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# COMMENTARY
# "Pseudodeficiencies" of Lysosomal Hydrolases

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## Introduction

In almost all cases, an inherited deficiency of a lysosomal hydrolase is associated with clinical disease. There are, however, individuals who, in spite of having greatly reduced enzyme activity, as determined by in vitro techniques carried out on their cells or plasma, remain clinically healthy. These persons are said to have a "pseudodeficiency" of the enzyme in question (Zlotogora and Bach 1983, 1985). In actual practice, this term is not limited to absolute deficiencies but, rather, is employed to describe those situations in which the enzyme values are sufficiently below the carrier range that carriers are confused with, or indistinguishable from, affected patients.

While the pseudodeficiency phenomenon may not be limited to lysosomal hydrolases, it is clearly more common in this group. To date, pseudodeficiencies have been reported to occur with at least nine lysosomal hydrolases. These include arylsulfatase A, β-hexosaminidase A, β-hexosaminidase A and B, galactosylceramidase, α-galactosidase, β-glucuronidase, α-L-iduronidase, α-glucosidase, and α-L-fucosidase.

## Arylsulfatase A (Defective in Metachromatic Leukodystrophy [MLD])

Arylsulfatase A, a component of cerebroside sulfatase, catalyzes the desulfation of cerebroside sulfate. Inherited deficiencies of this enzyme usually are associated with accumulation of cerebroside sulfate in the CNS. The resulting clinical phenotype, MLD, is divided into several subtypes according to severity, ranging from late infantile to adult.

There are, however, individuals who, in spite of having low levels of arylsulfatase A, lack clinical or biochemical evidence of disease (Dubois et al. 1977; Schaap et al. 1981; Tonnesen et al. 1983; Kihara et al. 1984). It has been concluded, therefore, that, while sonicates of white blood cells or fibroblasts from these individuals have low arylsulfatase A activity (<10%) against artificial substrates in vitro, they are able to catabolize the natural substrate in vivo sufficiently well to prevent disease (Wenger and Louie 1991).

Pseudodeficiencies of arylsulfatase A have generally been considered to result from one or more allelic mutations of the gene causing MLD, usually designated "ASAp" (Schaap et al. 1981). Healthy individuals, who lack activity against the artificial substrate in vitro, could be either homozygous for the pseudodeficiency allele (ASAp/ASAp) or a genetic compound for pseudodeficiency and MLD alleles (ASAp/ASA−).

Direct evidence for this was provided by Gieselmann et al. (1989), who described two molecular alterations in the only ASAp allele described to date. One causes a change (AATAAC→AGTAAC, at position 2725) downstream from the stop codon, resulting in a nonfunctional polyadenylation signal and a deficiency of the normal 2.1-kb mRNA species. This results in a 90% reduction in the enzyme (Gieselmann et al. 1989, 1991*b*).

A second A→G transition, at position 1788, leads to the substitution of asparagine 350 by serine (N350S) and to the loss of an N-glycosylation site. In transient-transfection studies this mutation does not affect the synthesis, stability, or catalytic properties of the arylsulfatase A. Thus it is concluded that the pseudodeficient arylsulfatase A activity results from a quantitative reduction in mRNA and that this reduction is due to the defective polyadenylation caused by the first mutation. To date, all examined pseudodeficiency alleles

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having the change in the polyadenylation site also have the second mutation (Nelson et al. 1991).

The clinical importance of the ASAp allele stems from high frequency of the pseudodeficiency allele (Herz and Bach 1984; Hohenschutz et al. 1989; Barth et al. 1993). Current evidence indicates that ~10%–20% of healthy individuals in the general population may be carriers of the arylsulfatase A pseudodeficiency mutation. Early estimates of this gene frequency ranged from 7.3% (Hohenschutz et al. 1989 ), to 13.7% (Schaap et al. 1981), to 17% (Herz and Bach 1984). More recently, Nelson et al. (1991), using allele-specific hybridization, found that 19% (14/73) of unrelated, healthy individuals in Australia were heterozygous for the pseudodeficiency allele.

