

ADAM10 and Alzheimer's disease

Amyloid precursor protein (APP) can be cleaved by β -secretase and γ -secretase proteases to generate amyloid- β protein, the main component of senile plaques in Alzheimer's disease, or can be cleaved by α -secretase proteases, precluding the production of amyloid- β protein and generating a secreted, non-amyloidogenic product. Rudolph Tanzi and colleagues previously identified mutations in the *ADAM10* gene, which encodes the major α -secretase responsible for cleaving APP, in families with late-onset Alzheimer's disease. Now, they have generated transgenic mice expressing two human *ADAM10* mutations in brain, and they report that these mutations increase amyloid- β plaque load (*Neuron* **80**, 1–17, 2013). The authors first showed that the mutant ADAM10 proteins had diminished α -secretase activity on endogenous APP. They then crossed the *ADAM10* transgenic lines with a transgenic mouse line that overexpresses human APP and showed that expression of the *ADAM10* mutants increased amyloid- β levels in the brain compared to in mice expressing comparable levels of wild-type *ADAM10*. The authors also used these mouse crosses to show that increasing the level of ADAM10 α -secretase activity in the brain reduced amyloid- β plaque load, plaque morphology and reactive gliosis in the brain. Finally, the authors showed that the ADAM10 alterations, which are located in the prodomain region of the protein, impair the prodomain's chaperone function. EN

sequence coverage of over 130 \times . Variants were classified as deleterious, of unknown clinical significance or benign on the basis of guidelines from the American College of Medical Genetics and Genomics (ACMG). After filtering, the authors identified approximately 400 to 700 potentially clinically useful variants per patient. Variants were confirmed with Sanger sequencing in each proband as well as in parental samples, when available. The authors determined the molecular diagnosis for 62 of the patients (25%), including for 33 individuals with autosomal dominant disease, 6 individuals with autosomal recessive disease and 9 individuals with X-linked disorders. For 30 of the patients, the authors also identified medically actionable incidental findings in 16 genes, 9 of which are recommended for reporting by the ACMG. OB

FunSeq for cancer genomics

Mark Gerstein and colleagues report a new method, FunSeq, to facilitate the analysis and functional prioritization of noncoding variation in cancer genomics studies (*Science* **342**, 1235587, 2013). They analyzed patterns of selection across noncoding regions using data from the 1000 Genomes Project Phase I data set that comprises genome sequences from 1,092 individuals. They used enrichment of rare SNPs as an estimate of purifying selection and further subdivided noncoding regions into 677 specific categories, finding that 102 of these categories showed significant evidence of selective constraint. The highest levels of negative selection were found in regions they term 'sensitive' and 'ultrasensitive', which have, respectively, a 40- and 400-fold enrichment in disease-causing mutations annotated in the Human Gene Mutation Database. Variants in regions with high connectivity (hubs) in protein-protein interaction or regulatory networks showed higher selective constraint. To demonstrate the usefulness of FunSeq in the analysis of cancer genomes to prioritize candidate driver mutations, the authors examined a data set including whole-genome sequences from 64 prostate, 21 breast and 3 medulloblastoma tumors, identifying 98 noncoding candidate drivers. FunSeq, which was also shown to be useful in identifying potentially deleterious variants in personal genome sequences, has been made publicly available as an automated web tool at <http://funseq.gersteinlab.org/>. OB

Ras pathway activation in breast cancer

Mutations in *RAS* genes are very rare in human breast cancers, but the Ras signaling pathway is hyperactivated in half of these tumors. Now, Karen Cichowski and colleagues identify a new driver of Ras pathway activation in breast cancer and show that it functions as a tumor and metastasis suppressor (*Cancer Cell* **24**, 365–378, 2013). The authors initially identified *RASAL2* in a cell-based screen for Ras GTPase-activating proteins with growth suppressive activity. By searching publicly available databases, they found that the catalytic domain of *RASAL2* is targeted by mutations in human breast cancers and other human tumor types. Mouse xenograft studies showed that *RASAL2* expression suppressed the growth of tumors derived from a *RASAL2*-deficient breast cancer cell line, and short hairpin RNA (shRNA)-mediated suppression of endogenous *RASAL2* in a breast cancer cell line promoted tumor growth. The authors generated genetically engineered mice that lack *Rasal2* and found that, although the *Rasal2*-deficient mice did not develop mammary tumors, loss of *Rasal2* increased the number of metastases in an engineered mouse model of mammary tumorigenesis. This work identifies a new mechanism by which Ras becomes activated in breast cancer. EN

Clinical diagnostic sequencing

Christine Eng and colleagues report clinical whole-exome sequencing of 250 individuals representing the first patients referred to the CLIA-certified laboratories at the Baylor College of Medicine for diagnostic exome sequencing (*N. Engl. J. Med.* doi:10.1056/NEJMoa1306555, 6 October 2013). All patients were referred on the basis of having an undefined genetic condition. The majority of patients were under the age of 18 years, and ~80% were children with neurological phenotypes. Sequencing was performed with either the Illumina Genome Analyzer IIX platform or the Illumina HiSeq 2000 platform, with mean

Genetics of immune cell levels

Francesco Cucca and colleagues (*Cell* **155**, 242–256, 2013) have applied a sequencing-based genome-wide association approach to analyze how genetic variants influence the relative abundance of immune cell types. The authors collected peripheral blood samples from 1,629 individuals from Sardinia and used fluorescence-activated cell sorting to purify 95 distinct immune cell types, with an emphasis on specialized T cell subsets. They then tested more than 8 million genetic variants for association with 272 different traits related to immune cell levels or function, with further replication testing in 1,241 additional samples. In total, they observed 23 genome-wide significant association signals at 13 loci, 3 of which were previously associated with altered disease risk. For example, in the *IL2RA* region, they found that a variant previously associated with reduced susceptibility to type 1 diabetes was associated with higher levels of a memory T cell subset characterized by high CD25 expression, suggesting that this cell type might confer protection against this autoimmune disease. Further exploration of coincident associations between disease risk and immune cell phenotypes could provide new insights into disease mechanisms or suggest possible strategies for therapeutic intervention. KV

Written by Orli Bahcall, Emily Niemitz & Kyle Vogan