This Month in Genetics

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Penetrance Estimates for Recurrent Pathogenic CNVs

One challenge to the incorporation of chromosome microarray in the clinical setting is outcome prediction in fetuses and young babies who have copy-number changes. It's one thing to find a copy-number change in a child whose parents are seeking an explanation for the child's developmental delays; it is another to find the same change in a younger sibling or a fetus. Even for well-documented pathogenic copy-number changes, the reduced penetrance and variable expression make it hard to explain to families what the future holds. Rosenfeld et al. used data from clinical samples collected by Signature Genomics over several years and compared these to more than 20,000 control samples in order to get penetrance estimates for specific recurrent copy-number changes. These estimates range from 10.4% for 15q11.2 deletions to 62.4% for distal 16p11.2 deletions. Although there was no attempt to parse out different phenotypes in this analysis, these data do provide one more piece of concrete information for use in genetic counseling.

Rosenfeld et al. (2012). Genet. Med. Published online December 20, 2012. 10.1038/gim.2012.164.

Universally Different

Although each mammalian cell has numerous mitochondria, each with its own genome, it is generally believed that they are identical, at least at birth, in any given individual. Not so, say Payne et al.—as determined by ultra-deep resequencing of mitochondrial genomes in healthy individuals, heteroplasmy is universal in both blood and skeletal muscle. This sequence variation is not simply acquired with age, as might be expected given the relatively high mutation rate for mitochondrial DNA; rather, the variant sequences are very often shared between maternally related individuals, suggesting that they are inherited. If this is true, we might have to rethink the inheritance of variation in mitochondrial DNA and the dynamics of these variants with age.

Payne et al. (2013). Hum. Mol. Genet. 22, 384–390.

Even Higher Throughput Sequencing for Mutations that Cause Autism

The extreme genetic heterogeneity of a disorder like autism means that it is very difficult to definitively identify causative mutations in the absence of a functional assay for the gene product. Although exome sequencing in large autism cohorts has identified a multitude of de novo mutations in candidate genes for autism, the fact that only a single or small handful of mutations have been observed for many of these genes has stifled attempts to discern the relevant sequence changes from the rest. To make large-scale screening of these genes more feasible, O'Roak et al. tweaked a molecular-inversion-probe assay to allow resequencing of a set of 44 candidate genes in a large autism sample for a reagent cost of $1 per gene per sample. The molecular inversion probes capture the target sequence, which is then modified with adaptor and barcode sequences before being pooled and sequenced. The 44 genes were sequenced in nearly 2,500 probands with autism from the Simons Simplex Collection. The authors uncovered 27 de novo mutations, of which six had been missed by exome sequencing. Probabilistic modeling indicated that there was a higher-than-expected mutation rate in the 44 genes sequenced in this study. This excess mutation burden was significant for six of the individual genes as well. Although the results aren't proof that mutations in these genes are sufficient to cause autism, this is a more feasible approach to sequencing the genes in large enough cohorts to build the evidence that this is so.

O'Roak et al. (2012). Science 338, 1619–1622.

Twin Controls

Rather than focus on sequence variation in a limited number of genes, another recent study in an autism cohort assessed de novo mutation in whole-genome sequences. In this study by Jonathan Sebat's and Jun Wang's research groups, whole-genome sequences from sets of monozygotic twin pairs concordant for autism and their parents were used for the identification of de novo germline mutations. The use of twins allows true germline mutations to be distinguished from sequence error and from mutations that occur somatically or in the sequenced cell lines. What the authors found actually tells us more about the mutability of the human genome than it does about autism. Germline mutation was distributed nonrandomly across the genome and varied by 100-fold; it even sometimes occurred as clusters of two or more de novo mutations within 100 kb of each other. Certain features of the DNA are correlated with the mutability of a region; these include—not surprisingly—DNA sequence but also DNase hypersensitivity, nucleosome occupancy, and the presence of simple repeat sequences. Disease genes

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http://dx.doi.org/10.1016/j.ajhg.2013.01.005.

and exons are more highly mutable, and, paradoxically, some of the most highly conserved sequences are also the most hypermutable. This and other recent work together define hypermutable regions of the genome and provide the opportunity to unravel the explanation for this susceptibility.

Michaelson et al. (2012). Cell 151, 1431–1442.

Phenotypes in *DMD* Mutation Carriers

Most of what we know about Duchenne muscular dystrophy (DMD) was discovered through observation of affected boys. Contrary to what some believe, though, girls who carry *DMD* mutations can also manifest a phenotype that can be indistinguishable from that seen in affected boys. On the other hand, the phenotype can be mild to completely unrecognized. To better understand this clinical picture, Mercier et al. put together the largest series of symptomatic *DMD* carriers to date. Although the sample of 26 patients is biased because the researchers intentionally collected females who manifested symptoms before age 17, they fall into three general phenotypic groups: DMD, Becker-like muscular dystrophy, and early exercise intolerance. Some of the relatively common findings in the sample were learning issues or cognitive impairment and cardiac dysfunction, which occurred even in childhood. Although the broad range of phenotype severity in females is generally attributed to differences in patterns of X chromosome inactivation, these patterns were skewed in 62% of cases in this sample and did not clearly correlate with the severity of the phenotype.

Mercier et al. (2013). Eur. J. Hum. Genet. Published online January 9, 2013. 10.1038/ejhg.2012.269.

This Month in Our Sister Journals

A Closer Link

The trait of interest in a gene-hunting study is often some disease phenotype for which the genetic underpinnings are unclear. However, making the connection between the genetic variation and the phenotype involves a whole lot of biology, from transcription and translation of the DNA to systems biology. Holdt et al. reasoned that proteomic data are more directly tied to genetic variation and that it might be fruitful to use these data as the phenotype of interest in a quantitative trait analysis. As proof of principle, they used F2 intercrosses of two mouse strains and attempted quantitative trait analysis for 176 peptides that differed in the two parental strains (as measured by high-throughput mass spectrometry). Of these peptides, 69 achieved significant LOD scores. From there, the authors pursued two of the strongest linkage signals and were able to identify the causative genetic variation that led to differences in two of the peptides, one for hemoglobin A and one for Apoa2.

Holdt et al. (2012). Genetics. Published online November 19, 2012. 10.1534/genetics.112.143354.