Mitochondrial Disease

GENETIC TESTING

Diagnosis and management of mitochondrial disease: a consensus statement from the Mitochondrial Medicine Society

Sumit Parikh, MD[1], Amy Goldstein, MD[2], Mary Kay Koenig, MD[3], Fernando Scaglia, MD[4], Gregory M. Enns, MD[5], Russell Saneto, MD, PhD[6,7], Irina Anselm, MD[8], Bruce H. Cohen, MD[9], arni J. Falk, MD[10], Carol Greene, MD[11], Andrea L. Gropman, MD[12], Richard Haas, MB BChir, MRCP[1] Michio Hirano, MD[14], Phil Morgan, MD[15], Katherine Sims, MD[16], Mark Tarnopolsky, MD, PhD[17], Johan L.K. Van Hove, MD[18], Lynne Wolfe, MS, CRNP[19] and Salvatore DiMauro, MD[20]

There are published diagnostic guidelines

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Available online at bit.ly/mitoconsensus

When Mitochondrial Disease is Highly Suspected

GENETIC TESTING IS NEEDED

Genetic Diagnosis is the Gold Standard

- Allows for diagnostic confirmation
- Allows for ending the “diagnostic odyssey”
- Allows for mimicking diseases to be excluded
- Allows the patient to better understand symptoms and prognosis
- Allows the clinician to personalize preventative care and health planning

Dual Genome Testing

As the Mitochondria use both the nuclear DNA (nDNA) and mitochondrial DNA (mtDNA) for synthesis and function, testing both genomes is necessary

Many Nuclear Genes Impact Mitochondrial Function

> 1500 nuclear genes are involved in maintaining mitochondrial function

> 350 nuclear genes have been linked to human disease

A broad gene panel or Whole Exome Sequencing (WES) is preferred over single gene testing

Inheritance

Most mitochondrial diseases due to nDNA variants are Autosomal Recessive (AR) **and need the finding of two pathogenic variants in a single gene on separate alleles for testing to be diagnostic**

Select mitochondrial diseases are X-linked or Autosomal Dominant

We do not yet know all the nDNA genes impacting mitochondrial function

AND WHOLE EXOME ONLY TESTS EXONIC MATERIAL (2% OF THE GENOME). INTRONS & NONCODING REGIONS ARE NOT YET TESTED

Whole genome testing is in its infancy but becoming more useful

THIS WILL GRADUALLY BECOME THE TEST OF CHOICE FOR MITOCHONDRIAL DISEASE PATIENTS

The mtDNA Genome is Compact and Easily Testable

As the mtDNA genome is around 16,000 base pairs, it can be assessed in its entirety

This testing can be performed in blood

Due to heteroplasmy (see prior lecture) - mtDNA changes may not be detected in blood and mtDNA analysis of other tissue may be needed

mtDNA analysis is selectively performed when needed in muscle, liver, heart or urine sediment

mtDNA Deletions and Quantifications

mtDNA deletions may also lead to disease but cannot always be detected in blood

mtDNA depletion due to disorders of mtDNA replication cannot be detected in blood

Analysis in muscle or other tissue is needed to exclude these problems

Variants of Unknown Significance (VUS)

These are DNA changes that may be benign/harmless but this is not certain yet

Familial/parental testing for variants may help us better understand the meaning of these types of findings

Proper genetic counseling is needed when VUS are found

VUS **should not** be associated to the patient's symptoms without further investigation and analysis

Diagnosis of 'possible' mitochondrial disease: an existential crisis

Sumit Parikh,[1] Amel Karaa,[2] Amy Goldstein,[3,4] Enrico Silvio Bertini,[5] Patrick F Chinnery,[6] John Christodoulou,[7,8] Bruce H Cohen,[9,10] Ryan L Davis,[11,12] Marni J Falk,[3,4] Carl Fratter,[13,14] Rita Horvath,[15,16] Mary Kay Koenig,[17] Michaelangelo Mancuso,[18] Shana McCormack,[3,4] Elizabeth M McCormick,[3] Robert McFarland,[19] Victoria Nesbitt,[19,20] Manuel Schiff,[21] Hannah Steele,[15,22] Silvia Stockler,[23] Carolyn Sue,[11,12,24] Mark Tarnopolsky,[25] David R Thorburn,[26,27,28] Jerry Vockley,[29] Shamima Rahman[30,31]

Stay away from "Possible Mitochondrial Disease" Diagnosis

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