HK J Paediatr (new series) 2024;**29**::108-109

# Letter to the Editor

## GATAD2B Associated GAND Syndrome

Dear Editor,

GAND syndrome (OMIM 615074) is caused by loss-of-function mutation of *GATAD2B* gene.[1,2] Only less 100 cases were reported[1-3] since its first described in 2013.[4] It usually onset in infancy, and characterised by global neurodevelopmental delay and poor speech acquisition. Patients have hypotonia and feeding difficulties in infancy and may relief later. Characteristic facial features, including frontal bossing, hypertelorism, deep-set eyes, posteriorly rotated ears, and elongated wide nose with prominent nasal tip, were common reported. More variable features may include macrocephaly, seizures, and cardiac abnormalities.[1-3]

A 5-year-old boy presented for language development retardation. He was G3P3 of non-consanguineous parents with a birth weight of 3.0 kg. He presented little cries after birth without feeding difficult. Global neurodevelopmental delay was noted. He couldn't walk until 3 years old, and couldn't speech and communication till now. His older brother and sister were healthy. Physical examination showed a height of 110.5 cm (about $P_{50}$), a weight of 20.5 kg (about $P_{75}$), and a head circumference of 50.2 cm (about $P_{50}$). Horseface, frontal bossing, hypertelorism, deep-set eyes, downslanting palpebral fissures, elongated wide nose with prominent nasal tip, a large and broad mouth, protruding tongue, pointed chin, and dentition irregularity were noted (Figure 1).

Liver and kidney function, blood gas and electrolyte, thyroid function, blood MS/MS, hepatosplenic ultrasonic, and echocardiography, were all normal. On the brain MRI, no significant was found except larger occipital cistern. Whole exon sequencing (WES) found a heterozygous mutation of c.1363del (p. Ala455Leufs*7) in the exon 8 of *GATAD2B* gene, which was not found in his parents (Figure 2). It was regarded as "pathogenetic" according to ACMG recommendation.

To our knowledge, this is the first case of GAND syndrome reported from China. Recently, Nikam et al[1] summarised 18 cases with GATAD2B mutation, Shieh et al[2] reported 50 cases, and Vera et al[3] reported 19 cases. These implied that the incidence of GAND syndrome may be underestimated.

As one of the neurodevelopmental delay diseases, the clinical features were variable and less specificity. Our patient presented serious mental and language development retardation, characteristic facial features,

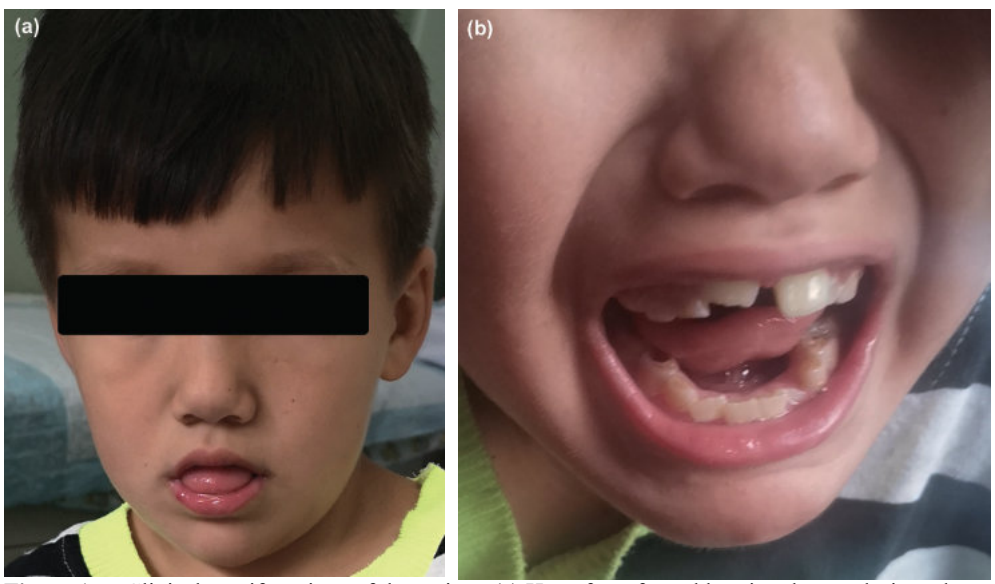


**Figure 1** Clinical manifestations of the patient. (a) Horseface, frontal bossing, hypertelorism, deep-set eyes, downslanting palpebral fissures, and elongated wide nose with prominent nasal tip, a large and broad mouth, protruding tongue, and pointed chin; (b) Dentition irregularity.

motor development delay, and larger occipital cistern. These were consistent with main clinical features in previous studies. It was notable that our case did not present the feeding difficulties, macrocephaly, seizures, or cardiac abnormalities, but showed protruding tongue, which is usually found in Down syndrome and never reported in other cases with GAND syndrome. Hence, further analysis on the clinical features with large samples may be required.

