This Month in the *Journal*

The extent of linkage disequilibrium varies widely between chromosomal regions and between populations. This month in the *Journal,* Jonathan Pritchard and Molly Przeworski contribute a review that addresses these differences, from both a modeling and an empirical standpoint (p. 1). They also discuss how the extent of linkage disequilibrium affects association and fine-mapping studies. In another review, Pragna Patel and Grazia Isaya (p. 15) provide an overview of Friedreich ataxia, including (*a*) possible mechanisms by which the GAA triplet-repeat expansion interferes with transcription of the *FRDA* gene, (*b*) the normal role of the frataxin protein, (*c*) the pathogenesis of this disorder, and (*d*) mouse models of Friedreich ataxia.

USH1F Caused by* PCDH15 *Mutations, *by Ahmed et al. (p. 25)*

Using three families with Usher syndrome type 1F (USH1F), which is characterized by profound congenital deafness and retinitis pigmentosa, Ahmed et al. were able to limit the *USH1F* locus to 1 Mb on chromosome 10q21.1. A mouse chromosomal region that is syntenic to the *USH1F* locus contains *Pcdh15,* a gene that is mutated in the deaf Ames waltzer mouse. Therefore, the authors sequenced the human homolog of *Pcdh15* in the affected families. Affected individuals in one family possessed a putative splice-acceptor–site mutation, IVS27-2A→G, that is predicted to lead to inclusion of sequence from intron 27 and loss of exon 28. A second family had an R3X nonsense mutation that should lead to complete loss of the encoded protein. *PCDH15* encodes protocadherin 15, a member of a family of proteins that is believed to play a role in cell adhesion during synaptogenesis. Alagramam et al. (see the citation in the article by Ahmed et al.) recently showed that the Ames waltzer mouse has abnormal stereocilia in the cochlear hair cells, indicating that *Pcdh15* is required for normal function of the inner ear. Its precise role in this function is unclear.

SDHB *Mutations in Familial Pheochromocytoma and in Familial Paraganglioma,* *by Astuti et al. (p. 49)*

Mutations in *SDHD* and *SDHC* are associated with hereditary paragangliomas, which are slow-growing tumors in the extra-adrenal sympathetic ganglia. These genes encode subunits of mitochondrial complex II, and they anchor the SDHA and SDHB subunits of this complex to the inner-mitochondrial membrane. Because of the interaction of these proteins to perform a common function in cellular respiration, Astuti et al. wondered whether *SDHB* mutations and additional *SDHC* mutations could be associated with paraganglioma or with pheochromocytoma, a related type of tumor that develops in the adrenal medullary tissue. An R91X mutation was found in *SDHB* in three families with pheochromocytoma; two of these families also had at least one case of paraganglioma. No haplotype in the *SDHB* region was shared between the families, so it was believed to be a recurrent mutation. Two additional *SDHB* mutations were discovered in this study: a conserved proline was changed to arginine (P198R) in one family with pheochromocytoma, and a c.725delC frameshift deletion was found in one sporadic case of pheochromocytoma. No *SDHC* mutations were found in the sample. The process by which these mutations lead to tumorigenesis is unclear. It has previously been suggested that cellular proliferation may occur through a defect in oxygen sensing (see the citation of Baysal et al. in the article by Astuti et al.). Astuti et al. propose an alternative explanation, in which tumors result from a failure of apoptosis.

A Nonsense Mutation in* MSX1 *Causes Witkop Syndrome, *by Jumlongras et al. (p. 67)*

Congenital absence of some permanent teeth, as well as dysplastic finger and toenails, are symptoms of Witkop syndrome, which is also known as "tooth and nail syndrome." Because *MSX1* mutations have previously been associated with tooth agenesis, this gene is a plausible candidate gene for Witkop syndrome. Markers around the *MSX1* locus show evidence of linkage to the phenotype in an affected family. Encouraged by this linkage, Jumlongras et al. sequenced the coding regions and flanking intron sequences of *MSX1* and identified a S202X nonsense mutation that cosegregated with Witkop syndrome in this family. *MSX1* is a homeobox gene. The mutation, which is in the homeobox coding region, is believed to result in haploinsufficiency, because it is predicted to encode a protein that is completely nonfunctional. It is curious that another nonsense mutation in *MSX1,* S105X, which would also be predicted to result in complete loss of protein function, has been associated with oral clefting in addition to tooth agenesis. The authors propose that the effects of modifier genes may explain the phenotypic differences between these families.

0002-9297/2001/6901-0001$02.00

Homocysteine Metabolism in Down Syndrome, *by Pogribna et al.* (*p. 88*)

With three copies of chromosome 21, individuals with Down syndrome are in a position to have overexpression of many genes. This view may be oversimplistic, because compensatory mechanisms may help to prevent the overexpression of some genes or may provide adaptive responses to the overexpression. Pogribna et al. feel that Down syndrome can be viewed partly as a metabolic disease due to overexpression of certain genes on chromosome 21. Their paper focuses on one such gene, that for cystathionine β-synthase (CBS). Overexpression of CBS activity has been documented in people with Down syndrome. CBS directs homocysteine to a cysteine and glutathione synthesis pathway, thereby depriving the methionine synthase reaction of its precursor, homocysteine. Progribna et al. demonstrate, in children with Down syndrome, decreases in such things as total plasma homocysteine, methionine, glutathione, and S-adenosylmethionine. Increases in cysteine, cystathione, and adenosine are also noted. Opposite to what might have been predicted on the basis of reductions in the methylation precursors, a global increase in DNA methylation is also observed in lymphocytes from individuals with Down syndrome. The authors propose that decreased homocysteine availability creates a functional folate deficiency that may play a role in Down syndrome pathology. On the basis of the demonstration of metabolite imbalances in children with Down syndrome, the authors perform in vitro nutrient-supplementation experiments on trisomy 21 cells, to determine whether some of these metabolites can be normalized. The supplementation significantly alters metabolite levels in the cells, allowing for the possibility that nutritional intervention may have a therapeutic effect on the metabolic pathology of Down syndrome, although it should be stressed that the significance of these findings in this regard are quite unclear and will require vigorous follow-up.

A Mutation in H-Ferritin mRNA, *by Kato et al.* (*p. 191*)

Kato et al. have identified a woman who has high serum ferritin levels, increased serum iron and transferrin saturation, and iron deposition in hepatocytes, Kupffer cells, and macrophages. Three family members also exhibited elevated serum ferritin levels, suggesting a genetic disorder. The prevalent *HFE-1* and *TFR2* mutations that are normally associated with hemochromatosis were not present in this family. However, there was a heterozygous A49T mutation in the *5′* UTR of the H-subunit of ferritin. This mutation falls in the iron-responsive element (IRE) of this gene, which is involved in translational control of gene expression. The mutation strengthens the interaction between the IRE and a translational repressor, thereby increasing this repression. Immunoblotting of a liver-biopsy sample from one of the affected individuals confirms the decreased expression of the H-subunit of ferritin, as well as an increase in the L-subunit levels. Cells transfected with a construct encoding the mutated H-subunit show increased uptake of iron but decreased incorporation of ^{59}Fe into ferritin. The authors believe that this results from reductions in the ferroxidase activity of the H-subunit, which are due to decreased production of the protein, because this activity is essential for the incorporation of iron into ferritin. These defects probably lead to the tissue iron deposition seen in the affected individuals.

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