Variation in recombination rate across the genome: evidence and implications

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Recent data from humans and other species provide convincing evidence of variation in recombination rate in different genomic regions. Comparison of physical and genetic maps reveals variation on a scale of megabases, with substantial differences between sexes. Recombination is often suppressed near centromeres and elevated near telomeres, but neither of these observations is true for all chromosomes. In humans, patterns of linkage disequilibrium and experimental measures of recombination from sperm-typing reveal dramatic hotspots of recombination on a scale of kilobases. Genome-wide variation in the amount of crossing-over may be due to variation in the density of hotspots, the intensity of hotspots, or both. Theoretical models of selection and linkage predict that genetic variation will be reduced in regions of low recombination, and this prediction is supported by data from several species. Heterogeneity in rates of crossing-over provides both an opportunity and a challenge for identifying disease genes: as associations occur in blocks, genomic regions containing disease loci may be identified with relatively few markers, yet identifying the causal mutations is unlikely to be achieved through associations alone.

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Current Opinion in Genetics & Development 2002, **12**:657–663

0959-437X/02/$ – see front matter
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DOI 10.1016/S0959-437X(02)00358-1

Abbreviations

CEPH	Centre d'Etudes du Polymorphisme Humaine
LD	linkage disequilibrium
MHC	major histocompatibility complex
N	effective population size
SNPs	single nucleotide polymorphisms

Introduction

Meiotic recombination — the exchange of genetic information between homologous chromosomes during prophase I of meiosis — is widespread among eukaryotes, and the rate at which this exchange occurs may vary substantially among species, among individuals, between the sexes, and among different regions of the genome. Variation in the rate of recombination can have profound consequences for the structure of genetic variation and consequently for our ability to map and identify disease genes. Historically, the rate of crossing-over was measured cytologically, by observing chiasmata through the microscope, or by the number of recombinant individuals recovered in genetic crosses using phenotypic markers. With the availability of complete genome sequences and thousands of molecular markers, it is now possible to describe the amount and distribution of recombination in great detail. The pattern that emerges is complex and varies strikingly in different species and in different genomic regions.

Theoretical models indicate that the level of recombination can affect the amount and pattern of genetic variation in many ways. For example, in regions of the genome where recombination is either reduced or absent, non-random associations among alleles at different loci are expected. As a consequence of selection at linked sites, genomic regions with little recombination may also harbor fewer polymorphisms in addition to polymorphisms at lower frequencies. Moreover, the efficacy of selection is expected to vary as a function of recombination rate: interference due to linkage may reduce the chances of fixing beneficial mutations in regions of low recombination.

