This Month in *The Journal*

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Reading Disability Deciphered

Powers et al., page 19

It would be difficult to overstate the importance of speaking and reading in modern human society. Fortunately for those affected by reading disability and/or language impairment, intervention efforts often succeed, but the cost is significant and success levels are highest when children are targeted from an early age. Years of work indicate a strong genetic component for these learning disabilities, but to date, a clear picture of the underlying genetics has yet to emerge. Now, Powers et al. propose a mechanism by which a region within 6p22 disrupts the development of crucial communication skills. The authors previously uncovered a putative risk variant—a short tandem repeat termed READ1—that resides within an intron of *DCDC2*. Their new work shows that READ1 disrupts binding of transcription factor ETV6, thus ascribing a functional role to this stretch of DNA. This work also opens the door for new explorations of ETV6 function; to date, it is best known as a proto-oncoprotein whose dysfunction can lead to leukemia. Given the highly polymorphic nature of READ1, this finding might provide some explanation for why reading disability appears to have a high level of "missing heritability." Although the book is certainly not closed on the genetics of language acquisition, this work might just have signified the end of a very long chapter.

Straight to the Heart of Things

Arndt et al., page 67

As might be expected for disorders caused by copy-number variants (CNVs), many individuals harboring CNVs display variable and often seemingly unrelated phenotypes. Tracking down the genes that contribute to discrete phenotypes requires careful clinical work-ups and large cohorts. In this issue, Arndt et al. describe their work in narrowing down the gene whose loss results in the cardiomyopathy found in ~25% of those affected by chromosomal region 1p36 deletion syndrome. Their analysis of deleted regions, in conjunction with studies of mutations in individuals with nonsyndromic cardiomyopathy, identified *PRDM16*, which encodes a transcription factor perhaps best known for its role in the development of brown fat. Notably, mutant zebrafish displayed reduced cardiac output and bradycardia, suggesting that, indeed, PRDM16 plays an important role in cardiogenesis. Further work should identify the relevant PRDM16 binding partners and target genes; a better understanding of this biology might aid the development of targeted therapeutic strategies and shed some light on the variable penetrance of cardiomyopathy observed in individuals with 1p36 deletion syndrome.

Truncating Mutations Are Found Not Guilty

Guo et al., page 78

Protein-network-based approaches for identifying candidate genes and for prediction of mutation pathogenicity often hinge on the idea that disruption of the interactions of a pathway results in a disease and that mutations in genes encoding components of a given pathway should result in the same phenotype. This idea is known as the "guilt-by-association" principle. However, it is still unclear whether this idea can be applied to both recessive and dominant mutations. In this study, Guo et al. evaluate over 20,000 cancer-associated mutations to investigate the guilt-by association principle, which proposes that dominant and recessive mutations are enriched in regions encoding protein interaction interfaces. After mapping the mutations onto their corresponding proteins in the 3D protein interaction network, they found that recessive mutations, but not dominant point mutations, are likely to be found in regions encoding interaction interfaces. Furthermore, dominant truncating mutations are enriched in regions encoding areas between interfaces, suggesting that these mutant genes might encode functional protein fragments that retain some, but not all, protein interactions. For example, an ovarian-carcinoma-associated mutation in *TRIM27* falls in a region encoding the area between two interaction interfaces and results in a loss of interaction with SIRPA; however, the truncated protein still retains the ability to interact with MID2 and TRIM42, as judged by a yeast two-hybrid assay. These functional truncated protein products are not limited to those with alterations in the extreme C terminus, supporting the idea that many truncated transcripts might escape nonsense-mediated decay. With a better understanding of the impact that mode of inheritance has on the protein change, programs for identifying candidate genes and predicting the pathogenic impact of mutations could be improved.

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What Lies Within (Runs of Homozygosity)?

Szpiech et al., page 90

Each genome contains numerous small changes that together create a unique individual. Within each genome, however, lie stretches of sequence—termed runs of homozygosity (ROH)—that are identical across a defined population owing to consanguinity, selection, and/or demography. The length of a given ROH stems from the relatedness of the population, and indeed, studies of consanguineous families have demonstrated that knowledge of these regions can aid in the discovery of variants linked to rare Mendelian disorders. From a population-genetics perspective, ROH can provide key insights into our evolutionary history; for instance, evidence of past bottlenecks, coupled with physical evidence, creates a compelling evolutionary story. To better understand the properties of ROH, Szpiech et al. studied individuals of various consanguineous backgrounds and spanning six global populations. They found that ROH, especially long ROH, harbor a much higher-than-expected burden of potentially damaging variants. These results suggest that just as inbreeding creates a safe harbor for strongly deleterious variants (such as those that cause Mendelian disorders), the resultant ROH are also home to a wide array of mildly damaging variants. Might the combinatorial effect of such variants underlie some complex diseases? Larger studies (e.g., see Gamsiz et al. in this issue) will be needed for addressing this question with certainty, but the findings of Szpiech et al. provide a solid foundation for a new way of looking at genomes.

When Chromatin Organization Goes Awry

Gregor et al., page 124

Chromatin organization is essential for regulating gene expression, and defects in genes that are involved in chromatin organization can lead to a variety of developmental disorders. In this issue, Gregor et al. identify mutations in *CTCF* in individuals with intellectual disability and growth defects. CTCF is a chromatin organizer that binds chromatin to prevent the spread of inactive heterochromatin into active regions and has a role in imprinting, X inactivation, and nucleosome positioning. The identified mutations resulted in reduced accumulation of the mRNA transcript and protein or interfered with amino acids required for interaction with the DNA backbone, suggesting that the phenotype could be due to haploinsufficiency of *CTCF*. Transcriptome data revealed that compared to controls, individuals with *CTCF* mutations had substantially more downregulated genes than upregulated genes. In addition, ChIA-PET interaction data showed that downregulated genes were enriched with promoters that interact with enhancers, suggesting that CTCF deficiency predominantly affects expression of enhancer-regulated genes. Taken together, these findings provide further evidence of the function of CTCF and underscore the importance of epigenetic regulation in development.