AN AUDIOLOGICAL AND GENETIC PROFILE OF HEARING OF LEARNERS SUSPECTED OF FAMILIAL HEARING LOSS ATTENDING SCHOOLS FOR THE DEAF IN KWAZULU-NATAL

BY

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DECLARATION

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Hereby declare that the dissertation, which is submitted to the University of KwaZulu-Natal for the degree of Master of Communication Pathology (Audiology), entitled:

AN AUDIOLOGICAL AND GENETIC PROFILE OF LEARNERS SUSPECTED OF FAMILIAL HEARING LOSS ATTENDING SCHOOLS FOR THE DEAF IN KWAZULU-NATAL

Represents my own work in completion and execution. The descriptive study performed for this dissertation was under the guidance and supervision of Dr Lavanithum (Neethie) Joseph and Dr Colleen Aldous.

The study is the work of the author and has not been submitted in any form to another University or Tertiary Institute. Where use was made of the work of others, it is duly acknowledged in the text.

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ABSTRACT

This study focused on genetic familial hearing loss, concentrating on learners attending schools for the Deaf in Kwazulu Natal .The study sought to identify the audiological profile characteristics of suspected genetic familial hearing loss in the learners and their family members with hearing loss. Currently there is a scarcity of research in the area of genetics and hearing loss in South Africa.

The study aimed at providing both an audiological and genetic profile of familial hearing loss of learners with a history of hearing loss in the family. A quantitative multicase study research design was chosen. Participants were identified based on a positive family history of hearing loss in learner records and the referral from the school Audiologists. An audiological assessment and family pedigree was conducted on affected learners and their families who volunteered to participate in the research. The study sample consisted of 40 learners from 25 families with 70 affected participants who underwent audiological assessments and a family pedigree analysis, of which 31 were male and 39 were female. The pedigree analysis of the 25 families also presented 417 individuals who were reported to have normal hearing and 20 individuals with a reported hearing loss that were unable to undergo audiological testing in the study.

The study identified an autosomal dominant inheritance present in 32% (8) of families an autosomal recessive inheritance in 56% (14) and a presumed co-incidental familial hearing loss in 12% (3) of families. The audiological and genetic profile of families within the study, revealed significant differences between the profile of autosomal dominant and autosomal recessive hearing loss. The autosomal recessive group revealed a profile of hearing loss that was predominately congenital, prelingual, sensorineural, severe to profound in severity and flat in configuration. The autosomal dominant inheritance revealed a profile that was both prelingual and postlingual in onset with a moderate to severe sensorineural hearing loss and a sloping configuration.

The results of the study are supported by other studies with regard to the description and auditory profile differences of autosomal recessive and autosomal dominant hearing loss. An understanding of the audiometric profiles of genetic familial hearing loss, will be useful to health professionals when assessing and managing these families with a history of hearing

loss. It is believed that a standard method of profiling genetic familial hearing loss and the use of a family pedigree analysis, would be beneficial to professionals who encounter families with hearing loss.

The role of the multidisciplinary team which includes Audiologists, geneticists and genetic counsellors in the family with a familial hearing loss are invaluable. This study provided data on the current incidence of genetic familial hearing loss at schools for the deaf in the province of KwaZulu-Natal. It is expected that with the advancement of research in the area of genetic familial hearing loss, an increase in professionals in the field of genetics such as geneticists and genetic counsellors will be available.

Key words: Genetics, familial hearing loss, pedigree, autosomal recessive hearing loss, autosomal dominant hearing loss, co-incidental familial hearing loss, geneticist, genetic counsellors.

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CHAPTER ONE

STUDY BACKGROUND AND RATIONALE

1.1 Introduction

This chapter introduces the key features of the study. It commences with an introduction of hereditary hearing loss and moves on to an overview of its incidence and prevalence. It describes the current status of genetics and familial hearing loss. The rationale of the study is presented. Key genetic and audiological terms mentioned in the study are defined. An outline of the chapters in the write-up of the study is presented.

1.2 Study background

Hearing loss is described as a reduction in hearing sensitivity as a result of auditory dysfunction (Stach, 1997), and is regarded as the most common sensory disorder being diagnosed (Torre, Zeldow, Howard, Hoffman,Buchanan,Siberry,Rice, Sirois,Williams ,2012). Tsuiki and Murai (1971), stated that the presence of a hearing loss in several close family members usually indicates a hereditary etiology which is recognized as familial deafness. Stach (1997), defines familial hearing loss as deafness occurring in members of the same family and due to a genetic cause.

Hearing loss in children affects not only hearing ability, but it hampers speech and language development as well. The lack of adequate speech and language development warrants educational intervention which is required in addition to medical intervention in a child with hearing loss (Matsunaga, 2009) . With congenital and early onset hearing loss, early assessment and timeous intervention can prevent delayed speech and language development. In most hereditary conditions it is rare to regain such a functional component (Matsunaga, 2009).

Hearing loss was reported to affect 120 million people worldwide in 1995, 278 million in 2005 and 368 million people in 2014, accounting for 5.3% of the world's population (Olusanya & Newton, 2007; WHO, 2006; WHO, 2014). More than 100 countries are considered to be "developing" countries and make up more than 80% of the world's inhabitants accounting for two thirds of the deaf population (Olusanya & Newton, 2007; Traynor, 2011). Sub-Saharan Africa records a higher rate of severe to profound hearing loss as compared to many developed countries (McPherson & Swart, 1997). It is estimated that

unknown causes of deafness still account for 30-40% (Morzaria, Westerberg, & Kozak, 2004; Schrijver, 2004), and due to a paucity of research on etiological studies, older studies are used as points of reference. Etiological studies and reviews such as the study by Mulwafu, Kuper, and Ensink (2016) are currently being conducted in developing countries to determine the causes of congenital hearing loss due to limitations in the literature.

The population of South Africa a country within sub-Saharan Africa is estimated to be 54 million (StatisticsSA, 2014). South Africa has been described by researchers as an upper middle income country with a fairly well developed infrastructure, and a developing health care system, in comparison to other regions within sub-Sahara (Swanepoel, Storbeck, & Friedland, 2009). The prevalence of hearing loss in South Africa was estimated to be more than 1,5million people affected with hearing loss in 2011(StatisticsSA, 2011). The incidence of hereditary hearing loss in South Africa is unknown.

Hereditary hearing loss is regarded as unique in comparison to other hereditary conditions as there are several genes involved in genetic hearing loss which makes identifying the cause and manifestations challenging for practitioners (Matsunaga, 2009). Genetics is estimated to be responsible for at least 50% of congenital hearing loss (Nance, 2003). Etiological studies conducted in South Africa almost three decades ago shed light on hereditary and familial deafness (Sellars, Beighton, Horan, & Beighton, 1977; Sellars & Beighton, 1978, 1983; Sellars, Beighton, & Groeneveldt, 1976; Sellars, Napier, & Beighton, 1975). Sellars and Beighton (1983) identified a genetic cause of hearing loss in 18% of learners attending schools for the Deaf, 11% of which accounted for familial hearing loss.

Studies on familial deafness in Africa are almost nonexistent and data is usually extrapolated from etiological studies. There is a scarcity of literature on etiological studies specifically in Africa and sub-Saharan Africa and thus identifying familial deafness in this context is almost impossible. There is a scarcity of research and diagnosis of hereditary and early onset hearing loss in Africa (Dunmade, Segan-Busari, Olajide, & Ologe, 2006). This situation is a reality for South Africa, were no such reference data is available and comparisons to statistics from developed countries are used. More recently a study conducted by Kabahuma (2010) and Bosch (2013), assessed the prevalence of the most common cause of genetic hearing loss, the Gap Junction Beta 2 (GJB2) Connexin mutation, to the South African population. These studies both identified this common mutation was not prevalent in the South African

population. Wonkam et al. (2013),indicated that due to recent advances in molecular testing in developed countries, only about 10% of the causes of childhood deafness are now unknown.

With regards to genetic hearing loss, studies conducted on a collection of large families indicated that non-syndromic autosomal recessive inheritance accounted for between 70-80% of hearing loss while autosomal dominant accounted for 10-20% of inheritance and 1-2% was due to x-linked and mitochondrial inheritance (Espeso, Owens, & Williams, 2006; Morton, 1991; Nance, 2003). A majority, at least 50-70% of prelingual hearing impairment is non-syndromic, autosomal recessive and sensorineural in nature (Hildebrand, Shearer, Smith, & Van Camp, 2012; Kalatzis & Petit, 1999; Zakzouk & Al-Anazy, 2002). These genetic estimates on hearing loss were based on the collection and analysis of the family pedigree of the deaf proband (Nance, 2003).

Pedigrees are challenging to obtain due to the associated stigma of hereditary hearing loss and therefore makes identifying familial hearing loss extremely difficult. Researchers conducting literature reviews on previous genetic hearing loss research identified that a standard systematic method of classifying genetic hearing loss is imperative in order to allow for comparisons between research findings (McPherson & Swart, 1997). It is important to identify the characteristics of hearing loss as it may assist in diagnosis of the hearing loss especially if the cause is of genetic origin (Rehm, 2005; Nance, 2003). Genetic hearing loss is classified by several criteria i.e.; causality, time of onset, age of onset, clinical presentation, anatomic defect, severity, frequency loss, ears affected and prognosis in order to understand the mode of inheritance (Hildebrand, Husein, & Smith, 2010). Profiling the genetic and audiological aspects of hearing loss will provide a clearer understanding of the characteristics of genetic hearing loss.

As genetics research and the human genome project continue to provide valuable information on disease, disorders and disabilities in communication disorders, it will become increasingly critical that audiologists understand principles of genetics, genetic testing and genetic counseling. The Joint Committee on Infant Hearing (JCIH, 2000) indicated that with recent advances in genetic research and the completion of the human genome project there will be several disease causing mutations identified in the near future. The identification of the cause of deafness in any individual carries diagnostic, prognostic and therapeutic information to

improve medical and audiological care (Mesolella, Tranchino, Nardone, Motta, & Galli, 2004). Wonkam, Noubiap, Djomou, Fieggen, Njock, Toure (2013), indicated that sub-Saharan Africa requires more research on the genetic aspects of deafness especially of the black African populations, to identify and make molecular screening available for common mutations as in the case of the GJB2 mutations in the European Caucasian population. South Africa is a diverse nation, with different races, cultures and languages and thus population studies are a necessity.

The psychosocial impact of hearing impairment on a family is exacerbated when there is more than one child or family member affected, and genetic counseling becomes essential. A sense of guilt may be experienced by parents, about having "bad genes" and feelings of despair about their children's future when hearing loss is considered (Arnos, 2008). A genetic counselor is essential in the management of families with genetic hearing loss, especially in these situations. In South Africa there is a scarcity of geneticists and genetic counselors. Genetic hearing impairment, like other genetic traits share similar ethical issues such as autonomy, confidentiality, prenatal diagnosis and most importantly children's rights (Nance, 2003). These rights are not being considered due to the lack of services and investigation in the field of familial deafness in South Africa. Identification of the accurate cause of deafness may have many advantages for those affected as well as their families (Arnos, 2008). For children newly identified with a hearing loss, genetic testing may aid in providing an exact diagnosis of hearing loss, and eliminating unnecessary medical assessments (Arnos, 2008). Identifying the exact genetic cause of deafness in future will also aid professionals in explaining the hearing loss progression in families as well as to explore treatment modalities (Arnos, 2008).

While working at a government hospital in rural Kwazulu-Natal, the researcher had observed in her clinical assessments, families with more than one member presenting with deafness. These families time and again sought assistance when affected offspring presented with delayed communication milestones, poor or no speech development and little or no response to sounds even at a school going age. A pattern was identified, however due to limited academic training on genetic and familial hearing loss, the researcher felt incompetent in providing information to these families on the etiology of genetic deafness as well as answering pertinent questions that these family members posed regarding genetics and making appropriate medical referrals. A review of available literature in the area of familial deafness revealed a scarcity of research in the field of familial deafness worldwide and a

dearth of research endeavors in South Africa. Exploring existing literature the researcher was unable to identify available studies focusing on congenital familial sensorineural hearing impairment and saw a need to investigate this area further.

Schools for the deaf were identified as data collection points for the project as it is rich in resources. School based research has proven to provide resource rich data in South Africa. Studies conducted by Kabahuma (2010); Sellars and Beighton (1983); Sellars and Beighton (1978); Sellars et al. (1977); Sellars et al. (1975), are the largest school based studies involving genetics and hearing loss in South Africa.

The Province of KwaZulu-Natal accounts for 19.8% (10, 69 million) of the population making it the second largest province in South Africa. There are currently forty seven schools for the deaf in South Africa, seven of those schools are located in Kwazulu-Natal. In 1996 there was an estimated 6000 pupils attending schools for the deaf (Rakau et al., 1996), 2000 of those attended schools in Kwazulu-Natal. This figure is expected to have increased substantially since, taking into account the increase in population and high rates of Human Immunodeficiency Virus (HIV) and infectious diseases leading to hearing loss. Statistics on children attending schools for the deaf are unavailable due to a lack of research. Families with hearing impairment living in rural areas have more challenges in obtaining services and support than their urban equivalents (McKellin, 1995). The distributions of schools for the deaf in Kwazulu-Natal are not equal, with schools predominately situated in urban areas. If parents are unable to relocate, learners are required to be fulltime boarders at the school, living away from home for lengthy periods of time. When these institutions reach capacity, pupils get placed on a waiting list for enrolment until boarding is available, losing out on essential academic time and getting lost in the school system, some never attending school at all. There are an estimated 16 000 deaf children that will never attend schools for the deaf, due to socio economic conditions, poverty and cultural beliefs (Rakau et al., 1996). It is expected that some families with hearing loss will be overlooked in this study due to these reasons.

However with the implementation of newborn hearing screening, the rate at which learners are being referred to schools for the deaf is expected to increase substantially. Up to 50% of congenital hearing loss is suggested to be of genetic origin (Hildebrand et al., 2010; Schrijver, 2004). Therefore research that focuses on audiology and genetics is important. This study focused on identifying an audiological and genetic profile of familial hearing loss of learners attending schools for the deaf in Kwazulu-Natal.

1.3 Definition of terms

The following terms have been utilized in the study

Allele – One or several possible forms of a certain gene, which may or may not be affected or pathological (Martini, Read, & Stephens, 1996; Read, 2001)

Carrier – A phenotypically normal individual who is has one mutated allele and one normal allele. Usually identified in heterozygotes for recessive conditions, (Martini et al., 1996; Read, 2001).

deaf – This term describes a group of people who have usable residual hearing and use speech reading as well as hearing aids, cochlear implants and other assistive hearing devices. They may use sign language, but use oral communication as their primary mode of communication (Hearing Loss Association of America (HLAA), 2012)

Deaf- Typically describes a group of people who have little or no residual hearing and use sign language as their main method of communication. This group reflects the culturally Deaf people with using the upper case "D" when writing the term (HLAA, 2012)

Genotype – The genetic makeup of a person (Martini et al., 1996; Read, 2001).

Hearing loss – Used to describe a person with any degree of hearing changes, ranging from mild to profound (HLAA, 2012).

Hearing impairment – This term often implies a deficit due to a hearing loss (HLAA, 2012)

Hereditary – Transmitted through a family due to a genetic mutation (Read, 2001).

Heterozygous – The presence of two alleles at a locus that are not the same (Martini et al., 1996; Read, 2001).

Homozygous –The presence of alleles at a locus that are identical (Martini et al., 1996; Read, 2001).

Kindred – An extended family (Read, 2001)

Locus – The position of a gene occupies on a chromosome (Martini et al., 1996; Read, 2001).

Non-penetrance – "The situation when a person does not manifest a character despite having a genotype that normally produces a character" (Martini et al., 1996).This is perhaps due to the effects of other genes or of environmental factors (Read, 2001).

Offspring – The children of a person (Read, 2001).

Proband – The person in the family that serves as the starting point for the genetic study (National human genome research institute (NIH), 2016).

Penetrance – The likelihood that a phenotype will be seen with a given genotype (Read, 2001)

Phenotype –The observable characteristics of a person (including the result of clinical examination, such as hearing loss). This is compared with genotype (Read, 2001)

1.4 Chapter outlines

Chapter 1 – Introduction

This chapter introduces the key components of the research topic. It provides an overview of the status of genetic familial hearing loss locally and internationally. It discusses the rationale for the study and concludes with a description of terminology used in the study.

Chapter 2: Genetic hearing loss and its manifestations

This chapter aims to give an in-depth review of genetic hereditary familial hearing loss. It outlines the most relevant literature, local and international articles have been included. The etiology and incidence of hearing loss and genetics are discussed. It explores the psychosocial impact of genetic hearing loss on the family and discusses professionals involved in the assessment and management of familial hearing loss.

Chapter 3: Methodology

This chapter focuses on the problem statement, the research question and the purpose of the study. It explores the aims and objectives of the study and the methods which the researcher adopted to attain these. Procedures and instruments used in data collection and analysis methods are described. Ethical and legal considerations as well as the validity and reliability of the study are explored.

Chapter 4: Results

Results obtained from the data collection process are presented in terms of graphs, tables, figures and charts.

Chapter 5: Discussion

The results from chapter 4 are discussed, using information from the methodology and literature review to explain and explore the findings.

Chapter 6: Conclusion

This chapter includes clinical and theoretical implications, suggestions for future research as well as limitations of the study.

1.5 Summary of chapter

This chapter provided an introduction to the study. It explored the causes of genetic hearing loss as well as its prevalence. The study of genetics and familial hearing loss in developed countries are well ahead in terms of advancements. There is a paucity of research in the area of familial hearing loss in Africa and the sub-Sahara and thus there is a critical need to develop ethnic specific data to assist this multi diverse population. This study aims at providing a basis for information in the area of genetics and familial hearing loss and touches on critical areas associated with this multifaceted condition.

CHAPTER 2

GENETIC HEARING LOSS AND ITS MANIFESTATIONS

2.1 Introduction

This chapter presents a review of the literature and aims to provide an understanding of hereditary hearing loss, and its relation to familial deafness. It discusses the incidence and etiology of hearing loss and genetics and reviews literature on familial deafness as well as recent advances in genetic research. It explores the impact of genetic hearing loss on the family unit. Professionals involved and essential in the management of familial hearing loss are discussed.

2.2 Incidence and etiology of childhood hearing loss linked to genetics

In developed countries at least 50% of congenital hearing loss is predicted to be inherited, while 50% is estimated to be due to environmental causes or a combination of both (Gorlin, Toriello, & Cohen, 1995; Schrijver, 2004).

Prevalence rates for a congenital hearing loss are estimated to be greater in developing countries due to poverty, lack of immunizations, poor access to health care, high rate of infectious diseases, prenatal, perinatal and postnatal infections, consanguinity, as well as ototoxicity (Arnos, Welch, & Pandya, 2013; Kral & O'Donoghue, 2010; Lasisi, Ayodele, & Ijaguola, 2006; Olusanya & Newton, 2007; Stevens et al., 2011).

Statistics from developed countries estimate that up to 40% of causes of congenital or early onset permanent hearing loss are unknown, possibly due to a genetic etiology (Olusanya & Newton, 2007). Fisch (1969), in assessing the etiology of congenital hearing loss in the United Kingdom, reported that 36% of congenital hearing loss was due to a genetic etiology.

Permanent congenital hearing loss can have an early onset, occurring before, during or shortly after birth or can manifest itself postnatally which is considered as late onset (Olusanya, Luxon, & Wirz, 2004). In developed countries congenital hearing loss is estimated to occur in two to four per 1000 live births (Bale Jnr, Smith, & White, 2005; Olusanya & Newton, 2007). The prevalence of congenital hearing loss in developing countries is estimated to be six per 1000 births or greater, double that of developed countries (Olusanya & Newton, 2007; Olusanya & Somefun, 2009; Swanepoel et al., 2009). This infers that of the 120 million babies born annually in developing countries, 718 000 infants will be

born with congenital or early onset permanent bilateral hearing loss (Olusanya & Newton, 2007; Swanepoel et al., 2009). The Health Professionals Council of South Africa (HPCSA) has identified a list of risk factors associated with childhood hearing loss (HPCSA, 2007). There are several genetic and environmental causes of hearing loss that can occur congenitally, early onset or late onset as represented in Table 2.1 (HPCSA, 2007; Morton, 1991; Morton & Nance, 2006).

Table 2.1 Risk indicators for childhood hearing loss

Acquired Causes

Prenatal causes

- In Utero infection : TORCHs
  - Toxoplasmosis
  - Rubella
  - Cytomegalovirus (CMV)
  - Herpes
  - Syphilis
- Human Immunodeficiency virus (HIV)
- Malaria
- Diabetes mellitus
- Drug /alcohol intake during pregnancy
- Ototoxicity due to Aminoglycosides

Perinatal causes

- Hyperbillirubinemia at a serum level requiring exchange transfusion
- Persistent pulmonary hypertension of the newborn associated with mechanical ventilation,
- Conditions requiring the use of extracorporeal membrane oxygenation (ECMO).
- Asphyxia
- Anoxia
- Meconium aspiration syndrome
- Neonatal convulsions
- Prematurity
- Low birth weight <1.5g
- Prolonged neonatal intensive care treatment
- Mechanical ventilation lasting longer than 5 days
- Birth trauma
- Severe intracranial haemorrhage
- APGAR score- 0-4 at 1minute 0-6 at 5minutes

Postnatal causes

- Bacterial meningitis
- Ototoxic medication including; aminoglycosides, chemotherapeutic drugs, loop diuretics.
- Meningitis,
- sepsis, varicella zoster
- Herpes zoster

Hereditary/Genetic

- Consanguinity
- Family history of hereditary childhood sensorineural hearing loss
- Craniofacial anomalies, including those with morphologic abnormalities of the pinna and ear canal
- Findings associated with a syndrome known to include hearing loss

South Africa which forms an integral part of Sub-Saharan Africa, has an estimated 6116 infants affected annually with congenital or early onset permanent bilateral hearing impairment (Swanepoel et al., 2009). The incidence of childhood hereditary non-syndromic

hearing loss in South Africa was possibly last reported by Sellars and Beighton (1983) to be an estimated 11%. Statistics of hereditary hearing loss in both children and adults are essential to provide appropriate services for people with hearing loss caused by genetic factors, in terms of both diagnosis and counselling (Parving & Davis, 2001).

Rehm, (2005), indicated that amongst neonatal intensive care (NICU) graduates, there are three factors aside from infectious diseases that cause hearing loss, namely hypoxia, resulting in prolonged ventilation, hyperbillirubinemia causing neurotoxicity in high levels of unconjugated bilirubin, and lastly ototoxicity largely found in aminoglycosides. A study conducted in South Africa assessing risk profiles for profound hearing loss revealed that admission to the NICU was the most common risk identified (Le Roux, Swanepoel, Louw, & Vinck, 2015).

Sub-Saharan Africa has the most severe epidemic of the Human Immunodeficiency Virus (HIV) Infection in the world (Bates, Musonda, & Zumla, 2013; Swanepoel, 2008), with Southern Africa being the worst affected, and South Africa having the largest prevalence in the world (AVERT, 2014; Bates et al., 2013). HIV exposure is thought to put children at a higher risk for hearing impairment (Torre et al., 2012). Research reveals that hearing loss is more common in children who are perinatally exposed to HIV and HIV positive children when compared to HIV unexposed children (Torre et al., 2012). Children born from HIV infected mothers are at a higher risk for acquired infections such as meningitis, encephalitis, CMV, low birth weight, meningitis and herpes (Spiegel & Bronwit, 2002) cited in (HPCSA, 2007).The incidence of childhood acquired hearing loss in South Africa is expected to be higher than other developed and developing countries due to the higher incidence of HIV infected children. Auditory and otological disorders are more common in patients with HIV and is said to increase with the progression of the disease (Van der Westhuizen, Heinze, Hofmeyr, & Swanepoel, 2013). Ototoxicity associated with the treatment of opportunistic infections associated with the HIV disease, such as antibiotics, antiviral and antifungal treatments are associated with hearing loss in developing countries (Swanepoel, 2008).

Acquired hearing loss in adults is most commonly due to environmental factors such as noise exposure and acoustic trauma (Kochhar, Hildebrand, & Smith, 2007). The susceptibility of acquiring hearing loss is possibly due to the genetic-environmental interaction (Kochhar et al., 2007). An environmental cause of hearing loss is suggested to account for 25%, with an unknown etiology possibly genetic, accounting for 25%. Half of the causes of hearing loss

are thought to be due to genetic causes. Of that 50%, the majority of 70% is non-syndromic in nature, with 30% accounting for syndromic hearing loss. Of the non-syndromic hearing loss, an autosomal recessive hearing loss accounts for 80% , autosomal dominant 15-20%, and an x-linked and mitochondrial inheritance 1 and 2% respectively. Figure 2.1 represents the breakdown of the cause of hearing loss as depicted by Schrijver, (2004).

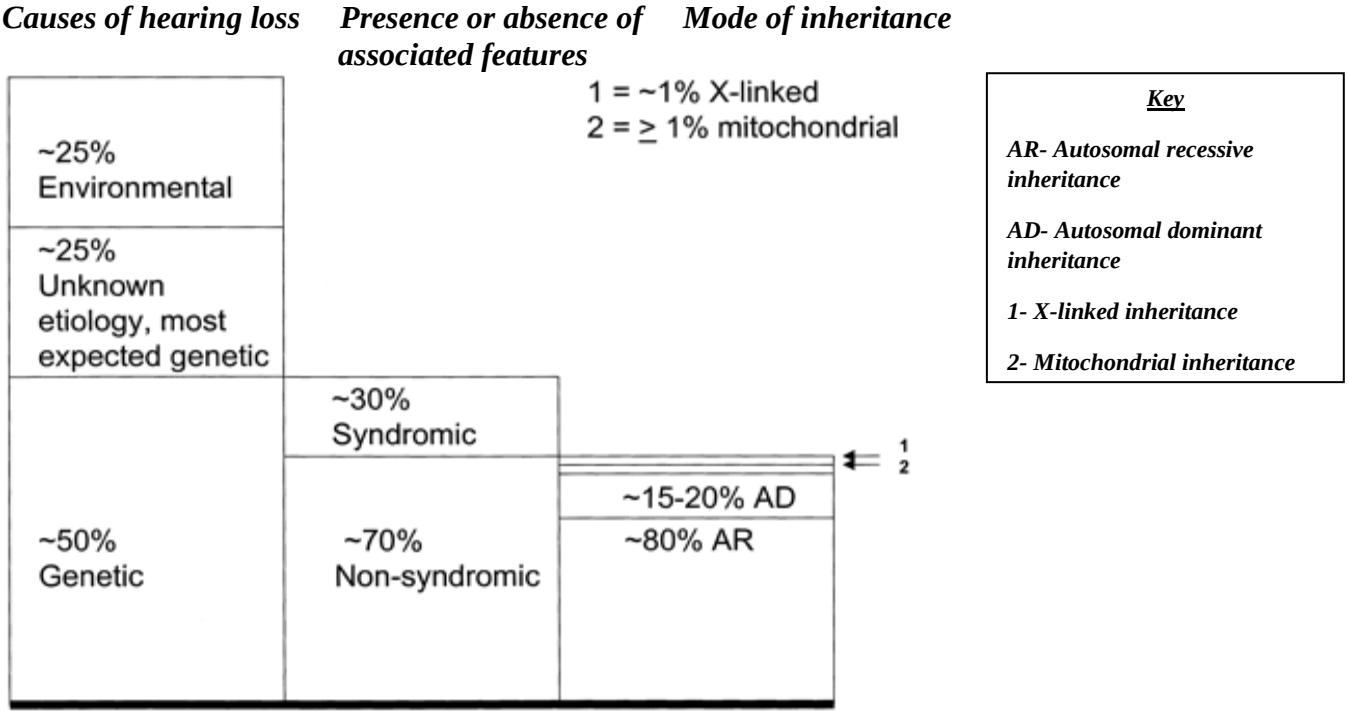

Figure 2.1 Etiology of hearing loss

2.3 Manifestation of genetic hearing loss

The history of genetic familial hearing loss is initially discussed below, to provide a background of how the etiology of familial hearing loss evolved. The basics of genetics and hearing loss, modes of inheritance and its audiological characteristics are described thereafter.

Familial deafness prompted researchers in the 16th century to identify genetics and its hereditary nature (Gorlin, 1995). This 16th century study showed many siblings with profound congenital hearing loss but with unaffected parents, indicating an autosomal recessive inheritance pattern (Gorlin, 1995). Later in the 17th century, the autosomal dominant inheritance pattern was described by Adams, by reporting a kindred affected in four generations and was identified as presenting with familial otosclerosis (Gorlin, 1995). It is assumed that the x-linked inheritance pattern was first described by Kramer in 1863 (Gorlin,

1995). In 1882 Politzer described genetic hearing impairment as the most frequent cause of hearing impairment (Gorlin, 1995) . Many centuries later in 1994, the first successful linkage study on autosomal recessive forms of non-syndromic hearing loss was identified and the first recessive genes, GJB2 and MYO7A were documented in 1997 (Petersen & Willems, 2006).

The human genome consists of 22 autosomes (1-22) and X and Y sex chromosomes that make 24 different genetic chromosomes (Keats, 2002). In a population a gene can have one allele or a great number of different alleles, however an individual can only have two alleles, This genetic behavior is regarded as autosomal (Read, 1996). Mendelian/monogenetic inheritance is the mutation of a single gene (Arnos et al., 2013). Genetic hearing loss is typically inherited as a simple mendalain trait (Gorlin et al., 1995). Humans are not ideal subjects for this type of analysis as they are non-experimental organisms, with small families with long life spans (Read, 1996).

Multifactorial inheritance are caused by a combination of environmental and genetic factors (Arnos, 2008). The genetic susceptibility of aminoglycoside antibiotics on hearing loss are an example of Multifactorial inheritance.

Mendelian inheritance is characterized by 3 patterns known as autosomal recessive, autosomal dominant, x-linked inheritance and mitochondrial inheritance (Arnos, 2008; Arnos et al., 2013; Gorlin et al., 1995). These inheritance patterns are dependent on the number of alleles mutated causing the hearing loss, as well as by the chromosomal location of the genes (Arnos et al., 2013).

2.3.1 Autosomal dominant inheritance

Affected individuals with autosomal dominant inheritance are heterozygote's presenting with two different alleles, one diseased and one normal (Arnos et al., 2013). The affected parent can pass the diseased allele or the normal allele to their offspring. The offspring has a 50% chance of inheriting a diseased allele or normal allele, and thus a 50% chance of being affected (Arnos et al., 2013). Those affected with autosomal dominant inheritance normally have one affected parent, and each offspring has a 50% chance of being affected (Read, 1996). In the autosomal dominant inheritance it is expected that some of the family members in each generation are affected (Keats, 2002) ,illustrated in Figure 2.2.

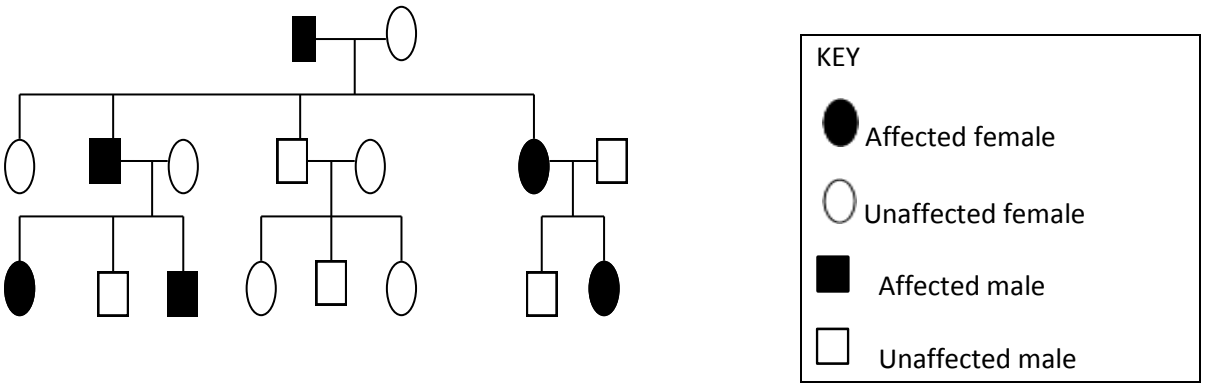

Figure 2.2: Autosomal dominant inheritance

Males and females are equally affected and likely to transmit the disease allele to their offspring. Research suggests that autosomal dominant inheritance accounts for up to 10-20% of genetic hearing loss (Hildebrand et al., 2010; Morton, 1991; Nance, 2003; Schrijver, 2004). A male to male (father to son) inheritance is observed eliminating a mitochondrial or x-linked consideration. Autosomal dominant hearing loss is characterized as late onset, postlingual, progressive and mild to severe in severity (Kalatzis & Petit, 1999) and accounts for 10-20% of hearing loss (Schrijver, 2004).

Occasionally a person is a carrier for the gene but it does not manifest as expected, this is regarded as non-penetrance, perhaps caused by the influence of other genes, age or environmental factors (Keats, 2002; Read, 1996).Complete penetrance is described when all individuals who inherit the mutated gene exhibit the disorder (Keats, 2002).

2.3.2 Autosomal recessive inheritance

A homozygous genotype is necessary for the disease to be expressed (Hildebrand et al., 2010; Read, 1996). Parents are phenotypically normal but are heterozygous carriers with one normal and one abnormal gene (Cohen & Gorlin, 1995; Hildebrand et al., 2010). The affected offspring inherits one mutated allele from each parent (Arnos et al., 2013). There is a 25% chance of an offspring receiving two mutant copies of the gene to express the disease phenotype, (Arnos et al., 2013; Cohen & Gorlin, 1995; Hildebrand et al., 2010) as depicted in Figure 2.3.

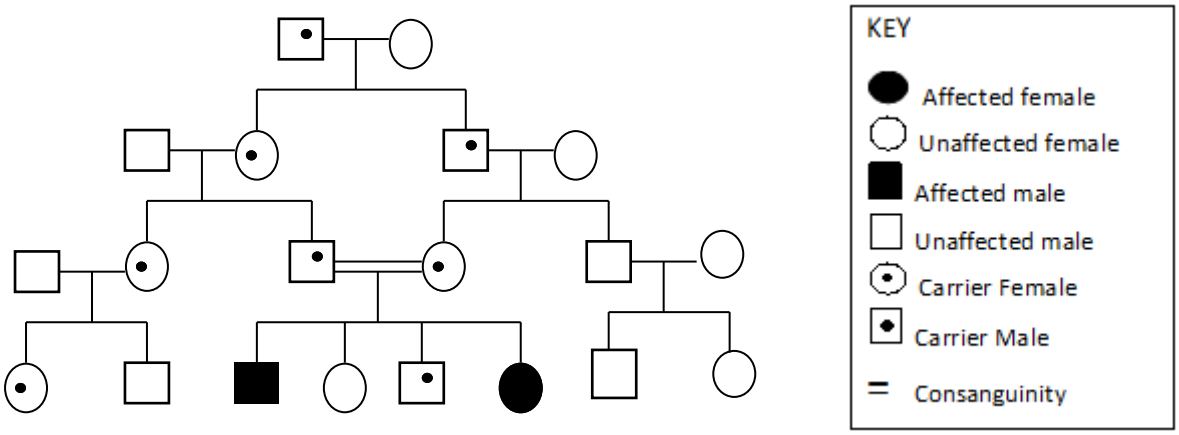

Figure 2.3: Autosomal recessive inheritance

Of phenotypically normal offspring it is suspected that two thirds will be heterozygous carriers for the disorder (Arnos et al., 2013; Cohen & Gorlin, 1995). Similar to autosomal dominant inheritance, both sexes can be affected (Cohen & Gorlin, 1995; Hildebrand et al., 2010). Sib ships of two or more children are common in recessive inheritance (Cohen & Gorlin, 1995) , however single affected children in a family are also a frequent occurrence (Arnos et al., 2013). As autosomal recessive inheritance is the most frequently occurring inheritance and the most common etiology for congenital hearing loss and should always be considered a cause of hearing loss even with a lack of environmental or syndromic causes and without a family history of hearing loss (Arnos et al., 2013). Most autosomal recessive mutations result in a severe to profound sensorineural hearing loss, with the exception of DFNB8 which causes a postlingual hearing loss that progresses rapidly (Hildebrand, Shearer, & Smith, 2015)

There is a possibility of autosomal dominant inheritance masking a recessive inheritance, according to Arnos et al., (2013), this is a commonality in the Deaf community with marriages within the community, where Deaf people marry and have children. This occurs when two people have the same autosomal recessive cause of hearing loss, thus their offspring will inherit both mutated alleles from their Deaf parents as there are no unaffected alleles to pass on , mimicking a dominant inheritance pattern (Arnos et al., 2013). An example of this is the GJB2 mutation which is the most common cause of deafness and chances of two people with deafness caused by this gene to marry and have children is not uncommon (Arnos et al., 2013).

There are communities that present with a more common gene pool than compared to other groups (Zakzouk, 2002) ,this is due to a higher incidence of mating with closely related individuals in communities due to social, cultural and religious beliefs (Kabahuma, 2010). The occurrence of hereditary hearing loss is more common in developing countries, perhaps due to the increased incidence of consanguinity (Zakzouk, 2002). Consanguineous marriages are still favored and socially supported in North Africa, Middle East and Asia (Barakat & Basten, 2014; Saggar & Bittles, 2008). Couples are defined as consanguineous if they have one or more ancestors in common, more often first or second cousins (Barakat & Basten, 2014; Hamamy, 2012; Saggar & Bittles, 2008). Sub-Saharan Africa is suspected to have high prevalence rates of consanguinity, however due to a lack of quantitative data and research this has yet to be documented (Barakat & Basten, 2014; Bittles & Black, 2010).

In 2010 it was estimated that 10.4% of the world's population were related by means of consanguineous unions (Bittles & Black, 2010). This figure does not account for areas such as sub-Saharan Africa were a paucity of research is evident. The majority of consanguineous families live in developing or underdeveloped countries were research is scarce (Kalatzis & Petit, 1999).

An etiological study conducted at a school for the deaf in Turkey revealed that 32% presented with familial deafness (Karatas, Kanlikama, & Mumbuc, 2006). Turkey is an area where consanguinity is a common occurrence, and the high incidence of the familial deafness has been attributed to this factor. A review of childhood etiological studies conducted in under developed areas in Turkey all revealed a high incidence of familial deafness, some as high as 63%, all suggesting a high incidence of consanguinity within the more under developed regions of Turkey. The absence of data, namely clinical characteristics in this population, is a disadvantage as it is a necessity for future research on these genetic mutations and for guiding genetic counseling (Kalatzis & Petit, 1999).

Consanguinity increases the chances of being carriers for the same type of autosomal recessive hearing loss, as the closer the relation between the couple the increased likelihood of them sharing the same mutated allele (Arnos et al., 2013). In the absence of a family history of hearing loss, with consanguineous parents, an autosomal recessive inheritance is strongly suggested (Arnos et al., 2013; Cohen & Gorlin, 1995; Hildebrand et al., 2010; Zakzouk, 2002).

It is not uncommon in a family to have generations of consanguinity with several people carrying the same affected gene. These families are particularly important for mapping of recessive hearing impairment and responsible for the majority of the genes for recessive deafness (Kalatzis & Petit, 1999; Read, 1996).

