This Month in Genetics

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This Is a Story about Controls

Unraveling the pathogenesis of a complex disease is daunting. Variation in multiple genes and multiple environmental factors could be at play, as could variation in the interactions of these risk factors with each other. Lest you despair, Cadwell et al. prove that it is possible to reveal features of the disease process through a careful set of experiments with good controls. The researchers previously reported a mouse model of Crohn disease that is hypomorphic for *Atg16L1*, an autophagy gene that was pulled out of a genome-wide association study for Crohn disease. When these mice were rederived in a different animal facility with higher containment procedures, however, the Crohn-like phenotype was not evident. The group tracked this phenotype difference down to a murine norovirus strain that contributes to the intestinal phenotype through establishment of a persistent infection. Once this infection is established, the mice have increased susceptibility to additional environmental insult in the form of dextran sodium sulfate (DSS), a toxin that injures the intestine. Altogether, *Atg16L1* hypomorphic mice that are infected with the norovirus and later given DSS exhibit several pathological features reminiscent of human Crohn disease. However, this is not the full story; the timing of the viral infection and DSS administration must be spaced if one is to see the intestinal damage, which also requires the presence of commensal bacteria in the gut. Treating the *Atg16L1* hypomorphic mice with broad-spectrum antibiotics to kill these bacteria prevents the damage induced by DSS. Truly, Crohn disease is complex, but this carefully executed set of experiments ties together at least one genetic risk factor with three separate environmental contributions to the disease process.

Cadwell et al. Virus-plus-susceptibility gene interaction determines Crohn's disease gene Atg16L1 phenotypes in intestine. Cell, 141:1135–1145.

Convergent Evolution of the Human X and Chicken Z Chromosomes through Gene Addition

The mammalian X and Y chromosomes are thought to have diverged from a pair of ancestral autosomes. Much of this divergence has been attributed to the degeneration of the Y chromosome, whereas the X chromosome has been assumed to be evolutionarily fairly stable. The same basic process is thought to hold true in birds, with the Z and W chromosomes evolving from an ancestral autosome and the W degenerating from there. A recent paper by Bellott et al. challenges the assumption of the static Z and X chromosomes. They use the completed chicken Z and human X chromosome sequences to show that, although these chromosomes share several features, they evolved independently from different parts of the ancestral vertebrate genome, meaning that their similarities arose through convergent evolution. The similarities include the acquisition of hundreds of genes but a paradoxically low gene density that is due not to loss of other genes but, rather, to expansion of intergenic regions. Most of the acquired genes are members of multigene families that are expressed in the testis, thereby biasing the gene content toward those involved in male reproduction. On the Z chromosome, this includes an 11 Mb tandem array of testis-expressed genes that encompasses almost 1% of the total chicken genome. This work puts a dent in the long-held notion that it is only the sex-specific chromosomes that have undergone drastic changes during their evolution.

Bellott et al. Convergent evolution of chicken Z and human X chromosomes by expansion and gene acquisition. Nature Advance Online Publication, published 7/11/10, doi:10.1038/nature09172.

Mutation-Guided Cancer Therapy

Defects in a pathway for DNA double-strand break repair are the underlying cause of cancer in people who inherit mutations in *BRCA1* or *BRCA2*. A recent set of clinical trials indicates that our understanding of this defect might improve treatment for cancer patients with hereditary breast or ovarian cancer. Tumorigenesis in these individuals involves loss of the second, wild-type allele of the relevant gene, thereby rendering cells incapable of using this particular DNA repair pathway. Because these tumors must rely on the remaining DNA repair pathways, the cells are susceptible to inhibitors of a DNA repair pathway for single-strand breaks, at least in vitro. Two recent papers report the clinical efficacy of such an inhibitor called olaparib, which targets poly(ADP-ribose) polymerase (PARP). In phase 2 trials of olaparib for patients with advanced breast or ovarian cancer due to mutations in *BRCA1* or *BRCA2*, the tumors in up to 33% and 41% of patients with ovarian and breast cancer, respectively, responded to treatment. If this drug is proven to be effective in a phase 3 trial, there will come a day when cancer

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patients will be grouped for treatment on the basis of the underlying genetic defect that caused their cancer.

Tutt et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: A proof-of-concept trial. The Lancet, published online 7/6/10, doi:10.1016/S0140-6736 (10)60892-6.