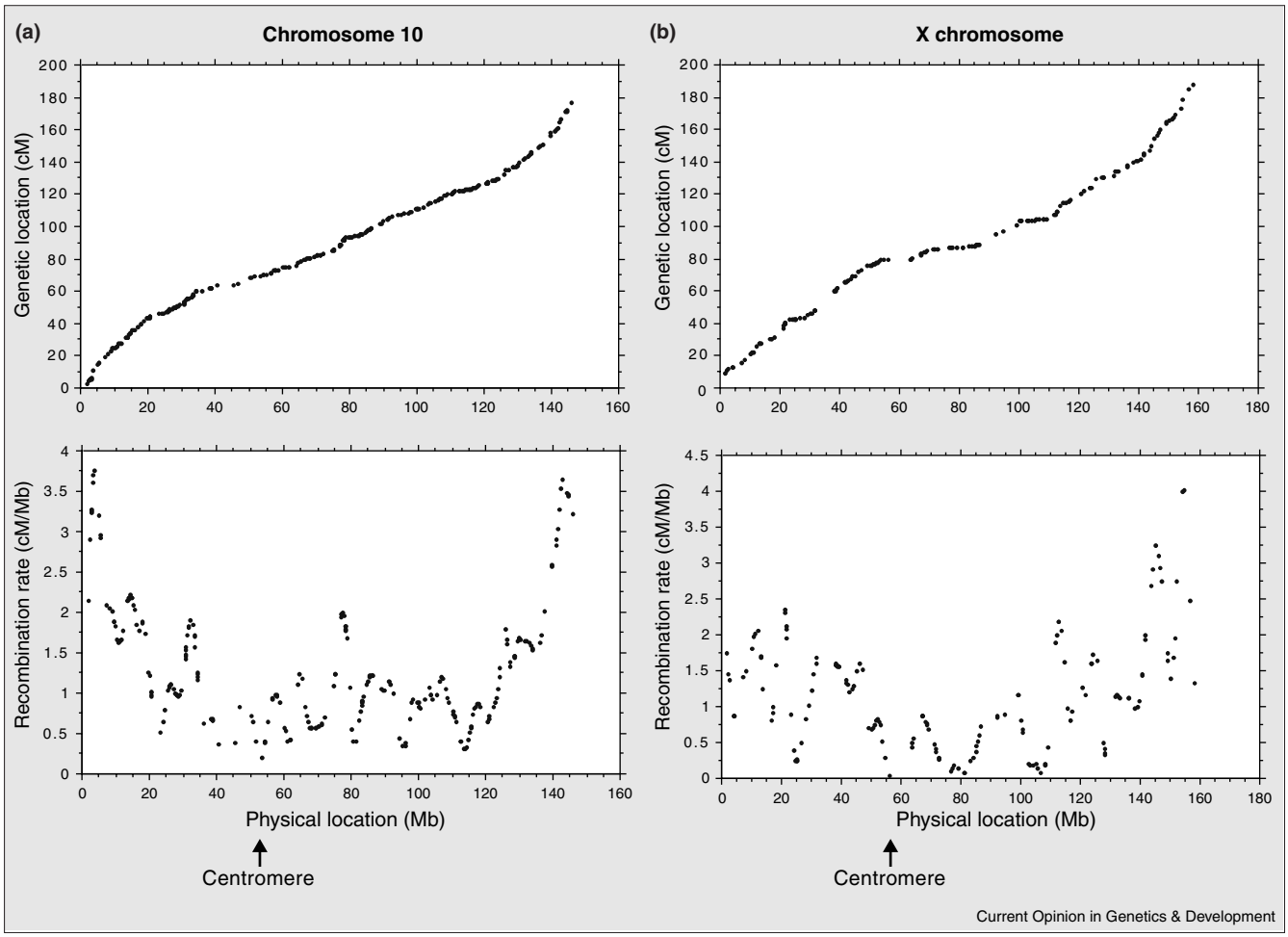
Here, I review evidence for variation in recombination rate, with special emphasis on humans and, to a lesser extent, *Drosophila*. I then discuss some of the theoretical predictions concerning the effect of variable recombination rate on patterns of genetic variation and I highlight recent data from flies and humans that address these predictions. Finally, I point to some of the implications of variation in the rate of meiotic crossing-over for our approach to mapping and identifying genes underlying complex traits, including many diseases.

Evidence for variation in recombination rate

Measurements of recombination can be made directly from exchanges that occur in meiosis. In organisms that are easily bred, such as mice and flies, recombinants are observed as progeny from genetic crosses; in humans, recombination is measured by comparing parents and offspring in pedigrees. More recently, recombination has also been measured in humans over very short intervals via typing of recombinant sperm using a PCR assay [1,2•]. To compare rates of crossing-over, rather than the absolute number of recombination events, genetic distances must be compared with some estimate of the physical distance between markers. The complete genome sequences of Drosophila [3], humans [4•,5], and several other eukaryotes [6,7] now makes it possible to compare detailed genetic and physical maps.

In *Drosophila melanogaster*, detailed genetic and physical maps were available before the era of genomics [8,9]. Precise physical maps are derived from *in situ* hybridization of markers to polytene chromosomes, which contain an

Figure 1



Recombination rate variation for two human chromosomes, **(a)** Chromosome 10 and **(b)** X chromosome, based on data from Kong *et al.* [16•]. The top panel for each chromosome depicts a plot of genetic versus physical position for microsatellite markers; the slope of this curve provides an estimate of recombination rate. The bottom panel gives the recombination rate estimates from Kong *et al.* for each marker based on a 3 Mb window. The amount of heterogeneity in estimates of recombination rate is strongly influenced by the choice of window size.

average of only 21 kb per band. Comparisons of markers on the genetic and polytene maps reveals a sex-average recombination rate of ~1.5 cM/Mb across the genome. The average rate for females is ~3.0 cM/Mb, and there is no recombination in males. This average value does not convey the substantial variation that exists in different regions of the genome, with low values approaching 0 cM/Mb, and high values of >5 cM/Mb [10,11]. Recombination is near absent on the small fourth chromosome, and is highly suppressed near the centromeres of the metacentric chromosomes 2 and 3. On the acrocentric X chromosome, recombination is only moderately reduced near the centromere, but is more suppressed near the telomere. Individual chromosome arms show substantial variation in recombination rate over distances of several megabases.

