second generation his descendants were engaged in technologies such as metallurgy and musical instrument production Genesis 4:21–22. Such technologies required a high level of intelligence. In certain fields and cultures, archaeology has shown there to have been a loss, not gain, in technology.[10] The science behind Egyptian eye make-up preparation and application, accords well with the biblical record of mankind's origins.

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1. Only one of these manuscripts is cited here; the pEbers. Regarding the age of the pEbers, there are some important pointers to the text's antiquity. Columns 103–110, which were written on the reverse, are in a different style of language compared to the rest of the papyrus. Whilst the handwriting is the same, different dialects are detectable. Although the writing style appears to be dated no earlier than 1600 BC by the Conventional Chronology, idiomatic usage indicates that the text belongs to an older period and some sections of pEbers can be traced back to the earliest Pharaonic dynasties.
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PRDM9: a link between meiotic ecombination hot spots and the origin of species

Jean K. Lightner

Creationists accept that changes occur within created kinds.[1] In fact, it has been pointed out that many times these changes can occur quite rapidly, surprising evolutionists who believe in only gradual changes over long periods of time.[2] However, the underlying causes for these changes, including those that can result in new species, have been unknown. Rapid changes may be either genetic or epigenetic.[3] Recent research suggests the gene PRDM9 is one factor that can be involved in rapid genetic changes.

What is PRDM9?

PR domain-containing 9 (PRDM9) is "a meiosis-specific histone H3 methyltransferase with a C-terminal tandem-repeat C2H2 zinc finger".[4] This means that PRDM9 is active during meiosis, or gamete formation. Histones are proteins associated with DNA that are important for proper packing and unpacking of DNA so it can be stored or used as needed. PRDM9 methylates a specific amino acid in histone H3 early in meiosis.[5] It plays an essential role in meiosis; mice lacking a functional *PRDM9* gene are sterile in both sexes due to severe impairment of the double-stranded break repair pathway and inadequate pairing of homologous and sex chromosomes.[6]

The zinc fingers at the end of this protein are predicted to bind DNA. A C2H2 zinc finger is a special structural motif where two cysteine (C) and two histidine (H) residues appear in an arrangement where they bind a zinc atom which helps to stabilize the structure (figure 1). One study in humans found that the number of zinc fingers varied from 8 to 18 in the over two dozen alleles examined.[4] It is this portion of the molecule that appears to play an important role in meiotic recombination by binding certain mini-satellite motifs in DNA.

Meiotic recombination hot spots

During meiosis, chromosomes pair up near the center of the cell, an event known as synapsis. During synapsis most, or all, chromosomes will undergo homologous recombination, or crossing over (figure 2). Portions of the matching chromosomes are swapped. This complex process begins with double-stranded breaks and, following a series of well-controlled protein-mediated steps, ends with the repair of those breaks. Important enzymes have been identified which are involved in the various steps.[7] Thus, crossing over is a complex, designed process that helps shuffle alleles between homologous chromosomes, allowing for greater genetic variation among the offspring.

Crossing over tends to occur most frequently at locations known as hot spots. Variation in PRDM9 appears to greatly influence hot spot activity. The previously mentioned study in humans shows that minor variation within the zinc finger domain can have profound effects. Alleles differing by a single amino acid can enhance hot spot activity, fail to activate hot spots, or even trigger the appearance of new hot spots.[4]

There was an interesting conundrum uncovered by this research. Some of the variants were not predicted to influence DNA binding, yet they had an impact on hot spot activity. Additionally, hot spot promoting alleles could activate hot spots that had no obvious corresponding binding motif. Uncovering further the details of PRDM9 activity in recombination should be a challenging and fascinating venture.

Unequal crossing over and genomic rearrangements

Hot spots are also associated with rearrangements. Unequal crossing over is one mechanism for changing

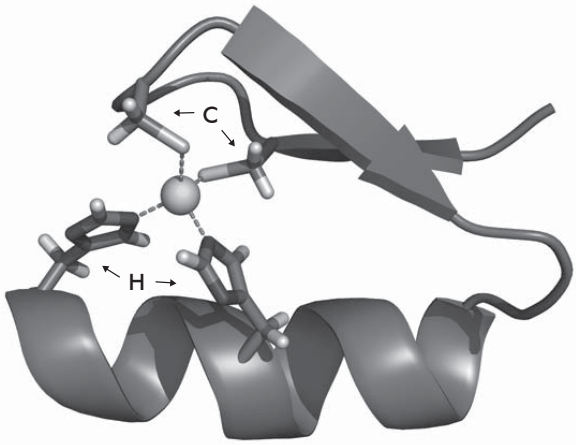

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Figure 1. Representation of the zinc-finger motif based on x-ray structure. The two cysteine (C) and two histidine (H) residues are shown bound to the zinc ion (ball).

the length of tandem repeats as well as duplicating (or deleting) a gene. Such copy number variants (CNVs) have been shown to be quite common, making them a major source of variation among humans. At times they appear to be adaptive;[8] others are known to be related to disease. However, the effect of most CNVs is unknown. The propensity for these and other rearrangements is known as genome instability.

The study also looked for a correlation between *PRDM9* variants and genome instability. Specifically, they evaluated sperm for unequal exchanges on a 1.5Mb region of chromosome 17 flanked on both sides by a particular repeat sequence. When unequal crossing over occurs, a deletion results in one disease (hereditary neuropathy with liability to pressure palsies) while a duplication results in another (Charcot-Marie-Tooth disease type 1A). These rearrangements were significantly less common in *PRDM9* variants associated with a decrease in hot spot activity. On the other hand, a common recurrent translocation between chromosomes 11 and 22 was not associated with *PRDM9* variation.[4]

Speciation

In addition to its critical role in meiosis and influence on the generation of genetic variability, *PRDM9* has been identified as a speciation gene in mice. Mating between two subspecies of the house mouse (*Mus musculus musculus* and *M. musculus domesticus*) results in infertile males. This follows Haldane's rule which states that if one sex of hybrid offspring is missing, rare, or infertile, it will be the heterogametic sex. This means that in mammals the males (XY) are more likely to be sterile, while in birds it is the females (WZ) which are preferentially affected.

