Genes with clonal monoallelic expression contribute disproportionally to expression variation in humans

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Variable expressivity of genotypes is a major challenge in understanding genotype-phenotype relationship. We hypothesized that a significant yet unappreciated source of phenotypic variability is clonally-stable allelic silencing. A classic example of such epigenetic mechanism is X chromosome inactivation (XCI). More recently, a widespread epigenetic phenomenon that resembles XCI has been described for autosomal genes (Gimelbrant, Hutchinson, Thompson, & Chess, 2007). This phenomenon, autosomal "random" monoallelic expression (MAE), controls gene expression such that transcription occurs only or mostly from one of two homologous alleles in a diploid cell, while neighboring cells show different stable pattern of allelic expression. Similar to X chromosome inactivation, MAE leads to expression variability between otherwise identical cells in a clonal cell lineage, thus potentially driving phenotypic variability.

To compare expression variability between MAE genes and genes with biallelic expression (BAE), we used tissue specific genes classification by chromatin signature (co-occurrence of H3K27me3 silencing mark and H3K36me3 active mark on the gene body), and expression data (Nag et al., 2013). We predicted MAE or BAE status for several human tissues, including heart, lung and gut tissues. Next, we assessed variance in RNA abundance between MAE and BAE genes in hundreds of GTEx donors (GTEx Consortium, 2015). For each gene for a given tissue we assessed variability between GTEx samples. At all expression levels, MAE genes had more variable levels of expression compared to BAE genes. That means that MAE genes contribute disproportionally to expression variation in humans, potentially increasing phenotypic variability. Moreover, our observations might be generally useful in interpreting genetic variation in the context of human disease.

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