This Month in the *Journal*

O'Donovan and Owen (p. 587) begin this month's series on genetic aspects of psychiatric conditions and treatment. They consider the merits of linkage and association studies for identifying genes related to schizophrenia and similar complex but heritable disorders, and they focus on three potentially relevant genes, including one, *KCa3,* that has generated both excitement and controversy in the past 2 years. Shih and Thompson (p. 593) discusses their work in a mouse system that models the pathological aggression seen in a large family segregating a mutation in the X–linked monoamine oxidase A (*MAOA*) gene. MAO A is required for the efficient degradation of serotonin and other neurotransmitters, and the absence of this activity causes similar metabolic and behavioral consequences in mice and humans. Reich et al. (p. 599) review the genetics of substance dependence and, especially, of alcoholism. These authors argue that comorbidity among different addictive behaviors makes it difficult to distinguish whether genes control them individually. Nevertheless, they suggest that large ongoing studies, such as the Collaborative Study on the Genetics of Alcoholism (COGA; data and materials from which are to be made public this month), have already provided crucial insights into the inheritance of this class of substance dependence. Finally, Catalano (p. 606) reviews the promise and the challenges of the new—or newly revitalized—field of psychopharmacogenetics, which aims to tailor psychiatric drug therapies to individuals on the basis of their genotype.

Stop-Codon Mutation in COX I Gene, *by Bruno et al. (p. 611)*

Most disease-associated mtDNA lesions directly affect the protein biosynthetic machinery in the mitochondrion and only indirectly interfere with oxidative phosphorylation. However, there is a growing list of point mutations and small deletions that occur in mitochondrially encoded structural genes for subunits of the respiratory complexes. Bruno et al. have identified a novel mutation in this class, a nonsense mutation that truncates the open reading frame of *COX I,* which encodes the largest subunit of complex IV. This lesion is present in ~75% of the mtDNA molecules in tissues of a woman who displays many of the hallmarks of mitochondrial disease, and the authors have generated transmitochondrial cybrids with varying proportions of wild-type mtDNA and mtDNA carrying this mutation. In this report, they show that 65% mutant mtDNA is sufficient to reduce the efficiency of oxidative phosphorylation by 90%. In these cybrids, the mutant protein does not accumulate to a detectable level, despite the presence of normal amounts of COX I mRNA. Bruno et al. suggest that the truncated protein is unstable and is degraded by endogenous proteinases because it fails to assemble with the other subunits of complex IV.

Splice-Donor–Site Mutation in COLQ, *by Ohno et al. (p. 635)*

In the course of studying a patient with congenital endplate cholinesterase (AChE) deficiency, Ohno et al. have identified an unusual splicing defect in the *COLQ* gene. COLQ anchors AChE to the endplate in the neuromuscular junction, and defects in this gene cause abnormal accumulation of acetylcholine and lead to chronic myasthenia. In the compound-heterozygous individual studied, one of the disease alleles carries an A→G transition at a site within a splice-donor sequence. Although the wild-type A nucleotide is predicted to interact with a complementary nucleotide in the U1 snRNA, which mediates splice-donor–site recognition, G nucleotides are found at this position nearly as frequently as A nucleotides, raising the question of why this mutation should be associated with inaccurate splicing. Ohno et al. have generated a minigene with the mutation, and they confirm that it causes exon skipping in heterologous cells. However, after analyzing large numbers of normal and mutant splice-donor sequences, they determined that G-containing sequences become more reliant on complementarity to the U1 sequence at two neighboring splice-donor sites. The authors verified this conclusion by introducing compensatory sequence changes into their minigene construct and by demonstrating accurate splicing.

Genetic Analysis of Presenile Alzheimer Disease, *by Campion et al. (p. 664)*

Campion et al. have surveyed the population of Rouen, France, for families with histories of early-onset Alzheimer disease (EOAD), in which the beginnings of dementia are seen in individuals <61 years of age. In this city of >400,000 people, the authors identify 39 probands, 24 of whom had affected relatives. In five of these cases, family histories are consistent with simple autosomal dominant inheritance, providing an estimate for the prevalence of autosomal dominant EOAD (ADEOAD). The authors have screened these families and 29 other French ADEOAD families, to determine

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whether mutations in the known AD genes might account for their disorder. In addition to previously reported disease alleles, this search identified four new missense mutations in the gene for PRESENILIN-1 and one in the gene for the amyloid precursor protein. None of the families appear to carry lesions in *PRESENILIN-2,* but the other two genes account for ⩾71% of the cases in this population.

