Case report: Tall stature, obesity and hip dysplasia in Weaver syndrome due to a loss-of-function variant in *EHZ2*

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INTRODUCTION

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

- macrocephaly, hypertelorism, retrognathia, 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	
DIS3L2	Perlman syndrome
DNMT3A	Tatton-Brown-Rahman syndrome
EZH2	Weaver syndrome
GPC3	Simpson-Golabi-Behmel (X linked)
NFIX	Marshall Smith syndrome
NSD1	Sotos syndrome
OFD1	Simpson-Golabi-Behmel (X linked)
PTEN	PTEN Hamartoma Tumor Syndrome
ZBTB20	macrocephaly

RESULTS

Clinical case

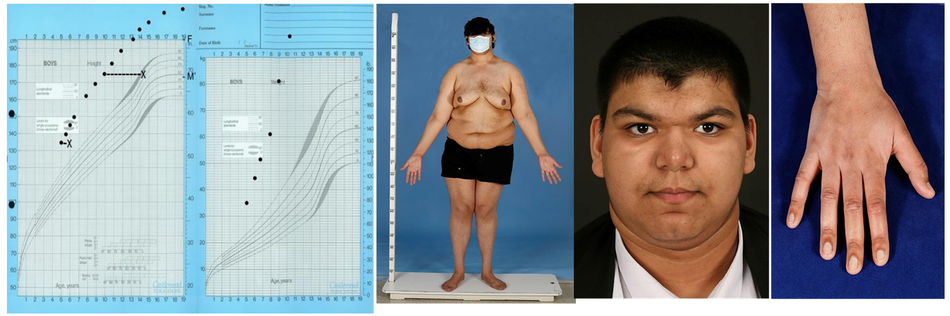
- consanguineous Pakistani parents, tall father 195 cm, mother 161 cm, brother 186 cm, 3 sisters
- Birth weight 4.6 kg (+2.2 SD), slightly delayed milestones
- Age 5: 136 cm (+6.2 SD), 33.4 kg (+4.2 SD), BMI 17.85 kg/m^2 (+1.69 SD), head circumference 54 cm (+1.82 SD), HV 10 cm/year
- Age 10: 177 cm (+6.4 SD), 98.6 kg (+4 SD), BMI 31.4 kg/m^2 (+3.4 SD), bone age 14.5 years

Age 19: 210.5 cm (+ 4.7 SD), 198 kg, BMI 44.7 kg/m^2, head circumference 62.5 cm (+5.5 SD).

- slightly coarse facial features, doughy skin, large hands, feet and prominent ears, mild squint, stork bite forehead
- Mild learning difficulties
- Obesity, mild acanthosis nigricans
- Mild scoliosis

Hip abnormalities

- Age 6: pain and restriction of hip movements
- Age 8: right hip subluxation, avascular necrosis
- Age 9: left femoral neck fracture
- Multiple orthopaedic interventions in childhood
- Age 18: total hip replacement



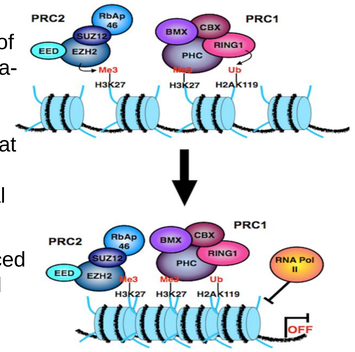
Investigations

FSH	1.1 unit/L	(ref range 1.5-12.4)
LH	8.0 unit/L	(ref range 1.7-8.6)
Oestradiol	135 pmol/L	(ref range 95-223)
Prolactin	302 mU/L	(ref range 0-323)
Testosterone	9.5 nmol/L	(ref range 8.6-29)
HbA1c	34 mmol/mol	(ref range 20-41)
FT4	18.4 pmol/L	(ref range 10.5-24.5)
TSH	1.06 mU/L	(ref range 0.27-4.2)
IGF1	361 ng/ml	(ref range 129-487.5)
IGFBP3	5 mg/L	(ref range 2.7-6.3)

- Urine homocysteine normal
- OGTT: normal suppression GH (max 0.45 ng/ml), normal glucose tolerance and insulin sensitivity
- MRI brain and pituitary: normal
- DXA: BMAD L1-4: 0.258 g/cm^3 (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
- Cardiology normal and ophthalmology examination: myopia, alternating exotropia
- Karyotype 46,XY, microarray normal, *FraX* normal
- *NSD1* (targeted Sanger sequencing): c.7636 G>A, p.Ala2546Thr (exon 23), common variant[2]
- Father with same *NSD1* variant
- *NSD1* MLPA analysis normal
- **Tall stature panel: heterozygous pathogenic loss-of-function missense variant in *EZH2*, c.1876G>A (p.Val626Met)**

DISCUSSION

EHZ2 forms with EZH1, EED (embryonic ectoderm development), SUZ12 (suppressor of zeste 12 homolog), and RbAp (retinoblastoma-associated protein) the PCR2 (Polycomb Repressive Complex 2), a histone methyltransferase responsible for histone H3 at lysine 27 (H3K27) trimethylation, resulting in chromosome condensation and transcriptional suppression.[3]



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.[3]

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, retrognathia 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.[6]

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.

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