EVOLUTION

Neanderthals help to tell our story

The availability of Neanderthal genomic sequence data is allowing us to date key events in our own evolution.

So far, only one gene has been convincingly associated with human language and speech — forkhead box P2 (*FOXP2*). Despite being a highly conserved gene, the human and chimapanzee versions differ at two positions in exon 7, and these substitutions have been implicated in our unique ability for speech.

Krause *et al.* found both substitutions in two Spanish Neanderthal samples. Further, they concluded that, for both substitutions, at least one of the individuals was homozygous for the derived allele that is predominant in modern populations.

Next, the authors analysed the Neanderthal samples for evidence of a selective sweep close to exon 7 of *FOXP2* that, from modern human genetic diversity data, was previously proposed to have occurred within the past 200,000 years. Seven polymorphic regions from the intronic region upstream of exon 7 were successfully amplified from the Neanderthal samples and, for six of these, all products from both Neanderthals represented the derived allele. These results suggest that the selective sweep in the *FOXP2* region began before the split from the human–Neanderthal common ancestor, which existed 300,000 to 400,000 years ago — much earlier than previously thought.

So, Neanderthal sequences can provide a useful tool to investigate our own evolution, making the extreme care that must be taken when retrieving genetic information from ancient samples worthwhile.

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ORIGINAL RESEARCH PAPER Krause, J. *et al.* The derived *FOXP2* variant of modern humans was shared with Neandertals. *Curr. Biol.* **17**, 1908–1912 (2006)

GENOMICS

Decoding the regulatory genome

A new computational tool can predict gene regulatory elements from diverse taxonomic groups and types of expression data.

Existing methods for predicting regulatory elements are limited to specific species or to particular types of element and expression data — this is because they rely on underlying assumptions about the relationship between elements and expression patterns. Elemento and colleagues developed a method — FIRE (Finding Informative Regulatory Elements) — that dispenses with such assumptions, instead directly quantifying the relationship between gene expression levels and potential regulatory motifs using information theory

The authors tested their approach on gene clusters derived from existing *Saccharomyces cerevisiae* microarray data, using FIRE to identify short sequence motifs that are highly informative about gene expression. FIRE predicted 17 DNA motifs from promoter regions and 6 RNA motifs from 3′ UTRs; 14 of these matched known yeast regulatory elements, indicating that the approach works well. Further validation came from conservation of the predicted motifs in a closely related yeast species, and from the fact that the target genes of a particular motif generally have related functions.

Unlike existing methods, large numbers of false positives are not a problem for FIRE: rates were found to be zero or close to zero across a range of genomes and data types — an important advantage, especially for application to larger genomes.

Elemento and colleagues applied and validated their method for different types of expression data from other species including fruitfly, worm, mouse and human. Their predictions included sequence motifs from the malaria parasite *Plasmodium falciparum*, which is inaccessible using other methods

> “…this versatile approach promises to be an important resource for studying the sequence determinants of gene regulation across diverse species.”

GENE THERAPY

Gene editors deliver

A major goal for gene therapy is to correct genetic defects in patient-derived stem cells, which could be put back into the patient to alleviate disease symptoms. However, the most widely used approach involves the genomic insertion of a transgene, which — owing to the non-specific nature of insertion — runs the risk of harmful side-effects. Advances using site-specific DNA-cutting enzymes are now showing promise for safer forms of gene therapy.

Zinc-finger nucleases (ZFNs) are engineered DNA editing enzymes that consist of a DNA binding zinc-finger domain and the nuclease domain of a restriction endonuclease. These enzymes produce double-stranded breaks, which can be targeted to a site of choice by altering the zinc-finger DNA binding specificity. ZFNs have been used previously to correct point mutations by inducing homologous recombination that brings about gene conversion from a donor DNA.

This approach avoids the insertion of new material into the genome. However, it requires the efficient delivery of three different constructs — two ZFNs (as the enzymes act as heterodimers) and the donor DNA — and current systems for delivery into clinically relevant target cells are highly inefficient. To overcome this problem, Lombardo and colleagues used an integrase-defective lentiviral vector (IDLV), which can infect most primary cells and deliver transgenes efficiently, but doesn't integrate into the host genome. For three human cell types, the authors showed that delivery of the necessary constructs using three IDLVs resulted in the desired gene editing outcome. For the different cell types, a variable but significant proportion of cells showed gene correction. In cases in which an endogenous gene was edited, there was normal expression of the gene product.