Auditory Dysfunction in Primary Mitochondrial Diseases: Genotype-Specific Impacts

N. Koohi [1], S. Holmes [1], A. Male [1], D-E. Bamiou [2], R. Pitceathly [1], D. Kaski [1].
[1]Queen Square Institute Of Neurology, University College London - London (United Kingdom), [2]The Ear Institute, University College London - London (United Kingdom)

INTRODUCTION

Background:
- **Primary mitochondrial diseases (PMD)** are genetic disorders that impair energy production in cells, affecting high-energy organs like the **auditory system**.
- Hearing loss in PMD is **multifactorial**, involving damage to both **cochlear pathways** (peripheral hearing loss) and **neural/central auditory pathways** (central auditory dysfunction).
- The involvement of central auditory dysfunction means **traditional hearing aids** often provide little benefit, as they are primarily designed to address cochlear issues.
- PMD-related hearing impairment is progressive and can significantly affect communication and quality of life.

Objective:
- To **investigate auditory deficits** in PMD patients, particularly focusing on the **m.3243A>G/T mutation**, a common pathogenic variant associated with hearing loss.
- To explore **genotype-phenotype correlations**, providing insight into how specific genetic mutations affect hearing, and to inform **personalised auditory assessments** and management strategies.

METHOD

Study Design:
- Cross-sectional study with 72 adults diagnosed with PMD.

Participants:
- Grouped by genetic diagnosis:
  - m.3243A>G/T (n=41), other mtDNA variants (n=18), nuclear gene variants (n=6), and clinicopathological diagnoses (n=7).

Audiological Assessments:
- **PTA**: Air/bone conduction thresholds.
- **QSiN**: Signal-to-noise ratio (SNR) loss.
- **LiSN-S**: Spatial auditory processing.
- **ABR**: Auditory pathway function.
- **DPOAEs**: Cochlear function.

Cognitive & Disease Severity:
- **MoCA**: Cognitive status.
- **NMDAS**: Disease severity.

Statistical Analysis:
- **MANCOVA**: Compared groups by adjusting for age, cognition, and severity.
- **Logistic Regression**: Assessed genetic influences on hearing loss.

RESULTS

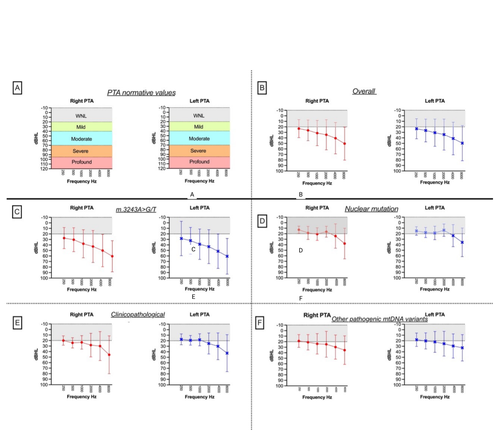


Figure 1: PTA Results in PMD Patients: Panels show PTA thresholds across various frequencies for right (red) and left (blue) ears, with data grouped by genetic mutations. The m.3243A>G/T group (*) exhibited significantly higher PTA scores compared to other groups. Error bars indicate standard deviations. MANCOVA revealed significant differences in PTA thresholds between genetic groups, controlling for age, cognition, and disease severity ($p < 0.001$).

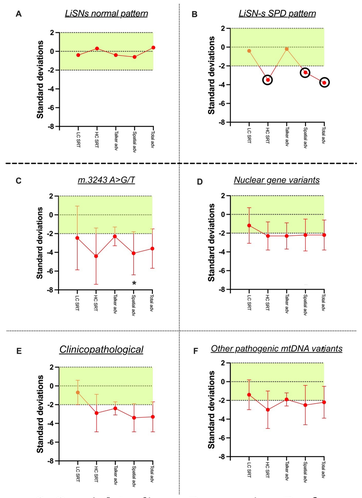


Figure 2: Spatial Auditory Processing Performance in PMD Patients: The figure shows LiSN-S test results, with performance across different test conditions. Panels C-F represent different genetic groups, with the m.3243A>G/T group (panel C) showing significantly lower spatial advantage scores compared to the nuclear gene variants (panel D) ($p = .025$). Error bars show standard errors.

