This new study [14] allows us to think about a host of further questions. For example, are memories of the same events stored in a similar way by different people, at least to the degree to which the content of their memories are shared? For this, the patterns of brain activation do not need to be equal, but the amount of information stored in different structures and their relative contribution to memory-associated patterns might be similar, as was indeed found by Chadwick *et al.* [14]. Similarity in activation patterns can even carry quite specific information: response patterns in the data of a group of subjects can be used to differentiate cognitive tasks in a separate individual [15,16]. Combining within-subject and between-subject classifiers might thus make it possible to differentiate the response patterns representing aspects of memories that are shared across people from those that differ, getting at the neural correlates of inter-individual differences in memory content.

Progress in neuroimaging techniques is followed with interest by the public, as neuroscience methods have started to be used to address legal questions. The judge of a court in India directly referred to a forensic analysis of electroencephalography data in his written opinion of a murder trial, and similar brain data analysis methods have been admitted in legal proceedings in the USA (see [17] for a recent review). Commercial applications have started to spring up, such as assessing the attractiveness of products (Neuromarketing) or quantifying the effect that movies might have on people's perception (Neurocinema). Further extensions of the method are to be expected: if what has been achieved for vision (reading observed letters from early visual cortex activity [18]) becomes possible for memory, then maybe one day we could be able to read the contents of a person's memory.

It might be possible to change stored memories too: conditioned fear responses can be erased with purely behavioural methods [19]. Combining reading and modification of memories brings closer a host of science-fiction scenarios, as for example in novels such as "We can remember it for you wholesale" by Philip K. Dick (adapted into the movie "*Total Recall*") and countless other Hollywood movies, for example, *Eternal Sunshine of the Spotless Mind*, *The Manchurian Candidate* and *Vanilla Sky*.

All these applications and fictional scenarios are of course seen with very cautious reserve by scientists, and rightly so: To convince researchers, a scientific method needs only to yield results reaching statistical significance (that is, beat chance). When considering the application of a method in everyday life, however, one must consider the consequence of any deviation from perfect performance. Discussion of ethical, sociological and legal aspects of the application of multivariate analyses promise a number of interesting debates.

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Meiosis: A PRDM9 Guide to the Hotspots of Recombination

During meiosis, homologous recombination occurs preferentially at defined hotspots. In mammals, the fast-evolving DNA-binding domain of PRDM9 has now been identified as a major hotspot determinant that may explain the rapid rates of hotspot redistribution during evolution.

Andreas Hochwagen[1] and Gabriel A.B. Marais[2]

In most sexually reproducing organisms, the homologous chromosome pairs of germ cells recombine during meiosis. That is, DNA sequences from one homologous chromosome are joined to the corresponding sequences on the other homolog, and vice versa, to produce what is known as a crossover. Depending on the organism, between one and half

a dozen crossovers occur per pair of homologous chromosomes. Crossing over is of key importance for the assortment of chromosomes into sperm or egg cells because it allows homologous chromosomes to be properly aligned during metaphase of the first meiotic division. In addition, because recombinant chromosomes are chimeras of the two parental chromosomes, they often harbor new allele combinations. Crossover formation therefore provides a central source of genetic diversity — the raw material for natural selection — and is of vital importance for adaptation of sexually reproducing populations to their environment.

Interestingly, crossovers occur preferentially in small hotspot regions, often not larger than 1–2 kilobases, that are separated by large cold domains, in which crossovers are only rarely observed [1]. How this non-random distribution of hotspots is achieved has remained enigmatic. During meiotic prophase, chromosomes adopt a highly structured conformation with chromatin loops extending from a central protein axis, and a variety of studies indicate that the DNA breakage that precedes crossover formation initiates in these loops. In addition, specific chromatin marks, most notably trimethylation of histone H3 lysine 4 (H3K4me3), are enriched at recombination hotspots in several organisms and inactivation of the sole H3K4 trimethyltransferase in yeast severely reduces the levels of DNA breakage at many hotspots [2,3]. However, because not all sites enriched for H3K4 trimethylation act as meiotic hotspots, additional hotspot determinants must exist.

