Molecular Genetics of Metachromatic Leukodystrophy

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Summary: Metachromatic leukodystrophy is a lysosomal storage disorder caused by the deficiency of arylsulphatase A. The disease is characterized by a progressive demyelination that causes a variety of neurological symptoms. Patients die within a few years after the age of onset. Clinically the disease is heterogeneous and according to the age of onset three different forms can be distinguished. The gene of arylsulphatase A has been cloned and several mutations causing metachromatic leukodystrophy have been characterized. The distribution of these alleles among patients with different clinical forms of the disease has revealed a genotype-phenotype correlation. A major determinant of the clinical phenotype is the residual enzyme activity that it associated with a particular genotype. Homozygosity for alleles that do not allow the synthesis of arylsulphatase A polypeptides causes the most severe form of disease, whereas homozygosity for alleles that encode arylsulphatase A with low residual enzyme activity is found in the mild late-onset forms of disease. A substantial arylsulphatase A deficiency can also be found in healthy individuals at high frequency. This phenomenon has been termed pseudodeficiency. It is often difficult to distinguish whether an arylsulphatase A deficiency is due to metachromatic leukodystrophy or harmless pseudodeficiency. The characterization of the mutations causing pseudodeficiency has allowed the detection of the pseudodeficiency allele in the DNA of probands and has thus improved the diagnosis and genetic counselling for metachromatic leukodystrophy.

INTRODUCTION
Metachromatic leukodystrophy is a lysosomal storage disease caused by the deficiency of the enzyme arylsulphatase A (EC 3.1.6.8). The inheritance is autosomal recessive and the frequency is estimated to be 1 in 40 000 (Gustavson and Hagberg 1971). Arylsulphatase A is involved in the degradation of sulphated glycolipids and one of its major substrates is cerebroside 3-sulphate. This lipid is mainly found in the myelin membranes, where it accounts for 3–4% of total membrane lipids. Arylsulphatase A initiates the degradation of this lipid by desulphation of a sulphated galactose residue. In this reaction arylsulphatase A needs the assistance of a small acidic protein, which has been called sphingolipid activator protein or briefly saponin B (Fischer and Jatzkewitz 1977). This protein solubilizes the hydrophobic lipid, so that it is accessible to arylsulphatase A. Deficiencies of this activator protein cause a disease that is indistinguishable from metachromatic leukodystrophy (Stevens et al 1981). This
variant form of disease, however, is very rare and this article will focus on metachromatic leukodystrophy caused by arylsulphatase A deficiencies.

Cerebroside sulphate accumulates in the lysosome and in the plasma membrane when aryl sulphatase A is deficient. In the affected patients cerebroside sulphate may constitute up to 30% of total myelin membrane lipids. Although the storage occurs in all tissues, it only clinically affects the nervous system. It leads to a progressive demyelination, which causes a variety of neurological symptoms. In the typical case the disease starts at the age of about 18 months. Children lose acquired capabilities, they develop a spastic tetraparesis, dysarthrias, ataxias, dementias and finally die in a decerebrated state.

The disease is clinically heterogeneous. Three different forms can be distinguished depending on the age of onset: a severe late-infantile form starting between the ages of 1 and 3 years, a juvenile form with an age of onset of 3–16 years, and adult forms that may not become apparent before the 3rd decade of life. The progression is slower in the late-onset forms and patients may survive for as much as 20 years after the disease has started. Psychiatric symptoms may prevail, particularly in the adult patients, before the neurological symptoms develop (for detailed review see Kolodny 1989).

Arylsulphatase A deficiency can also be observed in individuals who are clinically healthy (Dubois et al 1977). This phenomenon has been termed pseudodeficiency. These individuals have only about 10–20% of normal enzyme activity. Obviously these low activities are sufficient to prevent the manifestations of disease. Pseudodeficiency is caused by homozygosity for an arylsulphatase A allele that owing to certain mutations supports only the synthesis of reduced amounts of enzyme. The frequency of this arylsulphatase A pseudodeficiency allele is estimated to be between 7% and 15%, which predicts that 0.5% to 2% of the population are homozygous and thus pseudodeficient (Herz and Bach 1984; Hohenschutz et al 1989). Whereas pseudodeficiency is harmless for the carriers, it causes problems in the diagnosis and genetic counselling of metachromatic leukodystrophy because on the basis of in vitro determinations of enzyme activities it is difficult to differentiate whether an enzyme deficiency is due to a pseudodeficiency or metachromatic leukodystrophy.

This paper will summarize recent results of research on the molecular biology of metachromatic leukodystrophy. It will give a summary of all mutations known so far and will discuss some alleles that are relevant for the understanding of genotype–phenotype correlations in more detail.

**STRUCTURE OF THE ARYLSULPHATASE A cDNA AND GENE**

The arylsulphatase A cDNA has a 383-nucleotide 5' untranslated region, a coding sequence of 1521 nucleotides and a 3' untranslated region of 100 nucleotides (Stein et al 1989). The 1521 nucleotide coding sequence predicts a protein of 507 amino acids. Eighteen of these amino acids represent the leader peptide, so that the mature enzyme consists of 489 amino acids. The molecular weight of the enzyme that can be calculated from these data is in good agreement with the 62 kDa that has been determined in studies on the biosynthesis of arylsulphatase A. The cDNA sequence has revealed the existence of three potential N-glycosylation sites. In vitro mutagenesis