2.3.3 X-linked inheritance

Males (XY) with a mutated gene on the X chromosome will be affected as they do not have another normal X chromosome (Arnos et al., 2013). A female (XX) with an affected X chromosome , may be unaffected or have a milder form of hearing loss as they have another normal X chromosome (Arnos et al., 2013). Males (XY) pass the affected gene to their daughters (XX) but never to the sons (XY), as the son inherits the fathers Y chromosome. Thus there is never a male-male transmission. In the case of carrier females, with every conception they have a 25% chance of having an unaffected son, 25% chance of having an affected son, 25% chance of having a non-carrier daughter and 25% of having a carrier daughter (Arnos et al., 2013). X-linked can be recessive or dominant in men as reflected in Figure 2.4 and Figure 2.5

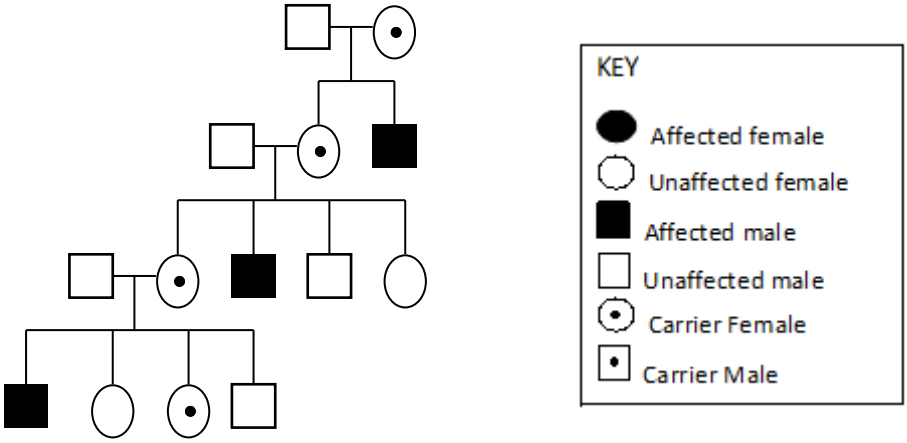

Figure 2.4: X-linked recessive inheritance

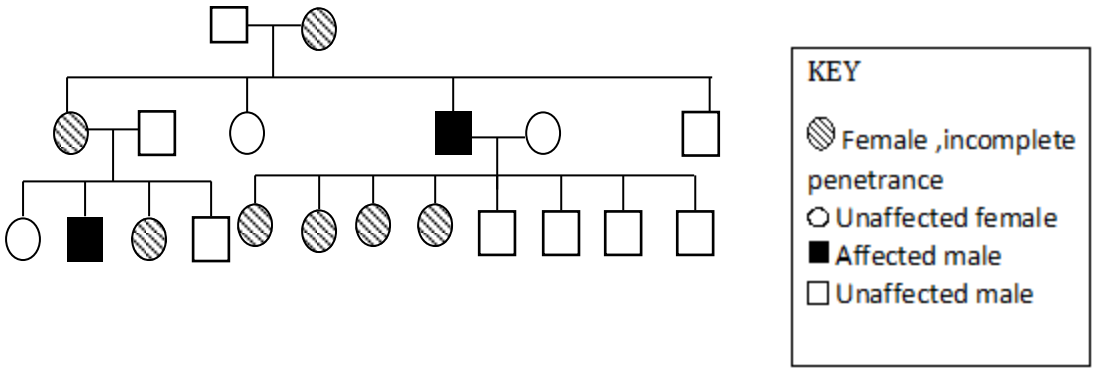

Figure 2.5 X-linked dominant inheritance

2.3.4 Multifactorial inheritance

Arnos et al. (2013), defines multifactorial inheritance as a deficiency resulting from a combination of environmental and genetic factors. Examples are cleft lip/palate, congenital heart disease and age related hearing loss and increased hearing loss susceptibility to aminoglycoside ototoxicity (Arnos et al., 2013). The reoccurrence risk is based on the frequency of the disorder in the population, e.g. the reoccurrence of cleft lip/palate is 4% if both parents are unaffected, and increases to 10% if one parent is affected (Arnos et al., 2013).

The susceptibility of acquiring hearing loss is possibly due to the genetic-environmental interaction (Kochhar et al., 2007). Age related hearing loss, also known as Presbycusis, is regarded as the most common age form of hearing loss in the world (Raynor et al., 2009). Studies on age related hearing loss reported that the interaction of both environmental and genetic factors perhaps plays a role in the aggravation and progression of Presbycusis (Raynor et al., 2009). Raynor et al, (2009), identified in their assessment of age related hearing loss, a clear familial pattern of Presbycusis suggesting a related genetic component.

Mitochondrial inheritance plays a substantial role in multifactorial inheritance, with aminoglycoside ototoxicity (Arnos et al., 2013). Schrijver (2004), reported that up to 25% of patients who receive aminoglycosides present with a hearing loss, even when issued a mild dosage, for a short duration. Schrijver (2004), reported that at least 50% of those affected present with the mitochondrial mutation which makes them susceptible to hearing loss from aminoglycosides. Bardien, Schaaf, Harris, Fagan, and Petersen (2009); Human (2009) and Human, (2010) reported that there are mitochondrial mutations, (A1555G, T1095C, C1494T, A827G, 961delT and T1291C) which make patients on aminoglycoside treatment susceptible for a sensorineural hearing loss. This is specifically important with the high incidence of multiple drug resistant tuberculosis (MDR) and extreme drug resistant tuberculosis (XDR) in South Africa where aminoglycosides are routinely used. Studies conducted by Human et al. (2010), suggested that a minimum of 0.9% of Black South Africans are susceptible to develop aminoglycoside induced hearing loss, due to underlying mitochondrial mutations.

Mutations as a result of mitochondrial inheritance are uncommon in congenital hearing loss, its prevalence increases with age (Matsunaga, 2009) . Mitochondria are structures within a cell that help to produce energy for the cell. Mitochondria have their own genes and own DNA. During reproduction the eggs of the mother and not the sperm of the father provides

mitochondria for the offspring. Therefore only females can pass on a mitochondrial characteristic to their child as reflected in Figure 2.5. A profound sensorineural hearing loss is associated with mitochondrial inheritance as well as other features Stach, (2003).

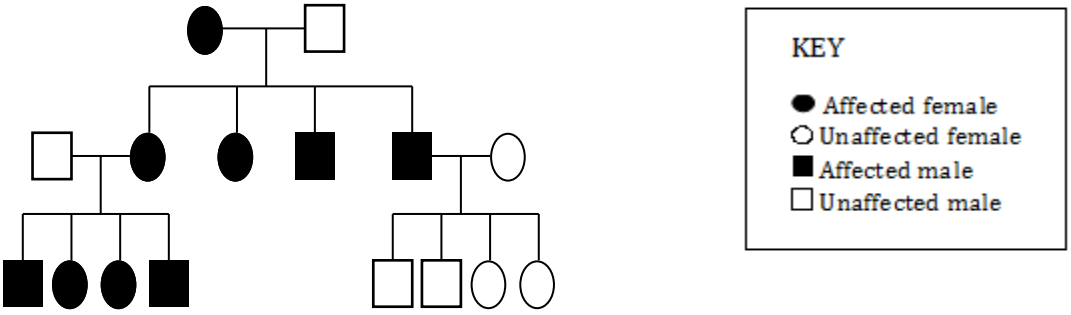

Figure 2.6 Mitochondrial inheritance

Mitochondrial inheritance constitutes for less than 1% of Hereditary hearing loss (as seen in Table 2.2), e.g. Kearns-Sayre Syndrome (Schrijver, 2004).

There are two main forms of genetic hearing loss i.e. syndromic hearing loss and non-syndromic hearing loss. These are discussed in the following section.

2.4 Syndromic and Non-Syndromic hearing loss

Of the causes of congenital hearing loss due to genetics, 30% are considered to be syndromic and 70% non-syndromic (Schrijver, 2004) as seen in Table 2.2. A syndrome is defined as a set of congenital abnormalities that occurs repetitively in a consistent pattern (Martini, Calzolari, & Sensi, 2009). Syndromic hearing loss accounts for up to 30% of hearing impairment, the majority of which is prelingual (Kalatzis & Petit, 1999; Zakzouk & Al-Anazy, 2002). Syndromic hearing impairment is the presence of other clinical anomalies as well as hearing impairment. More than 400 syndromes that include hearing loss have been described and in several of these cases the affected genes have been determined (Cohen & Gorlin, 1995; Martini et al., 2009; Nance, 2003). Hearing loss is genetically and clinically heterogeneous (Keats, 2002). The audiological manifestations of syndromic hearing loss vary and includes both conductive and sensorineural hearing loss, can be progressive or stable and unilateral or bilateral (ACMG, 2002).

Reflected in Table 2.2 are commonly occurring syndromes associated with hearing loss (Elsea, 2013; Griffith & Toriello, 2013; Haldeman-Englert, 2013; Keats, 2002; Kimberlin & Moller, 2013; Martini et al., 2009; Toriello, 2013a, 2013b).

Table 2.2 Syndromes and associated hearing loss

Syndrome and description of hearing loss
Autosomal recessive syndromes **Usher (I-III and subtype)** • USH1 – Congenital severe to profound sensorineural hearing loss across all frequencies • USH2 – Congenital moderate to severe sensorineural hearing loss • USH3 – Progressive sensorineural hearing loss **Pendred** • Congenital hearing loss. Bilateral and unilateral. • Mixed/ Sensorineural hearing loss • Enlarged Vestibular aqueduct causes hearing loss to range from mild to profound, with varying audiometric configurations **Jervell and Lange-Nielsen** • Congenital profound sensorineural hearing loss **Biotinidase Deficiency** • Early onset mixed/ sensorineural hearing loss. Severity ranges from mild to profound **Wolfram** • Onset 2nd decade. • Bilateral, sensorineural hearing loss. Slow progressive resulting in moderate to severe hearing loss
Autosomal dominant syndromes **Waardenburg (I-IV)** • Sensorineural hearing loss • Hearing loss ranges from mild to severe , and can be unilateral or bilateral **Branchio-oto-renal (I-II)** • Age of onset varies from early childhood to young adulthood • Conductive hearing loss in 30% of cases • Sensorineural hearing loss – 20% of cases • Mixed hearing loss – 50% of cases **Treacher Collins** • Absent / malformed ossicles, cochlear and vestibular system. • Bilateral hearing loss • Conductive/ mixed hearing loss **Stickler (I-III)** • Type 1-Mild to moderate sensorineural high frequency hearing loss. Present in 60% of those affected. • Type 2- Earlier onset than type 1, progressive, sensorineural hearing loss. Present in 90% of those affected. • Type 3 – Present in 100% of those affected. Mild to moderate non-progressive sensorineural hearing loss **Vohwinkel** • Congenital profound sensorineural hearing loss
X-linked syndromes **Alport** • Hearing loss onset, 1st or 2nd decade • Bilateral progressive sensorineural hearing loss **Norrie** • Progressive sensorineural hearing loss, develops after the age of 10years. • Sensory hearing loss ranging from mild – profound in severity. No retro-cochlear involvement suggested.

Non-syndromic hearing impairment is hearing impairment due to genetic insult without any other associated clinical anomalies. Non-syndromic sensorineural hearing impairment may be familial or sporadic. As depicted in Table 2.2 non-syndromic hearing loss accounts for 70% of genetic hearing loss, (Schrijver, 2004). Of the 70%, 15-20% are due to autosomal dominant inheritance, 75-85% are due to autosomal recessive inheritance and 1-2% are x-linked or a mitochondrial inheritance, as depicted in Table 2.2 (Schrijver, 2004). Currently there are up to 120 genes causing non-syndromic hearing loss (Schrijver, 2004; Smith, 2013). Non-syndromic hearing loss is categorized by mode of inheritance, type and progression of hearing loss, severity of hearing loss, configuration of the audiogram and the presence or absence of tinnitus and vestibular dysfunction, (Mazzoli et al., 2003; Smith, 2013). To further subcategorize into modes of inheritance of the non-syndromic hearing loss, the use of pedigree analysis and audiogram shape used in conjunction with the above categories is commonly used (Martini & Prosser, 1996). Martini &Prosser (1996) indicated that pedigree analysis and audiometric shape alone are not sufficient to assist in sub categorizing of genetic hearing loss. Pedigree analysis should consider consanguinity, paternity, and hearing status of the parents and siblings (ACMG, 2002).

2.4.1 Gene identification in non-syndromic hearing loss

There has been an immense growth in genetics and the localization and identification of new genes especially for non-syndromic hearing loss (Mazzoli et al., 2003). The Gap Junction Beta 2 (GJB2) was identified as the first deafness gene identified in 1997 (Petersen & Willems, 2006). The GJB2 gene encodes a gap junction protein called Connexin 26 (Cx26) that is expressed in the inner ear and plays an essential role in the maintenance of the endocochlear potential of the cochlea (Morell et al., 1998). A single GJB2 mutant allele called 35delG is said to be the most frequent cause of non-syndromic deafness in European countries. Cx26 mutations account for 50% of congenital non-syndromic recessive hearing loss, with the 35delG mutation accounting for more than 50% of the Cx26 mutations (Cohen, 1999). Studies conducted assessing GJB2 mutations revealed that ancillary testing such as; vestibular testing, CT scans, thyroid function tests, renal function tests etc., are not necessary as only hearing is affected (Cohn et al., 1999). A number of studies have reported that mutations in the Cx26 gene accounts for up to 60% in families with non-syndromic recessive sensorineural hearing loss and up to 40% of sporadic cases of non-syndromic sensorineural hearing loss (Mueller et al., 1999). The hearing loss associated with CX26 mutations are

severe or profound, symmetrical, sloping or flat audiogram configuration with a similar severity of hearing loss exhibited with other affected siblings (Mueller et al., 1999).

A pioneer study opening the doors for genetics and hearing loss research in South Africa was the investigation of the genetic aspects of hearing loss in the Limpopo Province of South Africa, (Kabahuma, 2010). The aim of the study was to investigate the role of the common GJB2 mutation, GJB6-D138 1830 deletion and the four most common mitochondrial mutations A1555G, A324G, A7511C and A7445G in the African hearing impaired population (Kabahuma, 2010). The study assessed 187 black learners presenting with non-syndromic sensorineural hearing loss attending two schools for the deaf in the Limpopo province. A significant number of these participants had a family history of hearing loss. Significant findings revealed that the most common genetic contributor to hearing loss the GJB2 and Gap Junction Beta 6 (GJB6) Connexin genes were not common in the South African population assessed (Kabahuma, 2010). The study did however suggest that the area assessed was in fact a high risk area for deafness, due to the pattern of distribution of the deaf participants and history of familial deafness. The researcher indicated that other unidentified genes may have a role in non-syndromic hearing loss of this population (Kabahuma, 2010).

A similar study conducted more recently also evaluated the significance of the Connexin gene in non-syndromic hearing loss in South Africa and Cameroon (Bosch, 2013).The findings were similar to that of Kabahuma, (2010) revealing that the GJB2 mutations were not significant in the African population with non-syndromic hearing loss and suggest that other possible undiscovered mutations may be involved (Bosch, 2013).Wonkam et al. (2015), further assessed the GJB2 gene prevalence in the black South African and Cameroonian population, and also confirmed that the GJB2 mutation was not associated with non-syndromic hearing loss in the African population. Similar studies in Ghana (Kenneson, Van Naarden Braun, & Boyle, 2002) and on the African American population all revealed that the GJB2 mutations were not prevalent in their population studies (Kenneson et al., 2002).

Thus studies in Africa (Bosch, 2013; Bosch et al., 2014; Kabahuma, 2010; Wonkam et al., 2015), have revealed that GJB2 mutations are not prevalent in this population, and suggest that population specific research is required in this context. From the studies above it is evident that the GJB2/ GJB6 gene mutations account for a significant amount of congenital non-syndromic recessive sensorineural hearing loss in other countries but has not been shown to be prevalent in the African studies conducted. Wonkam et al. (2015), further reported that

there is a great need for a genetic profile of hearing loss to be researched in the African population.

Other international studies include those conducted on the Ashkenazi Jewish population which revealed that congenital deafness accounts for 1.2 per 1000 of which 38% account for non-syndromic hearing loss (Morell et al., 1998). The Ashkenazi community is regarded as a population with high carrier rates for recessive conditions due to the large reduction in population sizes and endogamy in which there are a limited amount of people to marry in the communities' population (Morell et al., 1998). Studies conducted on families with non-syndromic hearing loss revealed that GJB2 mutations specifically the 167delT mutation is the most commonly occurring mutation in this population, and are possibly responsible for the majority of cases of non-syndromic hearing loss in this population (Morell et al., 1998). Generally the 35delG mutation is the most commonly occurring mutation in other populations, but the opposite has been identified for the Ashkenazi community with the 167delT mutation more frequently occurring (Cohen & Gorlin, 1995; Morell et al., 1998). This motivates for population specific research.

Studies investigating the incidence of the GJB2 mutations in familial and sporadic deaf families in the Iranian population revealed that GJB2 mutations were present in this population. The study emphasized the importance of GJB2 mutations as a factor in familial and sporadic hearing loss in Iran and also to be used as a tool for genetic counseling (Hashemzadeh, Farhoud, & Patton, 2007).The above is an indication that there are certain mutations more prevalent in specific population and racial groups, suggesting that certain mutations may be affected by different cultural backgrounds and ethnicities and thus vary among populations (Apps, Rankin, & Kurmis, 2007) . This is evident in the Caucasian and Mediterranean populations where several studies identified that Cx26 and its sub mutation 35delG were a commonly occurring mutation, with the 235delC commonly occurring in the Asian and Chinese population (Apps et al., 2007) and the 167delT occurring in the Ashkenazi Jewish communities (Morell et al., 1998).

The identification of these common mutations has led to genetic testing for these mutations forming part of the early hearing detection and intervention (EHDI) program in first world countries (Palmer et al., 2004). A study conducted on parents of deaf children identified that 96% were pro genetic testing of hearing loss (Brunger et al., 2000).

Almost 80% of genetic hearing loss is non-syndromic and sensorineural in nature, and it is often challenging to identify a non-syndromic hearing loss from others. There are also challenges identifying the differences between the different forms of non-syndromic sensorineural hearing loss (Steel & Palmer, 1996). Identifying GJB2 mutations as the most common cause of hereditary hearing loss has come from extensive research conducted on families with genetic hearing loss in European countries, and other first world countries.

2.5 The genetic evaluation

This is an essential service that enables those affected with hearing loss and their families to understand hearing loss as well as the possibility of other family members being affected (Arnos et al., 2013). The process involves an audiological assessment, extrapolation of family and medical history information, including a detailed pedigree, as well as a physical assessment and genetic testing (Arnos et al., 2013). The evaluation should include assessments to identify the etiology of hearing loss, as well as to identify related genetic syndromes with associated medical conditions that require treatment (Smith, Kimberlin, Schaefer, Horton, & Tinley, 1998). Table 2.3 lists the audiological assessments necessary in the assessment of genetic hearing loss according to Smith et al. (1998).

Table 2.3 Audiological assessments in genetic hearing loss

Audiological assessments in genetic hearing loss
• Otoscopy • Immitance Testing including acoustic reflexes • Pure Tone Audiometry • Speech Audiometry including Speech Reception Testing and Speech Discrimination Testing • Otoacoustic Emissions • Auditory Brainstem Response : For younger or difficult to test individuals

An important part of the genetic evaluation is to not only audiologically assess the first identified affected family member (proband), but all affected family members. An evaluation of several family members can indicate a specific diagnosis or mode of inheritance (Smith et al., 1998). The medical evaluation should include a detailed family and medical history, as well as a thorough physical examination to identify any dysmorphic features that may

represent a syndrome (Smith et al., 1998). The inclusion of a multidisciplinary team in the genetic assessment of a child with suspected genetic hearing loss is invaluable. Smith et al. (1998), suggested that the evaluations represented in Table 2.4, be used on a sliding scale based on the severity of the symptoms and individual patient needs.

Table 2.4 A medical genetic evaluation adapted from Smith et al. (1998)

STAGE 1	STAGE 2	STAGE 3
• Audiology • Otology • Genetics • Dysmorphology • Medical history • Pedigree analysis • Vestibular assessment	• Ophthalmology • CT scan of the temporal bones • Urinalyis, serum creatinine • Serology	• Electroretinogram • Electrocardiogram • Thyroid function/ perchlorate washout • Molecular DNA testing

Arnos et al. (2013) , suggested that the physical examination be conducted by a clinical Geneticist. The absence of a positive family history with a clear etiology of hearing loss, does not rule out a genetic hearing loss and these families should still have the option of a genetic evaluation, (Arnos et al., 2013). “New molecular disease mechanisms continue to be discovered thanks to age old clinical observations on disease transmission in families. A renewed look at a family tree led to the discovery of maternally inherited diabetes associated with deafness; this in turn led to further clues to the understanding of mitochondrial disease” (Vandenbroucke, 2001, p.330). A family pedigree is one of the most essential aspects of the genetic evaluation. According to Arnos et al. (2013), the following aspects need to be considered in a pedigree:

- It should include any relatives affected by hearing loss
- It should consider any medical conditions or physical features that may be associated with a hearing lose, e.g. Syndromes
- A vertical transmission of hearing loss over generations, is suggestive of an autosomal dominant inheritance
- The presence of consanguinity amongst parents with a child with hearing loss, is most often due to an autosomal recessive inheritance.

2.6 Professionals involved with familial deafness

With the high incidence of congenital hearing loss, and the enormous ramifications of late identification of hearing loss, new-born hearing screening has been the resolution for early identification. The Joint Committee on Infant Hearing (JCIH) following substantial research identifying the effectiveness of early hearing intervention and how it facilitates language development and socio-emotional development has recommended new-born hearing screening for every child born, and generated risk factors to identify children who may be at a high risk (HPCSA, 2007; JCIH, 2000; JCIH, 2007).

The goal of new-born hearing screening is to allow all children equal opportunities. The period from birth to five years of age is regarded as the most critical period for language acquisition and development (Yoshinagoa-Itano, Sedey, Coulter, & Mehl, 1998). Research revealed that early identification of hearing loss before three months of age and timely intervention before six months of age, allows for improved language development possibly in keeping with their hearing peers (Yoshinagoa-Itano et al., 1998). Children identified later may never catch up with their normal hearing peers, and have apparent delays in academic, social and emotional development, even with ongoing intervention (Olusanya et al., 2004). The use of objective hearing assessments such as Otoacoustic emission (OAE) tests and Auditory Brainstem Response (ABR) testing make newborn hearing screening cost effective and economically feasible (Cohn et al., 1999). The need for early hearing detection and intervention (EHDI) services is expected to be higher in families with a history of hearing loss (Olusanya et al., 2004).

The JCIH recommended that all families of children with an unknown etiology have the option of a genetic evaluation , JCIH (2000). Favoring this, in 2002, the American College of Human Genetics (ACMG) , formulated a team of multidisciplinary professionals in the fields of Audiology, Otorhinolaryngology, and Genetics to develop guidelines for the genetic evaluation of children (ACMG, 2002).

The high incidence of congenital hearing loss, the significant number of syndromes identified as well as the increasing underlying genetic etiology for congenital hearing loss makes the involvement of geneticists in the diagnosis and management of the child and family with genetic hearing impairment essential (Yaeger et al., 2006) With the implementation of EHDI services it provides a distinctive opportunity to include genetic testing in this new testing population. Increasing use of OAE and ABR in the assessment of children can increase the

identification of auditory neuropathy, which can also have a genetic origin (Smith et al., 1998). With the lack of professionals available, it is suggested that geneticists only be involved once a hearing loss is confirmed. It is anticipated that clinical geneticists become a part of the EHDI team, assessing and managing hearing loss.

A number of professionals are involved in the assessment of the patient with genetic hearing loss. The team includes but is not limited to the following professionals: Audiologist, Otolaryngologist, Radiologists, Medical technologists, Pediatricians, Medical Geneticists, and Genetic counselors, Ophthalmologists, Cardiologists and Nephrologists (ACMG, 2002; Smith et al., 1998). Genetic hearing impairment may be associated with other symptoms, e.g. heart defects, poor vision, etc., and thus a multidisciplinary team is essential in both the assessment and management of these patients (Smith et al., 1998).

Genetic counseling services in South Africa are almost non-existent (Madolo & Team, 1996) When families are faced with hearing loss that is of genetic origin or suspected of it in developed countries, they would seek assistance from a genetic counselor for different reasons (Smith et al., 1998). A portion of families would see hearing loss as a tragedy that will be avoided by not having subsequent children, while some do not see the transmission of the hearing loss as a problem (Smith et al., 1998). Genetic counselling for families with Deafness may only be effective and successful if the social values of the family and the Deaf community are taken into consideration (Schrijver, 2004). Without the availability of genetic counseling, the importance of genetic testing will be lost to families and professionals (Palmer et al., 2004).

2.7 Role of the Audiologist

Audiologists as hearing care professionals are frequently the first professional to have contact with a patient or families that present with familial hearing impairment. They have the most contact with parents of children with hearing loss and families with hearing loss, with these families relying on audiologists for knowledge, support and guidance (Steinberg et al., 2007). Often the first time that parents are confronted with a possible genetic diagnosis is when their audiologist refers them for genetic testing (Steinberg et al., 2007).

When audiologists are faced with a patient with hearing loss, it is common to be asked by the patient or family about the cause of hearing impairment as well as if there will be a progression and in most cases if subsequent offspring will be affected. Despite a detailed background history in some cases, a high number of patients have an unknown etiology of

hearing loss (Martini & Prosser, 1996). This makes counseling the patient and families challenging, not only for the audiologist but also for the geneticist and other team members.

Audiologists play a role in genetics by explaining the reason for referral and also assist by clearing misconceptions surrounding genetics and familial hearing loss (Martin & Clark, 1996; Steinberg et al., 2007). It is essential for audiologists to understand basic genetic mechanisms, modes of inheritance, congenital hearing loss and also the complex interactions between genes and the environment (Arnos, Della Rocca, Karchmer, Culpepper, & Cohen, 2004). Adequate training on genetics appears to not form part of the Audiology curriculum in South Africa and thus Audiologists when faced with counseling these patients seldom provide adequate or appropriate explanations of the disorder. Proper training is required for Audiologists in order to provide patients with insight on their condition, to provide the professional with insight on the patient's condition as well as to allow for appropriate referrals to medical geneticists and genetic counselors. The American Speech Language and Hearing Association (ASHA, 2004) recommends that audiologists should refer to a geneticist when an etiology of congenital hearing loss is unknown (ASHA, 2004).

A study conducted by Arnos et al. (2004), surveyed the genetic content of audiology academic programs in the United States, and found that 95% of the universities that took part in the research included genetics in their curriculum. Areas such as basic genetic mechanisms, syndromes and interpreting family history information, with a few institutions including information on molecular basis of hearing loss, ethics and legality as well as referrals to medical geneticists and genetic counselors. Little is known about the genetic aspects within the South African Audiology and Medical training curricula and it would be useful in guiding education and training on genetics in South Africa.

2.8 The role of genetic testing and counselling

The advancement of genetic research and the identification of genes responsible for hearing loss has resulted in genetic testing becoming standard practice in some developed countries, in the genetic evaluation of an affected child or adult (Arnos et al., 2013). Genetic testing involves either mutation specific testing, checking for the presence or absence of a specific mutation, such as connexin mutations. The second method, which is more time consuming and costly is gene sequencing, in which the DNA sequence is determined either completely or in part, to identify any abnormalities that may occur along the sequence that may be related to a hearing loss (Center for Disease Control and Prevention (CDC),2011).

The usual mutations screened for are mutations of the connexin mutations GJB2 / GJB6 which account for up to 50% of hearing loss in some countries (Arnos et al., 2013). Palmer et al. (2004), recommended that genetic screening for hearing loss form part of the EHDI process, incorporated with a genetic evaluation and genetic counselling.

If a mutation is identified it may aid families in the following way (CDC, 2011) :

- Awareness about the etiology of the hearing loss
- Awareness of the affected mutations, can assist medical professionals in understanding the severity and other related disorders that may be present
- The reoccurrence risk of future offspring being affected can be understood.

Genetic testing may be useful in determining the etiology of hearing loss , however with it are associated ethical and social issues (Arnos, 2008; Palmer et al., 2004). Arnos (2008), suggested that for genetic testing and its advances to be smoothly included into clinical practices, it requires "respect for patient autonomy" , their rights to informed decision making and to understand the specific needs of affected families and to be sensitive to their cultural and reproductive preferences.

The importance of genetic counselling in every stage of the genetic evaluation and management may assist in acceptance of information and with underlying issues (Arnos et al., 2013). Arnos suggested that the role of a genetic counsellor is to aid families with acceptance and understanding of information for appropriate decision making about their management and future. More recently a new method of genetic counselling called "non-directiveness" in which the genetic counselor remains neutral and does not in any way influence or sway the decisions of the family, while still giving them the accurate information has emerged (Arnos et al., 2013).

2.9 What does a genetic etiology of hearing loss mean to a family?

Smith et al. (1998), suggested that when families are faced with a diagnosis of hearing loss, there are several significant questions that arise such as:

- What is the cause of the hearing loss?
- Will the hearing loss change as the child gets older?
- Are there other physical or medical problems with the child?
- Could this happen if I have more children?

All of these questions can only be successfully addressed upon an accurate diagnosis of hearing loss (Palmer et al., 2004). Researchers suggest that identification of the cause of genetic hearing loss will provide benefit to parents by "removing the mystery of why their child has a hearing loss", aiding in treatment choices and providing parents with an accurate recurrence chance for future children (Palmer et al., 2004). Genetic professionals in the last decade have become sensitive to cultural differences, especially in the Deaf community.

2.10 Familial hearing loss research

Tsuiki and Murai (1971), stated that the presence of hearing loss in several close family members usually indicates a hereditary etiology and is recognized as familial deafness. Stach (1997), defines familial hearing loss as deafness occurring in members of the same family and due to a genetic cause. Read (2001), included that familial hearing loss is hearing loss that tends to run in the family due to possibly a genetic hearing loss or other causes.

Nance (2003), argued that if a genetic etiology was only considered in the presence of a family history of hearing impairment, simplex cases in which only one person in a family was affected would be impossible to identify and the incidence of genetic hearing impairment would be underestimated. Simplex cases can be due to environmental insult, and assuming that every simplex case has a genetic origin is also a challenge (Nance, 2003).

Studies on familial deafness are almost non-existent and the only data on familial deafness is usually extrapolated from etiological studies. There is a scarcity of literature on etiological studies specifically in Africa and sub-Saharan Africa and thus identifying familial deafness in this context is almost impossible.

In the mid 1970's to 80s a group of South African researchers endeavored to understand the prevalence and etiology of childhood hearing loss (Sellars & Beighton, 1983). Three thousand and sixty four (3064) children attending 16 schools for the deaf and 3 schools for the hearing impaired were assessed. This to date is the largest and possibly the most sophisticated etiological study conducted on the continent. The medical support team included otolaryngologists, geneticists, genetic nurses, radiologists, and pathologists. Initially specialized testing, including buccal smears, urine samples, electrocardiograms and skull radiographs were conducted, which were subsequently removed as it was found to provide little diagnostic information and deemed unnecessary. A diagnosis of genetic etiology was presumptive and based on background history of the learner. A high incidence of unknown

etiology was common, especially in schools that did not possess detailed background information on learners. Genetic causes of hearing loss accounted for 18%, 11% (347) due to familial hearing loss and 7% due to syndromic hearing loss. The researchers revealed that a high proportion of the unknown etiologies were presumed to be genetic in origin. Karatas et al. (2006), indicates that a detailed family history in a child with hearing loss is essential in identifying the etiology of deafness. There has been a dearth of research on the etiology of childhood hearing loss in South Africa since this study.

A similar study conducted in Zimbabwe assessed 885 children from five institutions for the deaf (Viljoen et al., 1987). The results revealed that 5.3% presented with familial hearing impairment while 11.9% presented with genetic hearing impairment without a familial pattern, (Viljoen et al., 1987). This study also included the services of a geneticist. These findings were similar to that of Sellers and Beighton, (1983). A high incidence of unknown etiologies with no additional anomalies was also identified. This lead to the conclusion that once more an under reporting of a genetic etiology was possible.

A retrospective chart review conducted in Nigeria in an ENT outpatient department assessed the etiology of deafness in 103 children with sensorineural hearing loss, who attended the hospital between the period of 2000-2005. The study revealed that genetics as an etiology of hearing loss accounted for 25% (Lasisi et al., 2006). The author indicated that some instances of genetic etiology may have been missed due to the lack of diagnostic facilities (Lasisi et al., 2006). The diagnosis of a genetic hearing impairment in this study was vague using a definition that included; family history of deafness, late maternal age, the presence of other physical abnormalities with deafness and the absence of other abnormalities with deafness only.

A similar retrospective review in Nigeria assessed 115 children with severe to profound hearing loss that attended a hospital outpatient department from 1999-2002. The researcher revealed that familial deafness was not identified in this study and attributed this, to challenges in obtaining family pedigrees with the stigma associated with familial hearing loss. Genetic studies in Nigeria are almost non-existent in most health care delivery centers (Dunmade et al., 2006).

A study conducted by McPherson and Swart (1997) reviewed published literature on the etiologies of childhood hearing loss in sub Saharan Africa conducted in either schools for the deaf or at hospital outpatient departments. Sub-Saharan Africa is made up of; East Africa,

Middle Africa, Southern Africa and West Africa. These studies have been mentioned below, along with other studies conducted on familial hearing impairment in Sub-Saharan Africa.

Table 2.5: Summarized findings of studies review on childhood hearing loss in Sub-Saharan Africa (McPherson & Swart, 1997)

Nigeria	▪ Holborrow, Martinson, and Anger (1982), assessed the etiology of deafness in 803 children most attending schools for the deaf. A possible etiology was obtained for only 64%. Familial etiology accounted for 3%. ▪ Ijadulo (1982), assessed the etiology of deafness in 298 profoundly deaf children from a school for the deaf and a hospital outpatient department. Familial deafness accounted for 13.1%. ▪ Obiako (1987) , conducted a 3 year survey on children presenting with profound deafness at a Nigerian hospital. Familial deafness only accounted for only a "few cases'.
Gambia	Holborrow et al. (1982), assessed 259 children from schools for the deaf. Only two thirds of the patients were assigned an etiology, of which a familial etiology accounted for 8%.
Ghana	Brobby (1988), conducted etiological assessments on 105 children attending a school for the deaf. The results did not mention familial hearing impairment. However a study conducted by David, Edoo, Mustaffah, and Hincliffe (1971) assessing Deafness in the high prevalence village of Adamarobe indicated that such cases of familial deafness have been known to occur in that area.
Angola	In an etiological study Bastos, Janzon, Lundgren, and Reimer (1990) assessed 105 children attending an Ear Nose and Throat clinic. The results revealed that 6% had hearing loss associated with familial deafness.

McPherson and Swart (1997) revealed that the studies that were discussed in the retrospective review were small in participants and sampling methods were not uniform, with different methods of assessment and criteria for defining hearing loss thus making comparisons between studies challenging. The researchers concluded that in order to substantiate

etiological data, prevalence studies need to have consistency and a standard classification system with transparency in methodologies. This was an issue that was prevailing as early as 1976 when researchers Gorlin and Koningsmark revealed that data regarding the etiology of congenital and early onset hearing loss was incongruent due to dissimilar definitions, varying degrees of completeness of assessments and differences in years of assessments (Gorlin, 1995).

Thus while increasingly more research is being undertaken, comparisons between studies is made difficult due to discrepancies in terminologies and descriptions. The GENEDEAF study group based on the recommendations of the EU HEAR project cited in Mazzoli, Kennedy, Newton, Zhao, and Stephens (2001) provided recommendations intended for researchers including audiologist and geneticists, who report families with non-syndromic hearing loss. Parving and Davis (2001), echoed the same message by stating that that there needs to be uniform terminology and descriptions when commenting on hearing loss in order to better determine new genetic disorders and for also improving patient care.

Parving and Davis (2001), reported several inconsistencies in studies when defining and diagnosing hereditary hearing loss, which resulted in the development of specific criteria for the diagnosis of hereditary hearing loss. Table 2.6 depicts the criteria suggested by Parving and Davis (2001).

Table 2.6 Criteria to be considered in hereditary hearing loss

1. One or both parents/grandparents affected.
2. Two or more generations affected.
3. Pedigree suggesting inheritance.
4. Two or more children with unaffected parents.
5. Consanguinity to any degree.
6. Only child with unaffected parents but with affected cousin(s).
7. Pedigree indicating X-linked inheritance.
8. Pedigree indicating mitochondrial inheritance;
9. Recognized syndrome.

Similarly the GENEDEAF study group after considering the predicament and challenges of discrepancies in data on non-syndromic hearing loss and genotype-phenotype correlation, sought to standardize the reported information by developing recommendations for the description of genetic and audiological data for families with non-syndromic hereditary

hearing impairment (Mazzoli et al., 2003). The recommendations were suggested for researchers, audiologists, and geneticists, who report on familial non-syndromic hearing loss, allowing a uniformity of definitions and descriptions. Table 2.7 reflects the recommendations suggested by Mazzoli et al., (2003).

Table 2.7 Recommendations of genetic and audiological descriptions for familial non-syndromic hearing loss

GENETIC ASPECTS

- **Nomenclature and localisation**
  - Locus name
  - Chromosomal localization
  - Gene name
  - Gene product name
- **Mutations and functions**
  - Mutations
  - Gene protein functions
  - Function change introduced by the mutation
- **Origin of family**
  - Geographical origin of the family
  - Ethnicity of the family
- **Pedigree and inheritance**
  - Pedigree figure
  - Pattern or inheritance
  - Penetrance
  - Complicating factors

AUDIOLOGICAL ASPECTS

- **Type of hearing impairment**
  - Conductive hearing loss
  - Sensorineural hearing loss
  - Mixed hearing loss
- **Severity of hearing impairment**
  - Mild: 20-40 dB HL
  - Moderate: 41-70 dB HL
  - Severe: 71-90 dB HL
  - Profound: ≥95 dB HL
- **Configurations**
  - Low frequency ascending
  - Mid frequency u-shaped
  - Gently sloping
  - Steeply sloping
  - Flat
- **Frequency ranges**
  - Low frequencies : ≤ 0.5 kHz
  - Mid frequencies : > 0.5 kHz ≤ 2kHz
  - High Frequencies : > 2 kHz ≤ 8kHz
  - Extended high frequencies : > 8kHz
- **Unilateral/ Bilateral**
  - With a bilateral hearing impairment it is essential to indicate symmetry of hearing loss i.e.>10 dB HL difference between the ears in at least 2 frequencies.
- **Estimated age of onset**
  - Congenital
  - Early onset
  - Late onset
  - Prelingual :Hearing loss present before speech and language development
  - Postlingual : Hearing loss that develops after normal speech and language development
- **Progression**
  - A hearing loss is regarded as progressive if there is deterioration in the hearing greater than 15 dB HL over frequencies of 0.5, 1 and 2 kHz over a 10 year period.
- **Presence/absence of vestibular dysfunction**
- **Presence or absence of Tinnitus-** Should include descriptions of tonal type and duration.

Several studies have questioned whether a specific audiometric configuration can be linked to a genetic mode of inheritance or cause of genetic hearing loss, (Fisch, 1955; Liu & Xu, 1994; Martini, Milani, Rosignoli, Mazzoli, & Prosser, 1997). Martini et al. (1997), reported that the thought behind genetic classification based on audiometric patterns is based on the relationship between the hair cell damage of the cochlea and the differences in hearing loss thresholds.

Liu and Xu (1994), in their study of familial hearing loss, assessed 28 families with non-syndromic hearing loss. The aim of the study was to identify the differences in audiometric severity and configuration between different genetic modes of inheritance and also to compare these results between families. The study included a thorough medical evaluation with pedigree assessments. The study also set out to identify any correlations between the genotype and audiogram. They reported that there were no specific genotype-phenotype correlation. They did however report that audiometric configurations and severity showed significant differences in the autosomal recessive families when compared to the autosomal dominant families. The autosomal recessive group revealed a severe to profound predominately flat audiogram, with the autosomal dominant inheritance revealing a varied severity from mild to profound, with varying audiometric configurations. Intrafamilial and interfamilial variations were marked in the autosomal dominant group.

A similar study was conducted by Martini et al. (1997), which assessed the audiometric patterns of non-syndromic sensorineural hearing loss. The study set out to identify if the audiometric pattern and severity alone could distinguish between a genetic and non-genetic cause of hearing loss and to correlate specific audiogram configuration to a genotype. Sixty five families underwent audiological assessments and were profiled according to hearing loss severity and set parameters of audiometric configurations. Results suggested that due to the severity of autosomal recessive hearing loss, the audiometric pattern cannot be used as a criterion to differentiate different genotypes. This may be possible in autosomal dominant hearing loss, with varying severity and audiometric patterns. Significant differences in audiometric severity and configuration were identified between the autosomal recessive group and autosomal dominant groups, similar to the findings of Liu and Lu (1994). Martini et al., (1997) suggested that audiometric configuration alone, may not be effective in the identification of genetic hearing loss and genotype, but the inclusion of other characteristics such as hearing loss progression, tinnitus and vestibular disturbances may be a more effective method of classifying and profiling families with non-syndromic hearing loss.

Arnett et al. (2011), assessed the genetic etiology in a family with an autosomal dominant progressive hearing loss, assessing 17 members, with 9 affected individuals and 8 unaffected. The findings identified that all affected members presented with a similar high frequency progressive sensorineural hearing loss, ranging from 1-21 years of age attributed to the KCNQ4 mutation. Arnett suggested that only utilizing family pedigrees and linkage analysis is a good method of identifying the etiology of hearing loss in larger families.

A study similar to the current study, evaluated the audiological profile of genetic hearing loss in a population in Greece assessing the common GJB2 mutations (Iliadou et al., 2003). One hundred and seven children underwent audiological and genetic evaluations, and were reported and described in keeping with suggestions by Mazzoli et al. (2003). Results of the study were similar to other studies assessing GJB2 hearing loss and revealed that the profile of hearing for patients with GJB2 hearing loss within the Greek population was found to be a severe to profound hearing loss with a sloping or flat configuration, predominately symmetrical, non-progressive and affecting more high frequencies.

