This Month in the *Journal*

This month in the *Journal,* Benjamin Neale and Pak Sham present their views on gene-based association studies, in which all common variation within a candidate gene is considered jointly. They advocate a movement toward this type of approach for association studies of complex disease, because it captures all potential risk-conferring variation and thus can make a negative result more meaningful because it is subject only to the power of the study. Gene-based approaches take into account local allele frequencies and linkage-disequilibrium structure and thereby avoid complications due to population differences. This will allow more meaningful interpretation of the results of replication studies performed in different study populations. Although this approach is not feasible for all genes at the present time, because of a lack of knowledge of complete variation within every gene, Neale and Sham feel that gene-based approaches are a wise choice when attempting to replicate previous associations and that they will be increasingly useful as additional gene variation is mapped.

Trisomy Recurrence, *by Warburton et al.* **(***p. 376***)**

Few studies have provided good estimates of recurrence risks for trisomy. To look at this more thoroughly, Warburton et al. collected data, from two sources, on >2,800 prenatal diagnoses for women with a history of a previous numerical-chromosome abnormality. The basic question they asked was: Were these women more likely to have either a trisomy of the same chromosome (homotrisomy) or a trisomy of a different chromosome (heterotrisomy) in a subsequent pregnancy? Their results confirm a previous finding that women who have trisomy 21 before age 30 years are at a significantly increased risk of having a second pregnancy with trisomy 21, but Warburton et al. also found an increased risk in women over age 30 years. One way to explain this recurrence is through gonadal trisomy 21 mosaicism, a possibility that is supported by other data. Things are not quite that simple, however, because there is also an increased risk of heterotrisomy subsequent to a trisomic pregnancy. This cannot be explained by gonadal mosaicism but, rather, suggests variation in risk of meiotic nondisjunction between women.

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Genomewide Linkage Scan for Myopia, *by Stambolian et al.* **(***p. 448***)**

Despite the fact that nearsightedness is obviously a very common condition with a genetic component, the underlying defects are unknown. Although many might not consider myopia to be an urgent problem, it actually increases the risk of more-severe eye conditions, including glaucoma and cataracts, so it is important from a public health standpoint. Stambolian et al. present the first genome scan for common myopia in a sample of Ashkenazi Jewish families. This relatively genetically isolated study population was chosen to reduce heterogeneity in the sample, because it is likely that several genes play a role in the development of myopia. In an effort to further reduce heterogeneity and bias in the study, myopia was treated as a binary—rather than a quantitative—trait. Perhaps surprising for a common trait with a large environmental component, the authors report a strongly suggestive linkage to chromosome 22q12. Although family-based association tests did not show an obvious genetic association with this region, the fairly wide spacing of markers at this stage of the study makes it difficult to draw conclusions from that result, so fine mapping of the region is under way.

Identification of BBS3, *by Chiang et al.* **(***p. 475***)**

Bardet-Biedl syndrome (BBS) is a genetically heterogeneous disorder, the cardinal features of which include obesity, mental retardation, polydactyly, and pigmentary retinopathy. Eight loci have been mapped so far, and some of the BBS genes have been identified through positional cloning and/or sequence comparisons with other BBS genes. However, the rarity of *BBS3*-linked families has precluded refinement of this locus. On the basis of the fact that some of the known BBS genes are involved in cilia function, Mykytyn et al. (2004 [see reference in Chiang et al.]) BLASTed BBS sequences against the genomes of a variety of organisms and found that, in general, there were sequences homologous to the BBS genes only in the ciliated organisms. Chiang et al. exploit this fact to identify the *BBS3* gene bioinformatically. They looked for a set of candidate genes that had homologs in ciliated organisms but not in unciliated organisms. None of the resultant 114 genes mapped to the *BBS3* interval, but one of them corresponded to the recently identified *BBS5,* providing support for the general strategy. From there, the authors looked for genes that were in common between humans and ciliated organisms and that localized to the *BBS3* interval. This led them to

identify *ARL6* as *BBS3*. Affected individuals in the kindred used to map *BBS3* carry a homozygous truncating mutation in this gene. ARL6 is a member of the RAS superfamily of proteins, which have diverse functions. Its precise role is unknown, but, on the basis of current knowledge of the other BBS and ARL proteins, Chiang et al. speculate it may be involved in intracellular transport.

Prenatal Molecular Karyotype Using Microarrays, *by Larrabee et al.* **(***p. 485***)**

Prenatal cytogenetic diagnosis by use of amniotic fluid (AF) samples takes at least a week, because viable amniocytes must be cultured to gain sufficient numbers for metaphase analysis. Once the amniocytes have been removed from a sample, some of the AF supernatant can be used for the analysis of cellfree proteins, but the rest of it is generally discarded. Larrabee et al. show that this discarded fraction can actually be useful for prenatal diagnosis of whole-chromosome aneuploidy because it serves as a source of cellfree fetal DNA that can be analyzed by comparative genomic hybridization microarrays. In this study, the number of each sex chromosome and chromosome 21 could be determined accurately through comparisons with euploid reference samples. A number of samples lacked sufficient amounts of cellfree fetal DNA or did not hybridize well to the array, so this technique is not ready for routine use. However, this could turn out to be a more rapid, more comprehensive way to look at prenatal samples in conjunction with standard karyotyping.

PTPN22 R620W Is Associated with Human SLE, *by Kyogoku et al.* **(***p. 504***)**

You may recall that two recent articles reported an association of *PTPN22 R620W* with autoimmune disease, one with rheumatoid arthritis (Begovich et al. 2004 [see references in Kyogoku et al.]) and one with type I diabetes (Bottini et al. 2004); for a refresher, see last month's installment of "This Month in the *Journal*." With the finding that PTPN22 R620W is associated with systemic lupus erythematosus (SLE), Kyogoku et al. now provide further evidence that *PTPN22* is an autoimmunity gene. In three independent cohorts of whites, this missense change was associated with a dose-dependent increase in risk of SLE. PTPN22 is a protein tyrosine phosphatase that regulates T-cell signaling. Perhaps it is not surprising, therefore, that *Ptpn22* knockout mice exhibit dysregulation of the effector/memory T-cell segment (Hasegawa et al. 2004). The authors propose that defects in the regulation of T-cell signaling in carriers of R620W facilitate the generation of the autoantibodies that are characteristic of these autoimmune disorders.

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