DNA chunks, chimps and humans

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Researchers have carried out the largest study of differences between human and chimpanzee genomes, identifying regions that have been duplicated or lost during evolution of the two lineages. The study, published in *Genome Research*, is the first to compare many human and chimpanzee genomes in the same fashion.

The team show that particular types of genes - such as those involved in the inflammatory response and in control of cell proliferation - are more commonly involved in gain or loss. They also provide new evidence for a gene that has been associated with susceptibility to infection by HIV.

"This is the first study of this scale, comparing directly the genomes of many humans and chimpanzees," says Dr Richard Redon, from the Wellcome Trust Sanger Institute, a leading author of the study. "By looking at only one 'reference' sequence for human or chimpanzee, as has been done previously, it is not possible to tell which differences occur only among individual chimpanzees or humans and which are differences between the two species.

"This is our first view of those two important legacies of evolution."

Rather than examining single-letter differences in the genomes (so-called SNPs), the researchers looked at copy number variation (CNV) - the gain or loss of regions of DNA. CNVs can affect many genes at once and their significance has only been fully appreciated within the last two years. The team looked at genomes of 30 chimpanzees and 30 humans: a direct comparison of this scale or type has not been carried out before.

The comparison uncovered CNVs that are present in both species as well as copy number differences (CNDs) between the two species. CNDs are likely to include genes that have influenced evolution of each species since humans and chimpanzees diverged some six million years ago.

"Broadly, the two genomes have similar patterns and levels of CNVs - around 70-80 in each individual - of which nearly half occur in the same regions of the two species' genomes," continues Dr Redon. "But beyond that similarity we were able to find intriguing evidence for key sets of genes that differ between us and our nearest relative."

One of the genes affected by CNVs is CCL3L1, for which lower copy numbers in humans have been associated with increased susceptibility to HIV infection. Remarkably, the study of 60 human and chimpanzee genomes found no evidence for fixed CNDs between human and chimp and no within-chimp CNV. Rather, they found that a nearby gene called TBC1D3 was reduced in number in chimpanzee compared to human: typically, there were eight copies in human, but apparently only one in all chimpanzees.

The authors suggest that it might be evolutionary selection of CNDs in TBC1D3 that have driven the population differences. Consistent with this novel observation, TBC1D3 is involved in cell proliferation (favoured category) and is on a core region for duplication - a focal point for large regions of duplication in human genome.

"It is evident that there has been striking turnover in gene content between humans and chimpanzees, and some of these changes may have resulted from exceptional selection pressures," explains Dr George Perry from Arizona State University and Brigham and Women's Hospital, another leading author of the study. "For example, a surprisingly high number of genes involved in the inflammatory response - APOL1, APOL4, CARD18, IL1F7, IL1F8 - are completely deleted from chimp

genome. In humans, APOL1 is involved in resistance to the parasite that causes sleeping sickness, while IL1F7 and CARD18 play a role in regulating inflammation: therefore, there must be different regulations of these processes in chimpanzees.

"We already know that inactivation of an immune system gene from the human genome is being positively selected: now we have an example of similar consequences in the chimpanzee."

CNVs in humans and chimpanzees often occur in equivalent genomic locations: most lie in regions of the genomes, called segmental duplications, that are particularly 'fragile'. However, one in four of the 355 CNDs that the team found do not overlap with CNVs within either species - suggesting that they are variants that are 'fixed' in each species and might mark significant differences between human and chimpanzee genomes.

DNA Samples and analysis

The project used DNA samples from 30 chimpanzees (29 from W Africa, one from E Africa): the chimpanzee reference was produced using DNA from Clint, the chimpanzee whose DNA was used for the genome sequence (www.nature.com/nature/journal/ … ull/nature04072.html).

Human DNA samples were obtained from following participants: ten Yoruba (Ibadan, Nigeria), ten Biaka rainforest hunter-gatherers (Central African Republic) and ten Mbuti rainforest hunter-gatherers (Democratic Republic of Congo). The human reference is a European-American male from the HapMap Project (NA10852).

CNVs and CNDs were detected using a whole-genome tilepath of DNA clones spanning the human genome used previously to map human

CNVs: this platform can reveal structural variants greater than around 10,000 base-pairs in size.

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