RESEARCHERS DISCOVER GENE MUTATION IN GAUCHER DISEASE; MAKES SCREENING POSSIBLE TO DETERMINE COUPLES AT RISK

LA JOLLA, CALIF. 6:30 p.m. (Eastern Time) Nov. 30, 1991 -- Screening for couples at risk for having a baby with Gaucher disease may now be possible with the discovery at The Scripps Research Institute (TSRI) of a gene mutation that plays a role in the disorder.

The research leading to the discovery is described in the December, 1991 issue of the Proceedings of the National Academy of Sciences.

Lead author Ernest Beutler, M.D., chairman of the TSRI Department of Molecular and Experimental Medicine, notes that Gaucher disease is caused by a deficiency of an enzyme needed for the elimination of cellular waste products. Although previous research had identified 75 percent of the mutant genes causing this disease in the Jewish population, screening couples for the potential of producing offspring with the disorder was not reliable until most of the remaining 25 percent of mutant genes could be found.

Some 15,000 Americans of Ashkenazic (Eastern European) Jewish descent are estimated to have inherited Gaucher disease. Manifestations vary from a rapidly fatal disease, with death...
occurring in the first year of life, to a disorder so benign that it is diagnosed quite by accident. Symptoms in moderate to severe cases can include enlarged spleens and livers, painful bone abnormalities, and even neurologic disorders.

The TSRI discovery identifies a single mutant gene, called 84GG, which accounts for most of the previously unidentified Gaucher disease mutations in Jewish patients, Beutler says. The mutation is an insertion of an extra guanine molecule in the DNA and this prevents the formation of the needed enzyme.

TSRI researchers also indicated that the 84GG gene appears to play a role in the severity of Gaucher disease. When a previously identified mutant gene labeled 1226G is found in a patient's DNA, the disease is usually mild, with symptoms often not appearing until middle age. When the 84GG gene, or a previously identified one called 1448C, is found along with the 1226G, the patient has a more severe form of Gaucher disease, with onset typically in early childhood. Although no cases of the 84GG alone have been identified, the TSRI researchers believe the resulting disease would most likely be fatal to the fetus during pregnancy or shortly after birth.

Just as most Jewish couples today routinely have DNA examination to detect Tay-Sachs disease, they will now be able to test for and receive genetic counseling about Gaucher disease, Beutler says.

For example, if both the male and female screened for Gaucher disease are found to be carriers, the chances of their child having the disease would be one in four, he notes. If only
one member of the couple was found to have a gene mutation, the risk of Gaucher disease would be one in 4,000, and less if enzyme activity is normal in the parent without a detectable mutation.

Although a DNA screening program might cost somewhere around $75 per person, it would be significantly less than the $50,000 to $800,000 a year cost of treating a Gaucher disease patient with currently-available enzyme therapy, Beutler says.

While optimistic about the benefits of genetic counseling for couples at risk, Beutler notes that further research is needed for more precise prediction of disease severity.

"Although patients with the mild mutation usually have less severe disease than those with mutations such as 84GG or 1448C, there is an overlap between the groups," he says. "Thus, some patients who have only the 1226G mutation may have relatively severe disease, while a few patients who carry a more severe mutation have milder disease. This produces difficulties in counseling and we're trying to address this with further research in the laboratory."

Additional authors of the article in the Proceedings of the National Academy of Science are Terri Gelbart; Wanda Kuhl; Joseph Sorge, M.D.; and Carol West.

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