In a remarkable convergence of research efforts recently reported in *Science*, the zinc-finger protein PRDM9 has now been identified as one such determinant in mammals [4–6]. Using human recombination data, Simon Myers and colleagues had previously identified a degenerate 13-mer sequence motif characteristic of a zinc-finger binding site that was present in approximately 40% of human hotspots [7]. Computational analysis of all predicted zinc-finger DNA-binding proteins in the human genome now yielded PRDM9 as the most likely binding partner [4,5]. At the same time, the laboratories of Bernard de Massy and Kenneth Paigen analyzed differences in crossover distribution between laboratory mouse strains. In detailed mapping experiments, they found that the differences in hotspot usage could be explained by sequence differences in *Prdm9* [4,6]. Importantly, de Massy and colleagues then showed that the same correlation between *PRDM9* alleles and hotspot usage holds true in humans, providing convincing evidence that this gene is a central regulator of mammalian crossover distribution.

The domain structure of PRDM9 immediately suggests a possible function in hotspot specification. Zinc-finger DNA-binding domains are modular arrays of different zinc-finger motifs whose number and arrangement governs and is strongly predictive of the sequence specificity of the domain (Figure 1A,B). Consistent with PRDM9 being selectively targeted to certain genomic sequences, it exhibits specific binding to the human hotspot motif in biochemical assays [4]. In addition to a zinc-finger domain, PRDM9 also harbors a SET domain with H3K4 trimethyltransferase activity, suggesting that PRDM9 enables the targeted deployment of H3K4me3 chromatin marks.

The fact that H3K4me3 serves as a mark for DNA break induction in yeast raises the possibility that PRDM9 may function at a similarly early stage in the mammalian recombination process. Consistent with this hypothesis, *Prdm9* allele status in the mouse not only affects the distribution of crossovers but also alters the distribution of non-crossovers (products of recombination that do not result in a rejoining of homologs) [8]. The simplest explanation for this observation is that *Prdm9* alters the pattern of the meiotic DNA breaks, which underlie both crossovers and non-crossovers. Indeed, the distribution of break-associated histone marks is noticeably distinct for different *Prdm9* alleles [9]. Unexpectedly, however, loss of *Prdm9* does not lead to a major reduction in the overall break signal in mouse spermatocytes [10]. One possible explanation for this discrepancy is that only a subset of mouse hotspots is controlled by *Prdm9*. Alternatively, sites of Prdm9-independent H3K4me3 enrichment may substitute as hotspots in *Prdm9* knockout mice.

The identification of PRDM9 also provided important evolutionary insights [5,11,12]. A key feature of hotspots is their rapidly evolving distribution: closely related species such as humans and chimpanzees share very few hotspots [13,14]. Even the subset of homologous regions with a conserved motif in both species that show elevated recombination rates in humans have normal recombination rates in chimps [5]. Interestingly, sequence analysis of PRDM9 in various mammals shows extraordinary evolution: zinc-finger domain numbers and sequences vary a lot among species [11,12]. Even more striking is the very clear signature of positive selection found specifically at the amino acids that bind to the DNA molecule in PRDM9 zinc-finger domains. Such fast evolution could clearly explain why humans and chimps and possibly other mammals have different hotspots. Their PRDM9 proteins must bind to different motifs.

Another important finding is that the rate of 13-mer motif loss is significantly higher in humans compared to chimpanzees, although rates of motif gain are similar in both species [5]. This relates to another key aspect of meiotic recombination: the sequence that initiates the DNA breakage will be replaced by the corresponding sequence on the homologous chromosome due the mechanisms of recombination itself. Thus, if hot and cold alleles coexist in a population, the hot allele should disappear, which raises the problem of how hotspots are maintained in the genome, the so-called hotspot paradox. The observation that the 13-mer motif is disappearing from the human genome is fully consistent with the idea that this motif is promoting hotspots. If meiotic recombination is to be maintained at the same levels, once the hotspot-promoting motif has ‘run out’ in the genome, selection will favor a new motif. This can be done in two complementary ways: PRDM9 can change its binding sites and bind to a new motif, and this is again fully consistent with PRDM9’s

