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MITO 101 – Genetic Counseling for Mitochondrial Disease

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Mitochondrial disease is not a single disorder but rather a collection of hundreds of different diseases, each with different prognosis and oftentimes extensive clinical variability, even when occurring in members of the same family. This clinical complexity stems from the extensive genetic heterogeneity of mitochondrial disease. Indeed, primary causes can be mutations in genes of the mitochondrial DNA (mtDNA) or of the nuclear DNA (nDNA). Potential genetic candidates abound, as well over 1,500 different proteins are found in mitochondria. In addition, mitochondrial *dysfunction* is increasingly recognized to occur as a secondary phenomenon in many other “genetic” disorders not typically considered to be mitochondrial *disease* (including chromosomal abnormalities and common disorders such as Parkinson’s Disease and Diabetes Mellitus) and may even result from environmental toxicities.

GENETIC COUNSELING INDICATIONS

Formal genetic counseling is clearly indicated in individuals with mitochondrial disease in order to: (i) interpret correctly genetic diagnostic tests performed in affected individuals and their relatives; (ii) review recurrence risk estimations for the siblings and offspring of affected individuals; and (iii) discuss prognosis. Another important aspect of genetic counseling is to help with the psychosocial concerns that accompany these diagnoses. Such concerns often include grief over the loss of an initially healthy infant or child, guilt for perceived failures in providing adequate assistance to an ailing child, bonding difficulties when symptoms are present in early infancy, confusion about unproven therapies, financial uncertainty related to long-term medical management and possible lifelong care, as well as the natural and appropriate concern whether other family members are at risk. Ethical issues may arise regarding whether to proceed with long-term support or surgical interventions, such as gastrostomy tube placement, in the face of a poor prognosis. Finally, it is important to recognize that families often are unable to move beyond their feelings and focus on their child’s symptomatic care until a clear diagnosis has been established. Genetic counseling can help address many of these areas of concern.

INHERITANCE PATTERNS

All of the causes of mitochondrial disease are genetic, with different inheritance patterns seen in different mitochondrial diseases. However, not all genetic problems are necessarily “running through” one’s family. Rather, a genetic change may arise anew (*de novo*) in the affected individual. An overview of the major genetic disease patterns associated with mitochondrial disease (maternal, autosomal recessive, autosomal dominant, and X-linked) are highlighted in **Table 1**, along with their specific implications for recurrence risk to an affected individual’s siblings and future children. As most primary mitochondrial diseases diagnosed in childhood (67% to 90%) are inherited in an autosomal recessive fashion, it is important to recognize that the stated recurrence risk is for full siblings; the likelihood of recurrence is rather low for most autosomal recessive disorders, should either parent have a different partner in future pregnancies. However, for maternally inherited or X-linked traits, a carrier or affected mother’s recurrence risk is independent of her partner.

mtDNA-RELATED MITOCHONDRIAL DISEASES

Genetic defects of mtDNA which are inherited in a maternal fashion include mtDNA point mutations, small deletions (several basepairs), and, rarely, large deletions with or without

duplications. Sensitive diagnostic testing for these possibilities is available, with the important caveat that an informative tissue based on a particular individual's symptoms need be tested (most commonly muscle). Should an mtDNA mutation be identified as causative in a child with a normal maternal family history, it is likely to be a brand new (*de novo*) mutation. This scenario would give a low recurrence risk on the order of 1% to 4% with each subsequent pregnancy, based on the theoretical possibility that even though the mother has no symptoms, some of her eggs might carry the same mutation (germline mosaicism). Of course, the mutation could be looked for in other tissues in the affected individual or in her/his maternal family members in an effort to further refine recurrence risk estimation. Furthermore, if the mutation is known to occur in an mtDNA transfer RNA gene, it is often not possible to predict the severity of symptoms expected should the mutation recur in other family members.