Assuming an ASAp allele frequency of 7.3%–15%, Gieselmann (1991) predicts that 0.5%–2% of the population will be homozygous for the pseudodeficiency allele. This increases the likelihood that the pseudodeficiency mutation will confound the interpretation of the results of both patients and families being evaluated for disorders involving the CNS (Baldinger et al. 1987; Gieselmann et al. 1991*b;* Kappler et al. 1991*a*). Because the pseudodeficiency allele is more frequent than the alleles causing MLD (the frequency of the latter is estimated to be 0.5%), it is likely that individuals with both a pseudodeficiency of arylsulfatase A and neurologic symptoms may be misdiagnosed as MLD (Li et al. 1992; Shen et al. 1993).

While there have been suggestions that the pseudodeficiency allele could contribute to a susceptibility for certain multifactorial diseases (Kappler et al. 1991*b*), other investigations have found no evidence for its involvement in such disorders (Herska et al. 1987; Francis et al. 1993). Several individuals shown to be compound heterozygotes for the pseudodeficiency allele and a mutation causing the most severe (late infantile) form of MLD lack any clinical or biochemical evidence of disease (Polten et al. 1991; Penzien et al. 1993).

Gieselmann (1991) has described an assay that allows for the direct and rapid detection of the ASAp allele by using PCR. It must be kept in mind, however, that the presence of the pseudodeficiency mutation does not exclude the existence of an MLD-causing mutation elsewhere on the same gene. Such an occurrence has been described in detail by Gieselmann et al. (1991*a*). Indeed, because of the high frequency of the pseudodeficiency mutation (15%–20% of all alleles), it is possible that almost a fifth of mutations causing MLD may be found together with the ASAp mutation, on the same allele. It is, therefore, important to be aware that the presence of the ASAp mutation does not rule out the existence of disease-producing mutations on the same chromosome.

Additional complications have also been reported (Shen et al. 1993). It therefore may be necessary to perform a combination of assays to determine the actual genetic makeup of a family or patient (Kappler et al. 1991*c;* Li et al. 1992; Penzien et al. 1993).

## β-Hexosaminidase A (Defective in Tay-Sachs Disease)

Hexosaminidase A catalyzes the cleavage of $GM_2$ ganglioside and related glycolipids. The deficiency of this enzyme usually results in Tay-Sachs disease. The measurement of β-hexosaminidase A, with artificial substrates, has been widely utilized for the detection of individuals who are either affected with or carriers for Tay-Sachs disease.

While most individuals identified as being heterozygous or homozygous for Tay-Sachs disease by standard procedures are identified correctly, there are exceptions. Such individuals have been described by Vidgoff et al. (1973), Kelly et al. (1976), O'Brien et al. (1978), Thomas et al. (1982), Grebner et al. (1986), and Navon et al. (1986).

The basis for the presence of normal individuals who lack hexosaminidase A activity has now been clarified by the discovery of two mutations resulting in pseudodeficiencies of Hex A. The first, a C→T transition at nucleotide 739 (Arg247Trp) was found in seven of eight pseudodeficient subjects, by Triggs-Raine et al. (1992). The remaining individual (a healthy 42-year-old female) was shown to have a C→T change at nucleotide 745 (Arg249Trp) (Cao et al. 1993). In this last individual the mutation was found as a compound with the adult-onset mutation (Cao et al. 1993); thus, there is at least a theoretical possibility that, if it were present as a compound with a classical Tay-Sachs allele, it might result in some form of mild, late-onset disorder.

In addition to the pseudodeficiency mutation, seven of these eight subjects had a disease-causing mutation on the other allele (Triggs-Raine et al. 1992). It is therefore concluded that most healthy individuals lacking Hex A activity are compound heterozygotes for a Tay-Sachs disease allele and a pseudodeficiency allele. In contrast to the reduced hexosaminidase A activity (as determined by heat inactivation using artificial substrates), these individuals (when examined) have been found to have substantial levels of enzyme activity in assays using the natural substrate ($GM_2$ ganglioside).

