This Month in Genetics

Kathryn B. Garber[1,*]

Putting Centrosomes at the Center of Human Growth

Centrosomes play a major role in mitotic-spindle organization and cytokinesis. By serving as a scaffold for cell-cycle regulators, they also influence cell-cycle progression indirectly. New data by Rauch et al. and by Griffith et al. implicate a major centrosomal protein, pericentrin, in two phenotypes associated with reduced body size and microcephaly—Seckel syndrome and microcephalic osteodysplastic primordial dwarfism type II (MOPD II)—and provide complementary data on the role of pericentrin in the cell. Pericentrin is not the first centrosomal protein to be implicated in microcephaly. In fact, prior reports of mutations that occur in centrosome genes and cause primary microcephaly allowed both groups of authors to zero in on the gene for pericentrin (*PCNT*) after initial homozygosity mapping in affected families. These results also implicate the centrosome in body-size determination. Additional data from Rauch et al. demonstrate that MOPD II mutations in *PCNT* cause abnormal mitotic morphology in fibroblasts, low-level mosaic variegated aneuploidy, and premature sister-chromatid separation, indicating that the cells have a defect in a spindle-assembly checkpoint. Griffith et al. link the Seckel-syndrome-associated defects in pericentrin to impaired ATR signaling, providing the first demonstration that a structural protein of the centrosome is involved in the ATR-dependent DNA-damage response. MOPD II has been clinically distinguished from Seckel syndrome largely on the basis of disproportionate shortening of the forearms and grossly normal brain development such that most individuals with MOPD II lack serious mental retardation. The finding that loss-of-function mutations in *PCNT* are found in individuals with either diagnosis places the two disorders on the same disease spectrum. They also suggest a central role for the centrosome in human growth.

A. Rauch et al. (2008). Science. Published online January 3, 2008. 10.1126/science.1151174; E. Griffith et al. (2007). Nat. Genet. Published online December 23, 2007. 10.1038/ng.1007.80.

The Role of Ataxin-2 in Both SCA1 and SCA2

The spinocerebellar ataxias (SCA) are a group of disorders that—although clinically quite similar—are genetically distinct. Because of the common neuropathologies seen with these disorders and the fact that several of them are caused by polyglutamine expansions in different genes, it is believed that there is some commonality to their underlying pathological processes. Al-Ramahi et al. now report that a change to the localization of Ataxin-2 may be a link between SCA1 and SCA2. These results come despite the fact that Ataxin-1 and Ataxin-2, the proteins mutated in SCA1 and SCA2, respectively, were not thought to be colocalized in cells, and their only similarity is the polyglutamine domain. In a screen for genetic modifiers of Ataxin-1 neurotoxicity in *Drosophila*, overexpression of Ataxin-2 was found to enhance, and underexpression to repress, the effects of expanded Ataxin-1. Ataxin-1 and Ataxin-2 interact in vitro, but, importantly, Al-Ramahi et al. also demonstrate that the proteins colocalize when there is a polyglutamine expansion in Ataxin-1. This pathogenic form of Ataxin-1 alters the localization of Ataxin-2 from the cytoplasm to the nucleus in cell culture and in pontine neurons from postmortem brains of SCA1 patients. The authors confirm their hunch that it is this change to the localization of Ataxin-2 that modulates neurotoxicity when they find that putting a nuclear localization signal on Ataxin-2 mimics some of the neurotoxic effects of expanded Ataxin-1. Whether Ataxin-2 is a common link in all of the forms of SCA remains to be seen.

I. Al-Ramahi et al. (2007). PLoS Genet. 3, 2551–2564. 10.1371/journal.pgen.0030234.

A Genetic Battle of the Sexes

Imprinted genes tend to be highly expressed in the placenta, and disruption of these genes often has effects on both fetal and placental growth. In fact, the evolution of imprinted genes has been suggested to be due to the conflict between the maternal and paternal alleles for maternal investment in the growth of offspring. In other words, fathers might want their offspring to suck as many resources as they can off the mother, but maximizing fetal growth and size might not be best for the mother. The human chromosome 14q21 region contains a cluster of imprinted genes, some of which are maternally and some of which are paternally expressed. Uniparental disomy (UPD) for this region is recognized clinically. In the case of paternal UPD, there are characteristic facial abnormalities, a small

[1]Department of Human Genetics, Emory University School of Medicine, Atlanta, GA 30322, USA
*Correspondence: kgarber@genetics.emory.edu
DOI 10.1016/j.ajhg.2008.01.004.