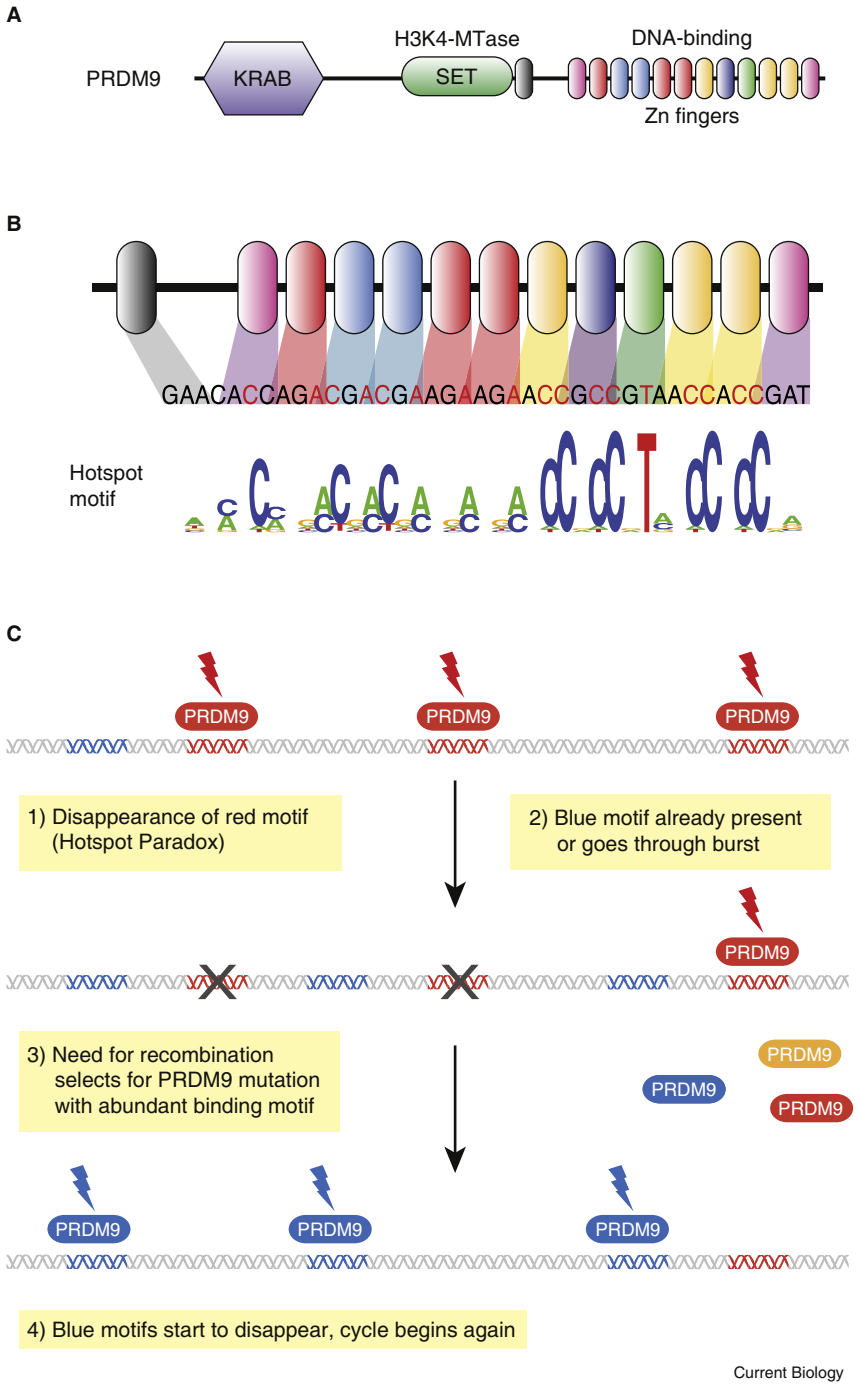

Figure 1. Function and evolution of PRDM9.

(A) Functional domains of PRDM9. The SET domain has H3K4 trimethyltransferase activity. KRAB is a domain of unknown function found in many zinc-finger DNA-binding proteins. (B) Alignment of the 13-mer hotspot motif in humans and the predicted PRDM9-binding motif. Bases in red are those aligning with the motif. Degeneracy in the hotspot motif is shown (adapted from [5]). (C) Co-evolution of motifs and PRDM9. Recurrent changes in the PRDM9/motif pair imply fast evolution of hotspot distribution as well as interspecies differences and possibly incompatibilities. (Figure courtesy of Tom DiCesare.)

extraordinary evolution, and new motifs can invade the genome, for instance through a burst of DNA repeats (Figure 1C).

Although these findings are a major breakthrough in meiotic recombination research, some important questions remain. Mice lacking *Prdm9* exhibit a strong meiotic arrest and persistent break signals [10]. This phenotype cannot be explained by a loss of break activity at hotspots, suggesting that *Prdm9* has a more intricate role in the control of meiotic crossover formation. Comparative data suggest *Prdm9* has been evolving the same way for a long time and may control hotspots in all mammals and possibly in other animal groups [11] but this remains to be investigated further. Indeed, some species, such as the dog, have lost functional *Prdm9*, which raises the question of how hotspots are distributed in this species [11]. Finally, *Prdm9* could also have a role in speciation since it is involved in hybrid sterility in mice [15] but the generality of this effect needs to be investigated.