Phenotype- Genotype correlations have over the years intrigued researchers and clinicians (Vona, Nanda, Hofrichter, Shehata-Dieler, & Haaf, 2015). The linking of genetic mutations to its effect on hearing loss type, severity and configuration, has to some degree provided a wealth of information thus far. However due to the genetic heterogeneity of non-syndromic hearing loss, more comprehensive correlations are challenging (Vona et al., 2015). With additional data becoming available and an enhanced understanding of the human genome, it may allow researchers an improved ability to combat this problem.

2.11 Research in genetics and hearing loss

The Human Genome Project initiated in 1990 by the National Human Genome Research Institute was the collaboration of researchers around the world, whose main aim was to identify, understand and map all genes of human (NIH, 2012). A combination of all of our genes is termed Genome (NIH, 2012). This project revealed that there are around 20 500 human genes. Due to the completed sequence the locations of these genes can now be identified. With the immense knowledge gained from the Human Genome Project, a great number of genes for deafness have been mapped. There are more than 120 genes identified causing non-syndromic hearing loss i.e. 60 prelingual and 60 postlingual (Smith, 2013)The identification of genes has been very significant in the diagnosis of hereditary hearing loss (Smith, 2013)

On the 9th of July 2015 researchers from the Swiss Federal Institute of Technology made a ground breaking discovery by assessing the use of gene therapy in a mouse that had TMC1 deletion in which both copies of the gene similar to that of congenitally deaf children, were deleted (Connor, 2015). The TMCI gene is known for being responsible for between 4-8% of human genetic deafness (Connor, 2015). The mice were injected with a healthy copy of the defective gene and then showed evidence of restored hearing. TMC1 and TMC2 are proteins found on microvilli of the sensory hair cells (Connor, 2015) According to the researchers using gene therapy to correct congenital hearing loss could be possible within the next five to ten years (Connor, 2015).

With the continual identification of new mutations that cause hearing loss, there is a need for research in hearing loss and genetics in South Africa, specifically focusing on families with deafness. Developed countries are decades ahead of us in terms of their research and findings in the area of genetics and hearing loss. They have maximized on their use of deaf family cohorts in research, to identify new mutations. As identified above, mutations such as GJB2, are not common in the African population but frequently occurring in European countries. Due to the differences in genetic mutations based on ethnicity and cultural backgrounds, we cannot compare findings of other countries to that of South Africa. Findings that are specific to the unique population of South Africa are needed.

A policy on human genetics was released in 1996 by the Department of Health in South Africa as guidelines for the management and prevention of genetic disorders, birth defects and disabilities (Madolo & Team, 1996). According to this policy, it was estimated that 150 000 infants presented annually with a serious genetic disorder by 5 years of age. These genetic disorders result in a disability throughout life and those affected may never reach their full potential. The genetic policy also raised the point that genetic professionals are scarce, and thus in South Africa patients are unable to obtain comprehensive genetic services if any at all.

When patients with familial deafness seek assistance at a hospital or clinic setting in South Africa, it is challenging to health care professionals to provide these families with the optimal support, and appropriate referrals. This is due largely to the lack of trained professionals namely geneticists and genetic counselors in South Africa as well as the lack of knowledge of other first line practitioners on how to appropriately identify and manage genetic hearing loss. The health system of South Africa does not have a structured system of identifying, assessing or managing patients with familial or genetic deafness and can therefore be seen as a major

contributor to why familial and genetic hearing loss in South Africa is a silent epidemic. Further, the above scarcity of genetic professionals in South Africa indicates the need for all disciplines of health to be educated and to be at the forefront of human genetics and genetic research. This would enable them to provide the best possible assessment and management of patients that present to them. As members of the genetic community, it is vital that we provide those with hearing loss and their families the best possible opportunities in line with primary health care, audiology and genetic services (Palmer et al., 2004).

2.12 Summary of chapter

This chapter explored both local and international research conducted on familial hearing loss and revealed that there is clearly a scarcity of research conducted on genetic familial hearing loss in South Africa. Familial genetic hearing loss is a complex condition and requires in depth research more specifically based on population specific data. The chapter explored the ethical and psychosocial aspects of genetic familial hearing loss and discussed the invaluable role that geneticists and genetic counselors play. It also discussed other key medical professionals involved with the individual and family with a genetic hearing loss, giving attention to the Audiologist who is frequently the first person to have contact with these families. The chapter concludes with recent advancements made in the field of genetic hearing loss.

CHAPTER 3

METHODOLOGY

3.1 Introduction

This chapter discusses the aims and objectives of the study. It explores the research methods used as well as the data collection process and analysis. It presents the method of the family pedigree compilation as well as the criteria used for audiological and genetic profiling in the study. It ends with ethical and legal considerations of the study.

3.2 Aims and objectives

3.2.1 Aims

The aim of the study was to determine and describe an audiological and genetic profile of learners suspected of familial hearing loss attending schools for the deaf in Kwazulu-Natal.

3.2.2 Objectives

In order to achieve the above aim, specific objectives were specified:

- To conduct an audiological assessment on all affected family members.
- To conduct a family pedigree dating back to a minimum of 3 generations if possible, on all families within the study.
- To determine the genetic inheritance pattern of each family using the pedigree and audiological information.
- To determine the audiological profile of the different modes of genetic inheritance based on the audiological information.
- To compare and contrast the inheritance patterns based on the audiological profiles.

3.3 Study design

This study was descriptive in nature and had both quantitative and qualitative elements in that participants presented key background case history information which allowed for the documentation, measuring and classification of hearing loss within families.

A quantitative, multicase study research design was chosen. A case study is a single unit that is researched in great detail over a few weeks to months (Bailey, 1997). It is “a research approach that is used to generate an in-depth, multifaceted understanding of a complex issue

in the real life context" (Crowe et al, 2011, p1). Stake (2006) in Crowe et al. (2011), characterised a case study in three specific types:

- Intrinsic – Used mainly to describe a unique phenomenon
- Instrumental – This uses a particular case to further understand a specific issue.
- Collective or multiple case studies – This involves studying multiple cases simultaneously, to gain a broader understanding of a particular issue.

A multicase study design is suggested over a single case study if

- Researchers want to build theories based on several studies, to allow for a stronger validated result (Bailey, 1997).
- It is "building general explanations that fits each of the individual cases, even though each case will vary in detail" (Bailey, 1997,p68).

Bailey (1997), suggested that cases studies are helpful and interesting ways for clinicians to learn about investigations and research. For unique research areas, such as rare pathologies the cases selected or available will be fewer (Stake, 2006). The objective of multiple case study design is to firstly understand the case, and then move on to study other aspects such as functioning and then on to comparing and relating it to other cases within the study (Crowe et al., 2011; Stake, 2006). When researching the multiple case study, researchers may opt to discuss each case on its own before combining the cases (Crowe et al., 2011).

Multiple case research requires the cases to have similarities. When studying multiple cases, the single case becomes helpful as it links to a collection of cases, with a common condition and features (Stake, 2006). In multiple case study research several cases are carefully chosen based on criteria, which allows an advantage to make comparisons amongst several cases.

The potential roles of case study and multiple case studies (Vandenbroucke, (2001, p.331):

- Recognition and description of new diseases
- Study of mechanisms of disease
- Medical education and audit
- Recognition of rare manifestations of a disease

A quantitative research design seeks to make predictions, generalizations, and "universal law like findings" in a structured environment (Rule & Vaughn, 2011). Quantitative research is

composed of three essential measures namely validity, reliability and generalizability (Rule & Vaughn, 2011). Validity is critical to ensure that the aim and focus of the study was maintained and was actually studied (Rule & Vaughn, 2011). Reliability in quantitative research ensures the replicability of the study, so others can conduct the same measures and expect a similar outcome (Rule & Vaughn, 2011). Generalization relates to the findings of the study being comparable to other studies of larger populations due to the expected high levels reliability and validity from the quantitative design (Rule & Vaughn, 2011). Researching human behaviour and social sciences, assessing feelings and experiences is not easily obtainable with quantitative research. Quantitative research is focused on "multiplicity and subjectivity of perspectives" (Rule & Vaughn, 2011). Qualitative research addresses this area of human behaviour , thoughts and feelings (Rule & Vaughn, 2011).

Henning, Van Rensburg and Smit (as cited in Rule & Vaughn, 2011, p. 61) reported that the two key components of qualitative research are "understanding" and an "in-depth enquiry". Rule and Vaughn (2011), indicated that both quantitative and qualitative research methods are useful in the investigations of social sciences. Making the choice of using a quantitative versus qualitative research method in case studies depends on the type of data obtained as well as the data analysis techniques (Rule & Vaughn, 2011). Rule and Vaughn (2011), reported that in order to fully understand a case, both qualitative and quantitative data are necessary as it provides an enhanced depth view of the cases and "yields data in the form of words and pictures".

An important issue with case study research is the ethical and social considerations for participants who make up the cases in the study. The researchers role is to ensure, anonymity and confidentiality , and to allow participants to make educated informed choices about entering into the research (Crowe et al., 2011). Crowe, et al., (2011), further suggested that the repercussions of divulging sensitive information can be an emotional burden and may result in participants declining participation in the study.

3.4 Study site

The study was conducted at four schools for the Deaf in the eThekwini region of Kwazulu-Natal province of South Africa. Kwazulu-Natal was chosen as the researcher worked within the Kwazulu-Natal province. Schools for the Deaf were chosen as research sites due to the following reasons:

- The majority of children with hearing loss were present at these institutions.

- These institutions had audiological testing equipment which allowed for a common point of testing affected learners and their families.
- All schools identified, reported good record keeping with background and family history information, making identifying learners suitable for this study easier.

Four schools were chosen based on the following criteria:

- Functioning audiological equipment that was calibrated for the year of testing (2013)
- An audiologist working at the school, with a knowledge of the background history of the learners.
- Approval from the schools to conduct the study

3.5 Study sample

Bailey (1997), described a study population as a total group of individuals that share the criteria and features that have been established by the researcher. The criteria for the population is predetermined prior to participant selection and the in-depth information regarding the participants is established later, after recruitment (Bailey, 1997).

A purposive sampling method was used. Rule and Vaughn (2011), indicated that making contact with everyone involved in a case study is a challenging task. Purposive sampling allows for the researcher to purposively choose research participants based on their suitability in meeting the research aims and objectives (Rule & Vaughn, 2011). The case study researcher is not interested in the representatives of a sample, but rather the ability of the sample to provide in-depth information about the case (Rule & Vaughn, 2011).

The study sample consisted of 70 participants with a history of familial hearing loss from 25 families who underwent audiological assessments and pedigree analysis in the study. Forty four of these participants were learners from the data collection points and 36 participants were affected family members who were available for testing.

The pedigree analysis described 417 family members that were reported to have normal hearing and 20 family members with a reported hearing loss that were not tested in the study. In total 507 individuals were discussed in the study.

3.6 Participants

3.6.1 Participant selection criteria

- Only learners with a history of familial deafness and their families were eligible for the study.
- Parents, siblings, cousins (1st, 2nd and 3rd generation), uncles, aunts, nieces, nephews of the proband were eligible for the study.
- Individuals who were adopted into the family were not be eligible, as only blood relatives were assessed (See Section 3).
- All participants who were able to join the study on a voluntary basis.

3.6.2 Description of participants

Normal hearing was reported in 417 individuals which included 202 males and 215 females. Twenty individuals were reported to have a hearing loss but did not undergo audiological assessments, which included 13 females and seven males. Seventy participants from 25 families underwent audiological assessments in the study, which included 39 females and 31 males.

The following families were recruited from each school:

- School 1 - Durban School for the Hearing Impaired: 2 Families (4 participants)
- School 2 - Fulton School for the Deaf : 5 Families (11 participants)
- School 3 - KwaThintwa School for the Deaf: 15 Families (44 participants)
- School 4 - V.N.Naik School for the Deaf : 3 Families (11 participants)

The majority of families (15), were identified and recruited from school 3. A smaller number of families, 5; 3 and 2 were identified and recruited at schools 2; 4 and 1 respectively. Due to the scarcity of schools for the deaf in Kwazulu-Natal, admission criteria is not dependant on the area that learners reside in. All schools have boarding facilities catering for learners from around Kwazulu-Natal, with no strict policies on admission regarding place of residence. The current study revealed that of the 967 learners attending four schools for the Deaf in Kwazulu Natal, a familial hearing loss was identified in 4.3% of learners.

Table 3.1 reflects that a majority of families within the study resided in eThekwini (36%), uMgungundlovu (32%) and uThukela (24%) municipalities, with a minority of 4% residing in the uMkhanyakude and Amajuba areas.

Table 3.1 Distribution of familial hearing loss within Kwazulu-Natal municipalities identified in the study.

Municipality	**Families (N=25)**	**Percentage**
Amajuba	1	4%
uMkhanyakude	1	4%
uMgungundlovu	8	32%
eThekwini	9	36%
uThukela	6	24%
Total	**25**	**100%**

3.6.3 Participants age and gender

The majority of participants tested ranged from 0-10yrs to 11-30yrs accounting for 34% and 37% respectively. A smaller number of participants fell within the 31-50yrs group accounting for 24%, with only 4% of participants in the >50years category (Figure 3.1)

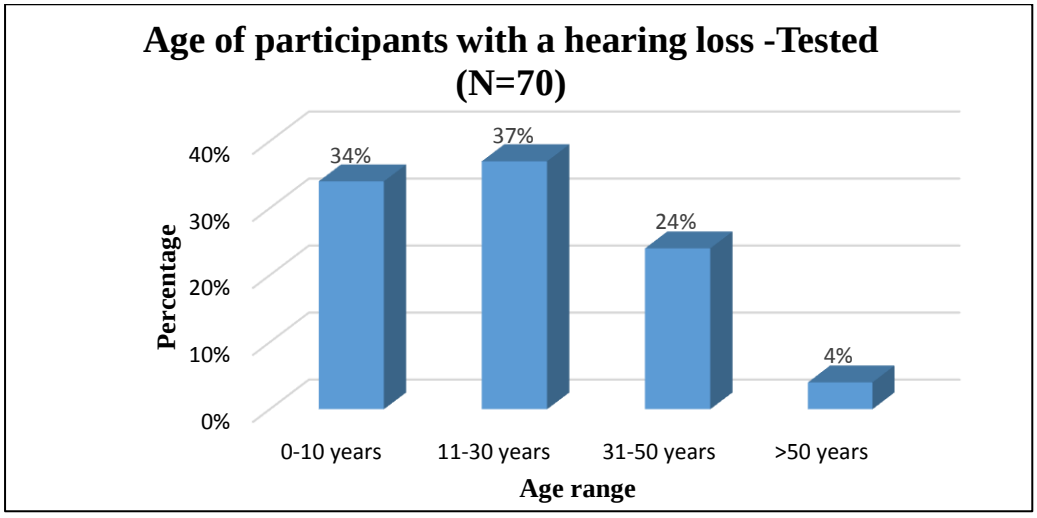

Figure 3.1 Age of participants with hearing loss – Tested

The inverse was identified in the group with a reported hearing loss who were not tested (Figure 3.2). The older categories of 31-50 and > 50years accounted for a higher percentage of 45 and 35% respectively, with the 11-30yr range accounting for 20%. None of the individuals within the reported group ranged in age from 0-10yrs. The normal hearing participants were not included in this group as not all ages were provided.

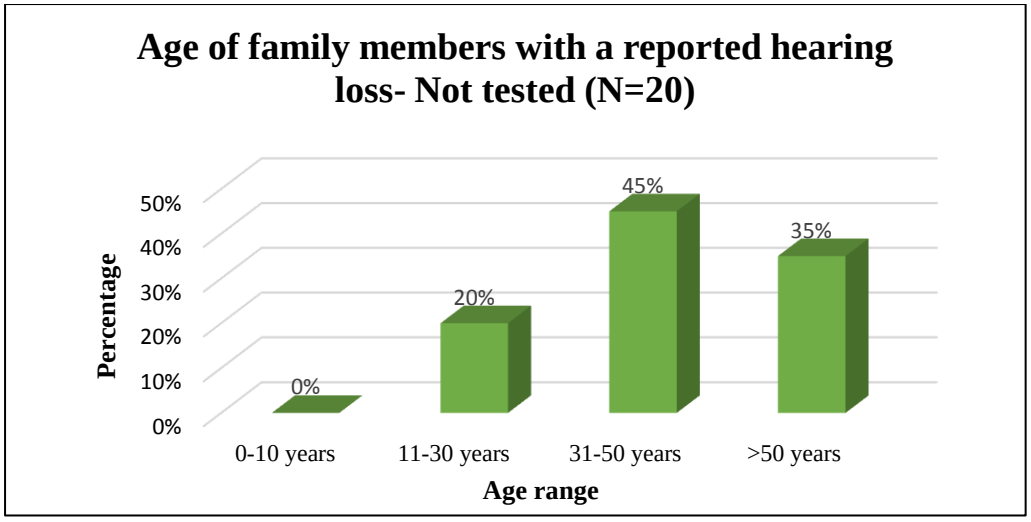

Figure 3.2 Age of participants with a reported hearing loss – Not tested

A total of 507 individuals were depicted and discussed in the study (Figure 3.3). The normal hearing individuals accounted for 40% (202) of males 42% (215) of females, and the not tested group with reported hearing loss accounted for 1% (7) of males and 3% (13) of females. A distribution of 6% (31) of males and females 8% (39) were present in the tested group.

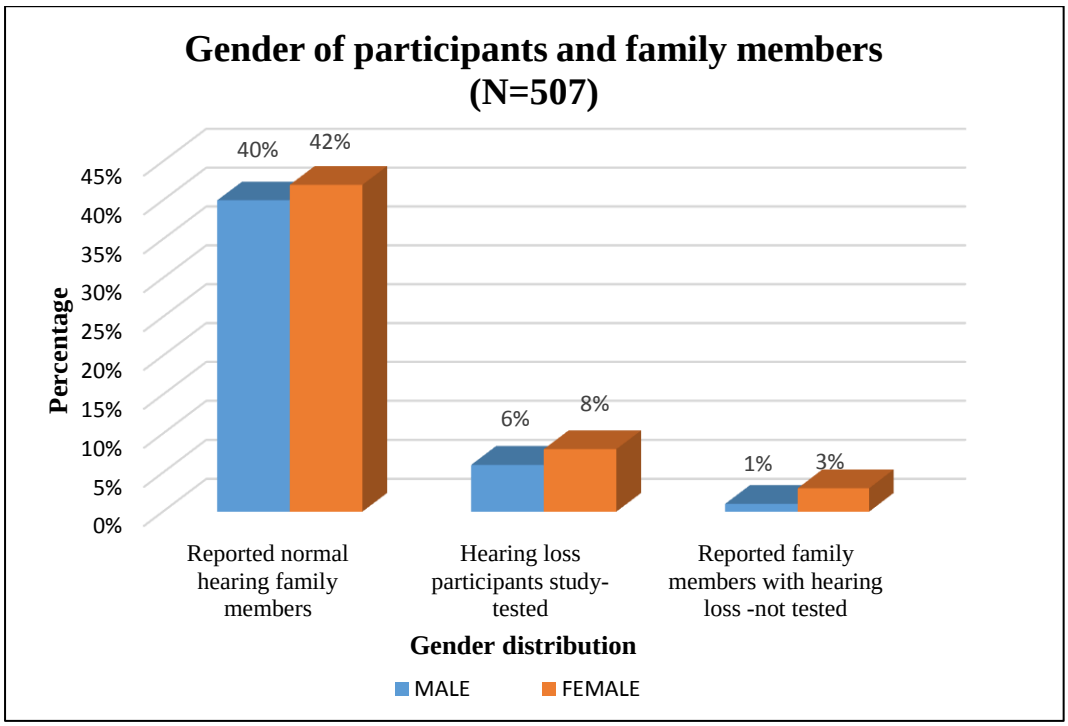

Figure 3.3 Gender of participants and family members

3.7 Data collection methods

3.7.1 Questionnaire

The questionnaire was developed to obtain critical information, pertinent to the objectives of the study. Rule and Vaughn (2011) , indicated that questionnaires are an effective method of obtaining information. A questionnaire which was adapted from Martin and Clark (1996) was utilised for the study. This questionnaire was chosen as it covered a wide range of areas, essential to this study, regarding, pregnancy history, prenatal exposure, acquired and genetic causes of hearing loss, including consanguinity and familial history of hearing loss. The questions were unambiguous and were tested in a pilot study before being finalized. The questionnaire consisted of six sections. The questionnaire contained yes/no and open ended questions. Refer to Appendix A for the questionnaire. A description of the questionnaire is presented in Table 3.2.

Table 3.2 Description of the questionnaire

Section of the questionnaire	Aspects covered	Motivation for inclusion
Section A: Biographical data **Questions 1-11**	• Age • Gender • Place of birth and current residence • Consanguinity of parents • Hearing status of parents	To identify the participant's geographical origin and current place of residence to identify trends if present. The identification of consanguinity provides a basis for the assumption of a genetic predisposition for a hereditary hearing loss.
Section B: Maternal Health and Prenatal history **Questions 1-5**	• Mothers health during pregnancy and if any illnesses acquired • Mothers emotional state during pregnancy	To determine the physical and emotional health of the mother during pregnancy to identify any conditions that may have resulted in a congenital acquired hearing loss of the participant.
Section C: Birth History **Questions 1-8**	• Birth history : - Prematurity - Length of pregnancy and duration of labour - APGAR scores - Birth trauma/ illness	To identify any significant birth history that may have resulted in an acquired hearing loss for the participant
Section D: Medical History **Questions 1-9**	• Health of the participant • Illnesses developed during childhood • Syndromic features	This section is critical to identify the health of the participant, to identify any illnesses that may have attributed to a hearing loss. To also identify any features associated with the hearing loss that maybe linked to a syndrome
Section E: Developmental History **Question 1-4**	• Motor development • Speech development	To identify any developmental delays in motor and or speech development, that maybe linked to a congenital or early onset hearing loss as well as other medical conditions.
Section F: Hearing History **Questions 1-4**	• Onset of hearing loss • Cause of hearing loss • Hearing assessment history • Recession in speech and language development	This section identifies age of onset of hearing loss, and the parent's idea of the cause of hearing loss. Hearing assessment history is ascertained to allow for an understanding of the participants hearing loss journey. To understand if speech and language development suddenly stopped, provides a reasoning for an acquired etiology.
Section G: Family History	• Family members with hearing loss • The age, relation and suspected cause of hearing loss are discussed here. This section leads to the pedigree compilation.	This section identifies information on familial hearing loss which is a critical aspect of the study.

A pilot study was conducted prior to data collection. The pilot study was conducted to identify any inconsistencies or weaknesses of the questionnaires and to evaluate if the appropriate answers would be easily obtained, (Bailey, 1997). Bailey (1997 p.184) suggested that undertaking a study without conducting a pilot study, opens the researchers to "uncertain methodologies" and "unclear justification for the study". The questionnaires were piloted on two volunteers. No discrepancies were identified in the questionnaire and nothing was altered.

The questionnaire was translated into isiZulu (Appendix B) by a Speech-Language Pathologist who is a first language isiZulu speaker. The translator was familiar with the study area and reported no challenges in translating the questionnaire due to her background in speech and hearing pathologies.

The questionnaire was administered by the researcher. Interpreters were used to assist participants with the questionnaire aspect during data collection. Hadziabdic (2011), suggested that an interpreter's role goes beyond just providing communication assistance, it also considers their professional attitude and dress , cultural and linguistic background and most importantly face to face interaction when translating. These were all considered with the translators utilised in the current study. There is a limited availability of professional translators in the healthcare industry, and thus it is not uncommon to use family members, friends and bilingual health care professionals (Gerrish, (2004) in (Hadziabdic, 2011). An isiZulu translator was present for all participants that required assistance in isiZulu. The translator was a first language isiZulu speaker who was a student studying an accounting degree at the time. She had recently matriculated with a higher grade pass in isiZulu.

A sign language interpreter was made available at each institution for the researcher to use as several participants and family members used sign language to communicate. Two sign language interpreters were Educators and two interpreters were Teacher Assistants at the schools for the deaf. They both had knowledge and experience in the use of sign language. The sign language interpreter were present to assist the participants and researcher to communicate effectively using sign language.

Prior to the data collection process, the interpreters were trained by the researcher on the ethical and appropriate behaviour expected during the questionnaire assistance and when liaising with participants and family members.

3.7.2 Audiological assessment protocol

The audiological protocol utilised in the study was adapted from, Stephens, (2001) who suggested the following investigations for proband as well as first degree relatives. Appendix C describes the audiological procedures, methods, and patient instructions. Table 3.3 outlines the audiological protocol recommended and conducted in the study.

Table 3.3 Audiological assessments conducted

Audiological Procedures
Otoscopy • Otoscopy was a critical tool in the audiological examination. It assisted in the identification of pathological conditions of the outer ear extending to the tympanic membrane (Gelfand, 1997).
Immitance • Immitance audiometry supplies information on various middle ear pathologies as well as middle ear muscle contractions. They are objective measures and require no physical response (Gelfand, 1997). - Tympanometry 220Hz Probe tone was used - Acoustic reflexes – Ipsilateral and contralateral reflexes, 500Hz – 4000Hz
Pure Tone Audiometry • Pure audiometry identifies an audiometric threshold, by assessing the lowest level of intensity at which the patient can hear a pure tone signal at least 50% of the time (Harrell, 2002) • The method that was used to obtain pure tone thresholds was the ascending/descending method developed by Carhart and Jerger (1959) in Harrell (2002). This was be done for the Air conduction frequency range of 250-8000Hz and Bone conduction testing frequencies of 250-4000Hz.

Table 3.4 indicates the audiological equipment utilised at each institution.

Table 3.4 Audiological equipment utilized at each school

School	Equipment	Make
School 1	Otoscope	Welch Allyn
	Audiometer	GSI 68
	Tympanometer	GSI 38
	Testing booth	3m X 3m
School 2	Otoscope	Welch Allyn
	Audiometer	Interacoustics
	Tympanometer	GSI 38 V4
	Testing booth	3mX3m
School 3	Otoscope	Welch Allyn
	Audiometer	Madsen Itera 2
	Tympanometer	GSI 31
	Testing booth	3mX 3m
School 4	Otoscope	Welch Allyn
	Audiometer	GSI 61
	Tympanometer	Madsen
	Testing booth	3x4m

All equipment utilized at the schools were calibrated for the year of testing (2013). (Appendix D).

3.7.3 Pedigree analysis

The pedigree drawing represented a family tree with its members and reflected those affected and unaffected with hearing loss over at least three generations when possible. According Kochhar et al (2007), a three generation family history with attention to other relatives with hearing loss and relative findings should be obtained to assist with information for a pedigree chart. Pedigree information was derived during the questionnaire administration with family members. Figure 3.4 represents the symbols utilized in the pedigree and its meaning. Studies conducted by Liu and Xu (1994) and Martini et al. (1997) suggested similar methods of categorizing inheritance patterns using pedigree and audiometric information.

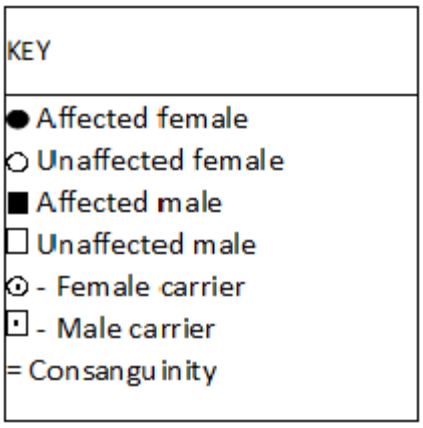

Figure 3.4 Key of symbols utilized in the pedigree

3.8. Data collection procedure

The data collection process is discussed below in 2 phases. Figure 3.4 provides an outline of the process.

Phase 1

- The schools principals and audiologists were contacted to discuss the research project. A letter of request (Appendix E) and power point presentation regarding the purpose of the project was sent to all schools of interest.
- Ethical clearance for this study was obtained from the Human and Social Science Ethics Committee at the University Of KwaZulu-Natal (UKZN) (HSS/0492/012M) (Appendix F).
- Approval to conduct the research was obtained from the school Principals (Appendix G).
- With the assistance of the schools Audiologist, school records of learners who were suspected of familial hearing loss were perused to check for a history of familial deafness.
- Learners who did not have a family history of hearing loss were not considered for further investigations
- Twenty eight (28) learners were identified with a positive history of familial hearing loss and met the criteria for the research study. These learners moved on to phase 2 of the data collection process

Phase 2

- All parents/ caregivers of learners identified in phase 1 with a positive family history of hearing loss were contacted telephonically to meet at the schools during the end of term. They were requested to come with all affected family members if possible.
- The 28 families were met at the schools end of term week. Informed consent was obtained from 25 families (Appendix H /Appendix I). Information regarding the research aim and procedures were detailed in the consent form (Appendix H/I). Three families declined and were then excluded from the study.
- An in-depth questionnaire (Appendix A/B) was administrated on each family, with the use of an interpreter when necessary.
- The same isiZulu interpreter accompanied the researcher to all testing points. A sign language interpreter was provided by each school. All interpreters were trained prior to data collection regarding the requirements as well as the ethical issues surrounding medical research.
- A family pedigree was drawn on each family with the assistance of the caregiver/parent.
- Audiological assessments were conducted on all members who were able to meet at the school for testing. Seventy participants were assessed, which consisted of 31 males and 39 females.

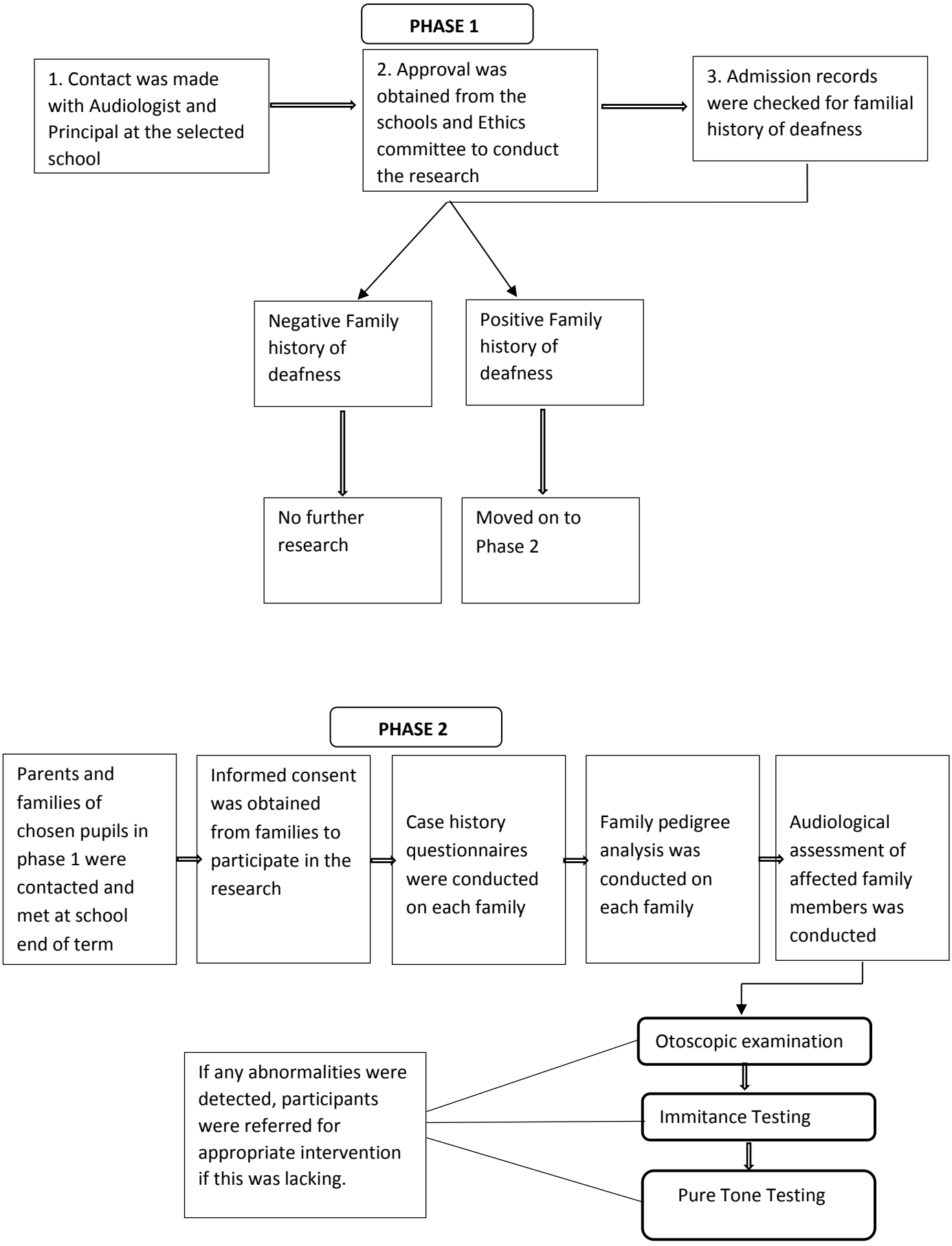

Figure 3.5 Data collection process

3.9 Validity and reliability

The principles of validity and reliability are critical in research to identify the credibility of the study (Bailey, 1997). Reliability considers the replicability of the study and its findings and validity considers the accuracy of the findings in the study (Bailey, 1997). The points below suggest how validity and reliability was considered and implemented in the study.

- None of the participants reported feeling uncomfortable at the data collection point. It is assumed that participants felt comfortable to reveal important information regarding family and relevant medical history. This was important for participant reliability.
- Questionnaires were translated into isiZulu by a Speech-Language Pathologist who had an advanced knowledge in this area of research. Both the isiZulu and sign language interpreters reported a higher education after matriculating.
- A pilot study was conducted on two volunteers to assess the usability of the questionnaire.
- All participants were tested by the researcher for consistency of data collection. Calibration certificates of equipment used were verified before data collection commenced. Audiological testing was conducted following American National Standards Institute (ANSI), and the South African National Standards (SANS) requirements.
- Inter-rater reliability was used to assess the consistency of the data analysis. This was conducted by another Audiologist. Twenty percent of the data (15 participants) was analysed, and found to correlate with the researcher's analysis .The percentage agreement was 100% (Table 3.5). The protocol used in the study recommended by Mazzoli et al. (2003) was specific in terms of categorising data and left little room for error.

Table 3.5 Inter-rater reliability of data analysis

Profile category	**Difference**
Hearing loss type	0
Hearing loss symmetry	0
Hearing loss severity	0
Hearing loss configuration	0
Age of onset of hearing	0
Prelingual vs postlingual onset	0
Presence/absence of tinnitus	0
Presence/absence of vestibular symptoms	0
Autosomal dominant group placement	0
Autosomal recessive group placement	0
Co-incidental group placement	0
Difference (1) = 0 No differences (0) = 11 **Percentage Agreement = 100%**	

Key -1 = Difference 0= No difference (McHugh, 2012)

3.10 Ethical and legal considerations

The following areas were considered:

- Ethical clearance for this study was obtained from the Human and Social Science Ethics Committee at the University of KwaZulu-Natal (UKZN) (HSS/0492/012M).
- The following principles were adhered to in order to maintain the highest ethical standards:
  - Consent was obtained from all participating schools.
  - The researcher provided each participant with information relating to the nature of the research. The aims were clearly stated by the researcher.
  - Informed consent was requested from each participant for each test procedure, in the event of a minor, parental / guardian consent will be obtained. (Appendix H and Appendix I)

The researcher adhered to the universal precautions, with regards to infection control during the study.

- Any participants with results suggestive of a genetic etiology, had the option of being referred for genetic counselling and further genetic evaluations
- Beneficence: Participants, their families and all individuals involved in familial hearing loss are expected to gain benefit from the research findings as it provides an improved understanding of familial hearing loss and genetics.
- Justice: The study targeted families with a suspected history of familial hearing loss. Participants were not excluded based on age, class, gender or race. The sensitive issue of a participant's adoption status was to be handled with the upmost confidentiality and all patients were numerically represented.
- Non-maleficence: Participants were informed that the study was harmless and posed no risk to them. All assessments were non-invasive in nature.
- Privacy- Confidentiality of the results were maintained in that no individuals beside the researcher had knowledge of them. All data will be locked in the UKZN Audiology Department for a period of 5years as per university requirements before being disposed of.

3.11 Data analysis

3.11.1 Statistical analysis

Descriptive and inferential statistics were used. Descriptive statistics are used to describe and summarize data in a meaningfully manner by means of percentages, frequencies, and in-depth descriptions of relative positions and central tendencies (Bailey, 1997). Inferential statistics allows inferences to be made from a study sample of the population, allowing for generalization and employing probability (Bailey, 1997).

A data base was created to allow for a simple method of profiling participants according to the profile characteristics. SPSS version 19.0 (SPSS Inc., Chicago, Illinois) was used to analyse the data. Both descriptive and inferential statistics were used. Data was analysed with the assistance of a statistician.

Categorical data was analysed by descriptive statistics and were presented in terms of frequency counts and percentages and bar charts. Inferential statistics such as the Fishers exact test to identify if the differences in scores between two categories were significantly different (Bailey, 1997). A p value <0.05 was considered as statistically significant.

3.11.2 Audiological profile characteristics

Descriptions for the audiological and genetic characteristics of familial hearing loss utilised in the study were taken from the GENEDEAF study group (Mazzoli et al., 2003). These characteristics and protocols was employed to profile the participants according to their genetic and audiological characteristics.

- Type of hearing loss
- Severity of hearing loss
- Audiometric configurations
- Frequencies affected
- Unilateral VS Bilateral hearing loss
- Estimated age of onset
- Tinnitus
- Intrafamilial/interfamilial variability
- Vestibular symptoms and function

3.11.3 Genetic characteristics

- **Criteria suggestive of an autosomal recessive inheritance**
  - Both males and females have an equal chance of being affected (Read, 1996).
  - There is a 25% chance of parents in each pregnancy both passing the mutations to their child and having a Deaf or hard of hearing child (Arnos et al., 2013).
  - A recessive inheritance is most likely if parents are consanguineous (Arnos et al., 2013).
  - A recessive inheritance is strongly assumed with affected offspring has 2 unaffected parents (Arnos et al., 2013).
  - Autosomal recessive inheritance is usually, congenital or early onset, prelingual onset and stable (Arnos et al., 2013).
  - A severe to profound sensorineural hearing loss is common in autosomal recessive inheritance (Hildebrand et al., 2015).
  - Autosomal recessive disorders are not usually seen in every generation of a family (Genetics-Home-Reference, 2017).

- **Criteria suggestive of an autosomal dominant inheritance**
  - Both males and females have an equal chance of being affected (Read, 1996).
  - An affected parent is often identified (Genetics-Home-Reference, 2017)
  - With every pregnancy there is a 50% chance the affected parent will pass the mutated allele and have an affected child (Arnos et al., 2013).
  - The pedigree usually depicts several affected family members in successive generations (Arnos et al., 2013) .
  - There is a variation in the age of onset of hearing loss and severity of hearing loss, due to variable expression, which is common in Autosomal dominant hearing loss (Arnos et al., 2013).
  - Autosomal dominant hearing loss is characterized as late onset, postlingual, progressive at times and mild to severe in severity (Kalatzis & Petit, 1999).

- **Criteria suggestive of an X-linked hearing loss**
  - Severe forms of hearing loss almost always identified in males with affected females presenting with normal hearing or a milder hearing loss (Arnos et al., 2013).
  - Inheritance from the pedigree is exclusively from females or affected males, lack of male to male transmission (Arnos et al., 2013).
  - All daughters from affected males are carriers (Arnos et al., 2013)
  - Mothers who are carriers of the X-linked mutation have a 25% chance of having a hearing son, 25% chance of having a son with a hearing loss, 25% chance of having daughter who is not a carrier and 25% chance of a having a daughter as a carrier (Arnos et al., 2013).
  - X-linked hearing loss can be prelingual or postlingual and ranges from mild to profound in severity, (Hildebrand et al., 2015).

- **Criteria suggestive of a mitochondrial hearing loss**
  - The mother is only parent that has the mitochondrial mutation.
  - All offspring of the affected mother, are at risk for a hearing loss, (Hildebrand et al., 2015)
  - Male offspring even if affected with hearing loss, are not at risk for passing the mutation (Hildebrand et al., 2015).

- Hearing loss ranges from mild to profound and can be early or late onset (Arnos et al., 2013).

- **Criteria suggestive of "co-incidental" hearing loss**
  - An acquired cause of hearing loss in a family member represented on the family pedigree that mimics a familial genetic etiology.
  - A family with one member affected with a syndrome and one member suspected of an acquired cause of hearing loss.
  - A pedigree that does not meet any one of the genetic inheritance criteria mentioned above

The criteria used for inheritance categorization of inheritance patterns against each participant was presented in Appendix J.

3.12 Summary of chapter

This chapter discussed the research protocol and procedures that formed the foundation of the study. A multi case study design was adopted. Issues of reliability and validity as addressed in the study were described. Data analysis was conducted with the assistance of a statistician. Inter-rater reliability of data analysis achieved 100% agreement. Ethical and legal considerations were discussed.

