Polygenic architecture

Peter Visscher and colleagues examine the genetic architecture of body mass index (BMI) and height using a within-family approach that uses realized genetic sharing between 20,240 sibling pairs from 9,577 nuclear families (*Am. J. Hum. Genet.* doi:10.1016/j.ajhg.2013.10.005, 31 October 2013). They calculate identity by descent (IBD) for each sibling pair using ~20,000 SNPs in linkage equilibrium. They estimate the narrow-sense heritability for BMI at 0.42 (s.e.m. = 0.17) and for height at 0.69 (s.e.m. = 0.14), and suggest that previous heritability estimates for BMI were likely overestimates. They find a positive correlation of partitioned genetic variance with chromosome size for both BMI and height, consistent with a polygenic architecture. They perform a within-family linkage study for height and BMI and show increasing genomic inflation factors proportional to sample size. Their simulations show that this linkage analysis is robust to population stratification as well as to genetic heterogeneity between cohorts. They further demonstrate that the observed data are consistent with simulations assuming a polygenic architecture including both common and rare variation. They also suggest that polygenic architecture has contributed to failures to replicate linkage studies. They estimate that 67% and 40% of variance for height and BMI, respectively, is captured by common SNPs. ***OB***

Super stretchy enhancers

Earlier this year, Richard Young and colleagues reported identification of clusters of enhancers, called super-enhancers, which are bound by the Oct4, Sox2 and Nanog transcription factors and the Mediator complex in embryonic stem cells (ESCs) (*Cell* **153**, 307–319, 2013). They showed that super enhancers can be identified in other cell types, are specific to cell type and are located near genes known to control cell identity. Now, Francis Collins and colleagues report identification of long 'stretch' enhancers that are cell-type specific and are associated with cell-type–specific expression of nearby genes (*Proc. Natl. Acad. Sci. USA* **110**, 17921–17926, 2013). These authors profiled histone H3 modifications and RNA expression in isolated human pancreatic islets and performed analyses with published histone profiles from nine other cell types. They tested two islet stretch enhancers for functional activity in transgenic mice and showed that they drive expression in pancreatic primordium. In addition, Young and colleagues now report a catalog of super-enhancers in 86 human cell types (*Cell* doi:10.1016/j.cell.2013.09.053, 10 October 2013). They use genome-wide profiles of H3K27ac, which they show is the most strongly predictive chromatin mark for super-enhancers in ESCs, and use this catalog to infer candidate master transcription factors that regulate cell identity in all 86 cell types. *EN*

PIK3CD mutations cause immunodeficiency

Two new studies report heterozygous gain-of-function mutations in *PIK3CD,* which encodes the catalytic subunit of phosphatidylinositol 3-kinase δ (PI3K δ), as the cause of a primary immunodeficiency syndrome. Sergey Nejentsev and colleagues (*Science* doi:10.1126/science.1243292, 17 October 2013) found a recurrent *PIK3CD* mutation leading to a p.Glu1021Lys alteration in seven unrelated families with a history of respiratory infections and progressive airway damage. In an independent study, Gulbu Uzel and colleagues (*Nat. Immunol.* doi:10.1038/ni.2771, 28 October 2013) identified three distinct *PIK3CD* mutations, resulting in p.Asn334Lys, p.Glu525Lys and p.Glu1021Lys alterations, in seven unrelated families presenting with sinopulmonary infections, chronic viremia and lymphoproliferation. Both groups showed that the mutations resulted in increased PI3K activity, increased phosphorylation of AKT and altered T and B cell function. In particular, Uzel and colleagues found that the mutations were associated with a deficiency of naive T cells and an excess of senescent effector T cells. Both studies also present preliminary data suggesting that individuals harboring these activating mutations in *PIK3CD* could benefit from treatment with selective PI3Kδ inhibitors or with mTOR inhibitors such as rapamycin. *KV*

Tumor suppressors, oncogenes and aneuploidy

Steve Elledge and colleagues have developed a bioinformatic method called TUSON Explorer to identify candidate tumor suppressor genes (TSGs) and oncogenes (OGs) based on sequence mutation parameters (*Cell* doi:10.1016/j.cell.2013.10.011, 31 October 2013). They applied the method to tumor sequence data from the COSMIC and TCGA databases and identified an estimated 320 TSGs and 250 OGs, including many new potential cancer drivers. Interestingly, their analyses predict that many TSGs are haploinsufficient, and they identified an enrichment of candidate TSGs on the X chromosome and 2 potential TSGs on the Y chromosome. The authors determined the density of TSGs and OGs on each chromosome arm and found that arms with a high density of TSGs have a high frequency of deletion and low frequency of amplification, whereas arms with a high density of OGs have a low frequency of deletion and a high frequency of amplification. A similar analysis of whole-chromosome aneuploidy also showed that density of tumor drivers associates with frequency of chromosome losses and gains. The authors conclude that there are likely to be many more cancer driver genes than previously thought and that there is a long tail of tumor driver genes with weak effects. *EN*

Capturing ancient DNA

Meredith Carpenter and colleagues report a new capture-based method for target enrichment in ancient-DNA sequencing libraries, which is important as these samples often contain <1% endogenous DNA (*Am. J. Hum. Genet.* doi:10.1016/j.ajhg.2013.10.002, 28 October 2013). Their method, called whole-genome in-solution capture (WISC), relies on the creation of RNA baits, covering the human genome from a modern reference individual, hybridized to the ancient-DNA libraries in solution and pulled down with streptavidin-coated beads. The unbound and largely nonhuman DNA is washed away, and the captured endogenous DNA is eluted and amplified for sequencing. The authors applied the WISC method to 12 human ancient-DNA libraries dating from 1500 BCE to CE 1500. Their capture method showed 6- to 159-fold enrichments of reads mapping to the human genome and 2- to 13-fold enrichments for unique fragments. To identify informative variation for population genetic analyses, they use SNPs overlapping with the 1000 Genomes Project reference panel. They were also able to generate coverage of mitochondrial DNA for five of the samples and tentatively call mitochondrial DNA haplogroups. ***OB***

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