Weaver syndrome [MIM 277590] is a rare condition characterized by tall stature, characteristic facial features and variable intellectual disability. Other features include:

- macrocephaly, hypertelorism, retrogнатhia, stuck-on chin appearance, large, fleshy ears
- soft and doughy skin, umbilical hernia, abnormal muscle tone, hoarse, low-pitched cry, dysarthric speech
- Skeletal abnormalities: advanced bone age, restriction of joint mobility, camptodactyly, prominent finger pads, clinodactyly of fifth finger and toes, broad thumbs, foot deformities (talipes equinovarus, talipes calcaneovalgus, metatarsus adductus, pes adductus and pes cavus), cervical spine anomalies and kyphoscoliosis
- Increased risk of cancer (neuroblastoma, haematological malignancies)

It is caused by mutations in the EZH2 gene (enhancer of zeste homolog 2, locus 7q35-q36). The condition is autosomal dominant, but the majority of the cases occur from de novo mutations.1

**AIM**

We describe a case of a male with tall stature and hip abnormalities.

**METHOD**

**Diagnostic evaluation of tall stature**

**Genetic panel for tall stature**

- DNM3TA
- Taton-Brown-Rahman syndrome
- EZH2
- Weaver syndrome
- GPC3
- Simpson-Golabi-Behmel (X linked)
- NFX1
- Marshall Smith syndrome
- NSD1
- Soltos syndrome
- ODF1
- Simpson-Golabi-Behmel (X linked)
- PTEN
- PTEN Hamartoma Tumor Syndrome
- ZBTB20
- macrocephaly

**RESULTS**

**Case report: Tall stature, obesity and hip dysplasia in Weaver syndrome due to a loss-of-function variant in EZH2**

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**INTRODUCTION**

**Weaver syndrome** is a rare disease characterized by tall stature, characteristic facial features and variable intellectual disability. Other features include:

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**Results**

**Clinical case**

- Consanguineous Pakistani parents, tall father 195 cm, mother 161 cm,
- brother 186 cm, 3 sisters
- Birth weight 4.6 kg (+2.2 SD), slightly delayed milestones
- Age 5: 113 cm (+4.9 SD), 23 kg (+4.4 SD), BMI 17.85 kg/m² (+1.69 SD), head circumference 54 cm (+1.82 SD), HV 10 cm/year
- Age 10: 177 cm (+4.4 SD), 98.6 kg (+4 SD), BMI 31.4 kg/m² (+3.4 SD), bone age 14.5 years

**Investigations**

- Urine hormone measurements
- OGTT: normal suppression GH (max 0.45 ng/mL), normal glucose tolerance and insulin sensitivity
- MRI brain and pituitary: normal
- DXA: BMD L1-4: 0.258 g/cm² (50-75th centile)
- Bone age: 6.3 years at chronological age 5 years, 15 years at age 10.5; almost fused at age 19
- Skeletal Survey: mild arachnodactyly, prominent supraorbital ridges, degenerative changes of hip joints
- Cardiomyopathy normal and echocardiography examination: myopia, alternating exotropia
- Karyotype 46.XY, microarray normal, FraX normal
- NFD1 (targeted Sanger sequencing): c.7636 G>A, p.Ala2546Thr (exon 23), common variant6
- Father with same NFD1 variant
- NFD1 MLPA analysis normal
- Tall stature panel: heterozygous pathogenic loss-of-function missense variant in EZH2, c.1876G>A (p.Val626Met)

**Discussion**

**EZH2 terms with EZH1, EED (embryonic ectoderm differentiation), SUZ12 (suppressor of zeste 12 homolog), and RBAp (retinoblastoma-associated protein) the PRC2 (Polycomb Repressive Complex 2), a histone methyltransferase responsible for histone H3 at lysine 27 (H3K27) trimethylation, resulting in chromosome condensation and transcriptional suppression.**

Loss-of-function EZH2 variants result in reduced H3K27 histone methyltransferase activity, and thus de-repression of transcription of growth promoting genes, therefore leading to overgrowth.2

54 patients with Weaver syndrome have been described in the literature.1

One more patient with the same mutation has been described: a 7-year-old boy, with birth length of 54.6 cm (+3 SD), increased height velocity, advanced bone age by 4 years, delayed development, macrocephaly, hypertelorism and large ears, large hands with thin, deep-set nails.4

In vitro expression of this variant in chondrocytes has proven reduced H3K27 methylation. A mouse with this EzH2 mutation shows mild overgrowth.4

Weaver syndrome can be associated with multiple musculoskeletal abnormalities, especially of the spine, hands and feet.

Hip abnormalities have only been described twice before:

- a 3-year-old girl with Weaver syndrome with typical features, and congenital dislocation of bilateral hips and congenital hypoplastic talus and subtalar dislocation of her ankle.5
- A father of 2 siblings with Weaver syndrome, also diagnosed with Weaver syndrome, with dislocated left hip in addition to bilateral talipes equinovarus.4

**Conclusion**

Early genetic evaluation with a gene panel in patients with tall stature is required to avoid unnecessary investigations. Hip dysplasia can be a feature of Weaver syndrome.

**References**

2. Turner et al. Mutations in NSD1 are responsible for Sotos syndrome, but are not a frequent finding in other overgrowth phenotypes. EJHG. 2003; 11: 85-85.3

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