Spectacular fossil animal embryos (*13*, *14*) of great evolutionary importance are found at Weng'an (some 375 km to the southwest of the authors' study area), where the Doushantuo Formation accumulated closer to the shoreline and records only a single surface of unconformity. In such nearshore environments, oceanic sediments are often exposed above sea level, resulting in the removal of underlying sediments and hence the erasure of some fraction of geological time. Which of the two hiatal surfaces from the deeper-water sections at the Yangtze Gorges correlates to the single unconformity at Weng'an? The data are more equivocal than presented by Condon *et al.*, and the choice carries important evolutionary consequences.

At the Yangtze Gorges, the extraordinary carbon cycle anomaly recorded in marine carbonates near the top of the Doushanto Formation is truncated by the uppermost unconformity. Condon *et al.* suggest that there is little time missing across the surface, thereby preserving a causal relation between the environmental perturbation and the rapid diversification of Ediacara organisms and associated faunas around 550 million years ago. However, correlation of this surface and the intervening sediments back to Weng'an tells another story. At Weng'an, both the carbon cycle anomaly and the sediments typical of the uppermost Doushantuo Formation at the Yangtze Gorges are missing, implying a substantial hiatus.

Comparison of broadly equivalent strata in southern Australia and the western United States suggests a stratigraphic architecture similar to that in southern China, where similar carbon cycle anomalies are truncated by unconformities (*15*). In the western United States, the post-anomaly unconformity removes a minimum of 130 m of section, more than the entire thickness of the Doushantuo Formation. These observations suggest that the unconformity separating the Ediacaran faunas and the carbon cycle anomaly in southern China may, in fact, hide a lot of time, thereby decoupling the environmental and biological events that the authors wish to connect. This is not meant to detract from the important radiometric calibration that Condon *et al.* provide, but rather to note that the stratigraphic relations between these dates, and therefore their connection to evolutionary events, are far from straightforward.

According to Condon *et al.*, the rapid diversification of complex multicellular organisms in Ediacaran oceans forced the carbon cycle anomaly seen worldwide, but this seems possible only if there is no real time missing across the upper Doushantuo unconformity. If this is not the case, then this interpretation may be placing the cart before the horse. Alternative models suggest that environmental changes may have driven evolutionary transformations. In particular, atmospheric oxygen—long believed to be an external forcing factor to evolution—appears to have built up rapidly during the Ediacaran Period, not because of a discrete biological event but as a result of the tectonic forces that lift and erode mountain ranges (*16*).

Through precise radiometric clocks and clever stratigraphic connections, geoscientists can increasingly correlate Ediacaran sediments that are separated widely in space and time. These tools allow us to piece together a complex puzzle of unforgettable biological events against a background of repetitive climatic and environmental perturbations. However, even with exact dates, the cyclicity of these events and the specter of a fragmentary rock record add uncertainty to our picture of Ediacaran Earth history.

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EVOLUTION

Where We're Hot, They're Not

Lynn B. Jorde

Homologous recombination, the exchange of material between chromosome pairs during meiosis, plays several key roles in diploid organisms. It produces new combinations of alleles, greatly increasing the potential for adaptive diversity. It is required for the normal separation of the two members of a chromosome pair during meiosis. It is an essential step in recombination-mediated repair of double-strand breaks in DNA. Defects in this crucial repair process can give rise to inherited diseases such as familial breast cancer.

The measurement of recombination frequencies has been the keystone of long-standing efforts to map the chromosomal locations of genes. As Winckler *et al.* (*1*) now report on page 107 of this issue, mapping of recombination hotspots in the human and chimpanzee genomes reveals a surprising finding. Despite 99% identity between human and chimpanzee DNA sequences, there is virtually no overlap between these two species in the locations of their recombination hotspots.

