This Month in *The Journal*

Sarah Ratzel[1] and Sara B. Cullinan[2]

Alu Elements in the Driver's Seat

Boone et al., page 143

Although copy-number variants (CNVs) are known to contribute to a range of Mendelian and complex disorders, our understanding of their molecular origins remains incomplete. Just as some elements render particular regions of the genome susceptible to errors at the single-nucleotide level, some loci appear to be especially prone to CNV formation. Previous reports have implicated *Alu* elements in driving recombination-mediated CNV formation at several loci, including *SPAST*, but technological limitations have hindered the type of in-depth analyses that are required for drawing clear mechanistic insights. Now, Boone et al. have mapped the breakpoint junctions of over 50 *SPAST* CNVs at nucleotide resolution, providing evidence that the genomic architecture of this locus predisoposes to a variety of CNV alleles, including several that generate chimeric transcripts. A better understanding of the phenotypic consequences brought about by the range of CNVs generated at this locus should prove helpful in both the diagnosis and the treatment of spastic paraplegia. More broadly, these findings add support to the notion that *Alu* elements possess inherent genome-destabilizing properties. Just how pervasive this activity is and what the consequences for human health are will no doubt be the focus of many future research endeavors.

De Novo Mutations Aren't Always what They Seem

Campbell et al., page 173

Although mosaicism can explain apparently de novo, recurrent disease in families, it is unclear how frequently mosaicism contributes to apparently de novo CNVs at a larger population level. To determine whether more sensitive detection methods could identify parental mosaicism as a source of apparently de novo CNVs, Campbell et al. screened 100 families with children harboring rare deletions. Using PCR designed for each individual breakpoint identified in these children, the authors detected low levels of somatic mosaicism in four of the families, suggesting that a substantial number of apparently de novo CNVs are inherited from mosaic parents. To better understand the results of this screen, they developed a probabilistic model that predicts that somatic individuals in whom the mutation originates before the germline lineage is established harbor 7–8 orders of magnitude more mutant gametes than the average individual. Clearly, these results have implications for family planning. Oftentimes, more intensive testing is not necessarily suggested for parents of a child with a single de novo mutation. This study hints that it might be beneficial to test parents for the specific allele identified in the child to more rigorously determine whether low-level parental mosaicism could be a contributing factor. As noninvasive prenatal testing improves, the application of this strategy to maternal plasma could be especially advantageous.

Every Exome Has Clinically Useful Incidental Findings

Tabor et al., page 183

One of the most hotly debated topics in returning incidental findings from whole-genome and exome sequencing relates to determining how useful these findings might be for an individual. Evidence suggests that, in general, people are interested in receiving findings that they can use in making healthcare and lifestyle choices. However, there is little information about how many incidental findings with a defined clinical utility (e.g., an established therapeutic intervention) a given exome might contain. In this study, Tabor et al. analyzed exome sequencing data from approximately 6,500 individuals from the NHLBI Exome Sequencing Project to evaluate the frequency of pathogenic variants with clinical utility in each individual and the curation required for delivering these findings to an individual. To evaluate a range of diseases and traits, the study focused on 39 genes commonly included in newborn-screening programs, 17 genes associated with age-related macular degeneration, and 14 genes that influence drug response. From these genes, over 10,000 variants were identified, and almost 400 variants were determined to be pathogenic by manual curation based on information from literature. On average, each person carried approximately 15 risk alleles and had a carrier burden of 0.57 for severe recessive disorders of childhood. These data suggest that every individual undergoing clinical exome sequencing most likely has variants of clinical utility. This study hints at both the potential for this information to make dramatic changes in medicine and the need to develop standard practices and tools for

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discussing and delivering these results to an extent that is reasonable and useful for individuals.

pQTLs Are an Independent Source of Phenotypic Diversity

Hause et al., page 194

Many investigations of complex traits have identified variants that influence mRNA levels—expression quantitative trait loci (eQTLs)—and assume that these effects are mirrored in protein accumulation. However, very few studies have directly evaluated this assumption because of the limitations of large-scale protein-quantification technologies. In this study, Hause et al. used micro-western arrays to quantify nearly 400 transcription factor levels in Yoruba lymphoblastoid cell lines from HapMap and evaluated the relationship between genome-wide genetic variation and mRNA and protein levels. Using this approach, they identified 12 *cis* and 160 *trans* protein-level QTLs (pQTLs). Although *cis* eQTLs are often pQTLs, it is not the case that pQTLs are associated with mRNA expression. Additionally, many pQTLs overlap SNPs associated with complex traits and therefore might provide additional insight into the functional implication of these variants in disease. Together, these results suggest that the effects of genetic variation contributing to differential mRNA expression are buffered in protein accumulation. Moreover, pQTLs might independently affect phenotypic diversity. Because this study focused on transcription factors, it will be interesting to see how these findings apply to different subsets of proteins and the proteome in general.

A Genetic Finding for AFND

Smith et al., page 235

Acromelic frontonasal dysostosis (AFND) is a rare disorder characterized by brain and limb malformations, along with intellectual disability. Phenotype-informed candidate-gene approaches have failed to identify causative mutations; moreover, the mode of inheritance has remained unclear. Now, Smith et al. have identified an identical, recurrent mutation in *ZSWIM6* as being causative for AFND. Little is known about *ZSWIM6*: its encoded protein contains a domain (SWIM) that is predicted to have both DNA-binding and protein-protein-interaction properties, but no functional characterization has been carried out. Expression and localization profiles in mouse and fish are consistent with the human phenotype, and preliminary work supports the hypothesis that aberrant activation of hedgehog signaling might be at play. Lending further support to this idea, the database DECIPHER includes several individuals (lacking the AFND phenotype) who harbor heterozygous deletions spanning *ZSWIM6*. Future biochemical and cell biological work should help to delineate the role of ZSWIM6, and perhaps also its family members, in key developmental pathways.