IN BRIEF

GENETIC TESTING

Classifying pathogenic variation

Amendola *et al.* refine estimates of the burden of incidental (also known as secondary) findings that may be identified during the course of clinical exome sequencing studies. They searched the exome sequences of 4,300 European and 2,203 African ancestry participants in the NHLBI Exome Sequencing Project (ESP) for single-nucleotide variants (SNVs) in 112 genes, selected by a panel of expert reviewers to be associated with medically actionable genetic disorders that may remain undiagnosed in adults. They estimate that 2.0% of European and 1.1% of African ancestry participants would be returned results with actionable, highly penetrant pathogenic or likely pathogenic SNVs. The authors highlight continuing challenges in variant classification, including high rates (~53%) of discordant classification of the same variant by two independent reviewers. They stress the importance of using multiple data sources and reviewers, as well as the need for developing improved consensus criteria for pathogenicity classification and a curated variant interpretation knowledgebase.

ORIGINAL RESEARCH PAPER Amendola, L. M. *et al.* Actionable exomic incidental findings in 6503 participants: challenges of variant classification. *Genome Res.* http://dx.doi.org/10.1101/gr.183483.114 (2015)

FUNCTIONAL GENOMICS

Multiallelic copy number variation

Multiallelic copy number variation (mCNV), for which more than two segregating alleles give rise to a wide range of copy numbers, have proved refractory to traditional analysis methods. Handsaker *et al.* now report the first large-scale characterization of the extent of large mCNVs based on an analysis of 849 human whole-genome sequences from the 1000 Genomes Project. They identified 1,356 mCNVs that showed 0–15 diploid copy numbers. They estimate that mCNVs are responsible for 88% of the variation in gene dosage, which is more than sevenfold greater than the combined contribution of deletions and biallelic duplications. They also find that most mCNVs affect expression levels of the genes that they contain. They further identify several examples of 'runaway duplication haplotypes' for which a small proportion of individuals showed much higher copy numbers emerging on specific haplotypes and within a single population, suggesting evolution by recurrent mutation on the same haplotype background.

ORIGINAL RESEARCH PAPER Handsaker, R. E. *et al.* Large multiallelic copy number variations in humans. *Nature Genet.* http://dx.doi.org/10.1038/ng.3200 (2015)

MODEL ORGANISMS

Updated *Drosophila* reference sequence

Hoskins *et al.* report Release 6 of the *Drosophila melanogaster* reference sequence, demonstrating improved accuracy and completeness, particularly in repeat-rich regions of heterochromatic portions of the genome. The authors used cytogenetic mapping to mitotic and polytene chromosomes, as well as clone-based finishing and bacterial artificial chromosome fingerprint verification. This updated reference sequence also offers improved ordering and orientation of sequence scaffolding, which was obtained by alignment to cDNA sequences. They validated the sequence assembly by comparison to a whole-genome optical restriction map. Further improvements to this reference sequence may require long-read sequencing technologies in order to span remaining gaps and further resolve highly repetitive heterochromatic regions.

ORIGINAL RESEARCH PAPER Hoskins, R. A. *et al.* The Release 6 reference sequence of the *Drosophila melanogaster* genome. *Genome Res.* http://dx.doi.org/10.1101/gr.185579.114 (2015)