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Recombination hotspots: Models and tools for detection

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ABSTRACT

Recombination hotspots are the regions within the genome where the rate, and the frequency of recombination are optimum with a size varying from 1 to 2 kb. The recombination event is mediated by the double-stranded break formation, guided by the combined enzymatic action of DNA *topoisomerase* and *Spo 11 endonuclease*. These regions are distributed non-uniformly throughout the human genome and cause distortions in the genetic map. Numerous lines of evidence suggest that the number of hotspots known in humans has increased manifold in recent years. A few facts about the hotspot evolutions were also put forward, indicating the differences in the hotspot position between chimpanzees and humans. In mice, recombination hot spots were found to be clustered within the major histocompatibility complex (MHC) region. Several models, that help explain meiotic recombination has been proposed. Moreover, scientists also developed some computational tools to locate the hotspot position and estimate their recombination rate in humans is of great interest to population and medical geneticists. Here we reviewed the molecular mechanisms, models and in silico prediction techniques of hot spot residues.

Contents

1. Introduction

Genetic variation is a certainty that a biological system – individual and population – is distinctive over space. It is the base of the hereditary variability of the diverse natural system in space. Hereditary variation is taking into account the variety in alleles of qualities in a quality pool. It occurs both within and among populations, upheld by individual bearers of the variation qualities. Hereditary variation is achieved by random mutation, which is a permanent change to the chemical structure of a gene. The process of recombination between chromosomes is one of the

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most paramount ways that mutation and genetic novelties are created. Meiotic recombination is vital for cell division and is a key process that produces hereditary differences. It furnishes little-girl cells with allelic arrangements that vary from those of their guardians. During the formation of egg and sperm cells, otherwise called meiosis, paired chromosomes from each parent align so that homologous DNA sequences from the paired chromosomes traverse each other. Traversing results in a rearrangment of hereditary material and is an essential process for the hereditary variation seen among posterity.

Homologous recombination defines the process of exchange of DNA fragments between non-sister chromatids of homologous chromosomes mediated by cleavage and ligation of DNA segments, guided by enzymes [1]. The phenomenon takes place in the prophase I of meiosis I, involving crossover between DNA segments by the formation of double strand breaks (DSBs), influenced by the DNA topoisomerase-II associated Spo11 protein endonuclease activity [2–4].

Recently, by applying genome-wide chromatin immunoprecipitation (ChIP) analyses followed by deep sequencing, Ito et al. (2014) [5] compared the genome-wide distribution of the axis protein Rec8 (the kleisin subunit of meiotic cohesin) with that of oligomeric DNA covalently bound to Spo11, indicative of double-strand break (DSB) sites. The frequency of DSB sites is overall constant between Rec8 binding sites. However, DSB cold spots are observed in regions spanning +/−0.8 kb around Rec8 binding sites. In addition, H3K4 trimethylation (H3K4me3) remarkably decreases at Rec8 binding sites. These results suggest that reduced histone H3K4me3 in combination with inactivation of Spo11 activity on the axis discourages DSB hotspot formation.

