This Month in Genetics

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Colon Cancer Risk Tied to Variation in *MYC* Enhancer

Genome-wide association studies don't necessarily point to coding SNPs that immediately identify a gene of interest and suggest some functionality. Sometimes, like in the case of chromosome 8q24 and colorectal cancer (CRC), the SNP of interest lies in a gene desert, which makes it a little less obvious how the marker contributes to disease risk. Tuupanen et al. and Pomerantz et al. were interested in the 8q24/CRC association because it is estimated to make a very strong contribution to CRC on a population level. Both groups reasoned that the 8q24 SNP might be in a regulatory element for *MYC* because it is the closest documented gene and it is known to participate in carcinogenesis. Indeed, through a variety of techniques, the two groups show that the SNP lies in a *MYC* enhancer that binds to the TCF4/TCF7L2 transcription factor. In vitro assays suggest that the CRC risk allele binds to TCF4 more strongly and is more active in reporter assays. Tuupanen et al. also find that in individuals heterozygous for this SNP, tumor samples exhibit preferential amplification of segments of chromosome 8q24 that contain the risk allele. The prediction from these data is that the risk allele is associated with increased MYC expression; unfortunately, neither group could document an obvious difference in *MYC* expression on the basis of genotype at this SNP.

Tuupanen et al. (2009). The common colorectal cancer predisposition SNP rs6983267 at chromosome 8q24 confers potential to enhanced Wnt signaling. Nature Genetics 41, 885–892.

Pomerantz et al. (2009). The 8q24 cancer risk variant rs6983267 shows long-range interaction with MYC in colorectal cancer. Nature Genetics 41, 882–884.

New Role for Phosphatidyl Inositol Signaling in Regulation of Cilia

Through studies of several genetic disorders, our understanding of the role of nonmotile cilia in development and in normal cell biology has greatly increased. One of these so-called ciliopathies is Joubert syndrome, a rare autosomal-recessive disorder that includes hypotonia, episodes of rapid breathing, ataxia, developmental delays, and the "molar-tooth sign," a disease hallmark that can be seen by cranial MRI. Through extensive sequencing around the *JBTS1* locus in affected families, Bielas et al. find an unexpected link between phosphatidyl inositol signaling and the function of nonmotile cilia. They find missense changes in *INPP5E* in several families affected by Joubert syndrome. The mutations cluster within the phosphatase domain of the encoded protein, inositol polyphosphate-5-phosphatase E, and impair the phosphatase activity of the enzyme. INPP5E localizes to cilia in the major organs affected by Joubert syndrome, including the renal collecting tubules, cerebellum, and retinal photoreceptor cells. Primary fibroblasts from affected individuals are ciliated normally. However, in response to serum stimulation in culture, INPP5E appears to control rates of ciliary disassembly and to affect the percentage of mitotically active cells. This is the first strong link suggesting that phosphatidyl inositol signaling regulates the primary cilium.

Bielas et al. (2009). Mutations in INPP5E, encoding inositol polyphosphate-5-phosphatase E, link phosphatidyl inositol signaling to the ciliopathies. Nature Genetics, in press. Published online August 9, 2009. 10.1038/ng.423.

Epistasis in Hirschsprung Disease

Hirschsprung disease (HSCR) is characterized by incomplete innervation of part of the gut. It can occur as an isolated disease, but it has also been found in conjunction with a variety of syndromes, including Bardet-Biedl syndrome (BBS). The key gene for HSCR appears to be *RET*; most people with isolated HSCR are heterozygous for a *RET* mutation or hypomorphic allele. However, the penetrance of HSCR is reduced, and variation at genes other than *RET* influences disease expression. de Pontual et al. wondered whether variation at multiple genes also contributes to the appearance of HSCR in the context of a syndrome. They identified families with both BBS and HSCR and found that penetrance of HSCR seemed to be influenced by variation in *RET*. In a zebrafish model, they show that whereas suppression of one of the *bbs* genes or *ret* individually reduces enteric neuron migration, suppression of *ret* in combination with a *bbs* gene results in a much more severe defect. The BBS proteins localize to cilia and basal bodies, whereas RET is a cell-surface receptor. No evidence links the activities of these proteins thus far, and the authors do not suggest that one exists.

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Instead, they propose that perturbation of two separate signaling systems happens to converge at the level of neuronal migration and survival in the gut and that the effects of these perturbations together are enough to prevent proper innervation of the gut.

de Pontual et al. (2009). Epistasis between RET and BBS mutations modulates innervation and causes syndromic Hirschsprung disease. PNAS Early Edition, in press. Published online July 31, 2009. 10.1073/pnas.0901219106.

Can IGF-1 Be Used to Treat Spinal and Bulbar Muscular Atrophy?

