Glaucoma risk variants

Glaucoma, a leading cause of blindness, is a heterogeneous group of disorders marked by optic nerve damage. Gudmar Thorleifsson and colleagues now report a very strong association between variants in *LOXL1*, encoding a member of the lysyl oxidase family, and a disease subtype known as exfoliation glaucoma (*Science*, published online 9 August 2007; doi:10.1126/science.1146554). Using the Illumina Hap300 chip, the authors performed a genome-wide association study of 195 Icelandic individuals with glaucoma and 14,474 population controls and identified a cluster of variants in *LOXL1* associated with the disease. Subgroup analysis revealed that the association was mainly with the exfoliation subtype of glaucoma, marked by abnormal deposits of fibrillar material in the anterior segment of the eye. The authors replicated the association in an independent Swedish case-control study. Additional fine-mapping studies showed that the association signal could be explained by two coding variants in *LOXL1*. The high-risk haplotype (GG) defined by these two SNPs was associated with a 27-fold higher disease risk compared with the less common low-risk haplotype (GA). The risk variants may influence disease susceptibility by directly altering the enzymatic activity of *LOXL1* toward extracellular matrix components. ***KV***

Sequencing cancer amplicons

The amplification of genomic regions is one of the hallmarks of cancer, although the mechanisms that underlie these events are not entirely understood. Graham Bignell and colleagues report the use of BAC-based end sequencing and shotgun sequencing to provide a high-resolution view of genomic rearrangements in human cancer cell lines (*Genome Res.*, published online 3 August 2007; doi:10.1101/gr.6522707). The authors sequenced 133 different genomic rearrangements in four cancer amplicons involving the genes *MYC*, *MYCN* and *ERBB2*. They observed a range of rearrangement architectures, with the majority showing evidence at the breakage-fusion junctions of either nonhomologous end-joining or nonallelic homologous recombination. The architecture of one particular inverted duplication at *ERBB2* is entirely consistent with a classical sister chromatid breakage-fusion-bridge process, which would be the first clear demonstration in a human cancer of the model proposed by Barbara McClintock. A few examples of rearrangements could not be attributed to any known mechanism, as they harbor complex arrays of small fragments of the genome. Finally, the authors show that several sequence motifs are significantly overrepresented in regions surrounding the breakpoints, suggesting that local sequences predispose certain regions to breakage and repair leading to amplification. *AP*

Mitochondrial fusion in neurons

Fusion between mitochondria is important in determining mitochondrial morphology and in protecting mitochondrial function by allowing content mixing. Proteins encoded by the *MFN1*, *MFN2* and *OPA1* genes are required for mitochondrial fusion, and mutations in *MFN2* and *OPA1* cause the neurodegenerative diseases Charcot-Marie-Tooth and dominant optic neuropathy, respectively. Mice lacking *Mfn1*, *Mfn2* or *Opa1* die embryonically because of placental defects. In order to gain insight into the role of mitochondrial fusion in neurons, David Chan and colleagues created conditional knockouts of *Mfn2* in mice (*Cell* **130**, 548–562; 2007). Mice lacking *Mfn2* in the embryo proper but not in the placenta survive to birth but die soon after owing to severe movement defects, and they have small cerebella. Knockout of *Mfn2* specifically in the cerebellum recapitulated the movement and lethality phenotype and revealed Purkinje cell degeneration. Knockout of *Mfn2* in mature Purkinje cells produced a progressive neurodegenerative phenotype, demonstrating the importance of mitochondrial fusion in normal cellular function. Investigation of the Purkinje cell defect showed reduced electron transport chain function, as well as defects in mitochondrial structure and cellular localization. This study demonstrates the critical role of *Mfn2*-mediated mitochondrial fusion in the development and function of Purkinje cells. *EN*

Written by Emily Niemitz, Alan Packer & Kyle Vogan

Exit Ptc1, enter Smo

Cilia are central in transducing Hedgehog (Hh) signals in vertebrate cells, but the precise mechanisms are not fully understood. Matthew Scott and colleagues (*Science* **317**, 372–376; 2007) now show that stimulation with Hh ligands results in dynamic changes in the subcellular localization of Patched1 (Ptc1), the surface-bound receptor for Hh proteins that acts as a negative regulator of the pathway by repressing the activity of Smoothened (Smo), a key positive effector of the pathway. Using immunofluorescence and live imaging methods, the authors show that Ptc1 localizes to cilia when the Hh pathway is inactive but exits cilia and relocalizes to a cytoplasmic pool in response to pathway stimulation. This relocalization of Ptc1 is accompanied by reciprocal changes in the localization of Smo, which accumulates in cilia in response to pathway stimulation. These findings suggest that reciprocal changes in the localization of positive and negative Hh signaling components in cilia function as a switch to regulate the activity of the pathway. These results also parallel earlier findings in *Drosophila*, where activation of the Hh pathway is accompanied by internalization of Ptc and accumulation of Smo at the cell surface. *KV*

Survey of common genetic variation

A complete picture of the architecture of human genetic disease will require an unbiased accounting of allele frequencies of common variants across multiple populations. At least some of the efforts thus far have been hampered by an oversampling of SNPs with a minor allele frequency of >5%. In a new attempt to address this concern, Stephen Guthery and colleagues report an analysis of variation identified by the Genaissance Resequencing Project, which involved resequencing the exons and flanking regions of more then 3,800 genes from 20 European Americans, 17 Latino Americans, 19 East Asian Americans and 20 African Americans (*Am. J. Hum. Genet.*, in the press). The authors found that most SNPs that were common in one population were present in multiple populations, but a substantial proportion was limited to one or two populations. In addition, SNPs that were common in two populations tended to differ in frequency from one another, with the difference in frequency of a given SNP in two populations being positively correlated with its minor allele frequency. They also confirm that African Americans carry the highest proportion of rare SNPs, and conclude by arguing for extensive sampling of African Americans and for new initiatives to canvass variation in individuals with a wider range of geographic ancestry. ***AP***