ANATOMICAL PATTERNS OF PRESENTATION OF CONGENITAL MELANOCYTIC NEVI

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PREFACE

This study was carried out in the Discipline of Clinical Anatomy, School of Laboratory Medicine and Medical Sciences, College of Health Sciences, University of KwaZulu-Natal, Westville, Durban, South Africa, and the Department of Plastic and Reconstructive Surgery, Inkosi Albert Luthuli Central Hospital (IALCH), Durban, South Africa, under the supervision of Prof L Lazarus, Prof M Daya, and Prof A Madaree. It is the author's original work and has not been submitted in any other way to another university. Where other people's work was used, it was duly acknowledged in the text.

DECLARATION

I, Mr Siphelele Nkosi, declare as follows that:

i. The work described in this thesis has not been submitted to UKZN or other tertiary institutions for the purpose of obtaining an academic qualification, whether by myself or any other party.

ii. This dissertation does not contain another person's data, graphs, tables, or other information unless specifically acknowledged as being sourced from other persons.

iii. This dissertation does not contain another person's writing unless specifically acknowledged as being sourced from other persons. Where other written sources have been quoted, the information used has been referenced accordingly.

iv. The research reported in this thesis unless where otherwise indicated, is my original work. My contributions to the project are as follows:

Development and design of research topic and protocol.
Conduction of research methodology.
Collection and analysis of data.
Interpretation of data obtained.
Formulation of manuscript.
Write-up of the final thesis.

v. The contributions of others to this project were as follows:

Prof L. Lazarus (supervisor), Prof A Madaree (co-supervisor), Prof M Daya (co-supervisor):

Development and refining of the research design and plan.
Assistance with data and statistical analysis.
Review of manuscript and thesis before submission.

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Mr. Siphelele Nkosi Date: 26/08/2024

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Professor Lelika Lazarus Date: 26/08/2024

[redacted]

Professor Anil Madaree Date: 26/08/2024

[redacted]

Professor M Daya Date: 12/09/2024

DEDICATION

To my mother, Christina K Nkosi, for her unconditional love, patience, encouragement, and support, thank you for making me the man I am today. Thank you for all the difficulties you had to overcome while raising me, the tears and sweat you shed trying to give us a better future. You exemplify a true ***'iMbokodo'*** *woman (South African term meaning 'rock').*

Thank you, Princess Buyisile Nkosi and Sabelo Nkosi, for the encouragement and for being there for me during my worst days.

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LIST OF ABBREVIATIONS

CMN	Congenital melanocytic Nevi
GCMN	Giant congenital melanocytic nevi
PNS	Peripheral nervous system
SA	South Africa
CN	Cranial nerves
CN V	Trigeminal nerve
CNS	Central nervous system

ABSTRACT

Background: Congenital melanocytic nevi (CMN) appear at birth and are caused by a proliferation of benign melanocytes in the dermis, epidermis, or both. Melanocytes are pigment-producing cells with a strongly polarized dendritic morphology that reaches the skin by the migration of neural crest cells from the neuroectoderm. They protect the skin against ultraviolet radiation by providing melanin from their cellular cytoplasm to neighbouring keratinocytes. Melanocytes may have a mutation resulting in a lack of dendrites, leading to melanin existing in the cytoplasm, which causes these nevi. Some areas of the skin rely on specific spinal nerves for their sensory distribution, called dermatomes. This study aimed to investigate the correlation between CMN distribution and a pre-existent dermatomal pattern. Due to the dermatomes on the body being different from that of the face, two subsets were conducted. The first subset investigated the correlation between the CMN on the overall body and its association with body dermatomes. Hence, this study also analyses the distribution of CMN and its association with facial dermatomes.

Methods: Clinical photographs of CMN (> 1.5 cm) obtained from the database of Inkosi Albert Luthuli Central Hospital were analysed. A total of 31 patients with CMN were collected.

Results:

Subset 1: The results for CMN distribution over the body revealed a higher preference for T10 (58.1 %), T11 (54.8 %), and T12 (51.6 %) dermatomes. Furthermore, facial dermatomes V1 and V2 (54.8 %), C5 in the cervical region (32.3 %), and L1 in the lumbar (41.9 %) were notably affected. Varied CMN patterns were observed in the head and neck region, emphasizing the complexity of the nevi distribution. *Subset 2*: Only 19 patients met the inclusion criteria in this subset. The zygomaticofacial, zygomaticotemporal, and supraorbital nerve areas of distribution emerged as the most affected, while the transverse cervical and mental nerve areas of distribution were the least affected.

Conclusion: This study provides evidence of a correlation between CMN distribution and dermatomes of the body/face and enhances our understanding of CMN presentation, shedding light on the potential for CMN to follow a dermatomal distribution, with CMN often mostly found in the trunk region around T10, T11, and T12. In the face, V1 and V2 dermatomes were found to be mostly affected, with sub-branches of V2 (zygomaticofacial and zygomaticotemporal) as the most affected branches. The findings contribute to broader knowledge and invite future investigations into the complex nature of CMN distribution across body regions.

Key words: congenital melanocytic nevi; dermatomes maps; South African

CHAPTER 1

INTRODUCTION

1.1. INTRODUCTION

Congenital melanocytic nevi (CMN) are benign (non-cancerous) pigmented skin lesions that are present at birth or appear shortly after birth. These lesions are caused by a defect in the development of melanocyte progenitors during embryology (Viana et al., 2013). Melanocytes are specialized pigment-producing cells that transfer melanin from their cellular cytoplasm to keratinocytes located in the epidermis, dermis, eyes, ears, heart, and leptomeninges (Van Raamsdonk and Deo, 2013). These nevi cells contain *N-Ras* or *B-Raf* hotspot mutations that result in a lack of dendrites, leading to melanin existing in the cytoplasm and not being disseminated to the cells, which then results in the brown-to-black colour of the cells called CMN. Congenital melanocytic nevi can vary in size, shape, and appearance, and they can occur anywhere on the body (Price, 2016). There are different patterns of presentation for CMN, which are typically categorized based on their size and distribution: The classification of CMN has historically been defined by size alone (Price, 2016). Recent publications have reported on predicted adult size (PAS), number of accompanying CMN (satellites nevi), and anatomic location- these parameters contribute to the classification of CMN (Krengel *et al.*, 2013).

These nevi may be small in infants but grow in proportion to the body and can eventually grow up to ≥20 cm in some cases (Price and Schaffer, 2010; Yeh, 2020). For the classification according to the projected adult size (PAS), any CMN ≤1.5 cm is considered as small, medium is described as being 1.5 to 20 cm, large being 20 to 40 cm, and giant ≥40 cm in diameter (Scard *et al.*, 2023). They can also vary in morphological traits such as colour, surface, and hairiness. As previously stated, the CMN may be solitary or accompanied by several widely dispersed satellite nevi (Viana et al., 2013). The incidence of small to medium-sized CMN ranges from 1% to 6% and roughly 1:20 000 for large or giant congenital melanocytic nevi (GCMN) (Masnari *et al.*, 2019).

Giant congenital melanocytic nevi are frequently surrounded by a ring of smaller satellite nevi, these congenital nevi are usually not treated surgically due to their size (Moustafa et al., 2020). The CMN (single or multiple) also extends vertically into the deeper dermis and, more rarely, into the hypodermis or even subcutaneous tissues (Kinsler *et al.*, 2014). No ethnicity group preference has been identified for CMN (Kinsler *et al.*, 2014). They can occur in both sexes (Kinsler *et al.*, 2014). People with this condition may experience psychological and low self-esteem because of the nevus's impact on their appearance. Due to its peculiar appearance and complicated treatment, CMN may have an impact on health-related quality of life and psychosocial adjustment in affected people, especially in paediatric patients (Masnari *et al.*, 2019). Children with CMN may experience emotional or behavioural issues as a result of its appearance. To date, there is no literature that correlates the distribution of CMN on the skin with dermatomes.

Dermatomes are unique areas of the skin's surface that are derived from somite cells, which are cells that develop into three types viz.: (1) dermatomes, which produce connective tissue, including the dermis; (2) myotomes, which produce some skeletal muscle and (3) sclerotomes, which produce vertebrae (Stecco *et al.*, 2019). These dermatomes are said to be the skin regions supplied by a sensory nerve branch from a single cranial and spinal nerve root and are an important concept in clinical practice and a fundamental concept in human anatomy (Whitman *et al*., 2023). The spinal cord is divided into thirty-one segments, each containing a pair of ventral and dorsal nerve roots that carry motor and sensory information, respectively (Whitman *et al*., 2023). These spinal nerves are formed when the anterior and posterior nerve roots unite on each side as they exit the vertebral canal via the intervertebral foramina or neuroforamina, giving rise to ventral and dorsal rami (Gkasdaris and Kapetanakis, 2015).

In these thirty-one spinal segments, there are eight cervical, twelve thoracic, five lumbar, five sacral, and one coccygeal spinal nerve. Except for the first cervical spinal nerve, dermatomes exist for each of these spinal nerves (Lee et al., 2008). Sensory information from a given dermatome is conveyed to the spinal nerve of a specific section of the spinal cord via sensory nerve fibres (Whitman *et al*., 2023). The face, in comparison to the body, does not have a similar dermatomal pattern as the body; rather, it receives cutaneous innervation from the trigeminal nerve (CN V) responsible for innervation of the entire skin of the face. The dermatome is a simple concept. However, there are a lot of variations across dermatome maps in mainstream anatomy and medical guideline textbooks (Lee et al., 2008). An analysis of fourteen distinct dermatome maps by Keegan and Garrett (1948) revealed variations in each map. Historically, this map was based on Foerster's (1933) dermatomal illustration.

Dermatological or cosmetic issues are extremely sensitive and majorly impact social interaction in individuals having these issues (Masnari *et al.*, 2019). Children with a CMN may experience emotional or behavioural issues as a result of its appearance. Currently, no existing literature has investigated a correlation between the distribution of CMN on the skin and dermatomes. Understanding whether there is a correlation between CMN distribution and dermatome mapping can provide valuable insights into the developmental processes and may have clinical implications.

1.1.1 **Resaerch question**

- Does the distribution of congenital melanocytic nevi follow the dermatomal pattern?

1.1.2 **Aim**

To investigate the distribution of CMN (any size greater than 1.5 cm in diameter) and its correlation to the distribution of dermatomes of the human body and face.

1.1.3 **Objectives**

- To assess the location and extent of correlation of CMN to dermatomes with spinal root values C2 to S5 and the face.
- To assess the location and extent of correlation of CMN to dermatomes related to branches of the trigeminal nerve as mapped on the face.

1.2 LITERATURE REVIEW

Congenital melanocytic nevi appear at birth and are caused by a proliferation of benign melanocytes in the dermis, epidermis, or both layers of the skin (Farabi *et al.*, 2021). Nevi that are not present at birth but are histologically identical to congenital nevi might develop gradually within the first two years of life. These are known as congenital nevus tardive (Moustafa et al., 2020). Congenital melanocytic nevi have been found to be one of the established risk factors for the development of malignant melanoma, particularly giant congenital melanocytic nevi (GCMN) (Prescher *et al*., 2023). The CMN are classified into two forms - the most frequent of which is a solitary plaque that grows in accordance with the child's size, and a second type composed of many lesions, at least one being large and surrounded by many others (satellites) and sometimes involving bone as well as the central nervous system (CNS) (Moustafa et al., 2020).

The classification for CMN first consisted of PAS, number of accompanying CMN (satellites nevi), and anatomic location. As time progressed, more classifications for this disease were implemented. According to the study by Price and Schaffer (2010) and Scard *et al.* (2023), the size-based classification of CMN was standardized and updated in 2012. Based on the highest projected adult diameter in centimetres, this approach categorized CMN into four groups: (1) small, < 1.5; (2) medium (M1: 1.5-10, M2: > 10-20); (3) large (L1: > 20-30, L2: > 30-40); (4) giant (G1: > 40-60, G2: > 60) (Krengel *et al*., 2013). Category 3 refers to sizes greater than 9 cm on the scalp and greater than 6 cm on the body of a neonate. Congenital melanocytic nevi develop between the fifth and twenty-fourth weeks of pregnancy (Ibrahimi *et al.*, 2012).

The literature states that during embryogenesis, a developmental complication occurs in the neuroectoderm, resulting in uncontrolled proliferation of melanoblasts, which are progenitor cells of melanocytes (Farabi *et al.*, 2021). The histogenesis of melanocytic nevi, on the other hand, is still controversial (Viana et al., 2013). However, a study by Saida (2019) stated that CMN develops at the embryonic stage as a result of transiently increased proliferation of mutant melanoblasts as they move from the neural crest to the tissue that will become the epidermis. It has been postulated that the N-ras gene mutation could be responsible for the proliferation of larger congenital nevi (Saida, 2019). Saida (2019) also stated that most cutaneous malignant melanomas result from pre-existing melanocytic nevi. Many clinical and histological research appears to confirm this theory (Saida, 2019; Prescher *et al.*, 2023), which supports or shows that the CMN, specifically the large/giant type, has a lifetime risk of becoming malignant melanoma.

1.2.1 Embryology of Melanocytes and Peripheral Nervous System

During embryology, the ectodermal cells form the notochord, which then secretes growth factors that stimulate ectodermal cells, causing the formation of the neural plate, which then forms the neural folds

(Fig. 1). As the plate folds, it forms the neural tube, which differentiates into the CNS and neural crest cells (Elshazzly, 2018). Melanoblasts, the primitive melanocyte cells, originate in the neural crest and travel to designated areas of the skin throughout embryonic development (Mort et al., 2015; Vandamme and Berx, 2019). Neural crest cells are regarded as multipotent stem cells that produce the majority of neurons and glia in the peripheral nervous system (PNS) (Sommer, 2018). This means both the melanocytes' cells and the neurons of the PNS that innervate the skin areas (dermatomes) are derived from the same primitive cells (Goldstein, 2001). Intrinsic and extrinsic cues regulate the neural crest cells' increasing lineage limitation towards the melanocyte lineage, whereby pathfinding ability and differentiation are inversely correlated (Vandamme and Berx, 2019). Only melanoblasts migrate via the dorsolateral pathway (Fig 1), which has been the subject of the greatest amount of research (Vandamme and Berx, 2019).