In humans, the first detailed genome-wide linkage maps came from analysis of 5,264 microsatellites in the CEPH families [12,13]. Comparison of these maps to radiation-hybrid maps [14] and to sequence-based maps [15•] also revealed dramatic variation in the rate of recombination in different genomic regions, as well as differences between the sexes. In the first detailed comparison of genetic and sequence-based physical maps in humans, Yu *et al.* [15•] reported a sex-average recombination rate of 1.3 cM/Mb across the genome, similar to the average value in *Drosophila*. The average rate for males (0.9 cM/Mb) was slightly over half the average rate for females (1.7 cM/Mb). Yu *et al.* further identified recombination 'deserts' and 'jungles' — regions several megabases in length displaying unusually low (<0.3 cM/Mb) and unusually high (>3.0 cM/Mb) rates of recombination. These analyses utilized genetic maps that were based on 184 meioses. Importantly, Yu *et al.* [15•] restricted their analyses of recombination rate to those portions of the genome with finished sequence assemblies >1.5 Mb in

length. They also restricted their analysis to regions for which the order of markers was the same in the sequence, radiation-hybrid maps, and genetic maps. This restricted the analysis to ~58% of the non-repetitive portion of the genome.

Recently, Kong *et al.* [16•] constructed a genetic map from 5,136 microsatellites genotyped in 146 Icelandic families, representing 1257 meioses. The resolution of this map is approximately five times the resolution of previous maps. Although the total genetic length (3615 cM, sex averaged) is very close to previous estimates, the average recombination rate (1.1 cM/Mb) is slightly lower than the estimate of Yu *et al.* [15•] that was based on subsets of the genome.

Examples of recombination rate variation from two human chromosomes (10 and X) are shown in Figure 1, using data from Kong *et al.* [16•]. Across the genome, recombination rate varies from low values near zero to high values close to 5 cM/Mb. In general, recombination appears to be low near the centromeres of metacentric but not acrocentric chromosomes. Recombination is generally elevated near the ends of the chromosomes, regardless of whether or not there is a centromere in proximity. There is a strong inverse correlation between the length of each chromosome and the average recombination rate per chromosome [4•,16•], implying that there is a minimum number of crossovers required for proper pairing of homologs in meiosis. For example, the average rate for chromosome 22 (2.11 cM/Mb) is more than twice the average for chromosome 1 (0.96 cM/Mb). Along individual chromosome arms, recombination rate fluctuates rather dramatically, sometimes over scales of several megabases, and no chromosome shows a monotonic change in rate from regions of highest to regions of lowest recombination. However, it remains unclear whether this megabase-scale variation reflects real differences in recombination rate or statistical fluctuations in the mapping data. Certainly the amount of fluctuation depends on the scale at which recombination rate is measured. Figure 1 shows the genetic and physical positions of markers as well as recombination rates calculated from 3 Mb windows. If rates are calculated on the basis of larger windows, much of the fine-scale heterogeneity disappears.

Although there is fairly good general agreement between the Iceland map [16•] and the Marshfield map [13,15•], there are also some differences in the estimates of the rate of recombination per physical distance between Yu *et al.* [15•] and Kong *et al.* [16•]. For example, only 8 of the 19 recombination deserts identified by Yu *et al.* were identified by the Iceland group. Some of these discrepancies may result from the higher resolution of the Iceland map. Some may also result from the fact that Kong *et al.* estimated recombination rates using a draft of the human genome sequence with many gaps. As these gaps are filled in, estimates of recombination rates for specific regions will need to be revised.

