This Month in Genetics

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Is It Rare to Be "Normal"?

Although we know that a significant percentage of conceptuses do not result in a live birth and that many of those that are spontaneously aborted have a chromosome abnormality, it still seems quite shocking that only 9% of a set of in vitro fertilization (IVF)-derived embryos analyzed by Vanneste et al. had a normal karyotype in all blastomeres. In fact, in close to half of the embryos they analyzed, not a single normal blastomere was found. In the analysis, each blastomere in a cleavage-stage embryo was individually analyzed with a BAC and a SNP array. Compared to fertilized oocytes, in which a low level of anueploidy was found, whole-chromosome imbalances were observed in 19 of 23 embryos studied. Out of these, only three had the same aneuploidy in all blastomeres, indicating that most of the imbalances were the result of mitotic, rather than meiotic, segregation errors. It was not that the embryos were from couples with fertility problems that could be associated with structural chromosome problems; they were from couples seeking preimplantation genetic diagnosis for inherited conditions not related to fertility. That makes this sample the closest that we can likely get to studying what goes on in vivo. Yes, in vitro manipulation of embryos could contribute to the chromosome imbalances found in this study, but the fact that IVF success rates are more than double the rate of completely normal embryos in this study suggests that the chromosomally normal cells in an embryo might out-compete the abnormal cells, resulting in a chromosomally normal individual.

Vanneste et al. (2009). Nat. Med. 15, *577–583. 10.1038/nm.1924.*

Good Old-Fashioned Gene Hunting Still Provides Insight

With genome-wide association studies being so in vogue, it's easy to forget that we can still learn a lot from rare Mendelian forms of disease. A recent issue of *The New England Journal of Medicine* proves just that with reports of consanguineous families possessing two new disease genes that give us insight into normal biological mechanisms. Picard et al. describe a set of siblings with a combined immunodeficiency that is associated with severe defects in T cell proliferation in response to stimulation. A homozygous mutation was identified in *STIM1*, which regulates the activation of Ca^{2+}-release-activated Ca^{2+} channels that are essential for T cell activation. Bockenhauer et al. describe a new syndrome, EAST syndrome, that includes epilepsy, ataxia, sensorineural deafness, and tubulopathy. In two consanguineous affected families, they report homozygous mutations in the potassium channel gene *KCNJ10*. The phenotype in these families, along with additional studies in mice, implicates KCNJ10 as a channel that is necessary for proper salt handling in the kidney. Together, these two papers identify new candidate genes for roles in normal physiological function: one might be involved in T cell activation, the other in the regulation of blood pressure.

Bockenhauer et al. (2009). NEJM 360, 1960–1970.
Picard et al. (2009). NEJM 360, 1971–1980.

Ubiquitin Pathway, Neuronal Cell-Adhesion Molecules, and Autism

Although the heritability of autism is predicted to be higher than it is for other disorders for which risk alleles have been identified, common susceptibility factors underlying autism have for the most part eluded us. Rather than trying to find a single jackpot SNP or copy-number change that relates to autism, a set of companion papers now uses pathway- and gene-based association methods to look for the types of genes that play a role in susceptibility to autism. In combinations of large samples, two gene classes rise to the top of the pile. Wang et al. first did a genome-wide association study that identified a single SNP that was associated with autism at a level that achieved genome-wide significance. This SNP resides in a linkage disequilibrium block that is located between the genes for cadherins 9 and 10 and that contained other SNPs strongly associated with autism. To further support the relevance of the cadherin genes, the authors used a pathway-based association analysis to show that a set of 25 cadherin-related genes was more significantly associated with autism than the rest of the genes in their analysis. The cadherins are neuronal cell-adhesion proteins; when Glessner et al. used segment- and gene-based approaches to identify copy-number variation associated with autism, other neuronal cell-adhesion molecules, such as neuroligin 1 and neurexin 1, were implicated in

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this disorder. The second class of genes that Glessner et al. found to be enriched for copy-number variation were members of the ubiquitin family, including *PARK2* and *UBE3A*. Rather than focusing on specific autism genes, these papers give the impression that we should be thinking about sets of variation that together influence the pathways that are mechanistically linked to the development of autism.

Glessner et al. (2009). Nature, in press. Published online April 28, 2009. 10.1038/nature07953.

Wang et al. (2009). Nature, in press. Published online April 28, 2009. 10.1038/nature07999.

Modifying Allele Influences Ciliopathy Phenotype

Several genes are known to be involved in the development of the ciliopathies, a group of related disorders with overlapping phenotypes that are all caused by defects in cilia. As these genes have been discovered, it has become obvious that the differences in the ciliopathy phenotypes are not simply related to the single gene that is mutated. Instead, genetic modifiers appear to influence the expression of the ciliopathy. Khanna et al. attempted to unravel this phenotypic variability by assessing the complete mutational load of the cilia in patients with ciliopathies. During this assessment, they noticed that a missense change, A229T, in *RPGRIP1L* was enriched in a group of patients with retinal degeneration but absent in a group of patients without this phenotype. This change is not the mutation underlying the overall disease in these patients; it is a polymorphism found in 2.8% of unaffected controls. In functional studies of RGRIP1L, A229T was not able to substitute for the wild-type protein, and it had greatly reduced ability to bind to RPGR. Recessive mutations in *RPGRIP1L* were already known to cause Joubert syndrome and Meckel-Gruber syndrome. These results indicate that variation in *RPGRIP1L* can also influence the development of retinal degeneration in the context of ciliopathies due to mutations in other genes.

Khanna et al. (2009). Nat. Gen., in press. Published online May 10, 2009. 10.1038/ng.366.

Making Sense out of Nonsense Mutations

Many different genes are known to cause X-linked mental retardation (XLMR). Still, there are many affected individuals for whom no causative mutation can be found. To figure out what might be going on in these people, Tarpey et al. undertook a large resequencing effort to look for rare mutations of the coding exons of more than 700 genes on the X chromosome. Their results tell us something new about XLMR but also highlight some cautionary notes on large-scale resequencing for disease mutations. The authors started with more than 200 families for whom the inheritance pattern was consistent with XLMR but in whom no mutations had been found in the previously reported XLMR genes. The authors systematically sorted through the more than 1800 coding sequence variants to tease out which are likely to be causal. Through these efforts, they identified nine genes for which point mutations are likely to cause XLMR. Going beyond disease gene identification, the authors' work illustrates a couple of other important issues. First, despite resequencing huge amounts of the X chromosome, causative mutations are found in only 25% of the affected families. This highlights the difficulties we will face in finding causative mutations in a large proportion of families, even if we know many XLMR genes and perform a very detailed sequence assessment. Second, although truncating mutations were identified in 30 genes in this study, additional analyses of these mutations suggested that fewer than half of these genes are likely to be related to XLMR. Particularly given the fact that some of the likely causative mutations are very rare, this emphasizes the difficulty in assigning causation to sequence variation, even nonsense mutations, in large-scale resequencing studies.

Tarpey et al. (2009). Nat. Gen. 41, 535–543. 10.1038/ng.367.