GENETIC VARIATION

When more is more

Much excitement has surrounded the finding of large amounts of structural variation in the human genome. But what contribution does this make to phenotypic variation? A recent study provides evidence that human copy number variants (CNVs) have had a role in the adaptation of humans to their surroundings.

Chris Ponting and colleagues looked at CNVs that were identified in previous studies and used a bioinformatics approach to compare features of CNVs with those of the genome as a whole. Among their findings, the authors showed that CNVs are enriched in genes, and that different gene types are present unevenly within them. Genes that are involved in Mendelian diseases are underrepresented, which could be explained if the extra gene copies provided by CNVs compensate for mutations that might otherwise lead to disease.

By contrast, CNVs are overrepresented in genes that function in innate and acquired immunity and olfaction, and those that encode integral membrane proteins. Interestingly, these classes of gene match those that are predicted to require the ability to evolve particularly rapidly, for example, in response to altered host–pathogen interactions. Consistent with this, the authors found that the genes that contain CNVs have accumulated an unusually large number of substitutions that affect protein sequence, indicating that they have been subject to positive selection. CNVs could contribute to the ability to adapt by providing increased gene dosage, and therefore an adaptive advantage.

The search for structural variants has only recently begun, but many more are likely to be found. The findings from this study indicate that studying these variants closely will be important in understanding how humans have adapted to new environments.

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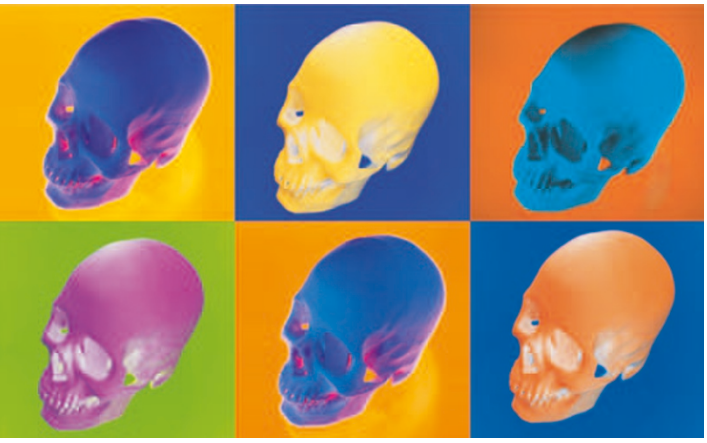
ORIGINAL RESEARCH PAPER Nguyen, D.-Q., Webber, C. & Ponting, C. P. Bias of selection on human copy-number variants. *PLoS Genet.* **2**, e20 (2006)
FURTHER READING Feuk, L., Carson, A. R. & Scherer, S. W. Structural variation in the human genome. *Nature Rev. Genet.* **7**, 85–97 (2006)



SYNTHETIC BIOLOGY

Building up a picture of gene regulation

Synthetic biologists have been making models of synthetic gene networks that describe the behaviour of these networks *in vivo*. Guido, Wang and colleagues now show that not only can such models quantitatively describe characteristics of gene expression but also they can be used to predict the *in vivo* behaviour of more complex systems.

The authors engineered the O_RO_{lac} promoter in *Escherichia coli* in a way that allowed them to study, in a controlled way, the effects of repression and/or activation on reporter gene expression. Four modules were constructed — unregulated, repressor-only, activator-only, and repressor and activator — in which the promoter was cloned upstream of a *GFP* ORF, and in which the activator and/or repressor were either present or absent.

A stochastic mathematical model that the authors developed correctly predicted the behaviour of the engineered modules, taking into account factors such as changes in the concentration of transcription factors and cell volume. Moreover, the model was able to make further predictions, for example, that a substantial amount of variability in gene expression in this system was due to fluctuations in the copy number of the plasmid — an expectation that the authors confirmed experimentally by re-cloning their engineered promoters into different plasmids. Strikingly, the model was also able to correctly predict the *in vivo* behaviour of a more complex system, in which a positive-feedback loop was added to the repressor–activator module.

When used to analyse how the different sources of noise contribute to the overall variability in expression, the model returned a surprising result — contrary to expectations, variability between cells seemed to

RNA WORLD

Behind the scenes

In the past decade there has been a surge of interest in microRNAs (miRNAs) — tiny, non-coding molecules of RNA. miRNAs have two functions: they base pair with partially complementary mRNAs to prevent the translation of mRNA into protein, and they reduce the cellular concentration of their mRNA targets. However, despite the significant insights into gene regulation that have been gleaned from the study of miRNAs, their modes of action have remained poorly understood. Two papers now highlight new biological functions and regulatory mechanisms of miRNAs.

Giraldez and colleagues set out to identify the *in vivo* targets of miRNAs, which are largely unknown. Using microarrays and *in vivo* target validation, the authors identified a large group of mRNAs that had a >85% probability of being direct targets of the miRNA miR-430. They estimated that, during early zebrafish development, there are, in fact, several hundred direct targets of miR-430 regulation. An analysis of the target set showed that most were expressed maternally, which indicated that miR-430 could have a crucial role in the maternal-to-zygotic transition in embryogenesis. Poly(A) tails stabilize mRNAs and enhance translation, and deadenylation can trigger translational silencing and mRNA decay. Giraldez *et al.* tested whether the decay of miRNA targets correlated with changes in the poly(A) tail length of mRNAs. They showed