Traditionally, gene mapping in humans has relied on the direct observation of recombination events in families (linkage analysis). This approach, while enormously successful, is limited by the small number of generations during which meiosis can be observed in humans. An alternative approach, based on the once-obscure concept of linkage disequilibrium (LD), has gained widespread attention during the past couple of decades. To understand LD, imagine that a disease-causing mutation has just occurred in a population. The chromosome on which this mutation occurred contains specific DNA variants (alleles) in neighboring polymorphic (variable) loci. At first, the mutation will be observed only in conjunction with these alleles, so the association (or LD) between the mutation and the surrounding variants will be high. Through time, these associations will dissipate because of recombinations between the mutation and nearby loci, and LD will drop (see the figure, A). The closest loci will experience the fewest recombinations and hence retain higher levels of LD with the mutation. Thus, LD patterns can reveal the approximate locations of disease-causing mutations. LD analysis, in contrast to linkage analysis, reflects the effects of dozens or hundreds of past generations of recombination and may therefore confer improved resolution and statistical power to localize mutations. Although its merits are still debated (*2*), LD analysis may be especially useful in the detection of mutations that underlie complex diseases (*3*, *4*), and it has yielded some recent successes (*5*, *6*).

As with all explorations, gene hunting based on LD benefits from a good map. The principal goal of the much-discussed International Haplotype Map (HapMap)

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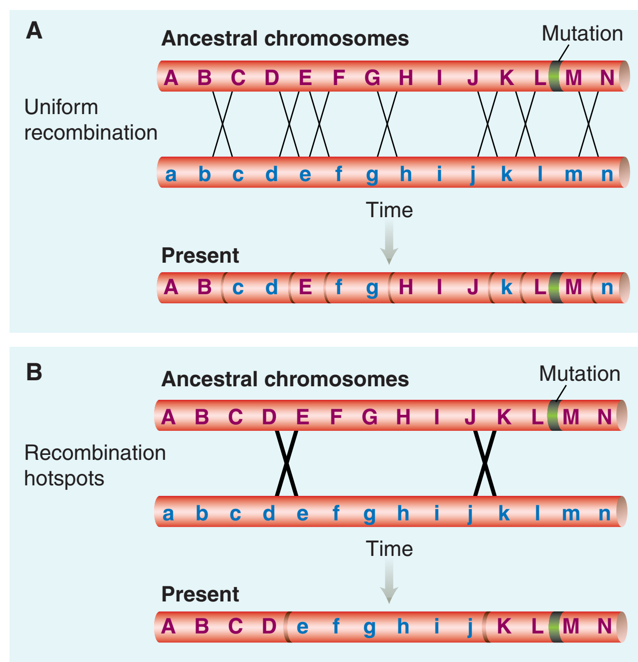
Project (*7*) is to generate such a map and to identify chromosomal regions, or "haplotype blocks," in which LD is maintained at a high level in populations (see the figure, B). By knowing which polymorphic loci are highly correlated with one another, investigators can avoid the wasteful collection of redundant information when searching for disease-causing mutations.

The LD patterns revealed by the HapMap Project and other studies have shown that recombinations appear to be concentrated in specific regions known as hotspots, which are found once every 50 to 200 kb in the human genome (*8*, *9*). A hotspot is defined as a 1- to 2-kb region in which the recombination rate, estimated here by LD, is at least 10 times that in the surrounding region (*9*). A better understanding of hotspots could have important implications for our ability to discover and exploit haplotype blocks (for example, determining how often haplotype blocks are defined by hotspots).



Mapping recombination hotspots. **(A)** Hypothetical ancestral chromosomes contain a series of polymorphic loci with alleles A, a; B, b; C, c and so on. If recombination occurs in a relatively uniform fashion, markers that are close to one another will maintain high levels of linkage disequilibrium (for example, loci A and B). In contrast, markers that are more distant will have low levels of linkage disequilibrium because of multiple intervening recombinations (for example, loci A and N). A mutation that occurs on the ancestral chromosome near loci L and M will be found in association only with those alleles in a chromosome sampled from the present population. **(B)** If recombination is concentrated in hotspots, linkage disequilibrium will be preserved over longer distances across the chromosome (haplotype blocks). Thus, loci A, B, C, and D will retain a high degree of linkage disequilibrium, but between loci D and E linkage disequilibrium will break down rapidly because of multiple recombinations that occur at the hotspot. The mutation located between loci L and M is associated with polymorphic loci over a longer chromosome distance (K, L, M, and N).

