

## Pathogenic variants and secondary results

Holly Tabor, Michael Bamshad and colleagues searched for pathogenic variants in the high-coverage exome sequences of 4,313 European-American and 2,204 African-American individuals from over 20 cohorts within the National Heart, Lung, and Blood Institute (NHLBI) Exome Sequencing Project (*Am. J. Hum. Genet.* doi:10.1016/j.ajhg.2014.07.006; 31 July 2014). They focused on variants in 39 genes for 31 mendelian disorders, 17 genes associated with age-related macular degeneration (AMD) and 14 genes implicated in drug response. In total, they identified 10,879 variants in these 70 disease-related genes and validated 399 risk variants, including 328 for mendelian disorders, 25 for AMD and 46 for drug response. The mean number of risk alleles per individual in the combined data set was estimated to be 15.3, with 0.57 for mendelian disorders, 3.16 for AMD and 11.5 for drug response. They found that 45% of individuals had at least one pathogenic allele for mendelian disorders and over 99.98% of individuals carried one or more risk alleles for AMD. Each individual also carried at least five functional alleles in genes associated with drug response. The carrier burden for severe recessive childhood disorders was estimated to be 0.57, significantly lower than previously reported estimates. This study highlights the striking prevalence of actionable incidental or secondary results, including ones of direct clinical usefulness, which might be obtained in patient sequencing. **OB**

## STING-mediated autoinflammatory disease

Mutations causing dysregulated interferon signaling underlie systemic autoinflammatory disorders such as Aicardi-Goutières syndrome. Raphaela Goldbach-Mansky and colleagues (*N. Engl. J. Med.* 371, 507–518, 2014) now show that a rare syndrome characterized by early-onset systemic inflammation, cutaneous vasculopathy and lung inflammation is caused by *de novo* activating mutations in *TMEM173*, which encodes an activator of interferon signaling called STING. Suspecting a genetic basis for this early-onset inflammatory disease, the authors performed exome sequence on an affected individual and her unaffected parents and identified a *de novo* missense mutation in *TMEM173* that altered a conserved residue in STING. They then performed targeted sequencing in five unrelated individuals with similar clinical manifestations and identified *de novo* missense mutations in *TMEM173* in all five cases. Next, they analyzed peripheral blood from affected individuals and observed a strong interferon response signature. They further assessed the activity of the mutant proteins and found that they resulted in strong activation of an interferon-sensitive reporter. Together, these findings show that gain-of-function mutations in *TMEM173* cause an inflammatory syndrome marked by vascular and pulmonary manifestations and expand the range of human diseases caused by dysregulated interferon signaling. **KV**

## Loss-of-function variants in the Finnish population

Mark Daly, Aarno Palotie and colleagues examined how genomic architecture in the Finnish founder population differs from that of other European populations (*PLoS Genet.* 10, e1004494, 2014). They analyzed the exome sequences of 3,000 Finnish individuals and 3,000 non-Finnish Europeans as part of the Sequencing Initiative Suomi (SISu) project. A higher proportion of low-frequency loss-of-function variants was identified in the

exomes of the Finnish individuals. They selected 83 loss-of-function variants showing at least 2-fold enrichment in Finns and genotyped these variants in an additional 36,262 Finnish individuals from 3 population-based cohorts. They tested for association to 60 quantitative traits as well as 13 disease outcomes, making use of access to data from the National Health Registers. Variants were identified in the *LPA* gene (encoding lipoprotein(a)) that were associated with lower plasma lipoprotein(a) levels. Using a mendelian randomization approach, they found that the *LPA* variants were protective against coronary heart disease. These analyses suggest that a reduction in lipoprotein(a) levels provides a protective effect against cardiovascular diseases and highlight a possible drug target. **OB**

## NF- $\kappa$ B signaling disrupted in neurodevelopmental disorders

Intellectual disability is present in 30–50% of people with autism spectrum disorder (ASD), suggesting that these disorders might share some genetic variants. Now, Mustafa Salih, Fowzan Alkuraya, Christopher Walsh and colleagues report the identification of loss-of-function alleles of *CC2D1A* causing multiple combinations of ASD, intellectual disability and seizure disorders in 16 individuals from 4 families (*Cell Rep.* doi:10.1016/j.celrep.2014.06.039; 24 July 2014). The authors performed linkage analysis on genome-wide SNP data for the three consanguineous families and homozygosity mapping for the one non-consanguineous family, identifying a single region at 19p13 containing *CC2D1A* that was strongly associated with affected status in all four families. *CC2D1A* regulates pathways involved in neuronal differentiation, including the NF- $\kappa$ B signaling pathway. The authors knocked down *Cc2d1a* in the developing cortex of mice *in utero* and observed abnormal, underdeveloped dendrites at postnatal day 11. They found that *CC2D1A* knockdown in neurons led to an increase in NF- $\kappa$ B target gene transcription and that chemical inhibition of NF- $\kappa$ B rescued the neuronal *CC2D1A* knockdown phenotype. **BL**

## Transcriptional cross-talk between tumor and stromal cells

Non-cancerous stromal cells in the tumor microenvironment, such as cancer-associated fibroblasts (CAFs), support tumor growth and malignancy and must undergo changes in gene expression to do so. A new study by Susan Lindquist, Luke Whitesell and colleagues identifies activated heat shock protein HSF1 as a key player in this transcriptional reprogramming (*Cell* 158, 564–578, 2014). The authors found that HSF1 localized to the nucleus in CAFs from breast cancer samples, indicating that it was active, in contrast to the predominately cytoplasmic (inactive) HSF1 in fibroblasts from normal breast tissue. Following co-culture experiments of wild-type and *Hsf1*-deficient mouse embryonic fibroblasts (MEFs) and D2A1 cancer cells, expression array analysis showed that 219 genes were specifically upregulated in cancer cells grown in the presence of MEFs expressing HSF1. This gene set was enriched for genes with roles in extracellular matrix (ECM) formation and cell adhesion, whereas genes involved in cytokine signaling and immune response were downregulated. Cancer cells similarly affected the transcriptome of co-cultured wild-type but not *Hsf1*-null MEFs, upregulating genes related to cell proliferation and wound response. The authors found that HSF1 exerts these effects through the TGF- $\beta$  and SDF1 signaling pathways. Finally, they showed that activation of HSF1 in tumor stromal cells from patients with breast and lung cancer was correlated with poor clinical outcome. **BL**

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