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REVIEW

Preventing the transmission of mitochondrial DNA disorders: Selecting the good guys or kicking out the bad guys

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Abstract Mitochondrial disorders represent the most common group of inborn errors of metabolism. Clinical manifestations can be extremely variable, ranging from single affected tissues to multisystemic syndromes. Maternally inherited mitochondrial DNA (mtDNA) mutations are a frequent cause, affecting about one in 5000 individuals. The expression of mtDNA mutations differs from nuclear gene defects. Mutations are either homoplasmic or heteroplasmic, and in the latter case disease becomes manifest when the mutation load exceeds a tissue-specific threshold. Mutation load can vary between tissues and in time, and often an exact correlation between mutation load and clinical manifestations is lacking. Because of the possible clinical severity, the lack of treatment and the high recurrence risk of affected offspring for female carriers, couples request prevention of transmission of mtDNA mutations. Previously, choices have been limited due to a segregational bottleneck, which makes the mtDNA mutation load in embryos highly variable and the consequences largely unpredictable. However, recently it was shown that preimplantation genetic diagnosis offers a fair chance of unaffected offspring to carriers of heteroplasmic mtDNA mutations. Technically and ethically challenging possibilities, such maternal spindle transfer and pronuclear transfer, are emerging and providing carriers additional prospects of giving birth to a healthy child.

KEYWORDS: chromosome–spindle transfer, mtDNA disease, nuclear genome transfer, preimplantation genetic diagnosis
VIDEO LINK: http://sms.cam.ac.uk/media/1400848

Introduction

Mitochondrial or oxidative phosphorylation disorders are complex diseases, caused by mutations in either nuclear genes or in the mitochondrial DNA (mtDNA). Nuclear gene defects segregate as Mendelian diseases, whereas mtDNA defects are transmitted maternally. The latter occurs in about 15% of the cases, affecting about one in 5000

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individuals (Rotig and Munnich, 2003). Carrier frequency for pathogenic mtDNA mutations in the population is higher — from 1:400 (Manwaring et al., 2007) to even >1:200 (Elliott et al., 2008) — but in general the mutation load remains below the level of clinical expression. Still, symptoms such as hearing loss can be present and undiagnosed individuals can turn out to be oligosymptomatic upon further investigation (Manwaring et al., 2007). Mitochondrial diseases can manifest with symptoms in many different organs and vary profoundly in severity and age of onset (reviewed in McFarland et al., 2010). Clinical manifestations may present in just a single affected tissue or organ, such as the loss of vision in Leber's hereditary optic neuropathy (LHON), but a multisystemic or multiorgan involvement is more common. The clinical spectrum (Chinnery and Hudson, 2013) involves the brain (ataxia, dementia, migraine, myoclonus, neuronal loss and stroke), the peripheral nervous system (neuropathy), the heart (cardiomyopathy, conduction disorders, Wolfe-Parkinson-White syndrome), skeletal muscle (fatigue, myopathy, weakness), the liver (hepatopathy), the pancreas (diabetes), the eyes (optic neuropathy, ophthalmoplegia, retinopathy), the ears (sensori-neuronal hearing loss), the kidney (Fanconi syndrome, glomerulopathy), the colon (pseudo-obstruction), the blood (Pearson syndrome) and the gonads (ovarian failure). Well-known neurological syndromes, caused by mitochondrial dysfunction and partly due to mtDNA mutations, are Leigh syndrome (subacute necrotizing encephalomyelopathy), mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS syndrome), neuropathy, ataxia and retinitis pigmentosa (NARP syndrome) and myoclonic epilepsy with ragged red fibres (MERRF syndrome). Fatally affected newborns represent the severe end of the spectrum. A frequent symptom in paediatric patients is developmental delay and failure to thrive. When at least two organ systems unexplained by other diseases are involved in a single person or in affected (maternal) relatives, then mitochondrial disorder must be considered. Clinicians should be aware that apparently unrelated symptoms might have a common genetic cause (McFarland et al., 2010). Given the potential for severe clinical disease in a child, the ability to prevent transmission of these inherited disorders using reproductive technology is highly desirable.

