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Variation in Patterns of Human Meiotic Recombination

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Abstract

In the last 30 years it has become evident that patterns of meiotic recombination can be highly variable among individuals. The evidence comes from both low and high resolution analyses of hotspots of recombination in human and other species. In addition, a comparison of the recombination profiles in closely related species such as human and chimpanzee reveals essentially no correlation in the position of hotspots. Although the variation in hotspots of meiotic recombination is clearly documented, the mechanisms responsible for such variation are far from being understood. Here we will review the available evidence of natural variation in meiotic recombination and will discuss potential implications of this variation on the functional mechanisms of crossover formation and control.

Meiosis is a key process in sexual reproduction and meiotic recombination is an intrinsic part of meiosis in most organisms. In mammals recombination intermediates provide a structural basis for the accurate segregation of chromosomes and meiotic recombination is necessary for completion of meiosis. A serious consequence of defects in meiotic recombination is aneuploidy. An important evolutionary consequence of meiotic recombination is the generation of genetic diversity.

A widely established paradigm of the initiation of meiotic recombination is the double-strand break (DSB) initiation model [1]. This model postulates that programmed DSBs introduced in the leptotene stage of the first meiotic division are used to initiate genetic recombination in all organisms including mammals [1–3]. These DSBs are then processed by a variety of meiosis-specific and non-specific proteins and result in the formation of crossover and non-crossover products. Although the molecular basis of crossover formation is being increasingly unraveled, the mechanisms of the regulation of meiotic recombination remain largely unknown. It is clear, however, that meiotic recombination is a highly non-random process. In most organisms that have been carefully examined meiotic DSBs are tightly clustered in hotspots instead of being uniformly distributed [4–7]. The hotspots of recombination themselves are also distributed non-randomly in the genome. The difference between the recombination rates inside hotspots and in surrounding ‘cold’ regions exceeds several thousand-fold. This preferential localization of meiotic crossovers to small regions of the genome strongly indicates that the site selection of programmed DSBs in meiosis is tightly regulated. Many genomic features are correlated with hotspots, but the correlations are weak and generally become weaker at higher resolution [4, 6–9]. Many, but not all, of the observed correlations are associated with a higher GC content. Thus, our ability to predict hotspots is still poor and the rules defining where hotspots are located in the genome remain mysterious.

Studies of meiotic recombination in humans are difficult. The large size of the genome and the relatively low frequency of human meiotic recombination (~1 cM/Mb) compared to budding yeast (~300 cM/Mb), for example, makes direct studies of recombination intermediates impossible using conventional molecular biology methods, such as gel electrophoresis. Thus the experimental techniques that are suitable for the analysis of meiotic recombination in mammals target identification and quantification of final recombination products, recombinant chromosomes. Although it is possible to detect all meiotic crossovers on a genome-wide scale, such studies have been limited to lower than 1 Mb resolution. Presently, the measurement of crossover frequency at high resolution is only possible on a limited scale. Thus, there is a potential problem between the small size of the hotspots that are believed to be the minimal functional unit of recombination and the inability to perform comprehensive analyses at high resolution. This makes a genome-wide analysis of mammalian meiotic hotspots rather challenging.

Accumulating evidence indicates that there are differences in meiotic recombination profiles between individuals and populations [see 10–12 for reviews]. Such differences are observed both at low resolution and at the level of individual hotspots. In this review we use ‘low resolution’ as the designation for the analyses that cannot resolve individual hotspots and ‘high resolution’ as the designation for the techniques that can separate individual hotspots or at least approach such resolution. For the human genome the boundary between high and low resolutions corresponds to around 100–200 kb. Here we will review and summarize the available evidence for the variation in hotspots of meiotic recombination in mammals with an emphasis on high resolution data. Male meiosis is very different from female meiosis. For example, the total number of crossovers in female meiosis is more than 50% higher than in male meiosis and while female crossovers are more frequent in centromeric regions of chromosomes, male crossovers are more common near telomeres [10]. These differences suggest a substantial divergence in the global regulation of meiotic recombination between sexes. Thus, we find it inappropriate to consider sex-specific differences in patterns of meiotic recombination as polymorphisms and do not discuss such sex variation in this review. Interested readers are referred to the excellent review by Audrey Lynn et al. [10].

