MPV17 and the mitochondrial genetic landscape in South Africa - the way forward

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INTRODUCTION

Mitochondrial disorders form one of the largest groups of inborn errors of metabolism. The birth prevalence is estimated at 1 in 5000[1] in well-studied populations, but little has been reported from Sub-Saharan Africa. The National Health Laboratory Services (NHLS) Inherited Metabolic Diseases (IMD) Laboratory in Cape Town, South Africa, has served as the primary referral diagnostic laboratory for mitochondrial disease genetics in South Africa, population 60 million, since 1991.

AIMS AND OBJECTIVES

To describe the mitochondrial and nuclear genetic variants found to cause mitochondrial disorders in the South African population from 1994 -2023 and to use this information to plan locally relevant prospective research.

METHODS

An audit was performed on all mitochondrial disease genetic testing performed in Cape Town, South Africa between 1994 and 2023. Request forms were retrieved and all available clinical data, as well as demographic and referral information was captured and analysed. Haplogroup context was captured for all positive cases, where this was available from diagnostic data or an associated NGS based study.

RESULTS

1950 samples were tested. There were 206 (10.6%) positive results.

Pathogenic mtDNA variants n = 135/206 (65.5%).

- **MELAS** (mitochondrial encephalopathy with lactic acidosis and stroke-like episodes), n = 42/135 (31%)
- **LHON** (Leber's hereditary optic neuropathy), n= 31/135, (23%)
- **Single large mtDNA deletions**, n= 27 (20%)/135.

RESULTS (continued)

Sixty six of 71 nDNA-positive results were homozygous (65 cases) or compound heterozygous (1 case) for the MPV17 pathogenic variant c.106C>T (p.[Gln36Ter, Ser25Profs*49]), causing MPV17 neurohepatopathy. Other nDNA variants were in POLG, TAZ1, CPT2, BOLA3 and SERAC1 . None were identified in SURF1 and PDHA1.

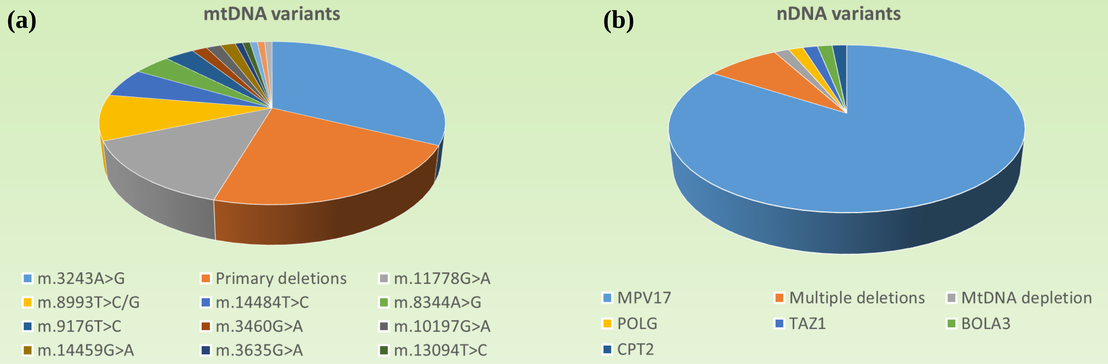

Fig. 1. Distribution of (a) mtDNA pathogenic variants, and (b) nDNA defects detected in the NHLS IMD mitochondrial disease cohort between 1994 and 2023.

Haplogroups were obtained for 82 patients, of which 67 had unique combinations of pathogenic mtDNA variants and haplogroup contexts.

L haplogroups accounted for 38/67 (56%) of the positive cohort.

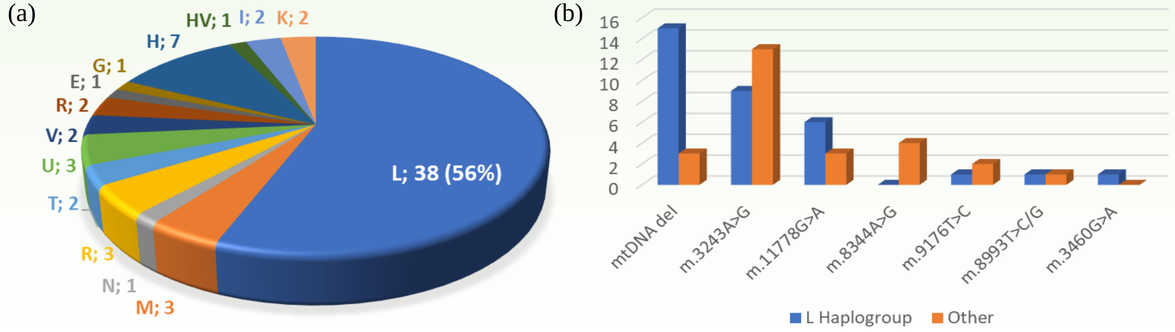

Fig. 2. graphs showing (a) the distribution of unique haplogroup/variant combinations detected across all mtDNA positive cases , regardless of the specific variants, and (b) the prevalence of L haplogroups for individual common mtDNA variants in the same cohort

CONCLUSIONS

This data represents the largest, most diverse cohort of patients with mitochondrial disease reported from Africa.

The finding of a large group of infants with a novel homozygous variant causing severe hepatocerebral disease in a non-consanguineous population emphasizes the importance of studying local populations for possible founder effects.

This data further confirms the presence of common pathogenic mtDNA variants in a Sub-Saharan African population in the context of L haplogroups for the first time. Haplogroup L is the root of the mtDNA phylogenetic tree, arising in Africa. This haplogroup is underrepresented in mitochondrial databases.

Haplogroup context has been implicated in disease expression by altering protection, pathogenicity, clinical expression or penetrance.[2]

The scarcity of commonly described pathogenic nDNA variants may be due to reduced prevalence or insufficient testing, and it is therefore critical to develop diagnostic platforms on the African subcontinent to further explore this.

REFERENCES

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