132cm final height due to poor pubertal growth: *FBN1* is the culprit

Additional features: neurocognitive manifestations

Brachet C[1], Boros E[1], Soblet J[2,3,4], Vilain C [2,3,4], Heinrichs C[1]
[1]Paediatric Endocrinology Unit, Hôpital Universitaire des Enfants Reine Fabiola, Université Libre de Bruxelles, Brussels, Belgium.
[2] Department of Genetics, Hôpital Universitaire des Enfants Reine Fabiola, ULB Center of Human Genetics, Université Libre de Bruxelles, Brussels, Belgium.
[3]Department of Genetics, Hôpital Erasme, ULB Center of Human Genetics, Université Libre de Bruxelles, Brussels, Belgium.
[4]Interuniversity Institute of Bioinformatics in Brussels, Université Libre de Bruxelles, Brussels, Belgium.

Introduction and objectives: Very short stature is a common presenting complain that gives rise to numerous investigations.
FBN1 heterozygous mutations cause acromelic dysplasia syndromes. The phenotypic spectrum of these growth disorders is broad, ranging from short stature with short extremities, stiff joints, skin thickening with tracheal stenosis and cardiac valvulopathy to nearly isolated short stature.
Here, we report on a girl with short stature, aortic bicuspidy, Arnold-Chiari type1 and behavioural and learning difficulties due to a previously described *FBN1* mutation.
Methods: case report and literature review. Sanger sequencing and targeted exome sequencing according to standard diagnostic laboratory techniques.
Results: Case Report: A 3.5y-old girl presented with short stature. Her parents were healthy, non-consanguineous, of Caucasian origin. Their height was 175,6 cm (father) and 166,8 cm (mother). She was born at 37 weeks of gestational age by caesarean section after a twin pregnancy obtained by IVF with 1900g and 44,5 cm. Her physical examination at 3.5 years revealed short stature (Height -3.1 SDS, ref Cole 1995), small hands, pseudomuscular build, dry but otherwise normal skin, short nose, broad nasal bridge (Fig. 1) and a relative macrocephaly (head circumference 0SDS), lumbar hyperlordosis. Parents repeatedly reported behavioural and learning difficulties. She also presented bicuspid aortic valve, asymptomatic Arnold Chiari 1 associated with minor syringomyelia. Growth hormone was administered at 4.9y when her height was at -3.5 SDS with a bone age equal to chronological age. It was given intermittently for a total duration of 6 years (height gain after 1 year: +0.4 SD with 25 mcg/kg/d and +0.5 SD with 50 mcg/kg/d) (growth curve see Fig. 2). Poor response was evident and total pubertal growth was only 11 cm.