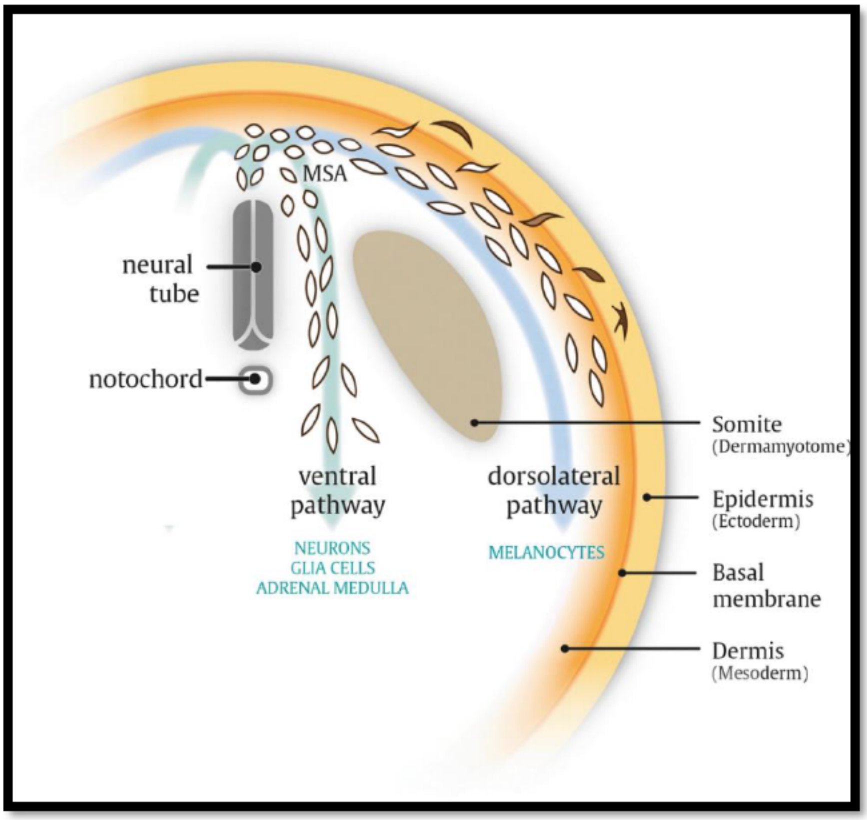

Figure 1: The migration of melanoblasts from the neural crest cells to the skin of a Human *(Adapted from Vandamme and Berx, 2019)*

1.2.2 Dermatome Anatomy

Dermatomes are distinct areas of skin that are innervated by sensory nerves that arise from a single spinal nerve root (Stecco *et al.*, 2019). The human body is divided into several dermatomes, each of which corresponds to a different spinal nerve. These dermatomes serve as a map of the body, helping healthcare workers determine the origin of sensory problems such as pain or numbness in individuals with neurological diseases or injuries (Congreve *et al.*, 2006). Understanding dermatomes is critical in identifying and controlling illnesses such as herniated discs, nerve compression, and spinal cord injuries because they assist in identifying which spinal nerve is afflicted and where the symptoms are originating from (Whitman *et al*., 2023).

Healthcare practitioners often clinically use dermatomes to evaluate sensory function in patients. They can identify whether there are any abnormalities or deficits in nerve function by assessing sensation in certain dermatomal locations (Lee *et al.,* 2008). Dermatome maps are essential tools in neurology, orthopaedics, and rehabilitation medicine, assisting in the localization of neurological abnormalities and directing therapy options for patients with nervous system sensory or motor impairments (Foerster, 1933). They are analysed in anaesthesia to determine the sensory limits of regional anaesthesia, such as pain localization. Given the clinical significance of dermatomes, it is remarkable that there is so much variation in dermatome maps in typical anatomical models.

a. **Foerster's map**

Foerster's map is a dermatome map that was developed by Otfrid Foerster in 1933 (Whitman et al., 2023). This map is based on clinical observations of anaesthesia after rhizotomy (Fig. 2). The Foerster map is the most commonly used dermatome map in healthcare and is used in the American Spinal Cord Injury Association Impairment Scale (ASIA Scale) (Downs and Laporte, 2011; Whitman *et al*., 2023). The dermatomes on the Foerster map are arranged in a way that correlates with the distribution of pain from angina or myocardial infarction (Downs and Laporte, 2011). The Foerster map depicts the medial area of the upper limb as being innervated by T1-T3, and the dermatome immediately below the C4 is the T2 dermatome (Lee et al., 2008). The dermatomes of the upper limb on the Keegan and Garrett map show that the C5 dermatome covers the skin below the clavicle, and C6 runs longitudinally from the shoulders, down the lateral aspect of the entire upper limb to the hand and thumb (Downs and Laporte, 2011). The dermatomes of the lower limbs on the Foerster map show a segmental arrangement, whereas the Keegan and Garrett map shows a spiral arrangement (Häggström, 2014). The exact area a dermatome may cover can vary by individual, and some overlaps are possible (Häggström, 2014). Multiple definitions of dermatomes exist, and several maps are commonly employed. At the same time, each map may have its own unique features or characteristics (Downs and Laporte, 2011; Häggström, 2014; Whitman *et al*., 2023).

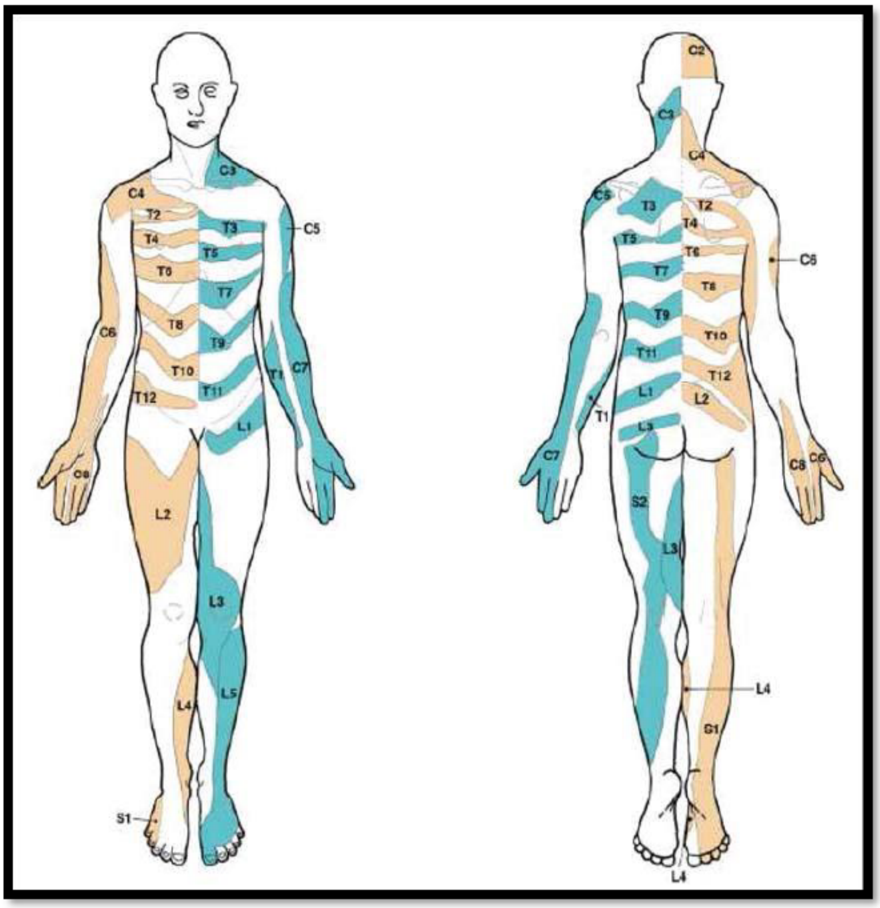

Figure 2: Foerster's tactile dermatome map (Foerster, 1933). Drawn from Foerster's clinical photographs. The posterior aspect of thoracic dermatomes included only T2. Overlapping dermatome areas are shown in lighter shades
(Adapted from Lee et al., 2008)

b. **Keegan and Garrett's map**

Keegan and Garrett's dermatome map is a specific dermatome map that was developed by Jay Keegan and Frederic Garrett in 1948 (Greenberg, 2003; Downs and Laporte, 2011) (Fig. 3). This map was derived largely by examining the compression of a single nerve root by a herniated disc or by anaesthesia of a single nerve root (Downs and Laporte, 2011). The Keegan and Garrett map shows all dermatomes as bands reaching the posterior midline and running the entire length of the body (Greenberg, 2003). The Keegan and Garrett map leans towards a developmental interpretation of dermatomes, and it differs from the Foerster map, which correlates better with clinical practice (Lee et al., 2008). The dermatomes of the upper limb on the Keegan and Garrett map show that the C5 dermatome covers the skin below the clavicles, and C6 runs longitudinally from the shoulders, down the lateral aspect of the entire upper limb to the hand and thumb (Whitman *et al.*, 2023). The T1 dermatome extends to the level of the upper pectoral region, whereas in the Foerster map, this area is represented by the T2 dermatome (Lee et al., 2008). The dermatomes of the lower limbs on the Keegan and Garrett map show a spiral arrangement, which differs from the more segmental arrangement on the Foerster map (Greenberg, 2003). The Keegan and Garrett map is one of several dermatome maps that are commonly employed, and each map may have its own unique features or characteristics (Greenberg, 2003; Downs and Laporte, 2011).

Foerster's and Keegan and Garrett's maps are commonly used dermatome maps, with Foerster's showing the medial upper limb as innervated by T1-T3, and Keegan and Garrett's showing C5 and C6 dermatomes (Whitman, Launico and Adigun, 2023). Foerster's map aligns better with clinical practice, while Keegan and Garrett's map leans toward developmental interpretation (Whitman *et al*., 2023). Foerster's map was developed in 1933, while Keegan and Garrett's map was developed in 1948 (Stecco *et al*., 2019). A study by Patton *et al*.(1976) on the dermatomal map shows the recently updated dermatome map, which is the one that was utilized in this study as it is more recent as compared to Foerster's and Keegan and Garrett's maps (Fig. 4).

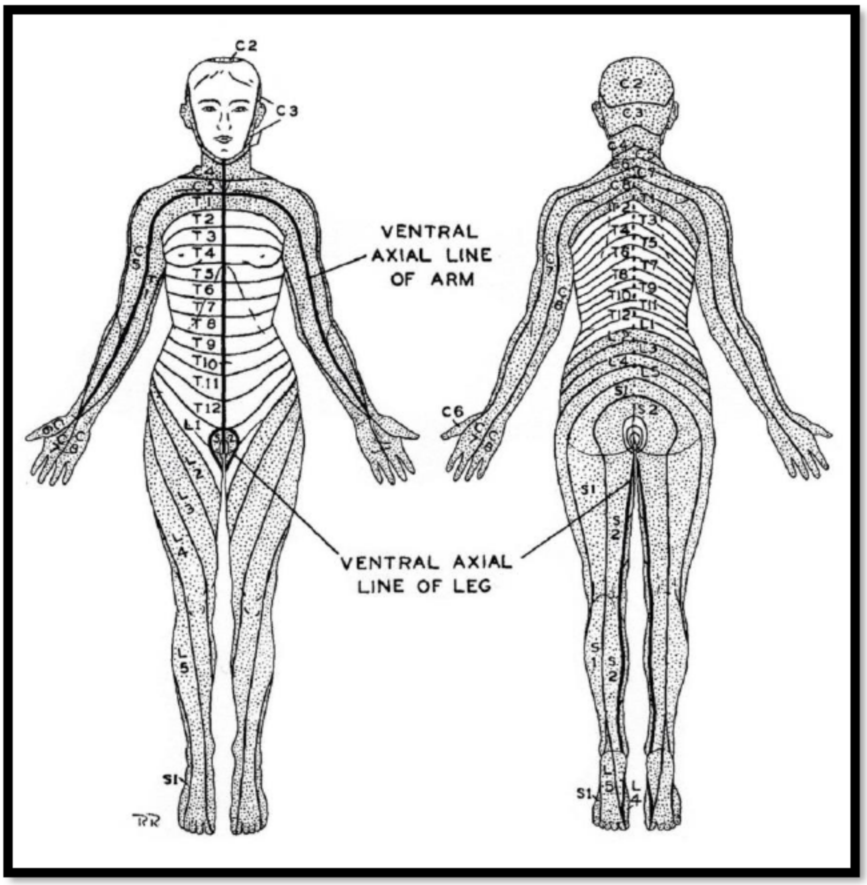

Figure 3: Keegan and Garrett's dermatome map, based on hypoalgesia produced by compression of a single nerve root by herniated disc or by anaesthesia of a single nerve root.
(*Adapted from Downs and Laporte, 2011*)

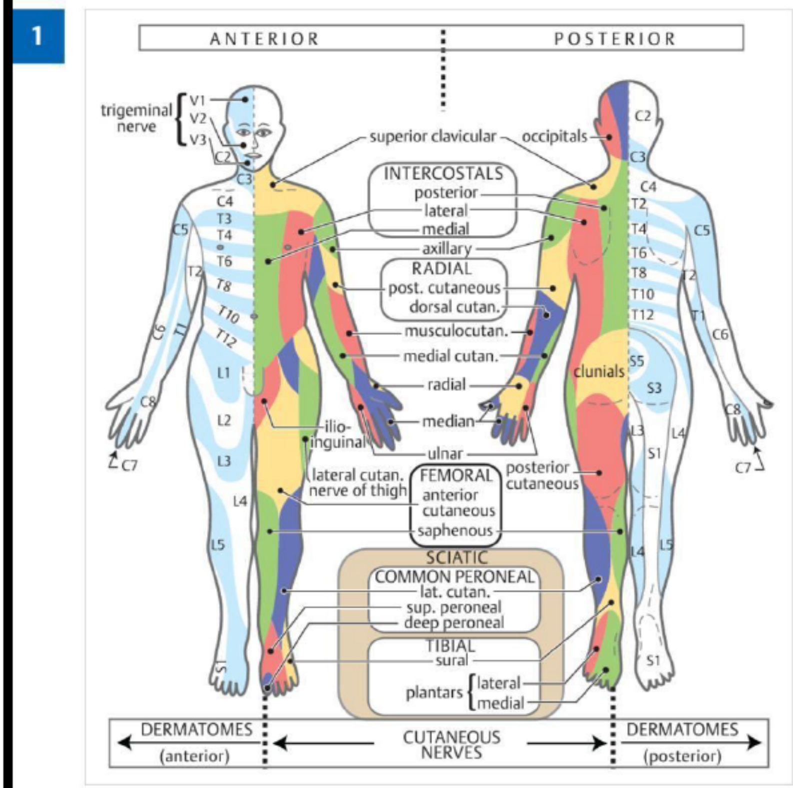

Fig. 1.16 Dermatomal and sensory nerve distribution. (Redrawn from "Introduction to Basic Neurology," by Harry D. Patton, John W. Sundsten, Wayne E. Crill and Phillip D. Swanson, © 1976, pp 173, W. B. Saunders Co., Philadelphia, PA, with permission.)