CHAPTER 4
RESULTS

4.1 Introduction

This chapter details the findings of the study. The chapter is broken down into five sections. It addresses the main aim of the study which was to determine and describe an audiological and genetic profile of learners suspected of presenting with familial hearing loss attending schools for the deaf in Kwazulu-Natal.

The results will be presented in terms of the objectives of the study

- To conduct an audiological assessment on all affected family members.
- To conduct a family pedigree dating back a minimum of three generations if possible, on all families within the study.
- To determine the genetic inheritance pattern of each family using the pedigree and audiological information.
- To determine the audiological profile of the different modes of genetic inheritance based on the audiological information.
- To compare and contrast the inheritance patterns based on the audiological profiles.

4.2 Study participants

4.2.1 Description of study participants

Twenty eight families were identified with familial hearing loss and met the selection criteria, of these, two families declined to be a part of the study due to cultural beliefs and stigma, and one family because of the travelling distance to the testing point. This left 25 families who completed the study.

The 25 families comprising of 507 individuals are discussed in this section. Only affected individuals who were willing to be assessed were included in the audiological testing. Table 4.1 depicts the study participants discussed in the study.

Table 4.1 Participants of the study (N=507)

Participants with hearing loss									**Participants who were not tested in the study with reported normal hearing**			**Total**
Audiological assessments conducted on participants with hearing loss			Reported hearing loss but not tested			**Total participants with hearing loss**						
Male	Female	Total	Male	Female	Total	**Male**	**Female**	**Total**	**Male**	**Female**	**Total**	
31	39	70 (14%)	7	13	20 (4%)	**38**	**52**	**90 (18%)**	202	215	**417 (82%)**	**507 (100%)**

Seventy individuals underwent audiological assessments in the study, which included 39 females and 31 males (Table 4.1). Twenty individuals were reported to have a hearing loss but did not undergo audiological assessments. These participants were not able to undergo an audiological assessment due to the distance to the hearing testing point, cultural choice, and in some instances personal unforeseen circumstances. These 20 participants were not included in the audiological descriptions in section 4.5, but are included in the earlier sections. All 70 affected participants were included in the family pedigrees. Four hundred and seventeen individuals were reported to have normal hearing and formed part of the family pedigrees. The participants in the study ranged in age from 3 to 72 years old. Forty four of these affected participants were learners from the schools and 26 participants were affected family members.

4.2.2 Race and geographical location of participants

All participants were of South African nationality. The majority 79% (55) participants were of Black South Africans (Table 4.2).White and Indian South Africans accounted for 7% (5) and 14% (10) respectively. None of the participants were of coloured ethnicity.

Table 4.2 Race of participants

Race Group	**Frequency (N=70)**	**Percentage**
Black South African	55	79%
White South African	5	7%
Indian South African	10	14%
Coloured South African	0	0%
Total	**70**	**100%**

All families reported originating from Kwazulu-Natal. The geographical distribution of families from this study as depicted in Table 4.3, revealed that the eThekwini, uMgungundlovu and uThukela districts presented with the highest number of affected families with 36 % (9), 32% (8) and 24%(6) of families originating from these areas respectively.

Table 4.3 Geographical distribution of families according to Municipalities

Municipality	**Families(N=25)**	**Percentage**
Amajuba	1	4%
uMkhanyakude	1	4%
uMgungundlovu	8	32%
eThekwini	9	36%
uThukela	6	24%
Total	**25**	**100%**

4.2.3 Case history information

A questionnaire (Appendix A/B) was utilized to identify background history of participants.

4.2.3.1 Risk factors for an acquired hearing loss

Six families, consisting of nine participants reported a history of risk factors associated with hearing loss (Table 4.4). Two participants were reported with a history of neonatal jaundice a few days after birth. Phototherapy was utilized. None reported bilirubin levels high enough where an exchange transfusion was necessary, putting them at risk for a hearing loss. Two participants reported the presence of a sudden hearing loss. Two participants presented with a hearing loss of an unknown etiology, presumed to be acquired. One participant reported a hearing loss following a motor vehicle accident, and two participants were reported to have a history of low birth weight of <1.5kg. Table 4.4 reflects the risk factors reported in the study.

Table 4.4 Risk factors for acquired hearing loss

Risk factor	**Participant (N=9)**
Neonatal jaundice	2
Low birth weight	2
Sudden onset hearing loss	2
Motor vehicle accident	1
Cause unknown, presumed to be acquired	2
Total	**9**

4.3 Audiological profile

This section presents the findings of the 70 participants from 25 families that underwent audiological assessments. These findings are depicted by tables and figures and discussed below.

4.3.1 Audiological characteristics

4.3.1.1 Otoscopy

Otoscopy did not identify any abnormalities of the outer ear and tympanic membrane bilaterally.

4.3.1.2 Tympanometry

Tympanometry results revealed Type A Tympanograms in all participants as depicted in Table 4.5. This is suggestive of normal middle ear function.

Table 4.5 Tympanometry Results

Tympanogram	**Right ear** (N=70)		**Left ear** (N=70)	
	Number	**Percentage**	**Number**	**Percentage**
Type A	70	100%	70	100%

4.3.1.3 Laterality of hearing loss.

All participants presented with a bilateral hearing impairment. One participant presented with an asymmetrical hearing loss.

4.3.1.4 Description of hearing loss

Sixty nine (99%) participants presented with a sensorineural hearing loss (Table 4.6). One participant presented with a neural hearing loss as well as Oculocutaneous Albinism. The neural hearing loss and Oculocutaneous Albinism was diagnosed at the participant's base hospital. The neural hearing loss was confirmed by normal outer hair cell function identified by Otoacoustic Emission testing and absent Auditory Brainstem Responses, tested at the participant's base hospital. These results were made available to the researcher for perusal. None of the participants presented with a conductive or a mixed hearing loss.

Table 4.6 Type of hearing loss exhibited

Hearing loss	**Frequency (N=70)**	**Percentage**	**Assessment method**
Neural	1	1%	Confirmed by the presence of outer hair cell function in the absence of auditory brainstem, responses, conducted at participants base hospital. Auditory neuropathy was suggested by previous audiologists who assessed this participant.
Sensorineural	69	99%	All confirmed by the audiological assessments in the study. Immitance testing was suggestive of normal middle ear function bilaterally.
Conductive	0	0	
Mixed hearing loss	0	0	
Total	**70**	**100%**	

4.3.1.5 Hearing loss severity

Severity of hearing impairment was based on the better hearing ear, averaged over 500, 1000, 2000 and 4000Hz (Liu & Xu, 1994; Mazzoli et al., 2003; Stephens, 2001). Only the better hearing ear was used to depict severity of hearing loss. As depicted in Table 4.7, of the 70 participants assessed a little more than half, 53% (37) presented with a profound hearing loss. Severe hearing loss was observed in 33% (23) of participants. A moderate hearing loss was present in 13% (9) participants with only one participant being identified with a mild hearing loss.

Table 4.7 Severity of hearing loss

Degree of hearing loss	**Frequency (N=70)**	**Percentage**
Mild hearing loss 20-40dB	1	1%
Moderate hearing loss 41-70dB	9	13%
Severe hearing loss 70dB-95dB	23	33%
Profound hearing loss >95dB	37	53%
Total	**70**	**100%**

4.3.1.6 Hearing loss configuration

Table 4.8 revealed that 4% (5) of participants presented with a low frequency ascending pattern. A steeply sloping pattern was present in 21% (29) of participants. A mid frequency u-shaped audiogram pattern was present in 6% (9) of ears. The second most common configuration identified was a gently sloping pattern identified in 25% (35) of participants with the majority, 44% (62) having a flat configuration. Table 4.8 below represents the audiometric configurations of individuals assessed.

Table 4.8. Hearing loss configurations

Hearing loss configuration	**Right ears N=(70)**	**Left ears N=(70)**	**Frequency**	**Percentage**
Low frequency ascending	2	3	5	4%
Mid frequency u-shaped	4	5	9	6%
Steeply sloping	14	15	29	21%
Gently sloping	18	17	35	25%
Flat	32	30	62	44%
Total	**70**	**70**	**140**	**100**

4.3.1.7 Suspected age of onset of hearing loss

Age of onset of hearing loss was derived from Mazzoli et al. (2003). The suspected age of onset of hearing loss was reported by parents/ caregivers and participants themselves. This information was derived from the questionnaire (Appendix A/B) conducted during phase 2 of data collection. Congenital hearing loss and hearing loss occurring between birth -10years were 47% (33) and 44% (31) respectively (Table 4.9). Hearing loss reported to have occurred

between 11-30years of age was reported in 9% (6) participants. A prelingual hearing loss was suspected in 81% (57) of individuals with a postlingual onset indicated in 19% (13) of participants (Table 4.10).

Table 4.9 Estimated age of onset of hearing loss

Age of onset	**Frequency (N=70)**	**Percentage**
Congenital	33	47%
Birth-10 years	31	44%
11-30 years	6	9%
31-50 years	0	0%
Total	**70**	**100%**

Table 4.10 Prelingual versus postlingual onset of hearing loss

	Frequency (N=70)	**Percentage**
Prelingual	57	81%
Postlingual	13	19%
Total	70	100%

4.3.1.8 Other ear related symptoms

Tinnitus was reported in 11% (7) of participants from 5 families. All participants reported a high pitched non-pulsatile tinnitus that was bilateral and intermittent. The majority 90% (63) did not indicate the presence of tinnitus. None of the individuals in this study reported any vestibular disturbances. This information was derived from the questionnaire and interview of the participants and caregivers.

4.4 Genetic profile

A family pedigree was conducted on 25 families. Detailed pedigree information regarding 507 people with 90 affected individuals from 25 families are discussed in this section. The pattern of hearing loss was determined based on the pedigree characteristics.

4.4.1 Inheritance patterns of families

Table 4.11 revealed that more than half of the families 56% (14) presented with an autosomal recessive inheritance pattern detailed in the pedigree analysis below. An autosomal dominant inheritance was suspected in 32% (8) of families. Also identified were three families whose hearing loss and background were suggestive of a co-incidental familial hearing loss, possibly acquired, this accounted for 12% (3) of families. None of the pedigrees were suggestive of an X-linked or Mitochondrial inheritance.

Table 4.11 Suspected Inheritance patterns

Suspected inheritance pattern	**Participants (N=70)**	**Percentage**	**Families (N=25)**	**Percentage**
Autosomal recessive inheritance	33	47%	14	56%
Autosomal Dominant	31	44%	8	32%
Mitochondrial	0	0%	0	0%
X-linked	0	0%	0	0%
Co-incidental familial hearing loss	6	9%	3	12%
Total	**70**	**100%**	**25**	**100%**

Group 1: Suspected autosomal recessive inheritance

Fifty six percent of families (1-14), presented with an autosomal recessive inheritance pattern (Table 4.13). Detailed below is a description of each family pedigree, who were suspected of presenting with an autosomal recessive inheritance.

Family 1

Family 1 were Black South African. The two generation pedigree (Figure 4.1) comprised of 6 normal hearing participants and five affected. The affected individuals are present in generation II of the pedigree. The family pedigree identified three affected females, including a set of identical twins (II-1, II-5, and II-6) and two affected males (II-4, II-7).

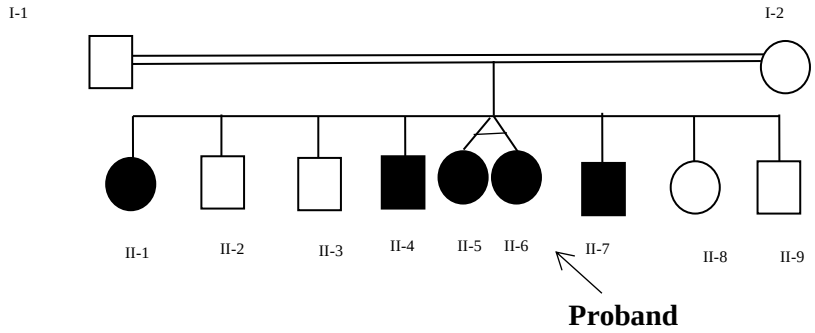

Figure 4.1 Pedigree Family 1

The circles represent females, the squares represent males. The shaded squares and circles represent affected individuals. The double line in generation I represents consanguinity. The short line between II-5 and II-6 represents identical twins.

The parents were unaffected and reported no other affected family members, dating back three generations. Consanguinity was suggested within the parents, who reported being related as second cousins. The parents reported a congenital hearing loss that was prelingual in onset in all affected individuals. No risk factors or acquired causes of hearing loss were indicated by the parents.

Audiological assessments revealed a profound hearing loss in all affected. All affected individuals used sign language for communication. All siblings presented with a flat audiogram and attend a school for the deaf. None of the participants reported tinnitus or vestibular difficulties. Only a two generation pedigree was provided by this family. They chose to not disclose the other family members as they did not feel it fair to discuss people that were not present and not affected with hearing loss.

Analysis of the pedigree indicated normal hearing parents with reported consanguinity, affected offspring presented with a congenital profound hearing loss, this is suggestive of an autosomal recessive inheritance pattern.

Family 2

Family 2 were Black South African

Family 2 (Figure 4.2) presented with three generations of twenty six normal hearing participants and three affected participants (III-3, III-4, III-7). This included one female (III-4) and two males (III-3, III-7). All affected participants were from the same generation and same parents. The parents did not report any other affected family members, dating back

three generations. No acquired causes and risk factors for hearing loss were reported by the parents.

Audiological assessments revealed a gently sloping pattern of hearing loss in affected male participants (III-4, III-7) which was profound in severity. A severe, mid frequency u-shaped configuration of audiogram was identified in the female participant (III-4). All hearing loss was reported to be prelingual with a congenital onset. All participants communicated via sign language. None of the affected siblings indicated the presence of tinnitus or vestibular complaints.

Intrafamilial variability was identified in the audiogram configurations and hearing loss severity between the affected male siblings when compared to the female sibling. All participants attended a school for the deaf, with the last affected sibling (proband) still in school. Analysis of the pedigree indicated normal hearing parents with affected offspring presenting with a severe and profound hearing loss which was of congenital onset. An autosomal recessive inheritance pattern was suspected.

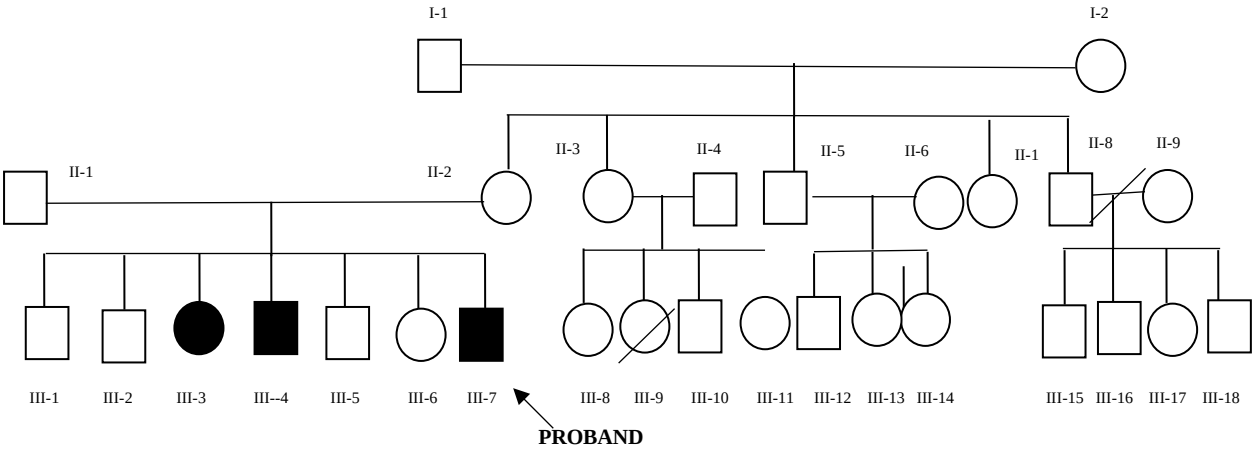

Figure 4.2 Pedigree Family 2

The circles represent females, the squares represent males. The shaded squares and circle represent affected individuals tested in the study. The line between II-8 and II-9 represents a separated couple. The line across III-9 represents a deceased child.

Family 3

Family 3 were White South African. A three generation family pedigree (Figure 4.3) comprising of 15 normal hearing individuals and three affected individuals (III-5, III-6, III-7,) were drawn. The affected individuals were female siblings and were of the third generation. Siblings III-5 and III-6 were identical twins. They all attend a school for the deaf.

The great great grandmother of 1I-5 was reportedly deaf, however no other information was available regarding the hearing loss. This was not included in the pedigree diagram as a detailed pedigree beyond 1-1 was unavailable. No other familial hearing loss was reported in this family. The father's father (grandfather) of 1-4 was of Jewish ancestry.

No acquired causes or risk factors for a hearing loss were reported for the affected individuals. The hearing loss was indicated to be of early onset and prelingual, identified between 3 to 4years of age. All siblings presented with a severe hearing loss with a steeply sloping configuration bilaterally identified on audiograms. No intrafamilial variability was identified. The presence of tinnitus or vestibular disturbances were not reported.

Genetic investigations were conducted on all three siblings previously according to the parents. A non-syndromic autosomal recessive inheritance was indicated. Testing for Connexin 26 mutations were negative. The parents opted not to pursue further investigations at that time.

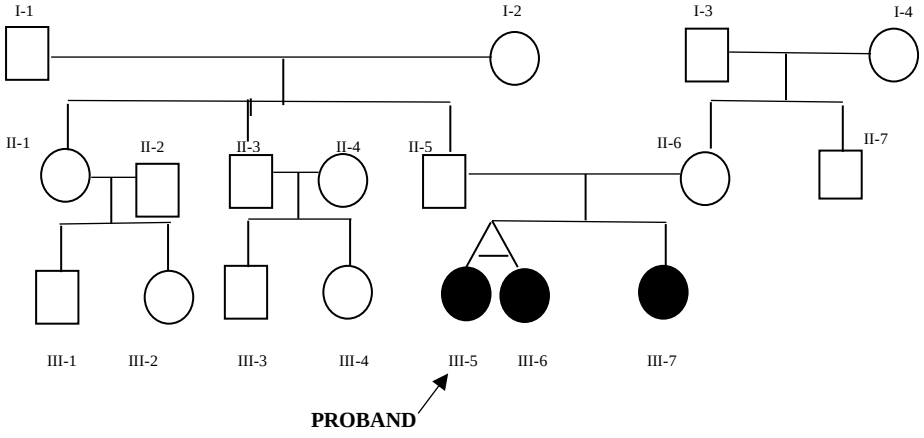

Figure 4.3 Pedigree Family 3

The circles represent females, the squares represent males. The shaded squares and circles represent affected individuals tested in the study. The short line between III-5 and III-6 represents identical twins.

Family 4

Family 4 were Black South African. A four generation family pedigree (Figure 4.4) comprising of 35 normal hearing individuals, one deceased individual at birth (IV-3), two affected individuals (I-2, II-7yrs) with reported hearing loss but not tested in the study and two participants (IV-1, IV-2) a set of twins with confirmed hearing loss. The parents of the twins were not certain if the twins were monozygotic or dizygotic.

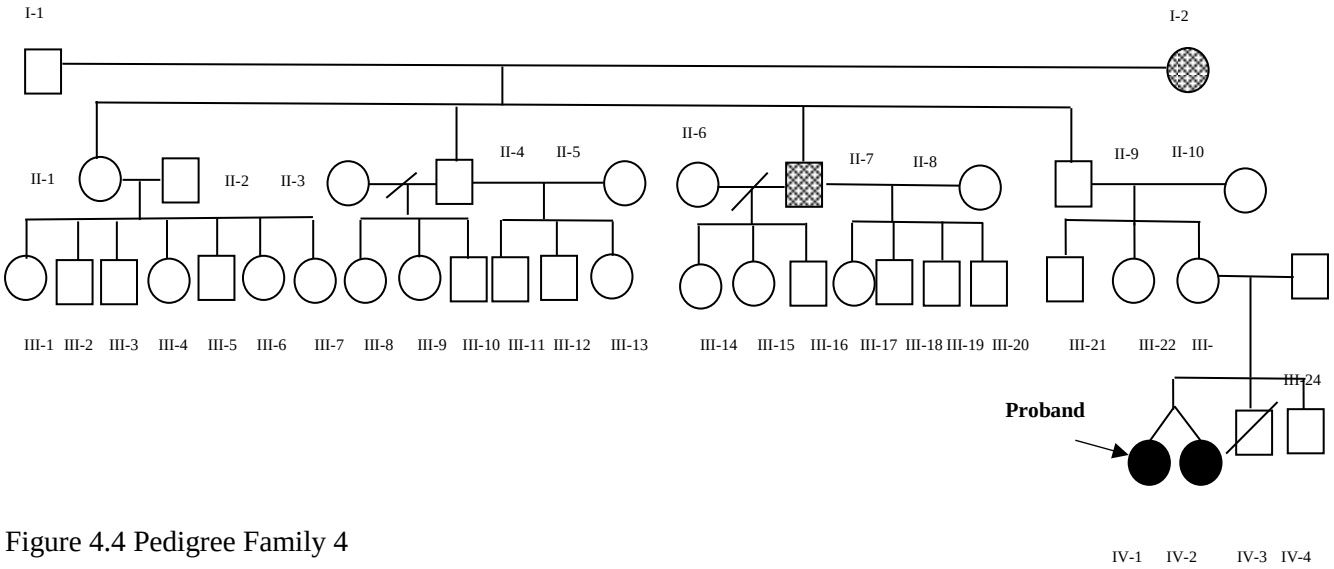

Figure 4.4 Pedigree Family 4

The circles represent females, the squares represent males. The light shaded square and circle represent reported hearing loss, but not tested in the study. The dark shaded circles represent affected females with confirmed hearing loss, tested in this study. Divorced couples are represented by a cross line through the linkage.

Affected individual I-2 was reported to have a hearing loss that was suggested by the family to be age related. The family reported the hearing loss possibly developed in the last 5 years. She was reported to have good speech development and had never used a hearing aid. She declined audiological testing as in the current study she was ill and not able to travel.

Affected individual II-7 was reported to have a hearing loss that was prelingual and of early onset. He was reported to use informal signs and gestures to express himself. This is suggestive of a hearing loss that is of a severe to profound nature. He was reported to use hearing aids bilaterally. He declined audiological testing in the current study.

Affected participants IV-1 and IV-2 were reported to have an early onset hearing loss, which was prelingual, and congenital in onset and used sign language for communication. No risk factors or acquired causes of hearing loss were indicated.

Audiological assessments revealed that participant IV-1 presented with a severe hearing loss that was gently sloping in audiometric configuration. Participant IV-2 presented with a profound hearing loss bilaterally with a steeply sloping configuration in the right ear and a flat configuration in the left ear. No tinnitus or vestibular difficulties were reported. The affected individual (II-7) was reported to have a hearing loss similar to that of the IV-1 and IV-2 in terms of severity and age of onset.

Intrafamilial variability was identified in audiometric configurations and hearing loss severity between the affected twins (IV-1, IV-2). The reported hearing loss of affected individual I-2 was dissimilar to that of the others affected with regards to age of onset and severity. The possibility of age related hearing loss cannot be excluded. Ten percent (10%) of this family presented with a hearing loss.

Based on the similarities in hearing loss profiles of individuals II-7, IV-1 and IV-2 and its correlation to the non-syndromic autosomal recessive phenotype of prelingual and severe to profound hearing loss, an autosomal recessive inheritance pattern was suspected.

Families 5-14

Ten (10) families, 14 males and 6 females presented with one affected sibling pair in the last generation, with no other affected individuals dating back three generations. Participant ages ranged from 4-16years old. Figure 4.5 depicts an example of one family (Family 5) represented in this group. The remaining 9 family pedigrees are presented in Appendix K.

In this group, 4 families presented with affected twins. One set were a dizygotic male and female pair. Three sets were males, it is unknown if they were monozygotic or dizygotic twins. Six sibling sets made up the remaining participants, with three sets of male and female combinations, two sets of male siblings and one set of female siblings.

One set of twins were born premature at 35weeks gestation and presented with a low birth weight of >1.4kg. They were not admitted to a neonatal intensive care (NICU) and spent three days in hospital. No risk factors or acquired causes for a hearing loss were reported in the other eight (8) families.

Five sibling sets were Indian South African, four siblings sets were Black South African and one sibling set were White South African,

Audiological assessments revealed that two participants presented with a severe hearing loss, with the remaining eight participants presenting with a profound hearing loss bilaterally. A gently sloping configuration was identified in 7ears with a flat configuration being the most commonly occurring present in 17ears. A flat configuration was identified in 14 ears. A steeply sloping configuration and a mid-frequency u-shaped pattern was identified in one ear each. All individuals were reported to have a hearing loss of congenital onset. All hearing loss was reported to be prelingual and all participants used sign language to communicate. None of the participants reported the presence of tinnitus or vestibular disturbances. Intrafamilial variability of audiometric configurations were identified in 6 sibling sets, with 4 sibling sets presenting with symmetrical audiograms.

All participants had normal hearing parents with a hearing loss that ranged from severe to profound with a congenital onset. An autosomal recessive inheritance pattern was suggested. Thus families 5-14 described above were suspected of presenting with an autosomal recessive hearing loss.

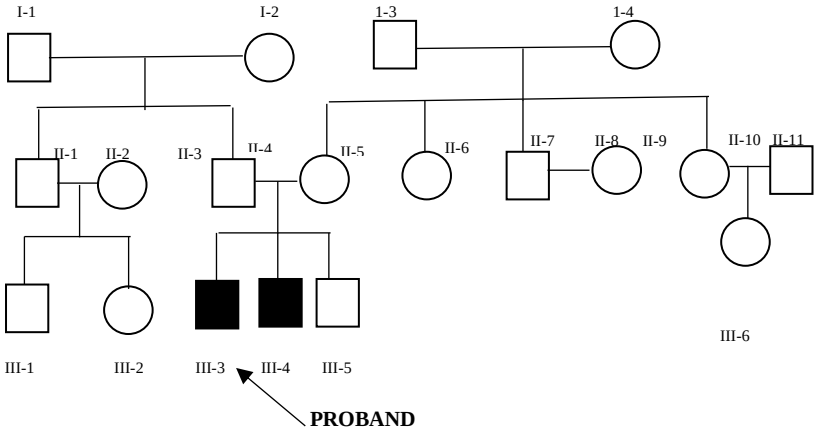

Figure 4.5 Pedigree Family 5

The circles represent females, the squares represent males. The shaded squares represent affected individuals tested in the study.

Summary of Group 1

Figure 4.6 depicts the hearing loss severity identified in families 1-14. A profound hearing loss accounted for a significant 76% (25) with a severe loss accounting for 24% (8). None of the participants were identified with a mild or moderate hearing loss.

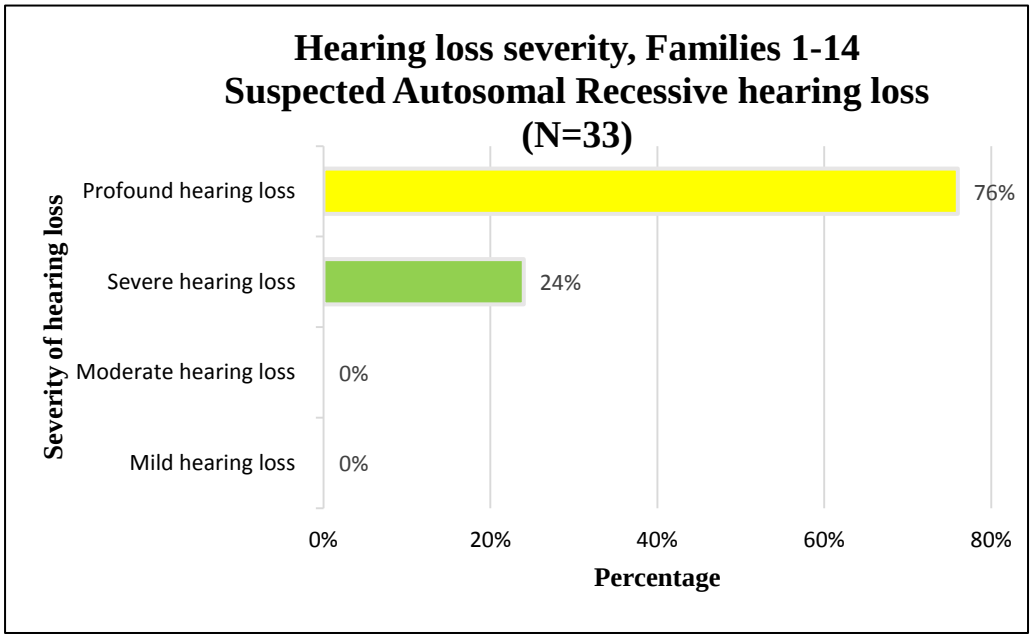

Figure 4.6 Hearing loss severity, families 1-14

Figure 4.7 represents the configuration of audiograms identified in group 1. A flat hearing loss configuration was the most commonly identified accounting for 64% (42). A gently sloping configuration accounted for a similar incidence of 20% (13) Less commonly occurring were the steeply sloping configuration accounting for 12% (8) and the mid frequency u-shaped pattern accounting for 4% (3).An ascending configuration was not identified in the autosomal recessive group

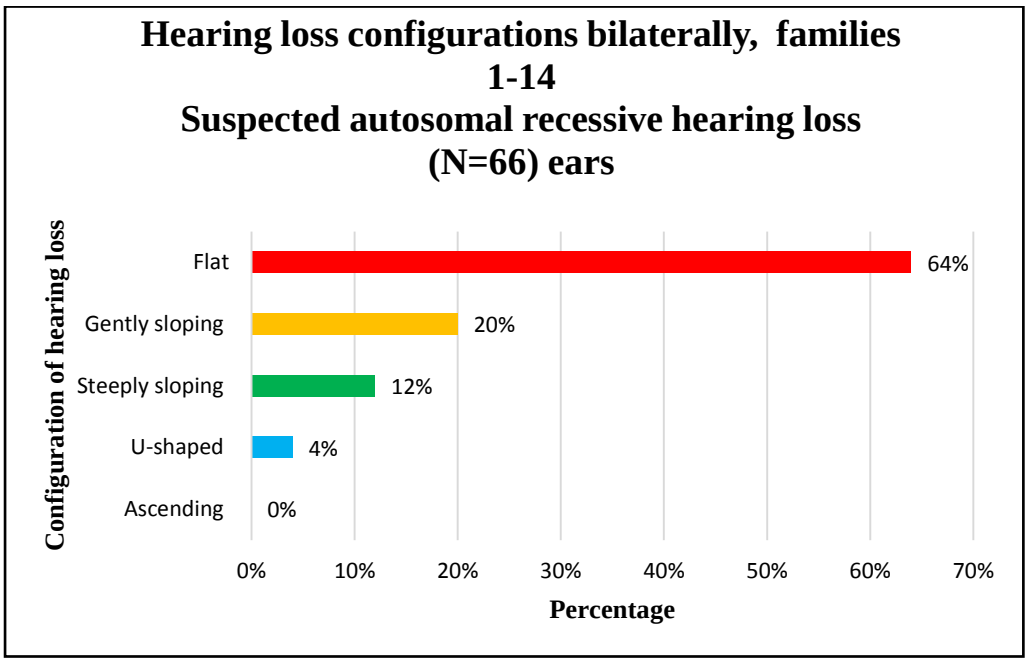

Figure 4.7 Hearing loss configurations, families 1-14

Group 2: Suspected autosomal dominant inheritance

Thirty eight percent (8) of families, families 15-22, comprising of 31 affected individuals presented with a vertical transmission of hearing loss suggesting an autosomal dominant inheritance pattern.

Family 15

Family 15 were Black South African. Family 15 (Figure 4.9) provided a four generation pedigree, with 15 normal hearing individuals and 8 affected individuals including four females (II-2, II-5, III-5, III-7,) and four males (II-1, II-6, III-6, IV-1).

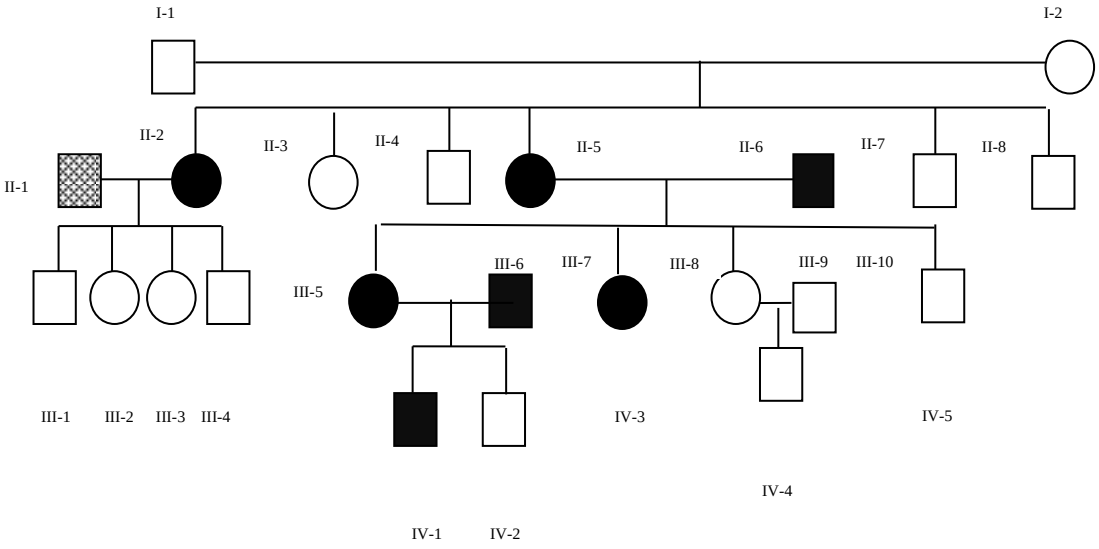

Figure 4.8. Pedigree Family 15

The circles represent females, the squares represent males. The light shaded squares represent reported hearing loss in a male, but not tested in the study. The dark shaded circles represent affected individuals with confirmed hearing loss, tested in this study.

Affected individual, II-1 married II-2 and had four normal hearing children. Affected individual II-5 married affected individual II-6 and had four children, two affected daughters (III-5, III-7) and one normal hearing daughter (III-8) and son (III-10).

III-5 married affected III-6 and had two children one affected son (IV-1) and one normal hearing son (IV-2).II-6 reported no family history of a hearing loss, he was one of seven children. He indicated that his hearing loss began at the age of 7 years and was postlingual.

II-1 was unavailable for audiological testing. His wife reported that he uses sign language to communicate but does have some speech. She was unsure of when the hearing loss began.

Audiological assessments were conducted on 7 affected participants (II-2, II-5, II-6, III-5, III-6, III-7; IV-1). Three individuals presented with a severe hearing loss and four with a profound hearing loss. A steeply sloping configuration was the most frequent configuration identified on 8 ears with a gently sloping and flat audiogram configuration being present in three ears each. A postlingual hearing loss was identified in one individual with the rest reported as prelingual. All participants reported having some speech, but used sign language to communicate. Two participants reported high pitched tinnitus. Intrafamilial variability was identified on the severity and hearing loss configuration of affected individuals.

A vertical transmission of hearing loss was identified over three generations, with a hearing loss ranging from severe to profound, with a prelingual and postlingual onset. An autosomal dominant hearing loss was suggested.

Family 16

Family 16 were Black South African. Family 16 presented with a five generation pedigree (Figure 4.8) with 18 affected individuals, (1-1),(II-3),(III-3,III-5,III-12,III-16,III-17,III-18,III-20,III-22,III-26,III-27),(IV-7,IV-9,IV-15,IV-23, IV-24),V-7,) and 51 individuals reported to have normal hearing.

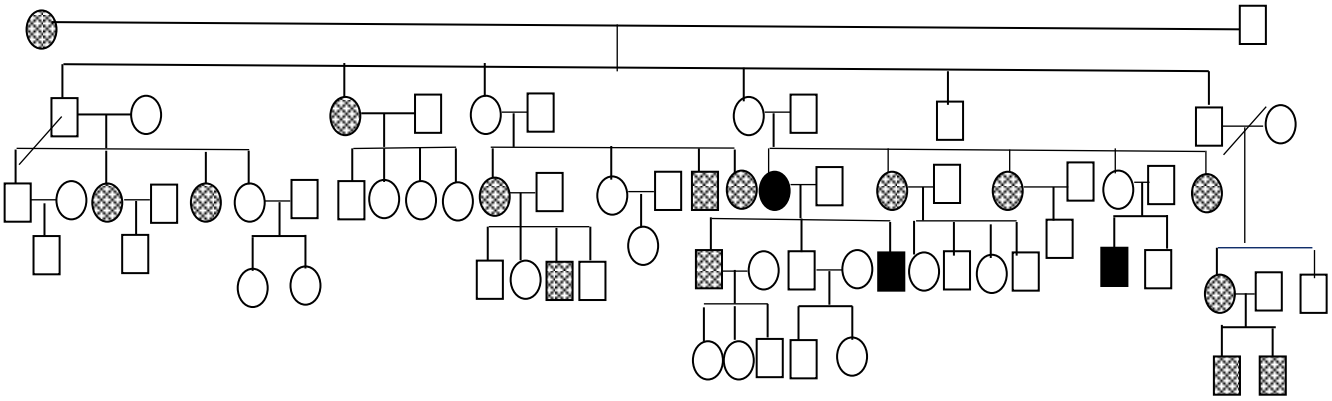

Figure 4.9 Pedigree Family 16

The circles represent females, the squares represent males. The light shaded squares and circles represent reported hearing loss, but not tested in the study. The dark shaded circles and squares represent affected individuals with confirmed hearing loss, tested in this study. The line across the squares/ circles represents a deceased individual.

A vertical pattern of inheritance was observed. Audiological assessments were not conducted on all affected individuals, as they were not able to travel to the testing point. I-1 and III-3

now deceased were reported to have a hearing loss at a young age possibly early adulthood, with speech development. All family members with a reported hearing loss, who were not tested were reported to have developed speech and used spoken language to communicate. The following were reported on affected family members that were not tested:

- None of the hearing loss was reported to be congenital
- All affected family members not tested used spoken language to communicate
- Eight affected individuals were reported to use hearing aids
- Seven affected individuals were not reported to use hearing aids

Audiological assessments were conducted on three participants (II-3, III-3, and III-11). All participants presented with a moderate hearing loss. One participant (III-3) presented with a symmetrical low frequency ascending configuration, with the other two participants (II-3, III-11) presenting with symmetrical mid frequency u-shaped audiometric configurations. All hearing loss was reported to be identified postlingually. Both III-3 and III-11 used hearing aids and attend a school for the deaf. They use spoken language and sign language to communicate. II-3 did not use hearing aids. A vertical transmission of affected individuals was observed.

Family 17

Family 17 was of Black ethnicity and presented with a five generation pedigree (Figure 4.9) with 15 normal hearing individuals, two deceased (I-I, 1-2) and 11 affected individuals (II-2, 1-4, III-1, III-4, III-9,IV-2, IV-3, IV-4, V-1, V-2, V-3). No other affected individuals were reported.

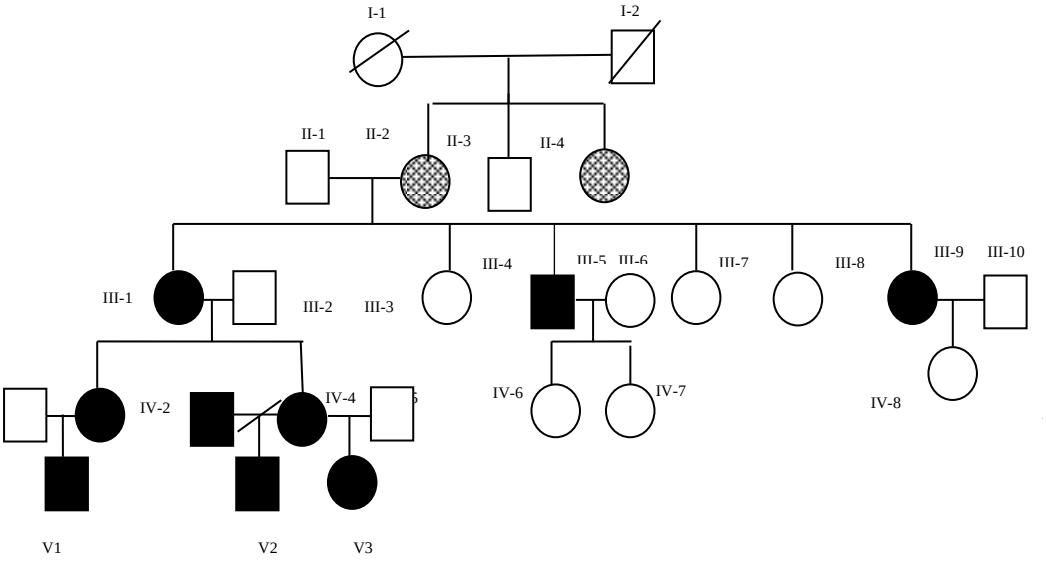

Figure 4.10 Pedigree Family 17

The circles represent females, the squares represent males. The light shaded circles represent reported hearing loss in females, but not tested in the study.. The shaded circles represent affected individuals with confirmed hearing loss, tested in this study. Divorced couples are represented by a cross line through the linkage. Crossed lines through circles and squares represent deceased individuals.

