This Month in *The Journal*

Kathryn D. Bungartz[1] and Robin E. Williamson[2]

Using the Common to Find the Rare

Li et al., page 728; Zawistowski et al., page 604

As the number of studies evaluating an association between common variants and a phenotype has increased, it has become clear that common variants aren't responsible for the majority of heritability in most cases. This has turned attention to searching for effects of rare variants. But, what are the best ways study rare variants? In this issue, Li and colleagues and Zawistowski and colleagues each present methods that contribute to the identification of rare variants that are associated with disease susceptibility. The methods share the goal of identifying disease alleles that have a minor allele frequency of $< 5\%$, and they both can use genome-wide association study (GWAS) data to study these rare variants. The thought is that although SNP panels are usually used to study common variants in GWAS, they can also be used to study low-frequency alleles if careful haplotyping is used or if imputation from external sequencing data, such as that from the 1000 Genomes Project, is incorporated. In the Li et al. manuscript, the authors focus on using haplotyping to assess rare variants in GWAS data and then demonstrate how imputation using sequencing data can add to their findings. Zawistowski et al. present a method with the goal of being able to handle the uncertainties involved with using low-coverage sequencing data and imputed data and similarly conclude that sequencing data can be used to impute rare variants from GWAS data. Both groups demonstrate the utility of their approaches by reevaluating previously published data.

How Can One Little Deletion Cause So Much Trouble?

Moreno-De-Luca et al., page 618

Identifying variants associated with disease not only contributes to the knowledge of which genes are likely to be involved in certain biological pathways but also can suggest links between pathologies when the same variant is found to be associated with more than one phenotype. Several association studies have found commonalities among the features that are found at an increased frequency in both patients with autism spectrum disorder (ASD) and patients with neurodevelopmental or psychiatric disorders such as schizophrenia. In this issue, Moreno De Luca and colleagues look closely at a recurrent deletion on 17q12. Genomic abnormalities of this locus have been identified previously in patients with renal disease, diabetes, and epilepsy. In addition, deletion carriers have been reported to have intellectual disability or ASD. When the authors examine their first data set of patients who were referred for intellectual disability or ASD, they also identify a high frequency of 17q12 deletion carriers. The authors also identify patients with schizophrenia who carry the deletion. Because the authors find the deletion in their patient populations but not in any controls, they suggest that the deletion is highly penetrant but that it has variable expressivity, on the basis of the wide range of phenotypes that have been observed in carriers. The deletion is a relatively common genomic abnormality, and the full characterization of the phenotypes that it can cause will assist in care and diagnosis of carriers.

Mutations in *FLVCR1* Cause PCARP

Rajadhyaksha et al., page 643

PCARP is the name given to a syndrome characterized by *p*osterior *c*olumn *a*taxia and *r*etinitis *p*igmentosa. Patients affected by PCARP suffer a progressive decline in visual function and proprioception, the ability to sense where body parts are in relation to the rest of the body. The onset of clinical features occurs in early childhood, some patients being diagnosed with RP before their one-year birthday and with ataxia by the time they are ten. Using data from three PCARP families, Rajadhyaksha and colleagues are able to link the syndrome to a region on 1q, but as often can be the case, when candidate genes in the linkage region are sequenced, no obvious etiologic mutations are identified. The authors then resequence the whole linkage region in members of one of their families and report a mutation in *FLVCR1* that encodes a heme-transporter protein. Two different mutations segregate with PCARP in the other two families. Each of the mutations affects a residue in a transmembrane domain of the channel protein. Previous functional work has supported that FLVCR1 is critical for erythropoiesis, and knockout mice present with features of Diamond-Blackfan syndrome. Here, the authors demonstrate that *Flcvr1* is highly expressed in the retina and posterior column of the spinal cord and suggest that a disruption in heme transport due to the PCARP-associated missense mutations might lead to a decrease in neuroprotective effects and an increase in apoptosis in these tissues.

[1]Science Editor, *AJHG*; [2]Deputy Editor, *AJHG*
DOI 10.1016/j.ajhg.2010.10.022.

Rare CNVs in an All-Too-Common Condition

Glessner et al., page 661

Obesity is a huge health risk with an incidence that is increasing throughout the world. This trend in children presents a serious public health concern as the majority of obese children grow to become obese adults. Obesity is a category of body mass index (BMI), which is calculated by dividing a person's squared height (in cm) by their weight (in kg). Averages depend on age, sex, and ethnicity, but in general, a BMI of 25 kg/ m^2 is the high end of normal. People having a body mass index (BMI) greater than 30 kg/m^2 are considered to be obese. This means that their bodies have accumulated a degree of excess fat that may have dire health effects. Obesity has been associated with increased risk of several different diseases, including type 2 diabetes, heart disease, cancer, and others. Although obesity can be effectively treated with diet and exercise, research is showing a small genetic contribution to this condition. In addition to several SNPs being associated with BMI and obesity, deletions on chromosome 16p11.2 have been associated with severe early-onset obesity and developmental delay. Here, Glessner and colleagues examine a cohort of children presenting with common obesity. They find a significantly higher incidence of copy-number variants (CNVs) in the obese children compared to lean controls. The products of several genes affected by the identified CNVs are highlighted in this study as being potential players in human BMI and obesity. With increased knowledge of the risk factors associated with childhood obesity comes increased hope for curbing this disturbing trend.

Language Impairment Out*FOX*ed

Hamdan et al., page 671

Language impairment describes communication disabilities that can take many forms. From difficulty distinguishing different sounds to inability to coordinate the muscles required for speech, language impairment can have an impact on the quality of daily life. It can be isolated or part of a syndrome. Language impairment often accompanies intellectual disability (ID), cerebral palsy, and autism spectrum disorders (ASD), as well as other developmental disabilities. Although language impairment may have many underlying causes, genetics are sure to play a prominent role. Verbal dyspraxia is a specific type of language impairment in which the affected individual has difficulty planning and executing verbalizations. Mutations in *FOXP2* have been associated with verbal dyspraxia. *FOXP2* transcribes forkhead box protein P2, a transcription factor involved in the regulation of several developmental processes. FOXP1 is the closest relative of FOXP2, and the two proteins interact to repress the transcription of target genes. However, the association between *FOXP1* mutations and language impairment has been elusive. Here, rather than looking directly at language impairment, Hamdan and colleagues investigate the role of *FOXP1* disruption in associated syndromes, including ID and ASD. In addition to identifying a de novo deletion in a patient with ID and autistic features, this group identifies a de novo *FOXP1* nonsense mutation in another autistic patient with ID. Both patients show language impairment, confirming the suspicion that both FOXP1 and FOXP2 are important for language development.