This Month in Genetics

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Risk of Pancreatic Cancer in Lynch Syndrome

Inherited mutations in mismatch repair genes are associated with dominantly inherited colon cancer. The shifting of the name of this cancer syndrome from hereditary nonpolyposis colon cancer back to Lynch syndrome reflects the fact that colon cancer is not the only form of cancer found in these families. Going back to some of the original families described by Lynch, one of the other cancers observed is pancreatic cancer. However, whether the cases of pancreatic cancer noted in these families were chance events or whether they were actually directly related to the mismatch repair defect has not been clear. Kastrinos et al. used two cancer registries to better estimate the risk of pancreatic cancer associated with Lynch syndrome. They had data from over 6000 individuals from 147 families with mutations in one of the mismatch repair genes. Overall, they observed nearly a 9-fold increased risk of pancreatic cancer in these families, compared to the general population. The relative risk is much higher at ages less than 50 years but then becomes more similar to the general population risk from ages 50–70. This work indicates that surveillance for pancreatic cancer in families with Lynch syndrome may be important, although the benefits and limitations of this type of surveillance, which may include radiographic and endoscopic imaging, has not yet been assessed.

Kastrinos et al. (2009). Risk of pancreatic cancer in families with Lynch syndrome. JAMA 302, 1790–1795.

Speech Networks

Ever since disruptions of *FOXP2* were found in individuals with severe language impairment, there has been research focused on the idea that if mutations in this single gene can take away language, perhaps this was a key gene in the evolution of human language. *FOXP2* appears to have undergone accelerated evolution in the human lineage, adding fuel to this idea, but no functional roles for the two human-specific residues in FOXP2 have been defined. To dissect out human-specific roles for *FOXP2*, Konopka et al. expressed the human or the chimp form of *FOXP2* in human neuronal cells lacking *FOXP2*. They compared the cell lines by using expression arrays and found 116 genes that were differentially regulated by the human and chimp proteins. Reporter assays with promoters from eight of these genes confirmed this differential expression in six cases. Even more striking is the in vivo evidence demonstrating that many of these genes are expressed at different levels in human versus chimpanzee brains. The authors surmise that networks of genes were actually key to the development of the language circuitry. They performed network analysis on the expression data and found two modules of genes that appear to be driven by the human-chimp differences in FOXP2. Some of these genes exhibit evidence of positive selection themselves, providing support for the idea that a coevolving gene network that included *FOXP2* might have been key to human speech development.

Konopka et al. (2009). Human-specific transcriptional regulation of CNS development genes by FOXP2. Nature 462, 213–218.

I'm Beginning to See the Light

Gene therapy seems to be the big promise that continually stays just over the horizon. The horizon seems like it just got closer with the report by Maguire et al. of their phase 1 trial of gene therapy for Leber's congenital amaurosis, an inherited retinal degeneration. In this trial, 12 patients with mutations in *RPE65*, ranging in age from 8 to 44 years, had injections of a gene therapy vector expressing *RPE65* into their most severely affected eye. All of the treated patients had stable improvements in retinal function in the treated eye, including improved visual field and pupillary light responses, and most patients had reductions in nystagmus. The greatest improvements were seen in children, presumably because retinal degeneration is not as widespread earlier in life. In fact, an 8-year-old child in the trial achieved nearly the same light sensitivity as age-matched control individuals. Video clips in the supplemental data show a remarkable improvement in one particular child's ability to navigate an obstacle course in dim light. These indications of treatment efficacy, coupled with a lack of adverse events, set the path for expanding this trial. Could we finally be seeing the light at the end of the tunnel for gene therapy?

Maguire et al. (2009). Age-dependent effects of RPE65 gene therapy for Leber's congenital amaurosis: A phase 1 dose-escalation trial. The Lancet 374, 1597–1605.

Cultural Evolution

More than 20 years ago, Richard Lenski started growing a single clone of *E. coli* in glucose-limiting medium. This culture has been kept going continuously since that day with daily transfer to fresh medium. At regular intervals, samples of this culture were frozen away until over 40,000 generations had passed, providing a wonderful

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system in which to study the evolution of a model organism. This group has now used next generation sequencing technologies to compare the complete genomes of clones that span the generations back to the ancestor. Over the first 20,000 generations, 45 mutations arose at a nearly linear rate, which would suggest neutral evolution. One might expect that changes in fitness would go hand in hand with changes to the genome, so you would also see a steady increase in fitness over time. However, their measures of fitness suggest that beneficial mutations appeared rapidly early in the culture, but this rate declined over time. Even in this simple system with a model organism and a constant environment, the relationship between genomic and adaptive evolution is not as straightforward as we might have assumed.