nDNA-RELATED MITOCHONDRIAL DISEASES

If mtDNA is extensively analyzed and found to be normal, nuclear inheritance becomes even more likely in children with mitochondrial disease. In this situation, it is important to recognize that the recurrence risk of mitochondrial disease for siblings does not exceed 50%. As affected children are most likely to have an autosomal recessive form of mitochondrial disease, the likely recurrence risk to parents of an affected child would then fall in the somewhat narrowed range of less than 1% up to 25%. Specifically, a recessive scenario suggests that both parents are asymptomatic carriers for the causative gene mutation, with a 25% (1 in 4) chance for each subsequent pregnancy to be similarly affected and a 67% (2 in 3) chance that unaffected siblings are themselves carriers. Autosomal dominant inheritance remains a possibility, but the absence of clinical findings in a parent would suggest a *de novo* mutation, which carries a low recurrence risk (less than 1%). Of course, the specific genetic cause has to be confirmed to provide the most accurate risk estimate.

In the event that a causative nuclear gene mutation cannot be identified, it is not possible to determine the expected severity for another affected individual regardless of the suspected genetic inheritance pattern. To date, pathogenic mutations causing a wide spectrum of mitochondrial disease have been identified in over 50 nuclear genes. As the number of genes implicated in mitochondrial disease continues to rise, testing methodologies improve, and additional diagnostic testing options become available, the potential to further pursue a genetic-based diagnosis of mitochondrial disease should be revisited with time.

PRENATAL GENETIC TESTING FOR MITOCHONDRIAL DISEASE

Prenatal genetic diagnostic testing may further clarify recurrence risk to offspring or siblings of an affected individual, but is only possible in the event that a definitive gene mutation can be identified in the affected individual; its use is more straightforward for nDNA genes than mtDNA genes because of the complexities of maternal inheritance. When the causative gene mutation is known, specific prenatal genetic diagnostic options that may be considered include pre-implantation genetic diagnosis (PGD, performed in the *in vitro* fertilization setting on a 3 to 5 day old embryo before it is implanted in the uterus to achieve a pregnancy), chorionic villus sampling (placental tissue testing available between 10 and 12 weeks' gestation), and amniocentesis (amniotic fluid sampling that is typically performed at 16 to 20 weeks' gestation). Further discussion about the risks, benefits, and availability of these individual prenatal genetic diagnostic options is available at www.genereviews.org. Newborn screening does not currently evaluate for mitochondrial disorders.

Table 1. Genetic inheritance patterns causative of primary mitochondrial disease.

Inheritance Patterns of Primary Mitochondrial Disease	Example	Recurrence Risk to Full Siblings	Recurrence Risk to Offspring of Affected Females	Recurrence Risk to Offspring of Affected Males
Maternal	mtDNA point mutations; mtDNA large deletions ± duplications (rare)	1-4% if no symptoms in mother; up to 50% if symptomatic mother	Up to 50% for both sons and daughters	None
Autosomal Recessive	Mutations in nDNA-encoded respiratory chain subunits or assembly factors; mtDNA depletion (<i>POLG1</i> , <i>TK2</i> , <i>DGUOK</i> , etc.)	25%	All children will be carriers (likely asymptomatic); Affected status depends on population carrier frequency	All children will be carriers (likely asymptomatic); Affected status depends on population carrier frequency
Autosomal Dominant	Progressive external ophthalmoplegia (<i>POLG1</i>)	50% if parent is affected; <1% based on germline mosaicism if parent is asymptomatic	50% for both sons and daughters	50% for both sons and daughters
X-linked	Sideroblastic anemia (<i>ABC7</i>); Barth syndrome (<i>tafazzin</i>); Mohr-Tranebjaerg syndrome (<i>DDP1</i>)	<u>If mother is a carrier:</u> 50% for brothers to be affected & 50% for sisters to be carriers (likely asymptomatic); <u>If <i>de novo</i>,</u> <1% for brothers to be affected or sisters to be carriers	If symptomatic mother, 50% for sons to be affected and 50% for daughters to be carriers/affected (depending on her x-inactivation pattern)	None for sons; 50% for daughters to be carriers (likely asymptomatic)
Sporadic	Muscle biopsy evidence of respiratory chain dysfunction without clear genetic etiology	Uncertain	Uncertain	Uncertain