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Research Focus

Can a genome change its (hot)spots?

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A new study by Jeffreys *et al.* shows that the rate of recombination in recombination hotspots in humans is not constant through time. This observation adds weight to the idea that hotspots are transient on evolutionary timescales. However, questions remain as to what controls their evolution and how these rapid changes influence broad-scale rates of recombination.

Variation in the rate of recombination

The rate of meiotic recombination (i.e. crossing over) in humans varies on many physical scales [1]. Much of the recombination appears to be concentrated into 1–2-kb hotspots [2–4]. Several recent papers have shown that the rate of recombination and the location of hotspots change rapidly through time, with hotspots varying within human populations [5]; research has also shown that hotspots are not conserved between humans and chimpanzees [6–9]. These results are somewhat surprising, because the low levels of human genetic variation and human–chimpanzee divergence would imply that hotspots should be better conserved than they appear to be. This lack of conservation raises questions about the mechanisms that control hotspots and what drives their rapid evolution. Recombination has two main functions: (i) it shuffles diversity, enabling different combinations of alleles to be tested together; and (ii) has a vital role during meiosis. If the rate of recombination is not constant through time, this has important implications for both of these functions.

To study recombination on a fine scale, two approaches have been developed. Using allele-specific PCR, the first directly observes crossing over in sperm. This produces a uniquely detailed picture of the current rate of recombination in males, but the procedure is time consuming. The second set of approaches utilizes a population genetic model (the coalescent, or approximations to it) to relate the patterns found in a current-day sample of polymorphism to the historical rate of recombination [3,4]. These estimates of the historic rate of recombination reflect thousands of meioses in the history of the sample, and so the rate estimated is an average of male and female rates over time. Encouragingly, given the dramatically different methods used by the two sets of approaches, good agreement has been found in the estimated locations of human hotspots [3–5].

Rapid evolution of hotspots

Two recent large-scale studies examined the conservation of hotspots between humans and chimpanzees by using estimates of the historical rate of recombination estimated from patterns of polymorphism [8,9]. The authors found that no hotspots were conserved between the two species. To better understand the evolution of hotspots within a species, Jeffreys *et al.* [5] identified eight human hotspots (seven new) through sperm typing [5]. Six of these hotspots were also identified by the use of methods for detecting hotspots from historical rates. In spite of this agreement, the estimated historical rates within the hotspots differed substantially from those found by the sperm study: historically, two of the hotspots were significantly more intense and one was significantly less intense than expected, given the current-day estimates obtained from sperm.

This disagreement between estimates might not seem surprising, because the methods for obtaining historical rates of recombination are estimating a quantity that can be affected by processes such as natural selection and demography, which alter the underlying amount of time for recombination to act historically. However, in a detailed analysis, Jeffreys *et al.* [5] found that neither statistical error in the estimation of the historical rate nor changes to the demographic model could account for the differences between the historical estimates and the sperm study. Even though the authors could not examine all possible demographic models, it is unlikely that any demographic model could increase the estimate of the historical intensity of some hotspots and decrease the estimate of the intensity of others, as demography will affect all regions similarly. Natural selection can lead to strong local differences in the underlying depth of history that could confuse historical estimation methods. However, two of the hotspots are hotter according to historical estimates of the rate, which is only consistent with a lengthening of the genealogical history of the sample. Forms of selection that lengthen the genealogy (e.g. multiallelic balancing selection [10]) are thought to be relatively rare in the human genome. If the rate of recombination in a hotspot was much high in females than in males, this could explain why two of the historical estimates of hotspot heat are higher than those found by the sperm study, but cannot explain the hotspot that appears cooler historically.