Evidence of Variation at Low Resolution

There are two major approaches used to analyze meiotic recombination at low resolution: direct visualization of recombination intermediates and analysis of genetic linkage maps. The inter-individual variation in meiotic recombination frequency in humans was first noticed by direct observation of chiasma (see [13] for overview and analysis of a number of early works). Later studies confirmed and advanced earlier findings [14]. The development of immunochemical techniques for visualization of proteins associated with crossovers significantly facilitated the analysis [see 10 for review]. In these assays for the detection of crossovers antibodies against the MLH1 protein are used most frequently, but not exclusively. These studies clearly prove that the total number of recombination foci varies significantly among individuals both in male [15–17] and female [18, 19] meiosis [for a detailed review see 10]. The observed numbers have been reported to be from 43 to 56 crossovers per cell and 50 to 95 crossovers per cell for male and female meioses, respectively. In addition, at least a three-fold variation in the numbers of crossovers [16, 19] was reported for cells isolated from the same individual.

An alternative to direct observation of crossovers using cytological methods is the comparison of genomic sequences of chromosomes that completed meiosis with those of parental chromosomes. Determination of genotypes at polymorphic markers allows mapping crossover position with a resolution that depends mostly on marker density. The analysis of the recombination frequency between polymorphic markers captured as a genetic distance in

linkage maps provides a sex-specific, population-averaged measure of meiotic recombination. Similarly to cytological methods, genetic maps constructed using short tandem repeats (STR)-based genotyping approaches show that recombination rate varies among individuals [20–23].

In addition to the inter-individual variation in recombination frequency or total map length, linkage maps provide some evidence of recombination rate variation in specific regions of the genome [24, 25; for a review see 10], although some of these findings have not been confirmed [26]. We must say however that classic linkage maps may not be very well suited for the regional comparison of recombination rates between populations. Potential problems include the effects of errors in genotype definition, suppression of recombination due to the presence of polymorphic inversions and the incorrect ordering of markers [see 24 for discussion]. A recent application of classic linkage analysis combined with application of a novel statistical approach proved the existence of extensive variation in meiotic recombination [27]. Cheung and coauthors performed a comprehensive analysis of 38 CEPH (Centre d'Etude du Polymorphisme Humain or Center for the Study of Human Polymorphisms, an international genetic research center where a collection of immortalized cell cultures from large reference families has been created) families and identified 17,461 genetic crossovers at roughly 0.5 MB resolution in 34 mothers and 33 fathers [27]. They found a highly significant variation of recombination rate among individuals in both males (range 16.9–28.9 recombination events per meiosis) and females (range 27.5–46.4 recombination events per meiosis) and strong evidence of positional variation in individual recombination rate profiles at 5 Mb resolution [27]. Similar findings were reported for high-resolution pedigree-based linkage analysis of a part of chromosome 22 [28].

An extension of linkage analysis particularly well suited for studies of recombination is called single sperm genotyping. In this case, genotypes are determined not in multi-generation nuclear families, but rather from multiple sperm cells from the same individual. A comparison of obtained genotypes allows determining the proportion of recombinant molecules and thus the frequency of recombination at a given locus. There are two major modifications of the method. In one, single sperm cells are first separated and then genotypes are determined for the region of interest for each of the individual cells [29]. In the other, potentially more sensitive approach, the fraction of recombinant molecules is calculated in small pools of sperm cells (for reviews on sperm genotyping see [4, 29, 30]). Although lately sperm genotyping is mostly used for high resolution analysis, the modifications of sperm genotyping where individual cells are analyzed separately can be efficiently applied to analyze regions of arbitrary size. Single-sperm genotyping applied to megabase-scaled loci found significant variation in position-specific recombination rates among individuals [10, 31, 32].

