Clinical and genetic complexity among patients with the progressive mitochondrial neurodegenerative disease LHON-Plus

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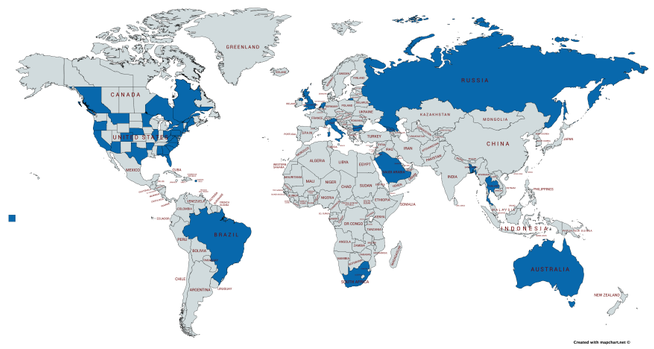
Introduction

The rare mitochondrial disease LHON-Plus (Leber's hereditary optic neuropathy-Plus) is a progressive neurodegenerative disease for which no curative treatment is available. LHON-Plus has a predominant adulthood onset and a gender bias with a female predominance. Patients harbor a maternally inherited pathogenic mitochondrial variant that affect the mitochondrial oxidative phosphorylation (OXPHOS) pathway, responsible for ATP synthesis. The three most prevalent mitochondrial variants for LHON-Plus, m.3460G>A, m.11778G>A, and m.14484T>C, map to mitochondrial genes encoding key subunits of the OXPHOS Complex I, resulting in Complex I deficiency and chronic energy deficit. Beside the well-documented predominant bilateral and subacute visual loss, the LHON-Plus extra-ocular symptoms remain scantily documented. This gap in knowledge has hampered our effort to design novel therapeutic strategies to mitigate mitochondrial dysfunction in LHON-Plus patients.

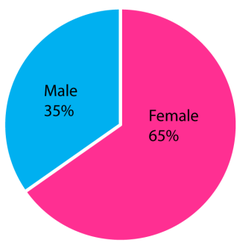
Therefore, we designed a comprehensive survey to assess the clinical spectrum among LHON-Plus patients using the only large international database from the LHON-Plus Global Project. About 120 patients filled the survey, which confirmed a female predominance among LHON-Plus patients with a 2 to 1 ratio. About 63% of the surveyed patients have a family history of LHON. Our survey revealed that LHON-Plus patients exhibit broad and heterogeneous clinical phenotypes with 65% of them having vision impairment. The two most frequent extra-ocular neurological symptoms are muscle weakness and hand tremors, while the two least frequent symptoms are bladder spams and seizures. Finally, our analysis on the correlation between the pathogenic mitochondrial variant and age of onset for symptoms revealed the unexpected finding that the three rare LHON-Plus mitochondrial variants, m.14459G>A, m.15512T>C, and m.14258G>A trigger early onset of symptoms between the age of 5 and 15. In contrast, the most frequent pathogenic mitochondrial variants have an adult onset.

In conclusion, our survey reveals phenotypic and genetic complexity among LHON-Plus patients. Moreover, LHON-Plus is not a mitochondrial disease limited to young adults, as three rare pathogenic mitochondrial variants trigger symptoms in pediatric patients. Our findings highlight the need to gain insight into the pathogenic mechanisms driving clinical heterogeneity with the objective to develop precise therapeutic strategies and interventions that can be applied on a patient-by-patient basis for personalized clinical care.

