This Month in the *Journal*

Yin Yang Haplotypes in the Human Genome, *by Zhang et al.* (*p. 1073*)

While working on the identification of haplotype-tagging SNPs using chromosome 21 data, Zhang et al. stumbled across an interesting phenomenon that they dub "yin yang haplotypes." These pairs of high-frequency haplotypes are composed of completely mismatched SNP alleles; that is, they differ from each other at every SNP position. To study these divergent haplotypes in a more systematic manner, Zhang et al. developed an algorithm to identify regions containing yin yang haplotype pairs and used it to characterize two genomewide data sets. They found that 75%–85% of the human genome is spanned by yin yang haplotypes and that these haplotypes make up a significant portion of the total haplotype diversity. Higher coverage with yin yang haplotype was achieved after removal of low-frequency SNPs from the analysis, which led the authors to suspect that these haplotypes are ancient. Further supporting this idea is the high degree of conservation of yin yang haplotypes across populations, suggesting these patterns emerged prior to the African diaspora. Although it might seem that evolution must have had a hand in the rise of opposing haplotype alleles, simulations indicate that yin yang haplotypes can occur under a neutral evolution model.

γ-Actin Gene Mutations and Progressive Deafness, *by Zhu et al.* (*p. 1082*)

Because mutations in several genes encoding actin-interacting proteins have been found to cause hearing loss, it is perhaps not surprising that Zhu et al. report mutations in the gene for γ-actin itself in four families with progressive deafness. What is unexpected, though, is the fact that, when this protein is widely expressed and highly conserved, the only phenotype in the affected individuals is hearing loss. All four mutations are missense mutations at conserved residues, and they occur in three of the four subdomains of the γ-actin protein. Zhu et al. speculate that the mutations have mild effects on protein function and that the auditory hair cells may be more sensitive to mutations in this gene because they do not regenerate, so subtle mutations can have long-term effects. This is in contrast to other γ-actin–expressing tissues in which cells are regenerated frequently, such as the intestinal epithelium. Hair cells may also be more susceptible to these mutations than other γ-actin–expressing cells because their function is dependent on precise control of their ultrastructural organization, which is determined by the actin cytoskeleton.

0002-9297/2003/7305-0001$15.00

Mutations and Clinical Correlations in XLRP, *by Sharon et al.* (*p. 1131*)

In an attempt to define genotype-phenotype correlations in X-linked retinitis pigmentosa (XLRP), Sharon et al. screened *RP2* and *RPGR* for mutations in a large sample of males with a diagnosis (or a suspected diagnosis) of XLRP or cone-rod degeneration. Mutations were found in 79% of the 135 people with a prior clinical diagnosis of XLRP, with the most common location being ORF15 of *RPGR*, a region that was overlooked in initial screens of this gene. Although there is a good deal of overlap in measures of ocular function, people with *RP2* mutations have, on average, a significantly lower visual acuity than patients with *RPGR* mutations. Subgroup analyses of the people with *RPGR* mutations indicate that those with ORF15 mutations have milder disease than those with mutations in exons 1–14. Within this ORF15 mutation group, the severity of the visual effects depended on the length of the wild-type amino acid sequence expressed. Confirming a previous report, mutations in ORF15 downstream of codon 445 were often associated with cone-rod degeneration rather than a strict XLRP phenotype, suggesting that these mutations are more deleterious to cones than to rods. These findings move us toward the ultimate goal of this research, which is to make mutation-based, long-term visual prognoses, but the heterogeneity in visual impairment within the mutation groups does not yet make this fully possible.

Mapping and Cloning the Gene for Mast Syndrome, *by Simpson et al.* (*p. 1147*)

In a recent *Journal* editorial, Crosby and Proukakis (71: 1009–1016) proposed that a common underlying mechanism in some hereditary spastic paraplegias (HSPs) may be a defect in cellular transport. Now, with the finding that mutations in *ACP33* are found in people with Mast syndrome, Simpson et al. believe they have found additional evidence for this model. Mast syndrome is a complicated form of autosomal recessive HSP that is found in Old Order Amish. The disorder is progressive, and onset generally occurs in young adults, although milestone delays and subtle cognitive and motor difficulties are often reported in childhood. Through use of a large Amish pedigree, Simpson et al. identified a single-nucleotide insertion in *ACP33* that leads to premature truncation of the encoded protein. ACP33 was originally identified as a CD4-

interacting protein that appears to regulate CD4-dependent T cell activation (see Zeitlmann et al. reference in Simpson et al.). The protein is partitioned between the cytoplasm and the endosomal/trans-Golgi network, and it has been proposed that it may be involved in intracellular trafficking and protein sorting. The HSPs result from degeneration of the longest motor and sensory axons in the spinal cord. Dr. Crosby's group has speculated that, because of their size, these axons are particularly susceptible to disruption of intracellular trafficking processes, which are vital for neuron survival. They propose that the *ACP33* gene product should be renamed "maspardin" for "Mast syndrome, spastic paraplegia, autosomal recessive with dementia."

PTEN Mutations Upregulate Akt in LDD, *by Zhou et al.* (*p. 1191*)

PTEN mutations cause a variety of disorders, including Proteus syndrome, Bannayan-Riley-Ruvalcaba syndrome, and Cowden syndrome (CS). The explanation for phenotypic differences in the expression of *PTEN* mutations and the relationship between these syndromes has not been fully uncovered. Lhermitte-Duclos disease (LDD) is another disorder associated with *PTEN* mutations, and it often occurs in association with features of CS, suggesting that these disorders share a common etiology. CS is characterized by multiple hamartomous lesions and typically involves neoplasms of internal organs, whereas LDD is a hamartomous overgrowth of hypertrophic ganglion cells. To better understand the relationship between CS and LDD, Zhou et al. gathered 18 subjects with LDD, without regard to the presence or absence of other features in these individuals, and performed mutational analysis on *PTEN*. They discovered 16 *PTEN* mutations in 15 adult-onset cases, both with and without features of CS. On the basis of six matched germline DNA samples, at least these six were germline mutations. Several points suggest that loss of PTEN is sufficient to cause LDD and that LDD is a component of CS. These include the high frequency of *PTEN* mutations, the complete or partial loss of PTEN staining in ~75% of samples, and the identification of loss of heterozygosity or a second-hit somatic *PTEN* mutation in three cases. In contrast to the mutations in the adult-onset cases, all three childhood LDD cases lacked *PTEN* mutations, both somatic and germline. In conjunction with three other reported patients with childhood LDD who never developed features of CS, this finding makes the interesting suggestion that adult-onset and childhood LDD may be distinct disorders, although this will require further study.

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