This Month in the *Journal*

TCF8 *Mutations Cause PPCD,* *by Krafchak et al.* **(***p. 694***)**

The corneal endothelium is normally composed of a single layer of cells that lose their mitotic potential. In posterior polymorphous corneal dystrophy (PPCD), these cells somehow retain their ability to divide, so that a multicellular layer resembling an epithelium develops. Although this condition is often asymptomatic, it can also be associated with glaucoma, and there can be a wide range of severity, even in the same family. Two genes for PPCD have already been found, but mutations have been reported in only a limited number of cases. These genes are *VSX1,* which encodes a transcription factor, and *COL8A2,* which encodes a collagen. Krafchak et al. focus on the *PPCD3* locus, which was previously defined on chromosome 10p11. Within *PPCD3* is *TCF8,* which encodes a transcription factor that is known to regulate the expression of a collagen. Krafchak et al. find that *TCF8* mutations appear to account for a large proportion of familial cases of PPCD. Closer examination of mutation-positive families reveals that the consequences of these mutations may not be limited to the eye; the frequency of inguinal hernia and hydrocele is higher than expected in affected individuals, and those affected may also have orthopedic anomalies, such as bone spurs and kneecap dislocations. PPCD can occur as a component of Alport syndrome. A link between the simple and syndromic forms of this phenotype is indicated by the finding that *COL4A3,* one of the Alport syndrome genes, is aberrantly expressed in the corneal endothelium of a proband carrying a *TCF8* mutation.

Pedigree Analysis with Clustered Markers, *by Abecasis and Wigginton* **(***p. 754***)**

Current linkage analysis methods generally assume linkage equilibrium between markers. With the increased use of high-density SNP linkage marker panels, this assumption will be often violated. But how much of a problem is this violation? Abecasis and Wigginton demonstrate, through simulations and a real-data example, that ignoring marker linkage disequilibrium (LD) can substantially inflate LOD scores, especially when parental data are missing. In fact, in the psoriasis data set they use as an illustration, one of the previously identified linkage peaks disappears when LD is taken into account. The authors tackle this problem with the development of an algorithm, for use with pedigree data, that accounts for LD by clustering tightly linked markers. Haplotype frequencies are used to model LD within each cluster, and a second algorithm is provided to estimate these frequencies. The authors' methods, which are implemented in MERLIN, overcome the biases in multipoint linkage analysis that are caused by marker LD, and they will allow for more-effective use, in linkage analysis, of the data from high-throughput genotyping technologies.

Human* RMRP *Is Essential for Cell Growth, *by Thiel et al.* **(***p. 795***)**

Anauxetic dysplasia is an autosomal recessive disorder associated with extreme short stature, hypodontia, and mild mental retardation. In an effort to elucidate new pathways involved in cell growth and division, Thiel et al. performed linkage analysis of families with anauxetic dysplasia and identified novel mutations in *RMRP,* the untranslated RNA subunit of the ribonucleoprotein endoribonuclease, RNase MRP. The gene, the yeast homolog of which is known to be involved in ribosome synthesis and the processing of cell-cycle mRNAs, is also mutated in cartilage hair hypoplasia (CHH) and metaphyseal dysplasia without hypotrichosis (MDWH). To determine how mutations in *RMRP* affects cell growth in mammals, the anauxetic dysplasia variants and one CHH variant are overexpressed in the poorly growing patient fibroblasts. In comparison with the wild-type *RMRP,* the anauxetic dysplasia mutants are able to stimulate cell growth and division only minimally. These dysfunctional mutants also generate an increase in uncleaved 5.8S rRNA, which suggests that an inability to process ribosomes might be a factor in their poor performance. Of note, although the CHH mutation also inhibits *RMRP* function, a moderate level of growth is observed. This potentially correlates to the less-severe skeletal dysplasia associated with CHH. The authors then observe another important difference between the alleles when they analyze the ability of the variants to process cell-cycle mRNAs: the CHH mutant is unable to degrade cyclin B mRNA, whereas the anauxetic dysplasia variants appear to function normally in this capacity. This reveals that the ability of *RMRP* to process mRNA is genetically separate from its involvement in ribosome synthesis.

Human Reticulate Evolution, *by Jackson et al.* **(***p. 824***)**

Reticulate evolution results in networks of sequences, rather than simple ancestor-descendant relationships,

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and can occur through such processes as gene conversion and unequal recombination. Approximately 5% of the human genome sequence is made up of recently formed segmental duplications and could have been affected by these processes, but the extent to which this has occurred is unclear. Jackson et al. use multiple alignments of recently duplicated sequences from across the human genome to compare the relative contributions of reticulation and of nucleotide substitution to their evolution. Although the patterns of reticulation vary greatly across these sequences, reticulate evolution appears to have played a strong role in their development; rather than evolving independently, these sequences appear to exchange sequence information frequently. The sequences selected for this study were required to have at least four copies of high identity. A less-stringent analysis of duplicated sequences might reveal that the role of reticulation in genome evolution is either more or less widespread. Certainly, it appears that one can no longer make naive assumptions about the evolutionary relationships between duplicon sequences when comparative analyses are performed.

Abrogation of* MPZ *Mutant–Induced Apoptosis, *by Khajavi et al.* **(*p. 841*)**

Mutations in the myelin protein zero gene, *MPZ,* cause a variety of neuropathies, ranging from Charcot-Marie-Tooth disease (CMT) to the more severe Dejerine-Sottas neuropathy (DSN) and congenital hypomyelinating neuropathy (CHN). It has been suggested that, among these diseases, the phenotype severity is correlated with the location and type of *MPZ* mutation. Some of the CMT mutations result in short transcripts that are degraded before translation and cause haploinsuffiency. Alternatively, DSN and CHN are associated with mutations that truncate the transcript far enough downstream to generate a stable mRNA that is translated into a mutant protein with presumable dominant negative function. But there are also CMT alleles for which the mRNA escapes degradation and a protein is produced, and yet the milder phenotype is seen. Khajavi et al. strive to elucidate the differences between the mutant proteins of CMT and DSN/CHN by transiently transfecting the variant constructs into HeLa cells and HEK293 cells. Localization studies reveal that the CMT and wild-type proteins are detected at least partially on the cell surface, whereas the DSN/CHN mutants are sequestered in the endoplasmic reticulum (ER). Also, in apparent connection to a toxic effect of the ER aggregation, cells overexpressing the DSN/CHN variants show significantly higher levels of apoptosis than those transfected with the CMT or wild-type alleles. The investigators then examine whether curcumin, a turmeric derivative recently shown to rescue misfolded protein in cystic fibrosis model systems, has any effect on the dying cells. They discovered that DSN/CHN proteins in cells treated with 10 μM of curcumin are released from the ER and subsequently localize to the plasma membrane. Accordingly, apoptosis levels in the treated DSN/CHN cells resemble those in the wild-type and CMT cells.

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