Despite our advances in describing recombinational variation in different genomic regions, we still remain quite ignorant of the factors responsible for this variation — although the density and intensity of recombination hotspots are clearly important, as discussed below. The fact that the amount of autosomal recombination in human females is 1.65 times the rate in males suggests that features other than the sequence itself contribute to variation in recombination rate, as the autosomes are not known to contain sex-specific differences in sequence [16•]. Moreover, the sex-specific variation revealed in the Icelandic map is complex: over much of the genome, male and female rates are highly correlated but there are several regions where peaks of recombination in one sex correspond to valleys of recombination for the other sex. Crossover rate tends to be higher for males near telomeres and higher for females near centromeres [13,16•]. Nonetheless, some aspects of the underlying sequence do correlate with the rate of recombination. In humans, the GC content, the CpG frequency, and the frequency of poly(A) or poly(T) tracts together explain ~32% of the variation in recombination rate [16•].

Comparisons of genetic and physical maps in other species suggests that variation in recombination rate in different genomic regions is quite widespread. The newly completed draft of the mouse sequence [17], coupled with the relatively dense mouse genetic maps [18,19] will soon enable us to provide precise estimates for recombination rate in another mammal, and these will serve as a useful reference to humans. This will allow us to test such things as whether homologous regions show similar rates of recombination.

The rate of recombination can also be inferred indirectly from patterns of linkage disequilibrium (LD) — the nonrandom association of alleles at different loci (or of nucleotides at different sites). Because mutations arise on a particular haplotype, the mutational process alone leads to associations; the rate at which these associations decay depends on the amount of recombination. Thus, all other things being equal (which they rarely are), we expect more LD in regions of less recombination. This general pattern is seen in humans [15•]. Among the factors that can complicate the simple link between LD and recombination are selection, recurrent mutations, and demographic processes such as admixture or population growth [20,21]. Even so, patterns of association among single nucleotide polymorphisms (SNPs) at different sites have provided insight into patterns of recombination. For example, the amount of LD is an inverse function of the population recombination rate, 4Nr (for autosomes), where N is the effective population and r is the recombination rate [20]. Thus, species with larger effective population sizes are expected to show less LD. In *Drosophila*, LD typically extends for much smaller distances than in humans, consistent with the notion that flies have larger effective population sizes than humans [21].

An accumulation of data from humans and mice over the last twenty years presents strong evidence for recombination

hotspots [22–25]. In particular, two recent papers describe patterns of LD in humans, one on chromosome 5q31 in a region implicated as containing a genetic risk factor for Crohn disease [26] and the other in the class II region of the major histocompatibility complex (MHC) [2•]. Both studies reveal blocks of linkage disequilibrium, extending on the order of 10–100 kb, separated by smaller regions with much less LD. Moreover, Jeffries *et al.* [2•] show that these regions of little LD correspond to regions with very high rates of recombination as measured directly from the frequency of recombinant sperm. The picture that emerges over a 200 kb region of the MHC is striking: the overall rate of recombination in males across the region is ~0.9 cM/Mb, very close to the genomic average, yet the region is made up largely of long stretches (~100 kb) with recombination rates of ~0.05 cM/Mb, punctuated with small hotspots (~1 kb) with recombination rates as high as 140 cM/Mb. Interestingly, not all hotspots are created equal: the different hotspots identified in this study vary in the amount of recombination by two orders of magnitude. The experimental measures of recombination from sperm-typing provide strong validation that the block-like patterns of LD reflect real underlying differences in the frequency of crossing-over in this genomic region. As pointed out by Jeffries *et al.* [2•] the strong concordance between patterns of LD and the locations of hotspots from PCR assays of sperm suggests that similar hotspots probably exist in females. One intriguing finding from this work is that hotspots appear to occur in clusters, with ~1–7 kb separating each hotspot within a cluster. The reasons for this spatial distribution remain unclear.

Patterns of LD from SNPs throughout the genome also suggest that nucleotide variation is organized into blocks of haplotypes [27]. Although these patterns appear consistent with the notion that many or most recombination events occur within hotspots, there has been no careful investigation of the pattern of LD expected under different spatial arrangements of crossing-over. For example, it is possible that block-like patterns of LD are expected even if a substantial amount of crossing-over does not occur in hotspots.