Thus, we can see that even at the relatively low resolution provided by cytogenetic and genetic mapping, variation in meiotic recombination can be clearly detected. One however should be cautious in interpreting these results. The analysis at low resolution provides an average of recombinational activity of tens to perhaps hundreds of individual hotspots. In addition, the use of classic linkage maps is associated with the potential artifacts mentioned above.

Evidence of Variation at High Resolution – Computational Approaches

A significant weakness of the analyses performed at low resolution is the inability to study recombination on a level of the individual functional units, meiotic hotspots. In contrast, high resolution analysis has the power to assess the functional activity of individual hotspots. Two approaches are frequently used to define profiles of recombination at high

resolution. The first approach is the reconstruction of high resolution recombination rate profiles from genetic variation data. The second approach, mentioned above, is sperm genotyping.

The first approach uses the genetic variation found in populations to estimate recombination rates. What is now seen as single nucleotide polymorphisms (SNP, the most frequent kind of sequence polymorphism) was at some time in the past a rare mutation in an ancestral chromosomal context. These ancient chromosomes have been mixed in thousands of generations to produce present-day chromosomes, but the historic association of SNPs is still detectable. These patterns of non-random association of genetic markers, called linkage disequilibrium (LD), are shaped by past recombination events [33]. Computer modeling allows reconstructing the population history backwards in time and estimating the likelihood of a given recombination frequency between pairs of polymorphic markers. An ever increasing number of methods have been developed for the estimation of recombination rates from population variability data, the most accurate of which are based on coalescent reconstruction [for review see 34, 35]. One potential drawback with many of these methods, in particular those that are more accurate in estimating rates, is the extreme computational demands. Full coalescent reconstruction is absolutely prohibitive from a computational point of view. Several approximations to the calculation of full-likelihood have been introduced (two programs, LDhat [36] and Phase [37–39], are most popular, and see [34, 35] for discussion). Although these approximate methods are still computationally-intensive, rapidly increasing performance of modern computers makes it possible to perform such calculations even on a genome-wide scale and such methods have been applied successfully to calculate high resolution recombination rate maps of the human genome [8, 36]. The advantages of computational methods are speed, throughput and cost-effectiveness. It is relatively easy to collect DNA samples from 30–50 individuals and determine their genotypes using modern genotyping techniques. These genotype data can then be used to calculate recombination rate profiles.

The variation between population-specific recombination rate profiles has been documented in several studies [8, 40–45]. The variation in calculated profiles of recombination was first comprehensively studied by Clark and coauthors [40]. They found evidence of population heterogeneity at ~100-kb resolution in many of the 538 SNP clusters studied [32]. Later studies were performed at higher resolution allowing analysis of individual hotspots. For example, by performing a computational analysis of 74 genes resequenced in 47 individuals as a part of the SeattleSNP program (<http://pga.gs.washington.edu/>), Crawford et al. found evidence of hotspots in 35 genes and in 16 of these 35 genes (45%) a hotspot was found only in one population [42]. A more sensitive recent analysis of a slightly larger set of SeattleSNP genes again found that 35% (43 out of 121) of all hotspots were detected only in one population out of two [43]. What has been missing from studies performed so far is an accurate unbiased estimate of the statistical significance of the observed differences on a genome-wide scale.

An interesting application of the LD-based computational methods is the comparison of profiles of recombination in closely related species [46–49]. In these studies the authors have reconstructed recombination rate profiles in the orthologous regions of the genome in human and chimpanzee based on population surveys of genetic variation. Despite a 98.7% identity in DNA sequence, there is no correlation in the positions of hotspots in up to 14 Mb of sequence [46–48]. Thus, hotspots of meiotic recombination have completely changed their positions in the ~7 MYR since the split between the human and chimpanzee lineages. At the same time, in an apparent contradiction to previous findings a recent study has shown that hotspots are found in the same location in paralogous genomic loci with an age of

duplication preceding the human-chimpanzee split [50]. It is unclear, however, how general is such a conservation in hotspot position.