Barrick et al. (2009). Genome evolution and adaptation in a long-term experiment with Escherichia coli. Nature 461, 1243–1249.

A Smaller, Recurrent Deletion at Chromosome 15q13.3

Recurrent deletions of chromosome 15q13.3 were discovered over the last couple of years and found to be associated with a range of phenotypes from epilepsy to schizophrenia to mental retardation and autism. The deletions result from nonallelic homologous recombination between low-copy-repeat elements in the region and include six genes. Shinawi et al. now report a smaller recurrent deletion in the same region that narrows the focus to one likely candidate gene, *CHRNA7*. Ten individuals from four families carried this 680 kb deletion, and it was associated with similar phenotypes to the larger deletion, including mental retardation, epilepsy, and global developmental delay. The 680 kb deletion was found in ~1 in 3000 individuals tested and appears to result from nonallelic homologous recombination between the "normal" and inverted variant of chromosome 15q13 in heterozygous individuals. Because the smaller deletion only encompasses two genes, *CHRNA7* and *OTUD7A*, and because *CHRNA7* is an ion channel that has been implicated in epilepsy and schizophrenia, the authors propose that haploinsufficiency for this gene might be key to the phenotype and a plausible therapeutic target.

Shinawi et al. (2009). A small recurrent deletion within 15q13.3 is associated with a range of neurodevelopmental phenotypes. Nat. Genet, in press. Published online November 8, 2009. 10.1038/ng.481.

This Month in Our Sister Journals

Interpreting Copy Number Variation

Compared to G-banded karyotypes, comparative genomic hybridization (CGH) arrays have given us much finer resolution for detecting copy number changes (CNCs) on a genome-wide level. But, of course, the more you look for changes, the more you find. There are a few different factors that one can use to determine whether a CNC is benign or pathogenic, including its size and gene content and whether it was inherited or de novo. Still, there isn't a systematic way of making this call. To assess variability in interpretation of CGH array results, Tsuchiya et al. asked 11 different clinical laboratories to interpret the significance of 13 different CNCs. Not a single test result was interpreted with 100% agreement. Although there may be common logic toward the interpretation of CNCs, many aspects of test interpretation were different, from the fact that number of classification categories (normal, abnormal, uncertain clinical significance, etc.) varied between the labs to the fact that size cutoffs for reporting CNCs ranged from 50 Kb to 500 Kb. The authors argue several points that could increase the interlab consistency in CNC interpretation, and these include the need for a good public database of CNCs to which all labs could compare their test results, common guidelines for CNC interpretation and lab report content, and a designated set of classification categories for CNCs.

Tsuchiya et al. (2009). Variability in interpreting and reporting copy number changes detected by array-based technology in clinical laboratories. Genet. Med., in press. Published online November 6, 2009. 10.1097/GIM.0b013e3181c0c3b0.

If You Thought Human Centromeres Were Difficult to Sequence, Try Wheat

We've completed the human genome sequence, so you might think that we could sequence any species' genome if we put our mind to it. Taking a human-centric view of the world, we're the most complicated organism, so ours should be the most complicated genome to get through, right? Not so. The wheat genome has proven to be a very difficult challenge. In addition to the fact that it is about 17 gigabases in size, it is a hexaploid organism with essentially three genomes within a genome, and these are referred to as the A, B, and D genomes. The three genomes arose from the hybridization of three related species of wild grasses. Each of these genomes is similar but not identical. Further complicating matters is the fact that ~90% of the wheat genome is repetitive. Maybe one of the hardest regions of any genome to sequence is the centromeres because of their repetitive nature. Qi et al. started to tackle the wheat centromeres, making use of the fact that some of the centromeres from rice have been assembled and that wheat and rice are evolutionarily related. Some rice centromeres actually contain genes. Qi et al. mapped genes from rice centromere 8 onto the wheat genome, and they were aided by the fact that there is an extensive set of wheat

aneuploid stocks that can be used to tease apart the A, B, and D genomes. This work gives us a picture of the evolution of the cereal chromosome centromeres, and it also outlines a general approach to deciphering other parts of the wheat genome, a problem that I am glad I don't have to tackle!

Qi et al. (2009). A molecular-cytogenetic method for locating genes to pericentromeric regions facilitates a genome-wide comparison of synteny between the centromeric regions of wheat and rice. Genetics, in press. Published online September 21, 2009. 10.1534/genetics.109.107409.