GENOMIC VARIATION

Copy number variation doesn't copy SNPs

Recent studies have characterized the extent of copy number variation in the human genome, but how important is its contribution to complex phenotypes? A new study shows that copy number variants (CNVs) have a smaller contribution to gene-expression phenotypes than SNPs do, but the CNV and SNP contributions are largely independent, so both types of variation need to be measured to completely understand the genetic basis of phenotypic variation.

Manolis Dermitzakis, Matthew Hurles and colleagues carried out an association analysis of gene expression in cell lines from the HapMap individuals with both SNPs and CNVs, focusing on the genomic regions around the expressed genes. Of the 14,072 genes for which expression levels were measured, they found association with a local SNP in between 323 genes (in Europeans) and 411 genes (in Africans). For CNVs, the numbers were lower — local CNVs were associated with the expression levels of between 44 genes (in Chinese) and 96 genes (in Africans). On the basis of these data and corrections for the proportion of total copy number variation observed in this study, the authors estimate that 8.75–17.7% of heritable variation in gene expression is due to copy number variation.

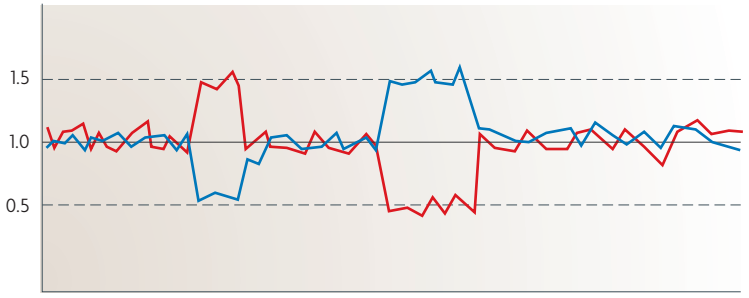
So what types of effect are the CNVs having? Altering gene dosage through deletion or duplication is the obvious possibility, but over half the CNVs were outside the probed region of the gene with whose expression they were associated. This implies that they are affecting gene structure or regulation rather than dosage. There were even a small minority of cases in which increased transcription was associated with reduced copy number, implying a complex relationship.

In principle, it might not be necessary to measure both types of variation when carrying out an association study. Just as some SNPs are representative of others through shared ancestry and therefore linkage disequilibrium, the SNP variation might overlap with and therefore represent the CNV variation. However, the authors found that fewer than 20% of their CNV associations had a corresponding SNP association.

This study shows the importance of copy number variation in complex phenotypes, and the need to measure it without relying on SNPs to represent it. However, only a fraction of copy number variation was measured — future work will look at larger and more distant variants. It will also be important to test associations with phenotypes other than gene expression.

Patrick Goymer

ORIGINAL RESEARCH PAPER Stranger, B. E. *et al.* Relative impact of nucleotide and copy number variation on gene expression phenotypes. *Science* **315**, 848–853 (2007)
FURTHER READING Feuk, L., Carson, A. R. & Scherer, S. W. Structural variation in the human genome. *Nature Rev. Genet.* **7**, 85–97 (2006) | Redon, R. *et al.* Global variation in copy number in the human genome. *Nature* **444**, 444–454 (2006)



IN BRIEF

EPIGENETICS

Dynamics of replication-independent histone turnover in budding yeast.

Dion, M. F. *et al.* Science **315**,1405–1408 (2007)

Histone replacement marks the boundaries of *cis*-regulatory domains.

Mito, Y., Henikoff, J. G. & Henikoff, S. Science **315**,1408–1411 (2007)

Characterizing the dynamics of chromatin remodelling is crucial to understand chromatin function. Two teams measured the levels of histone turnover, at high resolution, in budding yeast and fruitflies and found a huge variation in histone-replacement rate across the genomes of both organisms. Histone turnover is higher at promoters, rather than in coding regions, where it could transiently expose DNA *cis*-regulatory elements to other diffusible factors, providing the potential for a rapid and dynamic regulation. Rapid histone turnover was also found at chromatin boundaries, where it could serve to prevent the spreading of chromatin states and functionally delimit different domains.

TECHNOLOGY

Targeted gene addition into a specified location in the human genome using designed zinc finger nucleases.

Moehle, E. A. *et al. Proc. Natl Acad. Sci. USA* **104**, 3055–3060 (2007)

This study presents a new strategy for the insertion of ectopic DNA sequences in specific genomic locations. Engineered zinc finger nucleases (ZFNs) were used to induce DNA double-strand breaks (DSBs) at specific loci in human cells. The subsequent homology-directed repair of the DSBs was then allowed to occur in the presence of an extrachromosomal DNA donor, which carried the ectopic sequence of interest that was to be inserted flanked by two locus-specific homology arms. ZFNs guaranteed the site-specific integration of DNA fragments — of up to 8 kb — with high frequency, no need for selection and no increase in random integration.

CANCER GENETICS

A virus causes cancer by inducing massive chromosomal instability through cell fusion.

Duelli, D. M. *et al. Curr. Biol.* **17**, 431–437 (2007)

Chromosomal instability (CIN) is a hallmark of many human tumours, and tumours are often associated with viral infection. This work provides a new link between these two observations, showing that viruses can be tumorigenic by inducing cell fusion, which leads to CIN. The authors used the Mason–Pfizer monkey virus to fuse oncogene-expressing human fibroblasts, and showed through karyotype analyses that these hybrid cells were highly aneuploid, had many numerical and structural chromosomal aberrations and were tumorigenic in mice. As many viruses that infect human cells are fusogenic, preventing infection or cell fusion in infected individuals might help to reduce cancer incidence.