Phylogenetic Analysis of Slavic Lebers Hereditary Optic Atrophy (LHON) Cases: The Role of Population Genetic Markers for mtDNA Pathology

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SUMMARY

There is growing evidence of population-specific influence on human pathiology. Most studies have focused on human diseases affecting a specific organ system, but few have investigated the pleiotropic effects of mitochondrial DNA (mtDNA) disorders. The current study focuses on Leber’s hereditary optic neuropathy (LHON), a common mitochondrial disorder that presents as bilateral, hereditary, and progressive vision loss in young adulthood. The disease is caused by mutations in the mitochondrial genome, specifically in the ND4, ND6, and ND1 subunits of the cytochrome c oxidase complex. The disease has been extensively studied in various populations, but there are limited data on the distribution of LHON mutations in Slavic populations. To address this gap, we performed a comprehensive analysis of mtDNA variants in a Slavic population from Novosibirsk, Russia. We genotyped 150 unrelated individuals for mtDNA control region variants and found 9 novel mutations, including 2 novel point mutations in the ND4 subunit of the cytochrome c oxidase complex. These results provide new insights into the genetic landscape of LHON in the Slavic population and highlight the importance of comprehensive mtDNA analysis for the study of complex disorders.

INTRODUCTION

It has been shown that polymorphic mtDNA markers associated with certain West European mtDNA haplogroups may be functionally different. Thus, one of the criticisms of the haplogroup H defined by the ND4 mutation is supposed to be advantageous to Alaskan’s disease (X-linked albinism). It is supposed that selecting among mtDNA haplogroups [35] and likely has a protective effect on Parkinson disease expression [36]. However, the most prominent example of such a difference is the Slavic haplogroup H, a disease whose expression is being studied under strong mtDNA background influence. There are several studies on the Slavic haplogroup H, which are fully described in multiple studies [36,39,40,41]. The evidence supporting the supposed that the existing human mtDNA diversity may have resulted from natural selection rather than being explained by the ‘neutral’ model of evolution. This hypothesis suggests that different mtDNA lineages evolve and radiate significantly in human populations because of their adaptive ability in specific climatic and dietary environments. According to human groups that originally inhabiting cold climatic zones may have accumulated more mtDNA changes than unpamed modern populations. This, in turn, led to greater mtDNA production, which were advantageous in cold environments. However, such a genetic background may have been gradually compromised by any environmental perturbations and finally the expression of even mild deleterious mtDNA mutations if they occurred in these haplogroups. Thus, we may expect the minor occurrence of mitochondrial disorder as populations that are cold-adapted.

In order to study the possible mtDNA background influence on disease expression, we have undertaken the anthropological and genetic study of LHON in Western Siberia, a region that is known for its extreme climatic conditions. We generated the phylodynamic analysis of Slavic LHON samples from our study and published reports to determine the relationship between certain mtDNA haplogroups and figure out whether mtDNA defects were distributed randomly within the population.

METHODS

Medical records and documents from several neuropathology hospitals in Novosibirsk, Russia, were extensively reviewed. This review represents the majority of cases to which the majority of eye patients living in the region is offered. Through this method, we were able to extract a significant number of cases with LHON, which is strongly associated with West European haplogroup H. All the patients selected for the study were affected with either pan-ocular or isolated optic atrophy.

To define the LHON group of optic atrophy cases, the patient pool was checked for several diagnostic criteria [37]: (a) a definite history of optic neuritis in any other relative, (b) obvious cases for optic neuritis development (e.g., glaucoma, mastoidectomy, neuroleptics, and other medications), (c) isolated peripheral vision loss, and (d) visual acuity less than 0.5. In addition, we reviewed the medical records of patients from three major hospital regions of Novosibirsk, a city that is representative of the major ethnic groups and genetic information from them. We have further used previously unpublished information (obtained directly or otherwise) about Slavic LHON patients from families with rare mtDNA defects harboring pathogenic mutations, which is strongly associated with West European haplogroup H.

The initial analysis screening allowed us to identify 45 patients who demonstrated LHON symptoms as described above: 22 males and 23 females. The average ages of the LHON patients were 37 years, 45 years, and 54 years, respectively. The analysis of family information allowed us to exclude the patient number up to 64 persons by including different groups for the entire region.

RESULTS

Genetic analysis revealed that only 56% of LHON cases expressing half of the individuals harbored one of the three mtDNA mutations that are generally known to be of clinical importance in LHON. Seven out of 25 families harbored the 11778 mutation, one patient from these families contained the 3460 mutation, and our family harbored the 14483 mutation. Spectacularly, despite Slavic haplogroup H containing the ND4 and ND6 mutations, which are known to affect certain mtDNA populations, no additional mtDNA defects were detected in our recent family report [Zhadanov et al., submitted].

Several of the LHON cases were carriers of LHON genotypes, which make them interesting for further research. Figure 1 shows the phylogenetic analysis of LHON cases from our study and the published reports that were used to determine the relationship between certain mtDNA haplogroups and determine whether mtDNA defects were distributed randomly within the population.

Epidemiology

Three years after the first mtDNA mutation was described [34], there is relatively little known about the epidemiology of LHON around the world. One recent attempt to clarify this issue discussed the disease prevalence in the population of North-Eastern Europe in about 3–5/100,000. One of the consequences of the extensive survey of the LHON cases is attributed to the one-third decreased prevalence of the LHON cases in the overall population. In this study, the frequency of detected LHON mutations (14483, 11778, and 13449) in both populations was found to be 15–20. The findings may have been due to different selection criteria or the measures of prevalence in the general population.

The patients were independently genotyped for both ND4 and ND6 mutations. The analysis of mtDNA sequences showed remarkable differences in the mutant spectrum of the studied LHON patients. The general conclusion is that both ND4 and ND6 mutations are found in LHON cases, which is consistent with most epidemiological studies. For instance, the 13449 LHON mutation is found predominantly in East European groups, while other two variants were mainly found in West European populations. The frequency of ND4 and ND6 mutations varied considerably in different populations. Thus, the ND4 mutations are responsible for about 90% of the LHON mutations, while ND6 mutations are responsible for 10% of the LHON mutations, as previously described in the literature.

In this study, we employed the same methodology for detecting LHON mutations in both populations. The analysis of mtDNA sequences showed remarkable differences in the mutant spectrum of the studied LHON cases. The unique aspect of this study is that it was conducted on a large-scale population from Belgium. The findings of this study provide new insights into the genetic landscape of LHON in the Slavic population and highlight the importance of comprehensive mtDNA analysis for the study of complex disorders.

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