The genetic diagnostic analysis maybe the only method to confirm the diagnosis of this rare condition. In our patient, a new *de novo* mutation cause frameshift and terminate early was found. Combinate the clinical feasters, the diagnose of GAND syndrome were confirmed. Unfortunately, he was not diagnosed until he was 5 years old. Although microdeletion and 1q21.3 deletion involving *GATAD2B* gene[5] were also reported, high throughput sequencing (e.g. WES) should be considered as the first line methods and should be performed as early as possible to confirmed the diagnosis.

In summary, in patients with serious mental and language development retardation, and characteristic facial features, GAND syndrome should be considered in the differential diagnosis. Brain imaging and echocardiography should be considered to exclude other abnormalities, and genetic analysis should be performed early.

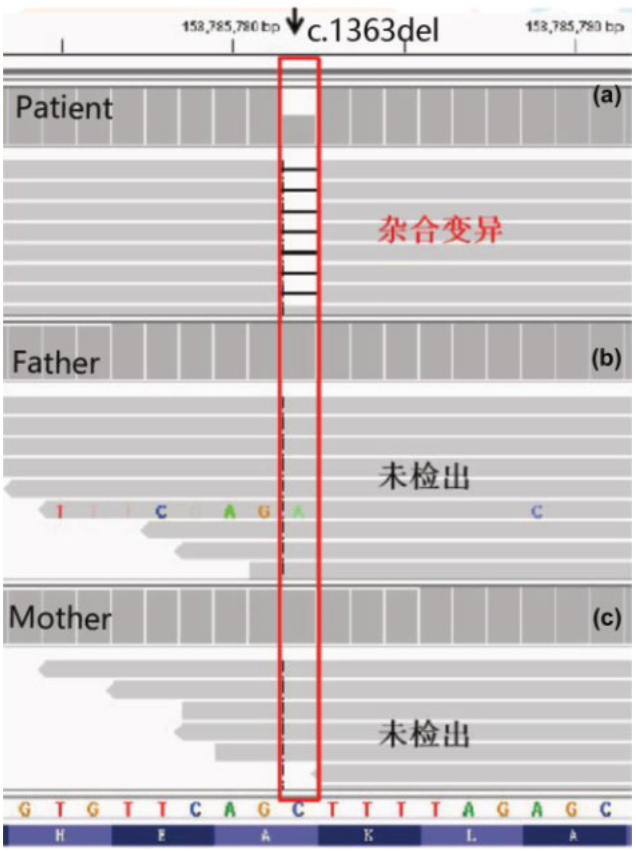


**Figure 2** Whole exon sequencing results of *GATAD2B* gene in the patient's family. (a) Heterozygous mutation of c.1363del in the exon 8 of *GATAD2B* gene in patient; (b) No similar mutation of *GATAD2B* gene in his father; (c) No similar mutation of *GATAD2B* gene in his mother.

## Acknowledgments

We are very grateful to the patient and his parents for allowing us to use the data.

## Conflict of Interest

None.

## References

1. Nikam V, Shaik Mohammad N. Tissue-specific DNase I footprint analysis confirms the association of GATAD2B Q470* variant with intellectual disability. J Genet 2021;100:61.
2. Shieh C, Jones N, Vanle B, et al. GATAD2B-associated neurodevelopmental disorder (GAND): clinical and molecular insights into a NuRD-related disorder. Genet Med 2020; 22:878-88.
3. Vera G, Sorlin A, Delplancq G, et al. Clinical and molecular description of 19 patients with GATAD2B-Associated Neurodevelopmental Disorder (GAND). Eur J Med Genet 2020; 63:104004.
4. Willemsen MH, Nijhof B, Fenckova M, et al. GATAD2B loss-of-function mutations cause a recognisable syndrome with intellectual disability and are associated with learning deficits and synaptic undergrowth in Drosophila. J Med Genet 2013; 50:507-14.
5. Tim-Aroon T, Jinawath N, Thammachote W, et al. 1q21.3 deletion involving GATAD2B: An emerging recurrent microdeletion syndrome. Am J Med Genet A 2017;173:766-70.

XY **Zou**
LH **Zeng**
Department of Clinical Medicine, Medical School of Hangzhou City University, China

YL **Dai**
Department of Endocrinology, the Children's Hospital of Zhejiang University School of Medicine, China

**Correspondence to:** Prof. LH **Zeng**
*Email: zouzouxinyi@163.com*