This Month in the *Journal*

The cellular protein biosynthetic pathway begins with the engagement of the ribosome but ends only when a fully folded and assembled protein reaches its ultimate intracellular or extracellular compartment, with all covalent modifications in their final form. Along the way, the nascent protein may interact with a wide range of chaperones, cochaperones, glycosyl transferases, glycosidases, kinases, and proteinases. Because many of these steps are critical for biological activity or for proper sorting of disease-related proteins, any of the genes for these protein-modifying factors may be implicated in a pathology. Our series this month focuses on three diseases in which the details of the biosynthetic pathway are critical for an understanding of etiology. Nichols and Ginsburg (p. 1493) discuss vesicular trafficking from the endoplasmic reticulum (ER) to the Golgi apparatus through the intermediate compartment (ERGIC). As they explain, a resident ERGIC protein is required specifically for the maturation and targeting of two coagulation factors, and a heritable bleeding disorder results when this protein is defective. Riordan (p. 1499) describes the "quality control" system that operates on misfolded proteins in the ER, and he considers the prospects for treating cystic fibrosis with drugs that interfere with this process. Smeitink and van den Heuvel (p. 1505) review the large number of recently cloned structural genes for components of complex I in the mitochondrial oxidative phosphorylation system. This complex presents the cell with one of the most unwieldy problems in biosynthetic assembly, because its 42 known components include both nuclear and mitochondrial gene products. As the various subunits have been discovered, the assembly pathway has also begun to come to light.

Sialuria Gene and Its Mutations, *by Seppala et al.* **(***p. 1563***)**

Nearly all N-linked sugars, as well as many lipid-linked sugar structures, acquire terminal sialic acid (NeuAc) on their reducing ends late in the biosynthetic pathway. Seppala and coworkers have studied a critical enzyme in the synthesis of NeuAc, UDP-N-acetylglucosamine 2-epimerase. They showed some years ago that sialuria, a metabolic disorder that causes hepatomegaly and mental retardation, results when this enzyme acts constitutively rather than being subject to feedback inhibition. Now they report the cloning of the human cDNA for this epimerase, and they identify lesions in cDNAs derived from the fibroblasts of three unrelated sialuric people. Each of these individuals is heterozygous for a different missense allele, but the three lesions all occur in one of two neighboring arginine codons. Seppala et al. also expressed the wild-type and mutant epimerase cDNAs in bacteria, and they confirm that the mutations leave the enzymatic activity intact but compromise its regulation by a downstream metabolite. The authors suggest that the affected region of the protein participates directly in allosteric regulation of epimerase activity.

0002-9297/99/6406-0001$02.00

Congenital Insensitivity to Pain with Anhidrosis, *by Mardy et al.* **(***p. 1570***)**

The TRK gene family encodes a group of receptors for nerve-growth factor (NGF) and related molecules. These receptors are expressed in overlapping patterns in different parts of the nervous system and are required for the survival of various classes of sensory and other neurons. Expression of *TRKA,* which is required in the dorsal root ganglia that transmit painful sensations and in the neurons that innervate sweat glands, is lost in familial dysautonomia type II. This autosomal recessive disorder causes anhidrosis, defective thermoregulation, and insensitivity to pain. Mardy et al. have screened through the exons and splicing junctions of *TRKA* genes from an international group of seven affected families, and they report 11 mutations, bringing the total of known disease alleles to 15. Missense mutations are scattered throughout the coding region, but all appear to represent strong loss-of-function alleles, since the phenotype is similar to that seen in individuals homozygous for early-truncation alleles. The two splice-site mutations identified appear to inhibit TRKA expression, since minigenes containing the relevant regions of the gene, cloned from affected individuals, cannot be spliced normally in transfected cells.

Heterogeneity in ADCA Type II and De Novo Mutation in* SCA7,** *by Giunti et al.* **(p. 1594***)**

Giunti and colleagues have identified 20 families with type II autosomal dominant cerebellar ataxia (ADCA), a neurological disorder that often presents with macular pigmentation and retinal degeneration. To date, all reported cases of ADCA type II have been ascribed to polyglutamine-tract expansions in the *SCA7* gene. In this report, the majority of affected families carry clinically benign predisposing alleles—intermediate-size CAG tracts 28–35 repeats long—as well as overt disease alleles of as many as ~220 repeats. Giunti et al. document the increasingly early onset of symptoms as the repeat length

climbs, evidence for intergenerational anticipation, and they show that tract lengths are particularly unstable when they pass from father to child. The remaining three families show CAG tracts in the normal range, but their phenotypes are not distinctive, either on clinical grounds or as assessed by neuroimaging, suggesting that other classes of mutations and perhaps other genes may be implicated in this disorder.

