This Month in the *Journal*

In the last installment of "This Month in the *Journal,*" I stated that Dr. Rando Allikmets wrote an editorial highlighting "the work of both Rivera et al. (p. 800), who find that mutations in *ABCR* are the major cause of autosomal recessive cone-rod dystrophy, and Maugeri et al. (p. 960), who provide further evidence that sequence variation in *ABCR* is associated with age-related macular degeneration." This should have read "the work of both Maugeri et al. (p. 960), who find that mutations in *ABCR* are the major cause of autosomal recessive cone-rod dystrophy, and Rivera et al. (p. 800), who provide further evidence that sequence variation in *ABCR* is associated with Stargardt disease." I apologize to both sets of authors for this error.

In this month's issue, Villavicencio et al. (p. 1047) have contributed a review on the Sonic hedgehog (SHH) pathway. They outline SHH signaling through the PATCHED receptors to the GLI family of transcription factors. They also provide an overview of the wide range of disorders, from holoprosencephaly to cancers, that result from dysregulation of this crucial developmental pathway. Next up are two invited editorials on the reconstruction of population histories. The first, by Peter de Knijff (p. 1055), discusses some caveats for the reconstruction of human genetic histories via unique mutation events and short tandem repeats on the Y chromosome. The second, by Mark Seielstad (p. 1062), discusses two articles—one by Mesa et al. (p. 1277) and the other by Carvajal-Cormona et al. (p. 1287)—that, in studies of the genetic histories of several South American populations, have found that the current population of Antioquia (Colombia) is probably derived from an original population that had a highly asymmetric mating pattern between European males and native females. Furthermore, they have found no evidence to suggest differences in sex-specific migration rates during the evolution of native Colombian populations.

Imprinted Genes* PWCR1/Pwcr1 *Encode Small RNA,
by de los Santos et al. (*p. 1067*)

The loss of paternal genes in the 15q11-q13 region leads to the neurodevelopmental disorder Prader-Willi syndrome (PWS). Although several genes in this region have been identified, mouse models for PWS suggest that an unknown gene may be responsible, at least in part, for the phenotype of this disorder. de los Santos et al. have identified an additional gene in the 15q11-q13 region and have named it "*PWCR1*." To facilitate an experimental model for studies of this gene, the authors have also gone on to find the mouse orthologue, dubbed "*Pwcr1*." *PWCR1* is an intronless, noncoding gene that is not expressed in cells from patients with PWS. A region of *PWCR1* is conserved in mammals, and it has similarity to the box C/D class of small nucleolar RNAs (snoRNAs). These RNAs are components of ribonucleoproteins that assist in the processing of certain rRNA transcripts and in RNA modification. The physiological role for *PWCR1,* including the snoRNA-like domains, is not yet clear, but the authors hypothesize that loss of *PWCR1* could lead to disrupted RNA modification, which, in turn, could lead to the phenotype of PWS.

ML4, *a Novel Gene Mutated in MLIV,* *by Bassi et al.* (*p. 1110*)*; and* **ALX4, *a Candidate for Parietal Foramina,*** *by Wu et al.* (*p. 1327*)

The work by Bassi et al. and Wu et al. demonstrates the powers of bioinformatics and the human genome databases. Through use of these tools, each group has identified a gene that is associated with a particular genetic disorder. Bassi et al. searched the region on chromosome 19p13.2-13.3 that had been identified, through linkage mapping, as being associated with mucolipidosis type IV (MLIV), a lysosomal storage disorder characterized by corneal clouding and psychomotor retardation. Several novel genes were identified in this search, and two mutations in one of these genes, named "*ML4*" by the authors, were identified in six patients with MLIV. Each mutation was associated with one of the two disease-associated haplotypes that have been reported previously, lending further support to their identification as the causative mutations for this disease. The protein encoded by *ML4,* mucolipidin, is predicted to be an integral membrane protein, and it possesses a region of homology to a putative Ca^{2+} channel. Since cells from patients with MLIV show alterations in the movement of endocytic markers, further studies of *ML4* may lead not only to an elucidation of the basis for mucolipidosis IV but also to a greater understanding of normal endocytic processes.

Wu et al. studied a contiguous deletion syndrome, of chromosome 11, that includes parietal foramina as a phenotype. Parietal foramina are defects in the parietal bones of the skull that result from either delay or loss of ossification. The authors hypothesized that a homologue of the *MSX2* gene, mutations in which cause autosomal dominant parietal foramina, could also be responsible for the parietal foramina in this syndrome. They performed a search for *MSX2* homologues and

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found a clone that mapped to chromosome 11p. Two patients with the contiguous deletion syndrome of chromosome 11 had deletions of the genetic region corresponding to this clone, indicating that this gene may indeed play a role in the phenotype of this disorder. Since this gene is expressed in bone but not in any of the other tissues tested, and since it has homology to the mouse homeobox gene *Alx4,* which is involved in skull development, the authors suggest that deletions of the gene may be responsible for the parietal foramina seen in this syndrome. These papers by Wu et al. and Bassi et al. provide excellent examples as to how genome databases can be used to hasten human genetics research.

FOXC1 ***Duplication Causes Iris Hypoplasia,*** *by Lehmann et al.* **(***p. 1129***)**

Mutations in the *FOXC1* transcription factor gene have been associated with glaucoma phenotypes. Some families that are affected by glaucoma, although they show linkage to the 6p25 region where *FOXC1* is located, do not have mutations in *FOXC1*. In their article, Lehmann et al. report that they have further genotyped one such family and present some unusual results for the microsatellite marker D6S967, which is located in the 6p25 region. As is seen in a PCR assay, affected individuals in this family possess either three alleles for D6S967 or two alleles for D6S967; in the latter case, one of the two alleles has twice the normal band intensity. FISH confirmed a statistically significant increase in the proportion of asymmetrical signals for the 6p25 probe in cells from the affected patients compared with controls. These results suggest that the glaucoma and iris hypoplasia phenotypes in this family result from a duplication of the genetic region containing *FOXC1*. Since FOXC1 is thought to be a transcription factor, the authors hypothesize that a change in *FOXC1* gene dosage leads to an altered pattern of downstream gene expression.

Cloning of a Fanconi Anemia Gene, *by de Winter et al.* **(***p. 1306***)**

Through complementation of a phenotype, Johan de Winter et al. have been able to clone a cDNA for the Fanconi anemia (FA) complementation group E. FA is a chromosomal instability syndrome characterized by a wide range of developmental disorders, bone marrow failure, and predisposition to malignancies. Cells from these patients exhibit hypersensitivity to mitomycin C and other DNA cross-linking agents. The authors have made use of this phenotype in a selection scheme. An FA group E cell line was transfected with an expression library and put under selection with mitomycin C. The cDNA isolated in this scheme was used to identify the corresponding human genomic sequence, termed "*FANCE.*" As is the case for the other FA proteins identified to date, *FANCE* lacks any significant homology to other proteins. FA has been a very puzzling disorder because none of the causative genes has given an immediate clue as to the underlying pathway that is disrupted in this disorder. The recent discovery that FANCC is involved in STAT1 activation (see Pang et al.'s article in *Molecular and Cellular Biology* [20:4724–4735; 2000]) may help to unravel the underlying mechanism for FA. Additional studies will further delineate the developmentally critical biochemical pathway involved in this disorder.

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