Figure 4: Introduction to basic neurology, the dermatomal map by Harry D. Patton et al. (1976)
(Adapted from Patton et al., 1976)

1.2.3 Neurosensory supply of the skin of the face

The face is also a highly specialized organ for receiving and transmitting sensory information from the environment to the brain. The cutaneous sensitivity of the face increases from the lateral areas to the midline, with the vermilion being the most sensitive and the forehead being the least sensitive, making facial sensations variable throughout the face (Von-Arx et al., 2017). The dermatome of the face differs from that of the body (peripheral region); the cutaneous innervation of facial skin is supplied by the CN V, one of the largest and most complex cranial nerves (CN). As the CN V is a primary source of cutaneous innervation of the face (Von-Arx et al., 2017), it has three main branches, viz. the ophthalmic nerve (V1), maxillary nerve (V2), and mandibular nerve (V3) divisions which have sub-branches that give cutaneous innervation to different parts of the face. The first branch (V1) has three major branches, viz. the frontal, nasociliary, and lacrimal, which innervate the forehead, scalp, eyelids, and (Von-Arx et al., 2017). The second branch (V2) gives rise to zygomatic and infraorbital nerves, which innervate the upper lip, cheek, nose, and anterior temporal regions. The third branch (V3) gives rise to the auriculotemporal nerve (which provides sensory innervation to the tragus, auricle, and posterior part of the temple), the long buccal nerve, and inferior alveolar nerve (which supplies the buccal, lower lip, and chin) (Von-Arx et al., 2017). Fig. 5 illustrates the cutaneous nerve distribution of the face and is utilized in this study.

The neck region also has its own unique distribution with respect to the anterior and posterior regions. The cutaneous innervation of the dorsal neck is primarily supplied by the dorsal rami of spinal nerves C2, C3, and C4, which include the lesser occipital (C2) and third occipital (C3) nerves (Kaiser and Lugo-Pico, 2023). While the anterior neck receives its cutaneous innervation from the ventral rami of spinal nerves C2 to C4 through branches of the cervical plexus. The cervical plexus gives raise to the great auricular nerve (C2 and C3) which innervates the upper-lateral region and the lower margin of the mandible; the transverse cervical nerve (C2 and C3) which innervates the anterior cervical region; and the supraclavicular nerves (C3 and C4) which innervate the skin over the upper chest and shoulders (Ginsberg and Eicher, 2000).

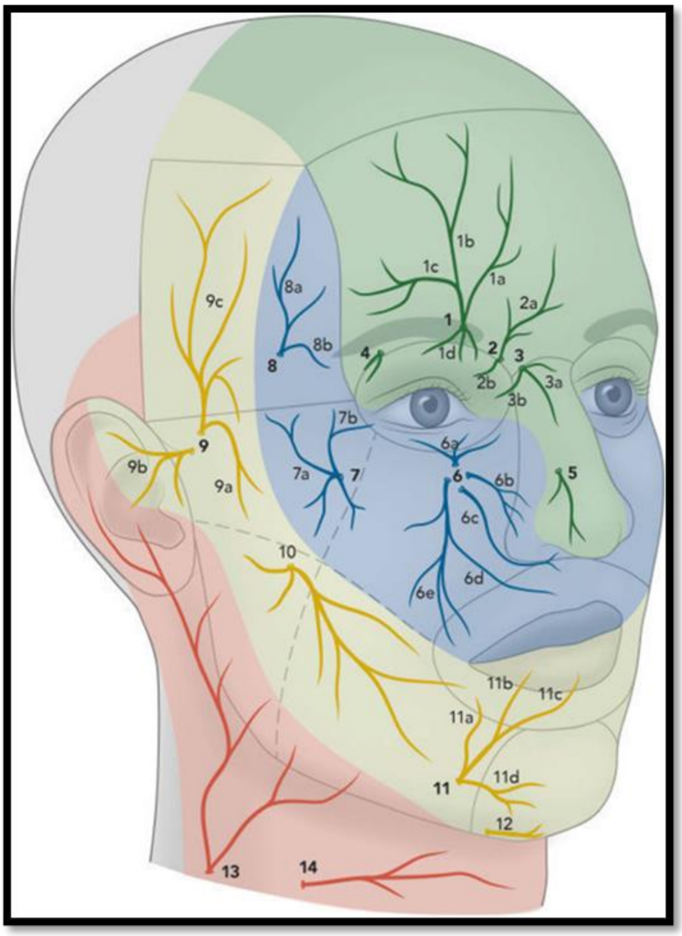

Figure 5*: *Illustration of the cutaneous, sensory nerves of the face
*(Adapted from Von-Arx et al., 2017)***

Key: Description of cutaneous nerves of the face

1.	**Supraorbital nerve** = (1 a = medial branch, 1 b = lateral branch, 1 c = horizontal branch, 1 d = palpebral branches).
2.	**Supratrochlear nerve** = (2 a = forehead branches, 2 b = palpebral branch).
3.	**Infra-trochlear nerve** = (3 a = nasal branches, 3 b = palpebral branch).
4.	**Palpebral branches of lacrimal nerve**.
5.	**External nasal branch of anterior ethmoidal nerve**.
6.	**Infraorbital nerve** = (6 a = inferior palpebral branches, 6 b = external nasal branch, 6 c = internal nasal branch, 6 d = medial branch of superior labial branch, 6 e = lateral branch of superior labial branch).
7.	**Zygomaticofacial nerve** = (7 a = zygomatic branches, 7 b = palpebral branch).
8.	**Zygomaticotemporal nerve** = (8 a = temporal branches, 8 b = palpebral branch)
9.	**Auriculotemporal nerve** = (9 a = zygomatic branches, 9 b = auricular branches, 9 c = temporal branches).
10.	**Long buccal nerve**.
11.	**Mental nerve** = (11 a = angular branch, 11 b = lateral labial branch, 11 c = medial labial branch, 11 d = mental branch).
12. 13. 14.	**Mental branch of mylohyoid nerve**. **Great auricular nerve.** **Transverse cervical nerve.**

To date, there is no literature that correlates the distribution of CMN on the skin with dermatomes (specific areas of skin innervated by individual spinal nerves) and non has explored a direct relationship between the distribution of CMN and dermatomes, leaving a notable gap in the understanding of CMN. Most of the studies focus mostly on dermoscopic patterns and the line of Blaschko, which are patterns that represent pathways of epidermal cell migration and proliferation during foetal development (Hanayama et al. 2007). These lines are invisible under normal conditions but become apparent when certain skin diseases manifest along these patterns. See Table 1 below.

Table 1: Summary of previous research and their findings

Author	Study Title	Key Findings
Effendy and Happle (1992)	Linear arrangement of multiple congenital melanocytic nevi	This study highlighted that the distribution of multiple congenital melanocytic nevi was reminiscent of the lines of Blaschko, indicating a patterned arrangement that aligns with these developmental lines
Hanayama et al. (2007)	Congenital melanocytic nevi and nevi spilus have a tendency to follow the lines of Blaschko: An examination of 200 cases.	A study examined 200 cases of congenital melanocytic nevi (CMN) and nevus spilus (NS) to investigate their relationship with Blaschko's lines. Results showed that 42.4% of CMN cases and 62.0% of NS cases followed the lines of Blaschko. The lines of Blaschko are believed to reflect the proliferation of epidermal cells during embryonic skin growth, possibly due to mosaicism and pigmentary gene anomalies
Martins da Silva *et al.* (2017)	Patterns of distribution of giant congenital melanocytic nevi (GCMN): The 6B rule.	A study highlighted that giant congenital melanocytic nevi (GCMN) follow reproducible distribution patterns represented by the 6Bs

1.3 MATERIALS AND METHODS

1.3.1 **Data Collection**

Clinical photographic images were obtained from the database of the Department of Plastic and Reconstructive Surgery at the Inkosi Albert Luthuli Central Hospital (IALCH) in Durban, South Africa. This database contains a collection of clinical images of patients with CMN on the head and neck, trunk, back, and limbs.

All data obtained from the database were anonymized to remove any personally identifiable information. Each image was carefully de-identified, ensuring confidentiality and ethical standards.

1.3.2 Inclusion Criteria

Photographic images of CMN with the following characteristics were included in the study:

- Projected size of 1.5cm in diameter or above.
- Presence of a visible site of the lesion(s).

1.3.3 Exclusion Criteria

Photographic images of CMN were excluded based on the following criteria:

- Size less than 1.5cm in diameter.
- Absence of a Visible site of lesions.

1.3.4 Ethical Considerations

Ethical approval for this study was obtained from the Biomedical Research Ethics Committee (BREC) of the University of KwaZulu-Natal (Reference number: BREC/00004680/2022). Gatekeeper permission was also secured from Inkosi Albert Luthuli Central Hospital. The study's ethical approval was contingent on the review by the medical institution and the Department of Health of KwaZulu-Natal to ensure patient privacy and safety.

Throughout the data collection and analysis stages, patient anonymity was emphasized, and the approach used was found to comply with high ethical standards. Respect for patient confidentiality and the honesty of scientific findings were maintained by dedication to ethical concerns, which guarantees the safekeeping of sensitive medical data.

1.3 Sample Size

Patients (both adult and paediatric) diagnosed with congenital melanocytic nevi (CMN) and who underwent nevi removal surgery between 2000 and 2023 were obtained from the database of the Department of Plastic and Reconstructive Surgery at IALCH. Clinical photographs of CMN with a projected size of 1.5cm in diameter or larger and having conspicuous site(s) were selected for analysis.

1.3.5 Data Analysis

Two investigators examined the clinical photographs to evaluate the size and dermatomes covered by the nevi. The following steps were performed:

- The observed nevi distribution was transposed onto a dermatome template [Harry D. Patton et al. (1976), Fig. 4, Page 10 and Von-Arx et al. (2017) Fig. 5, Page 11].
- Affected dermatome areas were tabulated.

In cases where there was disagreement between the investigators regarding the classification, the result was thoroughly evaluated. At each level of the classification process, any discrepancies between the reviewers were settled through discussion or with the assistance of a third reviewer. The aforementioned methodology of finding Interobserver Agreement (IOA%) was adopted from Bryson and Zea (2023), using the Exact Count Per Interval method with the following formula:

$$\text{Interobserver Agreement (IOA\%)} = \frac{\text{Reviewer Agreement}}{\text{Total sample size}}$$

These analyses were done in two (2) subsets. The first subset (subset I; n= 31) looked at the correlation between the CMN on the overall body and the body dermatomes adopting the dermatomal map of Patton et al., (1976) (Fig. 4*)*. The second subset (subset II; n= 19) looked at patients with CMN on the head and neck, and investigated the correlation of CMN and facial dermatomes (Trigeminal nerve) distribution using Fig. 5.

1.3.6 Statistical Analysis

Statistical data analysis was conducted using the R Statistical computing software (R Core Team, 2020, version 3.6.3). The results were presented in both descriptive and inferential statistics.

Descriptive statistics included:

- Minimum, maximum, quartiles, interquartile range.
- Means, standard deviation, and the coefficient of variation.
- Categorical variables were described as counts and percentage frequencies.
- Visual aids such as pie charts, simple bar charts, component bar charts, Pareto charts, and multiple bar charts were used to visually represent categorical variables.

Trend analysis included graphical displays to understand the behavioural patterns of dermatome prevalence over time.

This methodology ensured rigorous data collection and analysis while upholding ethical standards and patient confidentiality. The study's findings will contribute to our understanding of the relationship between CMN distribution and dermatomes.

1.4 Structure of the thesis

This thesis was prepared according to the guidelines outlined by the College of Health Sciences, University of KwaZulu-Natal, South Africa. The manuscript has been structured and formatted according to the guidelines of the respective scientific journal. The structural outline of the thesis is as follows:

1.4.1 Chapter 1: Introduction

This chapter supplies insight into congenital melanocytic nevi (CMN) and dermatomes as well as a comprehensive literature review and an overview of the study. The aims, objectives, research question, and detailed methodology are included in this chapter.

1.4.2 Chapter 2: Scientific manuscript

This chapter comprises an original scientific manuscript entitled Dermatomal Patterns and Congenital Melanocytic Nevi Distribution in the Head, Neck, Trunk, Back, and Limbs. This manuscript investigated the correlation of dermatomal patterns and CMN (with a size greater than 1.5 cm in diameter) distribution on the head, neck, trunk, back, and limbs.

1.4.3 Chapter 3: Synthesis, limitations, recommendations, and conclusion

This chapter discusses the findings of Chapter 2 and provides a synthesis of the findings of the potential correlation between the dermatomes and the distribution of CMN in this study. Limitations encountered and recommendations for future research have been outlined and highlighted.

Following chapter 3 are the Appendices.

1.4 REFERENCES

1 Congreve, K. et al. (2006) “Where is T5? A survey of anaesthetists,” Anaesthesia, 61(5), pp. 453–455. doi: 10.1111/j.1365-2044.2006.04609. x.

2 Downs, M. B. and Laporte, C. (2011) “Conflicting dermatome maps: Educational and clinical implications,” The Journal of orthopaedic and sports physical therapy, 41(6), pp. 427–434. doi: 10.2519/jospt.2011.3506.

3 Effendy, I. and Happle, R. (1992) “Linear arrangement of multiple congenital melanocytic nevi,” Journal of the American Academy of Dermatology, 27(5), pp. 853–854. doi: 10.1016/0190-9622(92)70265-h.

4 Elshazzly, M. (2018) “Embryology, Central Nervous System,” StatPearls.

5 Farabi, B. et al. (2021) “Congenital melanocytic naevi: An up-to-date overview,” The Australasian journal of dermatology, 62(2), pp. e178–e191. doi: 10.1111/ajd.13535.

6 Foerster, O. (1933) “The dermatomes in man,” Brain: a journal of neurology, 56(1), pp. 1–39. doi: 10.1093/brain/56.1.1.

7 Gkasdaris, G. and Kapetanakis, S. (2015) “Clinical anatomy and significance of the lumbar intervertebral foramen: A review,” Journal of the Anatomical Society of India, 64(2), pp. 166–173. doi: 10.1016/j.jasi.2015.10.003.

8 Goldstein, B. (2001) “Anatomy of the peripheral nervous system,” Physical medicine and rehabilitation clinics of North America, 12(2), pp. 207–236. doi: 10.1016/s1047-9651(18)30066-4.

9 Ginsberg, L. E. and Eicher, S. A. (2000) “Great auricular nerve: Anatomy and imaging in a case of perineural tumor spread,” AJNR: American Journal of Neuroradiology, 21(3), p. 568.

10 Greenberg, S. A. (2003) “The history of dermatome mapping,” Archives of neurology, 60(1), p. 126. doi: 10.1001/archneur.60.1.126.

11 Häggström, M. (2014) “Medical gallery of Mikael Häggström 2014,” Wikijournal of medicine, 1(2). doi: 10.15347/wjm/2014.008.

12 Hanayama, H. et al. (2007) “Congenital melanocytic nevi and nevus spilus have a tendency to follow the lines of Blaschko: an examination of 200 cases,” The journal of dermatology, 34(3), pp. 159–163. doi: 10.1111/j.1346-8138.2007.00242. x.

