This Month in the *Journal*

Identification of the Gene for MLC, *by Leegwater et al.* (*p. 831*)

Severe involvement of the brain's white matter and slow deterioration of motor functions with ataxia and spasticity are characteristic of the neurological disorder megalencephalic leukoencephalopathy with subcortical cysts (MLC). A locus for MLC has been identified on chromosome $22q_{tel}$, and Leegwater et al. were able to narrow the critical region to 250 kb. Four genes were localized to this region. Sequencing revealed 12 different mutations in the *KIAA0027* candidate gene from affected individuals; the gene was therefore renamed "*MLC1*." The function of the *MLC1* gene product is not known, but it is predicted to have eight transmembrane domains, and it is expressed in the brain, peripheral white blood cells, and spleen, as well as in other tissues. Five of the affected individuals had mutations disrupting one of two polyleucine motifs in the protein; this motif is a component of the predicted transmembrane domains. The MLC1 protein has similarity to the human voltage-gated potassium channel KV1.1, as well as to the signature of ABC-2 type transporters and of sodium:galactoside symporters, so the authors suggest that it may have a transport function.

Dimethylglycine Dehydrogenase Deficiency, *by Binzak et al.* (*p. 839*)

Binzak et al. characterize the first case of a new inborn error of metabolism, dimethylglycine dehydrogenase (DMGDH) deficiency. In addition to chronic muscle fatigue since adolescence, this patient has a lifelong history of a fish-odor smell that intensifies during physiological stress or increased physical activity. ^{1}H NMR analysis indicates that he has 20 times the normal level of dimethylglycine (DMG) in his urine and 100 times the normal level of DMG in his serum. Since DMGDH normally removes a methyl group from DMG during the process of choline metabolism, the authors suspected that DMGDH was deficient in this patient. Through use of the rat *DMGDH* sequence for comparison, clones that encompass the human *DMGDH* sequence were isolated. The DNA sequence revealed a homozygous H109R mutation in the patient. Expression of DMGDH in *Escherichia coli* indicated that the mutated protein was inactive; western blots for DMGDH in 293 cells transfected with a plasmid containing the *DMGDH* gene indicated that the mutant protein may also be unstable.

0002-9297/2001/6804-0001$02.00

Tourette Syndrome Studies on Human 7q31, *by Petek et al.* (*p. 848*)

Chromosomal rearrangements at 7q31 have been associated with Tourette syndrome, autism, and speech and language disorder. In this article by Petek et al., a boy with Tourette syndrome is found to have an inverted duplication of ~15 Mb on chromosome 7q. Characterization of the distal breakpoint region showed that there were actually two different breaks in the chromosome—the breakpoint of the duplication and that of the insertion site. A search for expressed-sequence tags in the region found that the gene for Leu-Rch Rep protein is ~75 kb proximal to the first breakpoint (DBP-1), whereas a large gene was directly disrupted by both breakpoints (DBP-1 and -2). This gene, termed "*IMP2*" by the authors because it has homology to yeast mitochondrial inner-membrane proteinase subunit 2, is expressed in many tissues—including weak expression in brain. Other genes could be involved in the phenotype, most notably the gene for Reelin, a glycoprotein involved in the layering of neurons in the cerebral cortex and cerebellum. The proband possesses three copies of this gene, which has recently been associated with lissencephaly. Given the intense interest in Tourette syndrome, these data implicating IMP2 and Reelin in the development of Tourette syndrome in this patient are intriguing, but additional research in other patients is necessary to prove a connection.

OR Clusters and Chromosome Anomalies, *by Giglio et al.* (*p. 874*)

A newly discovered, common inversion polymorphism on chromosome 8p increases susceptibility to recurrent rearrangements in this region. While studying recurrent rearrangements on distal chromosome 8p, which include inv dup(8p), del(8)(p23.1p23.2), and der(8)(pter-p23.1::p23.2-pter), Giglio et al. found two repeat regions (REPs) of ~400 kb each, and these contain olfactory-receptor gene clusters. Breakpoints for the recurrent rearrangements fall within the REPs, suggesting that the rearrangements result from unequal recombination between them. Since the inv dup(8p) and der(8) rearrangements occur in maternal meiosis, Giglio et al. studied the critical 8p region in mothers of individuals with these rearrangements. All of the mothers were heterozygous for an inversion, bounded by the 8p-OR gene clusters, that was subsequently found to be present in 26% of normal controls of European descent. Although chromosome 8p rearrangements occur at a low frequency in carriers of the

inversion polymorphism, the inversion does appear to facilitate chromosomal rearrangements.

Efficient Multipoint Linkage Analysis, *by Markianos et al. (p. 963)*

Although GENEHUNTER has been a very useful program for linkage analysis, it is limited in the size of pedigrees that it can handle, because of computational constraints. Markianos et al. present new algorithms, which are incorporated into GENEHUNTER version 2.1, that allow the analysis of larger pedigrees by reducing the computational requirements for the analysis. One improvement reduces the time and memory requirements of the analysis, through consideration of only those inheritance vectors with nonzero probability; in other words, for inheritance patterns that are incompatible with the observed marker genotypes, the algorithm does not calculate or store single-point–inheritance probabilities or multipoint-inheritance probabilities. GENEHUNTER version 2.1 also includes both an algorithm that accelerates computations of the NPL_all statistic and a method to evaluate the significance of transmission/disequilibrium-test results. Performance gains depend on the pedigree and markers that are analyzed but generally are 10–1,000-fold of those of GENEHUNTER version 2.0.

KATHRYN BEAUREGARD
Deputy Editor