Driven to destruction

Given the reported lack of sharing of hotspots between humans and chimpanzees [6–9], one plausible explanation of the findings of Jeffreys *et al.* is that hotspots are transient and vary between species and within human populations. Strong support for this argument is provided

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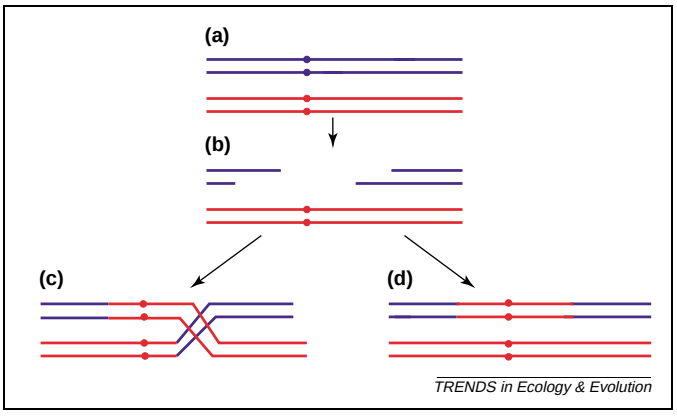

Figure 1. A simple representation of the process of recombination. Two nonsister chromatids (i.e. one of the two maternal and one of the two paternal chromatids) are shown in red and blue during meiosis **(a)**; both strands of the DNA are depicted. The red and blue circles are two different alleles (i.e. the individual is a heterozygote). Recombination in humans is thought to be initiated by a double-stranded break [DSB; **(b)**] on one of the chromatids. Genetic material surrounding the DSB on the broken chromatid is lost, and is replaced via gene conversion, using the nonsister chromatid as a template. The resulting structure is then resolved into either a crossover accompanied by gene conversion **(c)** or a gene conversion **(d)**. If, in heterozygotes, an allele (red circle) reduces the initiation of DSBs locally in *cis*, then it will be overtransmitted, because it will be used to overwrite the other allele (blue circle) by gene conversion more often than it itself is overwritten.

by the observation that several hotspots are polymorphic among human males in sperm studies [5,11–13]; in some cases, allelic variation that controls the level of recombination initiation has been identified [11–13].

The rapid evolution of hotspots is surprising given the high degree of sequence similarity within human populations and between chimpanzees and humans. If hotspots are controlled by a relatively short motif (e.g. tens of base pairs), then it seems that mutation and genetic drift alone are insufficient to explain their rapid evolution. An explanation of the rapid evolution of hotspots is provided by the fact that alleles that reduce the intensity of hotspots locally in *cis* are overtransmitted to offspring of heterozygotes as a natural consequence of the recombination mechanism (Figure 1). This overtransmission means that such alleles experience a form of drive and so increase in frequency in the population [14]. In fact, this drive is such an efficient way of removing hotspots from a population that their long-term persistence is something of a paradox [14,15]. Driven disruptive alleles have been observed in the DNA2 and NID1 hotspots in humans [12,13], which suggests that it is common for hotspots to segregate and go extinct as a result of such alleles. Interestingly, Jeffreys *et al.* found that the NID1 hotspot was hotter historically than in the current-day sperm estimates [5] (but not significantly so), which is consistent with the idea that the derived disruptive allele at this hotspot [13] is pushing it to extinction.

Evolution of broad-scale rates

Will the fast rate of hotspot evolution lead to relatively rapid changes in the broad-scale rate of recombination? Several factors speak against this simple hypothesis. First, there will be strong selection for the maintenance of a suitable rate of recombination on a chromosome arm, as at least one recombination must occur per arm to ensure correct segregation of the chromosomes at meiosis [1]. Heritable variation exists in broad-scale rates of recombination in humans [1], which perhaps implies that broad-scale rates of recombination are controlled at a higher level rather than being determined by the sum of individual hotspots. A third factor that might affect the evolution of broad-scale rates is the observation in yeast that, when one hotspot is removed, nearby hotspots increase in heat ([15] and references therein). This could enable the maintenance of recombination in a region where there are multiple hotspots, whereas individual hotspots go extinct.

