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New Genetic Syndrome Linked to Missing DNA

People who lack a certain large segment of DNA have a previously unrecognized syndrome characterized by mental retardation, seizures, and slight physical abnormalities, according to a genetic analysis conducted by HHMI investigator Evan E. Eichler at the University of Washington School of Medicine and a team of international collaborators. The deleted DNA segment is responsible for just a small percentage of cases of mental retardation, but when you think about how common mental retardation is, Eichler says, this deletion has a significant impact on human health.

The new discovery adds to a rapidly growing list of mental and physical disabilities caused by the loss or duplication of sizable pieces of DNA. While each individual structural variant is rare, together they constitute a major health issue. When you look at these things collectively, Eichler says, they contribute to a heavy burden of disease.

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— **Evan E. Eichler**

Eichler's team discovered the missing DNA segment after screening more than 700 British and Italian patients with mental retardation or seizure disorders. Two unrelated individuals had identical deletions of about a million and a half DNA letters on one of the two copies of chromosome 15. Once we found those patients, we knew that we needed to look at a bigger sample, says Heather C. Mefford, a postdoctoral fellow in Eichler's laboratory who helped conduct the study. It was published online in *Nature Genetics* on February 17, 2008.

A subsequent analysis of more than 2,000 people with mental retardation turned up nine people with missing DNA on the same part of chromosome 15. All nine had mild to moderate retardation and common physical characteristics, including full, upturned lips and abnormalities in their fingers and hands. Seven of the nine also had epilepsy or abnormal brain activity. Genetic tests of more than 2,000 people without mental retardation turned up none with the deletion.

Other researchers had already identified nearby regions on chromosome 15 as genetic trouble spots. Deletions and rearrangements of DNA in those areas cause several other genetic disorders, including Prader-Willi syndrome—which causes poor muscle tone, low levels of sex hormones and a constant feeling of hunger—and Angelman syndrome—which causes developmental delay and neurological problems. Eichler and his colleagues suspected the piece of DNA that was missing in the new syndrome was important because it contains six genes, including one previously linked to seizure disorders.

That part of chromosome 15 has many repeated DNA segments, Eichler points out. When a cell divides to produce germ cells, these duplicated segments can misalign through a process known as nonallelic homologous recombination, which can cause large segments of DNA to be missing in one of the daughter cells. This area is packed with duplications that have occurred over the last 10 to 15 million years of human evolution, Eichler says. Though the underlying cause of these duplications remains unknown, the result is a part of the genome where rearrangements are common and can have big consequences.

The newly discovered syndrome accounts for approximately 3 of every 1,000 cases of mental retardation. That may not seem like much, but Eichler estimates that similar deletions and rearrangements of DNA may account for 15 to 20 percent of mental retardation. In the paper, he and his colleagues recommend that people with mental retardation and seizures be tested to determine if their condition is caused by the deletion on chromosome 15. While no treatment for the syndrome exists, the information from such testing will contribute significantly to understanding a fraction of cases with mental retardation, he says.

Eichler expects that future genetic analyses will uncover other structural variants that cause physical and mental disorders. But many variants will be less common, which will require that more people be screened to find the variant. We've been able to find the rearrangements that occur with the highest frequency, Eichler says. Now we need to screen not 750 samples but 7,500. When we can do that in a cost-effective way, we will find all kinds of rare variants associated with disease.