This Month in Genetics

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Let's Talk

Reports of *FOXP2* mutations in individuals with speech and language disorders were heralded as providing a key to the development of human language. This may be the case, but the rarity of pathogenic *FOXP2* mutations indicates that this gene is probably not the major factor contributing to common speech and language impairment. Even so, FOXP2 is a transcription factor, making any of the genes it regulates candidates for involvement in common forms of speech and language impairment. In order to find these genes, Vernes et al. used antibodies to FOXP2 in chromatin-immunoprecipitation experiments and then did shotgun sequencing of the resulting DNA fragments. Although the range of genes pulled out of this experiment is not made available, the authors did pull out a compelling gene, *CNTNAP2*. This member of the neurexin family had already been associated with autism spectrum disorders, including, in one study, an association with language delay. Vernes et al. provide evidence that FOXP2 negatively regulates expression of *CNTNAP2,* and they use family-based association studies to support the role of this gene in language development. This was not the first attempt to use chromatin immunoprecipitation to isolate targets of FOXP2, but this was the first time that *CNTNAP2* was identified. Why is that? Previous studies used the chromatin immunoprecipitations to probe promoter-based microarrays. It turns out that the *CNTNAP2* fragment that binds to FOXP2 is located in an intron, meaning that it is in an unexpected regulatory region.

Vernes et al. N. Engl. J. Med. 359, 2337–2345. 10.1056/NEJMoa0802828.

You Do Need Your Calcium—Even If You're a Lysosome

Niemann-Pick disease is a lysosomal-storage disorder that causes a progressive neurodegeneration for which there is no treatment. The gene for the most common form of this disease, *NPC1*, is known, but neither its function nor the underlying pathogenic process of this disease is clear. A broad range of lipids accumulates in the lysosomes of NPC1 cells, but we don't know which are key to the development of the disorder. The work by Lloyd-Evans et al. teases out some of the initiating steps in NPC1. They show that one of the primary factors initiating the pathogenesis of NPC1 is sphingosine storage. This leads to calcium depletion in the acidic compartment of cells, where it would normally be involved in vesicle trafficking and fusion. Ultimately, these trafficking defects prevent glycosphingolipids, sphingomyelin, and cholesterol from getting to the endoplasmic reticulum, so they accumulate in the acidic compartments. Delineating the involvement of calcium in NPC1 pathogenesis gave the authors the idea of trying to modulate the process using thapsigargin or curcumin to increase cytosolic calcium and hopefully restore endocytic transport. These treatments normalized sphingolipid trafficking in cell culture and improved some aspects of disease in NPC1 mice, including an increase in life expectancy, further supporting the role of calcium in the disease process and making it a potential target for NPC1 therapies.

Lloyd-Evans et al. Nat. Med. 14, 1247–1255. 10.1038/nm.1876.

Serotonin: Not Just for Moods Anymore

Inactivating mutations in *LRP5* cause osteoporosis pseudoglioma, a rare syndrome characterized by decreased bone formation. Osteoblasts express this gene, so it is a logical assumption that studying LRP5 in osteoblasts can uncover the pathway through which it controls bone formation. Yadav et al. started to do just that, but they noticed that, ex vivo, *Lrp5-/-* osteoblasts proliferated just as well as wild-type cells, hinting that there might be more to this regulation. Using an extensive set of transgenic mice, they find that Lrp5 activity in the gut, not in the bone, is what regulates bone formation. Lrp5 does this by controlling expression of *Tph1*, the rate-limiting enzyme in serotonin biosynthesis in the duodenum. Loss of Lrp5 activity in the gut leads to increased *Tph1* expression, a corresponding increase in circulating-serotonin levels, and ultimately a decrease in bone mass. The authors are able to manipulate the bone-loss phenotype in *Lrp5-/-* mice by reducing circulating-serotonin levels either pharmacologically, by using a drug that inhibits serotonin synthesis, or through dietary means, by implementing a low-tryptophan diet. The ability to manipulate the phenotype in these mice means that clinical intervention for low bone density in

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DOI 10.1016/j.ajhg.2008.12.011.

people might be possible via this pathway. This has implications for more than just the people with osteoporosis pseudoglioma. It has previously been shown that common variation in *LRP5* is associated with osteoporosis in a general population. Moreover, Yadav et al. also show that knocking out *Tph1* expression in the gut prevents mice from developing ovariectomy-induced osteoporosis, a model of postmenopausal osteoporosis.

Yadav et al. Cell 135, 825–827. 10.1016/j.cell.2008.09.059.

When Two and Two Do Not Equal Four

As our ability to high-throughput genotype has increased, there has been an explosion in the number of confirmed genes associated with a variety of complex traits. Despite these huge advances, it is likely that we are still seeing only the tip of the iceberg. Many questions remain about the overall genetic architecture of these traits, such as the number of genes involved and how they interact to modify phenotype. To get at these problems, Shao et al. used chromosome-substitution strains in mice and rats to study a wide range of blood, bone, and metabolic traits. In these panels, a collection of strains is generated from two original inbred strains. Each single chromosome in the "host" strain is replaced individually with the corresponding chromosome from the "donor" strain, so that you have a series of inbred animals that each differ by one chromosome. On average, eight chromosomes significantly affected each trait, confirming that the traits are polygenic. But one can't simply add the effects of each chromosome together to explain the phenotypic differences between the two parental strains. In mice, for example, over half of the 41 traits examined had additive differences that were more than five times that seen between the parental strains, indicating a striking level of epistasis. This argues against the idea that we can simply add the effects of risk genotypes together to predict outcome for complex genetic traits.

Shao et al. PNAS 105, 19910–19914. 10.1073/pnas.0810388105.

Noncoding RNA Recruits Histone-Modifying Enzyme for Gene Regulation

Air is a large noncoding RNA that silences imprinted genes in *cis* on mouse chromosome 17, although its mode of action has not been clear. Nagano et al. show that, at least at some genes, *Air* does this by recruiting histone-modifying enzymes to the DNA to induce transcriptional repression. In mouse placenta, *Air* silences the paternal allele of *Slc22a3* in *cis*, although biallelic expression is observed later in development. At times when the paternal allele is silenced, Air RNA can be found associated with the *Slc22a3* promoter, but this diminishes by the time biallelic *Slc22a3* expression is observed. *Air* appears to recruit the G9a histone methyltransferase to transcriptionally repress *Slc22a3* through histone H3 lysine 9 trimethylation of the promoter. The significance of this recruitment is observed with embryos that lack G9a expression; in the placenta, there is a shift towards biallelic expression of *Slc22a3*. The recruitment of G9a clearly has significance for regulation of *Slc22a3*, but Air must have other tricks up its sleeve. Although *Air* is also involved in the regulation of expression of *Igf2r*, a gene found in the same imprinted cluster as *Slc22a3*, the same enrichment for *Air* and G9a are not observed at the *Igf2r* promoter, so the regulation at this gene must occur through a different process.

Nagano et al. Science 322, 1717–1720. 10.1126/science.1163802.