This Month in Genetics

Kathryn B. Garber[1,*]

Second Site Variation at a VNTR Influences ARTX Phenotype

When we discuss variable penetrance or expressivity of mutations, we often use a hand-waving argument that genetic variation in a second gene could be influencing penetrance of the disease mutation. With recent work by Law et al., this hand waving can become finger pointing, directed at a tandem repeat sequence that explains variable expression of the alpha thalassemia/X-linked intellectual disability (ATRX) syndrome phenotype. Even when two individuals have the same *ATRX* mutation, there is variability in the phenotype of the resulting ATRX syndrome, particularly in the severity of the alpha thalassemia component of the phenotype. Whereas some individuals with *ATRX* mutations have a microcytic anemia due to the downregulation of alpha globin expression, others have normal red cell indices. Law et al. tie these loose ends together through a chromatin immunoprecipitation-sequencing (ChIP-Seq) approach that indicates that ATRX has an affinity for G-rich tandem repeats. Indeed, ATRX seems to prefer to bind G-quadruplex structures, at least in vitro. One of the binding sites is a VNTR that is close to the alpha-like globin genes. As it turns out, variation in the length of this VNTR governs the variability in alpha globin expression in individuals with *ATRX* mutations. Cells from patients with the largest number of repeats at this VNTR have the biggest reduction in expression of alpha globin and, at the extreme, can exhibit monoallelic expression of the alpha globin gene.

Law et al. Cell 143, 367–378.

Accidents Do Happen; Quite Often, In Fact

It takes many, many genes to form a human brain and to facilitate normal postnatal brain development. This leaves many mutational targets that can lead these processes to go awry, making genetic testing for intellectual disability quite complicated. As our ability to detect genetic variation has improved, so has our ability to explain the genetic underpinnings of intellectual disability. The fact remains, however, that intellectual disability comprises a very heterogeneous group of disorders that can be the result of mutations at many different positions in the genome, leaving the underlying cause undiscovered in a significant fraction of cases. Recent work suggests that exome sequencing may help us find the needle-in-the-haystack mutations in many of these previously unexplained cases. Vissers et al. sequenced the exomes from ten individuals with sporadic, unexplained intellectual disability and their parents. Sorting through the variation, they honed in on changes that were predicted to be functional changes within genes and were de novo in the affected children. They found six different likely pathogenic mutations in six different patients, each in a different gene. These included two genes that were already known to cause intellectual disability when mutated, providing proof of principle for the analysis. Beyond finding a likely genetic cause in a number of affected people, this work also suggests that de novo point mutations could explain a significant fraction of sporadic cases of intellectual disability.

Vissers et al. Nature Genetics Advance Online Publication. Published online November 14, 2010. 10.1038/ng.712.

WDR62 Proves Multitalented in Brain Development

To form a normal brain, neural precursors must first undergo a set of symmetric cell divisions to produce a sufficient number of neural progenitor cells. Next comes a series of asymmetric cell divisions that give rise to cells that will differentiate into neurons and migrate to the appropriate location in the cortex. If too few of the symmetric cell divisions occur, there aren't enough neural progenitors, and you get microcephaly. It was thought that defects in other stages of this process would give rise to different malformations of cortical development. Recent work described in a series of recent papers has identified WDR62 as a protein that links the different phases of development. *WDR62* is mutated in individuals with primary microcephaly and in others with microcephaly and additional cortical defects. As with other proteins implicated in microcephaly, WDR62 is localized to mitotic spindles in dividing neural precursors, but it moves into the nucleus in young neurons and influences neuronal migration. The precise mutation in *WDR62* determines which function of the protein is affected. Missense mutations that are found in individuals with primary microcephaly prevent WDR62 from localizing to the spindle pole. On the other hand, more severe mutations affect both proliferation and neuronal migration and result in a more severe phenotype.

Nicholas et al. Nature Genetics 42, 1010–1014; Wollnik. Nature Genetics 42, 923–924; Yu et al. Nature Genetics 42, 1015–1020.

