**SEVERE SHOX GENE HAPLOINSUFFICIENCY IN A GIRL WITH A NOVEL MUTATION (M1T) INVOLVING THE FIRST CODON OF CODING REGION**

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SEVERE SHOX GENE HAPLOINSUFFICIENCY IN A GIRL WITH A
NOVEL MUTATION (M1T) INVOLVING THE FIRST CODON OF
CODING REGION

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List of abbreviations:
LWD – Leri-Weill syndrome
H - height
SH – sitting height
M –methionine
T - threonine
To the Editor:

Alterations of the pseudoautosomal SHOX gene represent a basic condition in Turner syndrome and have been reported in some individuals with idiopathic short stature and in many patients with Leri-Weill dyschondrostosis (LWD), an osteochondrodysplasia with mesomorphic short stature and Madelung deformity of the wrist (1). In addition, homozygous SHOX mutations have been shown to cause the more severe Langer type mesomorphic dwarfism.

According to a recent survey (2), more than 70% of the mutations underlying the SHOX phenotype are represented by deletions ranging between several kilobases and several hundred kilobases, whilst point mutations are detected in a minority of cases (3). All the 132 mutations that are currently included in the SHOX point mutation database (available at: http://hyg-serv-01.hyg.uni-heidelberg.de/lovd/search.php?select_db=SHOX&srch=a11) are spread across the entire coding region: from exon 2 to exon 6 (4).

The aim of the present letter is to report on one additional novel and very peculiar de novo mutation of SHOX gene in a Calabrian girl with LWD, that is not reported to now in the updated SHOX allelic variant database.

The proband was the only child of non-consanguineous parents and was referred to our Unit of Pediatric Endocrinology at the age of 6.9 years, due to disproportionate short stature and Madelung deformity (radial bowing, triangularization of the distal radial epiphysis and dorsal dislocation of the ulna). Her height (H) deficiency was -3.6 DS and sitting H (SH) / H ratio was distinctly supranormal (0.56). Growth curve from the first years of life onwards was retrospectively reconstructed with the help of the family
paediatrician (Fig.1). Birth weight and length had been -2.0 and -2.8 SDS, respectively. Maternal, paternal and target H were respectively 156.1 cm (-0.95 SDS), 170.0 cm (-1.0 SDS) and 156.7 cm (-0.9 SDS). None of the parents exhibited either dysmorphic features or body disproportions or Madelung deformity. Laboratory investigations enabled us to exclude the most frequent causes of pathological short stature and even Turner syndrome and GH deficiency (GH peaks in response to two pharmacological stimulations 12.3 and 16.1 ng/ml, respectively). 45, X0 mosaicsisms were excluded as well thanks to the analysis of one hundred mitosis. The patient was followed up for 4.6 years and at the time of the last evaluation (11.5 years, pubertal stages B2 P3, bone age 10.1) her height deficiency was -3.7 DS (Fig.1), with a persistently supranormal SH/H ratio (0.56) and a poor final H prognosis (144.2 cm).

This clinical picture as a whole suggested diagnosis of LWD, due to the coexistence of two features that may be found respectively in 100% and 50% of the children with LWD: supranormal SH/H ratio and Madelung deformity (1). This diagnosis was supported by the results of SHOX gene analysis, which revealed a novel thiamine to cytosine transition at codon 1 in exon 2, that resulted in a novel heterozygous missense mutation (M1T) with methionine (M) to be replaced by threonine (T) (Fig.2). No defects were detected in the SHOX gene analysis of both parents.

SHOX gene alterations have been found in approximately 4% of the children with either sporadic or familial short stature, but this prevalence increases up to 22% in a selected population of patients with supranormal SH/H ratio (1). According to the different estimates, the average H deficit caused by SHOX mutations is approximately 2 SDS (5). In the present girl
H defect at the last examination was -3.6 SDS, but it is to be considered that her target H was -0.95 SDS. Therefore, the calculated H deficit caused by SHOX defect in our case was actually -2.65 SDS, which is more severe than that generally reported (5). Moreover, this girl had also presented intrauterine growth retardation, as only infrequently observed in the cases with SHOX haploinsufficiency (5). However, it is known that growth failure is more severe in females than in males (5) and that only girls with a de novo mutation have a height SDS that is significantly different from their midparental height (2).

To conclude, in this patient with LWD we have detected a novel SHOX de novomutation, which is peculiar in that it involves the first methionine of the first coding exon and therefore it may have a deleterious functional impact on the protein biosynthesis as a consequent severe haploinsufficiency. This may account for both the early onset and severe growth impairment and the poor height prognosis observed in this case.

References


Legends for the figures

Figure 1
Proband’s height curve from the age of 1 month to 11.5 years and her target height (TG).

Figure 2
Electropherogram of SHOX gene exon 2 sequence with forward primer; the heterozygous pick indicates the thiamine (T) > cytosine (C) transition resulting in Methionine 1 Threonine mutation.