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

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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) .

Tatton-Brown-Rahman syndrome

Our case: red highlighted

- 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 (frequent: 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%)

Tatton-Brown K, *et al*. Wellcome Open Res. 2018 Apr 23;3:46.

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 165 cm (+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

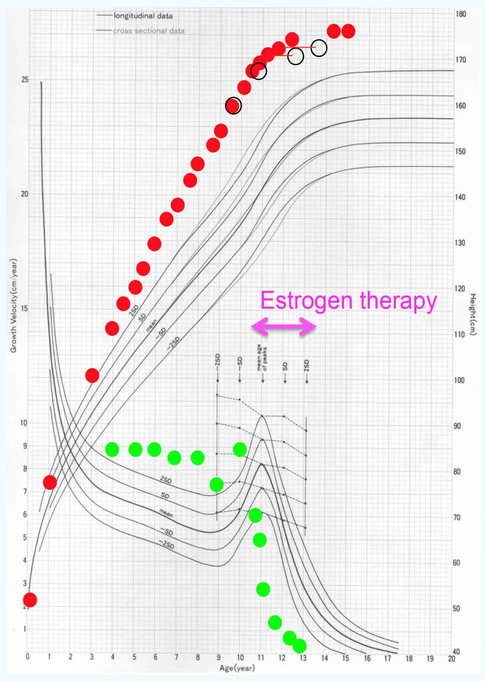
Breast: Tanner stage 4

Extremities: arm span172cm, cubitus valgus, arachnodactyly, thumb sign(+), wrist sign(+), marfanoid habitus

Spine: lumbar lordosis Skin: hirsultism

No abnormalities in muscle tonus. She was always reticent.

- Routine laboratory examinations were unremarkable.
- Major endocinlgical 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

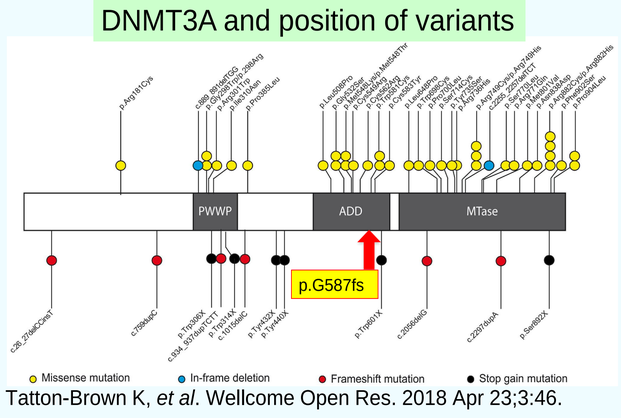


- Since final height is predicted to be excessive, she was treated with an oral estrogen from 10.8 (166cm) to 13.6 years old (175cm) in order to induce growth plate fusion.
- At 26 years old her height was176 cm and body weight was 63kg.
- She has spent her daily life without any special support and worked in disability employment.
- No hematologic malignancy has developed.

Whole exome sequencing at 25 years old

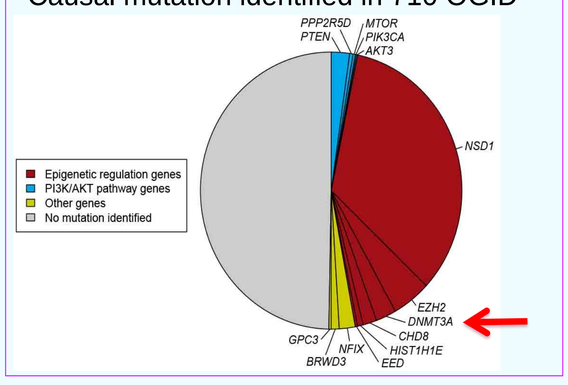
- We performed a whole exome analysis of the patient and her parents.
- It revealed de novo heterozygous mutation in the *DNMT3A (DNA cytosine 5 methyltransferase 3A)* gene (exon15, c.1761_1762del: p.G587fs. hetero) of 2p23, which was confirmed by Sanger Sequencing.
- This variant was not found in her parents, the previous reports and database. However, its predictive function was evaluated as disease-causing by SIFT Indel analysis.

DNMT3A and position of variants



Tatton-Brown K, *et al*. Wellcome Open Res. 2018 Apr 23;3:46.

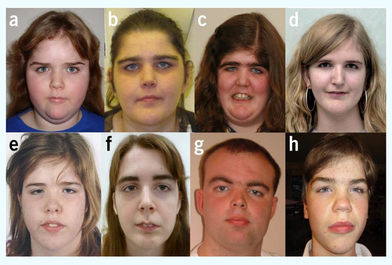
Causal mutation identified in 710 OGID



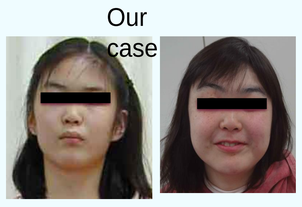
Tatton-Brown K, *et al*. Am J Hum Genet. 2017; 100: 725-36.

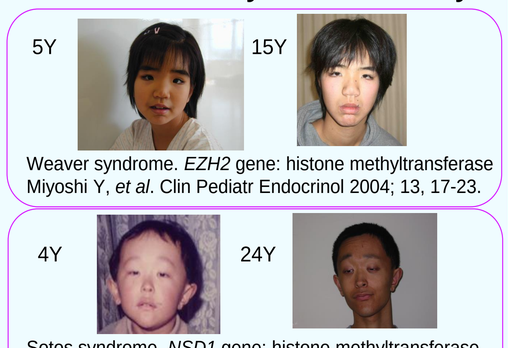
Tatton-Brown-Rahman syndrome

- 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.



Tatton-Brown K, *et al*. Nat Genet. 2014;46:385-8.





Conclusion

TBRS resulted from constitutional mutations in the epigenetic regulation gene *DNMT3A*. Other epigenetic regulation genes such as *NSD1* and *EZH2* cause OGID. Features specific to mutations of each gene should be elucidated. Case reports of OGID may help to make differential diagnosis.

1. Tatton-Brown K, *et al*. Mutations in the DNA methyltransferase gene DNMT3A cause an overgrowth syndrome with intellectual disability. Nat Genet. 2014; 46(4): 385-8.
2. Tatton-Brown K, *et al*. Mutations in epigenetic regulation genes are a major cause of overgrowth with intellectual disability. Am J Hum Genet. 2017; 100(5): 725-36.
3. Tatton-Brown K, *et al*. The Tatton-Brown-Rahman Syndrome: A clinical study of 55 individuals with de novo constitutive DNMT3A variants. Wellcome Open Res. 2018 Apr 23;3:46.

COI: The authors have no financial conflicts of interest to disclose.