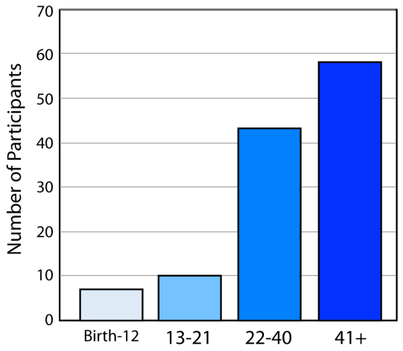
1 Demographics of our De-Identified Survey Using the Digital Platform of LHON-Plus Global Project



Gender Distribution of Survey Participants



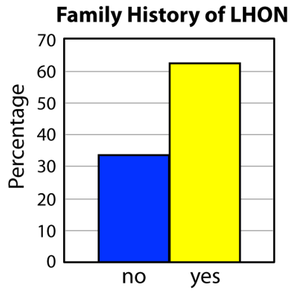
Age Distribution of Survey Participants



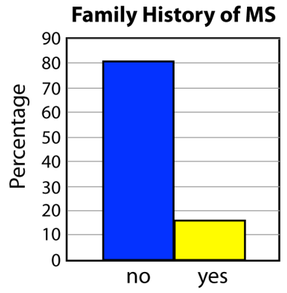
This online survey was performed in compliance with the tenets of the Declaration of Helsinki and the institutional board approval was obtained from the Office of Human Research at the Children's National Medical Center.

