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GENE REGULATION

# Characterizing monoallelic expression

> monoallelic expression is cell specific and dynamic during embryonic development

For many autosomal genes in diploid organisms, expression is almost exclusively from one allele (which is termed monoallelic expression). Unlike imprinting and heterozygous variants in regulatory sequences, which reproducibly favour expression from the same allele, random monoallelic expression results from a seemingly stochastic allele choice. New studies now characterize epigenetic features, and a dynamic form, of random monoallelic expression.

Nag *et al.* built on previous transcriptome analyses from their team that took advantage of expressed heterozygous single-nucleotide polymorphisms (SNPs) to distinguish between transcripts from each allele. Using microarray-based gene expression readout, these earlier studies revealed that a surprisingly large percentage (10–15%) of autosomal genes were randomly monoallelically expressed in clonal populations of human and mouse cells. In the latest study, they searched for underlying chromatin features of the genes that are known to be randomly monoallelically expressed in human lymphoblastoid cell lines using chromatin profiling data from the Encyclopedia of DNA Elements (ENCODE) project. They found that gene-body enrichment for histone H3 trimethylated at lysine 27 (H3K27me3) and H3K36me3 constitute a reliable signature of randomly monoallelically expressed genes, and high-throughput RNA sequencing (RNA-seq) further confirmed differential expression between the alleles at loci that displayed this signature. As expected for these modifications, the repressive mark H3K27me3 was associated with the silenced allele, whereas the activating mark H3K36me3 was associated with the expressed allele.

Further analyses showed that this chromatin signature is characteristic of randomly monoallelically expressed genes in multiple human cell types, even though different subsets of genes were monoallelically expressed. The authors thus proposed that the signature could be a universal indicator of randomly monoallelically expressed genes beyond the genes that can be directly interrogated through heterozygous SNPs. Overall, >20% of genes showed this chromatin signature of random monoallelic expression in at least one cell type; these genes were enriched for cell-type-specific and developmental genes, which indicates that monoallelic expression might have important roles in differentiation.

SNP-based analyses in bulk cell populations can only identify random monoallelic expression that is mitotically stable, as signals of transient random monoallelic expression from each allele will cancel each other out when averaged over the population. In a separate study, to capture both dynamic and stable monoallelic expression, Deng *et al.* carried out RNA-seq on single cells that were dissociated from pre-implantation mouse embryos of different developmental stages. The mouse strain used was a cross of two different inbred strains, which generates heterozygous SNPs for allele discrimination.

In their study, Deng *et al.* found that 12–24% of autosomal genes were randomly monoallelically expressed across the pre-implantation developmental stages studied. Interestingly, averaging the data across all cells of each embryo removed essentially all signals of monoallelic expression, which indicates that monoallelic expression is cell specific and dynamic during embryonic development, in contrast to the clonally stable form analysed by Nag *et al.* Furthermore, the patterns of monoallelic expression were consistent with a model in which the two alleles become active independently through transcriptional bursting. Finally, Deng *et al.* identified similarly widespread monoallelic expression in single-cell analyses of adult liver cells and fibroblasts, which further highlights the pervasiveness of monoallelic expression.

It will be interesting to fully decipher the mechanistic underpinnings of stable versus transient random monoallelic expression and to determine the biological implications, such as those for interpreting the expressivity of heterozygous disease-associated genetic variants.

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**ORIGINAL RESEARCH PAPERS** Nag, A. *et al.* Chromatin signature of widespread monoallelic expression. *Elife* **2**, e01256 (2013) | Deng, Q. *et al.* Single-cell RNA-seq reveals dynamic, random monoallelic gene expression in mammalian cells. *Science* **343**, 193–196 (2014)