This Month in the *Journal*

Murine Model for Human SPR Deficiency, *by Yang et al.* (*p. 575*)

Sepiapterin-reductase (SPR) is a member of the intricate network of enzymes necessary for the homeostasis of the essential cofactor tetrahydrobiopterin (BH_4). Patients with BH_4 deficiency can develop a variety of neuromuscular symptoms because of a decrease in activity of enzymes such as phenylalanine-4-hydroxylase (PAH), tyrosine-3-hydroxylase (TH), and tryptophan-5-hydroxylase (TPH). Though it was originally thought that mechanisms existed that compensated for loss of SPR, patients have recently been identified with SPR deficiency who have psychomotor retardation, spasticity, dystonia, tremors, and growth retardation. Yang et al. create a mouse model for SPR deficiency to study the pathways affected by the loss of the protein. Like the patients, the mice also show growth retardation and impaired body movement. BH_4 levels are significantly reduced, and, consequently, the activity of PAH, TH, and TPH is impaired. The authors then demonstrate that dietary supplementation of BH_4 is able to restore normal body growth and PAH activity. These mice will serve as a resource for additional studies of the effects of SPR deficiency and as a model for the progression of the human disease.

A Fine-Scale LD Measure, *by Wang et al.* (*p. 615*)

As high-throughput SNP genotyping technologies improve, more information is available to map complex diseases, study recombination, and analyze the genetic relationships within and among populations. It is important for these analyses that the linkage disequilibrium in a genomic region be accurately assessed. Traditionally, the two-point measures, D' and r^2, are used, but these statistics are not very robust to marker allele frequency and are highly variable across the physical distance between two markers. Wang et al. propose a new measure, Δ, that incorporates information from surrounding alleles to estimate common ancestral segments from shared haplotypes. In simulation studies, the authors demonstrate how smoothly Δ correlates with physical distance and how correct values are obtained at a variety of marker densities and frequencies. They also expand their simulations to establish conditions for using unphased genotypes. The three measures are then compared on real data from the HapMap project, and Δ is able to precisely correlate the LD of the region with physical distance and recombination rate. This new statistic should assist in making more-detailed measurements of LD throughout the genome.

***Reinitiation of Translation in* NEMO,** *by Puel et al.* (*p. 691*)

NF-κB essential modulator (NEMO) is necessary for normal NF-κB activation. Inactivating *NEMO* mutations cause incontinentia pigmenti (IP), a severe developmental disorder that causes death in utero in hemizygous males and various ectoderm abnormalities in heterozygous females. Hypomorphic mutations are associated with forms of anhidrotic ectodermal dysplasia (EDA) and immunodeficiency (ID). Peul et al. report a patient with a *NEMO* frameshift mutation that causes the most *5′* truncation yet identified. On the basis of analysis of the truncated protein alone, the new patient would be expected to suffer from IP but instead has ID without any obvious developmental defects. The authors explain the comparatively mild phenotype by demonstrating that an alternative downstream *NEMO* start codon is utilized. The smaller protein produced from this new start site is observed at low levels in wild-type and mutant cells. The variant protein is able to normally activate NF-κB and retains some κB DNA-binding activity but is unable to elicit a proper immunological response. This is an example of how reinitiation of translation of a mutant transcript can partially recapitulate normal protein function.

Mutation in* RAB3GAP2 *and Martsolf Syndrome, *by Aligianis et al.* (*p. 702*)

Martsolf syndrome and Warburg Micro syndrome are characterized by ocular and neurodevelopmental defects. Recently, mutations in *RAB3GAP1* were identified in a subset of Warburg Micro kindreds. *RAB3GAP1* encodes the catalytic subunit of the RAB3GAP protein complex, a regulator of proteins involved in the exocytosis of hormones and neurotransmitters. The other subunit is encoded by *RAB3GAP2*. Because of the similarities between Martsolf syndrome and Warburg Micro syndrome, Aligianis et al. look for linkage to *RAB3GAP1* in a family with a Martsolf-like phenotype. The *RAB3GAP1* locus is excluded, but the authors do find evidence for linkage to the region containing *RAB3GAP2*. Sequencing of the gene identifies a homozygous mutation in the affected members of the

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family. Expression analysis in zebrafish embryos then provides additional clues about the role of these proteins in development. Though *RAB3GAP1* is generally expressed throughout the embryo, its partner, *RAB3GAP2,* localizes to specific regions of the CNS. This restricted expression helps to explain the phenotype that results from the disruption of either subunit of the RAB3GAP protein.

The Power To Detect Disease Associations with mtDNA Haplogroups, *by Samuels et al.* (*p. 713*)

Mitochondrial DNA (mtDNA) sequences are often broken down into haplogroups on the basis of variation at specific SNPs. Human populations can be divided into these mitochondrial categories, and, for example, ~95% of Europeans belong to 1 of 10 haplogroups. A great deal of work has been done to compare haplogroup frequencies in cases and controls, to propose links between mtDNA variation and a number of disorders. Yet, as with any type of association study, even highly significant findings are difficult to replicate. Although other reasons may explain this lack of reproducibility in certain cases, Samuels et al. examine the power that is achievable in mtDNA studies. Their first analysis details the risk of generating false positives when analyzing infrequent haplogroups. Then, by simulating populations with varying haplogroup frequencies, the authors establish that very large cohorts are needed to have enough power to identify significant associations. These conclusions not only help to explain discrepancies among past studies but also will assist in future efficient study design.

This Month on the Cover

Archibald E. Garrod, commonly referred to as "the father of biochemical genetics," was one of the first geneticists to recognize "inborn errors of metabolism." In 1902, he described the incidence of alkaptonuria in nine families (Garrod AE [1902] Lancet 2:1616–1630). Garrod noted that a high proportion of the patients were born to consanguineous parents, and this, with the observations of Bateson et al. (Bateson W, Sunders ER [1902] Report to the Evolution Committee of the Royal Society 1:133), helped to predict that the disorder was due to the transmission of a rare recessive allele. Garrod observed that urine from alkaptonuria patients darkens on exposure to air or with the addition of base. Special thanks to Dr. Bill Gahl and Isa Bernardini for the photograph.

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