This Month in the *Journal*

USH3 *Gene,* *by Joensuu et al. (p. 673)*

Joensuu et al. add to the list of genes that are involved in Usher syndrome, through their discovery of mutations, in a novel gene, in people with Usher syndrome type 3. The Usher syndromes are characterized by retinitis pigmentosa and sensorineural deafness. A founder mutation for Usher syndrome type 3 exists in the Finnish population, and this aided in the refinement of the critical region for *USH3*. Contigs in this region were assembled, and expressed-sequence tags (ESTs) were examined for mutations. Three mutations in a retina-derived EST were found in affected individuals. The major Finnish founder mutation was a Y100X nonsense mutation. A second founder mutation, M44K, was also identified in this population. Finally, a 3-bp deletion that resulted in the substitution of a methionine for an isoleucine and a leucine was found in an Italian family. This gene, called "*USH3,*" is predicted to be a transmembrane protein, and it has a putative endoplasmic reticulum–retention signal. Mouse models of other forms of Usher syndrome indicate that some of the other genes that are associated with this disorder are involved in the development or maintenance of the stereocilia in the ear. The USH3 protein and gene have no homology to any known proteins or genes. As such, it remains to be seen whether *USH3* plays a similar role or whether it is the key to the discovery of a new pathway underlying the Usher syndromes.

Molecular Basis of Desmosterolosis, *by Waterham et al. (p. 685)*

On the basis of similarity to an *Arabidopsis thaliana* enzyme, Waterham et al. have cloned and characterized the gene responsible for desmosterolosis. This gene encodes 3β-hydroxysterol Δ^{24}-reductase, an enzyme that catalyzes one of the last steps in cholesterol biosynthesis. Desmosterolosis was originally identified through its phenotypic similarities to Smith-Lemli-Opitz syndrome (SLOS), which results from a deficiency of 3β-hydroxysterol Δ^{7}-reductase. Both are malformation syndromes that affect the development of such structures as the palate, limbs, genitalia, head, and circulatory system. Despite the enzymatic deficiency that has been proposed on the basis of biochemical data, the gene for desmosterolosis had not been characterized until this study. The enzyme believed to be deficient in desmosterolosis, 3β-hydroxysterol Δ^{24}-reductase, reduces the Δ^{24} double bond of desmosterol during the production of cholesterol. DWF1 catalyzes a very similar reduction reaction in *A. thaliana,* and a putative human ortholog for *DWF1* has been known. Waterham et al. decided to study this human ortholog to determine whether it is the gene responsible for desmosterolosis. When expressed in *Saccharomyces cerevisiae,* the enzyme encoded by this gene converts desmosterol to cholesterol in an NADPH (reduced nicotinamide adenine-dinucleotide phosphate)–dependent, FAD (flavin adenine-dinucleotide)–enhanced reaction. Mutations in this gene, which was dubbed "*DHCR24,*" were found in two patients with desmosterolosis, and the proteins produced by these mutated genes exhibited substantial reductions in enzymatic activity in the *S. cerevisiae* expression system. The development of SLOS and desmosterolosis in response to deficiencies in cholesterol biosynthesis indicates that cholesterol plays an important role in embryonic development. However, its role in this process is not yet clear.

CNGA3 *Mutations in Cone Photoreceptor Disorders,* *by Wissinger et al. (p. 722)*

The *CNGA3* gene encodes the α-subunit of the cone-photoreceptor cGMP-gated channel, which is crucial for cone phototransduction in the eye. Mutations in this gene, as well as some in the gene that encodes the β-subunit of the same channel (*CNGB3*), have been found in patients with complete achromatopsia, or total color blindness. To define more clearly the spectrum of disorders associated with mutations in *CNGA3,* Wissinger et al. performed a large-scale mutation screen in people with complete achromatopsia, incomplete achromatopsia, and progressive cone dystrophy. Mutations were identified in 53 of 258 families, the majority being missense mutations. In fact, four recurrent missense mutations account for almost 42% of those detected. Mutations were not restricted to families with complete achromatopsia but were found in families with all three of the diagnoses that were examined. These results widen the spectrum of phenotypic manifestations of mutations in *CNGA3*.

Mismatch Repair in Colon Cancer, *by Cunningham et al. (p. 780)*

Cunningham et al. have examined the prevalence of defective DNA mismatch repair, as well as the mechanism through which these defects occur, in a series of unselected patients with colorectal cancer. Twenty percent of this sample of 257 cases had defective DNA mismatch repair, but germline mutations in the mismatch-repair genes

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hMLH1, hMSH2, and *hMSH6* account for only ~2% of the total cases. Although somatic mutations in a mismatch-repair gene were also responsible for some of the mismatch-repair defects, promoter hypermethylation of *hMLH1* appears to be responsible for most of the cases of DNA mismatch repair in these tumors. Defective mismatch repair is one cause of hereditary nonpolyposis colorectal cancer (HNPCC). This disorder is diagnosed through use of a set of clinical criteria called the "Amsterdam criteria," which includes an assessment of family history of colon cancer. Cunningham et al. found that not all patients with germline mutations in a mismatch-repair gene fulfilled the Amsterdam criteria and that not all cases that fulfilled these criteria had defective mismatch repair. The authors propose that use of a molecular diagnosis of hereditary defective mismatch-repair syndrome, rather than HNPCC, might yield a more homogeneous group of patients and might facilitate the identification of individuals at risk for cancer.

Linkage Disequilibrium Decay in Humans, *by Frisse et al. (p. 831)*

Accurate characterization of population-specific linkage disequilibrium (LD) across the genome is very important for the design of disease-association studies. However, different studies and different approaches to the characterization of LD have yielded discrepant results. To be able to make more-accurate comparisons between samples, Frisse et al. performed an empirical characterization of LD in three distinct population samples: African, Asian, and European. Sequence variation in the same 10 noncoding regions of the genome was analyzed in each population, through the resequencing of these regions in every individual in the sample. This allowed an examination of the spectrum of allele frequencies in the different populations, as well as a comparison of the amount of LD with the amount of polymorphism in each sample. Although, in these types of studies, non-African populations are often grouped together for comparison with African populations, frequency-spectra differences between the Asian and European populations in this study imply that different population histories may have shaped the two groups and that the "non-African" group is not uniform. Because gene conversion is likely to play a role in the decay of LD, Frisse et al. used their data to estimate the parameters of the gene-conversion process. The amount of gene conversion calculated from their human sample was higher than that which previously had been estimated in model organisms, such as *Drosophila* and yeast. These new estimates of the extent of gene conversion in humans should allow more-accurate predictions, through computer simulation, of genomewide patterns of LD. Previous predictions of the extent of genomewide LD, which have been based on computer simulation (see the Kruglyak [1999] reference cited by Frisse et al.), are upheld in the African sample in the study by Frisse et al., in which relatively low levels of LD were observed. However, LD in the non-African samples was much higher than that predicted by the simulations. These results indicate that the marker density required for association studies will vary according to the population under examination, with African populations requiring a marker density much higher than that required by non-African populations.

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