This Month in *The Journal*

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Identification of Causal Variants

Zaitlen et al., page 23

As the number of variants identified as being associated with complex disease increases, one caveat about the results is that the variant identified may not be the functional variant contributing to disease risk, but may simply be in linkage disequilibrium (LD) with the causal variant. Regions of LD are advantageous in that they allow researches to "tag" a large amount of sequence with a small set of markers, but dissecting which variant within such an LD block is causal is difficult. Fine mapping via high-density genotyping or sequencing can help to break up the LD in an area, and work has begun to determine which populations should be used for such follow-up studies. By evaluating the regions in populations with different LD structure, it might be possible to differentiate the association signal of one marker from another. Here, Zaitlen and colleagues analyze which population or set of populations is most useful in the quest to successfully zero in on the functional variant. Although it has been hypothesized that using a population with as little LD as possible, such as the African population, would contribute the most to such a project, the authors find that a combination of populations often yields the best results. The authors also note that the best choice of population set is locus specific. These analyses are compiled into software called MULTIPOP which will allow users to establish their ideal study design in the most cost-efficient manner.

X Chromosome Evolution

Lambert et al., page 34

Because of the special characteristics of the X chromosome, studying its population structure can be a bit more complicated than the same type of analysis of the autosomes. The fact that males are hemizygous for the X chromosome leads to increases in the differentiation at X-linked loci and to a smaller effective population size, which contributes to increases in the effect of drift. It has been reported previously that the X chromosome has, on average, larger allele frequency differences than the autosomes. Here, Lambert and colleagues use X chromosome data from a number of populations to look more closely at the differentiation of X-linked markers on a region-specific basis. The authors start by looking at the X-linked SNPs in the HapMap data that have extreme allele frequency differences. They identify five distinct regions along the X chromosome in which these most highly differentiated SNPs reside. In support of these findings, the Perlegen X chromosome SNPs with high allele frequency differences cluster in the same regions. Closer analysis of these regions identifies evidence of recent positive selection. Of particular note is that Lambert and colleagues identify within the cluster that resides near the centromere a high concentration of markers for which the derived allele is at a very high frequency in African populations, but for which the ancestral allele is more common in non-African populations. This is contrary to the situation that is most frequently encountered. This suggests that this region of the X chromosome has undergone selective pressures in the African populations that differ from those that have affected non-African populations.

C16orf57 Poikiloderma with Neutropenia

Volpi et al., page 72

Next-generation sequencing (NGS) has the power to accurately sequence long stretches of DNA from diverse regions of the genome. This is possible through use of a sequencing technique called massively parallel sequencing. As the name implies, the technique amplifies DNA from different regions of the genome concomitantly. After assembly of the sequences produced, sequences of entire genes or even chromosomes can be deciphered. Although different companies use diverse approaches to obtain sequence information from different parts of the genome simultaneously, they all promise increased throughput for a reduced cost. Here, Volpi and colleagues use NGS to identify a mutation in patients displaying a genetic skin disease characterized by poikiloderma (a type of altered pigmentation), pachyonychia (thick nails), and chronic neutropenia. Although initially diagnosed as having Rothmund-Thomson syndrome (RTS), the chronic neutopenia and absence of *RECQL4* mutations, present in two thirds of RTS patients, changes the diagnosis of these patients to poikiloderma with neutropenia (NP). Linkage analysis is used to identify a 3.4 Mb candidate region on chromosome 16q containing more than 80 annotated genes. Because classical sequencing would take a tremendous amount of time and money, this group utilizes NGS, which reveals 17 unreported homozygous mismatches found within or very close

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to genes. Further analysis reveals a splice-site mutation in *C16orf57*. Additional *C16orf57* mutations are then found in a separate patient with NP, confirming that mutations in this gene as causative for NP. In addition to demonstrating the utility of NGS, these data can now be used to distinguish atypical RTS patients from those with PN.

A Mutation in the *PDE8B* Gene Causes ADSD

Appenzeller et al., page 83

PDEs are cyclic nucleotide phosphodiesterases that degrade phosphodiester bonds in the second messenger molecules cyclic AMP (cAMP) and cyclic GMP. These second messengers are involved in the process of signal transduction. For example, cAMP is responsible for transferring the effects of small molecules such as hormones across cell membranes. One way in which these second messengers act is through the activation of protein kinases. Currently, inhibitors of PDEs are being used to treat disorders that would benefit from delayed degradation of these second messenger molecules. Some of these disorders are erectile dysfunction, dementia, and hypertention. Here, Appenzeller and colleagues identify a frameshift mutation in *PDE8B* in a family affected with autosomal-dominant striatal degeneration (ADSD). ADSD is characterized by slow execution of movement (bradykinesia), dysarthria (a motor speech disorder), and muscle rigidity. Bradykinesia and rigidity are two key features of Parkinson disease (PD), indicating that the same region of the brain is involved in these two disorders. *PDE8B* encodes phosphodiesterase 8B and selectively hydrolyzes 3′,5′-cAMP to 5′-AMP. The authors suggest that PDE8B may influence dopaminergic neurotransmission in the striatum, the region of the brain affected in both PD and ADSD. This is plausible, given that dopamine receptors in the striatum are known to stimulate cAMP synthesis. More work is necessary to decipher the true role of PDE8B in neurological function; however, this work gets us one step closer to the answer and identifies a gene involved in ADSD.