This Month in the *Journal*

The 6 years I spent working on the *Journal* have been an honor and a privilege. I vividly remember walking into the office on my first day as an editorial fellow, seeing a stack of at least 25 manuscripts in my in-box, and wondering what the heck I had gotten myself into. But here we are, some 7,000 manuscripts later, and I can't believe how the time has flown. I am extraordinarily grateful to Steve Warren for the opportunity to work on the *Journal* and for his mentorship. Our work was much easier thanks to the people at the University of Chicago Press, especially Everett Conner, Peggy Perkins, and Alec Dinwoodie. The rest of the *AJHG* staff has been phenomenal, and I feel very fortunate to have worked with them. Without seeing an editorial office in action first hand, I don't think you can truly appreciate how difficult it is to juggle authors, reviewers, readers, and the publisher and to keep everybody relatively happy. Brava to our managing editor, Carissa Gilman, who has managed to do this with professionalism and grace under pressure. Although I am sorry that our time with the *Journal* is coming to an end, I am looking forward to seeing some of the exciting changes that Cynthia and her staff are cooking up. I hope they enjoy the work as much as I have.

KATE GARBER

Inconsistent Haplotype Blocks, *by Nothnagel and Rohde* **(***p. 988***)**

Haplotype blocks, the HapMap, tagging SNPs: we hear quite frequently about these concepts and their promise for use in genetic association studies. With increasing research, it is becoming apparent that haplotype blocks are not the concrete structural elements that they may at first have seemed; rather, they are impacted by such factors as SNP density and sample size. To determine the precision with which haplotype blocks capture genetic variation, Nothnagel and Rohde compared haplotype blocks that were defined through two complementary and interdigitated sets of SNPs. Their approach allowed them to circumvent confounding influences of marker density and population selection on haplotype-block definition, because the marker sets were of similar density, came from the same genetic regions, and were genotyped in the same sample. Even at high marker densities, the particular SNP set chosen had a large effect on the haplotype-block borders, haplotype frequencies, and tagSNP selection, so genetic variation is not fully captured when one relies on these marker-selection methods. Although these approaches can be useful, trade-offs still exist between reductions in genotyping effort and loss of information.

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Discriminating Three-Dimensional Facial Morphology, *by Hammond et al.* **(***p. 999***)**

Clinical geneticists often begin their examination of a patient with a careful appraisal of craniofacial abnormalities. Disorders such as Noonan syndrome, 22q11 deletion syndrome, Smith-Magenis syndrome, and Williams syndrome are associated with characteristic facies that can provide clues to the underlying disease. Here, Hammond et al. expand on their previous work in 3-D face analysis, using dense surface models to develop a system that, through comparisons of facial features, can distinguish patients of each of the above-named syndromes from each other and from controls. They began by using a large number of cases and controls to establish views of the average face of each group. During this process, they were also able to determine which specific regions of the face are instrumental in the discrimination procedure. Their system was successful in correctly classifying 89% of 320 randomly selected affected children. Smith-Magenis syndrome was the most difficult to distinguish, with 78% of cases correctly identified, and Williams syndrome was the easiest, with 96% correct. Hammond et al. then used the system to evaluate four adult males with unconfirmed Williams syndrome. According to the measurements, three of the four were recognized as patients with Williams syndrome. Indeed, when molecular testing was performed, the diagnoses based on facial morphology were confirmed: three patients have a deletion on 7q11.23, whereas the fourth individual has a wild-type allele at that locus. The system will not only be a great instructional tool for clinical geneticists, but it will also serve as an invaluable resource for obtaining additional data for evaluation of genotype-phenotype relationships and examination of how the facial abnormalities of a syndrome change with age.

Identification of* BBS9,** *by Nishimura et al.* **(p. 1021***)**

Bardet-Biedl Syndrome (BBS) is an autosomal recessive disorder involving obesity, retinopathy, polydactyly, renal abnormalities, learning disabilities, and hypogenitalism. Although eight loci have already been linked to BBS, mutations in the genes at *BBS1-8* account for only ~50% of the known cases of the disease. Nishimura et al. have identified the locus and the gene of *BBS9*.

