Novel *ACAN* mutation in a SGA short stature without accelerated skeletal maturation

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Introduction

Heterozygous mutations in the *ACAN* , encoding for aggrecan or cartilage-specific proteoglycan protein, exhibit a broad phenotypic spectrum of non-syndromic short stature associated with advanced bone maturation, osteochondritis dissecans (OCD), early-onset osteoarthritis, and mild dysmorphic features including mid-facial hypoplasia, brachydactyly, broad great toes, and lumbar lordosis, with no genotype-phenotype correlations.

Some reports *ACAN* mutation is a relative common cause of familial severe short stature without advanced bone age.

Others presented that *ACAN* mutations in children born SGA with persistent short stature, advanced BA, and midface hypoplasia, joint problems, or broad great toes are highly prevalent.

We report a case of novel *ACAN* mutation in a severe short child born as small foe gestational age without accelerated skeletal maturation, showing incomplete penetrance.

Methods

A 2 years 7 month-old girl born as small for gestational age presented with proportionate short stature (height 79.9cm, SDS -3.23).

She was born as small for gestational age.(GA38+5 weeks, birth weight of 2.3 kg (SDS, -2.25), birth length of 44.6 cm (SDS, -2.44) and head circumference of 30.4cm (SDS -2.94).

She didn't show dysmorphic features.
She has no history of arthralgia or other joint problems and developmental delay.

Her father and mother's height (SDS) are normal, 166 (-1.57), and 158 (-0.63) respectively.
However, her grandfather and late grandmother's height (SDS) are extremely short, 150 (-4.83) and 140cm (-4.73) respectively.

Bone age x-ray, chemical and genetic test were performed.

Results

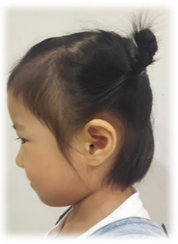
Two unprimed GH stimulation tests with glucagon and clonidine administration showed a peak GH value of 10.7 ng/mL

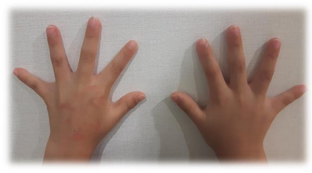
BA was delayed about 1year less than her chronologic age

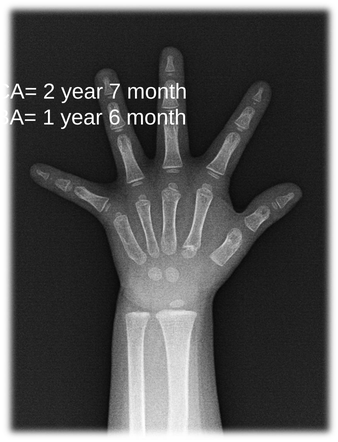
Karyotype test showed normal 46, XX.

Her father denying joint problem showed the same mutation.
A genetic test is underway for her short grandfather without joint problem.

Results

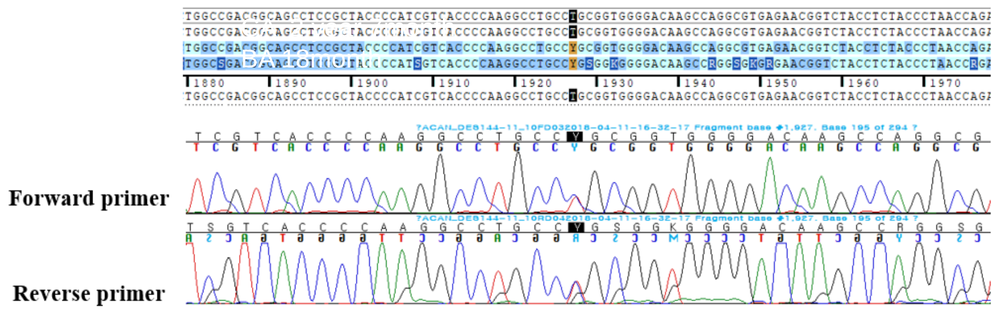




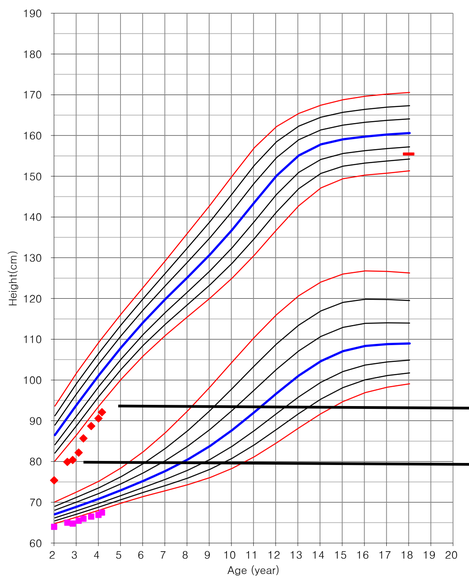


GHL sanger sequencing result

ACAN (c.1927T>C), heterozygous missense mutation
predicted to be deleterious by both SIFT and PolyPhen-2



Growth Curve



After one –year GH Tx,
the age of 4 year 1month,
Height 92.1cm, SDS -2.79

Start of GH 1.4mg/kg/wk
the age of 3 year 1month,
Height 82.2cm, SDS -3.61

Conclusions

A novel *ACAN* (c.1927T>C) mutation showed incomplete penetrance in this family.

Our findings extended the known clinical phenotypic spectrum of heterozygous *ACAN* mutations and suggest that this diagnosis should be considered in children without a family history of short stature and in children born as SGA without advanced bone age.

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Growth and syndromes (to include Turner syndrome)

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