[1]Department of Human Genetics, Emory University School of Medicine, Atlanta, GA 30322, USA
*Correspondence: kgarber@genetics.emory.edu
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BPA Quells Double-Strand Break Repair

"BPA Free!" read the stickers on water bottles near and far, as a result of accumulating evidence that bisphenol-A (BPA) could increase the risk of reproductive issues and certain diseases, such as diabetes and heart disease. Although some studies indicate that BPA has no significant health impact, data in rodents suggest that it disrupts meiosis, and at least one study found a correlation between urinary BPA and risk of miscarriage in women. To nail down the effects of BPA on meiosis, Allard and Colaiacovo turn to a simpler model system: *C. elegans*. BPA exposure, albeit at quite high levels, has drastic effects on fertility and on the survival of *C. elegans* embryos. Through its antiestrogenic activity, BPA decreases germline expression of genes involved in double-strand break repair, impairing this protective mechanism and leading to chromosome abnormalities in oocytes of exposed worms. Although the levels of BPA in these experiments were higher than what we'd expect for a typical human exposure, this type of study could tease apart the relevant pathways through which BPA is acting and lead to further understanding of its risks.

Allard and Colaiacovo. PNAS. Published online November 8, 2010. 10.1073/pnas.1010386107.

HLA Clamps Down on HIV

A small but significant fraction of the people infected with HIV, dubbed controllers, are able to limit viral replication and maintain high CD4+ T cell counts and low viral loads, even in the absence of antiretroviral therapy. A recent genome-wide association study (GWAS) compared the genomes of a large number of these controllers against those of people with advanced disease due to HIV and hit a bulls-eye in the binding pocket of HLA-B. The only significant associations from the GWAS were with SNPs in the major histocompatibility complex (MHC) region on chromosome 6. This region has been implicated in HIV control previously but has been a headache in genetic association studies in general because of high levels of linkage disequilibrium. To sort through the data and find the key variation associated with HIV control, the authors imputed amino acid residues from genotype data and used them in further association analysis. Five residues that line the binding groove of HLA-B are major players in this association, frequently differing between controllers and those with advanced disease. This groove is the portion of HLA-B to which viral epitopes are bound for presentation to CD8+ T cells, suggesting that activation of these cytotoxic T cells is the key to viral control. Understanding how these residues influence viral antigen presentation could leave us better able to manipulate this process in noncontrollers and potentially to design effective HIV vaccines.

The International HIV Controllers Study. Science Express. Published online November 4, 2010. 10.1126/science.1195271.

This Month in Our Sister Journals

Old Before Their Time

The chromosome ends, or telomeres, gradually get shorter as a person ages, because the DNA can't be copied all the way to the ends during replication. This normal telomere shortening is believed to contribute to aging phenotypes. However, some people start life with abnormally short telomeres due to single-gene mutations. A recent review by Savage and Bertuch provides a thorough overview of these telomere biology disorders, including the genes involved and the range of features associated with these mutations. Although the classic, and most severe, telomere biology disorder is dyskeratosis congenital (DC), we now recognize a range of phenotypes associated with telomere shortening. A triad of features is used to recognize DC—abnormal nail development, abnormal skin pigmentation, and oral leukoplakia—but the phenotype in affected individuals can also include bone marrow failure, cancer, and pulmonary fibrosis. The phenotype of a telomere biology disorder can be more subtle; some people with apparently isolated features, such as acquired aplastic anemia, idiopathic pulmonary fibrosis, or liver disease, have now been found to have mutations that result in short telomeres. Even within a single family, there can be quite varied expression of the same mutation, and genetic anticipation can be observed.

Savage and Bertuch. Genetics in Medicine. Published online October 15, 2010. 10.1097/GIM.0b013e3181f415b5.

Is There Really a Missing-Heritability Problem?

Although genome-wide association studies have been very successful at identifying risk alleles for complex genetic traits, many researchers have remarked on the problem of missing heritability; in other words, the fact that the identified risk alleles for a particular trait, together, don't fully explain the trait heritability. Various explanations for this missing-heritability problem have been proposed, but now Song et al. use modeling studies to support the idea that perhaps this heritability isn't missing at all, or at least not completely. Typically, we combine risk information from multiple alleles by using a multiplicative model, which assumes that the individual loci behave independently. Song et al. calculate recurrence risk to close relatives under different models and find that the results often yield higher estimated recurrence risk than is predicted under a multiplicative model, particularly when the risk alleles are rare. What this means is that gene-gene interactions

could account for more heritability than is often assumed. Although these results need to be confirmed with empirical data, they suggest that we don't necessarily need to go looking for more loci that contribute to complex genetic traits; we just need to be able to more effectively model gene-gene interactions by using the data we already have. This is easier said than done, as the effect of each individual interaction isn't going to follow the same model.

Song et al. Genetics Advance Online Publication. Published online September 20, 2010. 10.1534/genetics.110.119008.