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Incomplete penetrance in mitochondrial optic neuropathies

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ABSTRACT

Incomplete penetrance characterizes the two most frequent inherited optic neuropathies, Leber's Hereditary Optic Neuropathy (LHON) and dominant optic atrophy (DOA), due to genetic errors in the mitochondrial DNA (mtDNA) and the nuclear DNA (nDNA), respectively.

For LHON, compelling evidence has accumulated on the complex interplay of mtDNA haplogroups and environmental interacting factors, whereas the nDNA remains essentially non informative. However, a compensatory mechanism of activated mitochondrial biogenesis and increased mtDNA copy number, possibly driven by a permissive nDNA background, is documented in LHON; when successful it maintains unaffected the mutation carriers, but in some individuals it might be hampered by tobacco smoking or other environmental factors, resulting in disease onset. In females, mitochondrial biogenesis is promoted and maintained within the compensatory range by estrogens, partially explaining the gender bias in LHON.

Concerning DOA, none of the above mechanisms has been fully explored, thus mtDNA haplogroups, environmental factors such as tobacco and alcohol, and further nDNA variants may all participate as protective factors or, on the contrary, favor disease expression and severity.

Next generation sequencing, complemented by transcriptomics and proteomics, may provide some answers in the next future, even if the multifactorial model that seems to apply to incomplete penetrance in mitochondrial optic neuropathies remains problematic, and careful stratification of patients will play a key role for data interpretation. The deep understanding of which factors impinge on incomplete penetrance may shed light on the pathogenic mechanisms leading to optic nerve atrophy, on their possible compensation and, thus, on development of therapeutic strategies.

1. Introduction

In 1988 the first mutations affecting mitochondrial DNA (mtDNA) were described (Holt et al., 1988; Zeviani et al., 1988); amongst those there was, in particular, the first missense mutation in the complex I subunit gene ND4 associated with the maternally inherited blinding disorder Leber's Hereditary Optic Neuropathy (LHON) (Wallace et al., 1988). Since 1995, also mutations in the nuclear DNA (nDNA), transmitted with Mendelian inheritance, began to be associated with mitochondrial disorders (Bourgeron et al., 1995), and in 2000 dominant mutations in the OPA1 gene, encoding a mitochondrial dynamin-like GTPase involved in fusion of the inner mitochondrial membrane, were discovered as a major cause of dominant optic atrophy Kjer's type (DOA) (Alexander et al., 2000; Delettre et al., 2000).

1.1. Inherited mitochondrial optic neuropathies: incomplete penetrance

Both LHON and DOA are now regarded as frequent mitochondrial optic neuropathies, with an approximate prevalence of about 1 in 25–30,000 (Gorman et al., 2015; Yu-Wai-Man and Chinnery, 2013). They are both characterized by the common hallmark of a pattern of optic atrophy that preferentially affects the temporal quadrant of the optic nerve head, where the small fibers of the papillo-macular bundle provide the information for central vision (Carelli et al., 2004; Yu-Wai-Man et al., 2011). Thus, loss of central vision with relatively spared peripheral vision is the common clinical outcome of mitochondrial optic neuropathies. Interestingly, in both LHON and DOA many of the individuals carrying the primary pathogenic mutation in the mtDNA or nDNA do not seem to develop the disease, thus remaining unaffected lifelong (Howell and Mackey, 1998; Cohn et al., 2007). This issue of

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incomplete penetrance remains substantially poorly understood in both LHON and DOA, and this review will focus on the most recent advances on this topic.

1.2. LHON: clinical expression and mtDNA primary mutations

LHON is clinically characterized by a subacute loss of visual acuity, affecting prevalently young adult males, evolving in about four to six months into a profound defect of central vision, and stabilizing by one year in a chronic state of optic atrophy. Clinical expressivity may vary in LHON patients, as well as propensity to spontaneous recovery of visual function, in association with mutation type and age at onset; for details on the clinical features there are recent comprehensive reviews (Carelli et al., 2004; Yu-Wai-Man et al., 2011; La Morgia et al., 2014; Meyerson et al., 2015).

Genetically, three point mutations invariably affecting different ND subunits of complex I encoded by mtDNA (m.11778G > A/MT-ND4, m.3460G > A/MT-ND1, m.14484T > C/MT-ND6) are found in over 90% of LHON probands (Maresca et al., 2014). A growing list of other rare or private mtDNA mutations, validated for their pathogenicity, is also found in the remaining cases and similarly affect ND subunits of complex I (Achilli et al., 2012).

These “primary” mtDNA point mutations are found in the large majority of LHON maternal lineages as well established homoplasmic mutant (100% mutant) mtDNA variants, yet in a few families the pathogenic mtDNA mutation may be a recent event and segregate as a heteroplasmic (co-presence of mutant and wild-type) variant (Harding et al., 1995). In these cases, a few reports highlighted that penetrance may be reduced in the heteroplasmic individuals (Black et al., 1996; Juvonen et al., 1997; Carelli et al., 1997; Chinnery et al., 2001), even if caution should be used when counseling these patients about their diseases risk. In fact, there is evidence that the mtDNA assessment in peripheral blood cells may not reflect the heteroplasmic load in the target tissue such as the retinal ganglion cells (RGCs) (Howell et al., 1994). Overall, besides the few cases of heteroplasmic segregation of LHON mutations, in the homoplasmic families remains established that only about 50% of the male mutation carriers become affected, and only 10% of the female mutation carriers, highlighting a pattern of incomplete penetrance. Thus, the mtDNA primary mutations in LHON are a necessary, but not sufficient pre-requisite for developing the disease.

