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Consensus on managing mitochondrial disease

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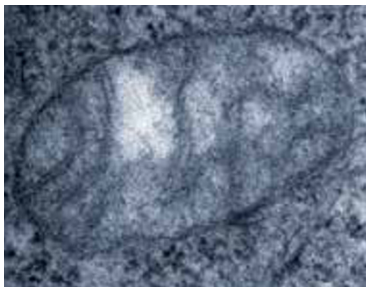

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The centrality of mitochondria to human health is never more on display than when something goes wrong with these multifunctional organelles. In recent years, it has become clear that diseases of mitochondrial origin are numerous and complex. Primary mitochondrial disorders can be caused by mutations in maternally inherited mitochondrial DNA (mtDNA) or in nuclear genes that encode mitochondrial building blocks. Next-generation sequencing methodologies have greatly improved the reliability and sensitivity of mtDNA genome analyses and have underscored the breadth of potential mitochondrial disorders, which affect at least 1 in 5,000 people. However, because hundreds of variants and disease manifestations have been identified, reaching consensus on proper diagnosis and treatment has been challenging. The Mitochondrial Medicine Society recently undertook a comprehensive review process that combined a literature search and evaluation with expert opinion to reach the consensus recommendations presented in this issue. The experts appointed by the society wrestled with the complexity of mitochondrial function and dysfunction, often finding that the literature yielded only isolated case reports and limited case series. Because mitochondrial disorders can affect a wide variety of tissues and can cause symptoms across a wide spectrum of organ systems, the path to diagnosis and treatment can be frustrating for both patients and physicians. This report attempts to standardize that process as much as possible, and covers recommended DNA, biochemical, and pathology diagnostic testing, as well as neuroimaging procedures. Best practices for treatment and preventive care are also discussed. *—Karyn Hede, News Editor*

New CNV resource available

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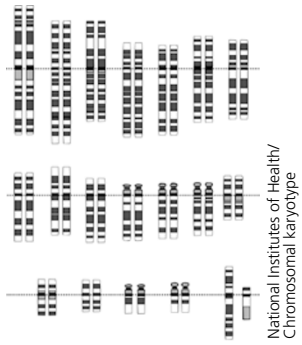

National Institutes of Health/ Chromosomal karyotype

Gain or loss of chromosomal DNA in the form of copy-number variants (CNVs) can result in unexplained neurodevelopmental disorders or other difficult-to-diagnose inborn abnormalities. Microarray analysis for CNVs is often the go-to diagnostic test for individuals with these conditions. But accurate diagnoses require a robust database of normal genomic variants for comparison. Now a Canadian consortium has produced a new CNV reference resource derived from a large, mostly Caucasian, North American population. Scherer and colleagues from the University of Toronto genotyped population-based samples from 873 adult volunteers using the high-resolution Affymetrix CytoScan–HD array. The group analyzed the CNV data in three stringency tiers (basic, research, and clinical) to serve investigators requiring different levels of clinical confidence. The analysis uncovered nearly 7,000 small CNVs in the range of 1 to 15 kb that had not been characterized previously. For potential use in a clinical genetics setting, the investigators suggest that the data be expanded to include diverse populations. However, for research use the publicly available database (http://dgv.tcag.ca) offers the first CNV reference data generated using a single platform, as well as the accompanying biospecimens to support clinical genetic research studies. DNA and cell lines from this unique biological resource are available to the research community. *—Karyn Hede, News Editor*

NEWS BRIEFS

Nominations open for ACMG secondary findings gene list

Scott Maxwell/LuMaxArt

The ACMG Secondary Findings Working Group is updating the secondary findings gene list, initially published in an ACMG policy statement (*Genet Med* 2013;15:565–574). The group's mission is to provide a dynamic and up-to-date list for use by laboratories performing clinical genomic analysis and clinicians returning genomic results, but we need your input. To nominate a gene to be added to or removed from the list, download and complete the nomination form from https://www.acmg.net/secondaryfindings, then e-mail the completed form to acmg@acmg.net.

Please keep in mind the following guiding principles. First, the genes should be medically actionable. "Actionable" means that a specific medical or surgical intervention is available that has demonstrated effectiveness to alter the disease course. Second, the genes should be associated with at least one clear phenotype that has serious medical implications.

For the first six months, the Working