Enzyme-based screening tests fail to distinguish between carriers of these apparently benign mutations and carriers of Tay-Sachs mutations (Tomczak et al. 1993). This fact is made more important by data indicating that the two known pseudodeficiency alleles appear to be the most common mutations responsible for "enzyme-defined" carriers of Tay-Sachs disease in the non-Jewish population. This conclusion is based on two studies that found 20 (32%) of 62 (Triggs-Raine et al. 1992) and 8 (42%) of 19 (Tomczak et al. 1993) non-Jewish enzyme-defined carriers to have the $C_{739}\rightarrow T$ mutation. Moreover, Cao et al. (1993) detected the second pseudodeficiency mutation ($C_{745}\rightarrow T$) in 4 (6%) of 63 of the same population. The incidence of these mutations in the Jewish population is less clear. Triggs-Raine et al. (1992) failed to detect the first ($C_{739}\rightarrow T$) mutation in 36 Jewish enzyme-defined carriers previously shown not to have any of the three common disease-related mutations. In contrast, Tomczak et al. (1993) found that 6 (32%) of 19 Jewish individuals carried the pseudodeficiency allele with the $C_{739}\rightarrow T$ mutation. Finally, Mules et al. (1992) also found the $C_{739}\rightarrow T$ mutation in a non-Jewish Pennsylvania Dutch kindred.

It is now possible to perform DNA-based analyses of enzyme-defined carriers. Conditions suitable for the detection of the $C_{739}\rightarrow T$ mutation have been described by Triggs-Raine et al. (1992) and Tomczak et al. (1993). The second mutation ($C_{745}\rightarrow T$) can be identified by methods described by Cao et al. (1993). Because a third of all non-Jewish enzyme-defined carriers may not be carriers for Tay-Sachs disease, it would be important to establish the nature of the mutation before genetic counseling is provided to such individuals.

## β-Hexosaminidase A and B (Defective in Sandhoff Disease)

Hexosaminidase A is a dimer made up of α- and β-subunits, while hexosaminidase B consists only of β-subunits. Mutations in the gene encoding the β-unit therefore result in the absence of both the A and B forms of this enzyme, leading, in most cases, to Sandhoff disease.

Exceptions to the above relationship include a healthy father of two children with Sandhoff disease whose hexosaminidase A and B activity was in the affected range when assayed with an artificial substrate (Dreyfus et al. 1975, 1977). With the natural substrate, a value in the heterozygote range for Sandhoff disease was found. It was concluded that this individual was a compound heterozygote with one classic Sandhoff allele (also carried by his wife and inherited by their two affected children) and one pseudodeficiency allele (hexosaminidase Paris) (Dreyfus et al. 1975). A normal daughter appears to be an unaffected compound heterozygote.

Dlott et al. (1990) showed the alteration in this individual to be a duplication of the junction of intron 13 and exon 14. This, in turn, generated an alternate splice site causing an in-frame 18-nt insertion into the mRNA. The resulting abnormal product was degraded rapidly. A small amount of correctly spliced messenger appeared to be responsible for ~10% of normal Hex A activity found in the asymptomatic individuals.

## Galactosylceramidase (Defective in Krabbe Disease)

Galactocerebroside β-galactosidase is responsible for the cleavage of galactocerebroside. A deficiency of this enzyme usually results in an inherited, lethal, neurodegenerative disease of infants.

In 1976 Wenger and Riccardi described a public health nurse with low galactosylceramidase (<10% of normal). Evidence that this deficiency resulted from a primary defect in galactosylceramidase was seen in the fact that complementation studies with cells from Krabbe patients failed to restore enzyme activity (Wenger and Louie 1991).

In a second family, the healthy father of two children with Krabbe disease had enzyme values indistinguishable from those of his affected children (Wenger and Riccardi 1976). The most satisfactory explanation for this finding is that the father is a compound heterozygote, i.e., has allelic mutations for both Krabbe disease and a pseudodeficiency.

Finally, Desnick et al. (1992) described a pseudodeficiency allele in the husband of a woman having prenatal diagnosis for Krabbe disease. In this case the significance of the low enzyme activity in both direct and cultured chorionic villi could not be determined, because of the presence of similar low values in the father's cells. The family chose to continue the pregnancy, which resulted in the birth of a child affected with Krabbe disease.

## α-Galactosidase A (Defective in Fabry Disease)

The lysosomal enzyme, α-galactosidase, cleaves the terminal galactose from the natural substrate, ceramide trihexoside. As the α-galactosidase gene is located on

the X chromosome, mutations in this gene usually result in an X-linked recessive disorder.

