***Early Pathogenic Events in Alexander Disease,* by *Perng et al.* (*p. 197*)**

Alexander disease is an intermediate filament disorder characterized by aggregates, or "Rosenthal fibers," that consist of a variety of proteins, including glial fibrillary acidic protein (GFAP). Heterozygous mutations in GFAP have been identified in patients with the disease, and R416W has been found in a number of familial cases. Here, Perng et al. examined the consequences of this mutation on filament assembly in a variety of cell systems. In contrast to the regular fibers formed in cells expressing wild-type GFAP, expression of the variant protein disrupts fiber elongation and leads to the production of shorter pieces. These short pieces are shown to clump together into insoluble aggregates. The authors then produced an antibody that specifically binds to the mutant protein, to evaluate, for the first time, whether the R416W GFAP is part of the abnormal fibers. By using the antibody on brain sections from a patient with Alexander disease, they were able to demonstrate that the mutant protein is stably produced in vivo and is part of both the normal filaments and the Rosenthal fibers.

***ZFYVE27 Is Mutated in HSP,* by *Mannan et al.* (*p. 351*)**

Spastic paraplegia (SP) is a genetically heterogeneous disease that has dominant, recessive, and X-linked forms. Although various genes have been identified that are associated with the disorder, several affected families remain for which no causal mutations have been found. Mutations in spastin, a protein involved in endosomal trafficking, are among the most common causes of autosomal dominant SP. By examining the binding partners of spastin, using a yeast two-hybrid assay, Mannan et al. established a pool of candidates that may also be important in the disease pathways. One of these proteins, ZFYVE27, contains domains suggestive of involvement in endosomal localization. The authors confirmed an interaction between the two proteins through localization and coimmunoprecipitation studies. *ZFYVE27* was then sequenced in families with autosomal dominant SP, and a mutation was identified that segregated with the disease. The mutation was found to disrupt binding between ZFYVE27 and spastin and to affect localization.

TRMU *Modifies Expression of mtDNA Mutation,* by *Guan et al.* (*p. 291*)

The penetrance and severity of hearing loss due to mutations in 12S rRNA are highly variable, and it has been predicted that other variant factors interact with the rRNA to affect the hearing process. Previous work has demonstrated that, in analysis of cells from individuals who carry a 12S rRNA mutation, the cells of affected individuals show a greater biochemical defect than do those from individuals with normal hearing. In addition, results of genome-wide linkage studies have suggested that nuclear loci exist that modify the effects of the 12S rRNA mutations. Some candidate genes for a modifier have been identified because of the way in which mutations of their orthologs in yeast and *Escherichia coli* interact with rRNA variants to influence phenotype. One of these genes, *TRMU,* is located in a previously identified modifier locus. In a screen of a large number of families with deafness due to 12S rRNA mutations, Guan et al. identified a *TRMU* mutation that appears to contribute to the hearing-loss phenotype. Examination of cells carrying variants of both 12S rRNA and *TRMU* revealed that modification of tRNAs was significantly affected and that there was a decrease in tRNA levels. These changes were not observed in cells with only 12S rRNA mutations.

***Hierarchical Bayes Haplotype Inference,* by *Zhang et al.* (*p. 313*)**

In mapping studies and evolution studies, more information can be learned from phased haplotypes than from the genotypes of isolated SNPs, but it is too slow and expensive to determine phased haplotypes by molecular means. Various algorithms have been proposed that allow the cost-effective conversion of SNP genotypes to inferred haplotypes. Incorporation of coalescence theory, the framework that takes into account ancestral origins of modern haplotypes, can improve the accuracy of these methods. Although the current leading coalescence algorithm performs well when applied to data sets, it may be limited by its inference results. In an effort to improve this, Zhang et al. introduce a new method, the coalescence-guided hierarchical Bayesian (CHB) model. When used with coalescence-based and empirically derived simulation data sets, the methods tested were comparable, but, when random data is missing, CHB outperformed the others. To extend further the application of CHB, the authors modified their model to incorporate recombination.

***Influence of Deletion on Gene Expression,* by *Merla et al.* (*p. 332*)**

Williams-Beuren syndrome (WBS) is caused by a deletion on the long arm of chromosome 7. It has traditionally been assumed that the WBS phenotype is due to a decrease in expression of the genes that are deleted. Here, Merla et

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al. looked at the expression of the genes in the deleted region as well as the expression of the genes in the 20 Mb surrounding the deletion. Many of the analyzed hemizygous genes showed an expected decrease in expression in patient cells. Unexpectedly, there was evidence that, dependent on cell type, the expression of two of the genes within the deleted region was not significantly lower in WBS cells. To evaluate the effects of the deletion on the genes near the breakpoints, the expression levels of 14 nonhemizygous genes in patient cells were compared with those in normal cells. Several of the genes with two normal copies showed a significant decrease in expression in WBS cells. It is presumed that critical regulatory regions for these genes are disrupted by the deletion. As the effort to make connections between the WBS phenotype and the involved genes continues, we might learn that the genes outside the deletion play a role as well.

This Month on the Cover

In 1980, David Botstein et al. proposed a method for mapping the human genome with use of RFLPs (Am J Hum Genet 32:314–331). It was their prediction that these markers could be used in linkage studies of human pedigrees. The cover image is a reproduction of figure 1 from their article, in which they describe how Southern blots could be used to visualize an RFLP.

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