This Month in the *Journal*

This month in the *Journal,* Kristin Waite and Charis Eng (p. 829) present a review of the tumor-suppressor gene *PTEN.* Along with an overview of the spectrum of diseases in which it is known to be mutated, Waite and Eng discuss PTEN's phosphatase activities and the role that this multitalented protein may have in the PI3K, MAP kinase, insulin signaling, and other pathways.

Rapsyn Mutations in Humans, *by Ohno et al. (p. 875)*

Congenital myasthenic syndromes (CMS), characterized by muscle weakness, result from defects in endplate-specific proteins. CMS-associated mutations are found in the genes for choline acetyltransferase, an acetylcholinesterase subunit, and the acetylcholine receptor (AChR) subunits. Ohno et al. find 10 patients who do not carry mutations in these genes, so they decide to expand their search for mutations. The researchers focus on the gene for rapsyn, *RAPSN,* because, in the postsynaptic membrane of the motor endplate, it binds to the AChR and links it to the subsynaptic cytoskeleton. Three mutations are identified in four of these patients, including two missense mutations and a small insertion. Endplate studies indicate that these individuals have AChR and rapsyn deficiencies and impaired morphologic development of the postsynaptic region but no evidence of decreased acetylcholine release in response to nerve impulse. In a cell-culture system, the *RAPSN* mutations significantly compromise AChR recruitment to rapsyn clusters. The severity of disease in these patients is variable, even between two patients who possess identical homozygous mutations, leading the authors to propose that polymorphisms in functionally related genes may play a role in phenotypic expression of this disorder.

SOS1 ***Mutation Causes HGF1,*** *by Hart et al. (p. 943)*

Hart et al. have identified the first mutation associated with nonsyndromic hereditary gingival fibromatosis (HGF). This is a benign fibrous enlargement of the gingiva that, in severe cases, can prevent tooth eruption. By use of a very large affected family, they are able to limit the critical region on chromosome 2p21-p22 to ~2.3 Mb. Sixteen genes in this critical region were sequenced, and only one polymorphism was found to segregate with the HGF phenotype. The polymorphism is a 1-base insertion in the *Son of sevenless-1* gene (*SOS1*), and it is predicted to cause a frameshift and premature truncation of the protein. HGF1 segregates as an autosomal dominant trait in this family, and both normal and mutant *SOS1* transcripts were demonstrated in the gingival tissue and white blood cells of affected individuals. The mutation appears to remove functional domains that maintain SOS1, a guanine nucleotide exchange factor, in a downregulated state. On the basis of previous studies of SOS1 carboxy terminal truncations in a variety of systems, it is believed that this mutation leads to a gain of function, although the mechanism by which it results in gingival overgrowth and the reason for its tissue specificity are, as yet, unknown.

Increased Alternative Splicing Causes Cardiac Fabry Disease (Report), *by Ishii et al. (p. 994)*

Ishii et al. describe a mutation, in individuals with cardiac Fabry disease, that substantially increases alternative splicing of RNA transcribed from the causative gene. Fabry disease is an inborn error of glycosphingolipid catabolism resulting from an α-galactosidase A (α-Gal A) deficiency. The cardiac form of Fabry disease is a relatively mild form of the disease, presumably due to residual α-Gal A activity, that generally presents with left ventricular hypertrophy and late-onset cardiomyopathy. In six patients with cardiac Fabry disease, an intronic mutation leads to inclusion of a 57-nt intronic sequence in α-Gal A transcripts. This alternative exon is used at low levels in normal human tissues and, in lymphoblasts, at rates ~10 times higher than normal when the mutation is present. The authors propose that this G→A mutation increases the A/C predominance in an already A/C-rich sequence and that the sequence may therefore serve as an A/C-rich exonic splicing enhancer. No matter the mechanism, the presence of this mutation in six people with the cardiac form of Fabry disease suggests that it is a prevalent mutation that should be considered in similar patients, particularly in the absence of mutations in the coding and flanking regions of this gene.

Premature Chromosome Condensation Syndrome (Report), *by Neitzel et al. (p. 1015)*

Neitzel et al. describe a unique, autosomal recessive cell-cycle disorder in a pair of siblings with microcephaly, profound mental retardation, and growth retardation. The disorder is characterized by premature chromosome condensation with a high rate of prophase-like cells that retain their nuclear membranes. Additional cell-cycle analyses did not indicate a prolongation of the G2/M phase, increased radiosensitivity, or malsegregation of

0002-9297/2002/7004-0001$15.00

chromosomes at anaphase. Although several factors are known to play a role in the regulation of the affected stages of the cell cycle, homozygosity mapping did not implicate any of these known candidate genes in this disorder. It is likely, therefore, that cell lines from these patients will be useful in further dissection of cell-cycle regulation and that they may lead to the identification of a novel factor in the regulation of early prophase.

***SNPs as Indicators of Deletions* (*Report*),** *by Huie et al.* (*p. 1054*)

Huie et al. suggest that apparent homozygosity for multiple contiguous SNPs be considered as a potential indicator of heterozygous deletions. Using this clue, they successfully identify the second mutation in a patient with autosomal recessive glycogen storage disease type II, in whom only a single splice-site mutation had been found by use of conventional methods. They noticed that 14 SNPs in the causative gene, *GDSII,* were apparently homozygous in the proband. Primers flanking this "homozygous" region were used to amplify the region, yielding a product much smaller than expected. Sequence analysis confirmed an 8.26-kb deletion in *GDSII*. This work shows how easy it can be to miss large deletions by conventional PCR and sequencing methods, but it also indicates that this problem can be overcome fairly easily if apparent long-range homozygosity is examined carefully. The authors also emphasize that apparent mutation homozygosity in probands with nonconsanguineous parents should be confirmed through the identification of the mutation in both parents.

KATHRYN BEAUREGARD
Deputy Editor