This Month in *The Journal*

Robin E. Williamson[1]

Population Structure of the Japanese

Yamaguchi-Kabata et al., page 445

It is quite well established that ignoring the effects of population stratification when performing association analyses can lead to the identification of false positives. One can minimize the influence of these spurious effects by selecting cases and controls from homogenous populations or by assessing the amount of stratification present and correcting for it. The Japanese population is often thought to be a homogenous population, but data from analyses of mitochondrial DNA and Y chromosomes have suggested that two subpopulations exist. Yamaguchi-Kabata et al. analyze the substructure of the Japanese people by performing a genome-wide SNP analysis of 7,001 individuals from seven regions of Japan. The authors demonstrate that two major clusters exist: one consisting predominantly of people from Okinawa (the Ryukyu cluster) and the other, larger cluster made up of people from the rest of Japan (the Hondo cluster). Of note, different proportions of the regions outside of Okinawa also contained members of the Ryuku cluster. The HapMap JPT samples fell within the Hondo cluster. The authors were then able to identify those regions of the genome that resided in the regions of highest differentiation between the two subpopulations. Simulations are used as a warning for how indiscriminate selection of cases and controls from Japan in general can adversely affect the results of association analysis.

Detection of Interactions in Pedigrees

Lou et al., page 457

Due to the complex nature of inheritance of many common diseases, methods that can measure the effects of interactions between genes and other genes, as well as between genes and the environment, have many advantages. Such combinatorial methods are often able to detect variants with small effects that work together; such variants can be missed by single-factor analysis strategies. Unfortunately, the multifactorial methods needed to evaluate the interactions of several terms can be computationally intensive and susceptible to false positives and negatives. A great deal of effort has been spent attempting to overcome the obstacles of multifactor analysis, and a number of strategies have been developed to make the work more feasible. The majority of methods previously developed were designed to handle population-based samples, and Lou et al. now extend their earlier work on the generalized multifactor dimensionality reduction method (GMDR) to handle family samples. The pedigree-based approach, or PGMDR, can incorporate covariates, can be used to evaluate both quantitative and qualitative traits, and can now utilize the important resource of family data available for genetic studies.

AAVshDyrk1A Attenuates Motor Abnormalities in a Down Syndrome Mouse Model

Ortiz-Abalia et al., page 479

Previous evidence has suggested that the increased dosage of *DYRK1A* may be responsible for some of the phentoypes observed in Down Syndrome (DS). Although the overexpression of many genes is most likely involved in the spectrum of DS features, transgenic mouse models that overexpress *DYRK1A* exhibit motor abnormalities and cognitive deficiencies. This has led to the hypothesis that attenuation of the expression of *DYRK1A* in DS patients might result in improvement of these aspects of DS. As an initial step toward this goal, Ortiz-Abalia et al. evaluate the ability of an adeno-associated virus (AAV) system to target *Dyrk1A* in a transgenic mouse model and to alleviate the established related symptoms. The authors are able to demonstrate that the virus successfully infects the targeted brain tissue of the mice and reduces the amount of Dyrk1A protein to levels similar to that observed in wild-type mice. The behavior of adult transgenic mice is analyzed, and those mice treated with the AAV show reduced hyperactivity and increased coordination as evaluated via a treadmill test. Additionally, the advantageous effects appear to be long lasting because they are still observed at an 8 month time point. The rescue of significant DS features in an adult transgenic mouse model through the normalization of gene expression may one day be able to translate into beneficial effects in the treatment of DS patients.

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CHD7 Mutations Cause Kallmann Syndrome

Kim et al., page 511

CHARGE syndrome is an autosomal-dominant disorder that affects a variety of systems including the eye, heart, genitor-urinary tract, and ear. A large proportion of CHARGE cases have been found to be due to mutations in *CHD7*. Researchers in the field have begun to recognize that the CHARGE phenotype can sometimes overlap with that of a different set of syndromes: idiopathic hypogonadotropic hypogonadism (IHH) and Kallman Syndrome (KS). A small number of CHARGE patients who present with features reminiscent of IHH or KS have been identified. IHH and KS are related to each other in that each involves a lack of sexual development. KS is additionally associated with the inability to smell. Although mutations in at least nine genes have been linked to either IHH or KS, the molecular basis for disease has only been determined in 25%–30% of cases. In their search for additional genes that are disrupted in IHH and KS, Kim et al. take advantage of the suspicion that IHH and KS may be allelic to CHARGE syndrome. Sequence analysis of *CHD7* in a population of patients with IHH or KS reveals several mutations and concretely establishes the relationship between these disorders.

GWAS for Plasma Liver Enzyme Levels

Yuan et al., page 520

Liver enzyme levels are thought to be affected by both environmental and genetic factors. Because the measurement of liver enzymes can reveal a variety of conditions or indicate the present of liver damage, understanding the factors that control liver enzyme levels can have important health benefits. Yuan et al. perform a genome-wide association study to identify genetic variants that influence the levels of four liver enzymes: ALT, AST, ALP, and GGT. In the first round of study, three large datasets (one from Switzerland, one from Italy, and one from the UK) are independently analyzed, and SNPs that are significantly associated with ALT, ALP, and GGT are identified. The authors then follow up on these variants in additional datasets from an Indian Asian population and a European white population. In addition to identifying a number of candidate genes that may be involved in liver disease and related phentoypes, the authors confirm an association between ALP and ABO blood groups, and they also report that the variants affecting ALP levels appear to be independent of those affecting levels of the other liver enzymes.