This Month in Genetics

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Mitochondrial Heteroplasmy Is Normal

Each cell in the body contains several mitochondria, which themselves contain multiple copies of the mtDNA. When a mitochondrial disorder is caused by an mtDNA mutation, the concept of heteroplasmy, or the presence of more than one distinct population of mtDNA, is key. Because mitochondria segregate randomly to daughter cells, the relative amount of mutant:normal mtDNA can vary widely between affected individuals within a family and between tissues within an affected individual. These features affect the phenotype and the recurrence risk in the family. In contrast, it is generally held that normal individuals have homogeneous mtDNA, or homoplasmy. Instead, He et al. find that normal individuals also have mtDNA heteroplasmy, as revealed by high-throughput sequencing of mtDNA from ten normal individuals. Each sample had, on average, four heteroplasmic variants, but each variant was not present in all tissues examined, and the level of heteroplasmy sometimes varied widely between tissues in a single individual. Segregation of heteroplasmic variants within families indicates that some of the variation in normal individuals is maternally inherited, whereas other variants arise as somatic mutations during development. Even more mtDNA variation arises in tumors. Matched colorectal cancer samples were compared to normal tissue and found to have additional homplasmic and heteroplasmic variation that might be useful for monitoring tumors.

He et al. (2010). Heteroplasmic mitochondrial DNA mutations in normal and tumour cells. Nature, in press. Published online March 3, 2010. 10.1038/nature08802.

Survival Estimates for Children with Congenital Anomalies

"Will they be okay?" is surely a question that parents of a newborn child with a congenital anomaly ask their healthcare providers. Unfortunately, particularly for more rare anomalies, good data are often not available to be provided to parents. A recent population-based study of congenital anomalies in the UK will go a long way toward changing that. The UK Northern Congenital Abnormality Survey (NorCAS) is a population-based register of congenital anomalies for northern England. Tennant et al. matched the NorCAS data with hospital and national mortality records to estimate survival rates for a large range of congenital anomalies, some as far as 20 years. This study included more than 13,000 cases of congenital anomaly that were referred to NorCAS between 1985 and 2003. Unlike other, similar studies, the authors consider the influence of associated anomalies in their estimates through use of a hierarchical classification system. This system allowed them to more accurately estimate survival for particular subtypes of anomalies. For example, they report the 20-year survival for isolated ventricular septal defect to be greater than 98%, but it would have been 91.7% had they not separately classified individuals with syndromic cases or multiple anomalies. This work will no doubt serve as a valuable resource for healthcare professionals guiding families who are affected by congenital anomalies.

Tennant et al. (2010). 10-year survival of children born with congenital anomalies: A population-based study. The Lancet 375, 649–656.

Breathing Easy

Although the underlying problem in cystic fibrosis (CF) is the absence of a chloride channel, the real pathologic issue is one of mucus—thick, excessive mucus that clogs the lungs, the pancreatic ducts, and the bowel. In a mouse model of CF, Harmon et al. show that, at least in the colon, the diabetes drug rosiglitazone can suppress this mucus accumulation. The authors started down this avenue of research with the finding that *Cftr*$^{-/-}$ mice have a defect in PPAR-dependent gene expression in their colons. Rosiglitazone, a known PPAR-γ agonist, normalizes expression of several genes and vastly improves survival of the mutant mice, who normally die within 6 weeks of life because of intestinal or colonic obstruction. Expression of PPAR-γ itself is normal in *Cftr*$^{-/-}$ mice; it is instead the production of its activating ligand 15-keto-prostaglandin-2 that is reduced, as a result of lower expression of the dehydrogenase that produces this lipid. Ultimately, the effects of rosiglitazone on PPAR-γ signaling do not improve chloride secretion in *Cftr*$^{-/-}$ mice but, rather, reduce mucus viscosity by increasing bicarbonate secretion, which is deficient in individuals with CF because of the role of the CFTR channel in bicarbonate and chloride exchange. This work not only outlines a pathway to explain the production of excess mucus in CF but also suggests PPAR-γ as a therapeutic target for intervention in this devastating disorder.

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Harmon et al. (2010). Pharmacological correction of a defect in PPAR-γ signaling ameliorates disease severity in Cftr-deficient mice. Nature Medicine 16, 313–318.

Blame It on Mom and Dad

The integration of mobile elements in the human genome has been an important force in its evolution, so viral integration is not a novel phenomenon. When we think of the viral integration that occurs in our population now, as with retroviruses, the inheritance of these integrated elements isn't considered because it occurs in somatic cells. Apparently, it can happen. Arbuckle et al. recently found families in which integrated human herpesvirus-6 (HHV-6) has been inherited. HHV-6A seems to integrate specifically into telomeres via homologous recombination, using a perfect TTAGGG telomere repeat in its genome. Fluorescence in situ hybridization on peripheral-blood mononuclear cells was used to document the insertion of the virus into telomeric segments, and this occurred on a different chromosome in each of the three families in the study. Within a family, multiple individuals had the same viral strain at the same integration site, so HHV-6 is presumed to have been inherited through the family. Moreover, HHV-6 could be reactivated from peripheral-blood cultures from these individuals, despite the absence of free viral genomes in these cells. HHV-6 is a ubiquitous virus that is believed to cause disease mainly in immunosuppressed or immunocompromised individuals. As yet, the consequences of HHV-6 integration and inheritance are unclear, and we do not know how widespread this phenomenon is.