Hearing loss in II-2 and II-3 was reported and not tested, as these affected individuals were not able to travel to the testing point due to illness. They were regarded as "hard of hearing", with their hearing loss occurring before the third generation was born. They used spoken language for communication.

All affected individuals from generation three to five underwent audiological assessments for the purpose of this study. A moderate hearing loss was identified in two individuals (III-1, III-4, with a steeply sloping configuration. Participants III-1 and III-4 had spoken language and reported that their hearing loss possibly began in childhood.

A severe hearing loss was identified in three individuals (III-9, V-1, and V-3). III-9 and V-3 presented with a gently sloping configuration with V-1 presenting with a low frequency ascending audiometric configuration. A profound hearing loss was identified in four participants (IV-2, IV-3, IV-4, V-2). IV-2, IV-3, IV-4 presented with a flat configuration with

V-2 presenting with a mid frequency u-shaped configuration symmetrical configuration. An early hearing loss was reported in these participants, with limited speech development. They used sign language to communicate. No acquired causes or risk factors for a hearing loss were reported in all affected individuals. None of the participants reported the presence of tinnitus. A vertical pattern of hearing loss was identified, which ranged from moderate to profound in severity with a prelingual and postlingual onset. An autosomal dominant inheritance pattern was suspected.

Family 18

Family 18 were Black South African and presented with a four generation pedigree (Figure 4.11) with 30 normal hearing individuals and 3 affected individuals (II-4, III-9, IV-9).

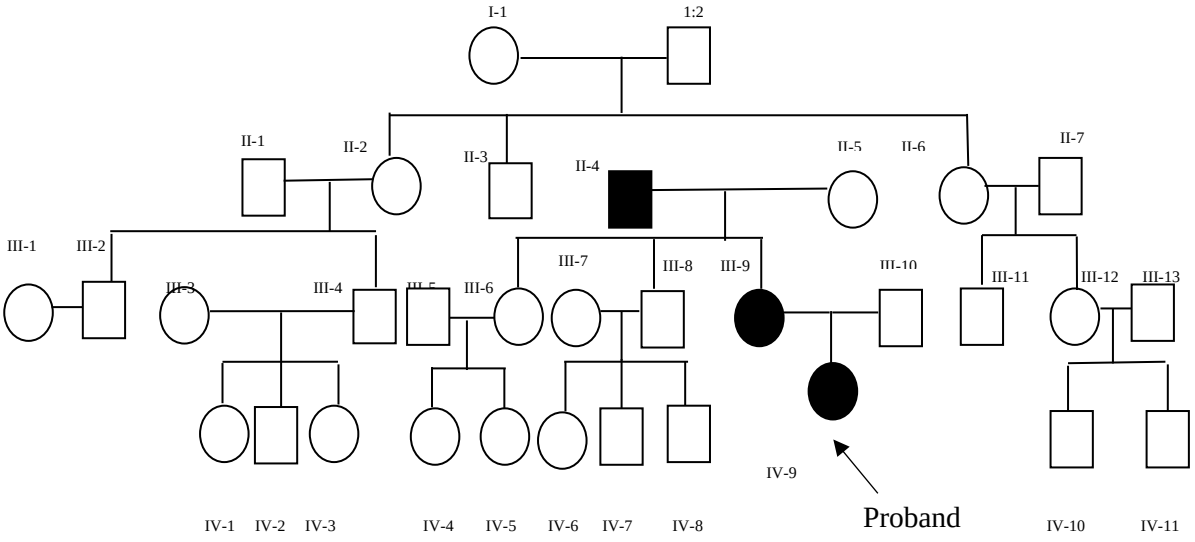

Figure 4.11 Pedigree Family 18

The circles represent females, the squares represent males. The shaded circles and square represent affected individuals with confirmed hearing loss, identified in this study.

A detailed history did not reveal probable acquired causes of hearing loss. No family history of hearing loss were reported in the spouses. II-4 married a normal hearing individual (II-5) and had one affected daughter (III-9). III-9 married a normal hearing individual (III-10) and had one affected daughter (IV-9).

All participants reported a postlingual hearing loss and used spoken language for communication. II-4 reported a hearing loss that began as a teenager and described it as a progressive hearing loss. His audiological assessment identified a severe hearing loss, with a steeply sloping symmetrical configuration. He did not indicate the presence of vestibular disturbances. The presence of age related hearing loss as well as a genetic hearing loss is a probability.

III-9 daughter of II-4, reported a hearing loss that was noticed while in school. She also described the hearing loss as progressive. Her audiological assessment revealed a moderate hearing loss that was steeply sloping in configuration bilaterally.

II-4 and III-9 indicated the presence of a high pitched tinnitus that is intermittent and began several years ago. They reported never undergoing a hearing evaluation until participating in the study.

IV-9, the daughter of III-9 and the granddaughter of II-4, presented with a mild hearing loss, which was steeply sloping in configuration bilaterally. Her hearing loss was identified at the age of 7 years.

All affected individuals exhibited a postlingual sensorineural hearing loss that was steeply sloping in configuration and used spoken language for communication. Hearing loss severity ranged from mild in the 4^{th} generation (IV-9), to moderate in the 3^{rd} generation (III-9) and severe in the 2^{nd} generation (II-4). A progressive pattern of hearing loss is suggested. Variability in severity of hearing loss was identified between all three affected individuals, with the similar steeply sloping configuration being consistent in all audiometric patterns.

A vertical pattern of inheritance was identified. A hearing loss ranging from mild to severe which was postlingual and possibly progressive hearing loss was identified. An autosomal dominant inheritance was suspected.

Family 19

Family 19 were Black South African and presented with a three generation pedigree (Figure 4.12) comprising of 16 normal hearing individuals and three affected individuals (II-9, III-8, III-9).

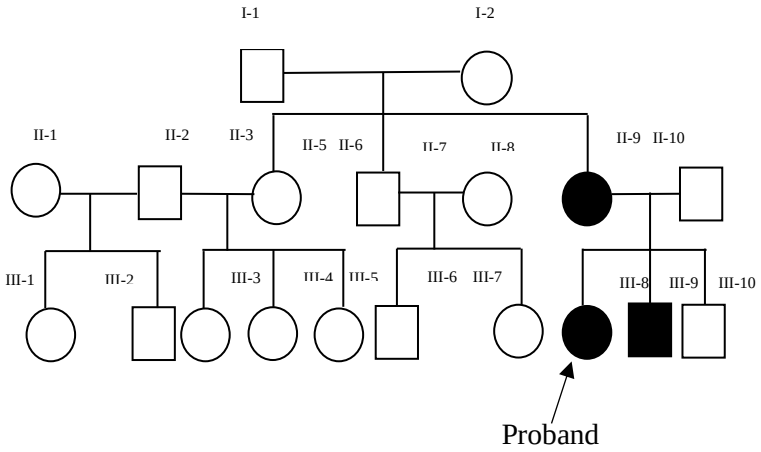

Figure 4.12 Pedigree Family 19

The circles represent females, the squares represent males. The shaded circles and square represent affected individuals with confirmed hearing loss, tested in the study.

The affected individuals belong to one family cluster, affecting generation II and III only. The affected individual II-9 married a normal hearing individual (II-10) and resulted in two affected children a female (III-8) and male (III-9). An in-depth history did not reveal an acquired cause of hearing loss. No familial hearing loss was reported from spouses.

The hearing loss was postlingual, with all individuals using spoken language for communication. All individuals presented with "deaf speech". All affected individuals presented with a moderate hearing loss. II-9 exhibited a steeply sloping audiometric configuration, with III-8 and III-9 exhibited a flat audiogram pattern. II-9 was the only affected individual that reported the presence of intermittent high pitched tinnitus. No vestibular complaints were reported. Intrafamilial variability was identified between audiometric configurations. A vertical transmission of inheritance is observered. A moderate postlingual hearing loss was identified, an autosomal dominant inheritance was proposed.

Families 20-22

Three Black South African families presented with only two affected individuals, a parent and offspring with no other affected individuals over three generations. A detailed history of all families did not reveal any acquired causes of hearing loss. The ages of affected individuals ranged from 10-35years. None of the individuals reported the presence of vestibular disturbances. All individuals reported a prelingual hearing loss and used sign

language to communicate. A vertical inheritance pattern is exhibited, suggestive of an autosomal dominant inheritance. The pedigree diagram of family 20 is depicted in Figure 4.13 below, the remaining 2 families are presented in Appendix K.

Family 20 comprised of an affected father and daughter who presented with a profound hearing loss and a flat audiometric configuration. Family 21 comprised of an affected father and son, who presented with profound hearing loss and a gently sloping configuration bilaterally. The father reported the presence of a high pitched tinnitus that was intermittent. Family 22 presented with an affected mother with a severe hearing loss and affected daughter with a profound hearing loss, both presenting with a sloping audiometric configuration.

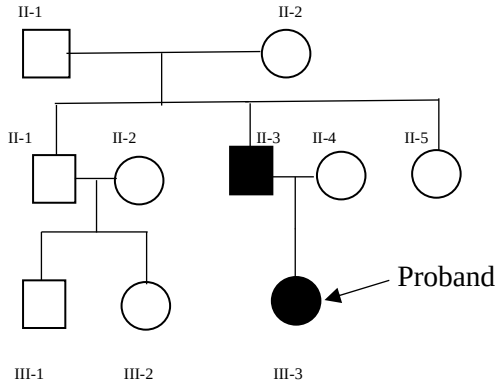

Figure 4.13 Pedigree Family 20

The circles represent females, the squares represent males. The shaded circle and square represent affected individuals with confirmed hearing loss, tested in the study.

Thus families 15-22 were suspected of presenting with an autosomal dominant inheritance pattern. As depicted in Figure 4.14, a profound hearing loss was identified in 32% (10) of participants with a severe loss accounting for 39% (12), a moderate loss accounting for 26% (8) and a mild hearing loss accounted for 3% (1).

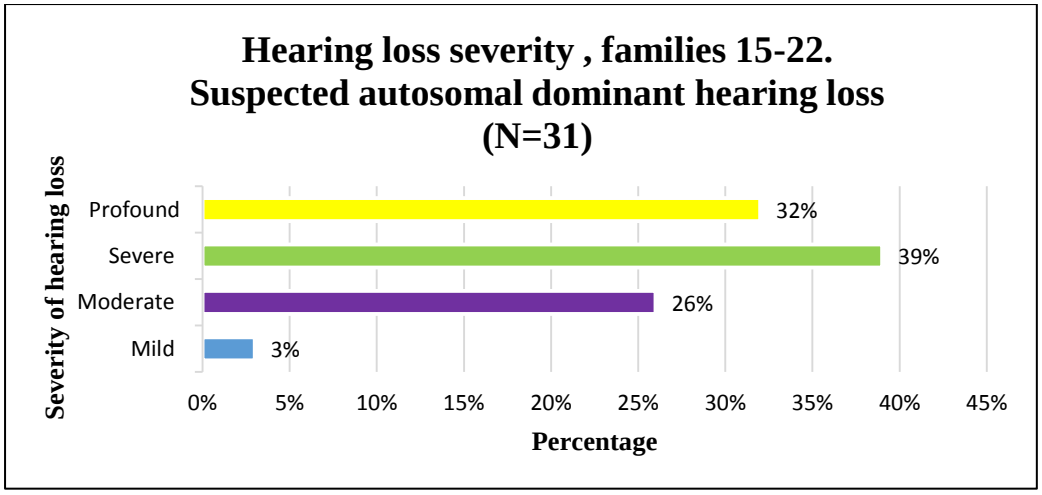

Figure 4.14 Hearing loss severity, families 15-22

Figure 4.15 depicts the configuration of hearing loss identified. Steeply sloping, gently sloping and flat configurations accounted for 32% (20), 32% (20) and 19% (12) respectively accounting for the most frequently occurring configurations in this group. A low frequency ascending and mid frequency u-shaped pattern were less commonly occurring configurations and accounted for 7% (4) and 10% (6) respectively.

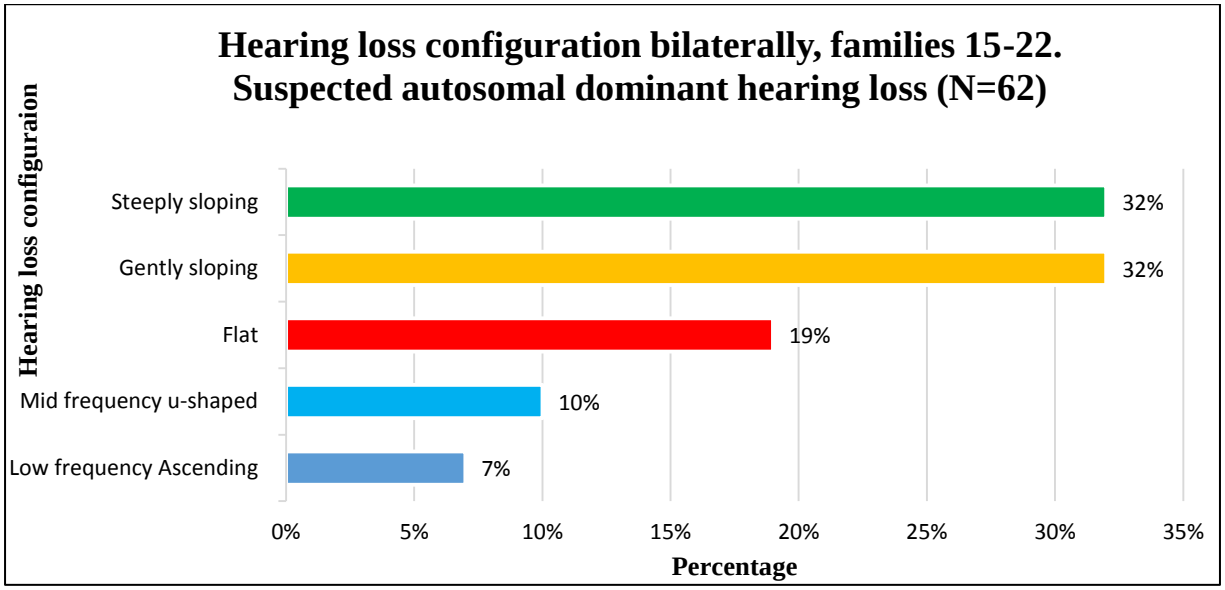

Figure 4.15 Hearing loss configuration, families 15-22

Presumed Co-incidental familial hearing loss

Three Black South African famililes (23-25) presented with a pattern of familial hearing loss that was assumed to be co-incidental and acquired, based on the background history, audiological profile and pedigree. Pedigrees and detailed history is presented in Appendix K. The ages of affected individuals ranged from 8-40 years old. Family 23 presented with an affected mother with late onset sensorineural hearing loss and daughter with a syndrome associated with a neural hearing loss. The mother reported the presence of high pitched tinnitus. Family 24 presented with an affected mother with a late onset sensorineural hearing loss during illness during pregnancy and a son with congenital sensorineural hearing loss. Family 25 presented with an affected mother who experienced a hearing loss after a motor vehicle accident when she was younger and a son with a congenital sensorineural hearing loss. The audiogram of all families in this group showed intrafamilial variability with audiological characteristics. Figure 4.16 revealed that 33% (2) of participants presented with a profound sensorineural hearing loss, 50% (3) presented with a severe hearing loss. One participant from the severe hearing loss group presented with a neural hearing loss and two participants presented with a severe sensorineural hearing loss. A moderate sensorineural hearing loss accounted for 17% (1). Figure 4.17 revealed that a flat configuration was the most common, identified in 68% (8) of participants, with a gently sloping accounting for 16% (2) and with a steeply sloping and ascending configuration accounting for 8% (1) each.

This group was not included in the descriptions made in section 4.5.

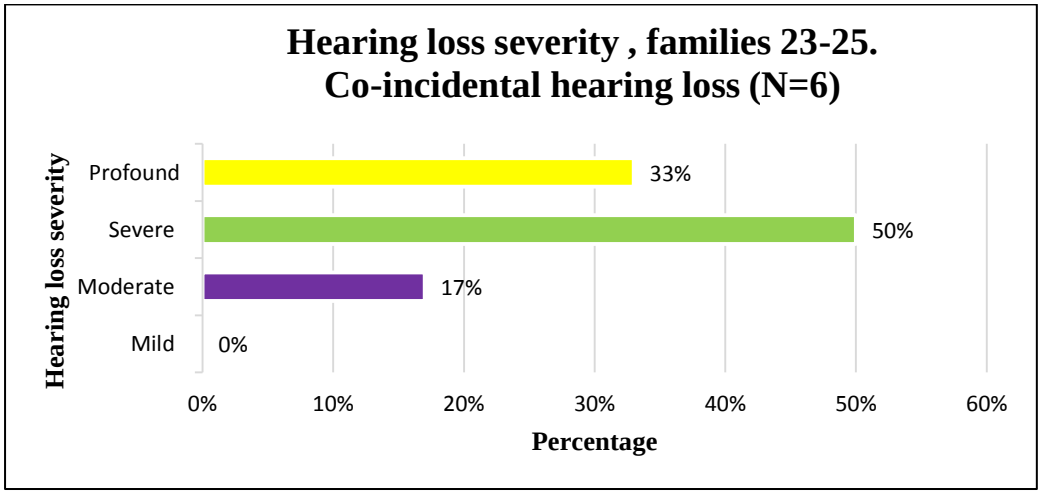

Figure 4.16 Hearing loss severity, families 23-25

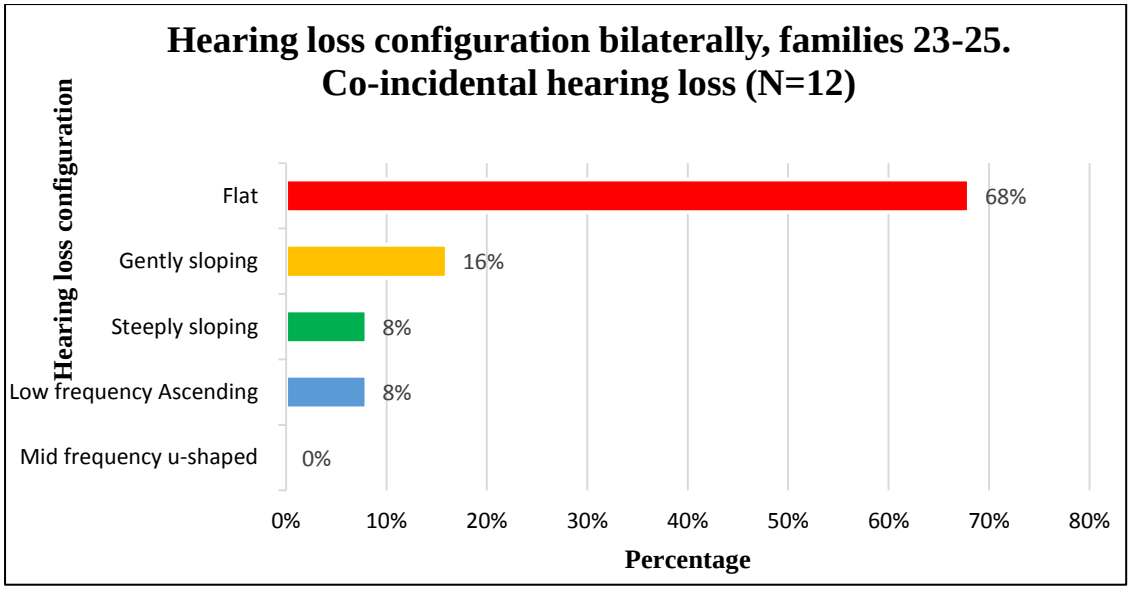

Figure 4.17 Hearing loss configurations, families 23-25

4.5 Genetic inheritance and audiological characteristics

A majority of 88% of families (22) were suspected of presenting with a genetic hearing loss as detailed in Table 4.13. Fifty six percent (14) of families with 33 affected individuals were suspected of presenting with an autosomal recessive inheritance pattern detailed in figures 4.1-figure 4.5 and pedigree analysis 1-14 depicted above. Thirty three individuals underwent audiological assessments.

Thirty two percent (8) of families with 37 affected individuals, were suspected to present with an autosomal dominant inheritance pattern detailed in figures 4.8- figure 4.13 and pedigree analysis 15-22 depicted above. Thirty one individuals underwent audiological assessments.

Detailed below are audiological characteristics identified in the autosomal recessive and autosomal dominant inheritance patterns. Every audiogram was categorized according to audiogram profile classification set out in the Chapter 3 and detailed in Appendix J

4.5.1. Severity of hearing loss

Hearing loss severity in the autosomal recessive (AR) and autosomal dominant (AD) inheritance groups are depicted below and compared against each other (Figure 4.18). In the AR group (Figure 4.6), a profound hearing loss accounted for a significant 76%, with a severe hearing loss accounting for 24%. None of the individuals presented with a hearing loss that was mild or moderate in severity. In the AD group, hearing loss severity ranged from mild to profound (figure 4.14). A minority of 3% of individuals presented with a mild hearing

loss, with a moderate loss accounting for 26%. A severe hearing loss was the most commonly occurring accounting for 39% with a profound hearing loss following with an incidence of 32%.

In the AR group a profound hearing loss was the most common hearing loss severity identified. In the AD group a similar distribution was identified between moderate, severe and profound categories. A statistical significance was found between the two groups with severity of hearing loss with a p-value of p=0.000 (Fischer's exact test).

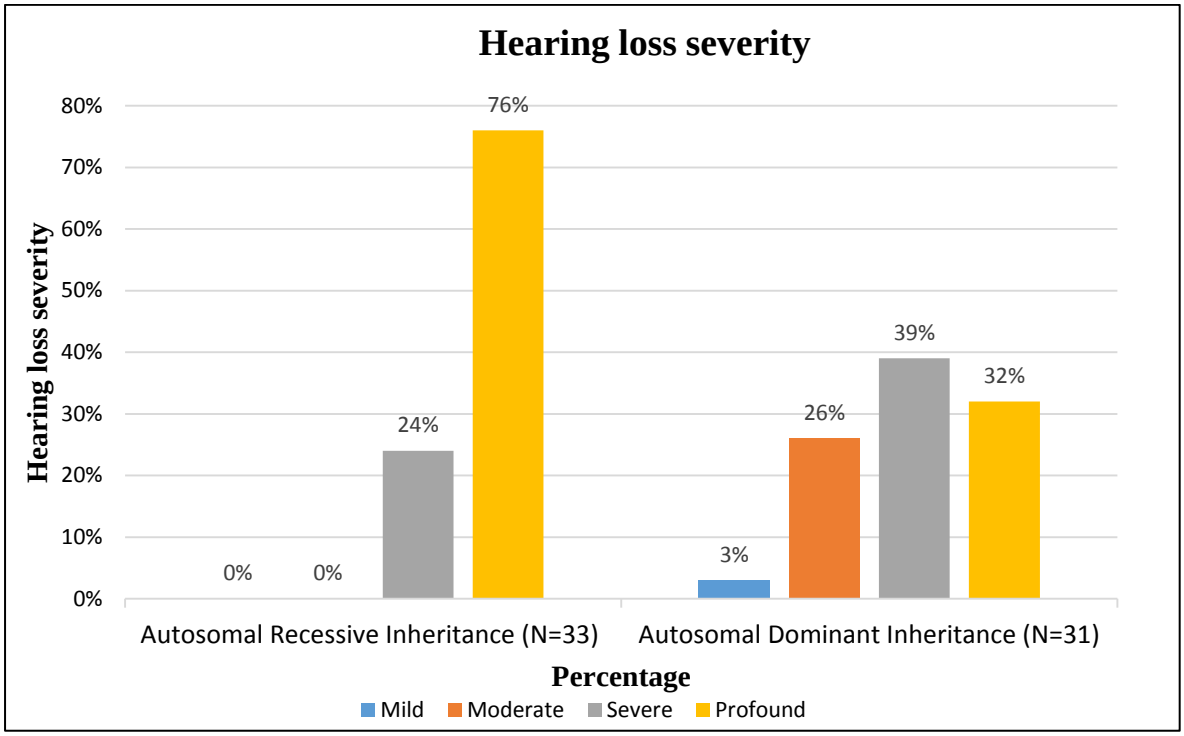

Figure 4.18 Comparison of hearing loss severity between AR and AD groups

4.5.2. Hearing loss configurations

In the AR group the audiograms of 33 affected individuals (66 ears) were evaluated to document the audiological configurations of hearing loss. In the AD group 31 affected individuals with 62 affected ears were evaluated. Figure 4.19 depicts the audiometric configurations of the AR and AD groups per ear and allows for comparison amongst them.

In the AR group, both left and right ears revealed that a flat pattern accounted for the majority of configurations, identified in 61% (20) and 67% (22) respectively. The flat configuration in the AD group accounted for the 20% (6) bilaterally, which was dissimilar to the incidence

identified in AR inheritance. Only the AR group was identified to have one specific configuration that accounted for more than 50% in each ear.

In the AD group, the steeply sloping and gently sloping configuration accounted for 32% (10) respectively for both right and left ears. The AR group revealed a lower occurrence than the AD in the gently sloping configuration accounting for 21% (7) and 18% (6) respectively for right and left ears. A steeply sloping configuration revealed a high incidence in the AD group of 32% (10) bilaterally but a lower incidence in the AR group with the 9% (3) identified in right ears and 15% (5) in left ears.

A mid frequency u-shaped configuration accounted for a similar distribution between AR and the AD group (right 3%, left 6%) with the AD group (10% bilaterally) presented with a slightly higher incidence.

A low frequency ascending configuration was identified only in the AD group. None of the individuals in the AR group presented with a low frequency ascending configuration.

The AR group revealed right and left ear differences of 6% with a flat hearing loss and steeply sloping configuration, with the gently sloping and mid frequency u-shaped revealing a difference in ears of 3%.

The AD group did not reveal any differences in right and left ears.

A statistically significant difference between the audiometric configurations were identified between the AR and AD groups with a significant p-value of p=0.001 (Fischer's exact test).

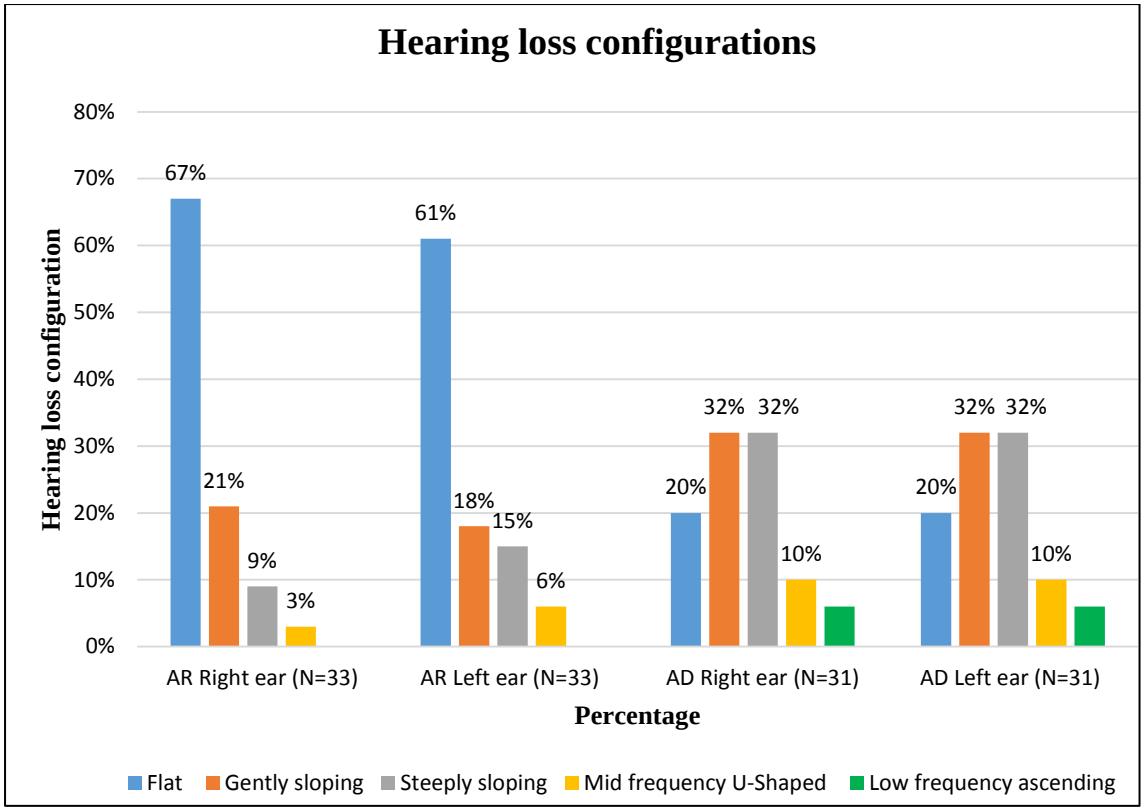

Figure 4.19 Comparison of hearing loss configurations between AR and AD groups.

4.5.3 Suspected age of onset of hearing loss

Figure 4.20 illustrates the suspected age of onset of hearing loss in both autosomal recessive and autosomal dominant groups and allows for comparisons to be made. Figure 4.21 depicts if the hearing loss was prelingual or postlingual in acquisition.

The vast majority, 85% (Figure 4.17) of individuals with an AR inheritance were suspected of having a congenital hearing loss. The remaining 15% were reported to occur between birth to 10years of age. As depicted in Figure 4.17 all individuals with an autosomal recessive inheritance presented with a prelingual hearing loss. All affected individuals in the AR group were reported to have no speech development, which correlates with the suspected congenital and early onset (birth to 10years) hearing loss reported above.

In the autosomal dominant group, the vast majority 77% (Figure 4.20) of affected individuals were reported to have a hearing loss that occurred anytime between birth to 10 years of age. A congenital onset was suspected in 13% of individuals. A hearing loss occurring between 11-30years of age was reported in 10% of affected individuals. Figure 4.21 revealed that 68% of individuals presented with a prelingual hearing loss and 32% were reported to present with a postlingual loss. During the audiological assessment and questionnaire it was observed and reported that the majority of individuals with a suggested prelingual hearing loss in the AD

group had limited speech. They all used sign language to communicate. All individuals with a postlingual hearing loss used either spoken language exclusively or sign language and spoken language to communicate. A statistical significance was identified between the age of onset of hearing loss between the AR and AD groups with a significant p-value of p=0.000 (Fischer's exact test). The onset of hearing loss before speech development (prelingual) or after speech development (postlingual) showed a significant difference between the AR and AD groups with a significant p-value of p=0.000 (Fischer's exact test).

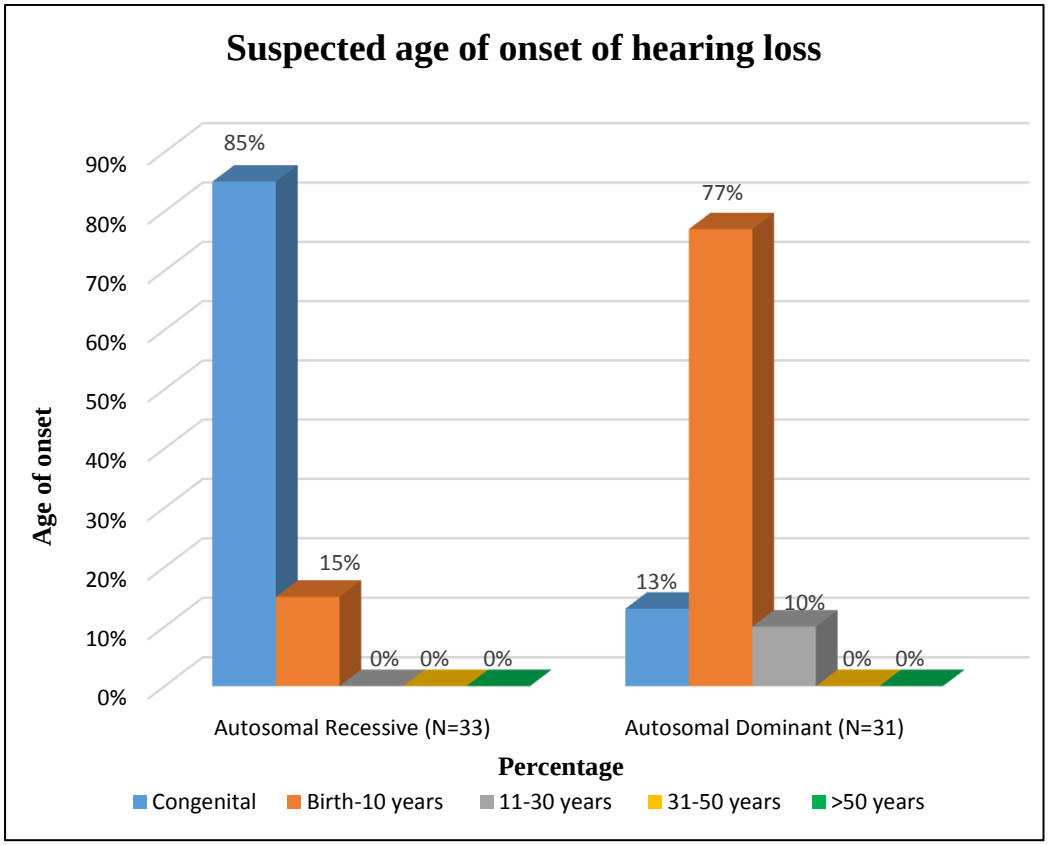

Figure 4.20 Comparison of suspected age of onset of hearing loss between AR and AD groups.

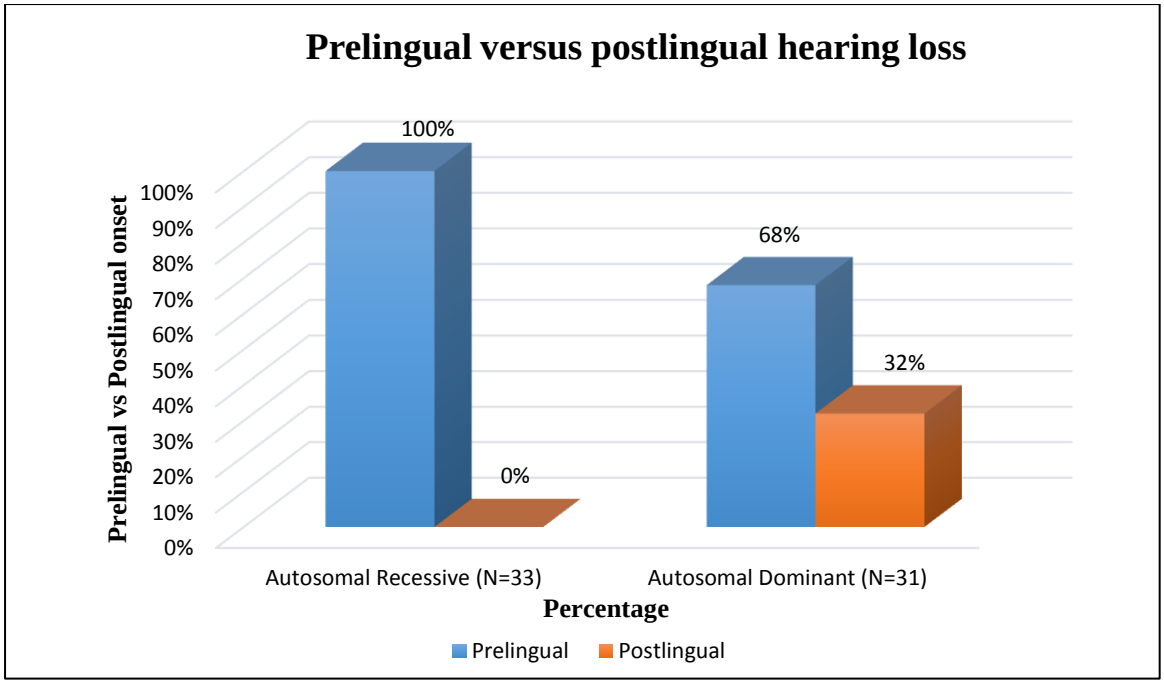

Figure 4.21 Prelingual versus postlingual onset of hearing loss

4.5.4 Other ear related symptoms

Six individuals reported the presence of tinnitus. All individuals with tinnitus presented with a suspected autosomal dominant inheritance. All participants that reported tinnitus, had a postlingual hearing loss, acquiring the hearing loss between 11 to 30 years of age. No tinnitus was reported in individuals with an autosomal recessive inheritance. A significant difference was identified between the AR and AD groups regarding the presence of tinnitus with a statistically significant value of p=0.0098 (Fischer's exact test).

4.5.5 Familial variability

Intrafamilial variability relates to differences in characteristics within the family in the AR and AD groups. The autosomal recessive inheritance group identified intrafamilial variability within the hearing loss severity and hearing loss configuration profiles (Table 4.12; Table 4.13 and Figure 4.22). The autosomal dominant group revealed intrafamilial variability in all categories discussed below.

The AD group revealed 75% of families with differences in severity of hearing loss and 7% of families in the AR group identified between affected members of a family .The AD group presented with 50% of families with variation in hearing loss configurations within the family, with 29% families in the AR group families.

The presence of tinnitus revealed intrafamilial variability in 50% of families within the AD group. The AD group identified intrafamilial variabilites with age of onset, prelingual and postlingual onset of hearing loss that accounted for 25% of families respectively. None of the families in the AR and AD groups reported the presence of vestibular disturbances. The AR group were identified with intrafamilial variability in only two audiological categories i.e. hearing loss severity and hearing loss configurations. The AD group were identified with intrafamilial variability in five audiological categories i.e. hearing loss severity, hearing loss configurations, age of onset of hearing loss, prelingual vs postlingual onset and the presence/ absence of tinnitus.

Table 4.12 Intrafamilial variability AD group

Hearing loss severity AD Group	**AD families (N=8)**	**Percentage**
Hearing loss severity (N= 8)	6	75%
Hearing loss configurations (N= 8)	4	50%
Prelingual/ postlingual onset (N= 8)	2	25%
Age of onset (N= 8)	2	25%
Tinnitus present/absent (N= 8)	4	50%

Table 4.13 Intrafamilial variability AR group

Hearing loss severity AR Group	**AR families N=14**	**Percentage**
Hearing loss severity (N=14)	1	7%
Hearing loss configurations (N=14)	4	29%
Prelingual/ postlingual onset (N=14)	0%	0%
Age of onset (N=14)	0%	0%
Tinnitus present/absent (N=14)	0%	0%

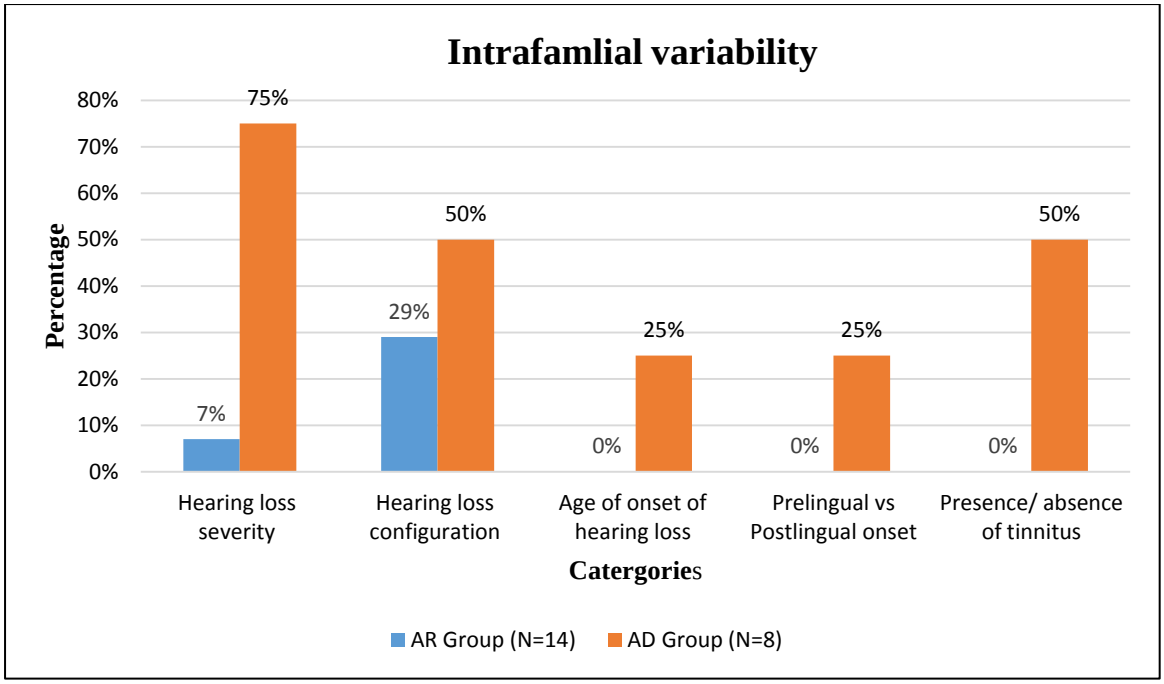

Figure 4.22 Intrafamilial variability of autosomal recessive versus autosomal dominant families

Interfamilial variations relates to differences in characteristics between families in the AR and AD groups. Variations were identified in severity of hearing loss of both autosomal recessive and autosomal dominant inheritance group (Figure 4.23).The AR group revealed that 71% of families presented with a profound hearing loss, 22% with a severe hearing loss and 7% family revealing a mixed severity within the family. Mixed severity suggests a range of hearing loss severity identified within one family due to intrafamilial variability. The autosomal dominant group presented with 12.5% of families with a profound hearing loss, 12.5% with a purely moderate hearing loss and the majority 75% identified with a mixed severity. None of the families with the AR group revealed a purely mild or moderate hearing loss severity. None of the families with the AD group presented with a purely mild or severe hearing loss.

