This Month in *The Journal*

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Potential Therapeutic Enzyme for Fabry Disease

Tajima et al., page 569

Patients with Fabry disease suffer from a wide range of symptoms, including pain, skin manifestations, renal problems, and cardiac disorders. The X-linked disease is caused by the lysosomal accumulation of globotriaosylceramide (Gb3) due to mutations in *GLA*, the gene encoding a-galactosidase A. Current treatment involves enzyme replacement therapy, wherein recombinant enzyme is introduced via infusion in an effort to break down the Gb3. The therapy has had its successes, but there is room for improvement. The therapy relies on mannose 6-phosphate (M6P) receptors to bind the recombinant enzyme and bring it into the cells. Because the recombinant enzymes do not contain a high level of M6P, this can be limiting, and some cells can not incorporate enough of the enzyme to significantly reduce the amount of Gb3 accumulation. Additionally, patients can have allergic reactions to the foreign proteins and develop antibodies that reduce the efficacy of the treatment. To alleviate these problems, Tajima et al. tweak a few amino acids in the active site of the endogenous enzyme a-*N*-acetylgalactosaminidase (NAGA) to create a modified version that will recognize and break down Gb3. The thought is that the modified NAGA contains more M6P and so will be better incorporated into cells, and that the enzyme also should not cause an immune response because it is similar enough to the natural form of NAGA. The authors demonstrate that, in mice, the modified NAGA is indeed well incorporated into a number of affected tissues. They also find that human patient serum shows no immunoreactivity to the modified enzyme. It is hoped that these results will translate into an improved and effective treatment for patients with Fabry disease.

Privacy in Biobanks

Kaufman et al., page 643

Involving the general public in genetic research is now more important than ever. Not only are new findings increasing the amount of useful information that can actually affect people's lives, but new study designs necessitate the participation of a large number of individuals. With this high level of public involvement has come the responsibility of ensuring that participants are well informed about the consequences of their contributions and that the privacy of each individual is maintained. Large biobanks have been created for the storage of participant samples and information, and many safeguards have been implemented for ensuring the safety of these data, but new reports have suggested that anonymous samples may not be as unidentifiable as originally thought. Discrimination by insurers and employers is not the only possible negative outcome; violating the right of individuals to share their personal medical information in a manner that suits them is also harmful. In addition, the public's perception that privacy might be breeched in these biobanks may hinder participation even if no such possibility does actually exist. Kaufman et al. report the results of a national survey that assesses how privacy concerns, study design, potential benefits, type of researcher, and data sharing affect the willingness of individuals to participate in a large cohort study. The authors conclude that, although many respondents do express concern about privacy, the majority say that they would share their data with researchers, particularly if they are confident that they will maintain control over the use of their information and if they benefit from the study.

GWAS of Lung Cancer by Histology

Landi et al., page 679

Carcinoma refers to the uncontrolled proliferation and migration of epithelial cells. Such malignant cancers can arise from different tissue sources, including glandular and squamous tissue. Malignant cancers arising from glandular tissue are referred to as adenocarcinomas, and those arising from squamous tissue are called squamous cell carcinomas. Lung cancer is most often a carcinoma and can be histologically classified as being either small cell lung cancer or non-small cell lung cancer. Treatment of lung cancer differs between these two types of carcinomas. Both adenocarcinomas and squamous cell carcinomas are non-small cell cancers and often respond to chemotherapy and radiation. Although long-term exposure to tobacco smoke is thought to be the primary cause of lung cancer, a genetic component does exist. Remarkably, there is little that is known about the genetics of the different histological subtypes of lung cancer. In this issue, Landi et al. set out to discover genetic variants contributing to lung cancer histology. Through performing a genome-wide association

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study of adenocarcinomas, squamous cell carnicomas, and small cell carcinomas, this group validates previous findings reporting association of 5p15, 15q25, and 6p21 with lung cancer. In addition, they identify a SNP in *TERT* that is significantly associated with adenocarcinoma in both smokers and nonsmokers. This study contributes to the task of ferreting out the interplay between smoking and genetics in the development of lung cancer.

Imputation Error and Power

Huang et al., page 692

SNP analyses of entire genomes are now commonplace in genetic studies. As the field evolves, the tools available for these analyses progress and change. One quickly evolving instrument is the platform used for genotyping; the SNP arrays are growing to include a larger and larger number of SNPs. Although many SNPs overlap between arrays, not all genotyping platforms contain exactly the same set of SNPs. Because of the growing number of genotyping platforms available, geneticists are using and sharing data and genotype information obtained from a variety of SNP arrays. In an effort to increase efficiency and decrease cost, scientists and statisticians have developed a means to substitute one SNP for another when data is missing from one genotyping platform or another. This process of substitution is called imputation. Use of imputation in genome-wide association studies (GWAS) is often limited by increased error rates and loss of power for the detection of association. Genotyping a larger number of people than necessary for nonimputed data can help to overcome these obstacles. Here, Huang et al. examine the degree of population inflation required for maintaining power in imputation GWAS. They find that even small errors in imputation require a large number of additional subjects to be genotyped in order to maintain power for the detection of associations. This number, however, is dependent on the population used. For example, fewer additional samples are needed when imputing European samples than when imputing African populations, who have more diverse genomes. This manuscript provides a guide for study design when imputing genotypes.

TRPM1 and Congenital Stationary Night Blindness

Audo et al., page 720; Li et al., page 711; van Genderen et al., page 730

Mutations in *NYX* and *GRM6* have been identified in patients with complete congenital stationary night blindness (cCSNB), but there remain cases in which the etiology remains unknown. Now, recent work in a horse model has shed some light on the topic. The Appaloosa horse suffers from a phenotype of night blindness that is very similar to cCSNB in humans, and expression studies in the horse have demonstrated that the gene *TRPM1*, which encodes a transient receptor potential channel, is downregulated in the retina. In addition, the proteins encoded by *NYX* and *GRM6* have been shown to modulate the TRPM1 channel. These findings have spurred three independent groups to screen for mutations in *TRPM1* in their patients with cCSNB. The groups, led by Li, Audo, and van Genderen, identify different *TRPM1* mutations in a large proportion of their patients. van Genderen et al. also further characterize the electroretinograms (ERGs) of their patients and compare them to those of patients with mutations in the other cCSNB genes. The authors report that the ERGs of patients with mutations in *TRPM1* are identical to those of patients with dysfunctional *NYX* and that they differ from those of patients with *GRM6* mutations. These collective data offer insight into the pathways involved in night vision and illuminate the genetic etiology of cCSNB in a significant percentage of patients.