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Researchers find new translocation; weak spots in DNA lead to genetic disease

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A genetics research team based at The Children's Hospital of Philadelphia continues to discover recurrent translocations—places in which two chromosomes exchange pieces of themselves. As many as 1 in 600 persons carry balanced chromosome translocations, which involve no loss or gain of DNA. Most such people appear healthy, but may have a child with abnormal chromosome composition and disabilities resulting from disrupted, extra or missing copies of genes.

While rare, such diseases originate a generation or two earlier in sequences of DNA bases spelled out as palindromes—lined up in reverse order of each other along the same strand of the double helix. These palindromic sequences are unstable spots where DNA strands are more likely to bend and break than in most other locations.

The research team now reports a new recurrent translocation between chromosomes 8 and 22. Study leader Beverly S. Emanuel, Ph.D., chief of Human Genetics and Molecular Biology at The Children's Hospital of Philadelphia, previously discovered a similar translocation between chromosomes 11 and 22, giving rise to a disorder that bears her name—Emanuel syndrome. "This new finding suggests that this type of genomic instability may be part of a more general mechanism lurking in the structure of our DNA," she said.

The study appears online today in the American Journal of Human Genetics. Emanuel led a team based at Children's Hospital of Philadelphia and the University of Pennsylvania, with collaborators from

other American and foreign institutions.

The current study summarizes data from 11 patients with the translocation designated t(8;22), involving an exchange of DNA that can ultimately result in a child with an extra chromosome. The presence of an extra chromosome is a trisomy, and it disrupts normal health and development. Two patients seen at Children's Hospital had abnormalities resulting from the extra chromosome derived from this translocation. The researchers searched the medical literature and found additional cases of translocations involving the same regions of chromosomes 8 and 22.

Some trisomies are fatal early in life; others cause a range of lifetime disabilities. Trisomy in t(8;22) causes less severe symptoms than the developmental disabilities and heart defects commonly found in Down syndrome (trisomy 21) or in Emanuel syndrome (a translocation between chromosomes 11 and 22). The 11 patients with +der(22) t(8;22) tended to have normal growth patterns, but mild mental retardation and developmental delays, and some deformities of the ears and fingers. Although the disorder is certainly rare, Emanuel said additional cases probably go unrecognized because of the disorder's nonspecific and mild features.

The roots of the disorder lie in sections of the genome having multiple repetitions of the DNA bases adenine and thymine. These sites, called palindromic AT-rich repeats (PATRRs) are sites at which DNA bends into fragile shapes called hairpins and cruciform structures which can break and rearrange with DNA from other chromosomes.

This DNA breakage tends to occur during meiosis, the period in which cells divide to produce gametes—sperm or egg cells. The researchers found that in sperm samples from healthy males, t(8;22) occurs at a low rate (between 1 sperm in 100,000 and 6 in 10 million). The chance that

an affected sperm will fertilize an egg is very low, but when this does occur, the child has a translocation in all their cells. Even then, when the translocation is balanced (i.e., there is an equal exchange of chromosomal material), the individual is healthy and unaffected, but that person may have a child affected by an unbalanced version of the translocation (an unequal segregation) or a (8;22) trisomy, with the range of symptoms mentioned above.

Among Emanuel's collaborators in the study was Elaine H. Zackai, M.D., director of Clinical Genetics at Children's Hospital, which provides a comprehensive array of multidisciplinary medical services for children and families with a broad range of genetic diseases.

For Emanuel, who in collaboration with Zackai has spent much of her career studying chromosome 22, the latest research provided a bit of a surprise. "The fact that we have now found recurring sites of instability along other chromosomes in addition to chromosome 22 suggests that there may be a more universal genetic mechanism that goes beyond the peculiarities of one chromosome," Emanuel said. "We have more to learn about exactly how these palindromic regions rearrange pieces of the human genome."

More information: "A Palindrome-Mediated Recurrent Translocation with 3:1 Meiotic Nondisjunction: The t(8;22)(q24.13;q11.21)," American Journal of Human Genetics, published online July 29, 2010, in print issue on Aug. 13, 2010.

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