iPS cell integrity

Correction of genetic defects in patient-specific induced pluripotent stem (iPS) cells is a potential therapeutic approach for many human diseases. However, recent work has shown that iPS cells generally carry several point mutations relative to the parental somatic cells. James Thomson and colleagues assessed the genomic integrity of an iPS cell line after reprogramming, gene targeting and removal of a selection cassette (*Proc. Natl. Acad. Sci. USA* published online, doi:10.1073/pnas.1103388108, 4 April 2011). The authors isolated iPS cells from an individual with gyrate atrophy carrying a deleterious mutation in *OAT*, the gene encoding ornithine-δ-aminotransferase, and corrected the mutation using homologous recombination. Analysis of both the parental fibroblast line and the iPS cell line showed that the mutational load at the time of initial reprogramming was fairly substantial, although they performed the subsequent genetic correction and removal of the cassette with minimal further changes. Specifically, they found two deletions, one amplification and nine protein-coding mutations in the initial iPS cell clone, but they observed no other mutations or copy number variants after the subsequent events. Further research is needed to determine if the mutational load differs between starting somatic cell types or whether it increases with aging. *PC*

De novo mutations and intellectual disability

Neuronal synaptic glutamate receptor complexes are involved in synaptic plasticity, learning and memory and have been implicated in neurocognitive diseases. Now, Jacques Michaud and colleagues report a systematic search for *de novo* mutations in glutamate receptor complexes in non-syndromic intellectual disability (NSID) (*Am. J. Hum. Genet.* **88**, 306–316, 2011). The authors sequenced 197 genes encoding glutamate receptors and their known interacting proteins in 95 individuals with sporadic NSID and identified 646 unique variants which were further tested for parental transmission. They identified ten *de novo* truncating, deletion, splicing or missense mutations in seven genes. Six of these mutations are in *SYNGAP1*, *STXBP1* and *SHANK3*, genes previously implicated in neurocognitive diseases. The remaining four candidate genes, *KIF1A*, *GRIN1*, *EPB41L1* and *CACNG2*, were sequenced in 50 additional sporadic NSID cases and 285 controls. This led to the identification of one additional duplication mutation in *GRIN1*. The authors documented functional effects of the mutations in *KIF1A*, *GRIN1*, *EPB41L1* and *CACNG2* in cell culture systems, but identification of mutations in additional patients will be needed to confirm their role in NSID. *EN*

Low-coverage sequencing

Gonçalo Abecasis and colleagues report an analysis of low-coverage sequencing designs for complex trait association studies (*Genome Res.* published online, doi:10.1101/gr.117259.110, 1 April 2011). They report a linkage disequilibrium–based method for SNP discovery and genotype calling from sequencing data as an extension of their previous genotype-based imputation methods. Their approach used a hidden Markov model to jointly analyze all sequenced individuals and draw on shared haplotypes. The linkage disequilibrium–based method has been implemented in the software program Thunder, which can combine information from sequenced, genotyped and imputed samples. Using simulations as well as application to the 1000 Genomes Pilot dataset, they examine the utility of low-coverage sequencing designs for SNP discovery, genotyping accuracy and genetic association studies. They also compare study designs based on genotyping tag SNPs, sequencing a limited number of individuals at high coverage or sequencing a larger numbers of individuals at low coverage. They find that low coverage sequencing study designs can provide greater power for genetic association studies, and that imputation can be used to further increase power. They also find that reference panels based on low-pass–sequencing study designs can provide greater utility for imputation into GWAS samples. *OB*

Written by Pamela Colosimo, Emily Niemitz, Orli Bahcall & Kyle Vogan

TDRD7 and lens development

Richard Maas, Simon John and colleagues (*Science* **331**, 1571–1576, 2011) identify the RNA granule component TDRD7 as an important regulator of gene expression in the developing lens. They initially identified a translocation disrupting *TDRD7* in a child with juvenile cataracts. They then discovered a small in-frame deletion in *TDRD7* in a second family with autosomal recessive congenital cataracts. Two affected individuals in this second family also developed increased intraocular pressure and open-angle glaucoma. Consistent with these findings, the authors showed that *Tdrd7*-null mice develop early onset cataracts that become more severe with age. The mice also develop increased intraocular pressure that results in a phenotype resembling open-angle glaucoma marked by severe optic nerve atrophy. Expression studies showed that TDRD7 is strongly expressed in the developing lens and is found in cytoplasmic RNA granules, where it co-localizes with the RNA-binding protein STAU1. *Tdrd7* mutant lenses showed reduced expression of several genes important for lens development, including some genes previously implicated in cataract formation. The authors propose that TDRD7 acts to stabilize specific mRNAs, thus promoting efficient translation of proteins such as crytallins that are required at high concentration for proper lens function. *KV*

Neuropeptides and starvation-induced food search

Feeding behavior in most animals is regulated by neuropeptides. In insects, neuropeptide F and short neuropeptide F (sNPF) promote feeding behavior when overexpressed in neurons. Although much is known about the control of feeding behavior, the mechanisms that modulate starvation are not well understood. Jing Wang and colleagues hypothesized that sNPF signaling may also regulate starvation-dependent enhancement of food-search behavior (*Cell* 145, 133–144, 2011). The authors knocked down sNPF in olfactory receptor neurons in *Drosophila* and found that starved flies lacking sNPF showed a longer latency in food finding. Starvation did not affect sNPF mRNA levels, but the authors observed a fourfold increase in sNPFR1 transcript levels in antennae of starved flies. Because levels of insulin-like peptide decrease during starvation, the authors hypothesized that ectopic expression of constitutively active insulin receptor would mimic the fed state. Indeed, activation of insulin receptor in olfactory receptor neurons prevents starvation-dependent food search behavior. The authors conclude that starvation increases sNPFR1, resulting in increased food-search behavior. *PC*