1.3. DOA: clinical expression and OPA1 mutations in nDNA

DOA presents many analogies with LHON, in terms of target tissue and pattern of RGC loss, however the main clinical difference is that onset is typically before the age of 10 and the natural history is described as a relentless, frequently stable for a long time or slowly progressive optic nerve atrophy, without evidence of spontaneous recovery of vision (Carelli et al., 2004; Yu-Wai-Man et al., 2011).

Genetically, over 60% of DOA families are associated with mutations in the OPA1 gene, encoding the major fusogenic protein of inner mitochondrial membrane (Landes et al., 2010; Yu-Wai-Man et al., 2010a; Lenaers et al., 2012). The pathogenic mutations affecting the OPA1 gene can be grossly distinguished in those leading to haploinsufficiency and others, missense mutations, which possibly act through a dominant negative mechanism. If the latter affect the GTPase domain of OPA1, these missense mutations frequently lead to a complex multisystem phenotype named “DOA plus” (Amati-Bonneau et al., 2009; Yu-Wai-Man et al., 2010b). Now that the molecular diagnosis is available, it became clearer also for DOA that penetrance is incomplete, even within the same family segregating dominantly the same OPA1 mutation (Toomes et al., 2001; Cohn et al., 2007). Thus, similar to LHON, also in DOA the OPA1 mutation is the necessary predisposing factor to disease, but in some cases it is not sufficient to develop a clinically relevant optic atrophy.

2. Incomplete penetrance: mtDNA haplotype

A first modifying genetic factor, potentially implicated in modulating penetrance in mitochondrial optic neuropathies, is the high sequence variability of the mitochondrial genome itself, characterizing the different mtDNA haplogroups (Wallace and Chalkia, 2013). This is particularly relevant for LHON, where the primary pathogenic mutations affect mtDNA, but there is now compelling evidence that mtDNA haplogroups may have different efficiencies in terms of oxidative phosphorylation coupling and production of reactive oxygen species (Moreno-Loshuertos et al., 2006; Latorre-Pellicer et al., 2016). Thus, the mitochondrial genome may also represent a genetic modifying factor for diseases associated with mutations in mitochondrial proteins encoded by nDNA, such as DOA (Strauss et al., 2013).

2.1. LHON: subclades of mtDNA haplogroup J play a role

Shortly after the identification of the three “primary” LHON pathogenic mutations in the early 90s (Wallace et al., 1988; Huoponen et al., 1991; Howell et al., 1991; Mackey and Howell, 1992; Johns et al., 1992), additional recurrent polymorphic mtDNA variants were also associated with LHON and called, for a long time, “secondary mutations” (Johns and Berman, 1991; Johns and Neufeld, 1991; Brown et al., 1992). The debate about the role of these “secondary mutations” (Mackey et al., 1996) ended once they were firmly established as mtDNA haplogroup-related polymorphic markers (Torroni et al., 1996). In 1997, multiple research groups provided the concordant evidence that the LHON m.11778G > A/MT-ND4 and m.14484T > C/MT-ND6 mutations were associated with a specific mtDNA haplogroup, haplogroup J (Torroni et al., 1997; Brown et al., 1997; Lamminen et al., 1997). Over the years, this association was refined to specific clades of haplogroup J, the J1c and J2b clades characterized by accumulation of missense variants affecting both complex I and III (Carelli et al., 2006; Hudson et al., 2007a). These studies were all carried out with large cohorts of LHON patients from European descent, but a similar scenario seems to apply also to the Asian cohorts of LHON patients (Ji et al., 2008; Kaewsutthi et al., 2011). Furthermore, the complete sequence analysis of mtDNA allowed revealing frequent private new variants, or polymorphic known variants on unusual haplogroup backgrounds, for which a possible modifying role could be hypothesized (Achilli et al., 2012). Multiple reports from Chinese LHON families indicated also the occurrence of mtDNA backgrounds characterized by an unusually high or complete penetrance (Yang et al., 2009; Zhang et al., 2008), frequently due to coexisting pathogenic mutations, as opposed to extremely reduced penetrance in other maternal lineages (Qu et al., 2009). Thus, different combinations including mtDNA haplotypes defined by specific arrays of polymorphisms, private variants and co-existing mutations may all impinge on the pathogenic potential and penetrance of the primary mutations. Remarkably, the role of the same mtDNA variant may vary drastically, for example, from an adaptation at high altitudes, due to an environmental positive selection on mtDNA sequence, to a pathogenic potential predisposing to develop LHON in different interacting environments (Ji et al., 2012).

A few studies tackled the issue of providing a functional evidence for the modifying role of the mtDNA haplotype and/or the private variants or co-existing mtDNA mutations. Initial studies based on MR-spectroscopy were unable to detect differences between LHON patients carrying the m.11778G > A/MT-ND4 mutation associated or not with the mtDNA haplogroup J (Lodi et al., 2000). Exploiting the cell model of transmitochondrial cytoplasmic hybrids, “cybrids”, it has been shown *in vitro* that different mtDNA haplogroups may have slight, but significant differences in bioenergetic efficiency, production of reactive oxygen species and stability of respiratory complexes assembly (Carelli et al., 2002a; Pello et al., 2008; Gómez-Durán et al., 2010, 2012), thus substantiating their possible role as modifiers for LHON penetrance. Controversial results were instead provided by the few studies on cases