What do we know about the expected evolutionary lifespan of hotspots? For example, do we expect them to be present at the same location in closely related species? One model suggests that hotspots should be short-lived because recombination-associated biased gene conversion will always favor mutants that suppress recombination [28]. One recent study [29•] provides support for this model by documenting a SNP in a hotspot for which alternative nucleotides affect the frequency of crossing-over. Moreover, individuals that are heterozygous at this site show significant over-transmission of the recombination-suppressing variant. In light of these observations, it will be interesting to see if humans and related species show the same hotspots for recombination.

Our knowledge of variation in recombination rate comes from two kinds of data that reveal patterns at different scales. On the one hand, comparison of genetic and physical maps reveals variation over scales of megabases, with some general patterns, such as elevation of recombination near the telomeres of some chromosomes and suppression of recombination near some centromeres. On the other hand, patterns of LD and experimental measures of recombination from PCR assays reveal variation on the scale of one to several hundred kilobases, and suggest that recombination occurs predominantly in hotspots in human and mouse (but not in *Drosophila*) genomes. One can imagine at least two ways in which variation at these two scales may be related. One possibility is that variation at the larger scale predominantly reflects differences in the density of hotspots in different regions of the genome [15•]. Perhaps telomeric regions contain more hotspots than some centromeric regions, for example. Alternatively, the number of hotspots may be roughly constant, but their intensity may vary [2•]. Whether genomic variation in the rate of crossing-over is due primarily to differences in the density or in the intensity of hotspots (or both) remains to be seen.

Predicted consequences of variation in recombination rate

A considerable body of theoretical work has addressed the ways in which selection and linkage may jointly affect patterns of genetic variation. Here, I focus on just two patterns: the amount of genetic variation and the distribution of allele frequencies. Because this work has been reviewed recently elsewhere [30,31], I only highlight several key predictions.

Models of selection at linked sites show that the amount of genetic variation may be reduced in regions of low recombination. Genetic hitchhiking refers to the fixation of adaptive mutations and the associated fixation of linked variants [32]. In the simplest case, if a new mutation arises and sweeps through a population to fixation in a genomic region devoid of recombination, a single haplotype will be fixed among all individuals. If there is some recombination during the course of the selective sweep, more than one haplotype may remain following the fixation of the adaptive mutant, and less variation will be eliminated. Thus, the process of genetic hitchhiking is expected to generate a positive correlation between the rate of recombination and the level of nucleotide variability. Another process based on selection and linkage, termed background selection [33], can also generate a correlation between the rate of recombination and the level of nucleotide variability; this process is based on the removal of deleterious mutations from a population by selection and the associated removal of linked neutral variants. These two processes are not mutually exclusive; on the contrary, both are likely to operate together at least to some degree [34]. Other more complex models of positive selection may also lead to reduced nucleotide variability in the absence of recombination, although for some of these models the reduction is rather slight [35,36].

Selection may also lead to a skew in the distribution of allele frequencies at linked sites, and this effect will be more pronounced in regions of lower recombination. Following a selective sweep, the return to steady-state heterozygosity depends on the input of new mutations, which typically arise at a frequency of 1/2N in a population of N diploid individuals. Thus, for a period of time after a sweep, an excess of rare alleles is expected [37–40]. Selective sweeps may also drive derived alleles to near-fixation, leaving behind an excess of rare ancestral alleles [41]. More generally, under some models of positive selection, the frequency distribution of polymorphisms may be correlated with the local rate of recombination [31]. Background selection may also lead to a skew in the distribution of allele frequencies, but only under conditions of rather small population sizes or selection coefficients [33].

What do the data tell us?

A correlation between recombination rate and nucleotide variability was first documented in *Drosophila* [42•]. Similar results have now been demonstrated for a variety of organisms, from plants to humans [43–48], although the strength of this relationship varies considerably among species. In both flies and in humans, variation in recombination rate explains >50% of the variability in nucleotide heterozygosity. Evidence that this correlation is not driven primarily by differences in mutation rate comes from the absence of a correlation between recombination and inter-specific divergence [42•,43,48], although there is some evidence that recombination is mutagenic in yeast [49]. There is weak evidence that a small amount of the variation in heterozygosity in humans may be attributable to differences in mutation rate [50]. It remains unclear whether background selection, hitchhiking, some combination of these processes, or more complex models of selection best explain the observations [31,34]. Nonetheless, the correlation between recombination and heterozygosity appears to be widespread and points to the importance of the joint effects of linkage and selection in shaping patterns of genetic variation.