13 Ibrahimi, O. A., Alikhan, A. and Eisen, D. B. (2012) “Congenital melanocytic nevi: where are we now? Part II. Treatment options and approach to treatment,” Journal of the American Academy of Dermatology, 67(4), p. 515.e1–13; quiz 528–30. doi: 10.1016/j.jaad.2012.06.022.

14 Kaiser, J. T. and Lugo-Pico, J. G. (2023) Neuroanatomy, Spinal Nerves. StatPearls Publishing.

15 Kinsler, V. A. et al. (2014) “Next-generation sequencing of nevus spilus–type congenital melanocytic nevus: Exquisite genotype–phenotype correlation in mosaic RASopathies,” The journal of investigative dermatology, 134(10), pp. 2658–2660. doi: 10.1038/jid.2014.195.

16 Krengel, S. et al. (2013) “New recommendations for the categorization of cutaneous features of congenital melanocytic nevi,” Journal of the American Academy of Dermatology, 68(3), pp. 441–451. doi: 10.1016/j.jaad.2012.05.043.

17 Lee, M. W. L., McPhee, R. W. and Stringer, M. D. (2008) “An evidence-based approach to human dermatomes,” Clinical anatomy (New York, N.Y.), 21(5), pp. 363–373. doi: 10.1002/ca.20636.

18 Martins da Silva, V. P. et al. (2017) “Patterns of distribution of giant congenital melanocytic nevi (GCMN): The 6B rule,” Journal of the American Academy of Dermatology, 76(4), pp. 689–694. doi: 10.1016/j.jaad.2016.05.042.

19 Masnari, O. et al. (2019) “Predictors of health-related quality of life and psychological adjustment in children and adolescents with congenital melanocytic nevi: Analysis of parent reports,” Journal of pediatric psychology, 44(6), pp. 714–725. doi: 10.1093/jpepsy/jsz017.

20 Mort, R. L., Jackson, I. J. and Patton, E. E. (2015) “The melanocyte lineage in development and disease,” Development (Cambridge, England), 142(7), pp. 1387–1387. doi: 10.1242/dev.123729.

21 Moustafa, D., Blundell, A. R. and Hawryluk, E. B. (2020) “Congenital melanocytic nevi,” Current opinion in pediatrics, 32(4), pp. 491–497. doi: 10.1097/mop.0000000000000924.

22 Patton, H.D. et al. (1976) Introduction to basic neurology. Saunders. Available at: https://ci.nii.ac.jp/ncid/BA25310169 (Accessed: 4 September 2023).

23 Prescher, H., Corcoran, J. F. and Bauer, B. S. (2023) “Congenital Nevi,” in Pediatric Surgery. Cham: Springer International Publishing, pp. 593–607.

24 Price, H. N. (2016) “Congenital melanocytic nevi: update in genetics and management: Update in genetics and management,” Current opinion in pediatrics, 28(4), pp. 476–482. doi: 10.1097/mop.0000000000000384.

25 Price, H. N. and Schaffer, J. V. (2010) “Congenital melanocytic nevi - when to worry and how to treat: Facts and controversies,” Clinics in Dermatology, 28(3), pp. 293–302.

26 Saida, T. (2019) “Histogenesis of cutaneous malignant melanoma: The vast majority do not develop from melanocytic nevus but arise de novo as melanoma in situ,” The journal of dermatology, 46(2), pp. 80–94. doi: 10.1111/1346-8138.14737.

27 Scard, C. et al. (2023) “Risk of melanoma in congenital melanocytic nevi of all sizes: A systematic review,” Journal of the European Academy of Dermatology and Venereology: JEADV, 37(1), pp. 32–39. doi: 10.1111/jdv.18581.

28 Sommer, L. (2018) “Developmental biology of melanocytes,” in Melanoma. New York, NY: Springer New York, pp. 1–17.

29 Stecco, C. et al. (2019) “Dermatome and fasciatome,” Clinical anatomy (New York, N.Y.), 32(7), pp. 896–902. doi: 10.1002/ca.23408.

30 Van Raamsdonk, C. D. and Deo, M. (2013) “Links between Schwann cells and melanocytes in development and disease,” Pigment cell & melanoma research, 26(5), pp. 634–645. doi: 10.1111/pcmr.12134.

31 Vandamme, N. and Berx, G. (2019) “From neural crest cells to melanocytes: cellular plasticity during development and beyond,” Cellular and molecular life sciences: CMLS, 76(10), pp. 1919–1934. doi: 10.1007/s00018-019-03049-w.

32 Viana, A. C. L., Gontijo, B. and Bittencourt, F. V. (2013) “Giant congenital melanocytic nevus,” Anais brasileiros de dermatologia, 88(6), pp. 863–878. doi: 10.1590/abd1806-4841.20132233.

33 Von-Arx, T., Abdelkarim, A. Z. and Lozanoff, S. (2017) “The Face - A Neurosensory Perspective,” Swiss dental journal, 127(12), pp. 1066–1075.

34 Whitman, P. A., Launico, M. V. and Adigun, O. O. (2023) Anatomy, Skin, Dermatomes. StatPearls Publishing.

35 Yeh, I. (2020) “New and evolving concepts of melanocytic nevi and melanocytomas,” Modern pathology: an official journal of the United States and Canadian Academy of Pathology, Inc, 33(Suppl 1), pp. 1–14. doi: 10.1038/s41379-019-0390-x.

CHAPTER 2

SCIENTIFIC MANUSCRIPT 1

Interface

Chapter 1 provided an overview of the congenital melanocytic nevi as well as its patterns of presentation in the head, neck, trunk, back and limbs regions. This chapter describes the clinical relevance and overview of the methodology.

Contributions of this chapter

This chapter comprises one scientific manuscript that investigates the correlation of dermatomal patterns and CMN (with a size greater than 1.5 cm in diameter) distribution on the head, neck, trunk, back and limbs. This scientific manuscript was **accepted for publication (In press)** by a European Journal of Anatomy (EJA) and has been formatted according to the guidelines outlined by the journal, with references set using the Harvard reference style.

Title:	Dermatomal Patterns and Congenital Melanocytic Nevi Distribution in the Head, Neck, Trunk, Back, and Limbs.
Authors:	S. Nkosi, A. Madaree, M. Daya, L. Lazarus
Journal:	European Journal of Anatomy
Manuscript Number:	240378ll (In press) please see Appendix A

TITLE PAGE

Title: Dermatomal Patterns and Congenital Melanocytic Nevi Distribution in the Head, Neck, Trunk, Back, and Limbs

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Total number of figures : 8

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Running headline : Congenital melanocytic nevi and dermatomal correlative patterns

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ABSTRACT

Congenital melanocytic nevi (CMN) are benign melanocyte nevi that appear at birth and can be found in the dermis, epidermis, or both layers of the skin. These CMN are caused by mutation in the melanocyte's cells. This mutation leads to them lacking dendrites and causes CMN. This study aimed to investigate the correlation between CMN distribution and dermatomes.

Clinical photographs of CMN (>1.5cm) from a quaternary hospital in Durban, South Africa, were analysed. Two investigators examined the clinical photographs to evaluate the size and dermatomes covered by the nevi (n=31). The observed CMN distribution was transposed onto a dermatome template, and the prevalence among dermatomes was compared.

The results showed a higher preference for T10 (58.1%) and similar patterns in T11 (54.8%) and T12 (51.6%). Facial dermatomes V1 and V2 (54.8%) were mostly affected with the areas of zygomaticofacial, zygomaticotemporal, and supraorbital nerves in the cervical region C5 (32.3%) and lumbar L1 (41.9%) were notably affected. Varied CMN patterns were observed in the head and neck region, emphasizing the complexity of CMN distribution.

The study enhances our understanding of CMN presentation, shedding light on the potential for CMN to follow a dermatomal distribution, with CMN often mostly found in the trunk region around T10, T11, and T12. V1 and V2 dermatomes in the face with zygomaticotemporal, zygomaticofacial, and supraorbital branches were mostly affected, suggesting embryological influences during the maxillary process fusion.

Keywords: *C*ongenital melanocytic nevi; Dermatomes maps; Trigeminal nerve; Distribution; South African

TEXT

INTRODUCTION

One of the most common skin lesions seen at birth is congenital melanocytic nevi (CMN), a skin disorder that appears as a pigmented patch on the skin (Macneal and Patel, 2023; Navarro-Fernandez and Mahabal, 2023). The size is the primary criterion for categorizing these lesions as small, medium, big, or giant (Macneal and Patel, 2023). Adult size is predicted using a scaling factor based on anatomical location. These CMN are expected to expand by a factor of 1.7 on the head, 3.3 on the lower limbs, and 2.8 on the upper limbs and trunk. The reason for classifying lesions by size is that larger lesions are more likely to develop into melanoma, have cosmetic implications, and have more challenging surgeries (Macneal and Patel, 2023).

Although most CMNs are completely harmless, a tiny number, particularly the bigger ones, can potentially develop into lifetime malignant melanoma (Hale *et al.*, 2005; Saida, 2019; Prescher *et al.*, 2023). Small and medium CMN do not indicate a greater risk of melanoma, and in the absence of additional surgical rationale, observation is the preferred management (Price and Schaffer, 2010). According to the literature search, CMN can be inherited in rare cases, but the pattern of inheritance is not Mendelian (de Wijn *et al.*, 2010). While CMN may manifest anywhere on the body, the most prevalent sites are the posterior trunk, the limbs, and the head and neck (Vourc'h-Jourdain *et al.*, 2013; Nikfarjam and Chambers, 2016). Embryologically, both the melanocytes and the neurons of the PNS that innervate the skin areas (dermatomes) are derived from the same primitive cells, which can be a potential explanation for CMN distribution on the skin (Goldstein, 2001).

To date, no existing body of literature has explored any potential connection between the distribution of CMN on the skin and dermatomes. Dermatomes are areas of the skin that rely on specific spinal nerves for their sensory distribution. Each dermatome corresponds to a distinct nerve root and is distributed in a segmented pattern throughout the body (Whitman, Launico and Adigun, 2023). There are several regularly used maps; Foerster's and Keegan & Garrett's maps are commonly used dermatome maps that differ in their arrangement of dermatomes (Whitman, Launico and Adigun, 2023). While dermatomes are helpful, there is a lot of variation in them from one map to another and even from person to person (Challoumas *et al.*, 2018; Whitman, Launico and Adigun, 2023). Overlaps on dermatomes vary among people, making studies on dermatomes quite complex (Lee *et al.*, 2008).

It is important to note that the face does not have dermatomes; rather, it receives cutaneous innervation from CN V due to the relationship in their embryological origin- the first pharyngeal arch (Von-Arx *et al*., 2017). CN V has three main branches viz the ophthalmic nerve (V1), which innervates the forehead, scalp, eyelids, and nose; the maxillary nerve (V2), which innervates the upper lip, cheek, nose, and anterior temporal regions; and the mandibular nerve (V3) which innervates the tragus, auricle, and posterior part of the temple (Von-Arx *et al.*, 2017). For the neck region, the cutaneous innervation arises from dorsal and ventral rami of cervical nerves, with the anterior part innervated by ventral rami via the cervical plexus nerve branches and the posterior part via dorsal rami of C2 to C4 (Kaiser and Lugo-Pico, 2023). The branchial arches are another essential structure during embryology in the neck region and contribute to the formation of the jaw, hyoid bone, and ear components (Ginsberg and Eicher, 2000). This is why the lower portion of the face has innervation from the cervical plexus via the greater auricular nerve (Ginsberg and Eicher, 2000).

When it comes to dermatomes, the Keegan and Garrett map is more in line with a developmental interpretation, but the Foerster map is more in line with clinical practice (Whitman, Launico and Adigun, 2023). A more recent dermatomal map by Patton *et al.* (1976), which was an updated version of Keegan and Garrett's map, was utilized in this study. The presentation of CMN on the skin remains enigmatic. Finding this ideological investigation of whether a correlation exists between the distribution of CMN and dermatome mapping could yield valuable insights into the processes of development and potentially hold clinical significance.

METHODS AND MATERIALS

Clinical photographs from the Plastic and Reconstructive Surgical Unit database at a quaternary hospital in Durban, South Africa, were used in this investigation. To determine whether there was a CMN correlation with the dermatomal pattern in the peripheral body, we anonymized the data and ran statistical analyses. All data analysed was treated with strict confidentiality. No photographic material with identification markers was retained, recorded, or published.

Sample size.

The medical records of 31 patients (adult and paediatric) diagnosed with GCMN and those eligible for surgical removal of the nevi between 2000 and 2023 were obtained from the database of the hospital.

Inclusion criteria

Photographic images of CMN with the following characteristics were included in the study:

- Projected size of 1.5cm in diameter or above.
- Presence of a visible site of the lesion(s).

Exclusion criteria

Any photographic images of CMN that are less than 1.5cm in diameter and did not have a visible site of lesions were excluded from the study.

Data Collection and Analysis

Clinical photographs of CMN with projected size ≥ 1.5 cm in diameter and having visible site of the lesion(s) were analysed. These analyses were done in two (2) subsets. The first subset (subset I; n= 31) looked at the correlation between the CMN on the overall body and the body dermatomes adopting the dermatomal map of Patton et al., (1976) (Fig. 1). The second subset

(subset II; n= 19) looked at patients with CMN on the head and neck, and investigated the correlation of CMN and facial dermatomes (Trigeminal nerve) distribution using Figure 2.

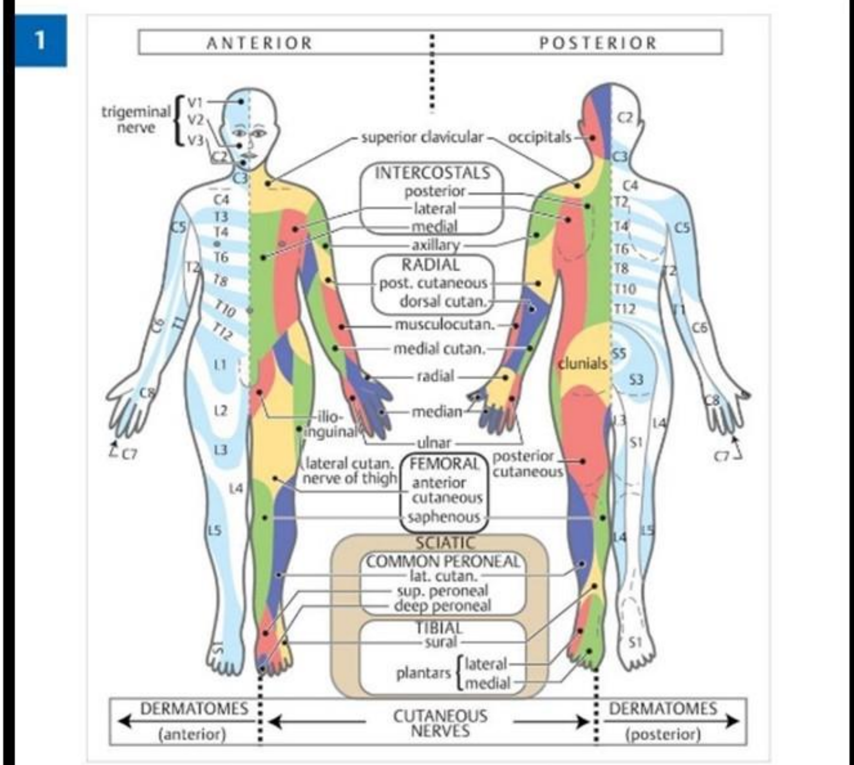

Fig. 1.16 Dermatomal and sensory nerve distribution. (Redrawn from "Introduction to Basic Neurology," by Harry D. Patton, John W. Sundsten, Wayne E. Crill and Phillip D. Swanson, © 1976, pp 173, W. B. Saunders Co., Philadelphia, PA, with permission.)

