This Month in Genetics

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The Sickly Kid

Do you remember the sickly kid in your class from elementary school? I do. No matter what was going around, he caught it. Even when I was six years old, I remember wondering why he was sick more than anybody else. This basic question of variability in susceptibility to infectious disease is what motivated a recent study by Khor et al. The "case" samples in their case-control genetic-association study included groups of people from various parts of the world who had bacteremia, tuberculosis, or severe malaria. Their study focused on variation in *CISH*, which encodes a suppressor of cytokine signaling, particularly the proinflammatory interleukin-2 (IL-2). Variation in *CISH* was reproducibly associated with susceptibility to all three infections. Functional studies support the role of CISH in governing variation in susceptibility to infection; peripheral blood mononuclear cells (PBMC) from subjects carrying the risk allele at a SNP in the *CISH* promoter expressed less CISH in response to IL-2 stimulation than did PBMCs from people with the major allele. The authors raise the idea that, rather than treating infections with standard antibiotics, perhaps tweaking this branch of the immune response might be a way to treat a diverse spectrum of infectious disease by helping the body help itself.

Khor et al. CISH and susceptibility to infectious diseases. NEJM 362, 2092–2100.

Treatment for α1-Antitrypsin-Deficiency-Associated Liver Disease

α1-antitrypsin deficiency affects two major organ systems: the lungs and the liver. The chronic obstructive pulmonary disease phenotype is due to a deficiency for α1-antitrypsin activity and is managed by augmentation of the protein via infusion. In patients with the most common Z mutation (ATZ), this therapy has no effect on liver disease, because it is the result of a toxic gain of function in which the mutant protein aggregates and causes liver damage. Because aggregated ATZ is at least partially degraded through the autophagic pathway, Hidvegi et al. explored whether they could further stimulate this response pharmacologically by using the autophagy stimulator carbamazepine. In cell culture, carbamazepine reduced levels of soluble and insoluble ATZ by stimulating intracellular degradation of the protein, an effect that was not observed in cells that lack an intact autophagy system. In a mouse model of liver disease due to α1-antitrypsin deficiency, carbamazepine reduced ATZ levels and hepatic fibrosis. Carbamazepine is safe for use in humans, so this suggests an intervention for α1-antitrypsin-deficiency-associated liver disease and could serve as a model for treatment of human disease due to protein aggregation.

Hidvegi et al. An autophagy-enhancing drug promotes degradation of mutant α1-antitrypsin Z and reduces hepatic fibrosis. Science Express. Published online June 3, 2010. 10.1126/science.1190354.

CFTR Influences Birth Rate in Fertile Men

Genetic variation in *CFTR* is classically associated with cystic fibrosis (CF), but the range of phenotypes associated with *CFTR* is broad—and getting broader. For one, the typical pulmonary phenotype can vary quite widely in severity, and mutations in *CFTR* have even been reported in people with a diagnosis of chronic rhinosinusitis. Another class of phenotypes attributed to *CFTR* relates to male infertility. Males with classic CF are infertile, but a majority of men with isolated congenital absence of the vas deferens also carry mutations in *CFTR* and are infertile. Because there is a spectrum of phenotypes associated with *CFTR* variation, Kosova et al. wanted to know whether even milder *CFTR* variation could influence male fertility. They measured the influence of the M470V *CFTR* polymorphism on fertility in healthy Hutterite men, a population in which contraceptive use is limited and large families are desired. Couples in which the man was homozygous for the Met470 allele had significantly lower birth rates and, on average, took longer to achieve each birth. The Met470 allele is the ancestral allele, and it predominates in most of Africa. In other populations, the derived Val470 allele reaches a frequency as high as 80%–90%, suggesting that it could be under positive selection, possibly because of its association with a relative increase in fertility.

Kosova et al. The CFTR Met 470 allele is associated with lower birth rates in fertile men from a population isolate. PLOS Genetics. Published online June 3, 2010. 10.1371/journal/pgen.1000974.

Evolution Shaped by Altitude

The Tibetan people are physiologically adapted to the high altitudes in which they have lived for thousands of

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DOI 10.1016/j.ajhg.2010.06.013.

years and are less susceptible to chronic mountain sickness. The typical reaction to high altitude is characterized by high hemoglobin levels and excess production of red blood cells and is associated with pulmonary hypertension, risk of stroke, and poor pregnancy outcomes, features that implicate high altitude as an environmental selective force. By looking for genetic signatures of selection, two groups recently sought the genetic variation that has conferred high-altitude adaptation to Tibetans. Using different statistical approaches, both groups combed through genetic variation in Tibetan populations and compared it to that of highly related Lowland Asian populations. Beall et al. zero in on *EPAS1*, which encodes a transcription factor that regulates red blood cell production. The same gene is implicated by Simonson et al., as is an upstream regulator of EPAS1 function, *EGLN1*. Both groups demonstrate that certain positively selected Tibetan alleles in these genes are associated with lower hemoglobin concentrations, relating the genetic variation back to the physiological adaptation observed in Tibetans.

