This Month in the *Journal*

This month in the *Journal,* David Kelsell and colleagues have contributed a review on the connexin family of proteins and their relationship to skin disease and hearing impairment. This work summarizes which connexins—and which mutations in the connexin genes—are involved in particular inherited disorders, and it highlights the importance of gap junctions in the epidermis and the inner ear.

SOST*, a Novel Gene Mutated in Sclerosteosis,* *by Brunkow et al.* (*p. 577*)

Sclerosteosis is a bone-overgrowth syndrome that particularly affects the skull and that leads to widening of the calvarium (i.e., the domelike part of the skull), with a resulting increase in intracranial pressure, as well as to a compression of the cranial nerves that can lead to deafness and facial palsy. The great majority of patients affected with sclerosteosis are from the Afrikaner population of South Africa, and the concentration of the disease in this population is believed to be due to a founder mutation. Brunkow et al. have identified sclerosteosis-associated mutations in a previously unidentified gene, which they term "*SOST,*" on chromosome 17q12-q21. As predicted, all of the Afrikaner patients in the study carry the same mutation, a nonsense mutation near the amino terminus of the predicted protein. An affected individual from Senegal has a *SOST* mutation that leads to aberrant splicing and, possibly, to nonsense-mediated decay of the message. The function of the protein encoded by *SOST* is unknown, but the authors speculate that it might be a negative regulator of a protein important for postnatal bone formation. They further suggest that, if their model is true, this protein could be considered as a potential target for the development of therapies aimed at bone-loss disorders; inhibiting this negative regulator of bone deposition could yield increased bone density in people with osteoporosis and related disorders.

IKBKAP *Mutation Causes Familial Dysautonomia,* *by Slaugenhaupt et al.* (*p. 598*)*; and* ***Familial Dysautonomia Is Caused by Mutations of IKAP (Report),*** *by Anderson et al.* (*p. 753*)

In this issue, two groups report that mutations in the *IKBKAP* gene, encoding the protein IKAP, cause familial dysautonomia (FD), an autosomal recessive disorder that is found almost exclusively in people of Ashkenazi Jewish origin. Affected individuals show poor development of and degeneration of the sensory and autonomic nervous systems, with symptoms including abnormal sweating, hypertension, difficulty in feeding and sucking, gastrointestinal dysfunction, and insensitivity to pain. These complementary articles illustrate how the same results can be achieved through different processes. The group led by Berish Rubin at Fordham University (see the Anderson et al. report) used the human genome sequence to identify mRNAs encoded in the area of the FD locus. Reverse transcriptase–PCR products for these messages were compared, for size and single-strand conformation polymorphisms, in a control individual and one homozygous for the major FD haplotype. One transcript in the region was found to be shorter in these patients than in controls; this was the *IKBKAP* message. In contrast, Jim Gusella's group at Massachusetts General Hospital (see the article by Slaugenhaupt et al.) used exon trapping and cDNA selection to clone all of the genes in the FD critical region. A screen for mutations in these genes led to the identification of several single-nucleotide polymorphisms that were used to narrow the candidate interval. The complete sequence of this smaller critical region was compared in a patient homozygous for the major FD haplotype and several controls. Only one unique change was identified in patients, and it was located in *IKBKAP.* The major FD mutation, which accounts for 99.5% of disease chromosomes, results in aberrant splicing of the *IKBKAP* RNA and, thus, to loss of one of the exons of the mRNA. Whereas Slaugenhaupt et al. found tissue-specific expression of this splicing defect, Anderson et al. detected both a shortened transcript and a truncated protein in lymphoblasts. A second, much less common mutation, R696P, was found in a consensus phosphorylation site. Anderson et al. demonstrated that this substitution resulted in a reduced level of phosphorylation for this protein. The normal function of IKAP is not well understood, so it is not clear how these mutations lead to disease. However, the discovery of the mutations corresponding to both the major and minor 2 FD haplotypes will greatly increase the efficiency of genetic testing for this disease.

Analyses of* FOXC1 *Missense Mutations, *by Saleem et al.* (*p. 627*)

In the February 2001 issue of the *Journal,* Nishimura et al. (68:364–372) found several *FOXC1* mutations in people with congenital anterior-chamber defects of the eye. Approximately half of these mutations were predicted to lead to truncated proteins. In addition, a du-

0002-9297/2001/6803-0001$02.00

plication of the region containing *FOXC1* was found in two affected families. The discovery of these mutations suggested that tight regulation of FOXC1 levels is crucial for proper ocular development. Following up on this story, we have an article by Saleem et al. They studied the effects of five different missense mutations on FOXC1's function as a transcription factor. These mutations are associated with Axenfeld-Rieger anomaly, a group of disorders characterized by defects in the anterior eye segment. Structural models based on the rat Genesis protein predict that none of the mutations disrupts the FOXC1 structure. In biochemical assays, the mutations proved to be variously affected at the level of protein stability, DNA binding, and transactivation ability. Although, when compared with wild-type protein, the defects in the mutant proteins range from a 95% decrease in protein levels to a 40% reduction in transactivation activity, all of the mutations led to an indistinguishable phenotype. These results lend further support to the idea that tight regulation of FOXC1 levels is important for proper development of the eye.

Enzyme Replacement in Fabry Disease, *by Eng et al.* (*p. 711*)

In our January issue (68:14–25), Robert Desnick's group reported a successful preclinical study of enzyme replacement in Fabry mice. This month, they report the next stage in this work, a phase 1/2 clinical trial. To date, treatment for Fabry disease, a deficiency of α-galactosidase A activity, consists of symptom management for pain and for complications of the cardiac, renal, and cerebrovascular systems, which are due to the accumulation of globotriaosylceramide (GL-3). In this paper, Eng et al. report that infusion of recombinant human α-Gal A leads to rapid, dose-dependent decreases in plasma GL-3. Clearance of GL-3 from tissues was more variable but generally decreased in the liver, skin, heart, and kidney. Patients participating in the trial reported significant improvement in overall pain and general health. A double-blind study is needed to further evaluate the efficacy of this treatment as a therapy for Fabry disease.

Clonal Expansion of mtDNA, *by Elson et al.* (*p. 802*)

In this issue, Elson et al. have contributed work designed to model in single cells the accumulation of mtDNA mutations. Although the overall level of mtDNA mutations remains fairly low in older people, individual cells may contain high levels of a single, mutated mtDNA species. Several models have been proposed to explain this finding, and most of them invoke a selective mechanism that leads to preferential replication of the mutated mtDNA molecules. Elson et al. perform simulations to examine the clonal accumulation of mutant mtDNA in single postmitotic cells. The simulations show that a gradual increase in the number of cells containing a high proportion of mutant mtDNA can result simply from random intracellular drift.

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