Infertile Testis Germ-Cell Nondisjunction, *by Huang et al.* **(***p. 1638***)**

Nondisjunction of sex chromosomes in male germ cells generates aneuploid sperm, which are detected with a frequency of 1:100 in normal men and at higher levels in men with idiopathic infertility. In the course of investigating this class of infertility, Huang and coworkers have found that this class of chromosomal mishap is far more common in normal spermatogenesis than had been appreciated. These authors have used FISH analysis to follow the formation of aneuploid mitotic and meiotic germ cells in testicular biopsies. Such cells are indeed more prevalent in men with idiopathic infertility than in the control group of men whose infertility could be explained by obstructions of the epididymis or vas deferens, suggesting that abnormal chromosome segregation may contribute to male infertility. However, even in the control group, who are assumed to be representative of men with normal fertility, more than a quarter of all postmitotic germ cells are aneuploid. Hence, selective cell death must account for the removal of >95% of such cells. Huang et al. raise the concern that intracytoplasmic injection of immature spermatocytes taken from testicular tissue of infertile—or even fertile—men could generate aneuploid zygotes.

LD Mapping of BP-I in Costa Rica, *by Escamilla et al.* **(***p. 1670***);** ***Localization of QTLs for HDL-Cholesterol,*** *by Almasy et al.* **(***p. 1686***);** *and* ***Extreme-Sib-Pair Blood-Pressure Screen,*** *by Xu et al.* **(***p. 1694***)**

Several papers this month deal with the mapping of complex traits. Escamilla et al. consider the use of linkage disequilibrium (LD) screening to identify loci involved in bipolar disease. This same group has worked with an extensive set of strictly defined bipolar type I (BP-I) families from Costa Rica, and they have reported linkage data indicating that some relevant genes likely reside at 18q22-23. Now they have followed up this report, using an independent group of Costa Rican BP-I probands. In an unusual instance of large-scale LD mapping, they provide suggestive evidence for BP-I loci at this site and at a previously unidentified telomeric locus on 18p. For a related strategy that may be of use in the mapping of BP-I genes, see the article by Service et al. (p. 1728). Almasy et al. use multivariate analysis to determine linkage of quantitative-trait loci (QTLs) that influence aspects of a person's lipoprotein profile, including HDL-cholesterol concentration, HDL particle size, and the degree of esterification of cholesterol within this plasma fraction. Each of these phenotypes has been correlated with risk of coronary heart disease, but their genetic basis and the interrelation among them are not certain. Almasy et al. follow all of these characteristics in 10 large Mexican-American pedigrees, and they identify two independent QTLs, one of which appears to regulate the unesterified cholesterol level in a particular subspecies of HDL particles, whereas the other affects the partitioning of HDL cholesterol into different classes of particles. Xu and colleagues have searched the genome for QTLs that might regulate blood pressure. Their study group includes 564 pairs of siblings, most of whom have blood pressure in the extreme high or low deciles of the distribution and who live in the Chinese city of Anqing, where blood pressure–regulating medication is not widely available. Xu et al. detect five loci whose maximum LOD scores suggest that they may modulate systolic—or, in one case, diastolic—blood pressure. When the authors consider blood pressure as a single measurement, pooling extreme systolic with extreme diastolic values, the LOD scores for the loci of interest drop below the suggestive range, indicating that the two parameters may be under separate genetic control.

LD Mapping in Founder Populations, *by Service et al.* **(***p. 1728***)**

Linkage disequilibrium (LD) mapping has been touted as a powerful approach to discover genes that contribute to complex traits, but there is little agreement on how best to implement it. One promising method involves multipoint LD (MLD) likelihood tests, which measure the combined likelihood of finding the calculated levels of LD for each marker in a contiguous region, under the assumption that no linkage to a disease gene exists. Service et al. suggest a mathematically similar approach that measures the likelihood of finding intact ancestral haplotypes that comprise these same contiguous markers. Power analyses with simulated marker data show that this ancestral haplotype reconstruction approach should be able to detect genes when markers are scattered too sparsely for the MLD method to reach a desired level of statistical significance. The method may also be helpful when the gene's overall contribution to the phenotype is small.

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