This Month in Genetics

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Role of microRNAs in 22q11 Deletion Syndrome

In addition to being at risk of physical abnormalities, such as heart defects and cleft palate, people with the chromosome 22q11 deletion syndrome can also have learning disabilities, autism, and delays in reaching motor milestones, and they are at increased risk of psychiatric illnesses, particularly schizophrenia. A well-delineated and recurrent microdeletion is the main culprit, but we haven't been able to translate the identity of the missing genes in this segment to a meaningful understanding of the development of this syndrome. In a mouse model of 22q11 deletion syndrome, Stark et al. found that impaired microRNA (miRNA) biogenesis underlies, at least partially, the behavioral and neuronal deficits associated with this microdeletion. They found several miRNA-containing transcripts among the genes that exhibited altered expression in the brains of mice with the deletion. Within the deletion is *Dgcr8*, a gene that encodes a part of the complex that processes primary forms of miRNAs to their mature counterparts. As expected if deletion of this gene limits processing of primary forms of the miRNAs, there is increased expression of certain primary miRNAs, and a corresponding downregulation of a smaller set of mature miRNAs, in the brains of mice with the microdeletion. The defects in miRNA biogenesis were attributable to loss of *Dgcr8* because they were recapitulated in mice with a specific heterozygous deletion of this gene. Further, the microdeletion and $Dgcr8^{+/-}$ mouse models share some cognitive and neuronal deficits. Although abnormal miRNA processing appears to contribute to the phenotype of 22q11 deletion syndrome, *Dgcr8* deficiency does not fully account for all features of the syndrome.

Stark et al. (2008). Nat. Genet. Published online May 11, 2008. 10.1038/ng.138.

Neural Crest Cells on the Move

Among the many features of Bardet-Biedl syndrome (BBS) are subtle craniofacial defects that have proven difficult to describe and characterize. That is, until computers got involved. Tobin et al. used three-dimensional dense surface modeling to analyze the faces of people with BBS compared to controls, and they have been able to define quantitatively the differences in facial structure. The changes they found are in the midfacial region and include nasal bridge hypoplasia and nasal shortening, midfacial flattening, and retrognathia. In addition to providing an objective way to recognize the facial features of BBS, this work opened a window in the search for similar changes in animal models. Indeed, parallel craniofacial features are seen in mouse models of BBS and in zebrafish embryos treated with morpholinos to the *bbs* genes. Detailed observations of the zebrafish embryos indicate that the craniofacial defects result from an inhibition of neural crest cell migration, and this inhibition can be mimicked through the induction of noncanonical Wnt signaling. An insensitivity to sonic hedgehog signaling when one of the bbs proteins is deficient contributes further to the craniofacial abnormalities. Another feature of BBS is Hirschsprung disease, the absence of enervation to a portion of the gut. This is another defect that can be attributed to neural crest cell migration; in zebrafish treated with morpholinos to *bbs8*, neurons fail to migrate properly into the hindgut. Whether and how cellular migration defects contribute to the other features of BBS remains to be elucidated.

Tobin et al. (2008). PNAS 105, 6714–6719. 0.1073/pnas.0707057105.

The Ins and Outs of the Nuclear Lamina

We know that specific regions of chromosomes are located near the nuclear lamina, but the complete identity of these regions—and how they contribute to spatial organization in the nucleus—isn't clear. Guelen et al. used the new DamID technique to map areas of the human genome that are associated with lamin B1. In this procedure, a fusion protein containing lamin B1 and the DNA adenine methyltransferase was introduced into fibroblasts. When lamin B1 interacts with DNA, adenines in the vicinity are methylated, and these regions are amplified by methylation-specific PCR and identified on microarrays. Over 1000 lamina-associated domains were identified, and there is a striking pattern of chromosomal domains that exhibit a high level of lamina association alternated with those that exhibit a very low level of association. Regions of the genome that are strongly associated with the lamina have several notable features that suggest that they represent inactive chromatin. These include a mean gene density that is half that of regions outside the domains,

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a reduction in gene expression within the domains, and an increased density of outwardly directed promoters just outside the domains. Also tending to flank the lamina-associated domains are CpG islands and binding motifs for the insulator protein CTCF, features that could help to delineate the lamina-associated regions. This map puts us on the road to understanding the architecture of the genome as it exists within the interphase nucleus.

Guelen et al. (2008) Nature. Published online May 7, 2008. 10/1038/nature06947.

A Mouse Model of Preeclampsia

Preeclampsia in pregnancy is marked by hypertension and the presence of protein in the mother's urine. If it is allowed to progress, seizures, coma, and even death of the mother can result. Preeclampsia also has implications for the baby; it can lead to restricted blood flow to the placenta, causing fetal-growth restriction and preterm birth. Although preeclampsia is a well-studied phenomenon, we don't fully understand the factors that trigger it in some women, and the key treatment is to deliver the baby. Kanasaki et al. find that mice that lack catechol-O-methyltransferase (COMT) expression have a phenotype that mimics preeclampsia, and this model has allowed them to identify additional contributors to this process. The effect of COMT deficiency is due to a lack of production of 2-methoxyestradiol (2-ME), which is a product of COMT activity and a metabolite of estradiol that is elevated during normal pregnancy. Decreased 2-ME induces expression of HIF1α and sFLT-1, two proteins thought to contribute to the development of preeclampsia. Not only does the phenotype of the *Comt*$^{-/-}$ mice mimic that of women with preeclampsia, but circulating 2-ME levels in women with preeclampsia are lower than those in other pregnant women, suggesting that the same pathologic process might occur in humans. The lower levels of 2-ME in preeclamptic women also suggest it might be possible to develop a much-needed screen or diagnostic test for preeclampsia on the basis of 2-ME measurements. Because administration of 2-ME to *Comt*$^{-/-}$ mice prevents the preeclampsia-like phenotype in this model, this pathway might yield clues as to how we might better treat preeclampsia.

Kanasaki et al. (2008). Nature. Published online May 11, 2008. 10.1038/nature06951.

A New Means to the End

Many human genes utilize more than one polyadenylation site, a phenomenon that generates transcriptional diversity. We know that site selection can be governed in a tissue-specific manner via changes in the concentration of RNA processing factors, but there are almost certainly other mechanisms by which the polyA site is determined. One of these other factors turns out to be genetic imprinting. Wood et al. report a novel imprinted domain on mouse chromosome 2 that contains two genes, *H13* and *Mcts2*. *Mcts2* is located within an intron of *H13*, and its promoter has a CpG island that is methylated in the female germline. This methylation influences the utilization of polyA sites for *H13*, with preferential use of polyA sites downstream of the differentially methylated region on maternal alleles. These preferences are abolished in embryos lacking maternally derived methylation imprints as a result of a *Dnmt3l* deficiency in the mother. Although we may not understand the mechanism, genetic imprinting is one way by which polA site selection can be controlled, even in early embryos.

Wood et al. (2008) Genes Dev. 22, 1141–1146. 10.1101/gad.473408.