Figure 1: Dermatomal map by Harry D. Patton et al., (1976) *(Adapted from Harry D. Patton et al., 1976).*

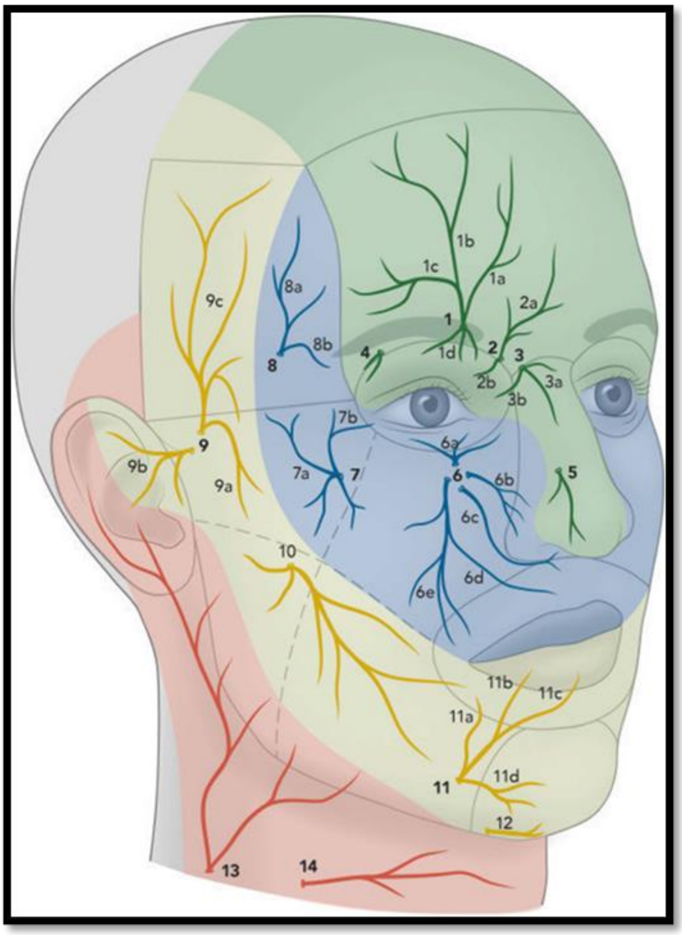

Figure 2: **Illustration of the cutaneous, sensory nerves of the face**

(*Adapted from Von-Arx et al., 2017*)

Two investigators examined the lesion(s) to evaluate the size and dermatomes that the nevi cover in the head, cervical, thoracic, lumbar, and sacral regions of the body. The extent of CMN was analysed on the photographs and transposed onto the dermatome templates and affected dermatome areas were tabulated. In cases where there was disagreement between the investigators regarding the classification, the result was thoroughly evaluated, and at each level of the classification process, any discrepancies between the reviewers were settled through discussion or with the assistance of a third reviewer. The aforementioned methodology of finding Interobserver Agreement (IOA%) was adopted from Bryson and Zea (2023), using the Exact Count Per Interval method with the following formula:

$$\text{Interobserver Agreement (IOA\%)} = \frac{\text{Reviewer Agreement}}{\text{Total sample size}}$$

Statistical analysis

The R Core Team's 2020 statistical computing program, version 3.6.3, was used for the statistical data analysis. Both descriptive and inferential statistics were used to present the findings. Standard deviation, coefficient of variation, minimum, maximum, quartiles, interquartile range, averages, and descriptive statistics of numerical measures were summarised where appropriate. Pie, basic, component, Pareto, and multiple bar charts were used to graphically represent the categorical variables, which were characterized as counts and percentage frequencies. To get insight into the behavioural patterns of dermatome prevalence over time, trend analysis was conducted using graphical presentations.

Ethical considerations

The study received institutional ethical approval from the Biomedical Research Ethics Committee (Reference number: BREC/00004680/2022).

RESULTS

A 23-year (2000– 2023) observational study yielded 31 patients (n = 31) presenting with CMN above 1.5 cm in size. For the first subset (subset I) the interobserver agreement (IOA) was 80,6%. The results for the (subset I) revealed the following demographics among the 31 patients: 41.9% were female, while 58.1% were male. The ethnicity distribution was 58.1% Black, 38.7% Indian, and 3.2% White. The age group distribution of the sample was as follows: 6.4% were younger than 16 years, 83.9% fell within the 16–30-year range, and 9.7% were in the 31–45-year range. Furthermore, the distribution of the skin condition across different body areas was observed as follows: back: 12.9%, upper limbs: 3.2%, lower limbs: and head and neck: 51.6% (Table 1).

Table1: Patient demographics

Parameter	**Overall (N=31)**
Gender	
Female	13 (41.9%)
Male	18 (58.1%)
Race	
Black	18 (58.1%)
Indian	12 (38.7%)
white	1 (3.2%)
Age group	
<16yrs	2 (6.4%)
16-30yrs	26 (83.9%)
31-45yrs	3 (9.7%)
Location	
Back	4 (12.9%)
Back; Head and neck	1 (3.2%)

Parameter	**Overall (N=31)**
Back; Head and neck; Trunk; Upper limbs	1 (3.2%)
Back; Lower limbs	1 (3.2%)
Back; Trunk	3 (9.7%)
Back; Trunk; Upper limbs	1 (3.2%)
Back, Trunk	1 (3.2%)
Head and neck	16 (51.6%)
Head and neck; Trunk	1 (3.2%)
Lower limbs	1 (3.2%)
Upper limbs	1 (3.2%)

| Valid % shown | Mode1-smallest mode | Nmodes-# of modes |

In Fig. 3, a combination of "C3-C4-C5-T2" represents the patients that had the CMN on the dorsal neck and running down the back region with a percentage of 9.7%. For those that had the CMN on the ventral neck and ran down the anterior trunk, it was represented by C3 with a percentage of 6.5%

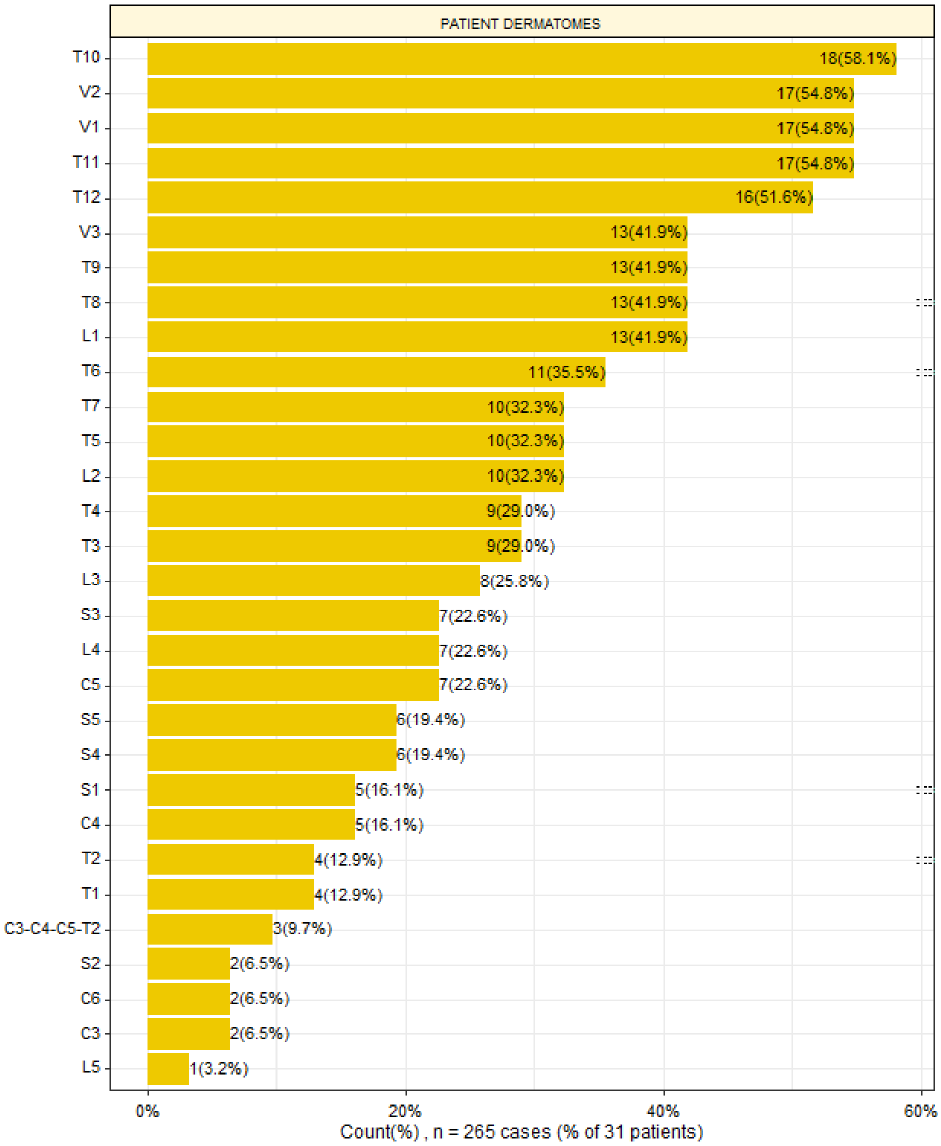

Figure 3: Incidence of CMN correlated with dermatomal pattern.

This investigation also sought to report on each dermatome, how many patients were found with CMN, and which dermatomes were the most/ least affected in each body region. T10 dermatome was found to be the most affected dermatome with (58.1%), followed by the T11 dermatome (54.8%) and T12 (51.6%). In the face region, V1 and V2 dermatomes were the most affected and had 54.8% of patients with CMN on them (Fig.3; Fig.4). In the cervical region, C5 was the most affected (32.3%) and the least affected was C6 (6.5%). The L1 dermatome was the most affected in the lumbar region (41.9%), while the L5 dermatome was the least affected (3.2%). In the sacral region, S3 was the most affected (22.6%) and the least affected was S2 (6.5%) (Table 2).

Table 2: Pattern of most and least affected dermatomes in each body region by root value

	Face	Cervical	Thoracic	Lumber	Sacrum
Most affected	V1; V2	C5	T10	L1	S3
Least affected	V3	C6	T1	L5	S2

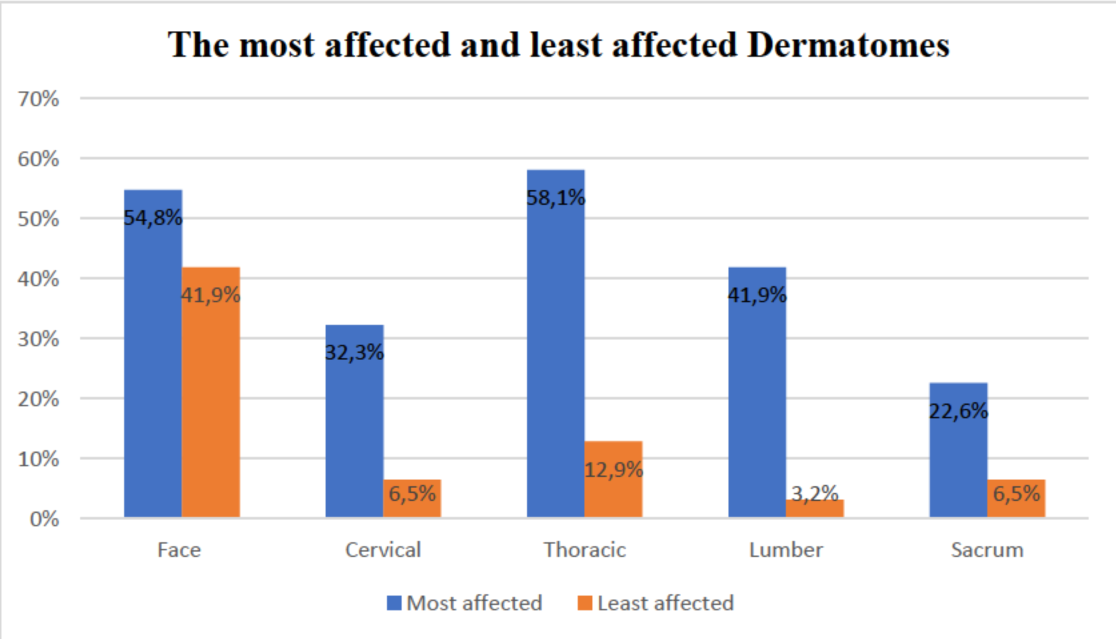

Figure 4: Most and least affected dermatomes in each body location.

Figure 5 illustrates the incidence of CMN patients affected by dermatomal combinations (spinal nerve root values). Concerning the head and neck region, the most prevalent dermatomal combinations impacted by the nevi were V1, V2, and V3, constituting 29.0% of patients. This was followed by the V1 and V2 combination, observed in 9.7% of cases, while

V1 on its own was present in only one patient, representing 3.2% of cases, as was V2. Other combinations were each noted in 3.2% of cases.

To demonstrate how many patients had CMN affecting various dermatomes, the respective percentages were used see figure 5, two patients exhibited CMN affecting a single dermatome (6.4%). In contrast, 12 patients had CMN affecting three dermatomes, accounting for a total percentage of 38.6%. Patients with two dermatomes affected constituted 9.7%, while the remaining cases represented 3.2% each.

