

This Month in Genetics

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Big Gene, Big Heart

Although the cardiomyopathies have a substantial genetic etiology, genetic testing for this class of heart disorders has been notoriously difficult. Indeed, the causative mutation is found in only 20%–30% of patients with dilated cardiomyopathy. Titin is a candidate gene for cardiomyopathy that has been examined for mutations to a limited extent due to its massive coding sequence, which is ~100 kb in size. Herman et al. recently published data showing that the sequence hurdle for this gene is worth the effort. Through next-generation sequencing, they identified a truncating *TTN* mutation in ~25% of familial cases of idiopathic dilated cardiomyopathy, moving *TTN* to the forefront of genes involved in this form of the disease. Although these mutations had very high penetrance after age 40 in familial cases, there is also a significant amount of *TTN* variation whose clinical significance is difficult to interpret at this time. This includes missense variation, which was not analyzed in this current paper, so its role in cardiomyopathy is unclear. Even with truncating mutations in *TTN*, interpretation is not always simple; these mutations were identified, albeit at lower frequency, in control individuals and in individuals with hypertrophic cardiomyopathy who also had a pathogenic mutation in a known disease gene.

Herman et al. (2012) *NEJM* 366, 619–628.

A Complex Balance

Perhaps it is not surprising that the more closely you look at something, the more you see. Certainly, the advent of whole-genome comparative genomic hybridization (CGH) arrays taught us that many people with normal G-banded karyotypes have cytogenetic aberrations when we look more closely. Even high-resolution CGH arrays don't give us a complete picture of chromosomes, as recently illustrated by Chiang et al. These investigators took a set of individuals who had apparently balanced chromosome translocations—at least based on G-banding and whole-genome CGH arrays—and they analyzed the breakpoints at the nucleotide level. What they found was an unexpectedly high level of complexity to the breakpoints. In almost 20% of cases, three or more breakpoints were involved, but in some cases, a shockingly complex interweaving of segments occurred, akin to what was recently described in cancer cells as “chromothripsis,” or chromosome shattering and reorganization. The cases

analyzed by Chiang et al. involved upward of ten breakpoints with inverted segments interspersed among segments of the expected orientation. This phenomenon is not limited to spontaneous rearrangements in humans; analysis of transgene insertions in mice and in sheep revealed that the sites of integration can be similarly complex.

Chiang et al. (2012) *Nat. Genet.* Published online March 4, 2012. 10.1038/ng.2202.

Good News for Men

The Y chromosome is just a degenerate of its former autosomal self that is on its way to extinction, or so some have proposed. If you compare the Y to the X chromosome, for instance, the Y has lost many of the genes that the chromosomes once shared, and without a companion chromosome with which to fully pair itself during meiosis, some think this sex-specific chromosome is doomed. David Page argues otherwise. His group does species comparisons of the Y chromosome in order to understand its evolution and to better predict the future fate of the Y. Page's group previously compared the human to the chimpanzee Y chromosome, which diverged about six million years ago, but, in order to look at a much longer evolutionary window, his group recently compared the human and rhesus macaque Y chromosomes, which diverged 25 million years ago. This comparison yielded a surprising level of evolutionary stability on the Y. In the majority of the male-specific regions of the Y chromosome, rhesus macaques and humans share the same ancestral genes, arguing for Y chromosome stability over the long haul. In only a very restricted segment of the Y has gene loss occurred in humans since the split from the Old World monkeys. Their data fit a model in which rapid degeneration of segments on Y was followed by marked slowing of this decay and chromosome stabilization. Don't count the Y out just yet; it looks like it may stick around a while.

Hughes et al. (2012) *Nature* 483, 82–86.

Enhancers Acting as Promoters

Just as we learn to group letters into words and bin words into different parts of speech in order to extract meaning from sentences, we try to interpret genome sequences by picking out the nucleotide sets that comprise genes and attempting to recognize the regulatory elements from strings of As, Cs, Gs, and Ts. But although we might think

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we understand what a particular type of genetic element does, recognition of one of its roles in gene expression sometimes doesn't tell the whole story. Take enhancers, for instance. These are well-studied *cis* elements that have a simple job: they bind transcription factors and enhance expression from gene promoters, hence their name. Kowalczyk et al. wondered whether that's all enhancers do, and they ended up with evidence that intragenic enhancers can also act as alternative tissue-specific promoters. The resulting mRNAs are spliced and polyadenylated but do not appear to be translated into protein. Because enhancers are much more common than classic promoters and because about half of enhancers are intragenic, this promoter-like activity could contribute substantially to the complexity of the mammalian transcriptome. The next step is to figure out how these untranslated transcripts are used.

Kowalczyk et al. (2012) Mol. Cell 45, 447–458.

A Common Turn-On

While we're on the subject of surprising roles for noncoding elements, a recent paper uncovered the coordinated

regulation of two neighboring, but nonparalogous, genes that both tie into an identical phenotype. Joe Gleeson's group focuses on ciliopathies, and they recently identified mutations in *TMEM216* at the JBTS2 locus that cause Joubert syndrome. Of the ten JBTS2-linked families, however, only about half of them had a *TMEM216* mutation, despite an identical phenotype to the mutation-containing families. When they resequenced the JBTS2 locus, they found mutations in a neighboring gene, *TMEM138*, that is not related to *TMEM216*, although it also encodes a transmembrane protein. Although your first thought might be that *TMEM138* simply contains a regulatory element for *TMEM216*, this is not the case. Rather, both genes are coordinately expressed via the action of an intergenic element, and they both encode proteins involved in the same process, ciliogenesis. Knockdown of either protein leads to defective ciliogenesis, which ultimately is central to the Joubert syndrome phenotype. Thus, despite the fact that the genes are very different, they have evolved a system of coordinated regulation and functional relatedness.

Lee et al. (2012) Science 335, 966–930.

This Month in Our Sister Journal

Yeast System for Characterization of Cystathionine-Beta-Synthase Mutations

Although we know that individuals with deficiency of cystathionine-beta-synthase (CBS) tend to have intellectual disability, a marfanoid habitus, ectopia lentis, and increased risk of thromboembolism, there is variable expressivity for this disorder, and it is difficult to predict outcome from genotype. Dietary protein and methionine restriction is the central approach to management, and supplementation with vitamin B6, a cofactor of CBS, can lead to further reductions in homocystine levels in some affected individuals, who tend to have milder disease. To address the challenge of genotype-phenotype correlations

in CBS deficiency, Mayfield et al. used a yeast system to characterize the function of all 84 CBS missense alleles that had been documented as of 2010. This system, in which the yeast ortholog of CBS is replaced by human alleles, allows them to assess the general level of function, as well as the responsiveness of each allele to vitamin B6 and to another cofactor, heme. The authors also propose that glutathione deficiency should be further explored in the context of CBS deficiency, because they noted reduced glutathione production in their system when CBS function was disabled.

Mayfield et al. (2012) Genetics. Published online January 20, 2012. 10.1534/genetics.111.137471.