This Month in the *Journal*

***Novel Mutations in* MATA1** *by Chamberlin et al.* (*p. 347*)

Methionine adenosyltransferase (MAT) activity produces *S*-adenosylmethionine (AdoMet), the source of methyl groups for most biological methylation reactions. In humans, MAT comprises three isozymes—MAT I, MATII, and MATIII—that are encoded on the *MAT1A* and *MAT2A* genes. Several mutations have been found in *MAT1A* that reduce MAT I/III activity, resulting in abnormal accumulations of methionine. Some of these mutations, including the most prevalent (R264H), are clinically benign, whereas others cause neurological problems, learning disabilities, and abnormal results on magnetic-resonance imaging. Chamberlin et al. present several patients with hypermethioninemia and correlate the type of *MAT1A* mutation with the level of MAT activity. The highest plasma methionine levels, which result from low MAT activity, are largely predictive of clinical symptoms due to hypermethioninemia. However, this correlation is not absolute, since two patients homozygous for a mutation, 539insTG/185X, that abolishes MAT activity do not show any symptoms. Further understanding of MAT I/III function is needed to allow us to understand this variability in the clinical expression of *MAT1A* mutations.

Splicing Mutations in Isovaleric Acidemia, *by Vockley et al.* (*p. 356*)

Deficiencies in isovaleryl-CoA dehydrogenase (IVD), an enzyme involved in leucine catabolism, lead to isovaleric acidemia (IVA), a disorder characterized by vomiting, severe ketotic acidosis, and an odor of sweaty feet. The characteristic odor comes from isovaleric acid, which is an intermediate in this pathway and which accumulates because of the deficiency. Clinical presentation of IVA ranges from a developmental delay to a fatal acidosis during the neonatal period, but the basis for this variability is not yet understood. Several classes of mutations in *IVD* have been identified, including those leading to defective protein processing, amino acid substitutions, shortened IVD precursors, and defective protein translation. Here, Vockley et al. characterize several new *IVD* mutations that lead to aberrant splicing of *IVD* mRNA and subsequent loss of IVD activity. Splicing mutations occur at an unexpectedly high frequency (9 of 20 *IVD* mutations characterized thus far) and are found both in the splice junctions and in the exons encoding IVD. Although splice-site recognition is directly affected by mutations in the conserved gt-ag sequence at the splice junction, single base mutations in the coding regions cause exon skipping, presumably because of a lack of exon recognition. These mutations weaken existing splice sites or strengthen cryptic splice sites, thereby altering recognition of the proper splicing components. The type of mutation in *IVD* affects the frequency of aberrant RNA splicing and, possibly, the stability of the resulting RNA. The range of protein defects that result from the splicing mutations may play a role in the clinical variability seen in IVA.

Imprinting Effect in Premature Ovarian Failure, *by Hundscheid et al.* (*p. 413*)

Premature ovarian failure (POF) is the complete, spontaneous cessation of menstruation at age <40 years. Although POF is genetically heterogeneous, evidence exists for an association with fragile X premutations. The question remains as to why only some women carrying these premutations develop POF. Hundscheid et al. have revisited this issue, evaluating women who carry fragile X premutations, to determine whether there is a predisposition to POF. These carriers were categorized according to the parent of origin for the premutation and were evaluated for POF. In general, 1% of the female population has a sporadic case of POF, but Hundscheid et al. found POF in 28% of women with a paternally inherited premutation. In contrast, only 1 (3.7%) of women with a maternally inherited premutation had POF. Moreover, the age at menopause was significantly lower in women with paternally inherited premutations, compared with those with premutations of maternal origin. These results confirm that women carrying a fragile X premutation are at increased risk for POF, but only when they have inherited the premutation from their fathers. The authors hypothesize that this parent-of-origin effect is due to genetic imprinting, although the mechanism remains obscure. However, these data should provide new avenues into the study of fragile X syndrome.

Admixture and Type 2 Diabetes, *by Williams et al.* (*p. 527*)

The American "melting pot" has given this country a population that inherently results from gene flow. New genotypes arise as once-isolated parental groups mix. Williams et al. have studied the relationship between this genetic admixture and disease prevalence in such a

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mixed population. In a 34-year study, they monitored the Pima Indians of the Gila River Community of Arizona, a group with a high prevalence of type 2 diabetes and obesity, two diseases that share a common linkage on chromosome 11q. Allele frequencies for both full-heritage Europeans and full-heritage Pima Indians were determined at several loci and were used to estimate individual genetic admixtures in the present Pima population. These admixture measurements were compared, between different members of the population, to determine the effect on disease risk. Nondiabetics had significantly more European admixture than did diabetics. In addition, both body-mass index and glucose levels varied inversely with genetic admixture. Lower-risk alleles from Europeans decreased the risk of obesity and type 2 diabetes in the admixed population, relative to that in full-heritage Pima Indians. If disease prevalence differs between two populations, these data suggest that the disease risk will be moderated in an admixed population that is derived from the two. As populations continue to mix, further alterations in allele frequencies are predicted for many loci.

Linkage Heterogeneity in Human PAR, *by Lien et al.* (*p. 557*)

The unequal frequencies of recombination between different regions of the genome have long been a puzzle. Generally, recombination frequencies are calculated as averages across all families studied. Although this provides a general estimate of physical distances between markers, it does not indicate how individual genetic variances translate to local recombination frequencies. To that end, Lien et al. have used single-sperm typing to study individual variation in recombination frequencies in the Xp/Yp pseudoautosomal region (PAR1). The availability of sperm has allowed them to study many meioses from single individuals, to calculate these frequencies. Nearly 2,000 sperm from four individuals were genotyped to create a linkage map for the PAR1 region, which was then used to assess recombination frequencies. Over certain intervals of PAR1 and in particular individuals, the recombination frequencies were hypervariable, yet the overall recombination frequency for the region was fairly constant between individuals. Compensatory reductions in recombination within neighboring intervals of PAR1, due to strong positive linkage interference, lowered the recombination frequency across the region. This interference is also evidenced by an unexpectedly low number of double crossovers in the region. To examine the relationship between this genetic information and physical distance within PAR1, the authors created a high-resolution map of the region, using radiation-hybrid mapping. Using this map, they discovered that, although recombination varies considerably between PAR1 intervals, the recombination per unit physical distance across PAR1 occurs at 20 times the genome average. Eventually, similar comparisons of genetic and physical distance at many loci can be used to determine the sequences and genetic structures controlling recombination.

New Locus for Generalized Epilepsy with Febrile Seizures Plus, *by Lopes-Cendes et al.* (*p. 698*)

Febrile seizures are fairly common in normal, healthy children, although most of these children have only one such episode. However, some children develop recurrent febrile seizures with episodes throughout their early childhood, and they can even go on to have generalized, afebrile seizures. A familial syndrome, termed "generalized epilepsy with febrile seizures plus" (GEFS+) is defined by these characteristics. Although inheritance of GEFS+ appears to be complex in some families, there is an autosomal dominant mode of transmission in others. A locus for GEFS+ has been mapped to chromosome 19q, where a mutation was found in *SCN1B,* which encodes a voltage-gated sodium channel (see the Wallace et al. [1998] entry in this article's References list). Since *SCN1B* mutations are not present in most families affected by GEFS+, Lopes-Cendes et al. have searched for further GEFS+ loci and have found one at chromosome 2q23-q31. Within this region are several candidate genes for GEFS+, including a cluster of Na^+ and K^+ channel genes and *GAD1,* which encodes a protein involved in production of the neurotransmitter GABA.

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