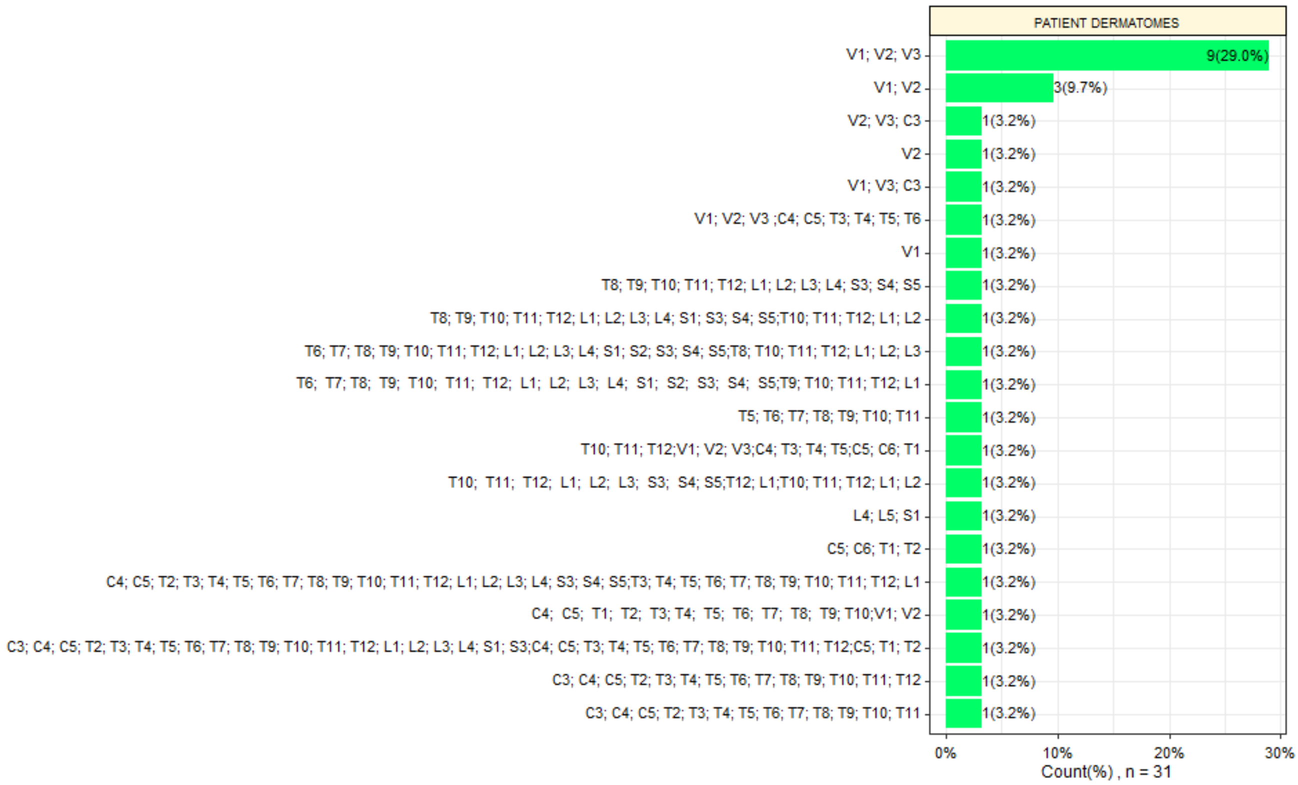

Figure 3: Incidence of dermatomal combinations affected by CMN.

The final comparison focused on the distribution of dermatomes across various locations. In terms of the number of affected dermatomes, the most prevalent location was the head and neck, accounting for 43.2%, followed by the back region at 27.3%, then the trunk region at 15.9%, and lastly, the upper and lower limbs with each accounting 6.8% (Fig. 6).

Among the patients with CMN in the head and neck region highlighted in blue, 10.5% had CMN localized on a single dermatome, 21.1% had CMN affecting two dermatomes, and the majority (68.4%) had it on three dermatomes. In contrast, among patients with CMN in the back region highlighted in pink, 8.3% had it affecting three or more dermatomes. The trunk area highlighted in red was affected by CMN in four and above dermatomes but not exceeding 12 dermatomes. The upper limbs highlighted in green exhibited CMN on 3 and 4 dermatomes, while the lower limbs highlighted in brown were observed with CMN affecting 2, 3, and 5 dermatomes, as shown below in (Fig. 6).

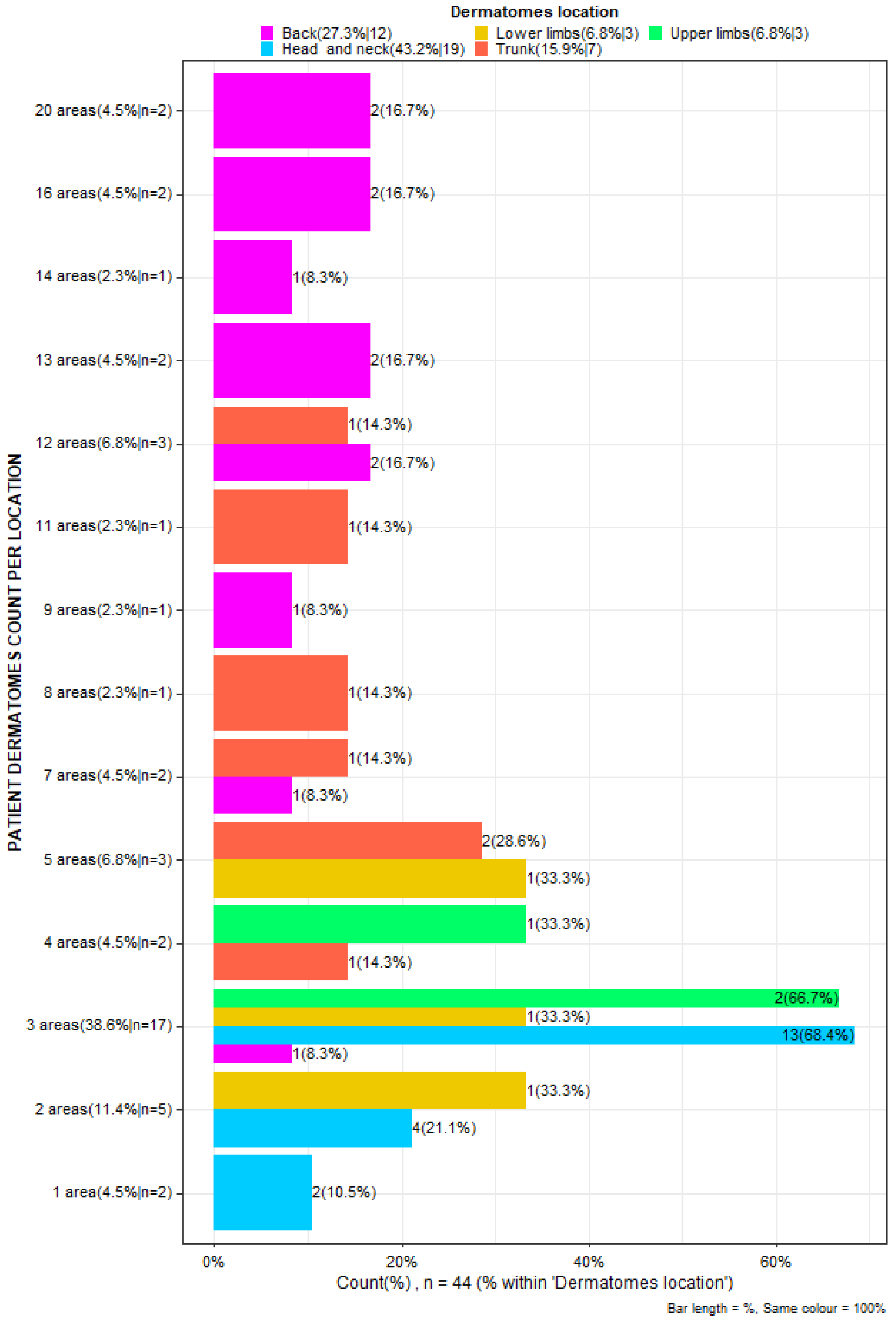

Figure 6: Dermatomes affected by CMN in comparison to their location.

For the second subset (subset II), we had patients (n = 19) presenting with CMN above 1.5 cm on the face (IOA here was 89%). Regarding gender analysis, 57.9% were found to be males, and 42.1% were females (Table 3). For age groups, the patients were distributed as follows: 78.9% were younger than 16 years, 15.8% fell within the 16–30-year range, and 5.3% were in the 31–45-year range. Laterality analysis showed that 47.4% of patients had CMN on the right side, 26.3% on the left, and 26.3% on both sides of the face.

Table 3: Patient demographics

	Overall (N=19)
Laterality	
Both	5 (26.3%)
Left	5 (26.3%)
Right	9 (47.4%)
Gender	
Female	8 (42.1%)
Male	11 (57.9%)
Age group	
<16yrs	15 (78.9%)
16-30yrs	3 (15.8%)
31-45yrs	1 (5.3%)
Race	
Black	12 (63.2%)
Indian	7 (36.8%)

| Group % shown | Mode1-smallest mode | Nmodes-# of modes |

Due to some of these patients having the CMN in multiple locations, each category that the patient had the CMN involved in was repeated count. The research results revealed the following demographics: among 19 patients, 16 had the CMN on the face only. The other 3 had it on the face plus multiple regions, including the neck, back, trunk, and upper limb. There is a discernible distribution of these nevi in the patients with CMN on the face and neck. Two of them had it running on the great auricular nerve and transverse cervical nerve, which are branches of the cervical plexus (Fig. 7).

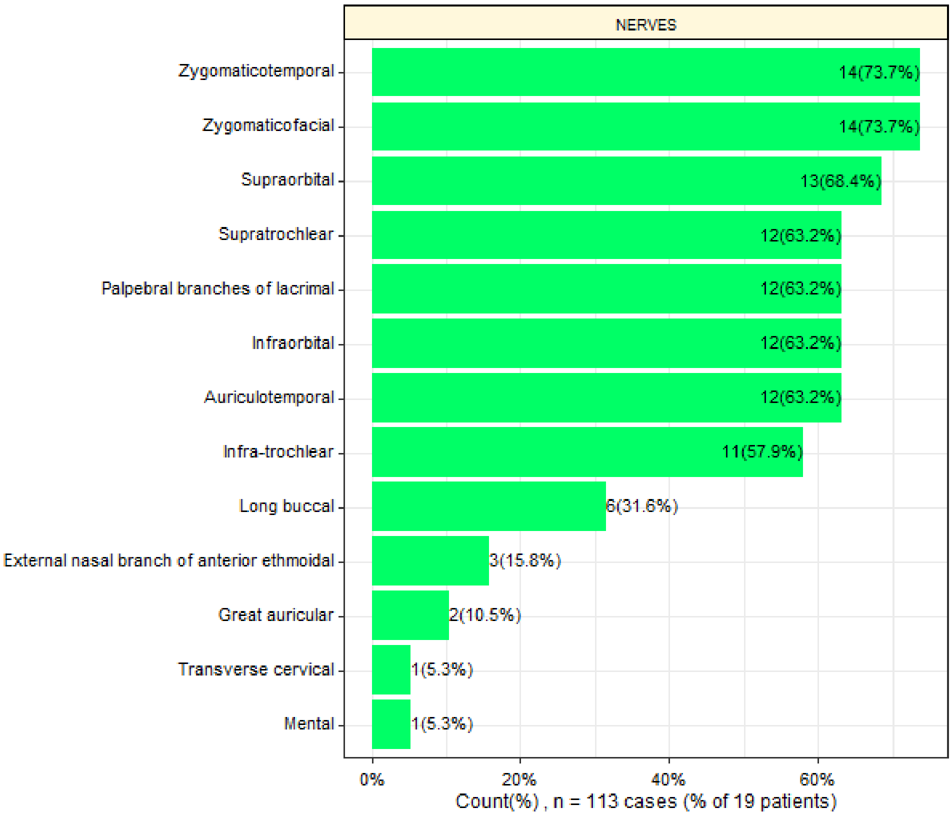

Figure 7: Number of patients in each nerve-supplying area affected by CMN.

The final comparison focused on the distribution of CMN in each CN V branch. Of the 34 % of patients affected by V1, 76.5% affected supraorbital, followed by supratrochlear (70.6%), palpebral branches of lacrimal (70.6%), infra-trochlear (64.7%) and external nasal branch of anterior ethmoidal (17.6%) dermatomes (Fig. 8). Out of the 36% patients affected on V2 region, zygomaticotemporal and zygomaticofacial dermatomes were the predominant with 77.8%, followed by infraorbital dermatome with 66.7%. Of the 26% patients affected on V3, 92.3% affected the auriculotemporal dermatome, 46.2% were on long buccal, while 7.7% were on mental dermatome.

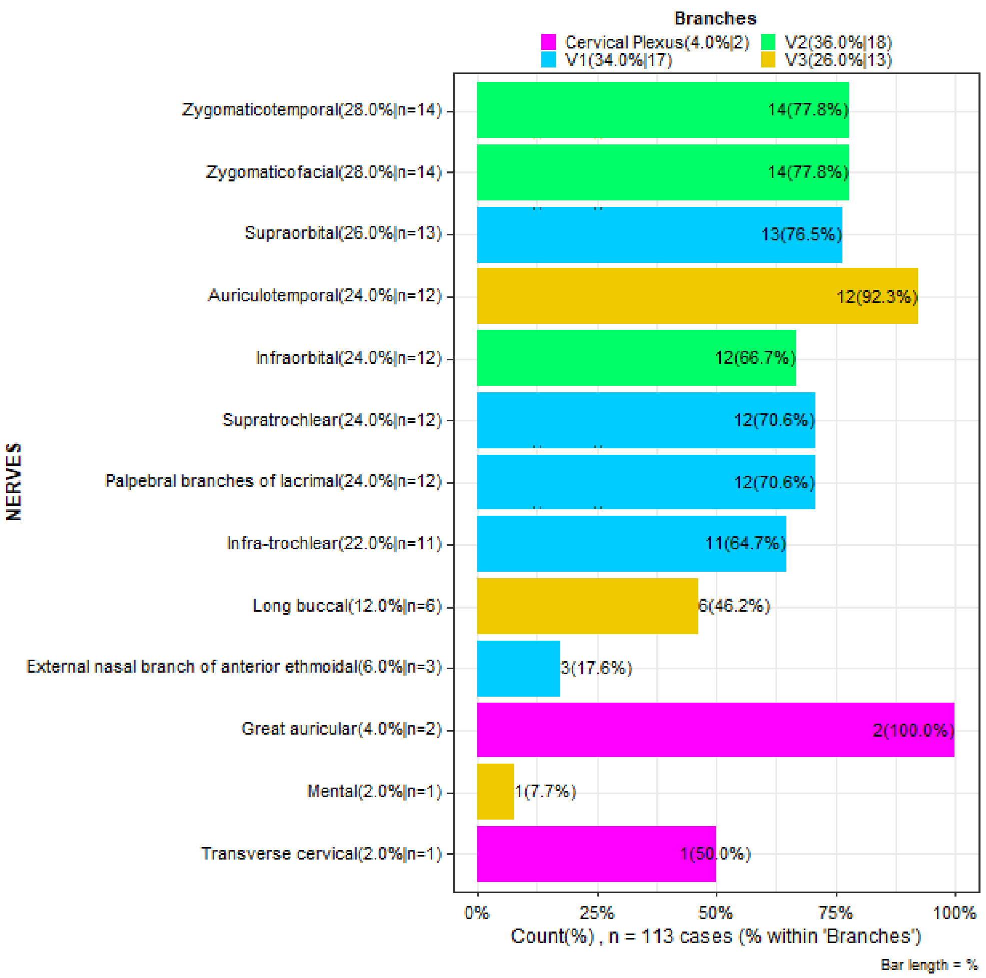

Figure 8: Incidence of trigeminal nerve and cervical plexus branches**.**

DISCUSSION

CMN is one of the most frequent skin lesions encountered at birth. The majority of CMN cases do not need treatment, but those that are highly visible, such as those on the face, neck, or hands, may be treated if patients are significantly bothered by them. Some need treatment due to it risks being malignant. Most importantly, the increased size of the nevi will cause the risk.