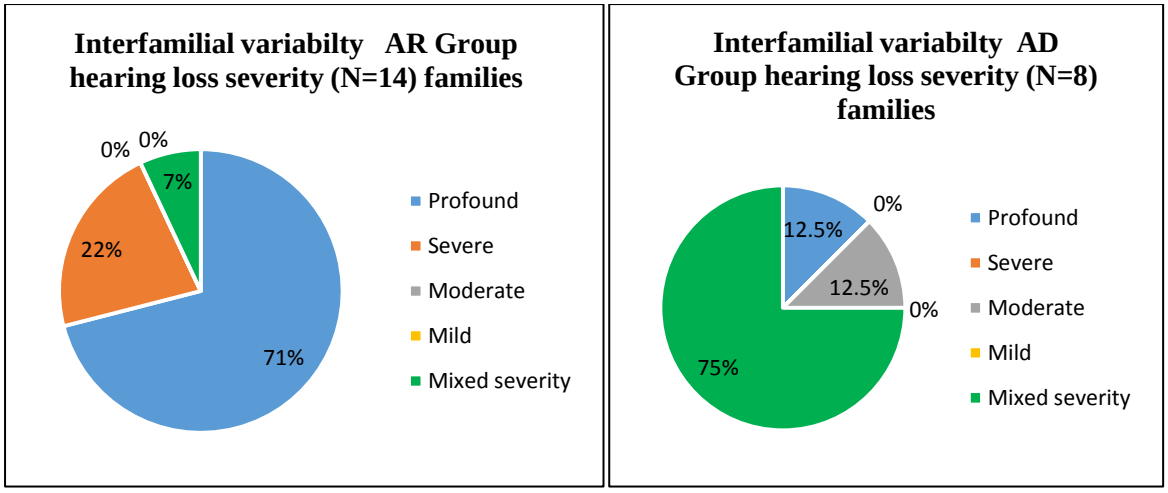

Figure 4.23 Interfamilial variability of hearing loss severity of autosomal recessive versus autosomal dominant families

Figure 4.24 revealed marked interfamilial variability between audiometric configurations of the AR and AD groups. The AR group revealed that 57% of families presented with a purely flat hearing loss only, 14% with a gently sloping configuration and 7% with a steeply sloping configuration within the family. A mixed configuration was identified in 22% of families. A mixed configuration is identified as different audiometric configurations present within a family due to intrafamilial variability. None of the families within AR group presented with a purely U-shaped mid frequency audiometric pattern.

The AD group revealed that a gently sloping and steeply sloping configuration was identified in 25% of families each. A solely flat configuration was present in 12.5% of families. Mixed audiometric configurations were identified in 50% of families. None of the families within the AD group presented with a purely U-shaped

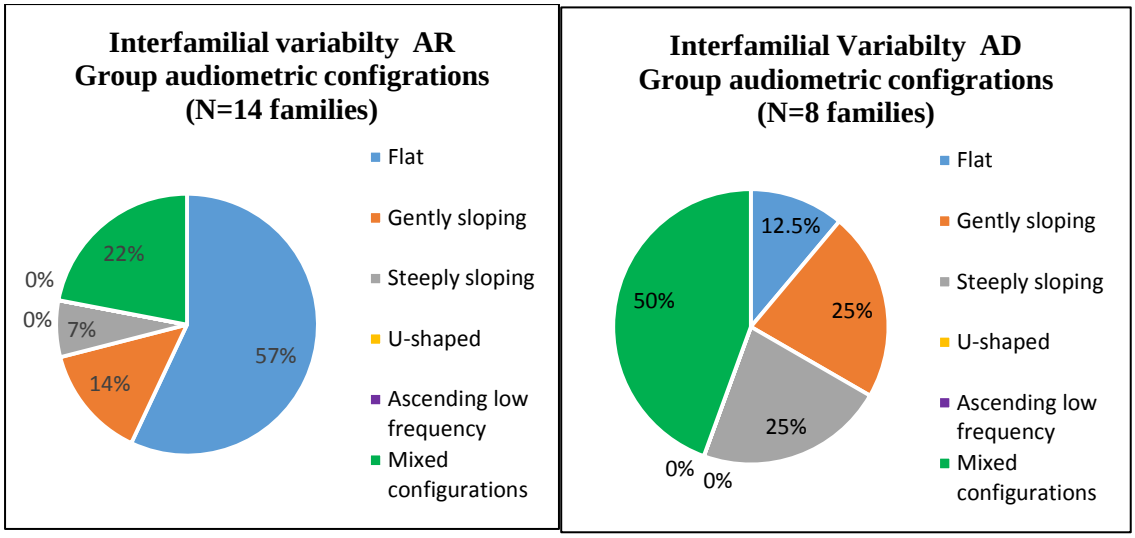

Figure 4.24 Interfamilial variability of audiometric configurations between autosomal recessive versus autosomal dominant families

Figure 4.25 revealed interfamilial differences in hearing loss onset between families of AR and AD groups. The AR group revealed a significant 86% of families with a congenital onset hearing loss and 14% of families all with an onset of hearing loss between birth-10yrs of age.

The AD group identified 37.5% of families with hearing loss with an onset of birth to 10yrs, 25% of families with a congenital onset and 37.5% of families with variable mixed onset of hearing loss in families. A mixed onset of hearing loss in Figure 4.25 and Figure 4.26 indicates hearing loss onset that varies within families due to intrafamilial variability in the AR and AD groups

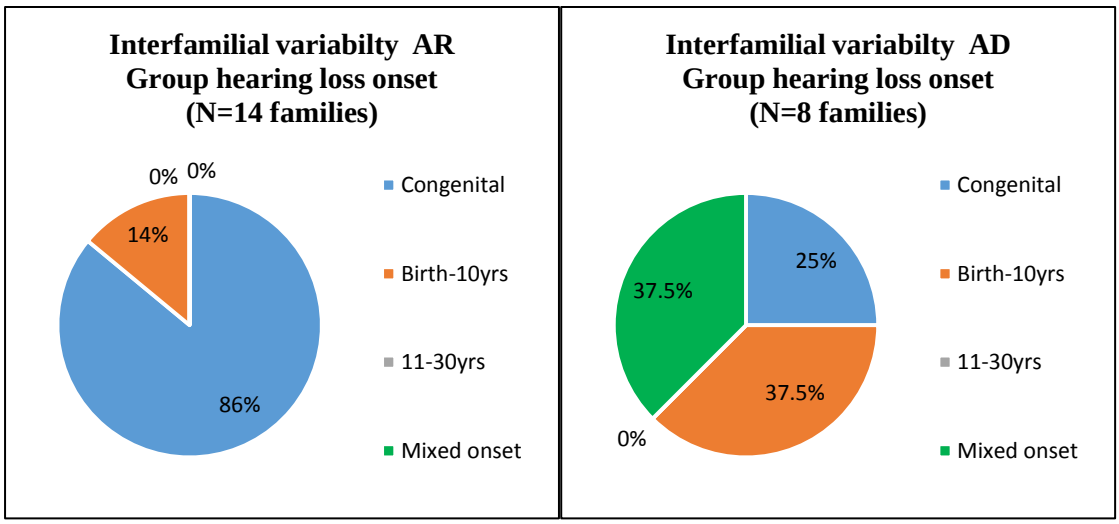

Figure 4.25 Interfamilial variability of hearing loss onset between autosomal recessive versus autosomal dominant families

Figure 4.26 revealed that the AR group did not present with interfamilial variability with prelingual versus postlingual onset of hearing loss, with all families reporting a prelingual hearing loss. The AD group revealed 50% (4) of families reporting a prelingual onset of hearing loss, 25% (2) families with a purely postlingual hearing loss and 25% (2) of families with a mix of prelingual and postlingual hearing loss.

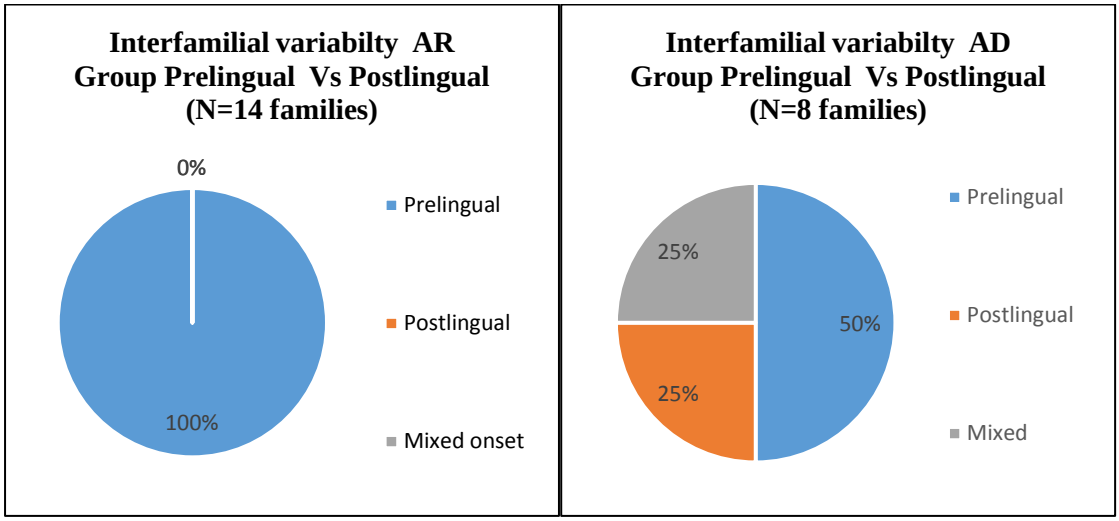

Figure 4.26 Interfamilial variability with prelingual versus postlingual hearing loss between autosomal recessive versus autosomal dominant families

Figure 4.27 revealed that the AR group did not present with any interfamilial variability within the tinnitus profile, as none of the families reporting the presence of tinnitus. The AD group revealed 50% (4) of families that reported the presence of tinnitus and 50% (4) of families without tinnitus.

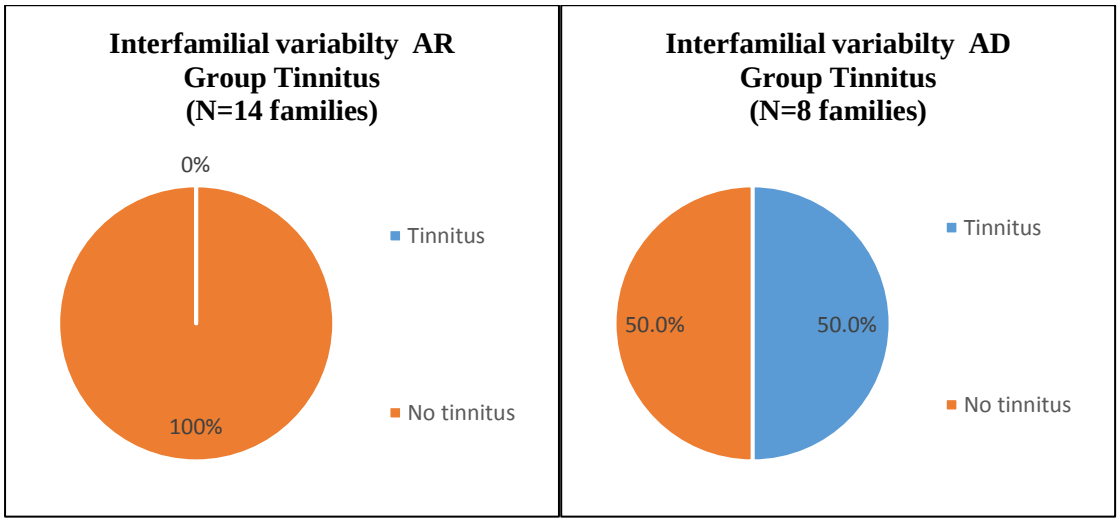

Figure 4.27 Interfamilial variability of the presence of tinnitus between autosomal recessive versus autosomal dominant families

4.6 Summary

This chapter presented the findings of the study with the help of tables and graphs to visually represent the results. The results provided a clear impression of the audiological characteristics of an autosomal recessive and autosomal dominant hearing loss. The use of profiling allows for an enhanced picture of the presentation for these inheritance pattern. These findings support literature in their idea of the audiological patterns of genetic hearing loss and also provide first-hand statistics for the South African population. The findings revealed that there are significant differences between the profile categories amongst the suspected autosomal recessive and autosomal dominant hearing loss groups. Chapter five presents an in-depth discussion of these findings.

CHAPTER 5
DISCUSSION

5.1 Introduction

This chapter serves to explore and discuss the findings and results from the study reported in Chapter 4.

5.2 A description of the study participants

Twenty five families completed the study with two families declining to be a part of the study due to cultural beliefs and stigma and one family due to the travelling distance to the testing point. Jeungst (2004) and Kabahuma (2010), reported that information regarding ancestry, genetics and hereditary hearing loss presents a social dilemma to some families, negatively affecting how they are regarded in their communities.

Dunmade et al. (2006), when investigating childhood hearing loss in Nigeria revealed that obtaining family pedigrees were challenging due to a stigma associated with familial hearing loss. Sankar, Cho, Wolpe, and Schairer (2006), in their study of genetics and stigma reported that hereditary hearing loss when compared to breast cancer, sickle cell disease and cystic fibrosis, yielded the most positive interpretation of hereditary hearing loss as it idealized growing up within a family with a shared communication system. Interestingly the study further stated that subjects with an autosomal dominant inheritance were more likely to accept hereditary hearing loss due to having multiple affected family members as opposed to autosomal recessive inheritance who are unlikely to see many deaf individuals in their families, and see it as rather an illness. Kabahuma (2010), stated that it is assumed that schools for the deaf represent all the hearing impaired children from the country, however a large number may be held back by their families, due to stigma.

Earlier studies on familial hearing loss revealed smaller groups similar to this study. Dar and Winter (1969), in their assessment of the cytogenetic analysis of familial deafness, identified 60 families. Martini et al. (1997), identified 65 families with familial hearing impairment from outpatient records collected over a period of 18 years. Liu and Xu (1994), identified 28 families with familial hearing loss also from outpatient records, also collected over several years. Choi et al. (2013), in their study of causative genes for hereditary hearing loss, identified 31 families who presented with 2 or more affected family members in the absence of syndromic hearing loss.

Studies conducted on childhood hearing loss in sub-Saharan Africa reported a similar lower incidence of familial hearing loss of 3-13%. Ijadulo (1982), when assessing 298 learners attending schools for the Deaf in Nigeria, identified a familial hearing loss in 13% of participants. Holborrow et al. (1982), also assessing childhood hearing loss in Nigeria, reported an incidence of 3% of familial hearing loss when assessing 803 learners attending schools for the Deaf. Holborrow et al. (1982), reported familial hearing loss in 8% of participants when assessing 259 learners from schools for the deaf in Gambia. Bastos et al. (1990), when assessing 105 children at an Ear Nose and Throat clinic in Angola, identified a familial history of hearing loss in 6% of participants. Sellars and Beighton (1983), assessed 3064 learners from 16 schools for deaf in South Africa, and identified a familial hearing loss in 11% of participants. Viljoen et al. (1987), when assessing 807 learners attending five schools for the Deaf in Zimbabwe, identified a familial hearing loss in 5.3% of participants. The current study revealed that of the 967 learners attending four schools for the Deaf in Kwazulu Natal, a familial hearing loss was identified in 4.3% of learners.

In order to identify suitable families that met the selection criteria, school admission forms were perused specifically of learners suspected of presenting with familial hearing loss. Not all school admission records reflected family history information. It was not possible to go through each learner's admission forms or conduct a telephonic interview with each parent/caregiver to identify familial deafness, as a limited time was allowed at each school. The school Audiologists were utilized to identify all learners with a familial history. This method may have limited the number of families identified as it was based on the Audiologist's knowledge of each learner. However all Audiologists were present at each institution for greater than 5years with a fair knowledge of all students at the institution.

The institutions used in the study were schools for the deaf, in which sign language was used as a first language. It is possible that learners with a milder and moderate hearing loss, may be placed at inclusive schools, with a unit for the hearing impaired and mainstream schooling. This would have limited the number of learners identified with milder losses. This study cannot be considered representative of all familial hearing loss in the childhood population of Kwazulu-Natal as data is confined to four schools within the Kwazulu-Natal region. It does however represent four of the largest institutions for the deaf within the region. Given the lack of studies on familial hearing loss in this area, the findings of this study maybe helpful in highlighting the presence of familial hearing loss, and its presentation within this population of South Africa.

5.3 Background information on etiology of hearing loss

A questionnaire was used to identify causes and risk factors for a hearing loss. Risk factors associated with a hearing loss were reported in three families within the autosomal recessive group. These risk factors included neonatal jaundice and low birth weight. These families were included in the autosomal recessive group as they presented with affected siblings without risk factors, suggesting a possible genetic cause of hearing loss. No other families within the autosomal dominant or recessive groups reported an acquired cause of hearing loss.

All families within the co-incidental group presented with hearing loss that appeared to be acquired. Family 23 presented a mother with sudden onset hearing loss with a child with oculocutaneous albinism. Oculocutaneous albinism with congenital deafness has been described as an autosomal dominant inheritance, characterized by congenital nystagmus, reduced visual acuity, hypopigmentation of the skin and hair, with a congenital neural hearing loss in a small percentage according to Smith (1995). No other family members presented with hearing loss or Albinism. The sudden hearing loss of the mother was co-incidental, presenting as a familial hearing loss. Family 24 reported a sudden hearing loss during her 5^{th} month of pregnancy, with a son that presented with congenital profound hearing loss. Her hearing loss was sloping bilaterally, possibly in keeping with ototoxicity. Family 25 identified a mother who reported a hearing loss after a motor vehicle accident, who later had a son, with a congenital profound hearing loss.

Consanguinity was reported in Family 1, with second degree cousins marrying. Consanguinity is suggested to increase the risks of an autosomal recessive inheritance. This family presented with 5 affected members from the same generation, with prelingual severe to profound hearing loss, in keeping with profile characteristics of an autosomal recessive inheritance. Wonkam et al. (2013), identified 15% of autosomal recessive hearing loss due to consanguinity, identified by pedigree analysis, in their assessment of childhood hearing loss in Cameroon. Arnos et al. (2013), reported that the closer the relation, the greater the incidence of both relatives being carriers of the mutation.

Obtaining information regarding consanguinity from the questionnaire was challenging as some participants overlooked the question. Similar findings were reported by Kabahuma (2010), with only 19 out 107 subjects responding to questions on consanguinity. Kabahuma, (2010) suggested that those who failed to divulge information regarding consanguinity may have a fear of stigmatization.

5.4 Genetic Profile

5.4.1 Inheritance patterns

A pedigree analysis was utilized to categorize inheritance patterns. Fourteen families (56%) were identified with an autosomal recessive non-syndromic hearing loss, while 32% (7) of families presented with an autosomal dominant non-syndromic hearing loss (Table 4.4). Literature supports an autosomal recessive inheritance incidence of 47-80%, and autosomal dominant inheritance of 10-30% (Cohen & Gorlin, 1995; Hildebrand et al., 2015; Kokitsu-Nakata, Guion-Almeida, & Richeri-Costa, 2004; Morton, 1991; Petersen & Willems, 2006)

Liu and Xu (1994), reported findings similar to the current study, when assessing the audiograms of 28 families with non-syndromic hearing loss. Their findings identified 43% of families with an autosomal dominant inheritance and 54% with an autosomal recessive inheritance. Kokitsu-Nakata et al. (2004), in their study of non-syndromic hearing loss revealed that of families that presented with a familial history of hearing loss, an autosomal dominant inheritance was identified in 31% and an autosomal recessive inheritance present in 69%. The current study correlates with other studies in that an autosomal recessive inheritance has a higher incidence than that of an autosomal dominant inheritance in non-syndromic familial hearing loss.

An X-Linked or Mitochondrial inheritance was not identified in any of the families assessed in this study. Martini et al. (1997), in their evaluation of audiometric patterns of genetic non-syndromic hearing loss, identified one family out of 65 with an X-linked hearing loss, with no mitochondrial loss identified. Wonkam et al. (2013) in their assessment of 75 pedigrees, did not observe any pedigrees suggestive of an x-linked or mitochondrial inheritance. A non-syndromic X-linked inheritance and Mitochondrial inheritance is regarded as “rare” and accounts for a small portion of hereditary hearing loss (Mazzoli, Orizan, & Stephens, 2001). It is not surprising that it was not identified in this study.

An unknown cause of hearing loss, possibly “co-incidental” familial hearing loss accounted for 12%. These families did not fit into an inheritance profile and affected participants had a possible acquired cause of hearing loss. These families were not excluded as the study was based on familial hearing loss and they presented with a familial pattern of hearing loss. It is important to include this group in the study as hearing loss that occurs in more than one family member has the potential to be genetic or acquired. Only with an in-depth questionnaire and assessments can the possibility of a genetic factor be eliminated. Acquired

causes such as HIV/AIDS and associated opportunistic infections such as Tuberculosis as well as trauma and sudden hearing loss cannot be ruled out as causes. With the high incidence of HIV and opportunistic pathogens related to hearing loss in South Africa, the incidence of acquired familial hearing loss may become a more frequent occurrence. When questioned on their medical conditions, few families reported medical conditions, and none reported being affected with any chronic illnesses. The stigma associated with HIV/AIDS and other medical conditions is common and cannot be ruled out as a cause of hearing loss in this study. A study by Crawford (1996) reported that the stigmas associated with HIV/ AIDS are much higher when compared to that of other illnesses.

5.4.2 Racial background and geographical location of participants

A majority, 81% of individuals were Black South African, with 13% percent being Indian South African and 6% being White South African. None of the individuals were Coloured South African background. The province of KwaZulu-Natal comprises of 86% of Black African nationals, 7.4% of Indians 4.2% of Whites and 1.4% of Coloureds (KZNONLINE, 2011).This perhaps correlates with the incidence of African, Indian and White individuals that were a part of the study. All families reported to originate in South Africa. The districts of eThekwini, uMgungundlovu, and UThukela, presented with the highest numbers of families with 36%, 32% and 24% respectively, and with the districts of Amajuba and uMkhanyakude presenting with 4% of families each. This study represented 4 out of 7 schools for the Deaf within Kwazulu- Natal. It is not a complete reflection, but rather a fractional view of the ethnicity of families and their familial geographical locations. Further research identifying at risk populations for genetic hearing loss within Kwazulu-Natal would be valuable.

5.5. Audiological Profile

5.5.1. Type of hearing loss

All participants with a suspected genetic etiology presented with a bilateral sensorineural hearing loss in this study (Table 4.6). One participant within the "co-incidental" group presented with a bilateral neural hearing loss, diagnosed with auditory neuropathy as well as oculocutaneous albinism. None of the subjects presented with a conductive or mixed hearing loss. Kokitsu-Nakata et al. (2004), revealed similar findings when assessing 137 participants with a genetic etiology, 99% presented with a sensorineural hearing loss with 1 presented with a mixed loss. A majority of genetic non-syndromic hearing loss is sensorineural in

nature, with the exception of the DFNX3 mutation which is characterized by a mixed hearing loss (Hildebrand et al., 2015). Petersen and Willems (2006), reported that autosomal recessive hearing loss is almost exclusively sensorineural in nature, which was identified in this study.

5.5.2. Hearing loss severity

The "co-incidental" group presented with a hearing loss severity that ranged from moderate to profound (Figure 4.16) similar to that found in the autosomal dominant inheritance group. Intrafamilial variability of hearing loss severity was apparent in all 3 families with none of the offspring presenting with similar losses as their affected parent. This also suggested an acquired cause of hearing loss.

In the autosomal recessive group, a profound hearing loss was present in 76% of participants, with a severe hearing loss accounting for the remaining 24% (Figure 4.18). None of the participants within the autosomal recessive group presented with a mild or moderate hearing loss. Similar findings were reported by Iliadou et al. (2003) when assessing 107 children with the autosomal recessive GJB2 mutation, pure tone audiometry revealed that a profound hearing loss was present in 85.2% of participants with a severe hearing loss accounting for the remaining 14.8%. Kabahuma, (2010) when assessing 182 participants in Limpopo South Africa, with suspected autosomal recessive non-syndromic hearing loss, identified a severe to profound hearing loss in 22.8% and a profound hearing loss 75%, similar to the findings of this study. Martini et al., (1997) reported in their study of audiometric patterns of genetic non-syndromic hearing loss, that most participants with autosomal recessive inheritance, presented with severe to profound hearing loss. An in-depth review of non-syndromic autosomal recessive hearing loss by Petersen & Willems, (2006), revealed similar findings to this study identifying that recessive forms of non-syndromic hearing loss are typically more severe, usually severe to profound and almost exclusively sensorineural. Review studies on non-syndromic genetic hearing loss and genotype-phenotype correlation echoed the same findings that recessive non-syndromic hearing loss tends to show a complete penetrance and are most often congenital , severe to profound and affect the entire frequency range (Angeli, Lin, & Liu, 2012; Cohen & Gorlin, 1995; Keats & Berlin, 1999; Mazzoli, Kennedy, et al., 2001).

Mazzoli et al, (2001) described autosomal dominant inheritance to have a variable penetrance, ranging from mild to profound in severity, in keeping with findings from this study. Martini et al, (1997) identified that autosomal dominant hearing loss typically

presented as a moderate to severe hearing loss. When compared to the autosomal recessive group, a clear distinction in the severity of hearing loss was identified. Liu and Xu (1994), reported that an autosomal dominant loss has been identified to be milder when compared to autosomal recessive hearing loss.

The autosomal dominant group studied revealed a hearing loss severity that was similar in distribution that ranged from mild to profound (Figure 4.18). A severe hearing loss was seen in 39% of participants, with profound hearing loss accounting for 32% and moderate hearing loss following closely behind accounting for 26%. Only 3% of participants were identified to have a mild hearing loss. Liu and Xu (1994), reported dissimilar results with a severe and profound hearing loss accounting for only 13% and 6% respectively and a moderate hearing loss accounting for more than half at 65% and a mild hearing loss accounting for 17%. A significant p-value of p=0,000 was identified using the Fischer's exact test, revealing highly significant differences between the severity of hearing loss between the AR and AD groups.

5.5.3. Audiometric configurations

In the autosomal recessive group (Figure 4.19) a flat configuration accounted for a marked 64% (67% for right ears and 61% for left) with a gently sloping configuration accounting for 20% (21% for right ears and 18% for left). This is in keeping with the findings of Kabahuma (2010) in which a flat configuration was identified in 70% with a gently sloping configuration present in 23% of participants with autosomal recessive inheritance.

In the autosomal dominant group (Figure 4.19) a steeply sloping configuration was the most common pattern, accounting for 32% bilaterally. Liu and Xu (1994), identified a similar incidence of 34% of the steeply sloping audiometric configuration when assessing audiometric patterns within the autosomal dominant inheritance group. Martini et al. (1997), when evaluating audiometric patterns in genetic non-syndromic hearing loss, identified 96 individual from 26 families that were identified with a high frequency steeply sloping hearing loss all of whom presented with an autosomal dominant inheritance.

The autosomal recessive group revealed a dissimilar incidence of the steeply sloping configuration revealing a lower occurrence of 9 and 15% for right and left ears respectively. Liu and Xu (1994), identified an occurrence of 21% within the autosomal recessive inheritance. Some studies gave no clear definition of a sloping configuration and may have grouped gently sloping and steeply sloping together as identified in Martini et al. (1997) and Frydman et al. (2000).

Less common was the mid frequency u-shaped pattern which accounted for 10% bilaterally in the autosomal dominant group and 3% for right and 6% for left ears in the autosomal recessive group. Kabahuma (2010) identified only one participant with a mid frequency u-shaped pattern with suspected autosomal recessive hearing loss, Liu and Xu (1994) also reported a lower incidence of 3.7%, of u-shaped configurations only occurring in the autosomal dominant group. Martini et al. (1997), identified a higher incidence of 14% of the u-shaped mid frequency pattern also occurring only in the autosomal dominant group.

The audiometric configuration with the least occurrence in both groups was the low frequency ascending pattern. It was identified in 6% of participants in the autosomal dominant group and was not present in the autosomal recessive group. Similar findings were observed by Liu & Lu, (1994) with 3.7% and Martini et al. (1997) with 7% in both studies also identified only in the autosomal dominant group. Liu and Xu (1994), described the low frequency ascending pattern as configuration of genetic origin, most commonly occurring in the autosomal dominant inheritance.

Audiometric configurations between autosomal dominant and autosomal recessive groups have been found to be significantly different (Liu & Xu, 1994; Martini et al., 1997; Petersen & Willems, 2006). Statistical analysis of this study revealed similar findings with a p-value of p=0.009 (Fischer's exact test), revealing highly significant differences between the audiometric configurations of the autosomal recessive and autosomal dominant group.

One participant from the autosomal recessive group was identified with an asymmetrical hearing loss. Liu and Xu (1994), identified an asymmetrical hearing loss in 12.5% of participants from both the AR and AD groups and a symmetric hearing loss in 87.5%, suggesting that a bilateral hearing loss was more significant than asymmetrical hearing loss, as identified in this study.

5.5.4. Onset of hearing loss

The assumed co-incidental group presented with 50% incidence of congenital hearing loss and 50% occurring between 11-30years. None reported an onset during birth-10years or greater than 30yearsof age. Interestingly in this group all affected parents presented with a hearing loss between 11-30years, with all affected offspring presenting with congenital hearing loss. This further suggests a non-genetic etiology of hearing loss. The co-incidental

group corresponding with the age of onset reported 50% with a prelingual loss and 50% with a postlingual onset.

In this study a congenital hearing loss accounted for 47% of all participants, with birth-10yrs onset accounting for 44%. An onset between 11-30 years was reported in 9% of participants (Table 4.9).

When further divided into genetic inheritance (Figure 4.20), a congenital loss was suspected in 85% of participants in the autosomal recessive group and 13% in the autosomal dominant group, revealing a marked difference. The onset of hearing loss suspected from birth-10years was reported in 15% in the autosomal recessive group and substantial 77% in the autosomal dominant group, showing dissimilarities once again between the two groups. No hearing loss was reported to occur later than 5years in the autosomal recessive group, with 10% reporting a hearing loss between 11-30years in the autosomal dominant group. Mazzoli et al (2001), reported that autosomal dominant inheritance has a variable penetrance and hearing loss onset can be congenital, but most frequently it occurs between 11-30yrs. This study identified a higher incidence of birth to 10years onset in the autosomal dominant group.

No similarities were identified between the autosomal recessive and dominant groups with regards to age of onset of hearing loss. In the autosomal dominant group a majority of 68% presented with a prelingual hearing loss with 32% reported a postlingual hearing loss (Figure 4.21). All participants, within the autosomal recessive group reported and were identified to present with a prelingual hearing loss. Statistical analysis revealed a high level of significance between the onset of hearing loss between the autosomal recessive and autosomal dominant hearing loss group with a p-value of p=0.000 (Fishers exact test)

It is regarded as a general rule that an autosomal recessive hearing loss has been reported to be predominately prelingual in onset, with an autosomal dominant inheritance identified as prelingual or postlingual presenting with a more variable phenotype (ACMG, 2002). Keats and Berlin (1999) in a review of genetic hearing loss reported that the onset of autosomal dominant hearing loss is often postlingual and consistent amongst the entire family. Rehm, (2005) reiterated that autosomal recessive hearing loss tends to be prelingual in onset with autosomal dominant inheritance being variable This was suggested due to most recessive mutations involving a complete loss of function of the gene, while autosomal dominant mutations reflect the interaction of the unaffected gene and the mutant gene (Rehm, 2005).

Gorlin (1995) in Van Camp, Coucke, and Willems (1996), extensively surveyed postlingual hearing loss in the autosomal recessive inheritance when compared to autosomal dominant inheritance. His findings identified three families with autosomal recessive postlingual hearing loss and at least 50 papers discussing autosomal dominant postlingual hearing loss (Van Camp et al., 1996). This findings suggested that postlingual hearing loss is most commonly considered to be inherited in an autosomal dominant manner (Hildebrand et al., 2015; Van Camp et al., 1996). This is in keeping with the finding of this study in which all postlingual hearing loss was reported from the autosomal dominant group only.

Olusanya et al. (2004); Swanepoel, Hugo, and Louw (2005) and Kabahuma (2010) indicated that little research has been reported on non-syndromic genetic hearing loss occurring in late childhood or adult onset. This study lends some information regarding later onset non-syndromic genetic hearing loss

5.5.5 Progressive hearing loss

This study did not test for progression of hearing loss due to the limited contact with patients, however family 18 were identified to show a hearing loss that appeared progressive over generations.

Family 18 (Figure 4.11) presented with an autosomal dominant hearing inheritance that appeared to be postlingual and progressive through generations. A longitudinal study based on several audiograms was not possible in this study. All hearing loss was steeply sloping with the higher frequencies being more affected than the lower frequencies. The youngest affected (IV-9) presented with a mild steeply sloping hearing loss, her mother (III-9) presented with a moderate steeply sloping hearing loss The father of III-9 and the grandfather of IV-9, II-4 presented with a severe steeply sloping hearing loss. Both II-V and III-9 reported the presence of high frequency tinnitus. To discriminate the effects of ageing against the progression of a genetic etiology is a challenge and needs to consider in progressive hearing loss. Martini et al. (1997), indicated that aging of the auditory system is not solely responsible for the deterioration of hearing loss, but can act in combination with an underlying genetic defect to show progression of hearing loss.

Similar findings were identified in a study conducted by Arnett et al. (2011), with 9 affected members in a family of 17 presenting with a high frequency sloping symmetrical sensorineural hearing loss, which progressed with age. In earlier years the hearing loss was identified to be mild to moderate, progressing to a severe to profound loss in the 7^{th} decade.

Arnett et al. (2011), attributed this hearing loss to DFNA2 deafness caused by the KCNQ4 gene.

The phenotype of progressive hearing loss is typical to that of DFNA2 deafness, at younger ages the hearing loss is milder, and in older persons the hearing loss is moderate in low frequencies and severe to profound in the high frequencies, and includes the presence of tinnitus (Arnett et al., 2011; Hildebrand et al., 2015; Martini & Prosser, 1996).

Martini and Prosser (1996), suggested that a DFNA2 Nonsyndromic hearing loss should be suspected in the following cases:

- A hearing loss that is milder in the low frequencies and moderate in the high frequencies at a younger age
- A hearing loss that is moderate in the low frequencies and severe to profound in the high frequencies at an older age.
- The family history is in keeping with an autosomal dominant inheritance
- No other clinical abnormalities are identified in the inner ears, e.g. enlarged vestibular aqueducts or Mondini dysplasia.
- The presence of tinnitus

Another mutation known to cause high frequency progressive hearing loss is DFNA5 mutation which starts at 5-15 years of age, and progresses to a severe hearing loss, with the lower frequencies being affected as well (Martini & Prosser, 1996). No tinnitus was reported with DFNA5 mutations. This mutation has not been associated with the presence of tinnitus, which was present in Family 18 (Martini & Prosser, 1996).

Audioprofiling reveals that the use of audiograms in the case of progressive familial hearing loss is a key element. Utilizing methods such as Audioprofiling by drawing audiograms of several family members on a single graph, allows for predictive hearing thresholds to be identified as a function of age, in cases with a progressive hearing loss, such as with Family 18 (Meyer, Nishimura, McMordie, & Smith, 2007).

Collecting data on families with a progressive hearing loss is not a simple task as data in not as easily available and available in large numbers like prelingual hearing loss collected at schools for the deaf (Van Camp et al., 1996). Research on familial hearing loss thus can be useful to for future studies.

5.5.6 Tinnitus

Six participants from 4 families within the autosomal dominant group reported the presence of high frequency non-pulsatile tinnitus. None of the participants from the autosomal recessive group reported the presence of tinnitus. The Fischer's exact test revealed a statistical significance with a p-value of p=0.0098, between the autosomal recessive and autosomal dominant group for the presence of tinnitus.

Martin and Raphael (2003), suggested that a combination of environmental and genetic factors are the most likely contributors to the pathophysiology of tinnitus. Autosomal dominant syndromes such as Neurofibromatosis type II (NFII), von Hippel-Lindau disease (VHL) and Wolfram syndrome have been known to cause tinnitus as a secondary occurrence (Martin & Raphael, 2003). An in-depth literature search by the researcher, did not identify any studies that linked tinnitus to non-syndromic hearing loss or specific modes of inheritance. There is a need for research in this area of tinnitus and non-syndromic hearing loss.

5.5.7 Vestibular disturbances

None of the participants were reported to present with vestibular disturbances. This was not directly assessed and information regarding vestibular disturbances were acquired from the case history interview. Moller (1996), suggested the vestibular information in a genetic evaluation can identify the effect of the genetic mutation on the labyrinth and provide a genotype phenotype relationship. The autosomal recessive non-syndromic genetic mutation DFNB12 has been linked to vestibular disturbances (Bork et al., 2001). It is not uncommon to for patients with non-syndromic hearing loss to not complain of vestibular dysfunction. Vestibular involvement is more common in syndromic hearing loss such as Ushers syndrome, (Moller, 1996) .

5.5.8 Intrafamilial and interfamilial variability

This study identified that intrafamilial variability (Table 4.12; Table 4.13, Figure 4.22) was common in both the autosomal recessive and autosomal dominant groups. The highest incidence of inter and intra familial variability were identified in families from the autosomal dominant group.

Between 25- 63% of families within the autosomal dominant group presented with differences within the family with variations in severity, audiometric configurations, age of onset of hearing loss and the presence of tinnitus. The autosomal recessive group revealed

intrafamilial differences between hearing loss severity and audiometric configuration only. Liu and Xu (1994), identified that a greater intrafamilial variability within autosomal dominant inheritance than autosomal recessive, similar to the findings above.

Interfamilial variability (Figure 23- Figure 27) was identified in both the autosomal recessive and autosomal dominant groups. The autosomal recessive group revealed differences of hearing loss severity, configuration and age of onset between families, with the autosomal dominant group revealing differences in families with all profile characteristics with the exception of type of hearing loss

Liu and Xu (1994), suggested that due to the variable penetrance in autosomal dominant inheritance a variation in most profile characteristics, such as hearing loss severity and configuration can be expected between and within families. Martini et al. (1997), suggested that intrafamilial variability can make determining a pattern of inheritance and phenotype challenging even with the presence of a hearing loss.

5.6 Audiological profile of genetic hearing loss

Significant differences in categories were identified between autosomal dominant and autosomal recessive inheritance. The profile of genetic hearing loss identified in this study is similar to the findings from previous studies as identified in Liu & Lu, (1994) and Martini et al. (1997).This trend is true for this study with the autosomal recessive losses presenting as severe to profound and the autosomal dominant losses appearing moderate to severe, with a progression only identified in the autosomal dominant group.

The most commonly occurring profile identified in this study of autosomal recessive inheritance was identified as congenital, prelingual, sensorineural, severe to profound in severity with a flat configuration .The most commonly occurring profile identified in the autosomal dominant group was identified as a moderate to severe sensorineural hearing loss, prelingual and postlingual with a configuration that was predominately sloping in configuration. Progressive hearing loss was suggested in one family within the autosomal dominant group.

