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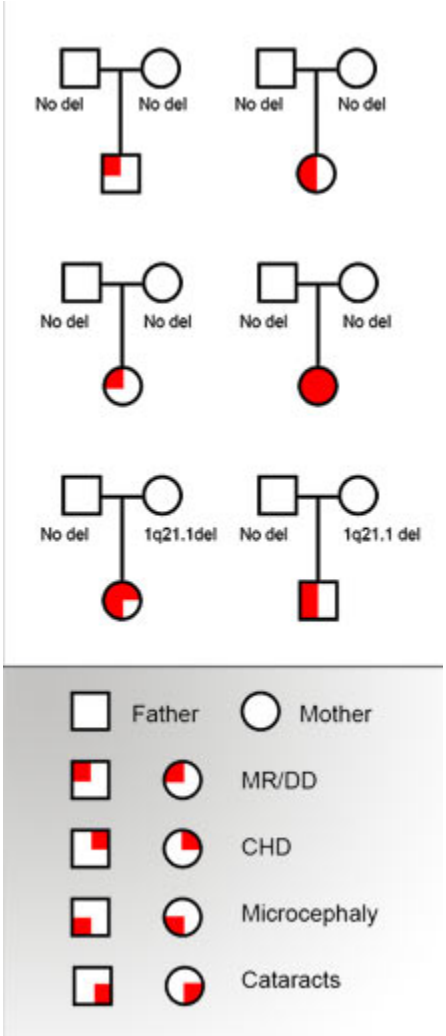
DNA Deletion Tied to Cognitive Problems

Detecting structural changes in the genome could bring new diagnoses.

By Emily Singer



Family tree: Pedigree charts of children with the 1q21.1 deletion demonstrate how variable the effects can be. Some have only mental retardation (top left) while others suffer mental retardation, heart problems, cataracts, and microcephaly, a smaller than average head (second from bottom, right). In most cases, the deletion arose spontaneously, but some children inherited it from unaffected (bottom left and right) or affected (second from top, right) parents. Credit: Mefford et al, NEJM, September 10, 2008

A small deletion in a specific chunk of DNA can trigger a wide variety of cognitive problems, including autism, mental retardation, and developmental delay, according to research published today in the *New England Journal of Medicine*. The findings, made possible by scientists' increasing ability to detect tiny architectural changes in DNA, could also signal a shift in how new disorders are identified and diagnosed. The same technology used to detect this deletion is now moving rapidly into clinical use, helping physicians diagnose the cause of unexplained developmental problems.

"This is really a paradigm shift in medical genetics. The genome scan is more informative diagnostically than patients' symptoms," says Jonathan Sebat, a geneticist at Cold Spring Harbor Laboratory, in Cold Spring Harbor, NY, who participated in the study.

Advances in gene microarray technologies have allowed scientists to screen the genome much more broadly than ever before, resulting in a flood of information linking specific genes to disease. Many of these studies have focused on single-letter changes in the DNA code. But a number of studies using similar microarray technology have shown that rearrangements of larger pieces of DNA--the equivalent of shuffling entire words, sentences, or pages--are surprisingly common and likely play a significant role in human health and disease.

Because these structural changes occur so frequently--scientists have found that everyone has them, often with no effect--it has been difficult to distinguish those that are harmful to our health from those that are benign. In the new study, Heather Mefford, a pediatric geneticist and scientist at the University of Washington (UW), in Seattle, in collaboration with Evan Eichler, a geneticist at UW, compiled data from clinical genetics labs around the world on variations in a specific region of the chromosome. They found that 25 patients in a screen of more than 5,000 people with mental retardation, autism, or congenital abnormalities were missing a similar 1.35 megabase piece of DNA. No one within a similar size group of healthy people harbored a variation in that region, meaning that the deletion is the likely cause--at least in part--of the patients' problems.

"Clearly, this region of genome is important for development," says

Mefford. "But the range of phenotypes is very broad. We found that the majority had cognitive problems that varied from learning disabilities to severe mental retardation." In addition, she says, some parents who were reportedly normal also carry the rearrangement.

The deletion encompasses at least seven genes, one known to play a role in development of the heart and a second in development of the lens of the eye. (Some patients with the deletion had heart and eye problems.) The function of the other genes is unknown, says Mefford, and it's unclear which contribute to abnormal cognitive development.

The new findings add to a growing body of evidence that small structural changes in DNA play a significant role in disease. Two studies published in *Nature* in June linked a deletion in the same region to increased risk of schizophrenia. And a third study identified structural variation in a different part of the genome that appears to be responsible for about 1 percent of autism cases--the largest genetic culprit found to date.

The same technology used in these research studies can be used to screen children with unexplained developmental disorders, and it's moving rapidly into clinical use. "I expect that within the next year or so, it will become the primary genetic test in the pediatric setting for children with any unexpected developmental abnormality," says David Ledbetter, a clinical geneticist at Emory University, in Atlanta. Microarray tests have 10 times the sensitivity of the conventional testing, which is based on microscopy and can only identify much larger structural changes, he says.

While it's not yet clear whether this information will help physicians make treatment decisions, Ledbetter and others say that it plays an important diagnostic role. "It's important for parents to understand what is causing the phenotype in their child," says Charles Lee, a cytogeneticist at Brigham and Women's Hospital, in Boston. Because the variations can either be inherited from a parent or arise de novo--meaning that the mistake occurred in the gametes or early in development--parents are usually tested as well. "If the parent has it, sometimes reexamination shows they are mildly affected," says Lee. The results can also be used for prenatal counseling. Parents whose children have a de novo variation are at no greater risk of having another affected child than the rest of the population is.

Scientists say that the next step in the research is to identify some of the other factors that modify the ultimate effect of the deletion--explaining why some people who carry it are unaffected and others severely mentally retarded. (While none of the healthy people in the study's control group had the deletion, follow-up testing revealed that some parents with no known cognitive problems did.) Sebat's group, for example, is searching for epigenetic changes--nongenetic factors that influence gene expression--that might impact a variety of deletions.

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