***Polymorphic X Inactivation of* TIMP-1,** *by Anderson and Brown* (*p. 699*)

Genes that are expressed from the inactive copy of the X chromosome in female cells are said to have escaped X inactivation. More than 30 genes with this epigenetic feature have been described, most of them residing in clusters. Brown and colleagues previously found indications that genes might escape inactivation in one individual but not in another. Now, Anderson and Brown have followed the expression pattern of the X–linked *TIMP1* gene, which had been identified in the original study, using hybrids made from the somatic cells of women known to inactivate a specific X chromosome in virtually all their tissues. This extreme skewing of X inactivation allows the authors to detect mono- or biallelic *TIMP1* expression, and they confirm that this gene escapes X inactivation in four of eight cell lines. Interestingly, this epigenetic difference appears to be highly specific for this gene, because four closely linked genes that flank *TIMP1* are uniformly silenced when the X chromosome that they reside on is inactivated.

Radiosensitivity and Cancer Predisposition, *by Roberts et al.* (*p. 784*)

Previously, Roberts et al. determined that the cells of women with breast cancer are unusually sensitive to chromosomal damage induced by ionizing radiation (IR), a phenotype that is also seen in conditions in which DNA repair mechanisms are perturbed. Now, these authors provide direct evidence that this cellular IR response is under genetic control. They report a dramatic incidence of lymphocyte hypersensitivity to IR in relatives of patients who are IR hypersensitive, compared with either control individuals or relatives of patients with normal radiosensitivity. This feature is characteristic for an individual and does not vary greatly over a 2-year period, nor does it correlate with age. Roberts et al. find that they can model the inheritance of the IR response as a single major locus modified by one minor locus. They argue that none of the known genes related to IR sensitivity or to breast cancer susceptibility are likely to account for this quantitative trait but that some variant of a still-to-be-identified gene that regulates it is enriched in families with high incidence of breast cancer.

ADH *and* ALDH *Polymorphisms and Alcoholism,* *by Chen et al.* (*p. 795*)

Two classes of genes for metabolic enzymes have been associated with predisposition to alcoholism: The alcohol dehydrogenase genes *ADH2* and *ADH3,* whose products generate acetaldehyde from ethanol, and the acetaldehyde dehydrogenase gene *ALDH2,* whose product degrades acetaldehyde. Individuals who carry catalytically activated variants of ADH genes (*ADH2*2* and *ADH3*1*) or who carry the catalytically inhibited *ALDH2* variant *ALDH2*2* appear to be protected from alcoholism, presumably because the excessive accumulation of acetaldehyde in each case makes it unpleasant to consume alcohol. In this report, Chen et al. confirm these findings, showing that homozygosity for *ALDH2*2* is fully protective from alcoholism, since no alcoholic individual with this genotype could be found in their group of 340 Taiwanese alcoholics, although more than half the control individuals were homozygous for this allele. The authors also investigate interactions among the ADH and ALDH genes, and they report that the apparent effects of *ADH3*1* in this population can be fully explained by disequilibrium with *ADH2*2*. They also argue that the protective effects of *ADH2*2* are independent of, and function additively with, those of *ALDH2*2*. For more on the genetics of alcoholism, see Reich et al. (in this issue).

Variation in Local Estimates, *by Roberts et al.* (*p. 876*)

Each of the authors in this month's series on psychiatric genetics emphasizes the need for replication of genetic linkage in the pursuit of complex traits, but the further question of exactly what replication might entail has not been adequately explored. Roberts et al. point out that regions of highest linkage for such traits often extend over a considerable portion of a chromosome and that it is difficult to know whether the identification of a similarly positioned region of linkage should be considered independent replication of a single locus—especially when two studies measure related but distinct phenotypes. Using simulated data, Roberts and colleagues find that, when traits are inherited in the complex manner (with incompleted penetrance, genetic heterogeneity, and a substantial rate of phenocopies), the standard error in the estimate of the location may cover 5–10 cM. Conducting studies with very large numbers of families can reduce this figure, but other remedies, such as screening with a denser array of markers, are of minimal help.

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