Although there are differences in the neurons that are affected and the specifics of the phenotypes that are produced, the polyglutamine diseases are all characterized by neurotoxicity that is associated with the formation of aggregates of the polyglutamine-containing protein. The polyglutamine expansion causing spinal and bulbar muscular atrophy (SBMA) occurs in the androgen receptor (AR). Normally, the AR binds its ligand, is internalized, and translocates to the nucleus. In the context of polyglutamine-containing AR, this nuclear localization is required for SBMA disease pathogenesis, which ultimately leads to loss of lower motor neurons in the brainstem and spinal cord but is preceded by pathology to the skeletal muscle. Knowing that AR could be inactivated through phosphorylation by Akt, which itself lies in a pathway that is stimulated by insulin-like growth factor 1 (IGF-1), Palazzolo et al. decide to see whether manipulation of these signaling pathways could be used to modify the outcome of SBMA in a mouse model. First, in cell culture, they demonstrate that, in an Akt-dependent fashion, IGF-1 reduces aggregation of mutant AR and increases degradation of AR through the proteasome. Then, in a mouse model of SBMA, they find that overexpression of a muscle-specific isoform of IGF-1 delays disease onset, increases the disease duration and lifespan, and reduces the pathology in the muscle and spinal cord of affected mice. Although IGF-1 itself promotes muscle growth, the amelioration of disease in SBMA mice does not solely occur by overstimulating muscle; the growth factor also reduces AR aggregate formation and motor neuron loss in affected mice. IGF-1 is thus a candidate therapy for SBMA and could also prove useful for other diseases that lead to muscle atrophy.

Palazzolo et al. (2009). Overexpression of IGF-1 in muscle attenuates disease in a mouse model of spinal and bulbar muscular atrophy. Neuron 63, 316–328.

Identification of Loci that Govern Cell-Type-Specific Gene Expression

The gene-expression pattern for each specific cell type is what gives a cell its unique properties. We recognize some of the general and even some of the specific regulatory sequences controlling gene expression, but there is still a lot to know, particularly in the realm of cell-type-specific gene expression. Many of the studies that have looked for genetic-variation-influencing gene expression (eQTLs) have been based on measurements of mRNA transcript levels from one cell type per individual in the study. To look more specifically at tissue-specific control of gene expression, Dimas et al. performed genetic association studies for eQTLs by using three cell types from each individual in the study. This was made possible by umbilical cord blood sampling, which yielded primary fibroblasts, lymphoblastoid cell lines, and T cells for testing. The authors searched for *cis* regulatory elements by testing for genetic associations between gene expression level and all SNPs within a 2 Mb window around the transcription start site for that gene. The majority of eQTLs that they found, nearly 80%, were cell-type specific. However, that did not mean that gene expression was restricted to one cell type; it appeared that many of the genes were expressed in all three cell types but that regulatory elements were used in a cell-type-specific manner to tweak the level of expression. Beyond influencing the transcript level for an individual cell type, Dimas et al. speculate that eQTLs might also influence alternative transcript choice because the number of eQTLs per gene correlates with the number of transcripts per gene. Clearly, we have a lot more to learn about the genetic variation that controls gene expression, and it is crucial that tissue-specific expression be taken into account in these studies as they move forward.

Dimas et al. (2009). Common regulatory variation impacts gene expression in a cell-type dependent manner. Science Express, in press. Published online July 31, 2009. 10.1126/science/1174148.

This Month in Our Sister Journals

Should Population-Wide Testing for BRCA1/2 Mutations be Pursued?

A key component to decision-making algorithms for *BRCA1/2* mutation testing is family history. The fact is that a significant percentage of *BRCA1/2* mutation carriers with no family history will go on to have breast or ovarian cancer. Would a population-based genetic screening program be an effective way to detect these carriers with no family history? This is the question explored by Rubinstein et al. They modeled the effectiveness of a population-based screening program for *BRCA1/2* founder mutations in the U.S. Ashkenazi Jewish population in terms of its effects on ovarian cancer. Using data from the literature on rates of uptake for screening programs and for risk-reducing surgery in *BRCA1/2* mutation carriers, they estimate that over 2800 cases of ovarian cancer could be prevented through such a screening program and that life expectancy in carriers would be increased by almost 1.5 years. The estimated costs of such a program are in line with other public health interventions that are well accepted. Although this study is limited by the fact that

breast cancer screening, prevention, and treatment were not considered, the authors advocate for a dialog among stakeholders as to whether such a population-based screening program should be pursued.

Rubinstein et al. (2009). Cost-effectiveness of population-based BRCA1/2 testing and ovarian cancer prevention for Ashkenazi Jews: A call for dialog. Genetics in Medicine, in press. Published online July 14, 2009. 10.1097/GIM.0b013e3181afd322.

Superoxide Radicals Paralyze Flies

Overproduction of superoxide radicals is toxic, as has been observed in several model systems. Approximately 10 hr or so after they emerge from the pupal case, *Drosophila* that lack the superoxide dismutase *Sod2* no longer move. But—to steal a line from *The Princess Bride*—are they all dead or only mostly dead? Godenschwege et al. find that at times when the flies are no longer mobile, they still have normal sensory and motor neuron outputs, so although they are alive, they just can't move. The lack of an early effect on neural transmission indicates that muscle is more sensitive to the effects of superoxide radicals than are neurons. This is further supported by the finding that muscle-specific, but not neuron-specific, expression of Sod2 prolongs the lifespan and mobility of these flies. This work suggest that the "mostly-dead" *Sod2* mutant flies still have some life in them and that they will be useful in further studies of the effects of superoxide radicals on different tissues.

Godenschwege et al. (2009). Mitochondrial superoxide radicals differentially impact muscle activity and neural function. Genetics, in press. Published online June 22, 2009. 10.1534/genetics.109.103515.