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Mitochondrial Function: OMA1 and OPA1, the Grandmasters of Mitochondrial Health

Two new studies have identified a key protease responsible for sensing mitochondrial dysfunction, leading to the inactivation of the fusion GTPase OPA1. These studies have broad implications in mitochondrial quality control.

Heidi McBride and Vincent Soubannier

The regulation of mitochondrial fusion has recently emerged as a critical factor in the exclusion of respiration-incompetent organelles, suggesting that the balance of fission and fusion is central to mitochondrial quality control [1]. Fragments of mitochondria that cannot generate or maintain their electrochemical potential become fusion-incompetent and are degraded through autophagy [1]. Mechanistically, it has been shown that uncoupling the mitochondrial membrane potential ($\Delta\Psi$) leads to the cleavage of the GTPase OPA1, which is localised to the intermembrane space and is required for mitochondrial fusion [2–4]. This sounds rather simple, yet the story of OPA1 processing has been complicated, with many candidate proteases proposed to participate in this regulated OPA1 cleavage. Two recent studies published in the *Journal of Cell Biology* have resolved this issue by identifying a novel zinc metalloprotease called OMA1 as the essential $\Delta\Psi$-dependent protease for OPA1 [5,6].

OPA1 is alternatively spliced, giving rise to eight variants that are expressed in a variety of patterns depending on the tissue [7]. The different splice variants possess either one or two cleavage sites, called S1 and S2 [3,4]. Previous work has shown that OPA1 must be present in both long and short forms for fusion to proceed, with the balance of those forms being maintained by constitutive processing [8]. The S2 site is a substrate for the intermembrane space AAA (i-AAA) protease YME1L, and it is generally agreed that this protease cleaves OPA1 constitutively following mitochondrial import [3,4] (Figure 1A). Although there is some constitutive cleavage at the S1 site, which is common to all variants, this site is the primary target of regulated cleavage upon loss of $\Delta\Psi$ [3,4]. In this case, or under conditions of low mitochondrial ATP levels or the presence of apoptotic signals, all long forms become cleaved at site S1, thereby disrupting the balance of long and short forms, abolishing mitochondrial fusion. The field has been searching for a convincing protease that mediates this regulated cleavage. A number of studies have suggested that various proteases, including PARL, paraplegin, and the AFG3L1/AFG3L1 mAAA protease complex, may be partly responsible [8].

The uncertainty surrounding the protease that mediates regulated OPA1 cleavage has now been resolved with the new papers characterising the mammalian inner membrane protease OMA1. These two groups have independently discovered that the loss of OMA1 through silencing completely abolishes the regulated cleavage of OPA1 [5,6]. In this way, the two new publications make it clear that OMA1 acts as a primary determinant of fusion competence. Mechanistically, however, the two studies focus on different aspects of how OMA1 activity may be regulated, and in this respect many questions are raised.

OMA1 is a zinc metalloprotease that spans the inner mitochondrial membrane with a number of predicted membrane spanning domains [9]. It has been most well characterized in yeast where it has overlapping activity with the matrix AAA (m-AAA) proteases (hence the name OMA1) [9]. The human orthologue of OMA1 (called MPRP-1) was originally mistakenly localized to the endoplasmic reticulum, where it went unnoticed since 2003 [10]. The current studies clearly demonstrate an exclusively mitochondrial localization of OMA1 [5,6]. The mammalian orthologue described in these two new studies has evolved a long 170 amino acid extension at the amino terminus that may impact the topology in higher organisms [10]. It will be essential to establish the topology of this multispanning membrane protein biochemically, and to localize the catalytic site in order to better understand its regulation.

The role of the amino-terminal extension is highlighted in the study by Head *et al.* [5], where they show that the 60 kDa precursor form of OMA1 is cleaved upon mitochondrial import to a 40 kDa mature form by an as yet unidentified protease. Upon dissipation of $\Delta\Psi$, the 60 kDa form of OMA1 rapidly accumulated concomitantly with the cleavage of all OPA1 variants, prompting the authors to consider that the 40 kDa form of OMA1 may be the inactive form, with the 60 kDa form being the active enzyme. In this way, the ongoing import of newly synthesized OMA1 into the inner membrane upon collapse of $\Delta\Psi$ would facilitate active cleavage of OPA1 at the S1 site. Although it is possible to generate mutants or chimeras of model proteins whose import into the inner membrane may become less sensitive to dissipation of $\Delta\Psi$, there are currently no known