This Month in the *Journal*

As Jost Schönberger and Christine Seidman describe in a review this issue (p. 249), there are many genetic loci—and many nongenetic etiologies—that are associated with dilated cardiomyopathy. Knowing the genes that are associated with dilated cardiomyopathy has allowed the identification and treatment of presymptomatic individuals in affected families, thereby reducing the symptoms and decreasing the morbidity and mortality of the disease. The genetic studies also give us a better understanding of the heart's action, as well as ways in which it can fail. This review article gives an overview of the genetic loci that are associated with dilated cardiomyopathy and of the mechanisms by which mutations are thought to lead to this disorder.

HAC-Mediated Rescue of HPRT Deficiency, *by Mejía et al.* (*p. 315*)

Mejía et al. have developed a human artificial chromosome (HAC) that is composed of centromeric sequences from chromosome 17, telomeric sequences, and a chromosome Xq26.1 segment containing the hypoxanthine phosphoribosyltransferase (HPRT) gene. Transfection of the HAC into $HPRT^-$ HT1080 fibrosarcoma cells resulted in relatively stable complementation of the HPRT defect of the cells. The HAC appears to be maintained as a minichromosome, although a low level of integration was detected in some cell lines. Structural characterization of the HACs in a few clones indicates that they consist of irregular, alternating segments of alphoid and nonalphoid DNA that were derived only from the input DNA. This system should be helpful in future studies of the generation and maintenance of de novo centromeres, but it also has potential as a gene-therapy vector.

Sequence Variation in* TCRB *V Genes, *by Subrahmanyan et al.* (*p. 381*)

The *TCRB* locus is a gene cluster, on chromosome 7, that encodes the β subunit of the T-cell antigen receptor. It is an interesting locus for association studies of disease susceptibility and of autoimmune disease, but a detailed characterization of polymorphisms in this locus, for use in these studies, had not been performed until the study by Subrahmanyan et al. In four populations, they sequenced 63 of 65 variable (V) segments in *TCRB*. Using these data, they generated one of the densest single-nucleotide polymorphism (SNP) maps to date, with approximately one SNP every 200 bp. Within exonic sequences, 74% of the variation identified was nonsynonymous. This is higher than has been seen in other surveys of human genetic diversity, but it is very close to the proportion (76%) of nonsynonymous changes predicted in the absence of any selection. Furthermore, the frequency spectrum of nonsynonymous changes at the locus did not deviate from neutrality. These data are consistent with the idea that *TCRB* diversity has been generated through a neutral evolutionary process. Another thing that may be surprising to readers concerns the finding that, across the *TCRB* locus, there are clusters of adjacent polymorphisms that are in strong linkage disequilibrium (LD) with each other. These clusters of LD could suggest local depressions in recombination rate or that the spaces between these clusters are hotspots of recombination. However, simulations under a neutral model with uniform rates of mutation and of recombination indicate that similar blocks of LD can be generated without these forces, meaning that the clusters could have been generated by the chance occurrence of a low level of local recombination.

Schizophrenia and Translocation t(1;11) (Report), *by Blackwood et al.* (*p. 428*)

Blackwood et al. describe a family that carries a balanced translocation, t(1;11)(q42.1;q14.3), that is linked to schizophrenia and affective disorders. Diagnoses that appear to be associated with the translocation include schizophrenia, bipolar disorder, recurrent major depression, and minor depression. A maximum LOD score of 7.1 was seen between the translocation and a phenotype that included schizophrenia, bipolar disorder, and recurrent major depression. This is certainly very strong evidence for linkage with a psychiatric disorder. The involvement of the 1q42 region in the phenotype is further supported by genome scans, for schizophrenia and bipolar disorder, that have achieved suggestive and significant LOD scores with markers in regions near the translocation breakpoint. Prolonged latency and reduced amplitude of auditory P300 event–related potential have been documented in both affected and unaffected members of families with schizophrenia. In this work, Blackwood et al. demonstrate that these measures of P300 amplitude and latency are altered in translocation carriers—as opposed to noncarriers—regardless of whether they are affected. This finding supports the idea that P300 measures are markers of risk for these disorders. Two genes, *DISC1* and *DISC2,* are directly disrupted by the translocation and are candidate genes for a role in these psychiatric disorders.

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***Maternal Folate Polymorphisms* (*Report*),** *by Hassold et al.* (*p. 434*)

The purported link between trisomy 21 and polymorphisms in the genes for methylenetetrahydrofolate reductase (MTHFR) and methionine synthase reductase (MTRR) was the first evidence for a genetic underpinning to chromosomal segregation abnormalities. Given the role of MTHFR and MTRR in folate metabolism, this finding brought the suggestion that nutritional prevention strategies might be employed to reduce nondisjunction, which is an intriguing idea. Hassold et al. have gathered samples to determine whether any associations exist between these genes and cases of trisomy of chromosomes other than 21. They genotyped the maternal *MTHFR* and *MTRR* polymorphisms in trisomy cases that were known to be of maternal origin. Sex-chromosome and some autosomal trisomies were studied. A significant increase in the T allele at position 677 of *MTHFR* in mothers of trisomy 18 conceptuses was the only allele-frequency difference that was detected between cases and controls. These results do not provide much support for a major effect of maternal *MTHFR* and *MTRR* polymorphisms on meiotic nondisjunction. As the authors explain, several confounding factors may explain the discrepancy between their results and those reported for trisomy 21. Further studies of the association between *MTHFR*, *MTRR*, and meiotic nondisjunction are certainly warranted.

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