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IN BRIEF

CANCER GENETICS

Oncohistone pathology explained

Researchers have elucidated the pathogenic mechanism underlying the histone H3 lysine-36-to-methionine (H3K36M) mutation, which is a frequent acquired mutation in children with chondroblastoma, a type of bone cancer. The H3K36M mutation disrupted the expression of genes involved in the differentiation of mesenchymal progenitor cells (MPCs) *in vitro*, and led to tumour formation after injection of mutated MPCs into severe combined immunodeficiency (SCID) mice. H3K36M mutations dominantly inhibited H3K36 methyltransferases, leading to H3K36 hypomethylation and subsequent H3K27 hypermethylation. Quantification by chromatin immunoprecipitation followed by sequencing (ChIP–seq) in H3K36M-mutant cells identified an intergenic gain of H3K27 trimethylation (H3K27me3). The shift in the ratio of gene-associated H3K27me3 to intergenic H3K27me3 led to the redistribution of Polycomb-repressive complex 1 (PRC1) and aberrant gene activation.

ORIGINAL ARTICLE Lu, C. *et al.* Histone H3K36 mutations promote sarcomagenesis through altered histone methylation landscape. *Science* **352**, 844–849 (2016)

GENETIC ENGINEERING

A new player in genome editing

The Argonaute endonuclease of the archaebacterium *Natronobacterium gregoryi* (NgAgo) is a precise and efficient tool for genome editing in mammalian cells. Using plasmid cleavage assays, Gao *et al.* found that — in contrast to the guide RNA (gRNA) needed by the Cas9 nuclease — NgAgo can cleave targets using single-stranded DNA of ~24 nucleotides in length as a guide. NgAgo was found to create site-specific DNA double-strand breaks in various mammalian cell lines with similar efficiency to the Cas9–gRNA system. Nucleotide mismatch at any position between the guide DNA (gDNA) and the target sequence substantially reduced target cleavage efficacy, and three consecutive mismatches abolished nuclease activity completely, suggesting high fidelity of the NgAgo–gDNA system. Correct insertion of donor DNA by homology-directed repair into a targeted genome locus was also achievable.

ORIGINAL ARTICLE Gao, F. *et al.* DNA-guided genome editing using the *Natronobacterium gregoryi* Argonaute. *Nat. Biotechnol.* http://dx.doi.org/10.1038/nbt.3547 (2016)

GENETIC VARIATION

Genetic associations with a social science outcome

Variants associated with educational attainment (the number of years of schooling completed by an individual, called EduYears) are identified in a new genome-wide association study (GWAS) of nearly 294,000 individuals of European descent. Okbay *et al.* identified 74 single-nucleotide polymorphisms (SNPs) — predominantly in areas associated with brain-specific gene expression — that explain 0.43% of the variation in educational attainment across sampled individuals. Analysis of data from 37 adult tissues assayed by the Genotype-Tissue Expression (GTEx) Project revealed that only the 13 GTEx tissues related to the central nervous system had significantly increased gene expression near EduYears-associated SNPs. Functional annotation on the basis of gene-set clusters suggested that many candidate genes from the GWAS-implicated loci are involved in fetal neural development. The authors caution against misinterpretation of their findings, as educational attainment is a complex phenomenon that is primarily determined by environmental factors.

ORIGINAL ARTICLE Okbay, A. *et al.* Genome-wide association study identifies 74 loci associated with educational attainment. *Nature* http://dx.doi.org/10.1038/nature17671 (2016)