Identification of 7th hexosaminidase A mutation of Tay-Sachs disease in the Turkish population

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To the Editor,

Tay-Sachs disease (TSD) is a form of GM2 gangliosidosis that results from the mutations in the alpha-subunit gene of N-acetyl-β-hexosaminidase (EC 3.2.1.52) (HEXA). Currently more than 100 mutations have been characterized in TSD[1,2]. At least six mutations were identified in Turkish Tay-Sachs (TS) patients to date: A donor splice site mutation (G412→A) and a stop codon mutation R137X in exon 3, a donor splice site mutation in intron 5 (INS-5 G→A), an in-frame 12 bp deletion in exon 10 (Δ 1096-1107 or 1098-1109), which seems the most frequent mutation in the Turkish population, a stop codon mutation R393X in exon 11 and a single G1362→A transition in exon 12[3,4,5,6]. This report describes the identification of a frameshift mutation in exon 13 (ΔC1510) of HEXA as the seventh mutation of TS patients in the Turkish population, and this mutation was present in both alleles of our patient.

The patient was born at term as the first child of healthy, nonconsanguineous parents. She was normal at birth. After three months, failure to develop was noticed by her parents. On admission she was one year of age. Her weight was 9000 g and her head circumference was 45 cm. She had poor head control, hypotonia, hyperacusia and increased deep tendon reflexes. Ophthalmoscopic examination revealed retinal pallor with cherry red spots on macula. Magnetic resonance imaging of the brain showed symmetric isointensity and hyperintensity on bilateral caudate nucleus, lentiform nucleus and periventricular white matter regions in weighted T2 scans. Background electrical suppression was observed on electroencephalogram. The enzymatic analysis showed a complete deficiency of Hex A (0%) by using fluorogenic substrate 4-methylumbelliferyl-N-acetylglucosaminide, consistent with the infantile type of TSD. For the mutation analysis, all 14 exons and flanking sequences of HEXA were amplified by polymerase chain reactions (PCR) using specified primers and conditions[4]. Each 14 exons were then subjected to single stranded conformational polymorphism (SSCP) analysis. Different migration patterns of exon 13 of HEXA were observed in SSCP (Fig. 1). DNA sequencing revealed a deletion of cytosine at position

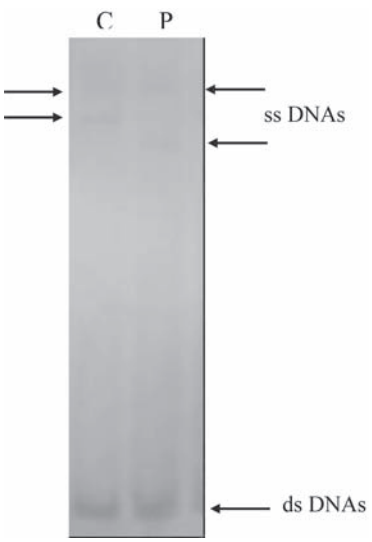

Fig. 1. SSCP analysis of exon 13 of HEXA. Lane 1, Control (C); lane 2, Patient (P). Mobility shifts of single stranded DNA (ssDNA) bands and double strand DNA (dsDNA) bands are indicated by arrows.

1510 of the coding sequence (ΔC1510 in exon 13) (Fig. 2). This frameshift mutation, which results in a premature termination of four codons downstream and a loss of a very hydrophilic stretch of 22 amino acids, was previously found in an Italian TS patient and leads to a truncated protein causing its retention in the endoplasmic reticulum and ultimate degradation[7].

Fig. 2. DNA sequence analysis of exon 13. The relevant portion of the sequencing is shown. The frameshift mutation is indicated by an arrow (ΔC1510). The match of normal sequence with the mutated sequence is demonstrated at the bottom.

In conclusion, the frameshift mutation in exon 13 (ΔC1510) of HEXA was identified as the seventh mutation of TS patients in the Turkish population and was present in both alleles of our patient. It is apparent that understanding the behavior of mutations discovered in patients would facilitate an understanding of the mechanism underlying TSD.

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