Inherited individual variations influence patterns of gene shuffling

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The first large-scale, high-resolution study of human genetic recombination has found remarkably high levels of individual variation in genetic exchange, the process by which parents pass on a mosaic-like mixture of their genes.

In an article appearing February 1, 2008, in *Science Express*, the online version of *Science*, researchers from the University of Chicago locate nearly 25,000 recombination events that occurred in the transmission of the parental genomes to 364 offspring. The high-resolution of their maps allows them to provide the precise location of where these genetic exchanges occur, and to assess the differences in recombination rates between individuals.

"Genetic recombination is a fundamental process, at the core of reproduction and evolution," said study author Graham Coop, PhD, post-doctoral fellow in the Department of Human Genetics at the University of Chicago, "yet we know very little about where it occurs or why there is so much variation among individuals in this important process."

"Now," he said, "we know where it occurs. Understanding where it happens provides us with important clues as to how it happens, how it is regulated and what the mechanisms are that control this essential biological phenomenon."

Recombination occurs during meiosis, a special kind of cell division that takes place only in the testicles and ovaries. In the process of making

sperm or egg cells, the parent-to-be takes the chromosomes inherited from each of his or her parents and reshuffles them, swapping parts of one chromosome for the matching segments of the other version of that same chromosome.

The result is a reproductive cell with a mosaic, or patchwork, of genes, about half from each parent, but shuffled together into entirely new combinations.

This process leads to offspring having different combinations of genes than their parents and is thought to have many advantages. Errors in this recombination process during the production of sperm or egg cells underlie a variety of chromosomal abnormalities and can cause deletions of regions of the genome, miscarriage, or genetic disorders such as Down syndrome.

The research team focused on the Hutterites, a genetically similar population of European immigrants who settled in the Dakotas in the 19th century and have maintained a communal agricultural lifestyle. One member of the research team, Carole Ober, PhD, professor of human genetics and of obstetrics and gynecology at the University of Chicago, has been working closely with this group for many years on health and inheritance issues.

The researchers collected DNA samples from 725 volunteers, representing 82 overlapping nuclear families, most of which included four or more children. These families are part of a larger 1650-person, 13-generation pedigree of the Hutterites in the U.S.

They used 500,000 markers of genetic variation (SNPs) to determine, along each chromosome, whether the genetic material transmitted from the mother (or father) came from the child's maternal (or paternal) grandmother or grandfather. The large number of markers allowed the

researchers to map out at high resolution the locations in the genome where ancestry shifts from one grandparent to another, which are known as recombination events.

Chromosomes from the mother (not including the X chromosome) averaged around 40 recombination events per gamete. Those from the father had only 26. The authors confirm a previous finding that older mothers have more recombination events in the transmission of their genome to their offspring, while the father's age has no such effect.

For both sexes, the majority of crossovers occur at genetic "hotspots," small regions where genetic exchanges are unusually common. Although the overall rate of hotspot use was similar between the two sexes, a subset of hotspots, "seems to be used mainly by one sex of the other," the authors note. Strikingly the pattern of hotspot used varied among individuals, but seemed to be passed on from generation to generation--a heritable difference potentially pointing to differences in the recombination machinery among individuals.

The study uncovered "tremendous variation in recombination rates over all genomic scales considered and in particular heritable variation in hotspot use," the authors conclude. Their ongoing efforts to map this variation should offer insights into the "genetic basis of recombination-rate variation and the selective forces governing the evolution of recombination rates."

Source: University of Chicago