This Month in *The Journal*

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De Novo Mutations in Autism Spectrum Disorder and Schizophrenia

Awadalla et al., page 316

De novo mutations (DNMs) may contribute to the development of complex disease and may explain some of the missing heritability that has not been identified via linkage analyses and association studies. Current indirect estimates of the neutral mutation rate in humans suggest that at least a couple DNMs will occur in each individual, and it is predicted that, if such mutations do affect disease susceptibility, they should occur at functional sites more often in patients with the disease than in those who do not have the disease. But are current estimates of the neutral mutation rate accurate, and is there yet enough evidence that DNMs really do play a role in disease risk? Awadalla et al. seek to evaluate these questions by resequencing synaptic genes in patients with autism spectrum disorder (ASD) or schizophrenia (SCZ). Variants that are identified are then determined to be de novo by evaluation of parent samples. The authors' direct estimates of the neutral mutation rate are similar to those reported previously. They then demonstrate that, in the patient cohorts, DNMs with functional effects are enriched over those that are predicted to affect nonfunctional sites. With the data at hand, Awadalla et al. are also able to compare the sites affected by DNMs with those that segregate in their patient families to show that segregating variants aren't as likely to affect functional sites. These analyses suggest that DNMs in synaptic genes are a risk factor for the development of ASD and SCZ.

Boost a Car or BOOST Your Analysis

Wan et al., page 325

Looking for gene-gene interactions that have an effect on disease is a bit more complicated than analyzing single markers for association with disease risk. Similar to playing a game of Memory, in which you get to progress through the game only if you flip over two cards that match each other, significant signals are observed only when two markers are assessed at the same time. This means that if a systematic analysis is to be done, each marker has to be tested alongside every other marker individually; with genome-wide SNP data, that works out to be a whole lot of tests. Some methodologies limit this number of tests by first discounting the markers that are unlikely to be contributing factors, but making such decisions ahead of time can mean discarding data that may be important. A central goal of some algorithms, then, is to look for an association between all pairs of markers and disease status without exhausting computational resources. In this issue, Wan and colleagues describe their answer to this problem: BOOST. The authors present the results of simulations to demonstrate the advantages of using BOOST in the study of gene-gene interactions. They then use BOOST to evaluate pairs of markers in the Wellcome Trust Case Control Consortium data from seven common diseases and find that BOOST is able to handle these data in significantly less time than is possible for other current methodologies. The differences that they report in the interaction patterns of markers in association with type 1 diabetes versus those in association with rheumatoid arthritis may reveal insight into the etiologies of the diseases.

Mutability of Y Chromosome Microsatellites

Ballantyne et al., page 341

Genetic analysis of the Y chromosome is an integral piece of population studies, forensic evaluations, and genealogical surveys. By looking at the nonrecombining region of the Y chromosome (NRY), researchers are able to follow the male lineage through generations and make estimations about the evolution of a population and the genetic distance of male relationships. All of these applications require an accurate assessment of the mutation rate of markers in the NRY. With evidence demonstrating that these rates are highly variable from one marker to the next, empirical determination of the mutation rate for each individual marker may be the best way to incorporate reliable data into calculations. In this issue, Ballantyne et al. closely investigate markers in the NRY and establish mutation rate values for each marker. They observe a wide range of values and evaluate how characteristics of the markers correlate with their mutability. In addition, the authors break the markers into groups on the basis of their mutability. Markers with low mutation rates can be useful in distinguishing distantly related male lineages from each other, but they will not be so useful in forensic applications that require the ability to differentiate close male relatives from one another. Such forensic analysis would benefit from the evaluation of markers with known

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higher mutation rates. In this regard, the authors' data not only provide mutation rate values for integration into better assessments of population history and evolution, but also establish which markers are best suited for particular applications.

TBC1D24 Mutations in Idiopathic Epilepsy and Intellectual Disability

Falace et al., page 365; Corbett et al., page 371

Idiopathic epilepsy (IE) is the name given to a seizure condition having no apparent cause. Seizures result from abnormal neuronal activity in the brain. The recurrent seizures in IE are present in the absence of detectable brain lesions or metabolic abnormalities and are the primary feature of IE. These seizures can impair consciousness and distort the electrical activity of the brain. Genetics are thought to play a prominent role in IE despite the fact than few mutations are currently associated with this condition. In this issue, Falace and colleagues and Corbett and colleagues both identify missense mutations in *TBC1D24* in patients with IE. Both groups combine different techniques to identify the mutations. Falace and colleagues use SNP genotyping and haplotype analysis followed by candidate gene sequencing to identify compound heterozygous *TBC1D24* mutations in a large Italian family. Corbett and colleagues perform linkage analysis and then utilize next-generation sequencing to sequence the entire linked region in a large Israeli family with IE and intellectual disability. After sorting through the identified variants, Corbett et al. confirm a *TBC1D24* homozygous missense mutation as segregating with disease in this family. Both groups of researchers find *TBC1D24* to be expressed in the brain. To define the function of TBC1D24, a largely uncharacterized protein, both groups perform in vitro analyses. They conclude that TBC1D24 has a role in neuronal outgrowth. Together, the localization of *TBC1D24* expression and the function of TBC1D24 support the role of the identified pathogenic *TBC1D24* mutations in IE.

Mutations in *FAM161A* Cause Autosomal-Recessive Retinitis Pigmentosa

Langmann et al., page 376; Bandah-Rozenfeld et al., page 382

Retinitis pigmentosa (RP) refers to a group of hereditary eye diseases. This heterogeneous condition is characterized by the accumulation of pigment-like deposits in the retina. Although the details of pathogenesis can vary greatly, all RP patients suffer from progressive retinal degeneration, often leading to complete blindness. Numerous genetic mutations in several different genes have been associated with different forms of RP. However, many cases of RP have no identified genetic cause. Here, two different groups of researchers identify mutations in a new gene associated with autosomal-recessive RP (arRP). Langmann and colleagues use a combination of two techniques to identify *FAM161A* mutations in an Indian arRP family. They utilize next-generation exon capture and sequencing of a region previously linked with RP in this family and simultaneously analyze chromatin immunoprecipitation data of murine retinal transcription factor target genes. *FAM161A* is found to be the top candidate in both assays. Nonsense mutations in this gene are then found in the original family and in additional arRP families. Bandah-Rozenfeld and colleagues take another approach. They use a combination of homozygosity mapping and candidate gene sequencing. Of the 12 candidate genes, only *FAM161A* is found to contain segregating pathogenic variants. In total, Bandah-Rozenfeld and colleagues identify three different mutations in 20 arRP families. Together, these data leave little doubt that *FAM161A* mutations lead to arRP.