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Finding recombination hotspots

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A new algorithm for revealing recombination hotspots, reported in the April 23 Science, has found that most recombination occurs outside genes. The mathematical method will be important in understanding the nature of recombination, according to the paper's authors. But others feel that claims that it will aid in mapping disease loci are unjustified.

"If we have a better sense of the way in which recombination rates go up and down in various places across the genome, we have a hope of learning more about the molecular mechanisms involved," said Peter Donnelly, coauthor of the paper and professor in the Department of Statistics at Oxford University.

Donnelly told us that the team's algorithm revealed that recombination occurs, on average, once every 200 kilobase pairs, with up to four-fold increases in frequency in these hotspots.

The method will enable comparison of recombination frequency in sequence motifs between species to discover what changes are driving recombination patterns, Donnelly said. "At a molecular biology level, we've got a whole new source of information of what's going on in recombination rates, and with the right kind of polymorphism data, you could apply it to other populations as well," Donnelly said.

That there is variation in recombination rates in humans has been recognized for some time through pedigree studies, said Donnelly. "[But] pedigree studies just don't have the resolution to go beyond megabase scales in determinations of recombination rates." At the other extreme is work carried out by groups such as Alec Jeffreys', which characterized male recombination hotspots, particularly in the HLA region, to a very fine resolution but over a much smaller area, he said.

"The point of our paper is we've developed a method - one might think of it as a telescope - which allows us to home in and see the variation in recombination rates over much finer scales than existing methods allow us to," Donnelly said.

Until now, researchers used family pedigrees to manually count recombination events. "The idea here is that you use individuals that are unrelated," said Carsten Wiuf, a professor at the Bioinformatics Research Center at the University of Aarhus in Denmark, who was not involved in the study. "Then you use some mathematical algorithm that helps you to do the counting; so they don't do it manually here."

A second reason for developing the mathematical method was its use in designing disease association studies and in their interpretation, according to Donnelly. "The hope is we'll soon be able to do association studies on pretty large scales across the genome," he said.

But Wiuf is not convinced the algorithm will be useful for fine-scale and association mapping, as suggested in the paper, nor is Mary Carrington from the US National Cancer Institute. Carrington, who was not involved in the study, said that the amount of detail generated by the method is simply too much for such basic studies.

"Knowing a recombination hotspot is in a region of say 100 bp for disease gene mapping may not be quite essential; we don't need to have it defined that precisely," said Carrington.

The authors estimated that for chromosome 20, about 50% of recombination occurs in less than 10% of the total sequence. In addition, for the HLA region, 80% of all recombination apparently occurs in less than 10% of the total sequence. "That really is not the case," said Carrington. "That's based on [Jeffreys'] data on a very short segment of the total [major histocompatibility complex (MHC)], so I think what they did is just extrapolate it from there."

Carrington said that current data suggest that about 20% of all the hotspots occur within 6% of the MHC. "It's really actually less than what they got from chromosome 20. The message from that is that everything depends on the scale at which you are looking at something," she said.

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