An early report of a pseudodeficiency of α-galactosidase was that of a healthy 51-year-old male whose daughter was being evaluated for features suggestive of Fabry disease (Bach et al. 1982). In spite of a low enzyme level against the artificial (4-methylumbelliferyl) substrate, the father had no clinical findings suggestive of Fabry disease, nor did he excrete increased amounts of ceramide trihexoside. His two daughters had intermediate levels of α-galactosidase. The interpretation of the findings in this man, however, was made difficult by the fact that his daughters had some accumulation of ceramide trihexoside (Bach et al. 1982).

Additionally, there have been reports of older males with low enzyme levels who lack most of the features found in Fabry patients. These include a male with rheumatoid arthritis and proteinuria who was otherwise normal at age 42 years (Bishop et al. 1981) and two unrelated males with proteinuria and kidney changes who lacked any other features of Fabry disease (Clarke et al. 1971; von Scheidt et al. 1991).

### α-L-Iduronidase (Defective in Hurler and Scheie Syndromes)

α-L-iduronidase catalyzes the cleavage of the terminal iduronic acid residues from dermatan sulfate and heparan sulfate. A deficiency of this enzyme usually results in a spectrum of clinical phenotypes ranging from severe (Hurler syndrome) to mild (Scheie syndrome) or in a disorder intermediate between these two disorders, the Hurler-Scheie syndrome.

There have been at least three descriptions of pseudodeficiencies involving this enzyme. Two of these reports concerned obligate carriers for mucopolysaccharidosis (MPS) I, i.e., unrelated mothers of children with the Hurler syndrome (Gatti et al. 1985; Whitley et al. 1987). These women, who had low levels of iduronidase activity, lacked any clinical findings expected from such a defect and were presumed to have both a Hurler and a pseudodeficiency allele.

More recently, Taylor and Thomas (1993) described a deficiency of α-L-iduronidase activity in a normal woman who served as a control for an unrelated family being evaluated for the Hurler syndrome. As with the previous cases, this individual also lacked any clinical or biochemical alterations suggestive of any form of MPS I. In this case, however, it was not possible to determine if she was a compound heterozygote or was homozygous for the presumed pseudodeficiency allele.

### β-Glucuronidase (Defective in Sly Syndrome)

β-Glucuronidase is responsible for the removal of terminal glucuronic acid residues from glycosaminoglycans. A deficiency of this enzyme usually results in moderate skeletal abnormalities and mild to moderate developmental delay (Sly syndrome).

The only reported pseudodeficiency involving this enzyme is in a healthy 25-year-old mother of a child with classical MPS VII (Chabas et al. 1991). This child lacked β-glucuronidase activity, while his father had approximately one-half the normal value. The child's mother also had very low levels (6%–10% normal) of this enzyme activity. She had normal glycosaminoglycan excretion and $^{35}S$ sulfate incorporation. It was concluded that this woman was a compound heterozygote for an MPS VII and a pseudodeficiency allele (Chabas et al. 1991).

### α-Glucosidase (Defective in Pompe Disease)

α-Glucosidase is the only lysosomal enzyme involved in the degradation of maltose and glycogen. An impaired ability to release glucose from these substrates usually results in one of several forms of glycogenosis type II, or Pompe disease. While the various forms differ in age at onset, organ involvement, and rate of progression, individuals lacking α-glucosidase usually have some form of the disease.

Nishimoto et al. (1988) described a family in which five members lacked the enzyme but only one exhibited clinical evidence of the disease. The affected individual, a 16-year-old female, suffered from the juvenile-muscular-dystrophy form of Pompe disease. While, as expected, she had <1% of glucosidase activity against the artificial substrate, her parents had ~15% of normal, not the 50% expected of obligate carriers. It was proposed that both parents could be compound heterozygotes for the juvenile form of Pompe disease and a pseudodeficiency allele.

### α-L-Fucosidase (Defective in Fucosidosis)

Fucosidosis is a disorder of oligosaccharide metabolism, resulting from a deficiency of the lysosomal hydrolase α-L-fucosidase. The more severely affected patients have psychomotor retardation, coarse facies, growth retardation, and dysostosis multiplex. A few, more mildly affected patients, who have a somewhat less severe course and angiokeratoma, have also been reported (Willems et al. 1991).

