MedicalXpress

Scientists discover second-oldest gene mutation

December 15 2011

A new study has identified a gene mutation that researchers estimate dates back to 11,600 B.C., making it the second oldest human disease mutation yet discovered.

Researchers with the Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute led the study and estimate that the mutation arose in the Middle East some 13,600 years ago. Only a mutation seen in cystic fibrosis that arose between 11,000 and 52,000 years ago is believed to be older.

The investigators described the mutation in people of Arabic, Turkish and Jewish ancestry. It causes a rare, inherited vitamin B12 deficiency called Imerslund-Gräsbeck Syndrome (IGS).

The researchers say that although the mutation is found in vastly different ethnic populations, it originated in a single, prehistoric individual and was passed down to that individual's descendents. This is unusual because such "founder mutations" usually are restricted to specific ethnic groups or relatively isolated populations.

The findings were published recently in the *Orphanet Journal of Rare Diseases.*

"Diagnosing IGS is often time-consuming and inconclusive mainly because vitamin B12 deficiencies have many causes, so identifying this

condition usually involves excluding other possibilities," says principal investigator Stephan M. Tanner, research assistant professor of molecular virology, immunology and medical genetics.

"Our findings permit reliable genetic diagnostics in suspected cases of IGS in that this mutation should be considered first when genetically screening patients from these populations."

Even in rare disorders, founder mutations can cause a significant fraction of all cases, he says. This mutation accounts for more than half of the cases in these populations and for about 15 percent of cases worldwide. "It is also often seen in expatriates living abroad," Tanner says.

IGS was identified just over 50 years ago. It occurs in children born with two mutated copies of either the amnionless (AMN) or the cubilin (CUBN) gene. When a genetic mistake is present in both copies of either of these two genes, a person cannot absorb vitamin B12 in the small intestine, resulting in the deficiency.

Children with IGS experience a high risk of infections, fatigue, attention deficit, paralysis and, ultimately, a form of anemia that can be fatal if left untreated. An estimated 400 to 500 cases of IGS have been described worldwide thus far. The incidence rate remains unknown. The syndrome is treatable with life-long injections of vitamin B12.

For this study, the researchers examined a total of 20 patients, 24 parents, 8 unaffected siblings, and 4 grandparents from 16 IGS families. Because the researchers found the mutation in such diverse populations, they were unsure whether it was a true founder mutation that first arose in one individual and was passed down through many generations, or whether it was simply a mutation that recurred frequently over time in different populations.

Careful analysis of the gene sequences on either side of the mutation (i.e., the haplotype in both the Muslim and Jewish families), however, pointed to a single mutational event rather than repeated events.

Provided by Ohio State University Medical Center