EXPRESSION OF GENETIC PERIPHERAL NEUROPATHIES IN SOUTHERN AFRICAN CHILDREN

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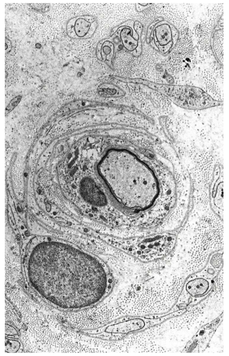
Introduction

- Peripheral neuropathies are a group of disorders of the peripheral motor, sensory and autonomic nerves
- Globally, an estimated 2-7% of the adults and children suffer from acquired and hereditary peripheral neuropathy (1).
- Genetic peripheral neuropathies are described in European ancestries, with a population prevalence of 1:2500 1:10000. In variance, these diseases are under reported and poorly understood in African populations.



Nerve Biopsy

- Few facilities in local setting have access to comprehensive molecular genetic work up
  - rely on clinical, neurophysiology and histology for a diagnosis.
- Sural nerve biopsy aid diagnosis and extent of nerve damage
  - Consider when clinical and electrophysiological data inadequate and pathogenic genes are not identified
- Peripheral nerve maturation occur between birth and 5 years
  - in fiber density, myelination fiber size and myelin thickness (20).
  - this impact normal ranges for NCS / histology interpretation

Methods

- A hospital based retrospective crosssectional study was conducted at Red Cross War Memorial Children's Hospital (RCWMH) in Cape Town, South Africa.
- From a database of 8850 children managed in the neurology service at RCWMH (2001-2023), 691 attended the neuromuscular service; of this group 196 had acquired or genetic peripheral neuropathies.
- Diagnostic work-up consisted of clinical phenotype, nerve conduction studies, family history and where available histology and limited genetics screens.

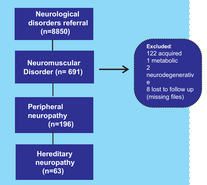


Table 4. Gene variants for 12 children with peripheral neuropathy

Case	Official symbol	Genomic Reference	Transcript Reference	Gene variants	Assembly	Chromosone	Location
A,B, C, D, E, F, G	PMP22	NG_007949.1	NM_000304.3	-	GRCh38.p14 (GCF_000001405.40)	17	NC_000017.11 (15229779..15265326, complement)
H	IGHMBP2	L361P	NM_0021180.2		GRCh38.p14 (GCF_000001405.40)	11	NC_000011.10 (68903891..68940601)
I	IGHMBP2		NM_0021180.2	-	GRCh38.p14 (GCF_000001405.40)	11	NC_000011.10 (68903891..68940601)
J	SLC12A6	LRG_270	NM_133647.1	c.3031C>t(p.R1011X; p.Arg1011Ter)	GRCh37	15	
K	SLC52A3	LRG_1394	NM_033409.3		(GRCh37/hg19	20	
L	MFN2	LRG_255	NM_014874.3	p.Arg104Trp(c.310C>T)	GRCh38.p14 (GCF_000001405.40)	1	NC_000001.11 (11980444..12013508)

CMT - Clinical features

- Heterogenous and slowly progressive.
- Common presenting symptoms include motor weakness and muscular atrophy affecting the feet, legs and hands
- But can have specific "markers"
  - marked sensory involvement
  - visual or hearing impairment
  - respiratory compromise
  - impaired speech and dysphagia
  - scoliosis
  - structural changes of the central nervous system with pyramidal signs and intellectual disability

Genetics

- Neuropathy genes have various function, including genes directly linked to
  - development
  - function
  - maintenance of Schwann cells, myelin sheaths, neurons and their axons.
- > 50% of peripheral myelin = 4 proteins:
  - myelin basic protein (MBP),
  - myelin protein zero (MPZ),
  - peripheral myelin protein 2 (PMP2)
  - peripheral myelin protein 22 (PMP22)

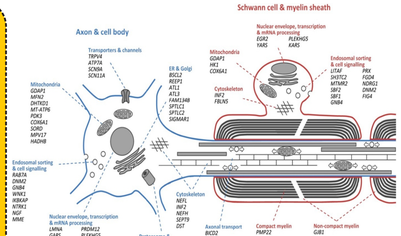


Figure 2: Proposed pathomechanisms of gene products in hereditary neuropathies. Genes causing axonal CMT or dHMN are marked in blue, genes causing demyelinating CMT are marked in red (9)

Demographics characteristics of 63 children

	Axonal (n=50, 79.4%)	Demyelinating (n=13,20.6%)	P value
Age onset symptoms (months)	39.1(SD 36.3)	40.8 (SD 30)	0.4
Age at diagnosis (months)	(N=35) 79.9 (SD 51.1)	(N=9) 127.1 (SD 138.04)	0.05
Sex			
Male	23 (76.6)	7 (23.3)	0.75
Female	26 (81.3)	6 (18.8)	
Ancestry			
African	11 (91.7)	1 (8.3)	-
Asian	1 (100)	0	
European	21 (87.5)	3 (13.5)	
Mixed	17 (65.4)	9 (34.6)	
Family history			
Yes	18 (75)	6 (25)	0.53
No	32 (82.1)	7 (17.8)	

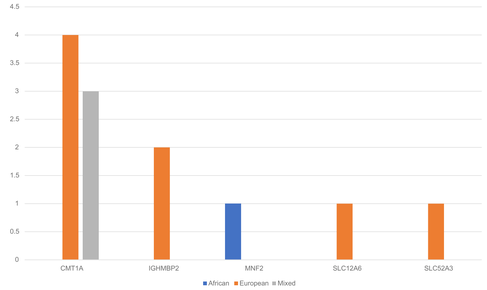


Figure 2: Genetic confirmed causes for peripheral neuropathy for 12 children by ethnicity.

Conclusion

- Axonal peripheral neuropathy is the most common genetic neuropathy manifesting in children of African ancestry in South Africa.
- CMT1A was not identified in children of African ancestry.
- The difference in genetic variants from those described elsewhere, will enable future directions for research and ideally targeted disease-modifying treatment options.

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Pathophysiology CMT

CMT was previously broadly categorized into 3 processes:

A predominant demyelinating process resulting in low conduction velocities (CMT1 & 4),

A predominant axonal process resulting in low potential amplitudes (CMT2)

An intermediate type where individuals demonstrate signs of both demyelination and axonal degeneration I -CMT.

OBJECTIVES

Aim:

To understand the spectrum of definite, probable and suspected hereditary peripheral neuropathy among children presenting with neuromuscular disorders from an African setting.

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Objective:

To compare clinical phenotype neurophysiology, histology and where available genetic variants of children with hereditary peripheral neuropathy

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