This Month in Genetics

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The Growth of the Family Tree

Family-history collection is one of the key strategies for identification of individuals at increased risk of certain types of cancer. Primary-care physicians are the gatekeepers of this information, which is used to decide who might require earlier, more frequent, or more sensitive cancer screening. The first time you visit a new doctor and fill out all of the required paperwork, a family history questionnaire is usually one component. But how often are these histories updated, and how might these updates influence screening recommendations? Ziogas et al. use retrospective and prospective data from the Cancer Genetics Network to explore this issue. This population-based registry included self-reported family history information on breast, colorectal, and prostate cancer for up to 10 years of follow-up. They found that between the ages of 30 and 50 years there are increases in the clinically relevant family history of colorectal and breast cancer and that these increases could change cancer screening recommendations, leading them to suggest that the family history of cancer be updated every 5 to 10 years. Family trees grow and change with time; these changes must be noted to maximize the usefulness of family histories in guiding cancer screening recommendations.

Ziogas et al. (2011). JAMA 306, 172–178.

Nonmuscle-Myosin Mutations Linked to Kidney Disease

Despite the discovery of mutations that cause the progressive kidney disease focal segmental glomerulosclerosis in more than 20 genes, the underlying cause of this disorder is unknown in about half of patients. The typical approach to therapy, which uses glucocorticoids, is also ineffective in a significant fraction of patients; at least half progress to end-stage renal disease. Mele et al. recently found mutations in a new disease gene, encoding the nonmuscle myosin Myo1E; this discovery gives insight into the pathogenesis of focal segmental glomerulosclerosis and could lead to improvements in treatment. Myo1E localizes to podocytes, a specialized type of epithelial cell that is a critical component of the glomerulus, which is the filtering unit in the kidney. In cells expressing wild-type but not mutant Myo1E, the protein is enriched in the characteristic foot processes of the podocyte and promotes podocyte motility, presumably through stabilization of the podocyte cytoskeleton. Cyclosporine is a second-line treatment for focal segmental glomerulosclerosis, although it is not effective in all patients. It was originally thought that it alleviated symptoms because of its immunosuppressive effects, but other data suggest that it acts through stabilization of the podocyte cytoskeleton. The fact that three of four patients with *MYO1E* mutations were responsive to cyclosporine therapy supports this idea and further emphasizes the importance of podocyte structure in maintaining the filtration barrier in the glomerulus.

Mele et al. (2011). NEJM. Published online July 13, 2011. 10.1056/NEJMoa1101273.

Getting Clearance to Avoid Alzheimer Disease

The strongest known genetic risk factor for typical, late-onset Alzheimer disease (AD) is the apolipoprotein E epsilon 4 allele (*APOE ε4*). ApoE4 influences the accumulation of the amyloid-β (Aβ) peptide, which is presumed to trigger the pathogenic cascade leading to the dementia that is the hallmark of this disease. As recently shown by Castellano et al., even in cognitively normal individuals, the level of Aβ in the cerebrospinal fluid of individuals with the *APOE ε4/ε4* genotype is lower than it is in individuals with other genotypes, and these levels reflect increased accumulation of Aβ in the brain. This is supported by imaging data indicating that the frequency of healthy individuals with evidence of amyloid plaques is increased in the group with an *APOE ε4* allele. One could imagine that apoE4 alters Aβ accumulation either by influencing its production or its clearance, but clear data had been lacking to distinguish the mechanism until Castellano et al. measured these parameters in mice expressing human apoE. They used in vivo microdialysis to demonstrate that mice expressing apoE4 are less able to clear Aβ from brain interstitial fluid than those expressing apoE2 or E3, whereas the generation of Aβ was not influenced by *APOE* genotype. Although it is unknown how apoE influences Aβ clearance, further understanding of this process could illuminate a pathway that could be targeted by therapies aimed at AD.

Castellano et al. (2011). Sci. Transl. Med. 3, 89ra57.

