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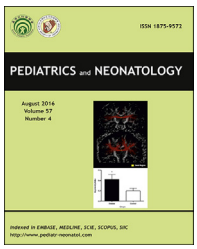

Letter to the Editor

Next-generation sequencing reanalysis identifies Coffin-Siris syndrome with an initial diagnosis of hypertrophic cardiomyopathy

Dear Editor

Coffin-Siris syndrome (CSS) is a multiple congenital anomaly and/or intellectual disability syndrome that is characterized by fifth digit and/or nail hypoplasias, coarse facial features, and a range of organ-system-related anomalies. However, cardiac diseases are rarely the initial presentation of CSS.[1] Here, we report a newborn baby who was initially diagnosed with hypertrophic cardiomyopathy, but CSS diagnosis was only established by a reanalysis of whole exome sequencing (WES) at the age of 2 years after the appearance of autism (see Fig. 1).

She was born at 40 weeks gestational age. Prenatal ultrasonography at 38 weeks reported dilated right atrium (RA) and right ventricle (RV). Unfortunately, hypothermia, respiratory distress, and poor activity were noted soon after birth. She was intubated with the use of assisted ventilatory support due to severe metabolic acidosis with a high lactic acid level (25.88 mmol/L). Echocardiography revealed dilated RA and RV, moderate tricuspid regurgitation, and pulmonary hypertension. Cardiac hypertrophy was found at 3 days of age, and propranolol was administered to abolish left and right ventricular outflow tract obstruction (LVOTO and RVOTO). Rapid trio WES revealed no hypertrophic cardiomyopathy-related disease.

She gradually recovered, and LVOTO and RVOTO disappeared at 5 months of age. However, hypotonia and developmental delay were noted. A brain magnetic resonance imaging at 11 months of age revealed a diffusely thin body and splenium of the corpus callosum. She was diagnosed with autism at 2 years of age and was then referred to a geneticist, and facial dysmorphisms, including hypertelorism, broad nasal tip, low-set ears, and flat philtrum, were noted. A previous trio WES data reanalysis, with autism, served as one of the human phenotype ontology terms for variant prioritization and identified a *de novo* mutation c.4691del [p.(Pro1564LeufsTer13)] in *ARID1B*.

Genes associated with CSS code for BAF chromatin remodeling complex components. The most frequently mutated gene in CSS is *ARID1B*, and the commonly associated phenotypes are mild-to-moderate intellectual disability, a facial gestalt reminiscent of CSS, hypertrichosis, and hypoplastic, and hardly ever absent fifth finger- and toenails. Cardiac anomalies, including ventricular septal defects, atrial septal defects, tetralogy of Fallot, and patent ductus arteriosus or patent foramen ovale, were occasionally reported. Hypertrophic cardiomyopathy was described in one patient with CSS[2] and a combination of biventricular outflow tract obstruction in another patient.[1] Currently, the cardiomyopathy mechanism in CSS is unclear. Cardiac hypertrophy in the current patient disappeared itself, but it could also be caused by premature closure of patent ductus arteriosus or patent foramen ovale.

Our patient presented life-threatening cardiac hypertrophy after birth. The first rapid trio WES failed to identify the etiology because CSS was not in our cardiac or mitochondrial disease panels at that time. Additionally, autism, which is a more specific keyword, appeared only after 2 years of age. Sequencing data reanalysis yields as much as 10% because of the continuous improvement in knowledge.[3]

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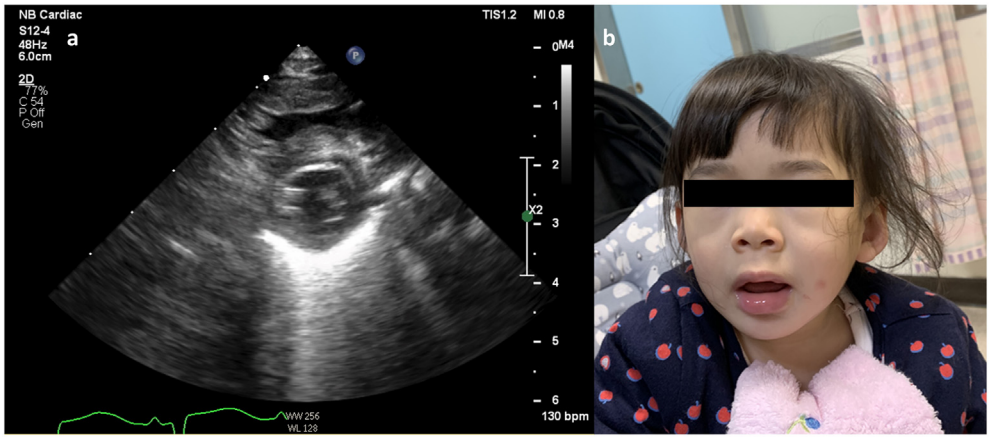

Figure 1 Clinical features of the patient. (a) Echocardiography which revealed cardiac hypertrophy and outflow tract obstruction. (b) Facial features of the patient.

Moreover, we recommend that CSS should be added to the cardiac panel of next-generation sequencing analysis.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pedneo.2022.07.010.

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Rai-Hseng Hsu
Ni-Chung Lee
Department of Medical Genetics, National Taiwan University Hospital, Taipei, Taiwan
Department of Pediatrics, National Taiwan University Hospital, Taipei, Taiwan

Ming-Tai Lin
Ting-An Yen
Department of Pediatrics, National Taiwan University Hospital, Taipei, Taiwan

Yin-Hsiu Chien
Wuh-Liang Hwu*
Department of Medical Genetics, National Taiwan University Hospital, Taipei, Taiwan
Department of Pediatrics, National Taiwan University Hospital, Taipei, Taiwan

*Corresponding author. Department of Medical Genetics and Pediatrics, National Taiwan University Hospital, 8 Chung-Shan South Road, Taipei, 10041, Taiwan.
E-mail address: hwuwlntu@ntu.edu.tw (W.-L. Hwu)

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