A single origin for the most frequent mutation causing late infantile metachromatic leucodystrophy

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Abstract

Metachromatic leucodystrophy is an autosomal recessive degenerative disease of the nervous system caused by the deficiency of the lysosomal enzyme arylsulphatase A (ARSA). We report here on the high incidence of late infantile MLD among Muslim Arabs originating from Jerusalem, most probably because of a founder effect. All the patients were found to be homozygous for 459+1 G→A, a mutation which destroys the splice donor site of exon 2 of the ARSA gene. This mutation has been reported to be the most common mutation causing MLD.

We studied the ARSA haplotype defined by three intragenic polymorphic sites in DNA samples from Muslim Arab patients from Jerusalem, a Christian Arab patient originating from the region, and eight other white patients, all homozygous for the 459 + 1 G→A mutation. All the alleles carried the same haplotype which is in complete linkage disequilibrium with the mutation. This finding indicates a common origin for the 459 + 1 G→A mutation which may have been introduced into Jerusalem at the time of the Crusades.

Metachromatic leucodystrophy (MLD) is a neurodegenerative disease most commonly caused by the deficiency of the lysosomal enzyme arylsulphatase A (ARSA). According to the age of onset the disease is classified into three forms: the late infantile and juvenile forms which are the most common and the adult form which is rare. The disease is found in all populations and its incidence is estimated to be 1 in 40,000 live births.

The ARSA gene is located in 22q13 and is about 3.2 kb long with a coding sequence of 1521 bp. Mutations in the ARSA gene may lead to the deficiency of ARSA causing MLD. In addition, a very low activity of ARSA can be found in persons without clinical symptoms, a phenomenon referred to ARSA pseudo-deficiency (PD). The most common mutation causing MLD, 459 + 1 G→A, is a G→A transition destroying the splice donor site of exon 2. This mutation is associated with a severe phenotype of MLD and has never been found in the homozygous state in patients with juvenile or adult MLD. Among 36 white patients affected with late infantile MLD, the 459 + 1 G→A allele was found in 41 alleles (37% of the mutant alleles) while in seven patients originating from Japan, none had the mutation. The mutation was also found in 14 alleles among 34 patients affected with juvenile MLD (20% of the mutant alleles).

We report on the high incidence of the mutation 459 + 1 A→G in the region of Jerusalem and on a study of the origin of this mutation in white patients.

Material and methods

SCREENING FOR THE 459 + 1 A→G MUTATION

During the last 15 years 27 patients have been diagnosed as being affected with late infantile MLD in the Department of Human Genetics at Hadassah Medical Centre. The diagnosis was based on clinical investigations and deficiency of ARSA in leucocytes and fibroblasts. These 27 patients originated from 17 unrelated families, four Jewish and 13 Arabs. Three of the Muslim Arab patients originated from Jerusalem. This represents a very high incidence, since in this period fewer than 50,000 Muslim Arab children were born in Jerusalem.

DNA samples from these patients were tested for the 459 + 1 G→A mutation using a MwoI polymorphism which is abolished by the mutation. The primers used for the amplification were 5' AGC CGG TGC CAG TGG AGG AG 3' and 5' CAA CAG TGG GAT GGG GAC 3'. The cycling conditions were 94°C for 30 seconds, 56°C for 30 seconds, 72°C for 12 minutes for 30 cycles with an extension in the last cycle at 72°C for 7 minutes. The amplified fragment of 350 bp was digested with MwoI according to the manufacturer's recommendations, and the products were analysed on a 2% agarose gel (figure).

DETERMINATION OF INTRAGENIC ARSA HAPLOTYPES USING THREE POLYMORPHISMS

Three intragenic polymorphic sites have been described within the ARSA gene: a BglII site in exon 3, a BsrI site in exon 7, and a BamHI site in intron 7. The polymorphisms were determined as previously described after the amplification of the ARSA gene in two fragments (Zlotogora et al, submitted). In a previous study we showed that the PD allele is in complete linkage disequilibrium with the haplotype (BglII (2), BsrI (2), BamHI (1)) and that the mean frequency of each of the polymorphisms in
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Digestion of a 350 bp fragment with MspI. The 459 + 1 G→A mutation abolishes the restriction site. Two fragments of 125 and 175 bp are seen in normal persons (lanes 1, 2) while only one fragment of 300 bp is seen in homozygotes for the mutation (lanes 3, 4).

non-PD alleles among random whites is BglI (1) 9-6%, BsrI (1) 54-4%, and BamHI (1) 74-9% (Zlotogora et al, submitted).

The intragenic polymorphisms were determined in three DNA samples from homozygous MLD patients from Israel as well as the DNA from both heterozygous parents of a fourth MLD patient. In addition we examined DNA samples from eight homozygotes for 459 + 1 G→A originating from Europe and the USA.

STATISTICAL ANALYSIS
In the analysis of the results the χ² test was used.

Results
Among the 27 patients with late infantile MLD originating from 17 unrelated families, four unrelated Arab patients (three Muslims and one Christian) were found to be homozygous for 459 + 1 G→A. This was determined by DNA analysis in three patients, while since no DNA was available from another unrelated Muslim Arab patient, both parents were examined and found to be heterozygous for the mutation.

All the three Muslim Arab patients originated from the same small village, which relatively recently has been included in the municipality of Jerusalem. Each of the patients was born to first cousin parents, and no relationship was known between the different families. The fourth patient was a Christian Arab from a small town situated a few kilometres from Jerusalem.

INTRAGENIC ARSA HAPLOTYPES IN HOMOZYGOTES FOR THE 459 + 1 G→A ALLELE
The three Arab patients homozygous for the 459 + 1 G→A allele in whom DNA was avail-
the third patient of Lebanese 
from the Galilee was also up to understand from Japanese origin. The mutation, which occurred in the region of Jerusalem, this may suggest that the mutation was introduced in Jerusalem at a period when both migration and religious conversion were frequent. For instance, the mutation may have been introduced from Europe at the time of the Crusades in the 11th and 12th centuries. Further knowledge of the distribution of the mutation is needed in order to understand its origin better.

Three other mutations which cause late infantile MLD have been reported to be frequent, each in a particular population. The G99D mutation was found in eight out of 12 alleles from Japanese patients (66% of mutant alleles) but up to now has not been found in white populations. In Australia a mutation, T274M, was found in the homozygous state in six patients of Lebanese origin. The same mutation was also found in two Israeli Christian Arabs from the Galilee and most probably has a common origin in Lebanon (in preparation). The third mutation, L377P, which occurred on the PD allele background, was found to be very frequent because of a founder effect in an isolate, the Hhabbanite Jews (17% carrier frequency), and relatively frequent among the Yemenite Jews who were living in the same geographical region (Zlotogora et al, submitted). The other mutations causing late infantile MLD which have been reported so far are rare or unique.

From the analysis of the different mutations causing late infantile MLD it seems that the difference between the mutation 459 +1 G→A and the other relatively frequent mutations is that 459 +1 A→G first occurred in Europe, a continent in which and from which migration has been frequent. The other mutations occurred in populations which have been, up to relatively recently, relatively isolated and therefore have not yet spread among other populations.

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