Metabolic link to gliomas

The gene encoding isocitrate dehydrogenase-1 (*IDH1*) has been shown to be somatically mutated, producing a single amino-acid substitution at Arg132 in approximately 70% of secondary gliomas, but its contribution to the underlying etiology of brain tumors is unclear. In the absence of any obvious inactivating mutations or apparent loss-of-heterozygosity in tumors, it has been speculated that Arg132 substitutions lead to oncogenic activation of IDH1. Now Zhao *et al.* (*Science*, published online 10 April 2009; doi:10.1126/science.1170944) examine glioma-derived mutations in *IDH1* and find that the tumor-derived mutants have reduced catalytic activity as a result of impaired substrate binding, limiting the activity and structural requirements critical for enzymatic function that occur under physiological conditions. They show that loss of IDH1 activity alters the cellular levels of α-ketoglutarate, the product of IDH1 catalysis, which is required to supply prolylhydroxylases and promote the degradation of hypoxia-inducible factor 1α (HIF-1α). As a result, the steady-state level of HIF-1α stably increases, leading to the upregulation of well-established HIF-1α target genes. These results highlight an emerging theme in which mutationally altered metabolic enzymes are thought to contribute to tumor growth by stimulating the HIF-1α pathway and tumor angiogenesis. ***LK***

Primary congenital glaucoma

Primary congenital glaucoma (PCG) is a relatively rare, early-onset glaucoma that is usually inherited as an autosomal recessive condition and whose incidence is elevated in populations with high rates of consanguinity. Manir Ali and colleagues (*Am. J. Hum. Genet.* in the press; doi:10.1016/j.ajhg.2009.03.017) now report mutations in *LTBP2* as a cause of PCG in several Pakistani and European Gypsy families. Previously, the authors used homozygosity mapping and linkage analysis to map a locus for PCG to a 4.2-Mb region of chromosome 14q24. In the current study, they selected *LTBP2* as a candidate gene for sequencing and identified two frameshift mutations and one nonsense mutation segregating with PCG in three unrelated Pakistani families. They then extended their analysis to European Gypsy families and found the same nonsense mutation previously discovered in one Pakistani family. This mutation is carried on an identical haplotype in both populations, suggesting it originated in a common founder. LTBP2 shares homology with TGFβ-binding proteins, and the authors hypothesize that it could have a role in maintaining ciliary muscle tone. The work also highlights *LTBP2* as a potential candidate gene for more common forms of glaucoma. *KV*

Modeling growth

In the past year, GWAS studies have reported adult height associated with over 50 variants. Marjo-Riitta Jarvelin and colleagues now examine these variants during the two most rapid stages of height growth, infancy and puberty, using longitudinal height growth measurements within the Northern Finland Birth Cohort 1966 (*PLoS Genet.* **5**, e1000409; 2009). For a sample of 3,538 individuals assessed at age 31y, height measurements were taken regularly from infancy to adulthood, with an average of 20 measurements per person. They fit individual growth curves to these longitudinal height measurements using a standard parametric model, and from this defined peak height velocities in infancy (PHV1) and puberty (PHV2). They examined 48 SNPs previously associated to adult height and found 26 associated with adult height in their samples; they suggest that this partial replication is due to limited power. Seven of these SNPs were associated with PHV1 and five were associated with PHV2. Further, they found a SNP in *SOCS2* showing age-dependent association, and modeled the combined impact of this association with age and sex on height growth velocity. They also tested for associations with age at PHV2 as well as sex–SNP interactions, but did not find any that passed thresholds for significance. *OB*

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DECIPHERing chromosomal imbalances

Thanks to technologies such as array comparative genomic hybridization and SNP genotyping array analysis it is now well established that previously undetectable genomic copy number changes can be pathogenic or polymorphic in the population. However, it can be difficult for disease researchers to determine whether a given change in an affected individual is causative for the phenotype. To assist in this task, Helen Firth, Nigel Carter and colleagues have developed the Database of Chromosomal Imbalance and Phenotype in Humans Using Ensembl Resources (DECIPHER) (*Am. J. Hum. Genet.* **84**, 524–533; 2009). DECIPHER is a web-based resource that catalogs human copy number data, including data generated from normal populations, and maps it to the human reference genome using the ENSEMBL genome browser. Researchers can use DECIPHER to interpret subject copy number data and to connect to other researchers who have similar subjects. By enabling collaboration, this resource can assist in the discovery of new syndromes and in the recognition of genes of clinical importance. DECIPHER requires the consent of research participants and uses security features and restricted access to protect privacy. DECIPHER is accessible on the web at https://decipher.sanger.ac.uk. *EN*

Persistent polycombs

It is known that the molecular basis of epigenetic states that are heritable during cell division involves histone chromatin structural proteins, as histone modifications can be inherited during DNA replication. Now, Nicole Francis and colleagues have determined that nonhistone chromatin factors of the polycomb family of proteins may also have a role in heritable epigenetic states (*Cell* 137; 110–122; 2009). The authors used a cell-free DNA replication system to show that polycomb repressive complex 1 (PRC1) remains bound to chromatin and is not released during DNA replication. Chromatin template containing a trimethylated histone H3 lysine 27 analog also permitted binding of PRC1 during replication. Inhibition of chromatin remodeling, a read-out of PRC1 function, was maintained through DNA replication. The authors also determined that polycomb proteins are bound to genomic polycomb response elements during S phase in synchronized *Drosophila* S2 cells. Immunoprecipitation experiments using the *Drosophila* cellular system showed that levels of polycomb protein associated with replicated DNA increase following the completion of replication, suggesting that additional polycomb complexes are subsequently incorporated. This study suggests that epigenetic inheritance during cell division may involve both histone and nonhistone chromatin factors. ***EN***