Figure 1. Photo of the patient at 8 years of age

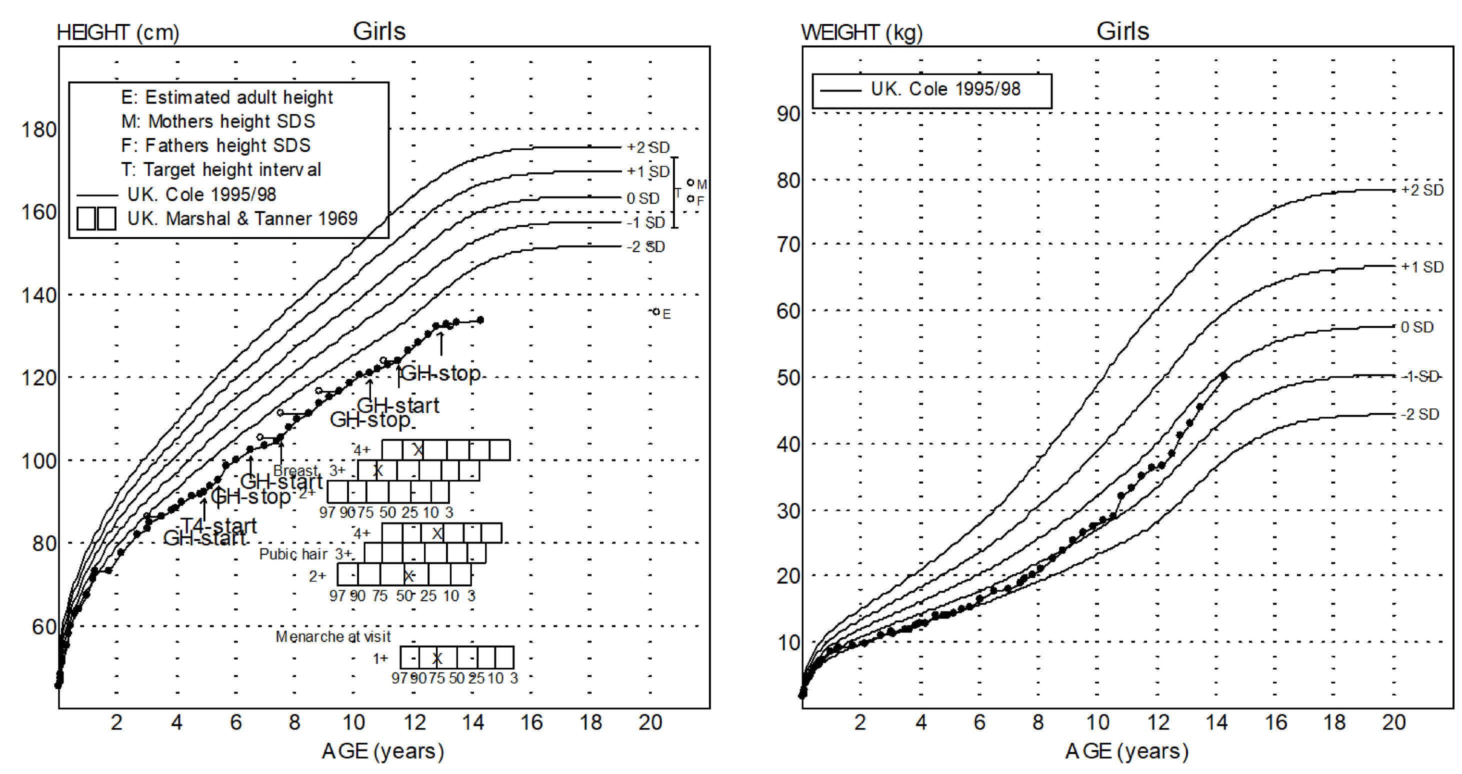

Figure 2. Growth curves of the patient

Extensive diagnostic work-up was negative:

- Growth hormone stimulation tests,
- Skeletal survey,
- Caryotype with FISH for SHOX,
- Microarray analysis,
- PTPN11 sequencing
- FGFR3 sequencing,
- 3M syndrome suspicion (bone dysplasia clinic advice).
- Targeted exome sequencing: c.5183C>T (p.Ala1728Val) heterozygous mutation in the *FBN1* gene

Start of puberty: 10.3 years of age; 122 cm; bone age 10 years (G and P).

Menarche: 12.7 years of age; 132.1cm.

Final height 133.5 cm; arm span 133cm; head circumference 58 cm (+2.5 SDS), sittingHeight/Height 0.56; BMI 25 kg/m2.

Recently, targeted exome sequencing showed a **de novo c.5183C>T (p.Ala1728Val) heterozygous mutation in the *FBN1* gene**. This gene encodes the protein fibrillin 1. Fibrillins assemble into micorfibrils which perform both structural and regulatory roles in the extracellular matrix. Regulatory roles may be determined by microfibrils-associated proteins which bind to TGF beta, for example. Microfibrils also directly bind bone morphogenetic proteins and growth and differenciation factors.

CONCLUSIONS

1.Very poor pubertal growth and very short adult height in this patient with acromicric dysplasia due to a FBN1 mutation.

2.This case highlights the importance of TGF beta signalling for somatic growth.

3.This mutation has already been described in 2 patients with acromicric dysplasia (de Bruin et al.) and in 1 patient with geleophysic dysplasia (Le Goff et al.). The patient reported by Le Goff had aortic stenosis, mitral and aortic valve insufficiencies. The patients described by de Bruine had some degree of hip dysplasia. Our patient has bicuspid aortic valve, Chiari 1 and neuropsychological difficulties. Identical mutations in the TGF beta5 domain of the FBN1 gene give rise to a variable phenotype sharing severe short stature.

4.This disease is a clinical diagnostic challenge for which targeted exome sequencing is of great help.

5.We confirm that growth hormone therapy response was poor.

6.The cardiac valvular disease being progressive (thickening), it requires follow-up, as do the tendency for carpal tunnel syndrome and hip dysplasia.

7.The neurobehavioral problems of the reported patient could be an aspect of her FBN1-related disease. This requires further study.The previously reported patients had normal development but no details were provided on their behavior. Other FBN1-related diseases include neurocognitive/psychiatric manifestations (Marfan syndrome, Shprinzen-Goldberg syndrome). The macrocephaly present in patients with acormicric dysplasia suggests a CNS effect of FBN1 mutation. This is not surprising, given that fibrillin microfibrils are part of the extracellular matrix which has mechanical functions but also shapes cell behavior and gene expression, including in the CNS.

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Matbio 2018 Fibrillin protein peliotropy: acromelic dysplasias Lynn Y Sakai et al.