2 Most Participants with LHON-Plus Have a Family History with LHON

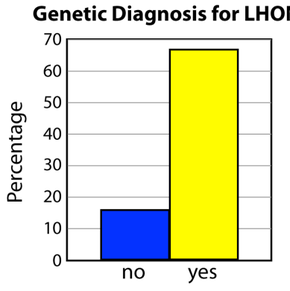
Family History of LHON



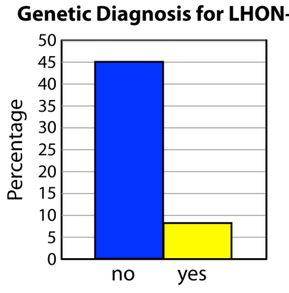
Family History of MS



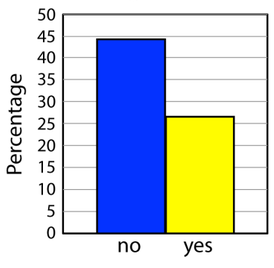
Genetic Diagnosis for LHON



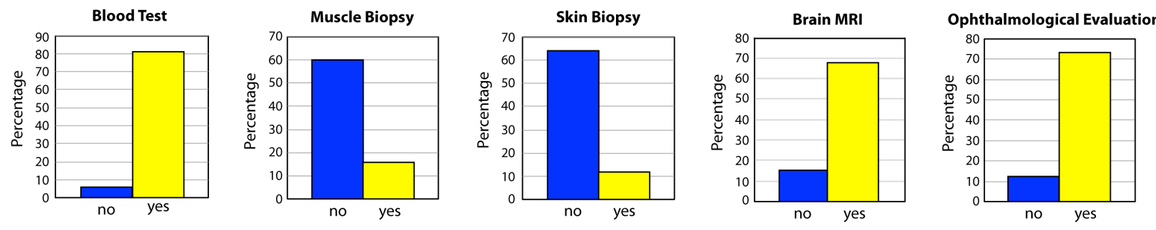
Genetic Diagnosis for LHON-MS



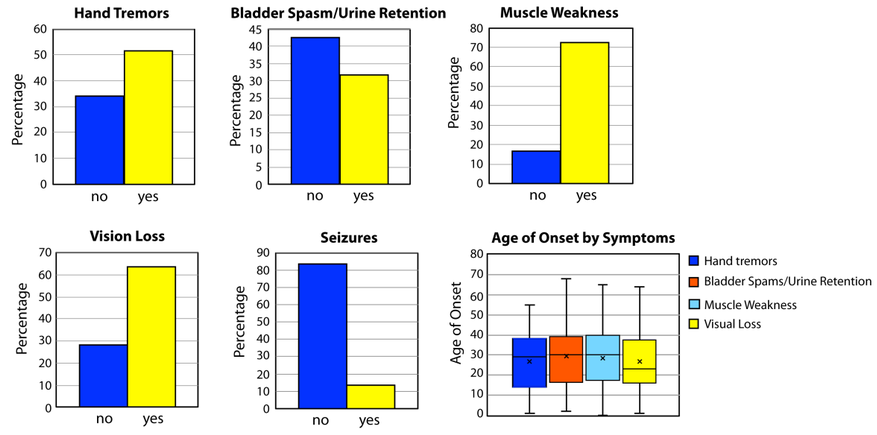
Genetic Diagnosis for LHON-Plus



4 The Clinical Diagnosis of LHON-Plus Patients Mostly Involves Blood Test, Brain MRI and Ophthalmological Evaluation

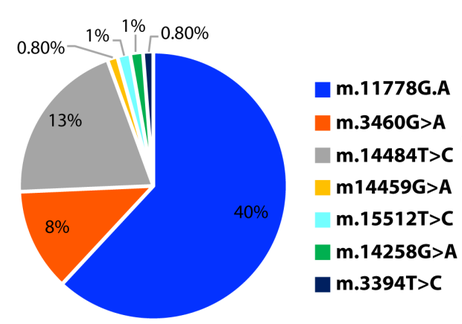


5 Broad and Heterogeneous Clinical Phenotypes Exhibited by LHON-Plus Patients

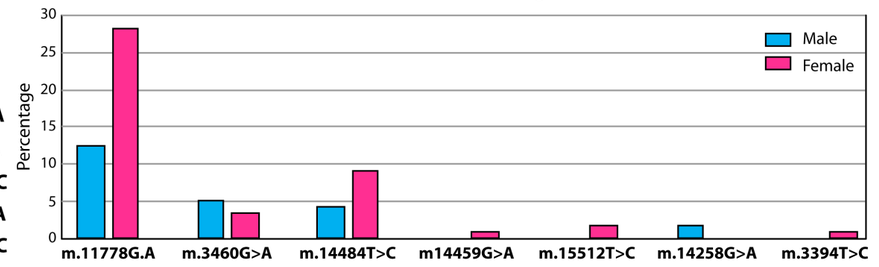


6 Frequency and Gender Distribution of Mitochondrial Variants Causing LHON-PLus

Frequency of Mitochondrial Variants

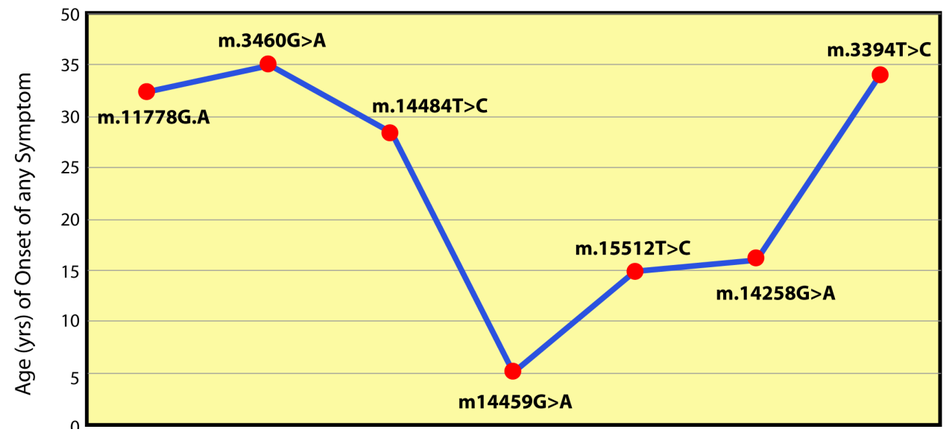


Gender Distribution Among Mitochondrial Variants



7 Three Rare Mitochondrial Variants Causing LHON-Plus Trigger Early Onset of Symptoms

Correlation between Mitochondrial Variants and Age of Onset



8 Conclusions

- The female bias of the LHON-Plus disease stands in contrast with the LHON disease, which predominantly affect male patients.
- Our survey reveals phenotypic and genetic complexity among LHON-Plus patients.
- All LHON-Plus patients exhibit symptoms specific to LHON-Plus, but 65% also share the symptom of vision loss with LHON patients
- The LHON-Plus disease is not limited to young adults, as three rare pathogenic mitochondrial variants trigger symptoms in pediatric patients between the age of 5 and 15.

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