Pancreatic cancer exomes

Pancreatic neuroendocrine tumors (PanNETs) are a rare but poorly understood form of pancreatic cancer. Nickolas Papadopoulos and colleagues now report (Science published online, doi:10.1126/science.1200609, 20 January 2011) exome sequencing of 10 PanNETs and a further analysis of 58 PanNETs. They found mutations in 149 genes in the ten tumor exomes. The genes mutated in PanNETs are quite different from those mutated in the more common form of pancreatic cancer, pancreatic ductal adenocarcinoma. Four genes had mutations in at least two of the PanNETs: MEN1, DAXX, PTEN and TSC2. ATRX, which forms a heterodimer with DAXX, was mutated in one tumor. These five genes were then sequenced in 58 other PanNETs. MEN1, a histone methyltransferase component that was previously known to be inactivated in PanNETs, was mutated in 44.1% of tumors. Forty-two point six percent of tumors had mutations in DAXX and ATRX, which are also involved in chromatin remodeling. There was evidence to suggest that mutations in MEN1, DAXX and ATRX are associated with better prognosis, as patients with metastatic disease and mutations in these genes survived at least 10 years after diagnosis, whereas over 60% of patients without these mutations died within 5 years of diagnosis.

Ant genomes

The genomes of three ant species were reported recently in the Proceedings of the National Academy of Sciences of the United States of America. Yannick Wurm and colleagues now report the draft genome of the fire ant (Solenopsis invicta), a major pest that causes crop and livestock loss (Proc. Natl. Acad. Sci. USA published online, doi:10.1073/pnas.1009690108, 31 January 2011). Odorant receptors are important for chemical communication, which is a trait that likely contributes to complex social behavior in ants. The authors identified more than 400 putative olfactory receptors, which is the most reported so far in insects. Jürgen Gadau and colleagues report the draft genome of the red harvester ant (Pogonomyrnex barbatus), which has a unique system of genetically controlled queen-worker caste determination (Proc. Natl. Acad. Sci. USA published online, doi:10.1073/pnas.1007901108, 31 January 2011). The authors manually annotated candidate gene families that may be involved in this process, including insulin/TOR-signaling genes, yellow/major royal jelly genes, biogenic amine receptors and hexamerin storage proteins. Finally, Neil Tsutsui and colleagues report the draft genome of the Argentine ant (Linepithema humile), a widely distributed invasive species that outcompetes and eliminates native ants (Proc. Natl. Acad. Sci. USA published online, doi:10.1073/pnas.1008617108, 31 January 2011). The authors discovered 231,248 SNPs that should be useful for future analyses of migration patterns of this invasive ant.

Catastrophes in cancer

Cancer development is usually described as a progressive process of mutation accumulation that eventually leads to the malignant phenotype. Now, Peter Campbell and colleagues show that many genomic rearrangements in cancer can occur in a single event (Cell 144, 27–40, 2011). The authors initially screened the cancer genomes of ten individuals with chronic lymphocytic leukemia for genomic rearrangements using paired-end sequencing. They identified a remarkable sample with 42 somatic rearrangements clustered on chromosome 4; the allelic state across the rearranged region alternated between heterozygosity and homozygosity. They then analyzed copy number profiling data from 746 tumor cell lines and 2,792 tumor samples and found that 2.5% of cancers of many different types have tens to hundreds of copy number changes localized to a particular genomic region. They also show that 25% of bone cancers have a similar distinct pattern of clustered rearrangement. Further investigation with spectral karyotyping and fluorescence in situ hybridization showed that the rearrangements involve one of the two parental copies of the chromosome, explaining the alternation between heterozygous and homozygous states. The authors suggest that the clustered rearrangements arise in a single event when a chromosome region shatters and is partially repaired; they call this process chromothripsis.

NT5E and arterial calcifications

Mutations in ENPP1, encoding ectonucleotide pyrophosphatase-phosphodiesterase 1, cause a rare disorder known as generalized arterial calcification of infancy (Nat. Genet. 34, 379–381, 2003). Cynthia St. Hilaire and colleagues (N. Engl. J. Med. 364, 432–442, 2011) now report biallelic mutations in the gene encoding 5’-ribonucleotide phosphodiesterase (NT5E) in three families affected with adult-onset arterial calcifications of the lower extremities. The authors performed homozygosity mapping in a consanguineous family with five affected individuals and found a single shared region of homozygosity at 6q14. One of the genes in the candidate region, NT5E, encodes the enzyme that acts downstream of the ENPP1 gene product to degrade extracellular ATP and its metabolites. Sequencing of NT5E in the index family and two other affected families identified homozygous or compound heterozygous mutations in all three families. Transduction of wild-type NT5E into cultured fibroblasts from an affected individual normalized the expression of tissue-nonspecific alkaline phosphatase, a key enzyme in tissue calcification, and prevented formation of calcium phosphate crystals. These findings highlight the importance of this metabolic pathway in preventing abnormal tissue calcification and suggest potential strategies to treat individuals affected with these disorders.

AIP and gigantism

Germline mutations in the aryl hydrocarbon-interacting protein gene AIP confer inherited predisposition to pituitary adenomas, symptoms of which include acromegaly and gigantism caused by elevated production of growth hormone. Previous work identified four families from Northern Ireland harboring the same mutation in AIP, suggesting that these families inherited the mutation from a common founder. Márt February 2011) now show that the same founder mutation is also present in an individual with gigantism from eighteenth-century Ireland whose skeletal remains are preserved at the Hunterian Museum in London. The skull of this individual was previously shown to have an enlarged pituitary fossa, suggesting that his gigantism resulted from a pituitary adenoma. To test whether this eighteenth-century case and the four contemporary families are ancestrally related, the authors extracted DNA from the skeleton and amplified the AIP region flanking the proposed founder mutation. Their investigation confirmed that this eighteenth-century individual with gigantism and the four contemporary families carry the same founder mutation, which the authors estimate arose roughly 60 generations ago and now persists in the contemporary population of Ireland.

Written by Pamela Colosimo, Emily Niemitz & Kyle Vogan