An intrinsic problem associated with the computational methods discussed is the fact that they are based on calculating population-averaged recombination rates from a sample of individuals. Thus, measuring the individual-specific recombination activity is impossible in principle. Another caveat is the fact that the inaccuracy in defining recombination rates from sequence variation data using coalescence-based approaches is rather high [8, 36, 51]. Thus, it is likely that many or even the majority of the observed differences between population-specific recombination rates do not reflect true biological variation. In addition, the definition of confidence intervals of recombination rate estimates with respect to true biological rates is not trivial [36, 51]. Another potential problem is that the majority of coalescent-based methods are based on a very simple model of DNA recombination that assumes that hotspots are completely conserved in a population. We now believe that this is an oversimplification and there is a great deal of variation in hotspot strengths among individuals. Recently introduced methods try to address this issue of the possible variability in hotspots and incorporate the heterogeneity explicitly in the likelihood calculations [52, 53], however, this is still an area of active development. The development of more realistic recombination rate models that incorporate hotspots explicitly, as such [54] will also improve the quality of predictions and the power of analysis.

Evidence of Variation at High Resolution – Experimental Approaches

A dominant experimental technique used to analyze meiotic recombination products at high-resolution is single-sperm genotyping [for review see 4, 29, 30]. It allows the direct measurement of recombination frequency at a given location by calculating the proportion of recombinant molecules in a sample of DNA purified from spermatozoa or oocytes. There are two major variants of the method. Proposed by the group of Norman Arnheim in late 1980s [55, 56] the first variant of the method is based on the determination of the genotypes of individual cells. In one of the most comprehensive efforts in single sperm genotyping, 20,031 cells were genotyped across the 3.3 Mb major histocompatibility complex (MHC) region on chromosome 6 and the authors found strong evidence of variation in recombination rates among 12 donors at a resolution approaching single hotspots [21].

An intrinsic problem associated with the testing of individual cells one by one is the lack of sensitivity in measuring recombination rates. The number of the cells that are assayed roughly determines the frequency of crossovers that can be detected. Typical hotspots recombine in less than 1 cell per thousand [4]. Thus, to somewhat reliably measure the activity of these hotspots at least several thousand cells must be analyzed. This intrinsic problem led to the development of pooled DNA sperm genotyping [57] which became the ultimate standard in high-resolution studies of meiotic recombination in mammals [for review see 4, 29, 30]. This method is based on the application of allele-specific PCR to determine the proportion of recombinant molecules out of all sperm DNA molecules. This modification achieves a superior sensitivity where even the weakest hotspots can be assayed but the drawback is the smaller region that can be analyzed in a single assay. The limit is imposed by the size of the PCR product.

An exceptionally high degree of polymorphism has been observed in male-specific profiles of recombination at the level of individual hotspots by pooled-sperm genotyping [58–63]; and for review see [11]. 6 out of 16 hotspots identified by high resolution sperm genotyping in the MHC2 region on chromosome 6 and in the MS32 locus on chromosome 1 by the group of Alec Jeffreys were found to be polymorphic [58–62]. In addition, a recent analysis of a 103-kb region on chromosome 21 identified 3 hotspots and 2 of them were polymorphic

[63]. In total, the recombinational activity of 8 of 19 hotspots of recombination studied in detail is polymorphic. Thus, polymorphic activity of meiotic hotspots in human appears to be the rule rather than the exception.

Some interesting facts are emerging from a comparison of the computational reconstruction of recombination profiles and experimental data. Although, overall coalescent reconstruction is rather accurate and correlates well with experiments, there are exceptions. For example, using sperm genotyping hotspots have been detected in regions where no hotspots were predicted computationally [59]. The opposite situation has also been seen: A hotspot predicted by computational methods has not been detected in some men [64]. These observations can be explained by polymorphic variation in hotspots or their rapid evolution.