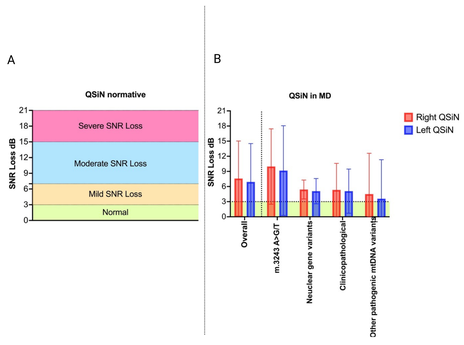


Figure 3: Quick Speech-in-Noise (QSiN) Performance in PMD Patients: The figure compares SNR loss in PMD patients to normative data. Panel B shows right (red) and left (blue) ear performance across different genetic groups. Error bars represent variability, and dotted lines indicate normative SNR loss ranges. MANCOVA analysis showed no significant differences across groups ($p > 0.5$).

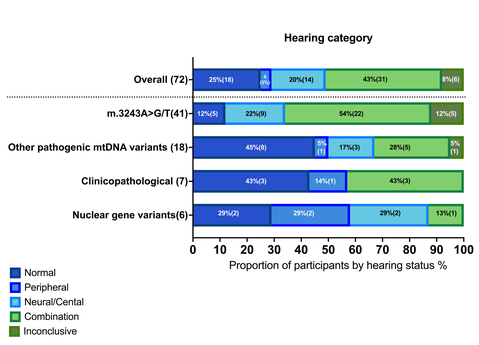
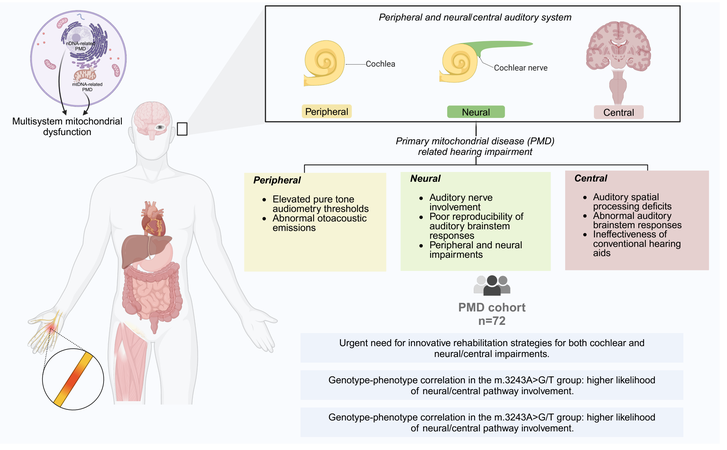


Figure 4: Prevalence of Hearing Impairment Types Across Diagnostic groups". Distribution of hearing impairment types including no impairment, neural/central, peripheral, peripheral & neural/central, and inconclusive across different diagnostic groups identified in mitochondrial disease patients. Each bar represents the percentage of individuals within a diagnostic group exhibiting a specific type of hearing function or impairment.

DISCUSSION

- **PMD-related hearing impairment** with specific **genotypes** affecting both **cochlear** and **central auditory** functions.
- The **m.3243A>G/T mutation** has a particularly strong impact, leading to significant hearing loss and central auditory processing deficits.
- **m.3243A>G/T group**:
  - Exhibited peripheral **hearing loss**.
  - Showed marked **spatial processing deficits** on the Listening in Spatialized Noise-Sentences (LiSN-S) test.
- **Central involvement**:
  - Abnormalities were found in the **ABR**, indicating issues in neural/central auditory pathways.
  - This suggests a **genotype-specific impact** on both peripheral and central auditory systems, particularly affecting spatial processing and brainstem function.
- **Personalised strategies needed**:
  - There is a need for **innovative rehabilitation approaches** that address both **cochlear** and **neural/central processing deficits** specific to genetic profiles like the m.3243A>G/T group.

CONCLUSION



REFERENCES

Kullar, P.J., Quail, J., Lindsey, P., Wilson, J.A., Horvath, R., Yu-Wai-Man, P., Gorman, G.S., Taylor, R.W., Ng, Y., McFarland, R., Moore, B.C., & Chinnery, P.F. (2016). "Both mitochondrial DNA and mitonuclear gene mutations cause hearing loss through cochlear dysfunction." *Brain, 139*(6), e33.
Santarelli, R., Cama, E., Scimemi, P., La Morgia, C., Valentino, M.L., Carelli, V. (2015). "OPA1-related auditory neuropathy: site of lesion and outcome of cochlear implantation." *Brain, 138*(3), 563-576.
Chinnery, P.F., Elliott, C., Green, G.R., Rees, A., Coulthard, A., Turnbull, D.M., & Griffiths, T.D. (2000). "The spectrum of hearing loss due to mitochondrial DNA defects." *Brain, 123*(Pt 1), 82-92.

ACKNOWLEDGMENT

We are grateful to the Lily foundation, and participants and families involved in this study.