OCA2 ***Haplotypes and Eye Color,*** *by Duffy et al.* **(*p. 241*)**

There is a great deal of evidence of an association between pigmentation levels and skin-cancer risk. One gene that plays a role in controlling pigmentation, *OCA2,* is located in a QTL that was identified, in a genomewide linkage scan, as being responsible for a high percentage of eye-color variation. Additionally, *OCA2* SNPs have recently been found to be associated with eye color. Here, Duffy et al. further examine the role of *OCA2* variants in the color of eyes, hair, and skin, as well as their relationship with freckling and mole count. Three SNPs were found to be associated with distinguishing blue eye color from non-blue eye color. Also identified was a haplotype of these three SNPs that acted as a recessive allele associated with blue eye color and fair skin, whereas other haplotypes acted as dominant alleles producing brown or green eyes and darker skin. One of these SNPs was also shown to be associated with freckling and mole count.

AAV-Mediated Gene Transfer in MoCo Deficiency, *by Kügler et al.* **(*p. 291*)**

Molybdenum cofactor (MoCo) is an essential cofactor for several enzymes. When synthesis of MoCo is disrupted because of a mutation in *MOCS1,* a gene encoding a member of the MoCo biosynthesis pathway, patients experience neuronal loss and death. A mouse model for this defect has been developed; because of *Mocs1* deficiency, these mice are unable to produce cyclic pyranopterin monophosphate (cPMP), a precursor in MoCo biosynthesis. In an effort to develop an effective treatment for MoCo deficiency, previous work with these mice focused on substitute therapy involving the injection of purified cPMP. Although improvements were seen, many technical difficulties existed with this course of action, so the authors, in the present study, tried a new strategy of somatic gene therapy to replace the missing *Mocs1* gene. When newborn mice were treated, the life span of the mice was significantly increased, although the mice were infertile and some did experience kidney failure. The authors then used the gene therapy on adolescent mice that had been treated with cPMP injections since birth. These mice were free of abnormalities and were fertile.

Inheritance of Recombinant mtDNA, *by Zsurka et al.* **(*p. 298*)**

It was generally accepted that human mtDNA does not recombine, but there is increasing evidence that the process does occur. The genetic consequences of this recombination have been unclear, because it is not yet known whether the recombinant mtDNA can be inherited. To address this issue, Zsurka et al. closely examined the mtDNA allele combinations in various tissues of heteroplasmic families. In each of two double-heteroplasmic families, two members were identified who carried all four possible pairs of the mtDNA alleles. It was proposed that the two unexpected combinations were the products either of recombination or of new mutations. Comparisons of the families' mtDNA sequences with those of mitochondrial databases suggested that the sites involved were not hypermutable, so it was considered unlikely that the new alleles arose by mutation. It was, therefore, concluded that the presence of the four allele combinations in more than one family member was the result of inherited recombinant mtDNA.

ALAD Porphyria, *by Jaffe and Stith* **(*p. 329*)**

ALAD (δ-aminolevulinate dehydratase) porphyria is a disorder in which heme biosynthesis is affected because of dysfunction of porphobilinogen synthase (PBGS). Traditionally, it was assumed that PBGS forms a homo-octamer, but characterization of variants has demonstrated that the protein can also assemble into a low-activity hexamer. This conversion between isoforms is characteristic of morpheeins, which are proteins that can associate into one functional conformation and can then disassemble and reassemble into a second functional conformation. The two structural isoforms of PBGS are in equilibrium with one another, and Jaffe et al. sought to determine whether the eight mutations associated with ALAD porphyria affect which conformation of PBGS is predominant. In comparison with the wild-type protein, which existed primarily as the octamer, five of the ALAD porphyria mutants favored the hexamer structure. An analysis of the equilibrium kinetics of the variants revealed that, for each, the reaction was shifted toward the hexamer conformation. These data helped to establish ALAD porphyria as a conformation disease.

A Weighted LD Score Test, *by Wang and Elston* **(*p. 353*)**

As the technology to gain vast amounts of data from large case-control association studies is improving, it is becoming increasingly important that the statistical methods used to analyze these data improve as well. A common dilemma researchers face is how best to balance the amount of information they include in their analysis with the loss of power introduced by additional degrees of freedom. Haplotype-based methods capture more information about a

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disease locus than do single SNP methods, but the phase uncertainty leads to a loss of power. Wang and Elston hoped to solve some of this problem by creating a statistic based on first consolidating the information from multiple correlated SNPs with a Fourier transform (FT). The FT components were then combined in a weighted fashion that accounted for the frequency of each. Comparisons with other methods demonstrated the utility of the new method.

This Month on the Cover

In 1969, Herbert A. Lubs identified a marker X chromosome in a boy who presented with mental retardation and minor anomalies (Am J Hum Genet 21:231–244). The marker chromosome was also found in four other male family members who had mental retardation. The female carriers in the family were unaffected. As shown in the cover image, the variant chromosome was characterized by "an unusual secondary constriction"$^{(p234)}$ at the end of the q arm of X. This disorder was later dubbed "fragile X syndrome," and, in 1991, it was discovered that the expansion of a trinucleotide repeat within the *FMR1* gene was etiologic (Science 252:1097–1102; Science 252:1179–1181; Cell 65:905–914; Science 252:1711–1714).

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