Arbuckle et al. (2010). The latent human herpesvirus-6A genome specifically integrates in telomeres of human chromosomes in vivo and in vitro. PNAS, in press. Published online March 8, 2010. 10.1073/pnas.0913586107.

A Murky Crystal Ball

Do you want to know your future? Several personal genomics companies will provide you with a risk assessment for various disorders, based on your genotype at several markers. These companies use data from population-based genetic association studies to identify markers whose allele distribution differs between people with a certain phenotype and those without. The problem is that the prospective value of this genetic information on an individual level is not clear. Paynter et al. assessed the prospective value of genetic-risk scores for cardiovascular disease in a systematic way. Using the National Human Genome Research Institute's Catalog of Published Genome-Wide Association Studies, they collected all SNPs associated with cardiovascular disease or its intermediate phenotypes and used them to calculate genetic-risk scores for cardiovascular disease in a prospective study of more than 19,000 women who were followed for a median of 12 years for cardiovascular disease events. After adjustment for traditional risk factors, the genetic-risk scores that they calculated were not associated with incident cardiovascular disease. In fact, self reports of family history of heart attack were better able to predict risk of a cardiovascular event in this group of women than were the genetic-risk scores. For each individual, the authors calculated genetic-risk scores by summing the number of risk alleles at all of the included SNPs. In the future, perhaps we will better understand how to combine and use this type of genotype information in a way that provides more accurate genetic-risk assessments for disease. For now, the view through our genetic crystal ball for complex traits remains pretty murky.

Paynter et al. (2010). Association between a literature-based genetic risk score and cardiovascular events in women. JAMA 303, 631–637.

This Month in our Sister Journals

***ACE* Modifies the Pompe Phenotype**

Because heterogeneity in the age of onset and the severity of the disease course for the non-infantile forms of Pompe disease does not always correlate with the level of residual acid alpha-glucosidase activity, it is believed that modifying genes influence the clinical course of this glycogen storage disorder. Non-infantile Pompe is characterized by progressive muscle weakness, which led Filippi et al. to consider candidate modifying genes based on their association with muscle function. A well-known insertion/deletion (I/D) polymorphism in the gene encoding angiotensin-converting enzyme (*ACE*) has been found by some researchers to associate with muscle strength and physical performance. Among a sample of 38 people with late-onset Pompe disease, the *ACE* DD genotype was associated with an earlier onset of disease and faster disease progression. The D allele is associated with increased ACE activity, which promotes vasoconstriction. The authors postulate that the modifying effect of the ACE polymorphism could be due to the reliance of Pompe-affected muscle tissue on circulating glucose as a result of its inability to use stored glycogen.

Filippi et al. (2010). The angiotensin-converting enzyme insertion/deletion polymorphism modifies the clinical outcome in patients with Pompe's disease. Genetics in Medicine, in press. Published online March 19, 2010. 10.1097/GIM.0b013 e3181s2900e.

Modifiers of Polyglutamine Aggregation

The intracellular aggregation of polyglutamine-containing huntingtin protein is a well-recognized hallmark of Huntington disease. Although these aggregates appear to be intimately linked to the disease, much remains to be

understood about their formation and role in neurodegeneration. Zhang et al. developed a quantitative fluorescence microscopy assay to measure aggregate formation in a *Drosophila* cell-based assay and performed a genome-wide RNAi screen to identify modifiers of aggregate formation. More than 100 genes were validated in their screens, including both enhancers and suppressors of aggregate formation. These include genes with a variety of functions, including protein biogenesis, cytoskeleton and protein trafficking, chaperones, signaling, and nonsense-mediated decay. Two of the aggregation-modifying genes were tested in a *Drosophila* model of Huntington disease neurodegeneration, and both also modified the neurotoxicity of polyglutamine-containing huntingtin. Additionally, homologs of several of their aggregation modifiers have previously been reported by other groups to modify toxicity of polyglutamine and other aggregate-associated disorders. Thus, the modifiers identified in this screen may have relevance for toxicity as well as aggregation of polyglutamine-containing huntingtin.

Zhang et al. (2010). A genome-wide RNAi screen for modifiers of aggregate formation by mutant huntingtin in Drosophila. Genetics, in press. Published online January 25, 2010. 10.1534/genetics.109.112516.