and bell-shaped thorax, abdominal-wall defects, and polyhydramnios, whereas maternal UPD is associated with prenatal and postnatal growth failure. Kagami et al. identified several individuals who had clinical features of UPD14 but had deletions or epigenetic changes in this region, and they used them to define the region further. They found that *RTL1* has a critical role in the development of both phenotypes and that over- and underexpression of the gene makes a major contribution to the paternal UPD and the maternal UPD phenotypes, respectively. At the same time, Sekita et al. found that, in mice, *Rtl1* is needed for proper placental development and maintenance of fetal capillaries at this interface. As in humans, tight regulation of *Rtl1* expression is necessary for proper development. The complexity of this regulation is apparent from the fact that *RTL1* is a retrotransposon-derived gene that is paternally expressed and regulated by a maternally expressed microRNA. Not only does this work place *RTL1* in a central role for the human phenotypes associated with this region, but it also suggests a major role for the gene in maintenance of the placenta and the evolution of this organ in mammals.

M. Kagami et al. (2008). Nat. Genet. Published online January 6, 2008. 10.1038/ng.2007.56; Y. Sekita et al. (2008). Nat. Genet. Published online January 6, 2008. 10.1038/ng.2007.51.

Variation of Breast Cancer Risk among BRCA1/2 Carriers

The options given to women who are found to have a mutation in either *BRCA1* or *BRCA2* are drastic and life altering, namely prophylactic oophorectomy and/or mastectomy. But exactly what is a mutation carrier's risk of developing breast or ovarian cancer? The literature on this point can be overwhelming, and penetrance estimates vary widely. Initial estimates calculated with high-risk, multiple-case families suggested a breast cancer risk of 70%–80% in mutation carriers by age 70, but estimates that used population-based ascertainment of breast cancer cases suggested that the early estimates could be halved. More comprehensive analyses put the estimate at somewhere in the middle, all of which makes counseling and decision-making based on these estimates difficult. The risk estimates in the previous studies were made on groups of mutation carriers considered as a whole. Begg et al. decided to look at this problem in a slightly different way—they wanted specifically to think about the variability in risk between different breast cancer families. Even after adjusting for specific characteristics of the proband, such as their age at diagnosis, whether they had unilateral or contralateral breast cancer, and the location of the mutation, they found strong evidence for between-family variation in risk of breast cancer in first-degree relatives. In fact, assuming a constant risk of breast cancer over most of adult life, the variance they see implies that there may be families in which the risk of breast cancer in mutation carriers is over 90% by age 70 and other families in which the risk is similar to the general population's risk for breast cancer. If not all "breast cancer families" are equal in terms of breast cancer risk to mutation carriers, certainly our penetrance estimates for mutation carriers found in general population screens are unlikely to be accurate. Now the charge is to determine the additional genetic and environmental factors that contribute to the residual cancer risk and to find ways of estimating family- and individual-specific mutation penetrance.

C.B. Begg et al. (2008). JAMA 299, 194–201.

Correction of Fragile X Syndrome in Mice

The central question in fragile X syndrome (FXS) research is this: How does the loss of a single protein lead to a disorder of neural development and cognitive impairment? The hypothesis that has come closest to addressing this question is the metabotropic glutamate receptor (mGluR) theory of FXS, which suggests that loss of the fragile X mental retardation protein, FMRP, leads to exaggerated signaling through mGluRs, particularly mGluR5. Most of the evidence for this idea is a result of pharmaceutical manipulation of mGluRs, and the drugs utilized in those experiments could have unintended effects. Dölen et al. set out to test this theory more directly through genetic reductions in the expression of mGluR5 in mice. They produced *Fmr1* knockout (KO) mice that expressed half the normal amount of mGluR5, and they found that the reduction in mGluR5 level rescued several phenotypes in the *Fmr1* KO mice, including changes to the density of dendritic spines, altered plasticity in the visual cortex, and increased susceptibility to audiogenic seizures. Additionally, the authors defined for *Fmr1* KO mice two new phenotypes—rapid extinction of a learned behavioral response and accelerated pubescent growth—that were also alleviated by the reduction in mGluR5. This was not a complete "cure" for mouse FXS; at least one phenotype, macro-orchidism, was not corrected by lowering of mGluR5. Not only do these results lend further credence to the idea that some components of the FXS phenotype are due to exaggerated mGluR signaling, but they also provide fuel for the current research into therapeutics—based on this idea—for FXS.

G. Dölen et al. (2007). Neuron 56, 955–962. 10.1016/j.neuron.2007.12.001.