Audeh et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer: A proof-of-concept trial. The Lancet, published online 7/6/10, doi:10.1016/S0140-6736(10) 60893-8.

Direct-to-Consumer Research

The growth of the direct-to-consumer personal genetics testing industry means that there are large samples of people who are interested in genetics and who have submitted a DNA sample for genotyping. What is the potential for these samples to be used for research? In a recent article in *PLOS Genetics*, Eriksson et al. illustrate the power of these samples in a genome-wide association study for 22 traits, using data collected through 23andMe. In their sample of people who ordered personal genome scans (and who consented to the use of their information for research), they replicated associations for pigmentation traits and identified novel associations for other personal traits, including the ability to smell asparagus in urine and the tendency to sneeze when entering bright light. Although powerful, the use of this type of sample is not straightforward. The accompanying editorial describes the complicated process by which the editors at *PLOS Genetics* assessed issues of consent, ethics, and data access related to this paper, including a debate over whether or not this constituted "human subjects research." As an interesting aside, the Eriksson et al paper touched on an aspect of personal genome scans that could have implications for the use of this type of scan in disease-risk assessment. They found that participants' answers to personal survey questions could be strongly biased if they were presented with their own genotype data and interpretation before they answered a question about that trait. Could this mean that genetic determinism trumps the benefit of patients being given risk information? This seems like an area ripe for further exploration.

Eriksson et al. Wed-based participant-driven studies yield novel genetic associations for common traits. PLOS Genetics, published online 6/24/10, doi:10.1371/journal. pgen.1000993.

Gibson and Copenhaver. Consent and internet-enabled human genomics. PLOS Genetics, published online 6/24/10, doi:10.1371/journal.pgen.1000965.

Man versus Parasite

The classic example of heterozygote advantage is the sickle cell mutation, which confers resistance to malaria in the heterozygous state and causes sickle cell disease in the homozygous state. Although it is unlikely that this type of selective force is unique to malaria, other examples of heterozygote advantage have been hard to pin down. Recent work by Genovese et al. suggest that *Trypanosoma brucei*, the parasite that causes sleeping sickness, may have selected for another detrimental mutation in humans. The authors were looking for genetic variation that might contribute to the high rate of kidney disease in African Americans and found an association with chromosome 22 that was originally attributed to *MYH9*. Further analysis of the region indicated that the strongest association was actually with *APOL1*, a gene that encodes the apolipoprotein L-1, a protein that has anti-trypanosomal activity. The authors find evidence of selection for the kidney disease risk allele in African populations and also demonstrate that plasma samples from people with the risk allele are better able to lyse *T. brucei rhodesiense*. Similar to the malaria story, the protective effect against trypanosomes is dominant, whereas the association with kidney disease is recessive. Thus, although the *APOL1* allele might have protected some of our ancestors from sleeping sickness, it is now found in more than 30% of African American chromosomes and could make a substantial contribution to renal disease in this population.

Genovese et al. Association of trypanolytic ApoL1 variants with kidney disease in African-Americans. Science Express, published online 7/15/10, doi:10.1126/science. 1193032.

This Month in Our Sister Journals

A 19p13.13 Microdeletion or Microduplication Syndrome

The increased use of whole-genome comparative genomic hybridization arrays for assessment of individuals with developmental delay has allowed us to recognize several novel microdeletion or microduplication syndromes. Dolan et al. add to this number with a description of individuals with deletions or duplications of chromosome 19p13.13. Four individuals with overlapping but unique de novo deletions in this region share three abnormalities in addition to developmental delay. These are: overgrowth, particularly macrocephaly with frontal bossing; eye abnormalities, including strabismus and optic nerve atrophy; and gastrointestinal symptoms, such as diarrhea, vomiting, and abdominal pain. Similar organ systems are affected in an individual with a duplication in this region. This child also had ophthalmologic problems and gastrointestinal issues

but was small for his age and had microcephaly. Three individuals with deletions in this region were previously tested for *NSD1* mutations to rule out Sotos syndrome. Because of this, the authors suggest that the 19p13.13 microdeletion syndrome might be considered in a child suspected of having Sotos syndrome when *NSD1* testing is negative.

Dolan et al. A novel microdeletion/microduplication syndrome of 19p13.13. Genetics in Medicine, doi:10.1097/GIM.0b013e3181e59291.