In their new work, Winckler *et al*. (*1*) have addressed this goal by using LD-based methods to compare hotspot locations in 1.5 megabases (Mb) of orthologous DNA sequences from the human and chimpanzee genomes. Human and chimpanzee DNA sequences are almost 99% identical. Thus, if hotspots are sequence-dependent, one might expect a high degree of concordance in their locations. Instead, Winckler *et al*. found that 18 recombination hotspots revealed in the human genome were absent from the chimpanzee genome. Hotspots in the human β-globin and human leukocyte antigen gene regions were also found to be absent in chimpanzees. The three recombination hotspots found in chimpanzees were absent in humans. Another recent study revealed the same lack of concordance (*10*).

What could account for this? One possibility is that LD, which can be affected by evolutionary processes such as natural selection, genetic drift, and admixture (*11*), is not a reliable indicator of recombination hotspots. Indeed, it is possible to generate haplotype blocks through genetic drift alone (*12*). However, Winckler *et al*. show that European and African populations, which have quite different demographic histories, reveal a high degree of concordance in the locations of hotspots (although, as in all such studies, there is generally more LD in the European than in the African sample). Other studies report generally similar findings (*9*, *13*). Even more convincingly, LD-based methods are quite successful in detecting hotspots previously documented by the direct assessment of recombination events in sperm cells (*8*, *14*).

Although the effects of human population history appear not to account for hotspot locations, it is possible that hotspot discordance could result from the substantial differences seen in the demographic histories or population structures of humans and chimpanzees (*15*). Winckler *et al*. used the well-known STRUCTURE algorithm to demonstrate a lack of population structure in the chimpanzee sample, but the number of loci they used (40) may be insufficient to detect meaningful population subdivision (*16*). Sperm typing in chimpanzees would allow a direct examination of recombination hotspots (at least in males) and would more conclusively exclude population structure and demographic history as explanatory factors.

As with any statistical analysis, the power to detect hotspots should be considered. Whereas the sample sizes on which most of the analyses are based are reasonably large (90 European-derived and 90 African individuals), the sample of 38 western chimpanzees is relatively small, as is the amount of DNA sequence (three 500-kb regions in the primary analysis). The authors have addressed this issue extensively and have shown that a lack of power would be unlikely to account for the startling absence of hotspot concordance. Also supporting their findings are the congruent results of Ptak *et al*. (*10*), which were based on an assessment of 14 Mb of DNA sequence in 71 humans but only eight chimpanzees.

Still another possible explanation for these results lies in genomic factors that are known to correlate with recombination rates. Recombination is elevated in GC-rich regions of the genome, and human recombination rates tend to be lower near centromeres and higher near telomeres (*17*, *18*). In addition, the overall human recombination rate is about 60% greater in female than in male meiosis. These factors, while related to recombination rates over relatively large regions, do not appear to correlate strongly with recombination hotspots in humans (*8*, *19*).

Lacking evidence that population history or local DNA sequence variation can account for hotspot location, Winckler *et al*. suggest that epigenetic factors that influence chromatin configuration (for example, acetylation and methylation) may be the key. Here it is useful to consider the budding yeast *Saccharomyces cerevisiae*, which has provided much of our knowledge about eukaryotic recombination. In yeast, meiotic recombination is initiated by DNA double-strand breaks, which occur in relatively open chromatin regions (*17*, *18*). The same appears to be true of mammalian recombination. Furthermore, many of the proteins necessary for this process, such as the DNA topoisomerase–related enzyme Spo11, are highly conserved from yeast to mammals (*19*). Yeast recombination hotspots occur roughly once every 50 kb (*20*), and, as in mammals, they do not appear to

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be consistently associated with specific DNA sequence motifs (*17*).