The use of the audiogram shape alone to distinguish between different genotypes and subtype non-syndromic hearing loss, has in previous studies been unsuccessful (Liu & Xu, 1994; Martini et al., 1997). Some authors reported that it is challenging to use audiometric criteria alone to sub-classify non-syndromic hearing loss (Martini et al., 1997). However when including several classification criteria and parameters such as mode of inheritance, the

presence of tinnitus, age of onset and variability with audiogram shape and severity ,can be useful in determining and categorizing mode of inheritance. Statistical analysis (Fischer's exact test) in this study identified highly significant differences between severity of hearing loss, audiogram configurations, onset of hearing loss, prelingual vs postlingual hearing loss and the presence of tinnitus between the autosomal recessive and autosomal dominant groups. This significant difference in audiometric profiles between autosomal recessive and autosomal dominant inheritance groups reiterates the importance of considering audiometric data when assessing an individual with genetic hearing loss.

From this study it is apparent that there is a scarcity of geneticists and genetic counsellors and this method of profiling may be useful to audiologists as they may be the first professional to have contact with these families.

5.7 Genetic evaluation and counselling

In the event of familial hearing loss, a clinical genetic evaluation is vital to help clients with hearing loss and their families. Although not directly evaluated, with the exception of Family 4, none of the other families reported undergoing a genetic evaluation or having genetic services offered to them. The key aspect of this investigation was to bring about awareness regarding genetic familial hearing loss and to further understand genetic familial hearing loss in the South African setting, with its diverse population. These families expressed a need for understanding the cause of their hearing loss and the probability of reoccurrence in future offspring. Rao et al. (2011), reported that the role of the geneticist would be to provide counselling and timely intervention, to identify risk reoccurrence in future offspring and the need for early assessment and intervention for an early diagnosis of future offspring. Interestingly if access to a geneticist or counselling was available, for some of these families, earlier intervention of affected siblings may have been possible. In the case of family 1, all affected 5 children even though presenting with a presumed congenital hearing loss, were all identified between 3-5years of age.

Audiologists and other professionals dealing with hearing loss are perhaps currently not adequately equipped with the knowledge to discuss the reoccurrence risks and to counsel grieving families. Rao et al. (2011), suggested that the role of the audiologists is not only characterizing the hearing loss, but also providing these families with counselling and referring them to the appropriate professionals. With that being said, audiologists perhaps require a more in-depth education of genetic hearing loss and counselling at an undergraduate level.

Beighton, Kieggen, Wonkam, Ramesar, and Greenburg (2012), reported that a scarcity of genetic professionals in South Africa leaves a significant percent of the population without access to vital services. Considering the essential role that geneticists play in monogenic disorders as well as common genetic disorders such as cancers, hearing loss and heart disease, they play a pivotal role in the journey of the patient with genetic disorders

Arnos et al. (2013), suggested that the most challenging aspect dealt with by a counsellor is when an exact cause of hearing loss has not been identified, but a genetic cause of deafness is still suspected. In this case the counsellor makes use of the family pedigree information to identify empirical risk. As in the case of most participants from the study and from sub-Saharan Africa, in the absence of genetic testing, this population still requires a similar method of counselling. Families are best managed when assisted by a geneticist and counselled with the appropriate information by a genetic counsellor, they are indispensable within the genetic hearing loss scenario. An important consideration regarding genetic counselling is that the family's socials values of deafness need to be taken into account for counselling to be effective.

Arnos (1997) reported that the emphasis of the genetic counselling session is to provide information in a setting that is supportive of the clients cultural differences and social needs, that may influence the decision making process. Genetic counselling in the Deaf community (culturally deaf), provides a challenge to the genetic counsellor. In the medical model, deafness is considered to be a pathological condition (Arnos, Israel , & Cunningham, 1991). The Deaf community do not regard hearing loss as a disability, but rather define themselves as being part of a minority group, with its own beliefs, language and customs. Linguistic and cultural beliefs play an essential role in the achievement of genetic counselling in the Deaf community (Arnos et al., 1991). Deaf parents may prefer to have deaf children, which should be considered in the genetic counselling process. The use of questionnaires, qualified interpreters and a revision of counselling material, should be considered when offering a service to remove cultural bias (Arnos et al., 1991). Arnos et al. (1991),suggested that the deaf community may not seek out genetic counselling to gain knowledge on reproductive risks, but are keen and open to genetic services, when provided in a linguistic and culturally appropriate manner, that is sensitive to their beliefs (Arnos et al., 1991). Members of the Deaf community are suggested to be ideal candidates to be genetic counsellors for deaf individuals and families (Arnos et al., 1991).

5.8 Childhood hearing loss and genetic research

Smith (2013), reported that more recently at least 72 recessive loci and 56 dominant loci have been identified to be responsible for hearing loss. Smith, (2013) further reported the identification of mutational genes in the diagnosis of hereditary hearing loss. Great advances have been made in our understanding of genes and its mechanism. With the high rate of molecular testing in first world countries, only 10% of childhood hearing loss is unknown (Wonkam et al., 2013). With the implementation of newborn hearing screening, a larger incidence of genetic hearing loss is suspected to be identified. In keeping with the early diagnosis of hearing loss in these babies as suggested by the JCIH, (2007) and HPCSA (2007) the assessment and diagnosis process should include a genetic evaluation, testing and counselling which will be helpful to the families, reducing the possibly negative emotions and trauma, that maybe experienced when and if subsequent affected children are born. It is essential that these stipulations in the JCIH, (2007) and HPCSA, (2007 regarding early intervention and the use of genetic services for hearing loss are upheld and not just placed on paper.

In sub-Saharan Africa, there is a need for genetic research to allow for the detection of specific mutations of the diverse African population to subsequently make molecular screening for these mutations easily available (Wonkam et al., 2013).

5.9 Summary

This chapter discussed the findings of this study in relation to other similar local and international research. The audiological and genetic profile of families within the study, revealed marked differences between the profile of autosomal dominant and autosomal recessive hearing loss. The method of using specific standardized criteria to profile genetic and audiological characteristics of familial hearing loss, has been useful when comparing and contrasting similar studies, and providing a clearer picture of the genotype-phenotype presentation of each inheritance pattern. The function of key team members such as the audiologist, geneticist and genetic counsellor are critical in the assessment and management of familial hearing loss. Families in this study and the majority of South Africa are without genetic services, due to the scarcity of these trained professionals.

CHAPTER 6
CONCLUSION

6.1 Introduction

This chapter discusses the culmination of the study by reviewing key elements from the results and discussion chapters. It includes a summary of the study, discusses its strengths and limitations. It explores the implications of this study as well as recommendations for future studies for research in this area. It ends with a summary of the chapter.

6.2 Summary of the study

The focus of this study was to understand the audiometric profile of familial genetic hearing loss in Kwazulu-Natal, looking at schools for the Deaf. This study intended to provide basic information regarding familial genetic hearing loss, which will allow for improving audiological and genetic related services in Kwazulu-Natal as well as continuing research for this forgotten etiology of hearing loss. Profiling of characteristics and compiling family pedigrees of genetic hearing loss as done in this study can be useful to medical practitioners and audiologists within South Africa, to identify characteristics such as mode of inheritance which would enhance counselling and to facilitate referrals to genetic professionals, as well as estimating the reoccurrence risk of the hearing loss if necessary. Participants had the option of being referred to a geneticist or genetic counsellor to assist with questions, concerns and information regarding their family pedigrees and family history of hearing loss.

Non-syndromic familial hearing loss is a challenge to the audiologist and geneticist. Defining inheritance of the hearing loss is still made on a probable basis using the audiogram and pedigree. The use of audiometric patterns, profiling parameters and pedigree analysis is still a useful method of sub-categorizing hereditary hearing loss (Martini & Prosser, 1996).

The results of the present study are in agreement with other studies description and auditory profile differences of autosomal recessive and autosomal dominant hearing loss. Autosomal recessive hearing loss profile has been identified as severe to profound, with an early onset which is predominately congenital, with flat and sloping audiometric configurations and sensorineural in nature. The most commonly occurring profile identified in the autosomal dominant group was identified as a moderate to severe sensorineural hearing loss, prelingual and postlingual with a configuration that was predominately sloping in configuration.

To the researchers knowledge this is the first study in South Africa focused on profiling familial deafness in learners attending schools for the Deaf in Kwazulu-Natal. The inclusion of 3 families with a co-incidental familial hearing loss, aimed at recognizing that familial hearing loss, is not always genetic in acquisition, but may have the same effects on communication, stigma and concerns that those with a genetic hearing loss present with.

In a setting where genetic professionals are unavailable, the onus is on the treating practitioner to intervene. A family's understanding of hearing loss and deafness is moulded by their exposure and interaction with professionals, other family members as well the Deaf and hearing communities. These different sectors play a vital role in shaping these families. Wonkam, Njamnshi & Angwafo, (2006) suggested that there is a great necessity to increase genetic literacy within sub-Saharan Africa. Prevalence studies and statistics of hereditary hearing loss in children and adults are essential to ensure adequate services for assessment and counselling are made available. Although not directly assessed in this study, stigmatization and different cultural views regarding genetic familial hearing loss was identified and should be regarded as an important issue that needs to be considered, when dealing with genetic hearing loss, especially familial inheritance.

6.3 Strengths of the study

- Knowledge of the profile characteristics of familial genetic hearing loss within the province of KwaZulu-Natal will be beneficial to medical professionals when assessing and managing these families and will optimistically aid to enhance and streamline service delivery to these families.
- Research on genetic familial hearing loss in South Africa is scarce, this study aims at renewing researchers interest in this growing and exciting field as well as providing a baseline of information regarding familial deafness and its characteristics.
- This study provides insights on the current incidence of genetic familial hearing loss at schools for the deaf in the province of KwaZulu-Natal.
- It is anticipated that with the development of research in the area of genetic familial hearing loss, more genetic professionals such as geneticists and genetic counsellors in genetic services will be available.
- The system of profiling genetic hearing loss is a useful standardized method of understanding this information and helpful when relating this information to other professionals. It is anticipated that this standard method of profiling genetic familial hearing loss, is utilized by all professionals who encounter families with hearing loss.

- The goals of early hearing detection and intervention of hearing loss especially in families with a genetic hearing loss are still not being met, even with prior knowledge of other affected family members. It is anticipated that with more awareness and interest in the area of genetic familial hearing loss, that these goals will be met.
- It is anticipated that families within this study have benefited by understanding the basis of their familial hearing loss and gained insight of the condition from genetic intervention (geneticist/ genetic counsellor) to be made available to them.

6.4 Limitations of the study

- This study provided an audiological profile of familial hearing loss within a limited number of schools for the Deaf. Including all schools for the deaf and Hearing impaired units within KwaZulu-Natal, may have provided an improved estimate of the incidence of familial hearing loss within this region.
- The method of acquiring participants for the study may have resulted in some eligible families being missed. The resident audiologist was used to identify suitable participants based on their knowledge of learners and as it was not possible to peruse all learners' records due to limited time available at each school.
- Not all affected family members underwent audiological assessments within the study, with some hearing loss being reported, limiting the contributing information used for profiling information.
- Family pedigree information was based on the families willingness to divulge information, as well as memory of ages, hearing status and order of births of all members of the pedigree. The accuracy of information provided is a factor.
- The psychosocial aspects of familial hearing loss were apparent during the questionnaire and pedigree aspect of the study. Feelings of guilt, confusion and inadequacies from the parents/ caregivers were just some of the emotions expressed. This was not the scope of the study and thus not explored or counselled in an in-depth manner. Some families may have felt that their psychosocial needs were not met in this study. They however were referred to a genetic counsellor.

6.5 Implications of the study

- This study provides theoretical and clinical insights on genetic familial hearing loss on learners attending schools for the deaf in Kwazulu-Natal.

- Research and investigations on hereditary hearing loss, and familial deafness is scarce in sub-Saharan Africa and South Africa. This study emphasizes the need for population specific research within Africa.
- This study highlights the role of the audiologist in the family with genetic hearing loss. There is a need for a revision of the genetic content in Audiology degrees at an undergraduate level to introduce the latest trends and research in genetic hearing loss and to include genetic counselling skills needed for an audiologist working with familial hearing loss. Methods such as profiling of audiometric and genetic information can be useful and should be included in the undergraduate programs.
- All families with genetic hearing loss should have access to genetic professionals, it is anticipated that the data from this study reveals the prevalence of familial hearing loss in Kwazulu-Natal and the need for skilled genetic professionals to assist this population.
- This study indirectly revealed the stigma and psychosocial aspects that accompany genetic familial hearing loss. These sensitive issues should always be considered by healthcare professionals when assisting these families.

6.6 Recommendations for future research

- Further ideas for these participants would be linkage analysis and possibly mutational analysis once the family has been mapped, moving towards identification of the genetic mutation responsible for the hearing loss. Keats and Berlin (1999), reported that studying sets of affected relatives who are assumed to have the same defective gene, can aid in genomic screening and is useful in genetic mapping.
- To investigate the emotional and psychosocial aspects of genetic familial hearing loss from the families perspective.
- To assess the stigma associated with genetic familial hearing loss
- To assess the availability and accessibility of genetic services to all affected individuals with genetic hearing loss in South Africa.
- To evaluate the sensitivity of current genetic counselling programs in dealing with the Deaf community and familial hearing loss.

6.7 Summary

This study investigated the audiological and genetic profile of learners suspected of presenting with familial hearing loss attending schools for the deaf in Kwazulu-Natal. The results of the study revealed marked differences between the audiometric and genetic profiles of inheritance patterns. The knowledge of the suggested audiological profile of genetic familial hearing loss will assist hearing health professionals when assessing and managing these families. The understanding of genetic hearing loss and its presentation in the South African setting even at a rudimentary level is useful as population based research is essential in the field of genetics. This study is perhaps the first at profiling audiological characteristics of familial hearing loss in South Africa. It is anticipated that this study will also bring about awareness and knowledge of genetic familial hearing loss as well as its features, to facilitate an improved rollout of genetic and health services to these families.

Audiologists play a vital role in the family with genetic hearing loss and are often the first clinicians to come into contact with these families. The role of audiologists within the family with genetic hearing loss needs to be highlighted.

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APPENDICES

APPENDIX A
QUESTIONNAIRE ENGLISH

Dear Parent/Care giver

INSTRUCTIONS

1. Please complete this form as best as you can
2. Participants are required to mark the appropriate answer to each question with an X, and give further detail if necessary..
3. There are ten sections, (A-J) to this questionnaire, please answer all the questions contained in each section.
3. A Zulu interpreter and the clinician will be assisting you with the Questionnaire.
4. Section B and C is required to filled by the mother/guardian of the child.
5. With your permission we will check your child's clinic booklet to determine birth and other medical information as well.

SECTION A

BIOGRAPHICAL DATA

1. SUBJECT NUMBER: _____
2. DATE OF BIRTH: _____
3. AGE: _____
4. SEX: _____
5. PLACE OF BIRTH:_____
6. PRESENT HOME AREA:_____
7. MOTHERS HOME AREA:_____
8. FATHERS HOME AREA: _____
9. RELATIONSHIP BETWEEN PARENTS (IF ANY) _____

_____

10. HEARING STATUS OF MOTHER _____

_____

11. HEARING STATUS OF FATHER_____

_____

.

SECTION B
MATERNAL HEALTH DURING PREGANANCY/ PRENATAL HISTORY

1. How was the mum's physical health during pregnancy?

Good ☐ Fair ☐ Poor ☐

If poor, state the nature and duration of the condition.
_____
_____
_____

2. How was the mum's emotional health during pregnancy?

Good ☐ Fair ☐ Poor ☐

If poor, state the nature and duration of the condition.
_____
_____
_____

3. Did any of the following occur during pregnancy?
If yes, explain.

Yes	No		Explain
____	_____	Bleeding	_____
____	_____	Measles (which months)	_____
____	_____	Accidents/ Trauma	_____
____	_____	Illness/Infections	_____
____	_____	Rashes (which month)	_____

4. Did the mum take any medication during the pregnancy?

Yes ☐ No ☐
If yes what was the medication for? _____
_____
_____

5, Did the mum take any recreational drugs /alcohol during pregnancy?
Yes ☐ No ☐

If yes what was the medication for? _____
_____

_____

SECTION C
BIRTH HISTORY

1. How long was the pregnancy?
_____
_____

Where was the child delivered? (At home, at clinic, at hospital?)_____
_____
_____

2. What type of delivery? (Normal, Breech, Caesarean)?
_____
_____
_____

3. Was the labor induced?
_____
_____
_____

4. How long was the labor?
_____
_____

5. Were forceps used? (A medical instrument used to help remove the baby during childbirth)
_____
_____

6. What was the child's Apgar score?
_____
_____

7. What was the child's birth weight?
_____
_____

8. Were any of the following present at the child's birth?

Yes	No		Explain
____	_____	Umbilical cord around neck	_____
____	_____	Jaundice (Kept under a light)	_____
____	_____	Convulsions	_____
____	_____	Blood transfusions	_____
____	_____	Breathing difficulty	_____
____	_____	Bleeding in the brain	_____
____	_____	Cyanosis (Bluish discoloration)	_____
____	_____	Oxygen given (how long)	_____
____	_____	congenital defects	_____
____	_____	Birth injuries	_____
____	_____	Incubator required (how long)	_____
____	_____	Meningitis	_____

SECTION D
MEDICAL HISTORY

1. How has the child's health been?

Good ☐ Fair ☐ Poor ☐

If poor explain

_____
_____
_____

2. Has the child ever had any of the following?

Yes	Date	No	
____	_____	_____	Mumps
____	_____	_____	Measles
____	_____	_____	Chicken pox
____	_____	_____	Pneumonia
____	_____	_____	Malaria
____	_____	_____	Meningitis
____	_____	_____	Sinus
____	_____	_____	Epilepsy

____	_____	_____	Poor coordination
____	_____	_____	Rheumatic fever
____	_____	_____	Polio
____	_____	_____	Diabetes
____	_____	_____	Earaches
____	_____	_____	Fluid Discharge from the ears
____	_____	_____	Head injury
____	_____	_____	Asthma
____	_____	_____	Allergies
____	_____	_____	Encephalitis
____	_____	_____	Broken bones
____	_____	_____	Chicken pox
____	_____	_____	chronic colds

3. Does your child have any medical conditions? E.g. epilepsy

_____
_____

4. Has the child ever been hospitalized?

Yes ☐ No ☐
If yes what was the reason?_____
_____
_____

5. Has the child undergone any surgeries?

Yes ☐ No ☐
If yes explain, _____
_____
_____

6. Does the child currently have or previously had any serious illnesses?

Yes ☐ No ☐
If yes explain, _____
_____

7. Has the child ever been diagnosed with a syndrome, (has other problems that accompany the hearing impairment?

Yes ☐ No ☐
If yes explain, _____
_____
_____

8. Has the child ever undergone an eye test?

Yes ☐ No ☐

If yes, when was the test done and what were the results?

_____
_____
_____

9. Is the child on any medication currently?

Yes ☐ No ☐

If yes, what medication is the child taking?

_____
_____
_____

SECTION E
DEVELOPMENTAL HISTORY

1. At what age did the child do the following?
   - Showed awareness to sound_____
   - Sit by himself _____
   - Walk _____
   - Began saying words_____
   - Age toilet trained _____

2. Compared to others in the family, was crawling, walking, running development
Fast ☐ Slow ☐

If answered slow explain,

_____
_____
_____

3. What is the child's present weight? _____

4. What is the child's present height? _____

SECTION F
HEARING HISTORY

1. When did you first notice you Childs hearing impairment? _____
_____

2. What do you think caused your Childs hearing impairment? _____

_____

3. Has the child's hearing been tested?
Yes ☐ No ☐

If yes, when was the test conducted and what were the results?

_____
_____
_____

4. Did the speech or language development ever seem to stop?

Yes ☐ No ☐

If yes when and at what age of the child did it stop?

_____
_____
_____

SECTION G
FAMILY HISTORY

1. Are there any family members that have any speech/ hearing problem?

Yes ☐ No ☐

1.1.If yes; please indicate the following

- What is their relation to your child_____
  _____
- Age _____
- Speech /hearing problem _____
- Cause of hearing impairment _____
  _____

1.2

- What is their relation to your child_____
  _____
- Age _____
- Speech /hearing problem _____
- Cause of hearing impairment _____
  _____

1.3.

- What is their relation to your child_____
  _____
- Age _____
- Speech /hearing problem _____
- Cause of hearing impairment _____

1.4.

- What is their relation to your child_____
  _____
- Age _____

- Speech /hearing problem _____
- Cause of hearing impairment _____
  _____

SECTION J
GENERAL

Please indicate any information you regard as relevant that has not been covered
_____
_____
_____
_____
_____

THANK YOU FOR YOUR TIME AND WILLINGNESS TO PARTICIPATE IN OUR RESEARCH PROCESS

Karen Pillay
Audiologist

Dr. L. Joseph
Supervisor

Dr. C.Aldous
Supervisor

APPENDIX B

QUESTIONNAIRE -ISIZULU

Mzali

Imigomo

1. Gwalisa ngemininingwane ngokuyikho.

2. Faka isiphambano empendulweni okuyiyo (X), bese unikeza neminye imininingwane uma ikhona.

3. Kuneziqephu eziyishumi okufanele ziphendulwe zonke.

4. Utolika kanye noDokotela bazosiza ukuchaza imbuzo.

5. Iziqephu- B kanye nesiqephu – C zidinga zigcwaliswe abazali.

6. Ngemvumo yomzali sizocela ukubana amakhadi aseklinini- sibone imininingwane mayelana nckuzalwa kanye nempilo komntwana.

ISEQEPHU A

UMLANDO WEMVELAPHI

1. Inombolo: _____

2. Usuku lokuzalwa: _____

3. Iminyaka: _____

4. Ubulili: _____

5. Indawo azalelwa kuyo: _____

6. Indawo ahala kuyo: _____

7. Indawo umama ahlala kuyo: _____

8. Indawo ubaba ahlala kuyo: _____

9. Ubudlelwane phakathi kwabazali (uma kukhona): _____

_____

10. Izinga lokuzwa loka mama_____

11. Izinga lokuzwa loka baba_____

ISEQEPHU B

Umlando nokuzalwa

1. Izinga lempilo likamama ekulelwe?

Kuhle ☐ Kungcano ☐ Kubi ☐

Uma kwaku kubi, wayephethwe yini? Isikhathi esingakanani.

_____

_____

_____

2. Ingabe umama waye patheke kanjani esingakanani?

Kuhle ☐ Kungcano ☐ Kubi ☐

Uma kwaku kubi, wayephethwe yini? Isikhatihi esingakanani.

_____

_____

_____

3. Ingabe wavelelwa okulandelayo ngesikhathi ukhulelwe?

Yebo	Cha		Chaza
_____	_____	Ukopha igazi	_____
_____	_____	Lisimungumungwane	_____
_____	_____	Lingozi	_____
_____	_____	Lukugula okuthize	_____
_____	_____	Lukuqubuka	_____

4. Ingabe umama kukhona amaphilisi/umuthi owaye wathatha ngesikhathi ekhulelwe?

Yebo ☐ Cha ☐

Uma yebo amaphilisi/umuthi ngabe ayesiza siphi isifo nama ukugula? _____

_____

5. Ingabe umama ubephuza utshwala noma izidakamizwa esakhulelwe?

Yebo ☐ Cha ☐

Uma yebo, ingabe wayesiza siphi isifo/ukugula?_____

_____

_____

ISEQEPHU C

UMLANDO NGOKUZALWA

1. Ingabe wakhulelwa izinyanga ezingaki?

_____

_____

2. Wazalelwa kuphi umtwana (ekhaya, ecliniki, esibhedlela?).

_____

_____

3. Wamthda kanjani? (Kahle, phuma ngezinyawo , isikele).

_____

_____

4. Ingabe umsiko wavuswa ngokuthi bakujove?

_____

_____

5. Ingabe wathatha isikhathi esingakanani umsiko?

_____

_____

6. Ingabe izinsimbi zasetshenziswa mhla uteta/umthola umtwana wakho?

_____

_____

7. Yathini i-Apgar score yamtwana?

_____

_____

8. Sathini isisindo somtwana ngesikhathi ezalwa?

_____

_____

9. Ingabe umtwana wayenako okulandelayo ngeikhathi umthela?

Yebo	Cha		Chaza
_____	_____	Inanga imbambe entanyeni	_____
_____	_____	Jandisi	_____
_____	_____	Isithuthwane	_____
_____	_____	Ukuphelewa yigazi emzimbeni	_____
_____	_____	Inkinga yokuphefumula	_____
_____	_____	Ukopha igazi engqodweni	_____
_____	_____	Ukushintsha kombala emzimbeni (ohlaza)	_____
_____	_____	Wafakwa kwi-oxygen, edinga umoya	_____
_____	_____	Ukukhubazeka emzimbeni	_____
_____	_____	Umtwana walimala yini ngesikhathi umthola	_____

_____ _____ Evazalwa isikhathi singaka fiki _____

_____ _____ Ikhanda elibuhlungu ngokunga bekezeleki_____

ISEQEPHU D

UMLANDO WEMPILO

1. Linjani izinga lempilo lomtwana?

Kuhle ☐ Kungcano ☐ Kubi ☐

Uma kwaku kubi,chaza

_____

_____

_____

Ingabe ungane yake yaphathwa:

Yebo	Usuku	Cha	
_____	_____	_____	Uzagiga
_____	_____	_____	Isimungu mungwane
_____	_____	_____	Utwayi
_____	_____	_____	Inumonia
_____	_____	_____	Malale vera
_____	_____	_____	Ikhanda elibuhlungu lingabekezeleki
_____	_____	_____	ukuvimbana kwamakhala/ ukucinana
_____	_____	_____	isifo sokuwa
_____	_____	_____	Ukuphelelwa ibhalansi
_____	_____	_____	Umkhuhlane omubi
_____	_____	_____	Polio
_____	_____	_____	Ushukela
_____	_____	_____	Izindlebe ezibuhlungu
_____	_____	_____	Izindlebe ziphuma ubomvu
_____	_____	_____	Ingozi ekhanda
_____	_____	_____	Isifuba
_____	_____	_____	Encephalitis (ikhanda elincane)
_____	_____	_____	Ukuphuka kwamathambo
_____	_____	_____	Utwayi
_____	_____	_____	Umkhuhlane

3. Ingabe kukhona ukugula ingane enakho? Isb. Isifo sokuwa?

_____

_____

4. Ingabe ingane yake yalala esibhedleki?

Yebo ☐ Cha ☐

Uma yebo,chaza kabanzi_____

_____

_____

5. Ingabe ingane yake yahlinzwa?

Yebo ☐ Cha ☐

Uma yebo, chaza kabanzi_____

_____

_____

6. Kukhona ukugula okuphethe ingane?

Yebo ☐ Cha ☐

Uma yebo, chaza kabanzi_____

_____

_____

7. Ingabe kukhona ukugula okuhambelana nenkinga zokuzwa ezindlebeni?

Yebo ☐ Cha ☐

Uma yebo, chaza kabanzi_____

_____

_____

8. Ingabe ingane yake yahlolwa amehlo?

Yebo ☐ Cha ☐

Uma yebo, kwenziwa nini ukuhlolwa kwamehlo?_____

_____

_____

9. Ingabe kukhona umuthi/amaphilisi athathwa ingane?

Yebo ☐ Cha ☐

Uma yebo, ingabe owoni_____

_____

_____

ISEQEPHU E

UMLANDO WOKUKHULA

1. Ingabe ingane yakwenza nini u-

- Utshengisa ukulalela imsindo_____
- Ukuzimela ngokwayo_____
- Ukuzihambela_____
- Ukukhuluma_____
- Usebenzisa indlu yangasese_____

2. Uma uqhathanisa nomdeni ingabe ukugaqa, uhamba, ukugijima, ingabe.

Kwashesha ☐ Kwahamba kancane ☐

Chaza uma kwahamba kancane, _____

_____

_____

3. Isisindo sengane?_____

4. Ubude bengane?_____

ISEQEPHU F

UMLANDO WOKUZWA

1. Kungabe waqala nini ukubona inkinga yokuzwa enganeni?

_____

_____

_____

2. Ingabe ucabanga ukuthi kwaqalwa yini?

_____

_____

_____

3. Wake wahlola ngaphambili ukuzwa kwakhe?

_____

_____

_____

4. Ingabe kwake kwabonakala sengathi ukukhuluma kuyaphela?

Yebo ☐ Cha ☐

Uma yebo,wayenaminyaka emingaki?_____

_____

_____

5. ISIQEPHU I

UMLANDO WAMDENI

1. Ingabe kukhona emindenini eninkinga yokukhuluma/ nokuzwa czindlebeni ekhaya?

Yebo ☐ Cha ☐

1.1. Uma yebo, chaza okulandelayo:

- Uhlobene kanjani lamuntu enganeni_____
- Iminyaka_____
- Inkinga yokukhuluma/ ukuzwa; chaza_____

_____

Ingabe kwaqalwa yini/enki nkinga yokuzwa ezindlebeni_____

_____

1.2. Uma yebo, chaza okulandelayo:

- Uhlobene kanjani lamuntu enganeni_____
- Iminyaka_____
- Inkinga yokukhuluma/ ukuzwa; chaza_____

_____

Ingabe kwaqalwa yini/enki nkinga yokuzwa ezindlebeni_____

_____

1.3. Uma yebo, chaza okulandelayo:

- Uhlobene kanjani lamuntu enganeni_____
- Iminyaka_____
- Inkinga yokukhuluma/ ukuzwa; chaza_____

_____

Ingabe kwaqalwa yini/enki nkinga yokuzwa ezindlebeni_____

_____

1.4. Uma yebo, chaza okulandelayo:

- Uhlobene kanjani lamuntu enganeni_____

- Iminyaka_____
- Inkinga yokukhuluma/ ukuzwa; chaza_____

_____

Ingabe kwaqalwa yini/enki nkinga yokuzwa ezindlebeni_____

_____

ISIQEPHU J

Uma enemininingwane ofisa ukusazisa yona engasiza wamukelekile ukuchaza kabanzi/ ukubhala ngaphansi.

_____

_____

_____

_____

_____

Siyabonga ngesikhathi sakho/nokuzinikela kwakho udlala indima ocwaningweni.

Ozithobayo

Karen Pillay

Audiologist

Dr L Joseph

Supervisor

Dr.C.Aldous

Supervisor

APPENDIX C

SCHEDULE OF ASSESSMENT PROCEDURES

1. Case History Questionnaire

Motivation

An in depth case history is required to provide valuable information about the participants background, family, medical, occupational, otological, communication and other relevant areas, Kochhar et al (2007).

Data Collection Instrument

Case history questionnaires will be utilized. Questionaires are available in English and IsiZulu.

Procedure

Participants/caregivers will complete the questionnaire on the day of the assessment. If the participants require clarification on any of the questions the researcher interpreter will be available for assistance.

A pilot study will be done regarding the questionnaire

2. Otoscopic Examination

Motivation

Otoscopy is a critical tool in the audiological examination. It assists in the identification of pathological conditions of the outer ear extending to the tympanic membrane (Gelfand, 1997). Collapsing ear canals, cerumen and congenital/genetic disorders of the external ear are important to identify e.g. aural atresia, microtia, anotia and stenosis of the external auditory meatus etc. In the light of an audiological profile of hearing being discussed the eardrum will be evaluated for colour, transparency, architecture, mobility, perforation, retraction and tympanosclerosis (Ramana et al, (2005).

Procedure

The external ear is examined for any congenital malformations. The ear canal is then inspected with the otoscope, which provides both illumination and magnification of the ear canal and tympanic membrane (Rappaport & Provencal 2002)

Instructions

Parent

"Sir/Madam please sit still and do not make any sudden movements, if you need to cough or move please inform me first and I will stop the examination".

Children

"I'm going to shine this bright light into your ears, so I can see what your ear looks like. It's not going to hurt. I want you to stay still, it'll be over shortly."

The reason for conducting the examination will be clearly explained to the participant. Instructions to the test procedure will only be done in the participant's first language.

3. Immittance Audiometry

Motivation

This serves to be an important component of the initial audiological assessment procedure as it is an objective means of assessing the integrity of the auditory mechanism/the mechanical status of the middle ear. Immitance audiometry supplies information on various middle ear pathologies as well as middle ear muscle contractions. They are objective measures and require no physical response (Gelfand, 1997).

Instructions

Adult

"Sir/Madam you will hear tones in your ear and may feel a slight pressure within the ear. Please sit still and do not make any sudden movements, if you need to cough or swallow please inform me first and I will stop the examination. Please do not chew during the test. You are not required to respond and I will inform you when the test is complete."

Child

"This machine is going blow air into your ears, it may tickle a little. I want you to stay still, it will be over shortly".

Instructions to the test procedure will only be done in the participant's first language.

4. Pure Tone Audiometry

Motivation

Pure audiometry identifies an audiometric threshold, by assessing the lowest level of intensity at which the patient can hear a pure tone signal at least 50% of the time (Harrell, 2002).

The use of pure tone testing is to find the clients threshold of hearing at various frequencies. The air conduction results can specify the degree but not the type of loss in the ear (Gelfand, 1997). During the test the whole conductive pathway is tested. (Outer, middle, inner ear and beyond.) Both air conduction and bone conduction pathways will be tested.

Procedure

Instructions will be provided for the test. The method that will be used to obtain pure tone thresholds will be the ascending/descending method developed by Carhart and Jerger (1959). This will be done for the frequency range of 250Hz to 8000Hz.

Instructions

Participants are required to remove earrings, glasses and hair accessories, if necessary. Chewing gum was disposed of. Clients will be seated in a comfortable chair. The objective of the test will explained, i.e. the participant is required to respond to the softest sound that they hear. "You are about to hear a tone (beep –beep) through the earphones. The tone will range from loud sounds to soft sounds, each time you hear the tone I want you to press the response button. Please do not press the response button if the tone is not heard. Some tones are extremely soft so please listen carefully. Instructions to the test procedure will only be done in Instructions to the test procedure will be done in the subject's first language.

5. Pedigree Chart

Motivation

A comprehensive family pedigree chart is required which should include at least 3 generations of family X. According Kochhar et al (2007), a three generation family history with attention to other relatives with hearing loss and relative findings should be obtained to assist with information for a pedigree chart. A pedigree chart allows a visual representation of other family members that present with hearing impairment.

Procedure

The chart will be drawn using universal symbols. The family pedigree focuses on hearing impairment. A family pedigree will include a 3 generation family history if possible.

Test 7 and Test 8 will only be conducted if behavioral audiological assessments ae unsuccessful

7. Auditory Brainstem Response (ABR) Assessment

Motivation

Auditory Brainstem response is a neurological test of the auditory brainstem function in response to an auditory stimulus. It is a test of auditory synchrony. It assesses hearing function up to the level of the brainstem.

Instructions

This test does not require a response from you. "I would like you to try to remain as still as possible while the test is commencing, you may even try to fall asleep. "I am going to place

these different colored wires at specific areas of your head. The wires will not harm you in any way." The wires are assisting in the hearing test. Instructions to the test procedure will only be done in the participant's first language.

8. Otoacoustic Emission Testing (OAE)

Motivation

Distortion Product Otoacoustic Emissions (DPOAE's) offer the clinician the ability to evaluate frequency specific regions of the cochlea (Northern & Downs, 2002). "DPOAE testing has the capability of delimiting quite accurately, the boundary between normal and abnormal hair cell function. This can be depicted best in patients exhibiting the effects of noise damage in which discrete notches and sharp reductions in high frequency hearing commonly occur" (Longbury, Martin and Martin, 1990).

Procedure

The participant was clearly instructed as to what is required from them during the test. An appropriately sized probe tip will be inserted into the participant's ear and the DPOAE will be recorded.

Instructions

"Please try to sit still and not make any sudden movements, as it would affect the results obtained .No chewing and limited swallowing is suggested during the testing procedure. Tones will to be heard and no physical response will be required from you during the test." Instructions to the test procedure will only be done in the patients their first language.

APPENDIX D

EQUIPMENT CALLIBRATION CERTIFICATES

HASS GROUP

Ear Institute, 1240 Webb Str. Queenswood Pretoria. Tel: (012) 333-3131 Fax: (012) 333-2298

H.A.S.S. Industrial (Pty) Ltd

Certificate of Calibration
No. C AS041510/13

Calibrated for:	**Fulton School** Speech and Audiology 8 Rooseveld Road Gillets Durban Kwa-Zulu Natal
Calibration of:	**GSI 38 V4**
Manufacturer:	GSI
Serial Number:	**AS041510**
Calibration procedure:	Complete probe, reflex, pressure and audio calibration as described in the manufacturer's specification. Earphones (TDH 39: Right s/n C76554; Left s/n C76553).
Traceability:	The calibration was performed using instruments traceable to national standards.
Date of Calibration:	**2013-03-01** **Cal. Due Date:** **2014-03-01**
Results:	The instrument complies with the requirements for use as specified by the manufacturer.
Remarks:	None.
Calibrated by:	Heinrich Kruse _____ Signature

NOTE: The values in this certificate are correct at the time of calibration. Subsequently the accuracy will depend on such factors as the care exercised in the handling and use of the instrument and the frequency of use. Re-calibration should be performed annually to ensure that the instrument's accuracy remains within the desired limits.

HASS GROUP

Ear Institute, 1240 Webb Str. Queenswood Pretoria. Tel: (012) 333-3131 Fax: (012) 333-2298

H.A.S.S. Industrial (Pty) Ltd

Certificate of Calibration
No. C 870688/13

Calibrated for:	**Fulton School** Speech and Audiology 8 Rooseveld Road Gillets Durban Kwa-Zulu Natal
Calibration of:	**AD229b**
Manufacturer:	Interacoustics
Serial Number:	870688
Calibration procedure:	Complete diagnostic calibration: Audiometer (AD229b), Earphones (TDH 39: Right s/n C509280; Left s/n C509073), Bone Vibrator (B71), Free Field (Unknown Speakers).
Traceability:	The calibration was performed using instruments traceable to national standards.
Date of Calibration:	**2013-03-01** **Cal. Due Date:** **2014-03-01**
Results:	The instrument complies with the requirements for use of a Type 2 Audiometer (Air Bone, Free Field).
Remarks:	None.
Calibrated by:	Heinrich Kruse  Signature

NOTE: The values in this certificate are correct at the time of calibration. Subsequently the accuracy will depend on such factors as the care exercised in the handling and use of the instrument and the frequency of use. Re-calibration should be performed annually to ensure that the instrument's accuracy remains within the desired limits.

Stanyer ELECTROSERVE
SALES, SERVICE & REPAIRS OF AUDIOMETRICS & MEDICAL INSTRUMENTATION
Ck 94/05783/23

Tel: 031-7090710
Fax: 031-7028778
Email: info@stanyersa.com
Website: www.stanyersa.com

P. O. Box 273, Gillitts, 3603
No. 2 Gilro Park
34 Gillitts Road
Pinetown, 3610

Certification of Standard Calibration

Company Name & Address

VN NAIK
Newlands, KZN

Make	Model	Serial no.	Left ear	Right ear	Pre. cal.	Post cal.	Cert. no.
Madsen	Itera II	407461	C563192	C563142	110,0	110,1	P130424D1

		Air/Pure tone			N.B. Noise			Bone con.		Free/Warble			Free/N/B		
Freq. Hz	Freq. Meas.	Left	SABS 70dB	Right	Left	SABS 70dB	Right	SABS 40dB	M.V	FF1	SABS 70dB	FF2	FF1	SABS 70dB	FF2
125	124,9	115,2	115	115,3	119,1	118	118,3			90,8	90	91,0	90,1	90	90,1
250	249,9	97,7	97	97,0	100,8	100	100,6	90.5	90,4	81,6	81	81,2	81,0	80.5	80,6
500	499,8	83,5	83.5	83,6	87,0	86.5	86,6	82.0	82,3	76,1	76	76,2	74,8	74.5	74,7
750	749,7	79,1	79	79,5	83,0	82	82,0	72.0	72,6	74,9	74.5	75,6	71,6	71.5	71,6
1 K	999,7	77,6	77.5	77,5	81,0	80.5	81,1	66.5	66,5	74,0	74	74,1	71,7	71	71,1
1K5	1499	77,2	77.5	77,3	80,9	80.5	80,8	61.5	61,5	72,7	72.5	72,5	72,3	72.5	72,0
2 K	1999	79,1	79	79,1	83,0	82	83,0	57.0	57,0	71,0	71	71,2	72,6	72.5	73,0
3 K	2998	81,1	81.5	82,0	85,6	84.5	85,0	55.0	55,8	66,6	66.5	66,4	68,1	68	68,3
4 K	3998	82,8	82	82,3	85,7	85	85,3	56.0	56,5	66,2	66	66,6	67,5	67	67,5
6 K	5997	86,7	86	86,8	89,5	89.5	89,3	53.0	53,4	76,5	76.5	77,0	73,1	73.5	73,6
8 K	7997	86,0	85.5	85,3	90,0	89.5	89,9	54.0	54,1	85,1	85	85,2	81,7	81.5	81,7

LIN	95	90	85	80	75	70	65	60	55	50	45	40	35	30
4000H	107,6	102,7	97,8	92,8	87,8	82,8	77,8	72,8	67,7	62,7	57,7	52,7	47,7	42,7

Booth Levels

Frequency	8 K	4 K	2 K	1 K	500	250	125
Screen	35.5	37.0	31.0	24.0	22.0	38.5	52.0
Diagnostic	35.5	37.0	31.0	24.0	20.5	21.0	29.0
Levels	15,2	15,3	16,0	16,0	15,2	16,0	24,0

Booth Type: .....