As with the other enzymes discussed in this review,

there are exceptions. In this case the difficulties arise from the presence of an alteration resulting in low serum α-L-fucosidase levels in serum or plasma. Details regarding this change have appeared in a number of reports, including those by Ramage and Cunningham (1975), Turner et al. (1975), Wood (1976), and Alhadeff and Andrews-Smith (1978).

While the deficiency in this situation appears to be most marked in plasma, Wauters et al. (1992) have shown that individuals with low plasma fucosidase levels also have ~30% of normal activity in fibroblasts. In addition, as with some of the other pseudodeficiencies, the incidence of this alteration appears to be very high, with estimates as high as 8%–10% of the normal population (Willems et al. 1991; Wauters et al. 1992).

## Conclusions/Recommendations

The presence of pseudodeficiencies can result in a variety of problems. In the case of Tay-Sachs carrier screening, pseudodeficiency alleles can (and have) resulted in the incorrect assignment of carrier status. Of even more serious concern is the possibility of an incorrect prenatal diagnosis of disease, because of the unrecognized presence of a pseudodeficiency allele.

Another problem may be encountered in attempts at early, presymptomatic treatment of individuals presumed to be affected because of apparent enzyme deficiencies. Our laboratory, for example, was involved in a situation in which a newborn sib of an older child with MLD was found to lack arylsulfatase A activity. This infant was offered a bone marrow transplant before the onset of symptoms. Prior to the transplant, it was determined that, while the older, affected sib was homozygous for MLD, the newborn was a compound heterozygote for the MLD allele inherited from his mother and the common pseudodeficiency allele inherited from his father, who was also a compound heterozygote, having both an MLD and a pseudodeficiency allele.

This case illustrates the potential pitfalls of a failure to recognize a pseudodeficiency allele. First, there is the danger of offering a potentially life-threatening procedure to an individual who is not at risk. Second, it points out the potential danger of an incorrect conclusion regarding the outcome of treatment. If this patient had undergone a successful bone marrow transplant and had remained symptom free, it would have been incorrectly concluded that the procedure had effected a cure.

Yet another complication is that the same apparent mutation may cause disease in some individuals and not in others. For example, Beutler et al. (1993, p. 88) have estimated that only a third of Ashkenazi Jewish individuals, homozygous for the 1226G (N370S) mutation in the gene coding for β-glucosidase, "are patients with Gaucher disease." Presumably, other factors (genetic or environmental) interacting with this mutation determine if it will result in disease or an apparent "pseudodeficiency."

Finally, the presence of pseudodeficiency mutations can lead to mistaken conclusions regarding the causal relationships between enzyme deficiencies and "atypical patients" with unrelated clinical disorders. In these cases, the occurrence of an enzyme deficiency and an abnormal phenotype might not be causally related. This is particularly true in those situations where it has already been established that pseudodeficiency alleles occur with a high frequency—i.e., arylsulfatase A gene and the hexosaminidase A gene—at least in the non-Jewish population.

For these reasons, one should use a variety of clinical and biochemical procedures before arriving at a final diagnosis. The information should include evidence of abnormal catabolism—i.e., increased urinary levels of the expected substrates of the enzyme in question, decreased catabolism of radiolabeled natural substrates by intact cells from the patient, histochemical evidence of abnormal storage in leukocytes and/or cells of the nervous system, etc.

Additionally, one should, whenever possible, carry out enzyme tests on the parents and sibs (both normal and abnormal) of the proband, to help identify those families having both disease-producing and pseudodeficiency alleles. This is particularly important when prenatal diagnosis and/or presymptomatic treatment of a newborn sib of an affected patient is considered.

Finally, when possible, enzyme-deficient individuals should be tested for the presence of mutations known to cause pseudodeficiencies. This type of testing should also be available to enzyme-defined carriers of diseases such as Tay-Sachs disease and MLD, because of the high frequency of pseudodeficiency alleles in the genes causing these disorders. It must be kept in mind, however, that the presence of a pseudodeficiency mutation does not exclude the presence of a pathological mutation in the same gene.

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