The main disadvantage of sperm genotyping is the relative complexity of the method and the inability to analyze larger genomic regions. At present, the longest region that has been studied at a time is 103 kb [63]. That leads to the most significant drawback of high-resolution studies, which is genome coverage. While several comprehensive genome-wide studies have been performed to date at low resolution, high resolution analyses (sub 100 kb) cover less than 1% of the genome. Studies performed at the level of individual hotspots cover less than 1 Mb in total. Considering the high regional variation in rates of recombination one should be careful in trying to generalize the limited data available to date. Thus, the extent of genome-wide variation of high-resolution recombination profiles is still not known. However, we still think that all the evidence suggests that the inter-individual differences in profiles of recombination are high. A potential for further development of sperm genotyping techniques lies in the application of high performance next-generation sequencing and genotyping technologies to single cell analysis.

Implications on the Mechanisms of Recombination

What kind of insights on recombination mechanisms can we gain from studies of the variability of recombination rate profiles? First of all, a model for crossover formation in humans must be able to explain the high degree of inter-individual variation in recombination profiles. There is a high degree of polymorphism in hotspots of recombination detected both by computational and experimental methods. The comparison of position of hotspots in human and chimpanzee also suggest that they evolve at a much higher rate than DNA sequence. In addition, the model must accommodate that while fine-scale recombination rates are highly variable, they are relatively conserved at low resolution [26, 64].

Although the influence of short DNA motifs on hotspots of recombination is unquestionable [6–9], it would be difficult to reconcile this degree of variation if the recombination is determined solely by the local DNA sequence. The more likely explanation is the involvement of epigenetic factors, nuclear architecture and/or distant DNA elements in the control of recombination [46, 47]. In such case one can easily imagine two layers of regulation where first the recombination is regulated at the level of chromosome domains and then at a finer scale where individual hotspots are chosen.

Independent evidence for a non-local mechanism determining recombination activity comes from an examination of the ‘recombination hotspot paradox’ [65] which consists in the contradiction between the relative persistence of hotspots and a strong pressure on intense hotspots to self-destruct due to the deletion of the allele that initiates DSB formation at the hotspot. A detailed population-genetic analysis does not provide a satisfactory explanation for the persistence of hotspots if they are determined solely by the local DNA sequence [52, 53, 66]. The presence of strong hotspots in humans is proven experimentally, however. This

contradiction again suggests that the strength of a hotspot is determined by non-local elements that would not be affected by gene conversion.

In yeast the importance of chromatin structure in determining the positions of meiotic DSBs is clearly established. A number of detailed studies of the regulation of meiotic DSB formation in yeast provide compelling evidence for the complex interplay and essential involvement of chromatin structure in hotspot formation [7, 67–70]. A recent study, for example, demonstrated that the loss of histone deacetylase dramatically changes the distribution of meiotic DSBs [71].

Strong evidence for the epigenetic control of recombination in human comes from two recent articles where male recombination profiles were studied using sperm genotyping [58, 63]. In the first work Neumann and Jeffreys found that the activity of hotspots is not determined by local sequence. Some men sharing the same haplotype have an active hotspot while it is suppressed in others [58]. In the study by the group of Arnheim and colleagues, the authors found that the decrease of the activity in one hotspot, as seen in yeast [68, 69], is compensated by an increase in one nearby [63]. This observation supports the idea that there is a regional control of recombination. An essential involvement of non-local elements in control of meiotic recombination was also seen in mouse [72]. Thus, we see that there is considerable evidence in support of the epigenetic control of meiotic recombination in mammals.

Conclusions

In summary, the combined evidence shows that there is a high degree of inter-individual variation in hotspots of meiotic recombination in humans, but the mechanisms responsible for this variation are mostly unknown. Further studies and comprehensive high-resolution analysis on a genome-wide scale in particular will allow us to more accurately quantify the variation in hotspots of meiotic recombination among individuals. However, it seems likely recombination may be one of the most variable biological processes. It would be very interesting to untangle the regulatory mechanisms responsible for such variation from the conservation of low-resolution recombination profiles and explain how this highly variable process can operate under the multiple constraints characteristic to meiosis.

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