Questions and prospects

The patterns used to estimate the historical rates of recombination reflect thousands of meioses. Therefore, in spite of the possible drive against hotspots, they do persist for relatively long periods of time. The small size and long-term persistence of hotspots points towards some strict control of their location, which seems to depend, in part, on the local sequence [13]. However, it is likely that larger scale factors will also have an important role. Jeffreys *et al.* [5] report that the MS32 hotspot appears to be cooler historically than it now appears to be in sperm data: is this an example of a newly arisen hotspot? How do hotspots reach high frequency in the population: do they randomly drift up in frequency or does selection act in their favor?

Finding polymorphic hotspots offers a unique chance to improve our understanding of the biological processes controlling fine-scale rates of recombination and how quickly rates of recombination can evolve. It is clear that, although historical estimates of rates and sperm typing methods both offer unprecedented information about the variation in fine-scale recombination rates, it will only be through more combined approaches, such as that of Jeffreys *et al.* [5], that a deeper understanding of the evolution and control of hotspots will be found.

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When bigger is better: the need for Amazonian mega-reserves

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The rate of forest destruction has accelerated sharply in Brazilian Amazonia, but there are also vital conservation opportunities with the ongoing designation of important new protected areas. In a timely paper, Carlos Peres argues that an extensive network of mega-reserves, operationally defined as those exceeding 1 million ha in area, is needed to ensure the long-term persistence of Amazonian species and ecological processes. Although such protected areas might seem excessively large to some, disparate lines of evidence suggest that mega-reserves are vital for the future of Amazonian biodiversity.

Introduction

During the past 15 years, rates of forest loss, degradation and fragmentation have accelerated sharply in the Amazon (Figure 1), the largest and most biologically diverse of all tropical wildernesses. These losses are being driven by a combination of factors, including rapidly increasing cattle ranching and soybean farming, a proliferation of industrial logging, forest-colonization projects, and an unprecedented expansion of new highways, roads and other transportation infrastructure [1,2].

Yet, this is also a time of unparalleled opportunity for conservation in the Amazon. Brazil, via various federal and state initiatives, is currently designating many new protected areas and sustainable-use forests within the Amazon (Box 1). These conservation units vary in the kinds of resource use that is legally permitted [3]; for example, intensive uses, including industrial logging, are permitted in some reserves, such as National Forests and Environmental Protection Areas, whereas others, such as National Parks, nominally allow only limited uses that include tourism and scientific research. Other conservation units, such as Extractive Reserves, permit intermediate activities, such as hunting, rubber tapping, and traditional swidden farming.

A related challenge is that, in reality, enforcement of environmental laws in the Amazonian frontier is patchy and inconsistent at best. Illegal logging is rampant, laws that regulate deforestation on private properties are rarely enforced, illicit forest invasions are common, and numerous reserves are being threatened by illegal deforestation, predatory loggers and gold-miners [4]. Such pressures will only increase as highways and other transportation infrastructure infiltrate throughout the basin [2], bringing conservation units and the expanding Amazonian population into ever-closer contact.

The need for mega-reserves

Into this mix of environmental promise and peril comes a new paper by Carlos Peres [5], part of a special section in the journal *Conservation Biology* about the Brazilian environment. Peres argues, based on several lines of evidence, that Amazonian reserves need to be large (>1 million ha) and embedded within a relatively benign matrix of sustainable-use forests to preserve their most vulnerable species and large-scale ecological processes. They should also be stratified across major vegetation types and key centers of endemism (Box 1). Finally, wherever possible, he and many others [6] assert, individual conservation units should be linked together into large-scale regional corridor systems.

At first glance, Peres' proposal might seem excessive to some policy makers, but the evidence for mega-reserves is compelling. One of the most important justifications is that our biogeographical knowledge of the Amazon is appallingly incomplete, even for relatively well-studied groups such as birds and mammals. As a result, apparent

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