This Month in the *Journal*

Somatic Mutations in TSC Lesions, *by Niida et al.* (*p. 493*)

According to the "two-hit model," cancer-predisposition syndromes are due to dominant germline mutations, and tumor formation results from a second somatic mutation in affected individuals. However, there has been some question as to whether haploinsufficiency, due to the original germline mutation, may itself promote tumorigenesis. Niida et al. examine evidence for the two-hit hypothesis in tuberous sclerosis complex (TSC), a disorder that is characterized by multiple hamartomas in many organ systems and that is associated with mutations in either the *TSC1* or *TSC2* gene. Multiple hamartomas from 10 patients were examined for evidence of second-hit mutations, by several methods. Although angiomyolipomas often exhibit loss of heterozygosity, other types of lesions often did not show any evidence of inactivation of the wild-type *TSC1* or *TSC2* allele. Some of the lesions in which a second mutation was not found were clonally derived. This rules out the hypothesis that the second mutation was not found because there was a mixture of normal and abnormal cells in the sample. This work suggests that haploinsufficiency for *TSC1* or *TSC2* may, in some cases, be sufficient for the formation of TSC lesions.

Behavior of Fragile X Mutations in Embryocarcinoma Cells, *by Wöhrle et al.* (*p. 504*)

Hypermethylation of expanded *FMR1,* the gene associated with fragile X mental retardation, has correlated with stability of the *FMR1* repeat. Wöhrle et al. determined whether this was also the case in undifferentiated cells. This led to the discovery of an exception to the correlation between hypermethylation and repeat stability in *FMR1.* These experiments started with fibroblasts from two males with *FMR1* expansions: one with fully methylated, stable expansions and one with unmethylated, unstable expansions. The fibroblasts were first fused with mouse A9 cells. Repeat stability was observed for the clones derived from both donors, despite maintenance of the difference in methylation. These hybrids were used as microcell donors to undifferentiated PC13 embryocarcinoma cells. This transfer resulted in complete demethylation of the previously methylated sequences. The demethylation was associated with destabilization of the *FMR1* expansion and with stable transcriptional reactivation of *FMR1.* However, if the *FMR1* expansions were then transferred from the PC13 cells back to differentiated murine A9 cells, mitotic stability of the *FMR1* repeat was regained, despite the fact that *FMR1* remained unmethylated. The factors contributing to this methylation-independent stability are unclear, as is the molecular mechanism of the initial expansion event in fragile X syndrome.

17q11.2 Microdeletions, *by Jenne et al.* (*p. 516*)

A minority of patients with neurofibromatosis type 1 (NF1) exhibit a clinical phenotype more severe than that generally seen with this disorder. In addition to the classic presentations of neurofibromas, café-au-lait spots, and an increased risk of malignancy, the more severely affected patients can have additional symptoms, which include mental retardation, a dysmorphic facial appearance, and an excessive number of neurofibromas for their age. In contrast to classic NF1, in which mutations generally lead to truncation or loss of the functional protein product, the more severely affected patients usually have a microdeletion of 1.5 Mb from chromosome 17q11.2. Jenne et al. have delineated the boundaries of the microdeletion in patients with the 17q11.2-microdeletion syndrome. The microdeletions arise from unequal recombination between two highly homologous DNA segments that appear to be derived from the *WI-12393* gene by partial duplication. This recombination leads to hemizygosity for at least 13 genes, including *NF1.* The loss of genes in addition to *NF1* may contribute to the more severe phenotype that is often associated with the 17q11.2 microdeletion. This finding adds to the growing list of disorders that are caused by rearrangements between duplicons.

Type 2 Diabetes in the U.K.: Genome Scan, *by Wiltshire et al.* (*p. 553*)

In one of the largest studies of type 2 diabetes to date, Wiltshire et al. have performed a genome scan of 743 sib pairs from the Diabetes UK Warren 2 Repository. Power studies indicate that their data set has high power to detect a locus with modest effects. In the collection of the samples, the authors attempted to reduce heterogeneity through use of a wide range of diagnostic criteria for inclusion in the sample. Their results provide confirmation, according to published guidelines, of a locus for type 2 diabetes, on chromosome 1q. Loci on chromosomes 8p21-22, 10q23.3, 5q13, and 5q32 also coincide with regions of interest that were identified in previous genome scans. These results, in combination with those from other large data sets, provide a basis for future genetic studies of type 2 diabetes, and addi-

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tional analyses of this large and carefully constructed data set may better delineate the candidate regions on which these studies should be focused.

QSAT for Population Samples, *by Zhang and Zhao* (*p. 601*)

The use of family-based association tests may help researchers to avoid the population-stratification problems that are encountered with case-control association tests. However, family-based tests are often less powerful than population-based ones, and the samples for the family-based studies are harder to collect. To combat this problem, some researchers have developed methods that are useful for case-control studies of qualitative traits, through use of genomic markers to control for population stratification. Zhang and Zhao have extended this approach to quantitative traits, through the development of the quantitative similarity-based association test (QSAT). Individuals in the samples are genotyped for a series of independent markers, and these genotypes are used to decide whether the individuals belong to the same subpopulations. This information is incorporated into an association test between a candidate marker and the quantitative trait. Estimates of type I–error rates for the QSAT are within reasonable limits, even in the presence of population stratification, and, for three sample sizes, the QSAT is more powerful than the two types of transmission/disequilibrium test to which it is compared. Although a number of markers (the authors use $\geqslant 500$) are needed to determine whether the individuals in the sample belong to the same subpopulation, the QSAT is likely to be a useful alternative to family-based association tests.

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