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Metachromatic leukodystrophy among southern Alaskan Eskimos: molecular and genetic studies

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Summary: Metachromatic leukodystrophy (MLD) is an autosomal recessive disorder resulting from the inability to metabolize sulphatide, an important component of myelin. Although there is significant clinical variability between patients, most have the late-infantile form. It is one of the most common lysosomal disorders involving mental deterioration and is found throughout the world. The great majority of the cases have a deficiency of arylsulphatase A activity. Accurate diagnosis of MLD is complicated by the presence of so-called pseudodeficiency alleles and the need to receive specimens for biochemical testing within 24–48 h of collection. We report the identification of the mutation (a g-to-a transition in the first nucleotide of intron 4) in the arylsulphatase A gene causing late-infantile MLD among the Eskimo population of southern Alaska. As all patients and family members from living and deceased patients had the same mutation, a mutation-based test was developed to identify patients and carriers that can be done on dried blood spots sent via regular mail service. A possible genetic link between this population and the Navajo Indians of the southwestern United States is proposed.

Metachromatic leukodystrophy (MLD, McKusick 250100) is a lysosomal disorder resulting from decreased metabolism of sulphatide, an important component of myelin (Kolodny, 1989). Most patients have mutations in the arylsulphatase A gene, but some have mutations in the prosaposin gene which codes for SAP-1 (or saposin B), a heat-stable protein required for interaction between sulphatide and arylsulphatase A (for review see Gieselmann et al 1994). A large number of mutations in the arylsulphatase A gene have been reported in patients with MLD (Gieselmann et al 1994). Mutation identification can be helpful in predicting the clinical course in patients with MLD (Polten et al 1991). Patients are usually classified as having either late-infantile, juvenile or adult MLD

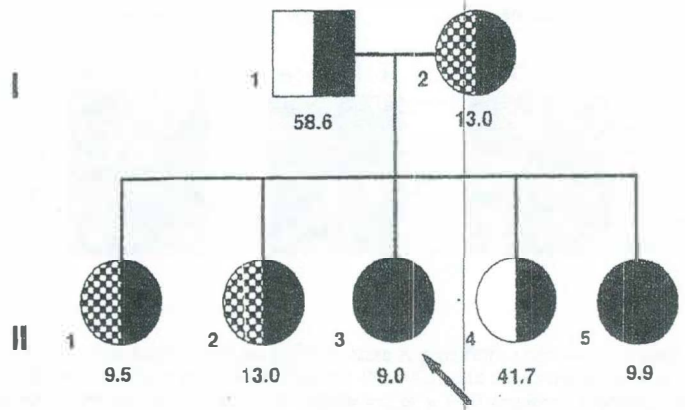

Figure 1 Pedigree from family 1 showing the proband (arrow) and the leukocyte arylsulphatase A activities (beneath each symbol). Arylsulphatase A activity in controls averages 71.1 nmol/h per mg protein. The black area denotes the presence of the IVS4nt1 mutation; the open area denotes the presence of the normal allele; and the chequered area indicates the presence of a pseudodeficiency allele

depending upon the age of onset of symptoms. While most patients are initially diagnosed by measuring low arylsulphatase A activity, the test is not conclusive owing to the high incidence of the so-called pseudodeficiency allele in the general population (Gieselmann et al 1989). Therefore, accurate diagnosis requires additional studies, such as measurement of urinary sulphatide excretion, radiolabelled sulphatide loading in cultured cells and, if possible, mutation analysis.

Arylsulphatase A is encoded by a relatively small gene of about 3 kb located on chromosome 22 (Kreysing et al 1990). While many mutations in the arylsulphatase A gene have been identified in the general population, common mutations may be found in certain ethnic groups such as the Habbanites in Israel (Zlotogora et al 1980) and the Navajo Indians in the southwestern United States (Pastor-Soler et al 1994). In addition, the finding of an identical mutation in geographically separated populations may indicate past intermixing between these peoples. The identification of a common mutation in a relatively homogeneous population permits accurate diagnosis of patients and identification of carriers by DNA analysis of small samples sent from locations that are hard to access. We describe the high incidence of late-infantile MLD in the Southern Eskimo population of Alaska, the identification of a common mutation found in all patients and all expected family members, and the development of a relatively simple method for securing samples for mutation analysis.

MATERIALS AND METHODS

Population studied: Initially, heparinized blood was received from family 1 who had a child considered to have late-infantile MLD by clinical symptoms. This Eskimo family lived in Alakanuk, a village at the mouth of the Yukon River in Alaska. The proband was