There has been no literature investigating the correlation between the distribution of CMN and the skin dermatomes. The results of this study indicate that there is a perceptible correlation between CMN and selected dermatomal areas. This investigation reports that even if a CMN is absent throughout an entire dermatomal region, it shows pattern distribution.

Our investigation reports on interesting distribution patterns, one of which is in a small sample of patients (6.5%), where they presented with CMN on the face, which also ran down the ventral surface of the neck. We believe that CN V may have an association with the ventral rami of the cervical nerve, which could be the explanation for us having 2 of our patients affected by CMN from the face running selectively down the ventral part of the neck, showcased some association/overlaps of CN V with the ventral rami of the neck (cervical nerves). Otherwise, the CN V was affected independently, which probably has much to do with brachial arch formation and mesenchymal penetration (Ginsberg and Eicher, 2000).

In the head and neck region, the most common dermatomal combinations affected by CMN were V1, V2, and V3, accounting for 29.0% of cases. Sub-branch observations were also reported in these cases. The V1 and V2 dermatomes were the second most affected combinations, indicating that these two dermatomes are frequently affected together. These findings support the study by Vourc'h-Jourdain *et al.* (2013) that CMN are also mostly found in the head and neck region. We also found 10.5% of patients having CMN localized on a single dermatome. We then found that the zygomaticofacial, zygomaticotemporal, and supraorbital regions are the most common locations of CMN on the face. The fact that the zygomatic nerve has two branches, which include the zygomaticofacial and zygomaticotemporal, might be the reason for this (Von-Arx *et al.*, 2017). This means that CMN might impact both locations it innervates if this nerve is compromised.

Another association that was noted was with the dorsal of the neck and back region. Three of our patients demonstrated discernible distribution of CMN on the dorsal part of the neck running down the back region. Here, the cranial-caudal folding and tubularization of the plate at the fourth and seventh week of gestation may also be investigated, examining the association of the dorsal rami of the neck and back. This study revealed that the T10 dermatome is the most affected, with 58.1% of patients presenting CMN in this area.

This high prevalence of CMN in the T10 dermatome is a significant finding and may indicate a predilection for the trunk region around T10. Similarly, the T11 dermatome (54.8%) and T12 dermatome (51.6%) exhibited notable levels of CMN involvement. Understanding this preference could lead to further research into the factors influencing CMN distribution in the trunk region and its potential clinical implications. These findings supported the study by Vourc'h-Jourdain *et al.* (2013) and Nikfarjam and Chambers (2016) that CMN are also often mostly found in the trunk region, which can be the reason most of our patients have CMN on T10, T11, and T12. The back and trunk have a tendency to develop CMN; however, an understanding of this type of etiology is unknown and could be due to embryological development (Kroon et al.,1987).

The lumbar region showed that the L1 dermatome was the most affected (41.9%), whereas the L5 dermatome had the lowest prevalence (3.2%). This distribution in the lumbar region could be associated with the anatomy of the lower back, as there are other lesions like congenital dermal melanocytosis, which are commonly found in the lumbosacral area (Gupta and Thappa, 2013). In the sacral region, S3 was the most affected dermatome (22.6%), while S2 had the lowest prevalence (6.5%).

In contrast, among patients with CMN in the back region, all of the patients had it affecting three and above dermatomes. This suggests that in the back region, there is a lower prevalence of CMN localized on a single dermatome in the back region. The Trunk area was observed to have CMN affecting four and above but not exceeding 12 dermatomes. The Upper limbs exhibited CMN on 3 and 4 dermatomes, indicating a moderate level of distribution in this region. Similarly, the lower limbs were observed with CMN affecting 2, 3, and 5 dermatomes.

CONCLUSION

In conclusion, this study contributes valuable insights into the distribution patterns of CMN across dermatomes in various body regions. Furthermore, it also illustrates how selective CMN is, showcasing the possible explanation for CMN to be selective on the head and neck region through CN V association with ventral rami of cervical nerves with face (CN V) and dorsal rami of cervical nerves associated with the back region. CMN are also mostly found in the head and neck region, frequently in the region of V1 and V2 dermatomes, precisely zygomaticofacial, zygomaticotemporal, and supraorbital regions and at T10, T11, and T12 dermatomal regions on the trunk of the body. This study illustrates a discernible correlation between CMN and selected dermatomes. This insight, although not covering the entire dermatome, suggests that these CMNs do (in certain cases) run/follow a dermatomal pattern, requiring further investigation.

LIMITATIONS

The small sample size limited our ability to reach a comprehensive conclusion to determine whether these CMN ran in one dermatomal region.

REFERENCES

1 BRYSON AM, ZEA MD (2023) The Effects of Motor Fluency on Dressing Tasks and Decreasing Escape Behaviors. *Behavior Analysis in Practice,* 17(1): 316–322.

2 CHALLOUMAS D, FERRO A, WALKER A, BRASSETT C (2018) Observations on the inconsistency of dermatome maps and its effect on knowledge and confidence in clinical students. *Clinical anatomy (New York, N.Y.)*, 31(2): 293–300.

3 DE WIJN RS, ZAAL LH, HENNEKAM RCM, VAN DER HORST CMAM (2010) Familial clustering of giant congenital melanocytic nevi. *Journal of plastic, reconstructive & aesthetic surgery: JPRAS*, 63(6): 906–913.

4 Downs MB, Laporte C (2011) Conflicting dermatome maps: Educational and clinical implications. *The Journal of orthopaedic and sports physical therapy*, 41(6): 427–434.

5 FARABI B, AKAY BN, GOLDUST M, WOLLINA U, ATAK MF, RAO B (2021) Congenital melanocytic naevi: An up-to-date overview. *The Australasian journal of dermatology,* 62(2): e178–e191.

6 Goldstein B (2001) Anatomy of the peripheral nervous system. *Physical medicine and rehabilitation clinics of North America*, 12(2): 207–236.

7 GUPTA D, THAPPA DM (2013) Mongolian spots: How important are they? *World journal of clinical cases*, 1(8): 230–232.

8 HALE EK, STEIN J, BEN-PORAT L, PANAGEAS KS, EICHENBAUM MS, MARGHOOB AA, OSMAN I, KOPF AW, POLSKY D (2005) Association of melanoma

and neurocutaneous melanocytosis with large congenital melanocytic naevi-results from the NYU-LCMN registry. *The British journal of dermatology*, 152(3): 512–517.

9 IBELLI TJ, KLEINMAN E, SCOPE A (2021) Novel classification system and surgical algorithm for facial congenital melanocytic nevi. *Journal of oral and maxillofacial surgery: official journal of the American Association of Oral and Maxillofacial Surgeons*, 79(10): e11–e12.

10 KAISER JT, LUGO-PICO JG (2023) Neuroanatomy, Spinal Nerves. In *StatPearls*. StatPearls Publishing.

11 KROON S, CLEMMENSEN OJ, HASTRUP N (1987) Incidence of congenital melanocytic nevi in newborn babies in Denmark. *Journal of the American Academy of Dermatology*, 17(3): 422–426.

12 LEE MWL, MCPHEE RW, STRINGER MD (2008) An evidence-based approach to human dermatomes. *Clinical anatomy (New York, N.Y.)*, 21(5): 363–373.

13 MACNEAL P, PATEL BC (2023) Congenital Melanocytic Nevi. *In: StatPearls. StatPearls Publishing, Treasure Island (FL)*. PMID: 33085315.

14 MORT RL, JACKSON IJ, PATTON EE (2015) The melanocyte lineage in development and disease. *Development (Cambridge, England)*, 142(7): 1387–1387.

15 NAVARRO-FERNANDEZ IN, MAHABAL GD (2023) Congenital Nevus. *Pathology of Melanocytic Disorders*, 2: 167–193.

16 NIKFARJAM J, CHAMBERS E. (2016) Congenital melanocytic nevi and the risk of malignant melanoma: Establishing a guideline for primary-care physicians. *The Einstein journal of biology and medicine: EJBM*, 27(2): 59.

17 PATTON, H.D. ET AL. (1976) Introduction to basic neurology. *W B Saunders*.

18 PRESCHER H, CORCORAN JF, BAUER BS (2023) Congenital Nevi. *In Pediatric Surgery. Cham: Springer International Publishing*, pp. 593–607.

19 PRICE HN, SCHAFFER JV (2010) Congenital melanocytic nevi - when to worry and how to treat: Facts and controversies. *Clinics in Dermatology*, 28(3): 293-302

20 RINKOFF S, ADLARD RE (2023) Embryology, craniofacial growth, and development. *In: StatPearls. StatPearls Publishing, Treasure Island (FL)*. PMID: 34283522.

21 SAIDA T (2019) Histogenesis of cutaneous malignant melanoma: The vast majority do not develop from melanocytic nevus but arise de novo as melanoma in situ. *The journal of dermatology*, 46(2): 80–94.

22 SOMMER L (2018) Developmental biology of melanocytes. *in Melanoma. New York, NY: Springer New York*, pp. 1–17.

23 STECCO C, PIRRI C, FEDE C, FAN C, GIORDANI F, STECCO L, FOTI C, DE CARO R (2019) Dermatome and fasciatome. *Clinical anatomy (New York, N.Y.)*, 32(7): 896–902.

24 THOMAS AJ, ERICKSON CA (2008) The making of a melanocyte: the specification of melanoblasts from the neural crest. *Pigment cell & melanoma research*, 21(6): 598–610.

25 VANDAMME N, BERX G (2019) From neural crest cells to melanocytes: cellular plasticity during development and beyond. *Cellular and molecular life sciences: CMLS*, 76(10): 1919–1934.

26 VOURC'H-JOURDAIN M, MARTIN L, BARBAROT S (2013) Large congenital melanocytic nevi: Therapeutic management and melanoma risk. *Journal of the American Academy of Dermatology*, 68(3): 493-498.e14.

27 WHITMAN PA, LAUNICO MV, ADIGUN OO (2023) Anatomy, Skin, Dermatomes. *StatPearls Publishing*.

CHAPTER 3

SYNTHESIS, CONCLUSION AND RECOMMENDATION

Interface

Chapter 3 analysed the facial distribution of CMN and assessed its potential correlation with dermatomal patterns. It analyses the CMN distribution distributions on the head and neck to assess whether this CMN has any relation to the dermatomal distribution of CN V.

Contributions of this chapter

The following chapter critically analyses and discusses the findings of Chapters 2 and concluded the findings on the potential correlation between the dermatomes and the distribution of CMN. Limitations encountered during the study as well as possible areas for future research, are outlined.

3.1 SYNTHESIS

Congenital melanocytic nevi (CMN) are pigmented lesions usually present at birth or develop within the first few months after birth. These lesions have a distinct patterned distribution on the skin. This study explored some of the potential dermatomes that CMN could be following.

This observational descriptive study analysed the correlation of CMN distribution on the head, neck, trunk, back, and limbs with the dermatomes of these areas. Analyses were conducted in two (2) subsets. Clinical photographs of patients diagnosed with CMN (>1.5cm) obtained from the database of the Department of Plastic and Reconstructive Surgery at Inkosi Albert Luthuli Central Hospital (IALCH) between 2000 and 2023 were analysed. The first subset (subset I; n= 31) investigated the correlation between the CMN on the overall body and the body dermatomes adopting the dermatomal map of Patton et al. (1976) (Fig. 1). The second subset (subset II; n= 19) documented patients with CMN on the head and neck, and investigated the correlation of CMN and facial dermatomes (Trigeminal nerve) distribution using Figure 2.

Subset 1

This study was based on the hypothesis that the CMN follows the distribution pattern of the dermatomes, and the results indicated a perceptible distribution, as it was found present in selected certain dermatomes. This study revealed that the thorax (T10) dermatome is most affected by CMN (58.1 %) and may indicate a predilection of CMN for the trunk region. Similarly, the T11 dermatome (54.8 %) and T12 dermatome (51.6 %) exhibited notable levels of CMN presence. Understanding this preference of the T10 dermatome may lead to further research into the factors influencing CMN distribution in this specific trunk region, such as its embryology and the spinal roots (dermatome) around the trunk region. These findings support the studies by Arneja and Gosain (2005) and Vourc'h-Jourdain et al. (2013) that CMN are often found in the trunk region, which corroborates the findings in our study where most of our patients presented with CMN in T10, T11, and T12 dermatomal regions. This study illustrates that CMN tend to present on the back and trunk; however, an understanding of this type of etiology is unknown, and it could be due to embryological development (Kroon et al.,1987).

According to Martins da Silva et al. (2017), CMN can be recognized in 6 repeated patterns (6B rule) (Patterns of distribution for CMN), one of which was the Bolero pattern (upper back and neck), which was recognized in this study (3 patients showed a trend of CMN presenting on the upper aspect of back including neck). This study hypothesizes that the pattern occurs due to the embryological development during cranial-caudal folding and tubularization of the plate at the fourth and seventh week of gestation and the overlapping of dorsal rami of the neck with dorsal spinal rami. This investigation paves the way for exploring the association of the dorsal rami of cervical nerves with the dermatomes of the back region, as the CMN was noted to be selective on those cutaneous innervation areas.

Furthermore, another pattern observed in this study was where the CMN were found running from the face down to the anterior part of the neck. This could be explained by an association between the ventral rami of the cervical nerve (cervical plexus) and CN V. The CMN could have followed the nerve branch from the cervical plexus, the greater auricular nerve which innervates the lower margin of the mandible and the skin over the parotid gland, and ran down to the neck via dermatomes (Rinkoff and Adlard, 2023). Another possible explanation is embryonic development and neural crest cells. Melanocytes are derived from neural crest cells that migrate from the neural tube. These neural crest cells migrate along specific pathways and spread across the skin. Dermatomes, which are areas of skin innervated by a single spinal nerve root, represent the segments of the body that these neural crest cells influence. If melanocyte migration is disrupted or abnormal in certain regions, it could lead to the formation of CMN in patterns that correspond to dermatomes (Jin et al., 2023).

