PS-13

A Novel Pathogenic Variant of *DNMT3A*: A Case of Heyn-Sproul-Jackson Syndrome with Craniosynostosis

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Background

- Pathogenic variants of *DNMT3A* have been implicated in Tatton-Brown-Rahman syndrome, an overgrowth disorder with macrocephaly and intellectual disability.
- An opposing clinical phenotype of microcephaly, growth failure, and impaired development was recently reported in 2019, arising from heterozygous variants in the same gene, named Heyn-Sproul-Jackson syndrome (HESJAS, OMIM #618724).
- Herein, we report a patient carrying a novel heterozygous *DNMT3A* variant identified by NGS, who showed clinical features of HESJAS.

Case Description

- A 5-year-old girl was referred to the department of rehabilitation medicine with severe developmental delay.
- Birth, past history:
  - Delivered by cesarean section at 37 weeks of gestation with a birth weight of 2.5 kg (-0.7 SD)
  - No known perinatal complications.
  - Third child of nonconsanguineous parents, her two older siblings had no developmental problems.
  - Started walking independently at 36 months of age
- At time of referral:
  - Weight 17kg (-1.3 SD), head circumference 48cm (-2.3 SD).
  - We could not take height measurement due to the patient's poor cooperation, but her parents stated that she was average in height compared to peers.
  - Facial dysmorphism: a prominent epicanthus, hypertelorism, a broad nasal tip, and a depressed nasal bridge.
- Bayley Scales of Infant and Toddler Development (3rd ed) done at age 5 years displayed profound global developmental delay.
  - Equivalent age of 26 months in cognition, 19 months in receptive language, 17 months in expressive language, 34 months in fine motor skills, and 24 months in gross motor skills.
- Laboratory tests revealed parameters within normal ranges.
- Brain MRI was normal; however, brain 3D CT revealed craniosynostosis (sagittal, bilateral lambdoid suture fusion state) (**Fig. 1**).
- NGS analysis revealed a *de novo* heterozygous pathogenic variant in *DNMT3A* in the form of a splicing variant (NM_175629.2: c.1012_1014+3del) (**Fig. 2**). This variant has not been previously reported in control databases.

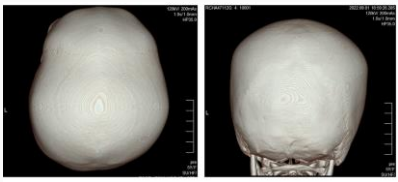

Figure 1. 3D CT reconstruction of the skull shows closed sagittal and bilateral lambdoid sutures.

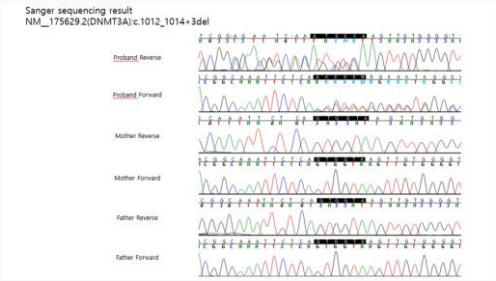

Figure 2. DNA sequencing chromatography for the patient and her parents.

Table 1. Summary of clinical findings in individuals with *DNMT3A*-related HESJAS.

Patient (source of study) Country of origin	Proband, this study South Korea	P1 (1) USA	P2 (1) New Zealand	P3 (1) Spain
Variant	c.1012_1014+3del (*de novo*)	c.968T>C (*de novo*)	c.968T>C (*de novo*)	c.99 TG>A (*de novo*)
Gender	Female	Female	Male	Male
Age at measurement	5 years 7 months	1 year	1 year 7 months	4 years 6 months
Birth weight	2.5 kg (-0.7 SD)	1.9 kg (-2.8 SD)	2.3 kg (-1.1 SD)	1.9 kg (-2.3 SD)
Height	Unchecked†	60.5 cm (-5.4 SD)	68.9 cm (-4.6 SD)	93.8 cm (-3.2 SD)
Weight	17 kg (-1.3 SD)	5.79 kg (-4.7 SD)	6.64 kg (-5.2 SD)	11 kg (-2.6 SD)
Head circumference	48 cm (-2.3 SD)	41.5 cm (-4.1 SD)	41 cm (-4.6 SD)	NR (microcephaly)
Craniosynostosis	+	NR*	NR	NR
Neurocognitive impairment	Severe Minimal expressive speech at age 5	Severe	Moderate	Moderate-severe
Dysmorphic features	Prominent epicanthus, hypertelorism, broad nasal tip, depressed nasal bridge	Sparse hair 11 pairs of ribs	Short broad metacarpals and phalanges	Strabismus, epicanthic folds, wide forehead, sparse hair; short broad metacarpals and phalanges; bilateral macro-orchidism
Brain MRI	Normal	NR	Normal	Normal

† Height measurement was not possible due to the patient's fear of the height scale. She was assumed to be about average in height compared to same age peers.

* NR: not reported

(1) Heyn P, Logan CV, Fluteau A, Challis RC, Auchynnikava T, Martin CA, et al. Gain-of-function DNMT3A mutations cause microcephalic dwarfism and hypermethylation of Polycomb-regulated regions. Nat Genet. 2019;51(1):96-105.

Conclusion

- To our knowledge, this is the first reported case of HESJAS since the initial report.
- While our patient shares some characteristics with previously reported patients (**Table 1**), an entirely new feature, craniosynostosis was discovered.
- Craniosynostosis formation may be explained in part by altered levels of a histone protein involved in osteogenic differentiation, caused by variants in *DNMT3A*.
- Further evaluation of our patient's variant is warranted to understand its exact and specific mechanism.