

Putative X-Linked Adrenoleukodystrophy Gene Shares Unexpected Homology With ABC Transporters

Adrenoleukodystrophy (ALD) is an X-linked disorder that leads to central nervous system demyelination and adrenal insufficiency. It can result in death within a few years, although the phenotype varies widely even within a family. The main biochemical abnormality found in this disorder is the accumulation of saturated very-long-chain fatty acids (VLCFA) due to impaired β -oxidation in peroxisomes.

ALD was the subject of the recent film, "Lorenzo's Oil." In this docudrama, a couple whose 6-year-old son, Lorenzo, has been stricken with the disease circumvent the medical establishment in an attempt to find a cure. The oil referred to in the title consists of erucic acid and oleic acid, which returned the raised plasma concentrations of saturated VLCFAs to normal. Unfortunately, this treatment (touted by the film as a cure for ALD) has since been shown in a 5-year controlled study to be ineffective for many ALD patients whose condition continues to deteriorate. Also of importance is that other patients who have not received the treatment remain stable for many years. Thus, it is likely that Lorenzo's condition remained stable due to chance and not to "cure" from the oil.

A gene that is thought to cause the ALD defect has been cloned recently by Patrick Aubourg's group in Paris. This gene was cloned utilizing a positional cloning approach, in which a gene is mapped to particular chromosomal region using restriction fragment length polymorphisms (RFLPs) and candidate genes in that region are then identified and used as probes for genes containing mutations in the affected families.

While it was originally thought that VLCF-CoA synthetase was the most likely candidate for the ALD gene, the gene identified by Aubourg's group bears no sequence resemblance to this or 3 other enzyme genes involved in peroxisomal β -oxidation. Instead, it is highly homologous with a peroxisomal membrane protein that is involved in peroxisome biogenesis and that belongs to a family of membrane proteins known as the adenosine triphosphate-binding cassette transporters. This family includes the multidrug-resistant gene product, the cystic fibrosis

transmembrane conductance regulator, and genes that map in the human major histocompatibility complex region. The members of this gene family are involved in transport of proteins, amino acids, inorganic ions, and peptides in both prokaryotes and eukaryotes. Thus, the sequence of this newly identified gene suggests that ALD may be caused by defective transport of VLCFA-CoA synthetase into the peroxisomal membrane, rather than by a deficiency in the VLCFA-CoA synthetase enzyme itself.

Mosser J, Douar A-M, Sarde C-O, et al. *Nature*. 1993;361:726-730.

Moser, HW. *Lancet*. 1993;341:544.

Editor's comment: *It is unfortunate that a popular film, "Lorenzo's Oil," would present as fact a hypothesis that has not withstood the test of a controlled trial, and would seek to further widen the rift that exists today between the general public and the medical and scientific establishment. The fallacies of treatment and flagrant misinformation in this film are duly recorded under the title "Pernicious Treatment," by Fred S. Rosen in Nature 1993;361:695, and in a film review by Dr. Hugo Moser in Lancet 1993;341:544. Both of these outstanding scientists are appalled at the the filmmaker's lack of responsibility in researching the truth and to patients with ALD, to physicians who are treating them, and to the United Leukodystrophy Foundation.*

However, the discovery of a gene that may represent the causal factor in ALD is very exciting, and brings with it the hope that in the near future, families afflicted with this tragic illness will have access to an understanding of why the disease happens and new therapies that may be effective in all cases. Prenatal diagnosis should be possible, and gene therapy is certainly a possibility as clinical trials are underway for gene therapy in a number of other disorders involving the central nervous system.

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