Experiments Identify an Xist-ing Bridge

A crucial player in the inactivation of one X chromosome in each female mammalian cell is the long noncoding RNA Xist. This RNA is preferentially expressed from what will be the inactive X chromosome and eventually coats the

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length of the chromosome, leading to gene repression and chromatin modification. A key aspect of this system that has been unclear is how Xist identifies and binds to the inactive X chromosome. Contrary to previous ideas, Jeon and Lee have recently shown that Xist is not inherently *cis*-acting. In fact, Xist RNA can diffuse through the cell and is stable when not bound to chromatin. Instead, the binding of Xist RNA to the X inactivation center is mediated by the protein YY1, which binds only to the inactive X chromosome. YY1 forms a bridge between Xist RNA and its DNA in the X inactivation center, thereby tethering Xist RNA to its chromosome of origin. In their model, Xist RNA cannot bind to the active X chromosome because the YY1 binding sites are blocked in an as-yet-unidentified fashion. This work defines a nucleation center for X chromosome inactivation; further work is needed to understand how Xist binding spreads in *cis* along the chromosome.

Jeon and Lee (2011). Cell 146, 119–133.

Molecular Analysis of 22q13.3 Deletions

Individuals with chromosome 22q13.3 deletions, otherwise known as Phelan-McDermid syndrome, tend to have global developmental delays, neonatal hypotonia, and severe speech issues. The long-term natural history of this syndrome has been less clear because of a dearth of reports of affected adults. Bonaglia et al. recently collected a group of 44 individuals with Phelan-McDermid syndrome, including three in their forties. Although the sample size is small, the syndrome does seem to be associated with progressive clinical decline. The authors also attempted to clone and characterize the deletion breakpoints in the sample in order to use 22q13.3 deletions as a model to study terminal chromosome deletions. A range of repair mechanisms was implicated in these patients as a group, but the data from one patient indicate that separate repair events can actually occur in different cells in the early embryo; these repair events result in mosaicism. This patient was mosaic for three cell lines with breakpoints ranging over 100 kb. Although not exceedingly common, this syndrome is of interest to a wider group of researchers because haploinsufficiency for *SHANK3*, a gene implicated in autism, is believed to be critical for many of the deficits associated with Phelan-McDermid syndrome. The group of patients analyzed in this study includes five who have microdeletions involving only *SHANK3*.

Bonaglia et al. (2011). PLOS Genet. 7, e1002173.

This Month in Our Sister Journals

Reduced Penetrance of Null Mutations in *COL3A1*

Vascular-type Ehlers-Danlos syndrome (EDS), otherwise known as EDS type IV, is caused by dominant mutations in the collagen gene *COL3A1*. Although null mutations make up the minority of known cases, data from other collagenopathies suggest that haploinsufficiency could be associated with a different clinical course than that seen with missense or exon-skipping mutations. Data from a recent study by Leistritz et al. suggest that this is, in fact, the case. Of their collection of more than 500 families with *COL3A1* mutations, 19 had premature termination codons, which were associated with nonsense-mediated decay in all patients tested. Using data from the index patients and 26 relatives who also tested positive for a *COL3A1* mutation and comparing them to previous data on the natural history of EDS type IV, the authors found evidence that null mutations are less likely to be penetrant. When complications do occur, they tend to happen at an older age than in individuals with missense or exon-skipping mutations, and they are limited to vascular events. The frequency of null mutations in their collection of EDS type IV patients also suggests underascertainment of these individuals. Perhaps contributing to this is the fact that minor clinical features of EDS type IV are absent in at least half of individuals with a null mutation, and these features are often used as a testing indicator. The authors propose relaxing the testing threshold for *COL3A1* mutations to include families with later-onset arterial aneurysm to determine whether more null mutations might be found in this group.

Leistritz et al. (2011). Genet. Med. Published online June 1, 2011. 10.1097/GIM0b013e3182180c89.

An Approach to the Use of High-Throughput Sequence Data in Population Genetics

The distribution of allele frequencies in a sample of individuals, or the site-frequency spectrum, is a useful parameter in population genetics. Although high-throughput sequencing generates reams of data for calculation of the site-frequency spectrum, it is not without problems. For one, sampling variation can mean that one allele at a heterozygous site is underrepresented—or even absent—from the sequence data. On the other hand, sequence errors can be misinterpreted as polymorphisms. This is a particular challenge in species with low nucleotide diversity, such as humans, where the frequency of errors is high relative to the frequency of true changes. Keightley and Halligan have developed a maximum-likelihood model to estimate site-frequency spectra from high-throughput sequence data. Their method is robust to nonrandom error and suitable for low-coverage data, such as the Yoruban sample from the 1000 Genomes Project that they use as an illustration.

Keightley and Halligan. (2011). Genetics. Published online May 19, 2011. 10.1534/genetics.111.128355.