Screening (N) (ATT+25Db		ATT LIN (1K TAPE+F	
Left	Right	Left	Right
94,8	94,7		

Calibration Date: 24/01/2013 Calibration Due : 23/01/2014

Calibrated by Mr. G.D. Stanyer / Mr. P.T. Stanyer Signature :

Member: Mr. G.D. Stanyer

Stanyer ELECTROSERVE
SALES, SERVICE & REPAIRS OF AUDIOMETRICS & MEDICAL INSTRUMENTATION
CK No. 1994/005783/23

Tel: 031-7090710
Fax: 031-7028778
Email: info@stanyersa.com
Website: www.stanyersa.com

P. O. Box 273, Gillitts, 3603
No. 2 Gilro Park
34 Gillitts Road
Pinetown, 3610

Certification of Standard Calibration (RION)

Name of Company: KWA-THINTWA SCHOOL	Certificate Number: P1342/16D3
Area: INCHANGA - KZN	Model: AC33
Make: INTERACOUSTIS	Serial number: 01300197

Left ear	Right ear	Pre. cal.	Post cal.
BS5001	BS5002	114,0	114,0

		Air/Pure tone			N.B. Noise			Bone con.		Free/Warble			Free/N/B		
Freq. Hz	Freq. Meas.	Left	SABS 70dB	Right	Left	SABS 70dB	Right	SABS 40dB	M.V	FF1	SABS 70dB	FF2	FF1	SABS 70dB	FF2
125	129,9	117,0	115	116,2	120,0	118	119,3			90,4	90	90,3	91,2	90	90,1
250	249,9	97,7	97	98,1	101,0	100	101,0	101.5	102,0	81,2	81	81,2	80,2	80.5	81,0
500	499,9	83,9	83.5	83,7	86,8	86.5	86,7	87.5	87,9	76,4	76	78,2	74,8	74.5	78,8
750	749,9	79,8	79	79,3	83,5	82	82,6	80.5	80,6	84,8	74.5	74,6	71,5	71.5	71,7
1 K	999,8	78,0	77.5	77,1	81,0	80.5	82,0	76.0	76,4	74,6	74	74,8	71,0	71	72,0
1K5	1498	78,2	77.5	78,0	82,6	80.5	82,0	68.5	68,1	72,2	72.5	73,0	72,0	72.5	72,7
2 K	1998	80,0	79	79,5	83,0	82	82,7	58.5	57,9	71,2	71	72,8	72,5	72.5	72,5
3 K	2998	82,0	81.5	82,0	85,3	84.5	85,0	59.0	59,5	66,5	66.5	67,0	68,2	68	68,2
4 K	3998	82,5	82	82,0	86,6	85	86,0	59.5	59,8	67,0	66	66,2	67,8	67	67,8
6 K	5998	86,5	86	86,8	90	89.5	89,8	72.0	72,5	77,0	76.5	77,2	74,0	73.5	73,9
8 K	7998	85,1	85.5	85,7	90	89.5	87,7	73.0	73,7	85,1	85	85,8	71,9	81.5	

LIN	95	90	85	80	75	70	65	60	55	50	45	40	35	30
4000H	107,5	102,5	97,5	92,5	87,5	82,5	77,4	72,4	67,4	62,4	57,4	52,4	47,4	42,4

Booth Levels

Frequency	8 K	4 K	2 K	1 K	500	250	125
Screen	35.5	37.0	31.0	24.0	22.0	38.5	52.0
Diagnostic	35.5	37.0	31.0	24.0	20.5	21.0	29.0
Levels	12,9	11,4	9,8	9,3	14,6	17,5	20,9

Booth Type: .....

Screening (N) (ATT+25Db		ATT LIN (1K TAPE+F	
Left	Right	Left	Right
94,5	94,3		

Date of Calibration 16/10/2013 (dd/mm/yyyy)

Due Date 15/10/2014 (dd/mm/yyyy)

Calibrated by: Mr. G.D. Stanyer / Mr. P.T. Stanyer

Signature: .....

Member: Mr. G.D. Stanyer

Stanyer ELECTROSERVE
SALES, SERVICE & REPAIRS OF AUDIOMETRICS & MEDICAL INSTRUMENTATION
CK No. 1994/005783/23

Tel: 031-7090710
Fax: 031-7028778
Email: info@stanyersa.com
Website: www.stanyersa.com

P. O. Box 273, Gillitts, 3603
No. 2 Gilro Park
34 Gillitts Road
Pinetown, 3610

Certificate of Impedance Calibration

Company: KWA-THINTWA School
Address: INCHANGA
Address: KZN

Make: GSI
Model: 38
Serial no: 2006117115
Cert. no: P134216T3

Test Cavity-O: 1,5/1,7
Test Cavity-N: 1,3/1,8
Compliance Cal: 0,3 @0.2ml
Compliance Cal: 0,6 @0.5ml
Compliance Cal: 2,1 @ 2.0ml
Compliance Cal: 5,2 @ 5.0ml

Probe Tone: 226,3 Hz
Probe Level: 86,1 dB
Pump Vacuum: -400 dapa
Pump Pressure: +200 dapa

IPSI @ 70dB	250Hz @	86.0dB		Contra @ 70 Db	250Hz @	95.5dB	
	500Hz @	80.0dB	✓		500Hz @	81.5dB	
	1000Hz @	76.0dB	✓		1000Hz @	77.0dB	
	2000Hz @	81.5dB	✓		2000Hz @	79.0dB	
	3000Hz @	81.0dB			3000Hz @	80.0dB	
	4000Hz @	74.5dB	✓		4000Hz @	79.5dB	
	6000Hz @	73.0dB			6000Hz @	85.5dB	
	8000Hz @	70.5dB	✓		8000Hz @	83.0dB	
				White Noise	@	80.0dB	

Calibration Date: 16/10/2013
Calibration Due : 15/10/2014

Calibrated by Mr. Geoff Stanyer
Signature :

Member: Mr. G.D. Stanyer

DISCIPLINE OF AUDIOLOGY
SCHOOL OF HEALTH SCIENCES
Tel: 031 260 7438/8986
Fax: 031 260 7622
E-mail: sitholep2@ukzn.ac.za
E-mail: naidoor1@ukzn.ac.za

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

APPENDIX E

SCHOOL PERMISSION LETTER

Date

TO: The Principal
Name of School

Re: Conducting of Clinical research at your institution

I am an Audiologist conducting a research project in fulfillment of my Master's degree. My research project is entitled:

An audiological and genetic profile of hearing in learners suspected of having congenital familial sensorineural hearing impairment attending schools for the deaf in Kwazulu-Natal.

Purpose of the study:

The purpose of the study is to evaluate the prevalence of familial (occurs in the family) hearing impairment in learners that attend schools for the deaf and their families, as well to evaluate and describe the audiological and genetic presentation of this familial hearing impairment.

The audiological profiling includes a diagnostic hearing assessment of the affected individuals. The genetic profiling includes a detailed case history and a family pedigree (family tree) composition that dates back at least 3 generations.

The aim is also to determine if there is a pattern of hearing impairment that is identified within the affected family members and also compared to other families within the study.

What is the research study all about?

Hearing impairment occurring within families is an area that requires research in South Africa. It has been identified that in schools for the deaf there are pupils within families with more than one person presenting with hearing impairment.

If members of the same family present with a similar hearing impairment, it is possible that this family may have familial (occurring in the family) hearing impairment, which may be caused by a genetic fault.

Genetic hearing impairment is due to a fault that occurs when a child is formed. This fault may be transmitted through many generations, resulting in some members presenting with hearing impairment and some family members with normal hearing, this is also regarded as hereditary hearing impairment. There is a scarcity of research endeavours in the area of familial hearing impairment in South Africa and thus research is essential.

Research indicates that a significant amount of congenital hearing loss is due to genetic causes. Schools for the deaf have been targeted for this study as it is assumed that a large number of learners attending schools for the deaf have either congenital or early onset hearing impairment.

Value of the study:

This study will provide the researcher with valuable information on hearing loss in families in Kwazulu-Natal. Genetics and hearing impairment is a rapidly growing area and literature and research in South Africa is very limited. There is an immense need for research to be done in the South Africa in order to provide future researchers and medical professional's research data that is within the South African context.

This information will also allow a better understanding to these families regarding the cause of their hearing impairment. It is presumed that if families are aware of familial hearing impairment, they will seek audiological assessments for future offspring at an early stage, allowing for early intervention of hearing loss if present. Research has indicated that early assessment and intervention of hearing loss before 6months of age will allow for better language, social and emotional development, possibly matching that of their hearing peers.

The study will also bring value to your institution by providing essential data that will assist in research development in the area of genetics and hearing impairment in South Africa.

Permission

The researcher seeks permission to include your institution in this research study. The research information acquired will be invaluable and will assist research development in South Africa. Only pupils who have a positive history of hearing loss in their families will be eligible for this study.

In order to obtain this information the researcher requires permission to conduct the following:

- Peruse pupil's admission files to determine a history of hearing impairment in the family.
- Obtain contact details of families who have been identified with a positive family history of hearing impairment to invite them to be a part of the research study.
- To utilise an area in your institution on an agreed day to conduct the study. The area will be used to brief families on the purpose for the study as well as to obtain informed consent.
- To utilise your audiology department and equipment to assess all families who complain of hearing impairment.

Please note the following:

- Informed consent will be obtained from each family before any research is conducted
- The participant's involvement in this study is voluntary, and may withdraw from the study at any time without negative consequences.
- The researcher will treat all information obtained with the upmost confidentiality.

All these assessments should be completed within a week.

Thank you for your time
Awaiting a favorable response

Kind Regards

_____

Karen Pillay

Audiologist (Postgraduate student in Audiology, UKZN)

Contact – 083 420 9513

Dr. L. Joseph
Supervisor
Senior Audiologist
Contact – 031 260 7476

Dr.C.Aldous
Supervisor
Geneticist
Contact - 031 260 4124

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

3 March 2015

Ms Karen Pillay200305276
School of Health Sciences – Audiology
Westville Campus

Dear Ms Pillay

Protocol reference number: HSS/0492/012M
Project title: An audiological and genetic profile of learners suspected of having congenital familial sensorineural hearing impairment attending schools for the deaf in KwaZulu-Natal

Full Approval – Expedited Application

In response to your application received on 4 July 2012, the Humanities & Social Sciences Research Ethics Committee has considered the abovementioned application and the protocol have been granted **FULL APPROVAL.**

Any alteration/s to the approved research protocol i.e. Questionnaire/Interview Schedule, Informed Consent Form, Title of the Project, Location of the Study, Research Approach and Methods must be reviewed and approved through the amendment/modification prior to its implementation. In case you have further queries, please quote the above reference number.

PLEASE NOTE: Research data should be securely stored in the discipline/department for a period of 5 years.

The ethical clearance certificate is only valid for a period of 3 years from the date of issue. Thereafter Recertification must be applied for on an annual basis.

I take this opportunity of wishing you everything of the best with your study.

Yours faithfully

.....
Dr Shenuka Singh (Chair)
Humanities & Social Sciences Research Ethics Committee

/pm

Cc Supervisor: Dr C Aldous & Mr CD Govender
Cc Academic Leader Research: Professor J van Heerden
Cc School Administrator: Ms P Nene

Humanities & Social Sciences Research Ethics Committee
Dr Shenuka Singh (Chair)
Westville Campus, Govan Mbeki Building
Postal Address: Private Bag X54001, Durban 4000
Telephone: +27 (0) 31 260 3587/8350/4557 **Facsimile:** +27 (0) 31 260 4609 **Email:** ximbap@ukzn.ac.za / snymanm@ukzn.ac.za / mohunp@ukzn.ac.za
Website: www.ukzn.ac.za

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

06 June 2017

Ms Karen Pillay (200305276)
School of Health Sciences – Audiology
Westville Campus

Dear Ms Pillay,

Protocol reference number: HSS/0492/012M
New project title: An audiological and genetic profile of learners suspected of familial hearing loss attending schools for the deaf in KwaZulu-Natal

Approval Notification – Amendment Application

This letter serves to notify you that your application and request for an amendment received on 26 May 2017 has now been approved as follows:

- Change in Title
- Change in Supervisor

Any alterations to the approved research protocol i.e. Questionnaire/Interview Schedule, Informed Consent Form; Title of the Project, Location of the Study must be reviewed and approved through an amendment /modification prior to its implementation. In case you have further queries, please quote the above reference number.

PLEASE NOTE: Research data should be securely stored in the discipline/department for a period of 5 years.

The ethical clearance certificate is only valid for period of 3 years from the date of original issue. Thereafter Recertification must be applied for on an annual basis.

Best wishes for the successful completion of your research protocol.

Yours faithfully

.....
Dr Shenuka Singh (Chair)

/ms

Cc Supervisor: Dr Lavanithum Joseph
Cc Academic Leader Research: Professor J van Heerden
Cc School Administrator: Ms Phindile Nene

APPENDIX G

SCHOOL APPROVAL LETTERS

024-077-NPO

All correspondence must be addressed to the principal

Fulton School for the Deaf

8 ROOSEVELT ROAD
PVT. BAG 9002
GILLITTS
3603
TEL: 031 - 767 1215
FAX: 031 - 767 1677

OFFICE: fsacc@iafrica.com
PRO: fultonfunds@iafrica.com
WEB: www.fulton.org.za
PRINCIPAL: fulton@iafrica.com

16 October 2014

TO WHOM IT MAY CONCERN

This letter serves to confirm that permission was granted to Audiology research student Ms Karen Pillay to conduct her Masters Data collection at Fulton School for the Deaf in November 2013.

She did collect all necessary data that was required in November 2013.

Yours faithfully

BW CAMPBELL (MRS)
PRINCIPAL

Audiology research

Durban School <dshi@telkomsa.net> Tue, Apr 30, 2013 at 9:05 AM
To: audio kp <kp.audiology@gmail.com>

Good Morning Karen

Permission is hereby granted to conduct your clinical research programme at the above school.

Please note that the Audiologist will be on accouchement leave from 16 May 2013.

Regards

Mrs T Naidoo

Principal

KWA THINTWA SCHOOL FOR THE DEAF

Private Bag X7018
Hillcrest 3650

Tel.: (031) 7834005
Fax: (031) 7834064

TO WHOM IT MAY CONCERN

This letter serves to confirm that permission was granted to Audiology research student Ms.Karen Pillay to conduct her Masters Data collection at Kwathintwa School for the deaf in November 2013.

She did collect all necessary data that was required in November 2013.

Kind regards

Dr. L. Naidoo

Headmistress

V N NAIK SCHOOL for the DEAF

LSEN Public School: SASA (84 of 1996)-Emis: 290783.
Non Profit Organisation: 002-444 NPO.

PO Box 76350, Marble Ray, 4035. 1201 Inanda Road, Newlands.
0315771280. Fax: 0315771214. Email: vnnaik@telkomsa.net

17 September 2014

Karen Pillay
UKZN

Dear Karen

Re: Permission to conduct Research at our School

This is a letter confirming that permission had been granted to you to conduct research at our school.

Yours Faithfully

Mr TM Govender
(Principal

VN NAIK SCHOOL FOR THE DEAF
Emis : 290783
22 -09- 2014
P.O. BOX 76350, Marble Ray, 4035
Tel : 031 577 1280
DEPARTMENT OF EDUCATION - KZN

DISCIPLINE OF AUDIOLOGY
SCHOOL OF HEALTH SCIENCES
Tel: 031 260 7438/8986
Fax: 031 260 7622
E-mail: sitholep2@ukzn.ac.za
E-mail: naidoor1@ukzn.ac.za

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

APPENDIX H

REQUEST FOR YOUR PARTICIPATION IN A RESEARCH PROJECT- ENGLISH

Date

Dear Sir/Madam,

REQUEST FOR YOUR PARTICIPATION IN A RESEARCH PROJECT

I am an Audiologist conducting a research project in fulfilment of my Masters degree. The title of the study is: **An audiological and genetic profile of hearing of learners suspected of having familial congenital sensorineural hearing impairment attending schools for the deaf in Kwazulu-Natal**. I would appreciate it if you would be willing to participate in this project. All the assessments conducted will be at no cost. Please see details of this research project below.

Purpose of the study:

The purpose of this study is to investigate and describe the audiological and genetic status of your families hearing. To determine if a hearing impairment is present and if there is a pattern of hearing impairment within your family.

What is the research study all about?

Hearing impairment in families is an area that requires research in South Africa. It has been noticed that in Schools for the deaf there are families with more than one person that present with hearing impairment. This study aims at understanding the cause of the hearing impairment in your family and to trace how many family members present with the impairment and for how many generations.

If members of your family present with a similar hearing impairment, it is possible that your family may have familial (occurring in the family) hearing impairment, which may be caused

by a genetic fault. Genetic hearing impairment is due to a fault that occurs when a child is formed. This fault may be transmitted through many generations, resulting in some members presenting with hearing impairment and some family members with normal hearing.

Procedure:

You will be requested to participate in the following assessments:

- Case History Questionnaire – You will be required to fill out a case history questionnaire, this includes questions regarding, family history, medical history, occupational history, audiological history, communication and other relevant areas.

  Time Taken – 15minutes
- Family pedigree- This is similar to a family tree. However here we are focusing on all the members of your family that present with hearing impairment

The following assessments will be conducted on family members who are in attendance who present with hearing impairment.

- Otoscopic Examination – This is an examination of the outer ear, ear canal and ear drum with the use of an otoscope.

  Time Taken – 5minutes per ear
- Immittance Test – This test assesses the functioning of the middle ear. It assesses the function of the eardrum, middle ear bones and Eustachian tube.

  Time Taken – 10 minutes per ear
- Pure Tone Testing – This is a test of hearing. Here the softest sounds that you can hear are assessed. Headphones and a sound proof booth are used.

  Time Taken – 20 minutes per ear
- Speech Testing – Here the softest words that you can hear are assessed. Headphones and a sound proof booth are used. The language of the test will be in English.

Risks and possible discomforts:

There are no risks involved in this study.

Value of the study:

This study will provide the researcher with valuable information on families with hearing impairment in Kwazulu-Natal. Genetics and hearing impairment is a rapidly growing area .Literature and research in the area of genetics and hearing impairment in South Africa is very limited. There is an immense need for research to be done in the South Africa in order to allow future researchers and medical professional's data that is from the South African context. This information will also allow you to understand your families hearing impairment better.

Participant's Rights:

Your involvement in this study is voluntary, you are not obliged to divulge information you would prefer to remain private, and you may withdraw from the study at any time without negative consequences. There will be no personal benefit to you for participating in this study.

Confidentiality:

The project team will treat the information you provide as confidential. You will not be identified in any document, including the research proposal or report, by your surname, first name, or by any other information. You will be referred to in the documents under a respondent code. No one, other than the project team, will be informed of your participation in this research. The information that you provide will be destroyed should you choose to withdraw from the study.

Dissemination:

The information and results of this research project will be available in the format of a dissertation at the Library of the University of Kwa-Zulu Natal as well as in a possible article publication. All raw data will be stored for 15 years before it is destroyed, in the event of future research on this study. If the results and data of this research project will be used for further research purposes, your permission will first be obtained by means of an informed consent letter.

Thank you for your willingness to participate in this project.

Sincerely

_____

Karen Pillay

Audiologist (Postgraduate student in Audiology, UKZN)

Contact – 083 420 9513

Please complete the tear slip below:

I, ……., understand the contents of this letter and hereby agree/disagree to participate in this research study according to the conditions stipulated and allow/do not allow the researchers to use information from my assessments for the purpose of this study.

…… **……**

Signature **Date**

DISCIPLINE OF AUDIOLOGY
SCHOOL OF HEALTH SCIENCES
Tel: 031 260 7438/8986
Fax: 031 260 7622
E-mail: sitholep2@ukzn.ac.za
E-mail: naidoor1@ukzn.ac.za

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

APPENDIX I

REQUEST FOR YOUR PARTICIPATION IN A RESEARCH PROJECT- ISIZULU

Usuku:

Ngokuzithoba Mnumzane / Nkosikazi,

Isicelo sokuhlanganela kanye nawe ocwaningweni/ Isicelo sokhuba ubambe iqhaza kulochwaningo

Ngingu dokotela wezindlebe (Audiologist) ngiphethe ucwaningo iwe: **An audiological and genetic profile of hearing of learners suspected of having familial congenital sensorineural hearing impairment attending schools for the deaf in Kwazulu-Natal**.

Kuzoba enkulu intokozo kithina ukubamba kwakho iqhaza kulolucwaninga. Akudingeki ukuba ukhokhe ukuze ugcwalise imininingwane yakho.

Inhloso yalolucwaningo:

Inhloso yalolucwaningo lizozama ukuthola futhi luchaze kabanzi ngezinkinga zokuzwa ezitholakala emndenini.

Kabanzi ngowaningo:

Izinkinga zokuzwa ngezindlebe emindenini eminingi eningizimu Afrika zidinga ucwaningo ulubanzi kakhulu.

Ezikoleni zabantu abangezwa kubanakale ukuba kukhona abantu abanezimpawu zokungezwa ezindlebeni.

Ugcwaningo luhlose ukuthola kabanzi ngembangela yokungezwa ezindlebeni kulemindeni, kanye nasezizukulwaneni ezedlule.

Uma emndenini owodwa kunabantu abalahlekelwa ukungezwa ezindlebeni ngokufana kungenzeka ukuba lenkinga ibangwa ukuthi khona lapho kulowondeni kukhona owayenaso kudala.

- Ukubuza/ ukuphendula imibuza
  - Uzophendula imibuzo,ngomlando womndeni wakho, umlando wezempilo, umlando ngokomsebenzi, umlando wokuzwa ngezindlebe, kanye ukukhuluma.

  Isikhathi: imizuzu engu-15

Amalunga emindeni azocutshunglwa ylawo anezinkinga zokuzwa ngezindlebe

- Otoscopic examination: ukuhlolwa kwezindlebe ngokufaka isisiza kuzwa ngaphezu kwamadlebe akho.
  Isikhathi: imizuzu engu – 5 indlebe iyodwa

- Immitance Test: Ukuhlolwa ukuzwa kanye nokusebenza kwezindlebe zakho.
  Isikhathi:imizuzu engu – 10

- Pure tone testing : Kuhlolwa ukuzwa kwakho ezindlebe zombili.
  Isikhathi: imizuzu engu – 20 (amashumi amabili) indlebe iyodwa ngesikhathi

- Speech testing: Kuhlowa ukuzwa amagama emisindweni ehlukene ephezulu naphansi. Ukuhlolwa kuzokwenziwa ngolimi isiZulu.
  Isikathi: Imizuzu engu – 5 (emihlanu), indlebe iyodwa.

Ubungozi balolucwaningo

Akukho okungaba ubungozi kulolucwaningo.

Ukubaluleka kwocwaningo

Lolucwaningo luzosinika ulwazi alubalulekile mayelana nezinkinga zokuzwa ngezindlebe emindenini endaweni yakwa-Zulu Natal.

Izinkinga zokuzwa ngezindlebe emindeni zibonakala zikhula ngokudlondlobala kanti ulwazi eningizumu Afrika lungcane. Kubalulekile sicwaninge ngalolu daba, ukuze imindeni isizakale ikakhulu imindeni enabantu abanezinkinga zokuzwa ezindlebeni.

Amalungelo akho

Ngokubamba iqhaza kulocwaningo-yazi ukuthi awuphoqiwe ukuveza imininigwane eyimfihlo. Uvumelekile ukuhoxa noma yinini ocwaningweni.

Inhlanipho kanye nemifihlo

Imininingwane osinicela yona izoba yimfihlo, iphathwe ngenhlonipho ngaso sonke isikhathi. Amagama, izibongo kanye neminye imininingwane izohoxwa. Abaphathi bocwaningo kuphela abazokwazi,hayi umphakathi.

Imiphumela yocwaningo izotholakala unyuvesi ya Kwazulu-Natal ngenhuku, kuzodingeka imvumo uma imphumela izosetshenziselwa dunye ucwaningu ezikhathini ezizayo.

Sidlulisa ukubonga ngokuzinikela ekubeni ubambe iqhaza ecwaningweni ozithobayo

Karen Pillay
Audiologist (udokotela wezindlebe)
Post graduate student in Audiology , UKZN)

Consent Form

Glowalisa imininigwane ngaphansi

Mina……, ngiyavumelanal ongivumelani necwadi yokubamba iqhaza ……,futhi. Ngiyavuma /Angivumi ukuba abacwaningi bengusebenzisa imiphumela yami ukuae basizakale ekuphumeleleni locwaningo abafisa ukulenza.

…… ……

Signature Date

APPENDIX J

CRITERIA FOR THE DETERMINATION OF INHERITANCE PATTERN

Table 1. Criteria suggestive of an autosomal recessive inheritance

Criteria	Present	Absent
Both males and females have an equal chance of being affected		
Consanguineous parents		
Affected offspring has 2 unaffected parents		
Hearing loss is typically • Congenital / early onset • Prelingual • Stable • Severe to profound / profound in severity • Sensorineural		
Hearing loss is not seen in every generation of a family, tends to skip a generation		

Table 2. Criteria suggestive of an autosomal dominant inheritance

Criteria	Present	Absent
Both males and females have an equal chance of being affected		
An affected parent is identified		
The pedigree usually depicts several affected family members in successive generations		
Hearing loss onset, severity and configuration is variable. Variable expression is expected. Some expressions include- Early onset / late onset • Prelingual/ postlingual • Stable / progressive • Mild to profound in severity		

Table 3. Criteria suggestive of an X-linked hearing loss

Criteria	Present	Absent
Severe forms of hearing loss almost always identified in males with affected females presenting with normal hearing or a milder hearing loss		
Inheritance from the pedigree is exclusively from females or affected males, lack of male to male transmission		
Mothers who are carriers of the X-linked mutation have a 25% chance of having a hearing son, 25% chance of having a son with a hearing loss, 25% chance of having daughter who is not a carrier and 25% chance of a having a daughter as a carrier.		
X-linked hearing loss can be prelingual or postlingual and ranges from mild to profound in severity		

Table 4. Criteria suggestive of a mitochondrial hearing loss

Criteria	Present	Absent
The mother is only parent that has the mitochondrial mutation and is unaffected.		
All offspring of the affected mother, are at risk for a hearing loss		
Hearing loss ranges from mild to profound and can be early or late onset		
Male offspring even if affected with hearing loss, are not at risk for passing the mutation.		

Table 5. Criteria suggestive of a co-incidental familial hearing loss

Criteria	Present	Absent
An acquired cause of hearing loss in a family member represented on the family pedigree that mimics a familial genetic etiology.		
A family with one member affected with a syndrome and one member suspected of an acquired cause of hearing loss.		
A pedigree that does not meet any one of the genetic inheritance criteria suggested in Tables 1 to Table 4 above		

APPENDIX K

PEDIGREES AUTOSOMAL RECESSIVE AND AUTOSOMAL DOMINANT NOT INCLUDED IN THE RESULTS SECTION

1. Families 6-14, suspected autosomal recessive hearing loss

1.1 Family 6

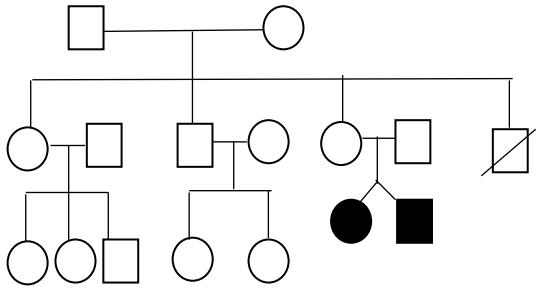

Figure 4.28 Pedigree – Family 6

The circles represent females, the squares represent males. The shaded squares and circles represent affected individuals tested in the study. A line across II-7 represents a deceased individual. The short line between III-6 and III-7 represents twins.

1.2 Family 7

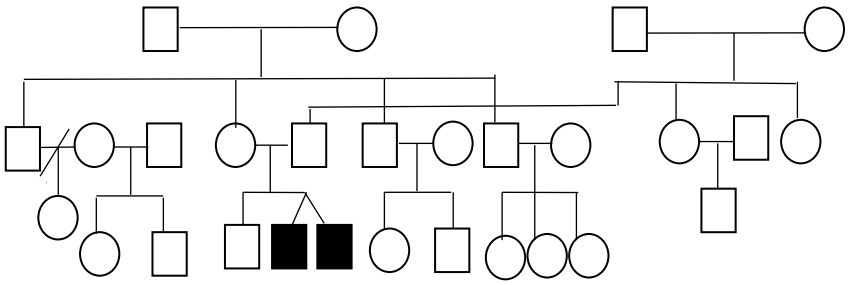

Figure 4.29 Pedigree – Family 7

The circles represent females, the squares represent males. The shaded squares and circles represent affected individuals tested in the study. The short line between III-4 and III-5 represents twins. The line between II-1 and II-2 represents a separated couple.

1.3 Family 8

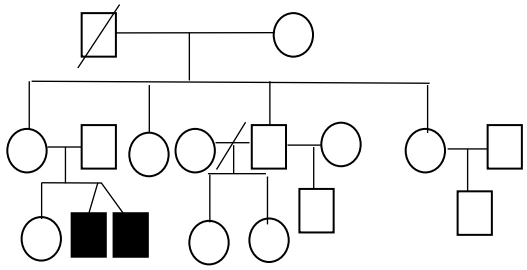

Figure 4.30 Pedigree – Family 8

The circles represent females, the squares represent males. The shaded squares and circles represent affected individuals tested in the study. The short lines between III-2 and III-3 represents twins. The line between II-4 and II-5 represents a separated couple. A line across I-1 represents a deceased individual.

1.4 Family 9

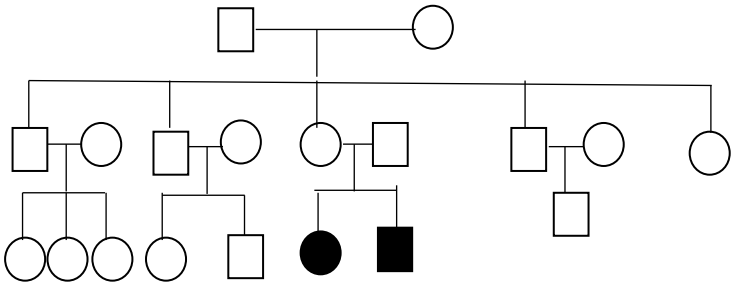

Figure 4.31 Pedigree – Family 9

The circles represent females, the squares represent males. The shaded squares and circles represent affected individuals tested in the study.

1.5 Family 10

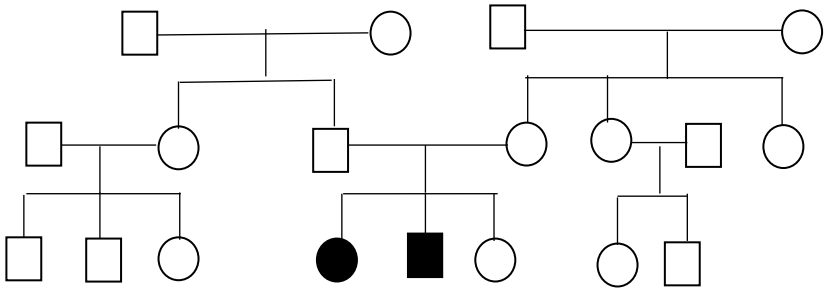

Figure 4.31 Pedigree – Family 10

The circles represent females, the squares represent males. The shaded squares and circles represent affected individuals tested in the study.

1.6 Family 11

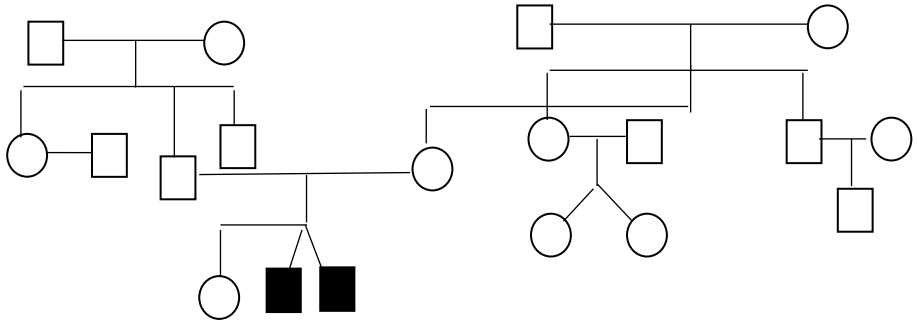

Figure 4.32 Pedigree – Family 11

The circles represent females, the squares represent males. The shaded squares and circles represent affected individuals tested in the study. The short lines between III-2 and III-3 represents twins

1.7 Family 12

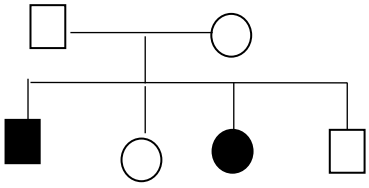

Figure 4.33 Pedigree – Family 12

The circles represent females, the squares represent males. The shaded squares and circles represent affected individuals tested in the study.

1.8 Family 13

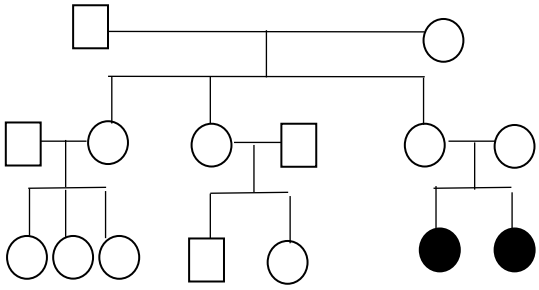

Figure 4.34 Pedigree – Family 13

The circles represent females, the squares represent males. The shaded squares and circles represent affected individuals tested in the study.

1.9 Family 14

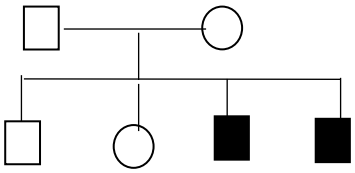

Figure 4.35 Pedigree – Family 14

The circles represent females, the squares represent males. The shaded squares and circles represent affected individuals tested in the study.

2. Families 21-22 suspected autosomal dominant hearing loss

2.1 Family 21

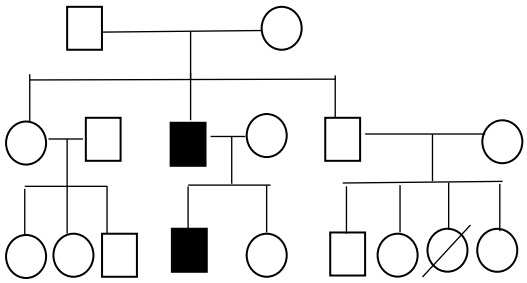

Figure 4.36 Pedigree – Family 21

The circles represent females, the squares represent males. The shaded squares and circles represent affected individuals tested in the study.

2.2. Family 22

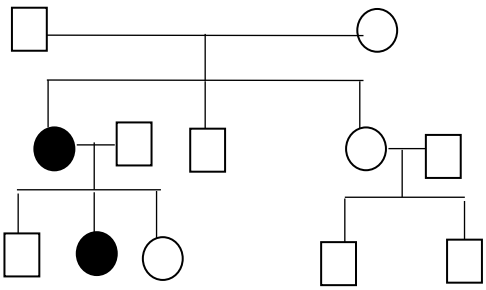

Figure 4.37 Pedigree – Family 22

The circles represent females, the squares represent males. The shaded squares and circles represent affected individuals tested in the study.

APPENDIX L

PEDIGREES AND DESCRIPTIONS – SUSPECTED CO-INCIDENTAL FAMILIAL HEARING LOSS, FAMILILES 23-25

Family 23

Family 23, presented with an affected African mother and daughter from the second and third generation, with no other history of hearing loss dating back three generations. The affected mother presented with a postlingual sensorineural hearing loss that was of sudden onset when she was a teenager. She did not report any illness or acquired causes of hearing loss. Her audiometric pattern identified a profound hearing loss that was flat in configuration. She married a normal hearing individual and had two children. Her second born was a normal hearing son and her first born was an affected daughter. Her daughter presented with a severe flat prelingual neural hearing loss and oculocutaneous albinism (OCA). The OCA and neural hearing loss were diagnosed at the individual's base hospital. She presented with green eyes, congenital nystagmus with blonde hair and a pale face. She reported photophobia. She had obvious speech discrimination challenges during the in-depth interview, presumed to be due to the neural hearing loss. Her assessment at the base hospital in 2010 revealed the presence of normal outer hair cell function during diagnostic Otoacoustic Emission (OAE) testing with absent auditory brain stem responses (ABR) bilaterally. Her pure tone assessment in this study revealed a severe hearing loss with a flat audiometric configuration. She was unable to discriminate any words during speech testing. She uses some spoken language for communication, but in the last three years joined a school for the deaf and now predominately uses sign language. No other individuals in the family presented with albinism.

Intrafamilial variability was identified in the type of hearing loss, severity and the configuration of loss, with the presence of OCA only in the daughter. An inherited hearing loss between the affected individuals and is not suspected and presumed to be a coincidental occurrence.

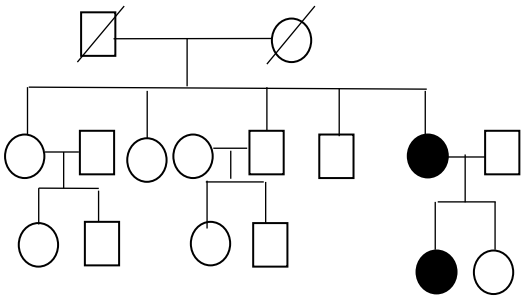

Figure 4.28 Pedigree- Family 23

The circles represent females, the squares represent males. The shaded squares and circles represent affected individuals tested in the study. A line across the figure represents a deceased individual.

Family 24

Family 24 presented with an affected African mother and son, with no other children and no affected family dating back three generations. The affected mother reported normal hearing until the age of 17 during the fifth month of her pregnancy, were she became severely ill, and bleeding. She reported being admitted to hospital for a month, were she experienced a sudden onset of hearing loss. Her audiological assessment revealed a severe hearing loss with a flat configuration in the right ear and a gently sloping configuration in the left ear with a moderate hearing loss. She reported a constant high pitched tinnitus that began shortly after the onset of hearing loss. Her son was born full term and healthy, and presented with a prelingual hearing loss that was identified at 1year of age. His audiometric assessment revealed a profound sensorineural hearing loss with a flat configuration on the right ear and a steeply sloping configuration on the left ear. He did not report the presence of tinnitus. He uses sign language to communicate and has no spoken language.

Variability in the hearing loss was identified in the severity, audiometric configurations, as well as the age of onset. Substantial evidence from the in-depth case history as well as variability in audiometric data suggested an acquired cause of deafness during pregnancy affecting both individuals, which mimicked a genetic familial pattern.

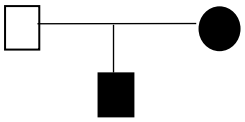

Figure 4.29 Pedigree- Family 24

The circles represent females, the squares represent males. The shaded squares and circles represent affected individuals tested in the study.

Family 25

Family 25 presented with a similar background of an affected African mother and son. No other affected individuals were reported over three generations. The affected mother reported a sudden hearing loss that occurred in her twenties after a motor vehicle accident. She uses spoken language to communicate. Her audiological assessment revealed a moderate hearing loss with a low frequency ascending pattern on her left ear and a steeply sloping configuration of the right ear. She married a man with normal hearing and had two sons, one with normal hearing and one affected. Vacuum extraction was used during the birth of the affected son, with a normal Apgar score and birth weight reported. A measles infection was reportedly occurred at 2years of age. The hearing loss was identified at 3years of age when the affected child portrayed absent speech development. His audiological assessment revealed a prelingual sensorineural hearing loss that was profound in severity with a flat audiometric configuration bilaterally.

An intrafamilial variability in the onset, severity and configuration of hearing loss was identified between the affected individuals. An acquired cause of hearing loss in both individuals is suspected.

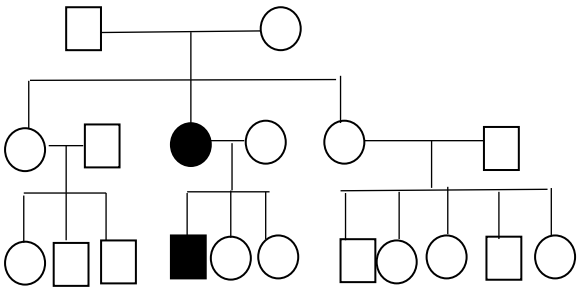

Figure 4.29 Pedigree - Family 25

The circles represent females, the squares represent males. The shaded squares and circles represent affected individuals tested in the study.