Mitochondrial DNA

The first description of a circular DNA located in the mitochondria dates from more than 40 years ago (Nass, 1966). The mtDNA has a number of unique characteristics that discriminates it from its nuclear counterpart. First, the mtDNA is a double-stranded circle (16,569 bp) with a structure and code different from the nuclear DNA. The mtDNA contains 37 genes, of which 13 genes encode OXPHOS subunits and 22 tRNA and two rRNA genes. Approximately 6% of the mtDNA is noncoding, located predominantly in the D-loop and involved in the replication and transcription of the mtDNA (Anderson et al., 1981). The mtDNA is compact. It contains no introns, several overlapping genes and incomplete termination codons. It mutates somatically during life as a result of reactive oxygen species, produced by the OXPHOS system, and through age-related damage.

Next, the mtDNA is not a diploid but a multicopy genome. A cell contains hundreds of mitochondria and, dependent on the tissue involved, each cell carries between 500—10,000 mtDNA molecules, except for mature oocytes which have between 100,000 and 600,000 mtDNA molecules (Reynier et al., 2001). The higher the energy demands of a cell, the more mitochondria and mtDNA molecules it contains. In a cell, all mtDNA molecules can be identical, which is called homoplasmy. Alternatively, two (or more) types of mtDNA molecules that differ in sequence can coexist in the same cell, tissue or even in the same organelle, which is called heteroplasmy. Heteroplasmy levels may range between 0% and 100% and the majority of severe pathogenic mtDNA mutations is heteroplasmic. Clinical manifestations depend to a certain extent on the mutation load and no symptoms occur unless the mutant load (proportion of mutant mtDNA) exceeds a certain threshold of expression (Hellebrekers et al., 2012). This threshold varies between tissues and between different mutations. In some mtDNA disorders, onset and severity of symptoms are clearly related to mutation load (Black et al., 1996; White et al., 1999). Often, however, phenotype and mutation load correlate poorly (Chinnery et al., 1997; Thorburn and Dahl, 2001).

Finally, the mtDNA is transmitted entirely through the maternal lineage. The mutation load inherited by the fetus from a heteroplasmic mother is affected by a segregational bottleneck, which is a restriction in the number of mtDNA molecules to be transmitted followed by a strong amplification of these molecules. During oogenesis, the number of mtDNA molecules is reduced and the resulting few mtDNA become the founders of all the 100,000 to 600,000 mtDNA molecules in the mature oocyte, resulting in considerable variation in mtDNA mutant load among individual oocytes and subsequently among offspring (Jacobs et al., 2006; Poulton et al., 2010). The 'size' of this bottleneck is still under debate, but seems to depend on the type of mtDNA mutation and may even be individual-dependent for certain mutations (Blok et al., 1997; Brown et al., 2001; Monnot et al., 2011). Also the mechanism by which mtDNA mutations segregate, either randomly or preferentially, is poorly understood and appears to differ among mutations and nuclear backgrounds. Apparently, homoplasmy based on uniparental inheritance seems to be the preferred and most healthy situation (Sharpley et al., 2012).

mtDNA defects and recurrence risks

Disease causing mutations in the mtDNA can be due to large rearrangements, point mutations or a reduced copy number, in some cases leading to depletion of the mtDNA. One has to be aware that a mtDNA defect can be the primary cause of disease, but that it also can be the manifestation of nuclear gene defects (e.g. defects in genes involved in mtDNA maintenance causing multiple mtDNA deletions and/or mtDNA depletion), mitotoxic drugs (e.g. nucleoside reverse transcriptase inhibitors can induce mtDNA depletion) or ageing (e.g. multiple deletions). It is obvious that the recurrence risk — the likelihood that the mtDNA disease present in a patient will occur again in his or her offspring or sibling — is highly dependent on the