They began with a comparative genomic analysis that exploited the fact that the genomes of both *Trypanosoma cruzi* and *Leishmania major* but not those of *Giardia lamblia* or *Saccharomyces cerevisiae* contain BBS orthologs. By determining which of the 35,838 human genes have orthologs in *T. cruzi* and *L. major* and excluding those with partners in *G. lamblia* and *S. cerevisiae,* the authors were left with a set of 366 potential BBS genes. Of these 366, 19 were also found to be aberrantly expressed in the eyes of *Bbs4*-knockout mice, a model in which photoreceptors are absent. Support for the involvement of these 19 genes with BBS is provided by the fact that 7 of the 8 known BBS genes are within this group. To further narrow the number of candidates, Nishimura et al. identified new potential BBS loci by homozygosity mapping in small consanguineous BBS-affected families. Nineteen candidate regions were identified, and comparison of these loci with the set of potential genes identified through genome comparisons suggests that three genes might play a role in BBS: *DPCD, UNCII9,* and *B1*. A *B1* splicing mutation was identified in one of the BBS-affected families, and six other *B1* mutations were then found in a different set of unrelated probands with BBS. The search continues for new genes that contribute to this heterogeneous syndrome.

Mannose Receptor in Enzyme Therapy, *by Du et al.* **(*p. 1061*)**

There are a couple of phenotypes associated with deficiency of lysosomal acid lipase (LAL), the enzyme crucial for hydrolysis of triglycerides and cholesteryl esters in lysosomes. These are cholesteryl ester storage disease (CESD) and the more severe Wolman disease (WD), which is fatal within a few months of birth because of the accumulation in several organs of macrophages containing cholesteryl esters and triglycerides. Enzyme replacement therapy shows promise for the treatment of these disorders. In an LAL-null mouse model, treatment with human LAL produced in *Pichia pastoris* results in significant improvement of hepatosplenomegaly and lipid accumulation. Improvement in the liver of these animals is due primarily to reductions in lipid storage in Kuppfer cells, whereas there is no improvement noted in hepatocytes. In an attempt to better understand the uptake and delivery of the LAL replacement therapy in this model, Du et al. compared the use of *P. pastoris*–produced human LAL (phLAL), which is highly mannosylated, to CHO cell–produced human LAL (chLAL), which includes more-complex structures. In contrast to phLAL, chLAL is able to clear the accumulated lipids from hepatocytes. Previous work had indicated that incorporation of phLAL into the lysosomes of J774 cells was dependent on the macrophage mannose receptor (MMR). Du et al. show that this process can be altered when phLAL is used to treat $lal^{-/-};MMR^{-/-}$ double-knockout mice. In this case, phLAL is cleared much more slowly from plasma and is able to mediate clearance of lipids from hepatocytes. The work of Du et al. highlights the importance of the uptake mechanisms for the efficacy of enzyme replacement therapy. It also has greater implications than the treatment for WD and CESD, because LAL has also been shown to have use in treating atherosclerosis in a mouse model.

X-Chromosomal Haplotype in LHON, *by Hudson et al.* **(*p. 1086*)**

Since association studies for the analysis of complex disorders have become common practice, it is clear that, in many diseases, a number of factors interact to affect the penetrance of a phenotype. In Leber hereditary optic neuropathy (LHON), a disease consisting of bilateral visual failure, 95% of cases are due to one of three mitochondrial mutations: 3460G→A in *MTND1,* 11778G→A in *MTND4,* or 14454T→C in *MTND6*. Yet only ~50% of males and ~10% of females carrying a mutation develop symptoms. What other factors are involved with LHON? Previous work has suggested that a modifier locus resides on the X chromosome, but studies have been unsuccessful in identifying the region involved. Here, by restricting their cases to those with the mitochondrial mutations at >70% heteroplasmy and by starting their search with nonparametric linkage analysis in an isolated cohort of Finnish families, Hudson et al. mapped a region on the X chromosome that is strongly associated with LHON. After the association with this region was confirmed in other European populations, a sample of 150 European men with LHON were used to define a high-risk haplotype that is more highly represented in males with LHON than in controls. Similarly, females who are homozygous for the X-chromosomal haplotype also demonstrate a higher risk of developing LHON. The identification of this nuclear modifier of LHON-associated mitochondrial mutations should help us to better understand the expression of this phenotype, and, in the future, it also may assist in genetic counseling of families with LHON through better predictions of disease outcome.

KATHRYN GARBER AND ROBIN E. WILLIAMSON
Deputy Editors