While the correlation between recombination rate and heterozygosity appears general, no strong, general pattern has appeared from comparisons between the frequency distribution of alleles and the rate of recombination. In African *Drosophila melanogaster*, a correlation is observed between the frequency distribution of polymorphisms and the rate of recombination; rare polymorphisms are more common in genomic regions experiencing little recombination, consistent with models of genetic hitchhiking [51]. However, one locus experiencing low rates of recombination in *Drosophila* has low levels of variability but no preponderance of low-frequency polymorphisms [52]. In humans, there is a weak trend for genes with low rates of recombination to harbor more low-frequency variants [48] but more extensive surveys are needed to test the generality of this result.

One of the challenges for theoreticians over the next several years will be to incorporate the complexities of the recombinational landscape — including hotspots that vary in density and intensity — into population genetic models. Most current population genetic models treat recombination as a single parameter. It is not clear how selection at linked sites will be affected, for example, by the presence of hotspots. Will an adaptive mutant effectively be uncoupled from surrounding sites if it is bracketed by high-intensity hotspots on either side? Incorporating these complexities into theoretical models may help us to evaluate our data better and may help resolve whether genetic hitchhiking or background selection is more consistent with the patterns we see.

Implications for mapping disease genes

Recombination is a double-edged sword for mapping disease genes. For mapping genes involved in complex diseases, where the effects of individual loci are relatively small, association studies may offer more power than transmission studies [53]. Association studies rely on LD between markers and traits. Thus, in genomic regions with low rates of recombination and high levels of LD, markers at considerable distances may associate non-randomly with genes conferring increased risk to a disease of interest. Because a greater region of the genome is likely to be associated with the gene of interest, this makes it easier to pinpoint the general region. On the other hand, in this situation, identifying the causal mutation becomes impossible from associations alone because many sites in the region will be associated with the trait.

Patterns of genetic variation (other than LD) that are correlated with recombination rate may also have important implications for mapping disease genes. If heterozygosity is lower in regions of low recombination (as seems to be the case), then we can expect to find fewer SNP markers in low recombination regions. If there is a skew in the distribution of allele frequencies in low recombination regions (as may be the case) then we can expect to find fewer informative, intermediate-frequency SNPs in low recombination regions.

Conclusions

Data from complete genome sequences, particularly in humans, provides convincing evidence for variation in recombination rate in different regions of the genome. Our understanding of this variation in recombination comes from observations at different scales. On a fine scale, patterns of LD and sperm typing in humans reveal hotspots of recombination separated by distances of 10–100 kb, and some of these hotspots recombine at rates (>100 cM/Mb) over three orders of magnitude higher than surrounding sequences (<0.1 cM/Mb). Comparisons of genetic and sequence-based physical maps reveal variation in recombination rate over distances of megabases, and average rates across this scale differ by about one order of magnitude (from ~0.2–5 cM/Mb). Variation at these two scales may be related by differences in the density and/or intensity of hotspots. A key challenge for better understanding the

nature of recombination in humans now is to describe the distribution and relative intensity of hotspots. Interestingly, hotspots such as those observed in humans and mice, appear to be missing in *Drosophila*, although they are well known in other organisms such as yeast and maize [54,55]. The factors responsible for variation in recombination remain obscure, although some features of the underlying sequence do correlate with differences in the amount of crossing-over [16•,29•].

Theoretical models incorporating selection and linkage predict reduced genetic variation in low-recombination regions, and this prediction is supported by data from several species. We are still struggling to distinguish between two different models of selection to explain this pattern, one based on adaptive mutations and the other based on deleterious mutations. Models incorporating the complexity of the recombinational landscape, including hotspots of different density and intensity, will be useful for merging theory with data.

Acknowledgements

My work is supported by grants from the National Science Foundation. I thank HE Hoekstra, BA Payseur, and SP Otto for comments on the manuscript.

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