Beall et al. Natural selection on EPAS1 (HIF2α) associated with low hemoglobin concentration in Tibetan highlanders. PNAS Early Edition. Published online June 7, 2010. 10.1073/pnas.1002443107

Simonson et al. Genetic evidence for high-altitude adaptation in Tibet. ScienceExpress. Published online May 13, 2010. 10.1126/science.1189406.

FMRP Controls Neural Stem Cell Proliferation in Flies

The fragile X mental retardation protein, FMRP, influences synaptic plasticity by regulating local protein synthesis at the synapse. Experiments in in vitro model systems suggest that FMRP also has a hand in neuron production in the brain. Callan et al. now provide detailed in vivo data in *Drosophila* that—early in brain development—FMRP controls the reentry of quiescent neural progenitors into the cell cycle. This leads to an increased number of neurons in the larval brain of *dFmr1* mutant flies, a change that persists in adults. Although this increase in neuron number is not large enough to cause a striking difference in brain size between mutant and wild-type flies, it is interesting to note that several reports indicate that certain parts of the brain are larger in children with autism, a behavioral phenotype that is often a part of the fragile X syndrome phenotype.

Callan et al. Fragile X protein controls neural stem cell proliferation in the Drosophila brain. Human Molecular Genetics. Published online June 4, 2010. 10.1093/hmg/ddq213.

This Month in our Sister Journals

Mutational Analysis of GSD III Yields Testing Implications

The gene for glycogen storage disease type III (GSD III), *AGL*, is a 35-exon gene that encodes the glycogen debranching enzyme. In some patients, the disease is restricted to the liver and is designated GSD IIIb, whereas the majority of patients also have myopathy, designated as GSD IIIa. Distinguishing between the two subtypes, which can be important for patient management and monitoring, has traditionally relied on a muscle biopsy for measurement of enzymatic activity in muscle. In order to get a better handle on the mutational heterogeneity associated with this disorder, Goldstein et al. sequenced the complete *AGL* gene in 32 patients with GSD III and did targeted sequencing in two additional patients. They report 38 mutations that, together with the published literature on GSD III, confirms the mutational heterogeneity of this disease and supports full-gene sequencing for identification of the causative mutations in patients with GSD III. Their data also confirm that having one copy of either of two exon 3 mutations is sufficient to restrict disease to the GSD IIIb subtype, a finding that should mean that patients can avoid a muscle biopsy in classifying their disease.

Goldstein et al. Molecular analysis of the AGL gene: Identification of 25 novel mutations and evidence of genetic heterogeneity in patients with glycogen storage disease type III. Genetics in Medicine. Published online April 27, 2010. 10.1097/GIM.0b013e3181d94eaa.

Modeling Metabolic Syndrome in Flies

Genome-wide association and heritability studies have begun to tease out the genetic contribution to metabolic traits, including blood glucose levels, body mass index, and cholesterol level. And from the environmental angle, we are barraged with news about the effects of high-fructose corn syrup, trans fats, and the "Western diet." What we really need to understand is how genes and the environment together influence metabolic traits and contribute to the massive increases in the prevalence of metabolic syndrome over recent decades, something that is hard to tease out in human populations. To simplify this research question, Reed et al. tackled it in flies. They measured a series of metabolic traits in many different *Drosophila* lines that were fed a range of foods. Diet accounted for far less of the variance in these metabolic traits than did the genetic variance, but when they took into account the genotype-by-diet interactions,

they could explain a much larger fraction of the phenotypic variance in these traits. The genotype-by-diet interactions were sensitive to the type and amount of sugar in the food, with changes in the sugar concentration leading to large changes in how much the flies weighed. Changes to the dietary fat content also influenced the metabolic traits, with a high-fat diet leading to increased phenotypic variance. The authors use these data to speculate about the increased prevalence of complex metabolic traits in the human population by using a threshold model of liability.

Reed et al. Genotype-by-Diet interactions drive metabolic phenotype variation in Drosphila melanogaster. Genetics. Published online April 12, 2010. 10.1534/genetics.109.113571.