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Case Report

The presence of diminished white matter and corpus callosal thinning in a case with a *SOX9* mutation

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Abstract

SOX9 is responsible for campomelic dysplasia (CMPD). Symptoms of CMPD include recurrent apnea, upper respiratory infection, facial features, and shortening of the lower extremities. The variant acampomelic CMPD (ACMPD) lacks long bone curvature. A patient showed macrocephaly (+3.9 standard deviations [SD]) and minor anomalies, such as hypertelorism, palpebronasal fold, small mandible, and a cleft of soft palate without long bone curvature. From three months of age, he required tracheal intubation and artificial respiration under sedation because of tracheomalacia. Cranial magnetic resonance imaging was normal at one month of age but showed ventriculomegaly, hydrocephaly, and the corpus callosum thinning at two years of age. Exome sequencing revealed a *de novo* novel mutation, c. 236A > C, p (Q79P), in *SOX9*. Sox9 is thought to be crucial in neural stem cell development in the central and peripheral nervous system along with Sox8 and Sox10 in mice. In humans, neuronal abnormalities have been reported in cases of CMPD and ACMPD, including relative macrocephaly in 11 out of 22 and mild lateral ventriculomegaly in 2 out of 22 patients. We encountered a two-year old boy with ACMPD presenting with tracheomalacia and macrocephaly with a *SOX9* mutation. We described for the first time an ACMPD patient with acquired diminished white matter and corpus callosal thinning, indicating the failure of oligodendrocyte/astrocyte development postnatally. This phenotype suggests that SOX9 plays a crucial role in human central nervous system development. Further cases are needed to clarify the relationship between human neural development and *SOX9* mutations.

Keywords: *SOX9*; Campomelic dysplasia (CMPD); Acampomelic CMPD (ACMPD); Macrocephaly; Ventriculamegaly

1. Introduction

SOX9 is responsible for campomelic dysplasia (CMPD). The incidence of CMPD is 1 in 2,000,000 newborns, making it a rare skeletal dysplasia. Symptoms include recurrent apnea, upper respiratory infection, facial features, shortening of the lower extremities, progressive kyphoscoliosis, short stature, and dislocation of hips. In some cases, central nervous symptoms such as developmental delay are reported [1]. The prognosis is poor, as it is usually lethal in the first few years of life. Acampomelic CMPD (ACMPD), a variant of CMPD, lacks long bone curvature, with other phenotypes almost the same as normal CMPD.

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We herein report a two-year-old boy presenting with few skeletal dysplasia features, tracheomalacia, diminished white matter and corpus callosal thinning with *de novo* novel missense mutation, c. 236A > C, p (Q79P) in *SOX9*.

2. Patient report

The patient was an 18-month-old boy. He was the second child born to nonconsanguineous healthy parents. The patient was born by spontaneous delivery at 40 weeks and 2 days. At birth, his height and weight were 49.2 cm (−0.2 standard deviations [SD]) and 3155 g (−0.3 SD), respectively. His occipito-frontal circumference (OFC) was 37 cm (2.8 SD). After birth, he had breathing distress and was given oxygen for one month. He presented with mild laryngomalacia visualized with a laryngoscope. Cranial magnetic resonance imaging (MRI) and X-ray of the bones was normal at one month (Fig. 1(a, b)). However, from three months of age, he required tracheal intubation and artificial respiration under sedation of phentanyl and midazolam due to obvious retractive breathing and recurrent apnoea. A bronchoscopic examination revealed tracheomalacia. He was referred to our hospital for an evaluation at 18 months of age.

At the time of the referral, his height and weight were 80 cm (−0.18 SD) and 11.8 kg (+1.1 SD), respectively, and his OFC was 53.3 cm (+3.9 SD). He showed macrocephaly and minor anomalies, such as hypertelorism, palpebronasal fold, small mandible, high-arched palate, cleft of soft palate, low set ear, and micropenis. Furthermore, his limbs showed clinodactilia in the second fingers in the bilateral hands and bilateral sandal gap in the feet. His developmental milestones were delayed, as he could not control his head nor understand simple words. His neurological evaluation revealed hypotonia and normal deep tendon reflex. He showed severe hear-

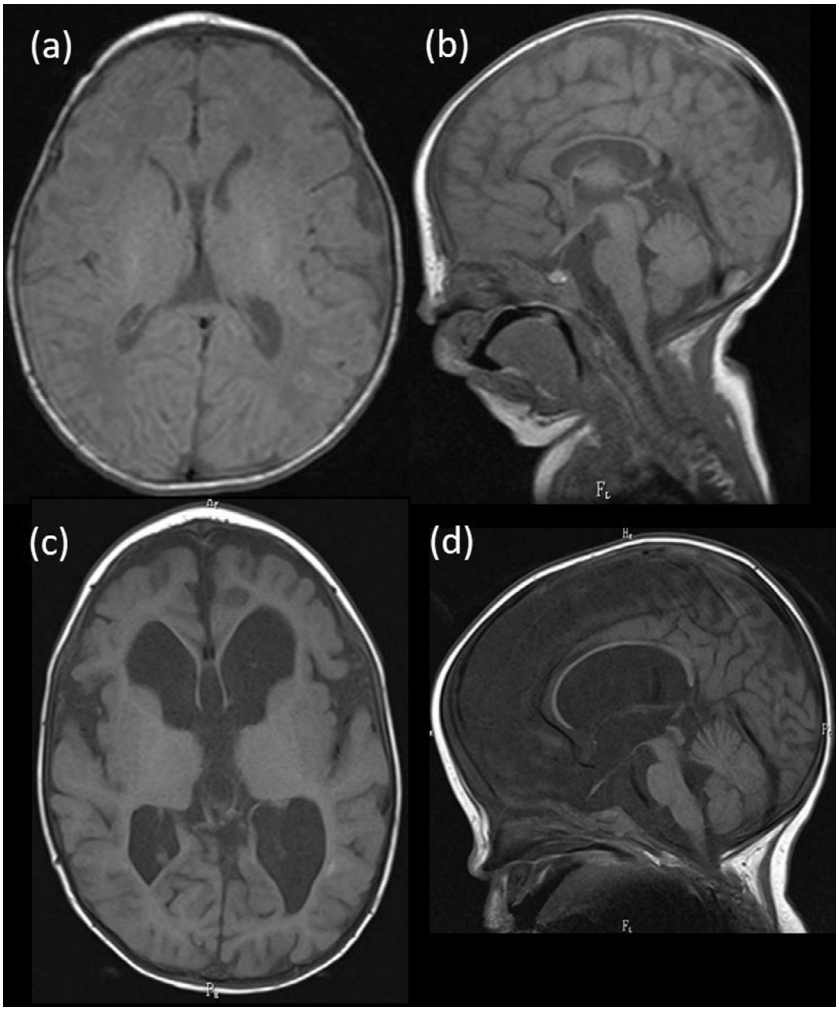

Fig. 1. Cranial MRI findings at one month of age (a, b) and two years of age (c, d). Both axial (a) and sagittal (b) T1-weighted images show a normal brain morphology. An axial T1-weighted image shows ventriculomegaly with diminished white matter areas (c). A sagittal T1-weighted image reveals hypoplasia of the corpus callosum, indicating white matter volume loss (d).

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