Seventeen-year observation in a Japanese female case of Tatton-Brown-Rahman syndrome: overgrowth syndrome with intellectual disability

Yoko Miyoshi, Keiko Yamamoto, Yukako Nakano, Kenichi Yamamoto, Takuo Kubota, Keiichi Ozono
Department of Pediatrics, Osaka University Graduate School of Medicine, Osaka, Japan

Background

Advances in genetic analysis techniques have greatly contributed to the recent discovery of causative genes associated with overgrowth with intellectual disability (OGID). Tatton-Brown-Rahman syndrome (TBRS; OMIM: 615879) was one of them, characterized by tall stature, distinctive facial appearance, and intellectual disability. This syndrome was first reported in 2014. Thus, long-term clinical courses are unknown.

Aim

To present a Japanese case with OGID who was diagnosed TBRS by Whole Exome Sequencing supported by the IRUD (Initiative on Rare and Undiagnosed Diseases).

Case report

<Chief complaint> Tall stature, intellectual disability
<Present history> A 9-year-old Japanese girl first visited our outpatient clinic, complaining of tall stature. After an uncomplicated pregnancy, she was delivered at 40 weeks’ gestation with a length of 51.4 cm (+1.03SD), a weight of 3604 g (+1.28SD) and a head circumference of 35.0 cm (+1.20SD). Developmental delay was pointed out at six years old. She had a distinctive face, marfanoid habitus and intellectual disability (IQ 68). She was evaluated at 10 years and 7 months old in hospitalization.
<Past history> Two episodes of unconsciousness at 10 years old
<Family history> No consanguinity. No similarly affected individuals
Father: 179cm (+1.4SD), Mother 165cm (+1.3SD)
Younger brother: final height 183cm (+2.1SD)

<Pubertal development> breast development: 10y2m~<, no menstruation

<Physical findings>
Height: 166.4cm (+3.77SD) Body weight: 44.1kg (+1.25SD)
Head: round face, heavy horizontal eyebrows, narrow palpebral fissures
Breast: Tanner stage 4
Extremities: arm span 172cm, cubitus valgus, arachnodactyly, thumb sign(+), wrist sign(+), marfanoid habitus
Spine: lumbar lordosis
Skin: hirsutism
No abnormalities in muscle tonus. She was always reticent.

Whole exome sequencing at 25 years old

• We performed a whole exome analysis of the patient and her parents.
• It revealed de novo heterozygous mutation in the DNMT3A (DNA cytosine 5 methyltransferase 3A) gene (exon15, c.1761_1762del; p.GS871s. hetero) of 2p23, which was confirmed by Sanger Sequencing.
• This variant was not found in her parents, the previous reports and database. However, its predictive function was evaluated as disease-causing by SIFT Indel analysis.

Conclusion

Tatton-Brown-Rahman syndrome

• Intellectual disability (100%): Mild (18%), moderate (65%), severe (16%)
• Postnatal overgrowth (83%)
• An evolving facial appearance with low-set, heavy, horizontal eyebrows and prominent upper central incisors (frequency: 20-80%)
• Joint hypermobility (74%)
• Obesity (weight +2SD) (67%), Hypotonia (54%)
• Behavioural/psychiatric issues (most frequently autistic spectrum disorder) (51%)
• Kyphoscoliosis (33%), A febrile seizures (22%)


• Routine laboratory examinations were unremarkable.
• Major endocrinological findings are listed below: IGF-1 325 ng/mL (+0.22SD), TSH 4.30 μU/mL, FT4 1.3 ng/dL, LH 5.4 mIU/mL, FSH 8.2 mIU/mL, estradiol 63 pg/mL. Serum GH and IGF-1 levels were not elevated.
• Chromosomal analysis: normal female karyotype (46,XX).
• Urinary homocysteine: not detected
• Bone age: 11.1 yrs
• Brain MRI and cardiac/abdominal ultrasonography: no abnormalities
• Ocular investigation: no dislocation of lenses

Since final height is predicted to be excessive, she was treated with an oral estrogen from 10.8 (166cm) to 13.6 years old (175cm) in order to induce growth plate fusion.
• At 26 years old her height was 176 cm and body weight was 63kg.
• She has spent her daily life without any special support and worked in disability employment.
• No hematologic malignancy has developed.

Tatton-Brown-Rahman syndrome

• Tatton-Brown-Rahman syndrome (TBRS; OMIM 615879), also known as the DNMT3A-overgrowth syndrome, is an overgrowth intellectual disability syndrome. It was first described in 2014 with a report of 13 individuals with constitutive heterozygous DNMT3A variants (Nature Genetics, 2014).
• DNMT3A encodes a DNA methyltransferase essential for establishing methylation during embryogenesis and is commonly somatically mutated in acute myeloid leukemia.


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