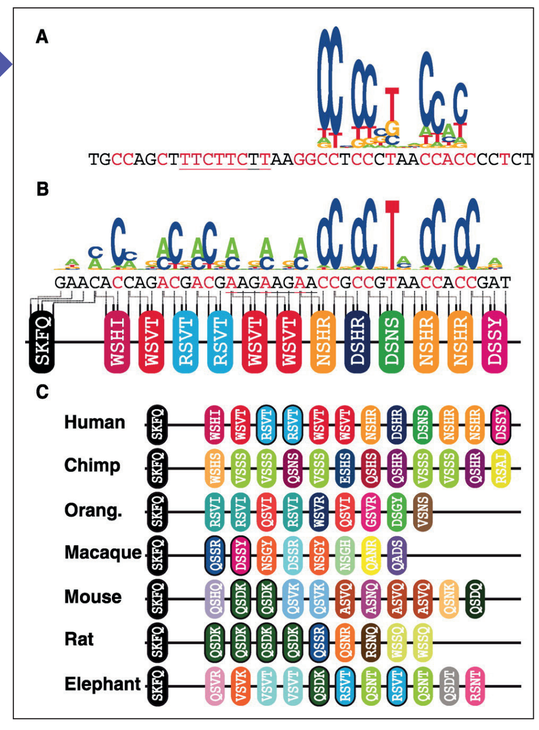
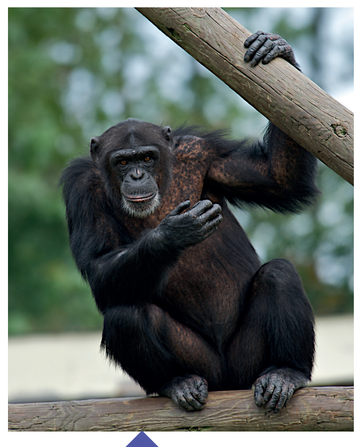
The Wellcome Trust Centre for
Human Genetics

UNIVERSITY OF OXFORD

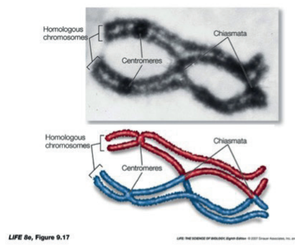
Discovery of key protein, PRDM9, responsible for localising recombination events



A) The degenerate 13-bp hotspot motif. (B) In silico prediction of the binding consensus for PRDM9*, aligned with the 13-nucleotide oligomer. Below the text is the sequence of four predicted DNA-contacting amino acids for the 13 successive human* PRDM9 *zinc fingers (one oval per finger, differing colors for differing fingers, and the separated finger is gapped N-terminal from others) and their predicted base contacts within the motif. (C) Sequence of four predicted DNA-contacting amino acids for the* PRDM9 *zinc fingers in seven mammalian species showing their rapid evolution between species*

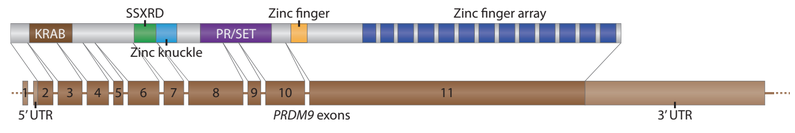


Recombination hotspots are different in humans and chimpanzees



Recombination events (chiasmata) linking homologous chromosomes during meiosis

The PRDM9 gene and protein domains



WHAT WAS KNOWN

- Recombination plays an essential role in meiosis in ensuring proper chromosomal segregation. Along with mutation, it is also responsible for generating genetic variation in natural populations
- Errors in the process result in aneuploidy, which is still the leading cause of pregnancy loss. In addition, deletions and duplications resulting from recombination-like events can cause a range of genomic disorders
- Crossover events typically cluster within narrow regions termed recombination hotspots
- Despite sharing nearly 99 per cent of their DNA sequences, chimpanzees and humans do not share recombination hotspots
- Relatively little is understood about the molecular mechanisms in meiosis, including recombination

WHAT WE DID

- We identified a degenerate 13-base pair DNA sequence motif associated with recombination hotspots in humans. Based on periodicity in sequence specificity around the motif we hypothesised that a zinc-finger binding protein would be responsible for localising recombination events. We used computational methods and evolutionary approaches to identify the specific protein, PRDM9, which binds to the hotspot sequence motif

WHAT THIS ADDS

- Identification of *PRDM9* explains the key first step in recombination: the positioning of the programmed DNA double-strand breaks which initiate meiotic recombination. It has provided a foothold from which to investigate other molecular aspects of this important process
- The zinc-finger array encoded by *PRDM9* is one of the fastest evolving parts of the genome. This rapid evolution explains why humans and chimpanzees, and indeed different humans, have completely different recombination hotspots: their distinct zinc-finger arrays mean that different *PRDM9* alleles bind to different DNA sequence motifs
- Although recombination hotspots, and hence crossover locations, differ completely between humans and chimpanzees, recombination rates over megabase scales are highly correlated, implying that there are other factors regulating recombination at these scales
- Because they are used as templates for repair, mutations which disrupt PRDM9 binding sites are preferentially passed on to offspring – a form of meiotic drive. Over time the best binding sites of a particular *PRDM9* allele will thus be lost. This effect leaves signatures in modern-day genomes
- Since Darwin, evolutionary biologists have been interested in identifying so-called speciation genes: the genes responsible for the reproductive barriers between species. Relatively few speciation genes have yet been identified across all species, with only one, *Prdm9*, known in mammals. In subsequent work we have tied together PRDM9's roles in recombination and hybrid sterility, and shown that it is also likely to have a role in meiosis downstream of localizing recombination events

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