Subset 2

The second part of this study investigated the distribution of CMN with the cutaneous branches of CN V (dermatomes of the face).

Dermatological or cosmetic issues are extremely sensitive topics, having a major impact on the perception and treatment in society (Macneal and Patel, 2023). CMN-specific individuals, especially children, may endure neurological issues, skin-related discomfort, or high levels of perceived stigmatization and psychological adjustment and, therefore, may require special monitoring and psychological support (Masnari et al., 2019). The dermatomes or the skin distribution of CN V on the face and its association with the CMN have not been previously published.

The main hypothesis of this study was that CMN follows the distribution pattern of the CN V branches. It does not provide a definitive solution, but the CMN did present itself in several dermatome branches of CN V with a discernible distribution. According to this study, the most common locations for CMN on the face were the zygomaticofacial, zygomaticotemporal, and supraorbital areas of distribution. In the present study, the fact that the zygomaticofacial and zygomaticotemporal are branches of the zygomatic nerve may be the reason for CMN to affect both these areas as they come from the same main nerve (Shafique and Das, 2023).

3.2 CONCLUSION

The correlation of the dermatomes and CMN distribution is a unique notion that has not been studied previously. The aim of this study was to investigate whether CMN distribution correlates with dermatomes of the body and face. The findings revealed that specific dermatomes, including the T10 dermatome, were more susceptible to CMN. This means CMN are more commonly located in the lower thorax. This aligned with previous studies emphasizing the predominance of CMN in the lower back and trunk region (Kroon et al.,1987). For the facial region, different dermatomes showed different patterns of CMN prevalence; the areas most impacted were the zygomaticotemporal and zygomaticofacial regions. This pattern of distribution indicates that there may have been an embryological relation that influenced the preferred development of CMN in certain parts of the face during the maxillary processes of fusing, which is another hypothesis that could be applied to this study. The study paves the way for exploring the association of ventral rami of cervical nerves and the CN V distribution through the selective distribution behaviour of CMN that was noted on the face and neck. This shows that the overlaps of these nerves (ventral rami of cervical plexus and CN V) can be an explanation for the selective distribution of CMN in these connecting regions. This study presented a perceptible distribution of CMN, which supports the idea that CMN correlates with the dermatomes.

3.3 Recommendations and suggestions for future studies

Further studies with a larger sample sizes are recommended to investigate the correlation of CMN distribution on the face or the body with dermatomal patterns. The type of dermatomal map utilized should be taken into consideration when conducting this type of study.

3.4 LIMITATIONS

The current study had a limited sample size, which limited our abilty to draw conclusions about the direct relationship between dermatome patterns in the human body and the distribution of the CMN. Only patients from a single plastic surgery clinic were utilized.

3.5 REFERENCES

1 Arneja, J. S. and Gosain, A. K. (2005) “Giant congenital melanocytic nevi of the trunk and an algorithm for treatment,” The journal of craniofacial surgery, 16(5), pp. 886–893. doi: 10.1097/01.scs.0000183356.41637.f5.

2 Jin, Q. et al. (2023) “Referred pain: characteristics, possible mechanisms, and clinical management,” Frontiers in neurology, 14. doi: 10.3389/fneur.2023.1104817.

3 Kroon, S., Clemmensen, O. J. and Hastrup, N. (1987) “Incidence of congenital melanocytic nevi in newborn babies in Denmark,” Journal of the American Academy of Dermatology, 17(3), pp. 422–426. doi: 10.1016/s0190-9622(87)70223-0.

4 Macneal, P. and Patel, B. C. (2023) “Congenital Melanocytic Nevi,” StatPearls.

5 Martins da Silva, V. P. et al. (2017) “Patterns of distribution of giant congenital melanocytic nevi (GCMN): The 6B rule,” Journal of the American Academy of Dermatology, 76(4), pp. 689–694. doi: 10.1016/j.jaad.2016.05.042.

6 Masnari, O. et al. (2019) “Predictors of health-related quality of life and psychological adjustment in children and adolescents with congenital melanocytic nevi: Analysis of parent reports,” Journal of pediatric psychology, 44(6), pp. 714–725. doi: 10.1093/jpepsy/jsz017.

7 Rinkoff, S. and Adlard, R. E. (2023) Embryology, craniofacial growth, and development. StatPearls Publishing.

8 Shafique, S. and Das, J. M. (2023) Anatomy, head and neck, maxillary nerve. StatPearls Publishing.

9 Vourc, H.-J., Martin, M. and Barbarot, L. (2013) “Large congenital melanocytic nevi: Therapeutic management and melanoma risk: A systematic review,” Journal of the American Academy of Dermatology, 68(3), pp. 493–498.

APPENDICES

Appendix A: Journal submission

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Editorial Decision

Accepted
03/09/2024 1 0:51
31st July 2024

Dear Dr. Lazarus,

Thank you for the opportunity to review your manuscript for European Journal of Anatomy. The reviewers and I concur that your manuscript has been accepted with no further changes.

Sincerely yours,

J Safiudo
Former Editor-in-Chief of EJA

Appendix B: Full ethical approval

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

28 October 2022

Mr Siphelele Nkosi (218012656)
School of Lab Med & Medical Sc
Westville

Dear Mr Nkosi,

Protocol reference number: BREC/00004680/2022
Project title: Giant Congenital Melanocytic Nevi: Patterns of Presentation
Degree: MMedSc

EXPEDITED APPLICATION: APPROVAL LETTER

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application.

The conditions have been met and the study is given full ethics approval and may begin as from 28 October 2022. Please ensure that any outstanding site permissions are obtained and forwarded to BREC for approval before commencing research at a site.

This approval is valid for one year from 28 October 2022. To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on RIG on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2020) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be noted by a full Committee at its next meeting taking place on 13 December 2022.

Yours sincerely,

[redacted]

Prof D Wassenaar
Chair: Biomedical Research Ethics Committee

Biomedical Research Ethics Committee
Chair: Professor D R Wassenaar
UKZN Research Ethics Office Westville Campus, Govan Mbeki Building
Postal Address: Private Bag X54001, Durban 4000
Email: BREC@ukzn.ac.za
Website: http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx

Founding Campuses: Edgewood | Howard College | Medical School | Pietermaritzburg | Westville

INSPIRING GREATNESS

Appendix C: IALCH Gatekeeper permission

health

Department:
Health
PROVINCE OF KWAZULU-NATAL

Inkosi Albert Luthuli Central Hospital
Department of Plastic & Reconstructive Surgery
Private Bag X 03, Mayville, 4058
800 Vuzi Mzimele Road, Mayville, 4091
Tel.: 031 240 1171
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Email.:madaree@ukzn.ac.za
www.kznhealth.gov.za

28 August 2022

Dr Linda Mtshali
Medical Manager
Medical Service
Inkosi Albert Luthuli Central Hospital

RE: PERMISSION GRANTED TO CARRY OUT RESEARCH WORK AT IALCH – SIPHELELE NKOSI

This letter serves to notify you that permission is granted to Siphelele Nkosi to carry out research in Masters in Medical Science entitled "Giant congenital melanocytic nevi: Patterns of presentation" at the Inkosi Albert Luthuli hospital.

The research will have no cost implication to the IALCH institution.

Yours sincerely

[redacted]

PROF ANIL MADAREE
Head of Department, Plastic & Reconstructive Surgery

uMnyango Wezempilo . Departement van Gesondheid

Fighting Disease, Fighting Poverty, Giving Hope

Appendix D: DOH Permission

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

DIRECTORATE:

Physical Address: 330 Langalibalele Street, Pietermaritzburg
Postal Address: Private Bag X9051
Tel: 033 395 2805/ 3189/ 3123 Fax: 033 394 3782
Email: [illegible]
www.kznhealth.gov.za

Health Research & Knowledge Management

NHRD Ref: KZ_202210_015

Dear Mr S Nkosi
(UKZN)

Approval of research

1. The research proposal titled **'GIANT CONGENITAL MELANOCYTIC NEVI: PATTERNS OF PRESENTATION'** was reviewed by the KwaZulu-Natal Department of Health (KZN-DoH).

   The proposal is hereby **approved** for research to be undertaken at Inkosi Albert Luthuli Centre hospital.

2. You are requested to take note of the following:
   a. ***Kindly liaise with the facility manager BEFORE your research begins.***
   This is to ensure that conditions in the facility are conducive to the conduct of your research. These include, but are not limited to, an assurance that the numbers of patients attending the facility are sufficient to support your sample size requirements and that the space and physical infrastructure of the facility can accommodate the research team and any additional equipment required for the research.
   b. *All research conducted in KwaZulu-Natal must comply with government regulations relating to Covid-19. These include but are not limited to: regulations concerning social distancing, the wearing of personal protective equipment, and limitations on meetings and social gatherings.*
   c. *Please ensure that you provide your letter of ethics re-certification to this unit, when the current approval expires.*
   d. *Provide an interim progress report and final report (electronic and hard copies) when your research is complete to* ***HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200*** *and e-mail an electronic copy to* hrkm@kznhealth.gov.za
   e. *Please note that the Department of Health shall not be held liable for any injury that occurs as a result of this study.*

For any additional information please contact Dr. G Khumalo on 033-395 3189.

Yours Sincerely

[redacted]

Dr E Lutge
Chairperson, Provincial Health Research Committee
Date: 17/10/2022

Fighting Disease, Fighting Poverty, Giving Hope

Appendix E: Data sheet 1 sample

Patient number	Race	Age group	Gender	Dermatomes	Laterality	Location
1b	Black	Pediatric group	F	T10; T11; T12; L1; L2; L3; S3; S4; S5	Both	Back; Lower limbs
2b	Indian	Pediatric group	F			Head and neck
3b	Indian	Pediatric group	F	C4; C5; T1; T2; T3; T4; T5; T6; T7; T8; T9; T10	Both	Back; Head and neck
4b	Indian	Pediatric group	F			Head and neck
5b	Black	Pediatric group	F			Head and neck
6b	Indian	Middle age group	F			Head and neck
7b	Black	Pediatric group	M	T6; T7; T8; T9; T10; T11; T12; L1; L2; L3; L4; S1; S2; S3; S4; S5	Both	Back;Trunk
8b	Indian	Pediatric group	M			Head and neck
9b	Black	Pediatric group	M			Head and neck
10b	Black	Young group	F	T10; T11; T12	Right	Back; Head and neck; Trunk; Upper limbs
11b	Black	Pediatric group	F	T8; T9; T10; T11; T12; L1; L2; L3; L4; S1; S3; S4; S5	Both	Back; Trunk
12b	Black	Pediatric group	M			Head and neck
13b	Black	Pediatric group	M			Upper limbs
14b	Black	Pediatric group	M			Head and neck
15b	Black	Pediatric group	M			Head and neck
16b	Black	Pediatric group	M			Head and neck
17b	White	Middle age group	F	C3; C4; C5; T2; T3; T4; T5; T6; T7; T8; T9; T10; T11; T12	Both	Back
18b	Black	Young group	F			Head and neck
19b	Indian	Pediatric group	M			Head and neck
20b	Black	Pediatric group	M	C3; C4; C5; T2; T3; T; 4; T5; T6; T7; T8; T9; T10; T11; T12; L1; L2; L3; L4; S1; S3	Both	Back; Trunk; Upper limbs
21b	Black	Pediatric group	M			Head and neck
22b	Black	Pediatric group	F	T8; T9; T10; T11; T12; L1; L2; L3; L4; S3; S4; S5	Both	Back
23b	Indian	Pediatric group	F	T6; T7; T8; T9; T10; T11; T12; L1; L2; L3; L4; S1; S2; S3; S4; S5	Both	Back; Trunk
24b	Indian	Pediatric group	M	C3; C4; C5; T2; T3; T4; T5; T6; T7; T8; T9; T10; T11	Both	Back

Appendix F: Data sheet 2 sample

Head & Neck					
No. of patients	***Race***	***Age group***	***Gender***	***Dermatomes***	***Laterality***
1					
2	Indian	Pediatric group	F	V1 V2	Right
3	Indian	Pediatric group	F	C3	Both
4	Indian	Pediatric group	F	V1 V2 V3	Right
5	Black	Pediatric group	F	V1	Both
6	Indian	Middle age group	F	V3	Right
7					
8	Indian	Pediatric group	M	V1 V2	Right
9	Black	Pediatric group	M	V1 V2	Left
10	Black	Young group	F	V2 V3	Right
11					
12	Black	Pediatric group	M	C2 C3	Both
13					
14	Black	Pediatric group	M	V1 V2	Left
15	Black	Pediatric group	M	V3 C3	Right
16	Black	Pediatric group	M	V1 V2 V3	Left
17					
18	Black	Young group	F	V1 V2	both
19	Indian	Pediatric group	M	V2 V3	Right
20					
21	Black	Pediatric group	M	V1 V2	Left
22					
23					
24					
25					
26					
27	Black	Pediatric group	F	V1 V2 V3	Right
28	Indian	Pediatric group	M	V3 C3	Both
29	Black	Pediatric group	M	V1 V2	Left
30					
31	Black	Young group	M	V1	Right

Appendix G: Data sheet 3 sample

Patient	Branches	Nerves	Finding	Laterality	Gender	Age group	Race	IOA
2	V1	Supraorbital		Right	F	Pediatric group	Indian	Agree
2	V1	Supratrochlear	A	Right	F	Pediatric group	Indian	Agree
2	V1	Infra-trochlear	A	Right	F	Pediatric group	Indian	Agree
2	V1	Palpebral branches of lacrimal		Right	F	Pediatric group	Indian	Agree
2	V1	External nasal branch of anterior ethmoidal	A	Right	F	Pediatric group	Indian	Agree
2	V2	Infraorbital	A	Right	F	Pediatric group	Indian	Agree
2	V2	Zygomaticofacial	A	Right	F	Pediatric group	Indian	Agree
2	V2	Zygomaticotemporal		Right	F	Pediatric group	Indian	Disagree
2	V3	Auriculotemporal		Right	F	Pediatric group	Indian	Agree
2	V3	Long buccal		Right	F	Pediatric group	Indian	Agree
2	V3	Mental		Right	F	Pediatric group	Indian	Agree
2	V3	Mental branch of mylohyoid		Right	F	Pediatric group	Indian	Agree
2	Cervical Plexus	Great auricular		Right	F	Pediatric group	Indian	Agree
2	Cervical Plexus	Transverse cervical		Right	F	Pediatric group	Indian	Agree

Appendix H: Turnitin report

ANATOMICAL PATTERNS OF PRESENTATION OF CONGENITAL MELANOCYTIC NEVI

ORIGINALITY REPORT

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