This Month in the *Journal*

AD Associated with* APP *Regulatory Mutations, *by Theuns et al.* (*p. 936*)

It is well established that there is a relationship between alterations in the gene for the amyloid precursor protein, *APP,* and Alzheimer disease (AD). Autosomal dominant AD is caused by various mutations in *APP* that lead to increased amyloid β peptide, which has been found, on autopsy, in plaques of brains of patients who had had AD. It is less clear whether higher expression of wild-type *APP* increases susceptibility to AD. Previous work has examined promoter polymorphisms that were associated with patients with AD, but these SNPs had no apparent effect on expression. Theuns et al. examined the *APP* promoter regions more closely and identified new polymorphisms that were observed only in patient samples. The ability of these variant promoters to increase transcription is compared with that of the wild-type promoter; in neuroblastoma cells, expression differences are seen. These functional effects are predicted to be related to changes observed in the binding and formation of nuclear protein complexes at these sites.

β-Actin Mutation with Multiple Abnormalities, *by Procaccio et al.* (*p. 947*)

The maintenance of many cellular functions, including cell movement and structure, relies on the proper activity of members of the actin family. The actins can be broken down into two subgroups: muscle actins—which are major cytoskeletal proteins in skeletal, aortic smooth, and cardiac muscle—and nonmuscle actins. Various disease-causing mutations have been identified in the muscle actins, but the nonmuscle actins are rarely reported to be involved in diseases. While investigating brain tissue from two patients with ventral midline malformations, hearing loss, and progressive dystonia, Procaccio et al. observed unusual protein inclusions that contained actin. Sequence analysis of several actin-related genes revealed a missense mutation in the β-actin gene, *ACTB*. The mutation affects cell morphology, and the patient cells have abnormally long, spiky processes. Structure modeling predicts that the mutant residue interferes with interactions at or near the ATP-binding pocket. This theory was evaluated by treating cells with Latrunculin-A, a drug that binds near the pocket and normally disrupts actin polymerization. The mutant cells were resistant to the drug.

Germline and Somatic* EFNB1 *Mutations, *by Twigg et al.* (*p. 999*)

Traditionally, X-linked diseases cause a more severe phenotype in hemizygous males than they do in heterozygous females, but this is not the case in patients with craniofrontonasal syndrome (CFNS). There also appears to be a skewed sex effect, with significantly fewer males affected by CFNS than is expected. Such a phenomenon is seen when a disease is lethal in hemizygous males, but several CFNS pedigrees exist in which male obligate carriers present with mild features and pass CFNS on to their daughters. Recently, mutations in *EFNB1* were linked to CFNS, and the differences between patches of tissue created by random X inactivation are suspected to be responsible for the dysmorphology seen in females. Here, Twigg et al. strove to determine the molecular basis for the unusually low number of CFNS-affected males by closely examining the sequence of *EFNB1* in several unrelated patients with CFNS. In 14 of 20 unrelated females with de novo mutations, the authors were able to determine which parent's chromosome contains the disease-causing mutation. In 13 of those 14, the mutation was on the paternal chromosome. It is suggested that such an increased tendency for *EFNB1* mutations to be created in sperm can explain the observed sex ratio, because a father's X chromosome can be passed only to his daughters.

Covariance with Ordered Genotypes, *by Dai et al.* (*p. 1035*)

The imprinting status of a locus is increasingly being recognized as a factor in disease. Allowing for imprinting effects in association studies requires that methods be able to handle ordered genotype data in which the maternal allele is distinguished from the paternal allele. Methods have been developed that assess the relationship between individuals, but many do not take into account from which parent each allele is inherited. The ITO method is used to predict the genotype of a relative if the genotype of an individual is known. Here, Dai et al. add two more matrices to handle parent-offspring transitions, to properly keep the maternal allele separate

from the paternal allele. With this new extension, they were able to derive equations for the covariance between full siblings in the presence of imprinting. The authors also developed a more general method that can handle individuals of any relationship.

Haplotype Homozygosity and Derived Alleles, *by Fry et al.* **(***p. 1053***)**

To evaluate the age and evolution of genetic variants, it is useful to determine the extent of haplotype homozygosity. This is a measure of the length of linkage disequilibrium (LD) surrounding an allele. It is expected that the homozygosity of younger alleles is longer than that of older alleles because, as time passes, recombination occurs and breaks up the LD in the region. Fry et al. developed a simple and quick metric, H_X, to apply to windows surrounding a target allele, to establish whether the homozygosity is higher or lower than expected. Simulations are used to show that the observed homozygosity of younger derived alleles is higher than that of the older ancestral alleles. Real data from HapMap and ENCODE are compared with the chimpanzee sequence to separate ancestral alleles from derived alleles, and H_X values, again, follow the same pattern.

This Month on the Cover

In 1949, Murray L. Barr and Ewart G. Betram described "a well-developed nucleolar satellite" in female nerve cells (Barr ML, Bertram EG [1949] Nature 163:676–677). This "Barr body," seen in the cover image on the left edge of the nucleus, was later recognized to be the condensed form of the inactivated X chromosome in female cells. Mary F. Lyon, in 1961, on observing the "mottled" coat of female mice (Lyon MF [1961] Nature 190:372–373), developed the Lyon hypothesis, which predicted that only one X chromosome is active in cells. She deduced that the variegated coat color of some female mice was due to the patchwork formation of a group of cells expressing one X chromosome next to a group of cells in which the other X chromosome was active. This variable X inactivation is also suspected of playing a role in the phenotype observed in females affected by CFNS discussed by Twigg et al. in this issue. Special thanks to Dr. Fred Dill, Department of Medical Genetics, University of British Columbia, for the photograph.

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