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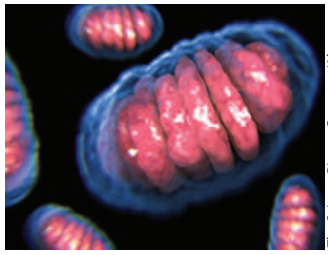
IN THIS ISSUE

A simplified approach to diagnosing mitochondrial disorders

see page 962



The Science Picture Company/Alamy

Disorders affecting the mitochondria are estimated to affect one in 5,000 people. But diagnosing mitochondrial disease is exceedingly frustrating and tricky; its symptoms, including muscle weakness, fatigue, intestinal problems and neurological deficits, are compatible with a host of diagnoses. Furthermore, mitochondrial disorders are attributable to a large number of potential genetic defects in both nuclear and mitochondrial DNA (mtDNA), making the route to diagnosis even more difficult. Genetic testing typically proceeds through a stepwise investigation starting with potential large-scale deletions and targeted gene sequencing, and it now often progresses to sequencing of both the mitochondrial and nuclear genome/exome. Griffin et al., of the Wellcome Trust Centre for Mitochondrial Research, Newcastle University, UK, describe a simplified method using readily available nuclear exome capture kits to identify DNA sequence variation in the mitochondrial genome, while simultaneously detecting heteroplasmy. The study also showed that sequencing of mtDNA works with patient samples from skin, blood, and muscle, although the muscle samples gave more complete sequence coverage, presumably due to the presence of more mtDNA that "carries through" during nuclear exome capture. The research team reports an error rate equivalent to that for traditional Sanger sequencing and suggests that mtDNA analysis should become a routine part of the diagnostic exome in a patient with suspected mitochondrial disease. —*Karyn Hede, News Editor*

NIPT drills down to single-gene level

see page 972

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Combining whole-genome sequencing with determination of parental haplotypes, researchers from Shanghai, Shenzhen, and Beijing, China, identified a pathogenic, single-base-pair defect in fetal DNA derived from noninvasive prenatal testing (NIPT). The study represents the first clinical foray into noninvasively identifying small, single-gene defects by reconstructing the fetal genotype using DNA derived from maternal plasma. The technology hinges on construction of maternal and paternal haplotypes, which are then used to discern fetal DNA sequence. In the reported clinical case, investigators took samples from three generations of a family in which a pregnant woman had given birth to a child with congenital deafness. Using a mathematical method the group had previously developed, they calculated linkage relationships using parental haplotypes and base distribution to deduce the inherited fetal haplotype. In this case, the fetus was determined to be a heterozygous carrier of the c.235 delC mutation in the *GJB2* gene, with maternal inheritance. If the technique is replicated and the cost of next-generation sequencing continues its current decline, it may be feasible to use this approach to greatly broaden the range of genetic defects that can be diagnosed via NIPT, including Mendelian diseases and small chromosomal changes such as microdeletions not detectable using current technology. As this potential develops, it will be critical to simultaneously address the attendant ethical issues associated with the ability to identify even minute genetic defects early in pregnancy. —*Karyn Hede, News Editor*

NEWS BRIEFS

Genomics illuminates mysteries of monarch flight, color

The mystery of how ephemeral monarch butterflies migrate thousands of miles each year has yielded at least some of its secrets to detailed genomic study. A collaborative research team reports in *Nature* that its genome-wide single-nucleotide polymorphism analysis of 101 geographically dispersed specimens revealed the underlying pattern of species dispersal from the monarch's ancestral home in North America. The research team compared the genomes of migratory and nonmigratory monarchs to identify several genetic variations associated with long-distance migration. These genes, which affect flight muscle, result in more efficient energy consumption and lower resting metabolic rates. The pattern of genetic variation also revealed that, after dispersing to Europe, South America, and Hawaii, among other locations, the monarchs reverted to a nonmigratory form. In the process, a single collagen gene changed in the same way in all dispersed nonmigrating populations.

Jaap de Roode

Monarch butterflies catching sun at a Mexican overwintering site.

Additional comparison between the genomes of five white monarchs and seven orange monarchs from Hawaii identified variation in a single gene—the myosin gene DPOGS206617—as being responsible for wing pigmentation. The gene previously had no known role in insect pigmentation but was known to affect mouse-coat coloration. This finding was a surprise to investigators, who had expected the gene