Nature Reviews Genetics | AOP, published online 11 February 2014

IN BRIEF

DISEASE GENETICS

Networks for functional insights into disease genes

To characterize the biology underlying hereditary spastic paraplegias (HSPs), which are a heterogeneous group of neurodegenerative disorders, Novarino *et al.* carried out exome sequencing of cases and controls from 55 HSP-affected families. They found genetic variants in 14 genes previously associated with HSP, as well as variants in 15 novel genes. The products of these genes were used to seed a protein–protein interaction network, which revealed key roles for endosomal trafficking and purine metabolism in HSP aetiology. Furthermore, the network uncovered additional HSP candidate genes and biological connections to other neurodegenerative diseases.

ORIGINAL RESEARCH PAPER Novarino, G. *et al.* Exome sequencing links corticospinal motor neuron disease to common neurodegenerative disorders. *Science* **343**, 506–511 (2014)

EVOLUTION

Taking advantage of drug resistance

Resistance to antimalarial drugs is common in the *Plasmodium falciparum* parasite, which causes the most lethal form of malaria. Using high-throughput small-molecule screens, Lukens *et al.* found that resistance to the commonly used antimalarial chloroquine and resistance to the in-development inhibitors of dihydroorotate dehydrogenase conversely caused sensitization to the compounds IDI-3783 and IDI-6273, respectively. Thus, mutations that cause resistance to antimalarials can sensitize to alternative agents, and the sequential or combinatorial use of different drugs might combat the spread of drug resistance.

ORIGINAL RESEARCH PAPER Lukens, A. K. *et al.* Harnessing evolutionary fitness in *Plasmodium falciparum* for drug discovery and suppressing resistance. *Proc. Natl Acad. Sci. USA* **111**, 799–804 (2014)

CANCER GENETICS

Tetraploidy tolerance promotes cancer evolution

Aneuploidy has been long associated with genetic instability and tumorigenesis. Dewhurst and colleagues examined the evolution and consequences of chromosomal aberrations in long-term culture of a diploid colon cancer progenitor cell line over time. Rare cells that survive genome doubling, tetraploids, have a greater tolerance for further chromosomal abnormalities. Furthermore, tetraploidy was found to be associated with a low probability of disease-free survival.

ORIGINAL RESEARCH PAPER Dewhurst, S. M. *et al.* Tolerance of whole-genome doubling propagates chromosomal instability and accelerates cancer genome evolution. *Cancer Discov.* http://dx.doi.org/10.1158/2159-8290.CD-13-0285 (2014)

MOLECULAR GENETICS

Insights into nucleolar formation and propagation

The nucleolus is a cellular compartment, with roles in ribosome biogenesis and cellular proliferation, which breaks down during mitosis and reforms around uncharacterized chromosomal features called nucleolar organizer regions (NORs). Grob and colleagues used a synthetic biology approach to investigate nucleolar propagation through mitosis in a human cell line. They identified the protein UBF1 as key for regulating NOR competency and they characterized the DNA sequence requirements for a functional synthetic nucleolus. In addition, they showed that NORs occupy distinct territories in nucleoli and that nucleolar biogenesis is a conserved process.

ORIGINAL RESEARCH PAPER Grob, A. *et al.* Construction of synthetic nucleoli in human cells reveals how a major functional nuclear domain is formed and propagated through cell division. *Genes Dev.* http://dx.doi.org/10.1101/gad.234591.113 (2014)