Infertile hybrid males share many features in common with males lacking a functional *PRDM9* gene. They have small testes with spermatogenic arrest, mostly during the stage when crossing over would occur. There is evidence of impaired synapsis, particularly involving pairing of the sex chromosomes. A gonad specific gene known to be directly induced by PRDM9 had barely detectable mRNA transcripts. Tests revealed decrease methylation of H3 was associated with this lack of expression. These deficiencies in sterile hybrids were rescued by use of bacterial artificial chromosomes carrying the appropriate version of *PRDM9*.

There is an important difference between sterile hybrids and mice with no functional *PRDM9* gene. Hybrid sterility appears only in the male; *PRDM9* knockout animals are infertile in both sexes. The hybrid sterility appears to be from epistatic interactions between *PRDM9* and other important genes. This is consistent with a Dobzhansky–Muller incompatibility, where two lines have diverged in several interacting genes to the point where they are no longer compatible between the two groups.[9]

Designed to change?

There is considerable diversity in the *PRDM9* gene among humans as well as among species of mice (*Mus*). There are two types of variation that are readily apparent: variation in the number of zinc fingers (each coded by one of the tandem repeats), and variation in the DNA sequence of the zinc fingers. In each case, diversity in this gene has increased since the population bottleneck at the Flood.

For humans, a *maximum* of ten alleles could have been carried through the Flood (two each for Noah, his wife, and the sons' wives) unless the sons carried *de novo* mutations. Currently, dozens of alleles have been identified in humans. These alleles not only vary in the number of zinc fingers (8–18),[4] but are also enriched in non-synonymous nucleotide changes affecting the DNA-binding portion of the zinc fingers.[10] The latter phenomenon has been considered strong evidence for positive selection. It is believed the changes in DNA-binding codons of PRDM9 parallel changes in the DNA mini-satellite motifs to which PRDM9 binds.

Mice are unclean animals which would have carried a maximum of 4 alleles through the Flood. There are 5 alleles currently known in *Mus musculus*[11] and several additional alleles in related *Mus* species.[12] These

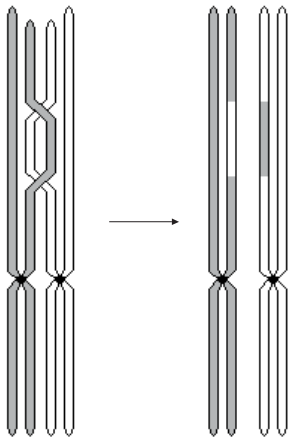

Figure 2. The crossing over of two homologous chromosomes during synapsis results in the swapping of chromosome portions.

vary between 8 (*Mus pahari*) and 14 (*Mus musculus*) zinc fingers. Another observation was that within species of rodents, there is a surprising similarity in the sequence of the zinc fingers. It is common for two or more of the zinc fingers to contain identical sequences, indicating these genes 'evolved' in the same direction. This is called 'concerted evolution'. Two known mechanisms are hypothesized to contribute to this phenomenon: rounds of duplication and deletion (possibly from unequal crossing over) and gene conversion.

It is possible that positive selection plays a role in the enrichment of non-synonymous nucleotide substitutions in the region of DNA-binding codons of PRDM9. In arriving at that conclusion, the researchers have assumed that the underlying mutations are essentially random, so this strong pattern must be the result of selection. However, within the creation model it is quite reasonable to question this assumption. In fact patterns of mutation have been identified which do not appear explicable by natural selection, suggesting there could easily be molecular mechanisms designed to bias the placement and/or type of mutations which occur.[13–15] If that is so, the diversification of PRDM9 may well indicate a designed phenomenon important in allowing for adaptation.

Conclusion

PRDM9 is an important protein essential for proper alignment of chromosomes during synapsis of meiosis. It also plays an important role in maintaining diversity through facilitating crossing over at various hotspots. It is somewhat ironic that it can influence unequal crossing over, which can vary the length of tandem repeats. PRDM9 itself carries tandem repeats, each corresponding to a zinc finger, which are variable within a species. Perhaps this variability is the result of unequal crossing over. Gene conversion may also play a role in maintaining the sequence identity of many of these repeats.

The changes that have appeared in *PRDM9* since the Flood are concentrated in the zinc finger region. This is the domain of the protein that determines which hot spots are used and the level of activity at these hot spots. Diversity at this location provides one mechanism for generating diversity throughout the genome and may contribute to some of the rapid genetic changes that have occurred within created kinds. Since the other domains of the protein appear to be related to proper synapsis, it is possible that positive selection contributed to the pattern of diversity seen in PRDM9 today. However, it is also possible that certain mechanisms within the genome may bias the placement of mutations. If the latter were the case, then directed mutation has played a role in the observed diversity of *PRDM9*.

Taken together, *PRDM9* diversity can contribute to variation in offspring and even lead to speciation events. Within the creation model, speciation may be more a side effect of the generation of diversity, rather than an intended goal of the Creator. Generation of diversity would allow for adaptation, enable creatures to reproduce and fill the earth as God intended.[16] Unfortunately, the other genes that are believed to be involved in epistatic interactions with PRDM9 have not been identified and characterized. This locus will be interesting for creation researchers to watch as more details are forthcoming.

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