Scientists opine that, most of the recombinations in humans remain confined within short regions of range 1–2 kb termed as recombination hotspots [6,7] and it is in these regions that the frequency, and the rate of recombination aremost favorable. Meiotic crossovers causing recombination are due to the nonuniform distribution of DSBs that cause recombination initiation [3]. The optimal rate of recombination within the hotspot are hundred to thousand of times more relative to the adjacent region [7,8]. The zinc-finger protein PRDM9 is believed to be the root cause of hotspot generation in mammals, including humans [9]. Furthermore, recent studies reveal that hotspots mark a ubiquitous feature in case of mammalian genome [7,10,11]. The nature and extent of recombination rate can therefore be studied by a high-resolution genetic map [6]. The region involving moderate hotspots, is found to have the average recombination of 0.075 cM (involving 1 cross-over per 1300 meioses), whereas the extreme hotspot region possesses a map length of 0.9–1 cM (or one cross-over event per 110 meioses) [6,12]. Reports on the heritability of human recombination hotspots were obtained from several recent studies [13]. However, variation in recombination rate was also reported to be based on variation in the density and intensity of hotspots, across the genome [14,15]. According to other reports, some motifs exist in the hotspots that repeat DNA sequences in humans [12]. Recombination hotspots are the regions for initiation and resolution of crossover as well as gene conversion events [16]. Increased frequency of gene conversion on either side of the DSB, as analysed from the three human hotspots, *i.e.*, DNA3, DMB2 and SHOX indicated the presence of shorter conversion tracts in both directions from the DSB site [3,16,17]. On the other hand, three commonly found hotspots in humans, namely NID1, MS32 and MSTM2 show significant variation in their recombination rates in men than in women. Other human hotspots include: NID2a, NID 2b and NID3 present around the NID gene and newer hotspots like MSTM1a and MSTM1b is also found in between MS32 and TM7SF [18]. The Mini-satellite MS32 contains 62% GC-content and is highly variable [19]. It is neither palindromic nor it influences the distribution of crossover sites across the hotspot [20]. In contrast, MSNID shows moderate variability, possesses 20% GC content and has a palindromic sequence. Because crossovers are rarely resolved within this minisatellites, it, therefore, constitutes a cold spot within the *NID*1 hotspot. This effect has nothing to do with its increasing AT content, then the adjacent AT-enrich domain, having fewer palindromic sequences than MSNID, and is found to play an active role in the crossover [21]. Hence, the occurrence of hotspot and coldspot therefore relies on the availability of palindromic sequences and/or occurrence of tandem repeats in MSNID. An important probable explanation may be that palindromes perhaps cause fold-back of resected 3′ ends, which tend to stop recombination from occurring in MSNID by preventing the strand invasion phenomenon into the homologous chromosome. Another alternative interpretation for the generation of MSNID cold spot is that crossover resolution sites do not seem to be symmetrically distributed across the *NID*1 hotspot, but show excessive cross-over exchanges, which map upstream of the interval containing MSNID [21]. Evidence from various research reports revealed that genomic regions that harbor maximum recombination accumulate GC-nucleotides overevolutionary time [22], which indicates the fact that a positive correlation exists between recombination and GC content of the genome [23].

Researchers reported the recombination event to be sex-averaged, and more recently it was observed that the recombination rate varies between human males and females [24–26]. Meiotic recombination is generally found to be highly suppressed near the region of centromeres while, highly elevated near the region of telomeres, but this increased and decreased recombination is not common in case of all chromosomes [27]. Variation in recombination rates occurs over multiple physical scales, from the site-specific hotspots, to vary over the scale of chromosome arms [27]. Here, we tried to illustrate the various models mediating recombination and tools used for their detection. Then we tried to put forward some of the research gaps, which needfurther study for a full-proof understanding about the factors influencing meiotic recombination in humans.

2. Human recombination hotspot evolution

Evidence regarding the presence of recombination hotspots in humans and chimpanzees has been put forward based on research reports comparing human linkage disequilibrium (LD) patterns with those of the disequilibrium patterns in chimpanzees [28]. Understanding of the evolution of human recombination hotspots and their frequencies and rates rely mainly on the phenomenon of 'biased transmission' at recombination hotspots [13,29]. Despite more than 98% of sequence identity between the chimpanzee and human genomes, no commonality exists in their hotspot positions [26,30,31]. Different human ethnic groups are also found to possess variations in the locations of their recombination hotspots [32–34]. Moreover, there is evidence for inter-individual variations in recombination positions and their rates [35,36].

Selection is more efficient in regions of high recombination [37]; and mutation rate appears to be higher in regions of high recombination rates [38]. The regions of high recombination have substitution rates approximately 50% higher than the regions of low recombination [23]. In addition, as stated by Wahls and Davidson (2011) [39], from a population genetics perspective, allelic drift could influence positioning of recombination hotspots in humans due to small effective population sizes as well as population bottlenecks [29]. Further, it has been shown that recombination hotspots appear to be enriched around the evolutionarily conserved non-coding regions [40].

Based on the DSB model of recombination, the mutations that damage hotspots by preventing DSBs formation also have an evo-