These comparisons suggest a number of potentially useful studies. Although technically challenging, it may prove fruitful to examine regional variation in chromatin accessibility in mammalian meiotic cells. How does this affect the action of recombination-related proteins such as Spo11? In addition to Spo11, at least 11 other proteins are involved in the initiation of double-strand breaks and recombination in yeast (*21*), and many of the responsible genes have orthologs in humans (such as, *RAD50*, *RAD51*, and *MRE11*). Comparisons of these genes in humans and chimpanzees could reveal differences that affect recombination patterns. In yeast, recombination hotspots can be eliminated by the insertion of the Ty transposable element, which suppresses recombination in nearby sequences (*22*). Thousands of *Alu* and *LINE1* mobile elements have been differentially inserted in humans and chimpanzees since their divergence 5 million to 6 million years ago (*23*). Could these elements act in a fashion similar to yeast Ty, contributing to the rapid divergent evolution of recombination hotspots in humans and chimpanzees?

Studies such as that by Winckler *et al.* demonstrate the value of comparative genomic analysis for understanding basic biological processes such as recombination, and for potentially improving the design of genetic association studies. Their work also demonstrates the utility of analyses of within-species diversity and underscores the need for DNA sequence information from large samples of humans and other species. As this information accumulates, our understanding of biology, as well as our ability to design well-conceived gene-mapping studies, will continue to evolve and improve.

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PSYCHOLOGY

Beyond a Joke: From Animal Laughter to Human Joy?

Jaak Panksepp

In the beginning was the word…but was the word funny? Research suggests that the capacity for human laughter preceded the capacity for speech during evolution of the brain. Indeed, neural circuits for laughter exist in very ancient regions of the brain (*1*), and ancestral forms of play and laughter existed in other animals eons before we humans came along with our *hahahas* and verbal repartee. Recent studies in rats, dogs, and chimps (*2*, *3*) are providing evidence that laughter and joy may not be uniquely human traits.

The capacity to laugh emerges early in child development, and perhaps in mammalian brain-mind evolution as well. Indeed, young children, whose semantic sense of humor is marginal, laugh and shriek abundantly in the midst of their other rough-and-tumble activities. If one looks carefully, laughter is especially evident during chasing, with the chasee typically laughing more than the chaser. As every aspiring comedian knows, success is only achieved if receivers exhibit more laughter than transmitters. The same behavior patterns are evident in the "play panting" of young chimps as they mischievously chase, mouth, and tickle each other (*2*).

Laughter seems to hark back to the ancestral emotional recesses of our animalian past (*3*, *4*). We know that many other mammals exhibit play sounds, including tickle-induced panting, which resembles human laughter (*2*, *4*, *5*), even though these utterances are not as loud and persistent as our sonographically complex human chuckles (*6*). However, it is the discovery of "laughing rats" that could offer a workable model with which to systemically analyze the neurobiological antecedents of human joy (*3*). When rats play, their rambunctious shenanigans are accompanied by a cacophony of 50-kHz chirps that reflect positive emotional feelings (*7*). Sonographic analysis suggests that some chirps, like human laughs, are more joyous than others.

Could sounds emitted by animals during play be an ancestral form of human laughter? We have shown that if rats are tickled in a playful way, they readily emit these 50-kHz chirps (*3*, *8*). The rats we tickled became socially bonded to us and were rapidly conditioned to seek tickles. They preferred spending time with other animals that chirped a lot rather than with those that did not (*3*). Indeed, chirping in rats could be provoked by neurochemically "tickling" dopamine reward circuits in the brain (*9*), which also light up during human mirth (*10*). Perhaps laughter will provide a new measure for analyzing natural reward/desire circuits in the brain, which are also activated during drug craving (*7*, *11*).

Deciphering the neural circuitry of play-

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