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IN BRIEF

CLINICAL GENETICS

Pathogenic non-coding variant identification

A new analysis framework called Genomiser combines a pathogenicity score to assess Mendelian non-coding variation with other measures — such as predicted regulatory regions, allele frequency or the phenotypic relevance of associated genes — to improve the identification of regulatory variants from whole-genome sequences. Genomiser takes as input a variant call format (VCF) file obtained from whole-genome sequencing, a list of human phenotype ontology (HPO) terms matching the clinical signs and symptoms observed in the individual under investigation, and optional user parameters. Focusing on small (<25 nucleotides) non-coding mutations, the authors report that Genomiser was able to identify the causative regulatory Mendelian mutation as the top candidate in 77% of simulated whole genomes.

ORIGINAL ARTICLE Smedley, D. *et al.* A whole-genome analysis framework for effective identification of pathogenic regulatory variants in Mendelian disease. *Am. J. Hum. Genet.* **3**, 595–606 (2016)

EVOLUTION

Mapping adaptive mutations in an evolving system

Researchers have used a lineage tracking method to characterize both the genetic basis and the fitness effects of hundreds of independent adaptive mutations in a laboratory evolution experiment of *Saccharomyces cerevisiae*. A previous study identified 25,000 lineages that gained an adaptive mutation within the first 168 generations of evolution. Now, the authors produced a comprehensive genotype-to-fitness map by isolating 4,800 colonies from the 88th generation — a point at which most adaptive lineages are likely to carry single adaptive mutations — and determining their barcodes. DNA barcode frequencies were monitored in pooled clones over the short term to measure the fitness of each clone. High-throughput genome sequencing of hundreds of known adaptive clones with varied fitness, as well as neutral clones, was performed to build a comprehensive genotype-to-fitness map of adaptation-driving mutations, highlighting two particular classes of adaptive mutations that drive early evolution.

ORIGINAL ARTICLE Venkataram, S. *et al.* Development of a comprehensive genotype-to-fitness map of adaptation-driving mutations in yeast. *Cell* http://dx.doi.org/10.1016/j.cell.2016.08.002 (2016)

DNA ELEMENTS

Sequence and shape help target the X chromosome

A newly discovered DNA motif determined by its sequence and shape, named PionX (pioneering sites on the X), allows the dosage compensation machinery in *Drosophila melanogaster* to distinguish X chromosomes from autosomes. In fruitflies, the male-specific lethal dosage compensation complex (MSL-DCC) doubles gene expression from the single male X chromosome. Using an *in vitro* DNA immunoprecipitation assay, Villa *et al.* showed that MSL-DCC recognizes the X chromosome at specific sites through one of its components, MSL2. Deletion of various protein domains revealed that MSL2 interacts with DNA through two domains. A subset of genomic regions required a functional CXC domain for binding, and these sites were enriched on the X chromosome. Sequence analyses comparing CXC-dependent and -independent binding sites for MSL2 yielded two distinct motifs. Further analyses confirmed that MSL2 relies on both DNA sequence and structure to identify its binding sites.

ORIGINAL ARTICLE Villa, R. *et al.* PionX sites mark the X chromosome for dosage compensation. *Nature* http://dx.doi.org/10.1038/nature19338 (2016)