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NOTE

Cohesinopathy presenting with microtia, facial palsy, and hearing loss caused by *STAG1* pathogenic variant

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Cohesinopathies are a various multisystem malformation syndromes including neurodevelopmental disorders, which are caused by pathogenic variants in the genes coding for the cohesin complex or its cofactors.[1,2] The cohesin complex plays a crucial role in the chromosome segregation, DNA repair, and genomic stability during DNA replication and cell division.[1,2] The *STAG1* gene encodes a subunit of the cohesin complex. Currently, only a few cases of cohesinopathies with *STAG1* pathogenic variants have been described.[1,2] Herein, we describe a 3-year-old Japanese boy with a *STAG1* missense variant.

The patient was born spontaneously at 38 weeks of gestation. The pregnancy was marked by intrauterine growth retardation. His birthweight was 2257 g (3–10 percentile), his length was 46 cm (3–10 percentile), and his head circumference was 32 cm (10–25 percentile). He presented bilateral microtia (dysmorphic and low-set ears), bilateral atresia of the external auditory canal, a dextral accessory ear, hypoplasia of the mandible, and dextral facial palsy at birth (Figure 1). Furthermore, he showed feeding difficulties, cryptorchidism, and bilateral hearing loss. He was fed by a tube during the first year of life after birth. He also received cryptorchidectomy and removal of the accessory ear 3 months after birth. Moreover, he wore audiphone for bilateral hearing loss 6 months after birth. At 18 months of age, he showed mild global developmental delay. A brain magnetic resonance imaging study at 2 years of age revealed no abnormalities. At 3 years of age, he displayed a short stature for 2.5 SDs below the mean for that age and received growth hormone therapy. His occipitofrontal circumference was within the normal range. Genetic analysis with a next-generation DNA sequencer revealed the genotype of a heterozygous *STAG1* missense variant (NM_005862.2: c.901C>T, p.Arg301Cys) and normal *STAG2*. The *STAG1* missense variant was located in a stromalin conservative domain and was hypothesized to induce instability in both cohesion and cohesin binding to chromosomes.[3]

Recently, Yuan et al. reviewed 19 cases of patients with a pathogenic variant in *STAG1* from 18 families (10 males and 9 females aged 2–33 years), including 17 cases reviewed by Lehalle et al.[1,2] The phenotypes in human patients with a deletion or single base substitution in the *STAG1* gene are characterized by dysmorphic features, growth retardation, developmental delay or intellectual disability, and microcephaly.[1,2] Our patients displayed only mild developmental delay as a neurological feature, only a wide mouth as a common facial features, and growth retardation and feeding difficulties as phenotypes seen with a high frequency in cohesinopathies. In addition, our patient showed auricular abnormalities including microtia, dextral facial palsy, and hearing loss. Of 19 patients reviewed,3 patients (16%) had any auricular abnormalities (Table S1).[1,2] In contrast, pathogenic variants of *STAG2* gene, which has both shared and distinct mechanisms of action compared with *STAG1* gene,[4] caused auricular abnormalities in seven (88%) of eight patients.[2,5–7] This suggests that there may be difference of the molecular interactions between *STAG1* and *STAG2* in auricular development.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

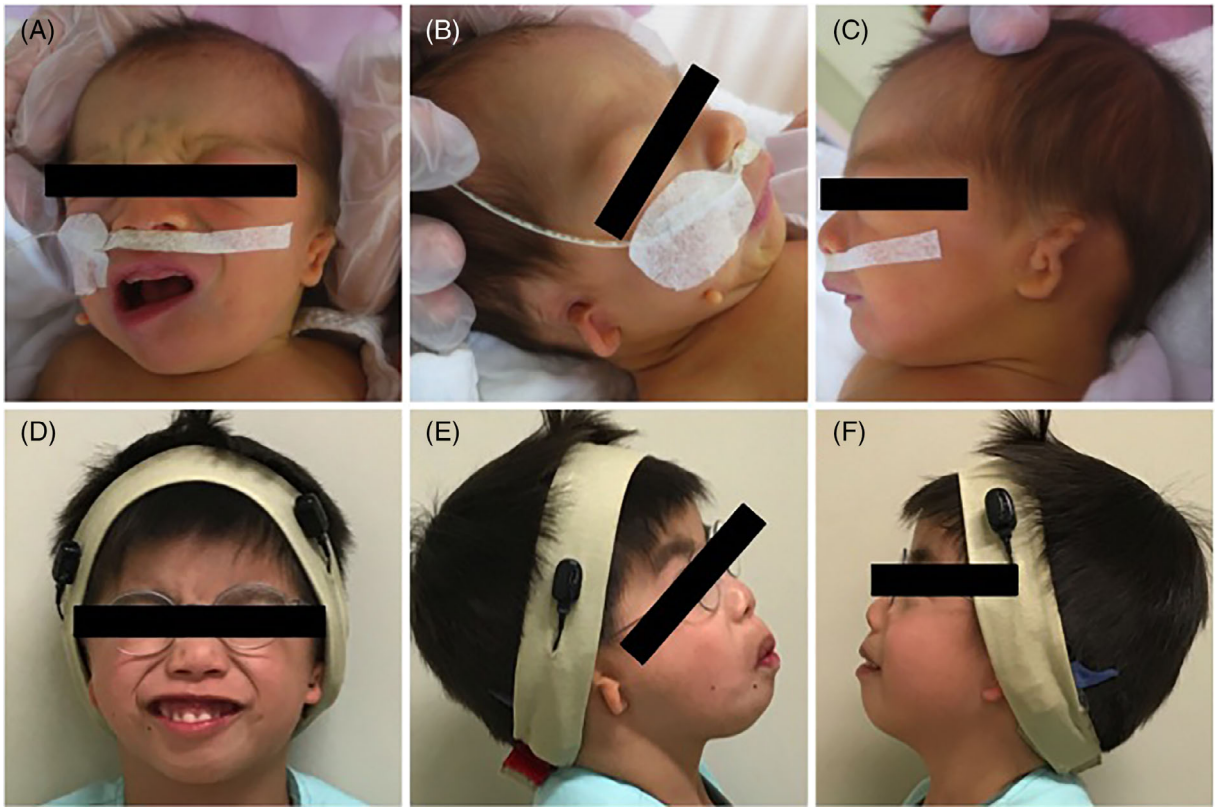

FIGURE 1 Facial phenotype of our patient with a *STAG1* pathogenic variant at birth (A–C) and at 3 years of age (D–F). (A) Dextral facial palsy. (B) Dextral atresia of the external auditory canal, dextral dysmorphic and low-set ears, and a dextral accessory ear. (C) Sinistral atresia of the external auditory canal, sinistral dysmorphic and low-set ears, and hypoplasia of the mandible. (D) Improved facial palsy. (E,F) Resected accessory ear and wearing audiphone. Written informed consent was obtained from his parents regarding the publication of these images

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SUPPORTING INFORMATION

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