A Fetus with Ciliopathy Caused by a *RSPH4A* Variant Diagnosed Due to Increased Ventricular Size

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Dear Editor,

A 27-year-old Chinese woman had a normal first-trimester nuchal translucency scan in her third pregnancy. Both partners were healthy and nonconsanguineous and had a nonsignificant family history. They had a healthy 3-year-old son. Their second pregnancy ended in termination at 16 weeks because of fetal cleft lip and palate [Figure 1]. Fetal microarray was normal. In the current pregnancy, the ultrasound at 20 weeks showed borderline ventricular size (left 9.3 mm and right 9.5 mm). A repeat scan at 22 weeks showed bilateral mild ventriculomegaly (left 10.1 mm and right 10.3 mm) [Figure 1]. Amniotic fluid cytomegalovirus polymerase chain reaction and chromosomal microarray (Affymetrix CytoScan 750k SNP array) were both negative. Rapid trio exome sequencing was further performed for amniotic cell DNA sample, using an Illumina HiSeq 2500 Analyzer platform with a mean sequencing coverage of more than 90×, with more than 98% of the target bases having at least 20× coverage. This approach revealed a homozygous variant c.1774_1775del, p.(Leu592Aspfs*5) of *RSPH4A* (NM_001010892.3) in the fetus, inherited from the heterozygous parents. This variant, combined with a *RSPH4A* c.2T>C, p.(Met1Thr), has been reported in a Chinese patient with typical primary ciliary dyskinesia and infertility[1] and might be a hotspot *RSPH4A* variant in Chinese subjects. The couple opted for pregnancy termination at 24 weeks. The aborted male fetus showed normal appearance. The parents declined autopsy. This like pathogenic variant was also studied in the family members, including the archived DNA of previous abortus. The previous fetus also had this variant in a homozygous state, and the healthy sibling was a carrier [Figure 1].

Cilia are almost ubiquitous cellular organelles. There are two subcategories of cilia, namely motile and immotile/primary cilia. The dysfunction of cilia causes disorders known as ciliopathies. Accordingly, motile ciliopathies and primary ciliopathies are clinically quite different. The radial spoke head component 4A (RSPH4A) is involved in the assembly of radial spokes, which is essential for motile cilia function. Therefore, our case is a motile ciliopathy. Motile cilia are highly complex hair-like organelles of epithelial cells lining the surface of various organ systems. The ciliary structure is a highly complex one, consisting of over 600 proteins orchestrating in a coordinated manner for various functions in different organs and tissues.[2] Genetic variants that impair ciliary beating cause a heterogeneous group of motile ciliopathies. The pathogenetic mechanisms, depending on the specific affected genes and the tissues in which they are expressed, are associated with clinical symptoms and severity of the disease.

In humans, variants in *RSPH4A* lead to primary ciliary dyskinesia, a life-shortening disease characterized by chronic respiratory tract infections, abnormal organ positioning, and infertility. In this study, we first presented a hydrocephalus case associated with the *RSPH4A* defect, although *Rsph4a* KO mice showing hydrocephaly have been known.[3] The increased ventricular size or hydrocephalus was reportedly associated with primary cilia syndrome in a number of cases as illustrated by our case,[4,5] whereas no ventricular enlargement was reported prenatally in such cases. Cilia as a structural component of ependymal cells are thought to be evolved in the pathogenesis of hydrocephalus. We also showed that phenotypically heterogeneous, ciliopathy features can manifest from variation at the same single locus, even in the same family. Approximately 30% of ciliopathies involve craniofacial and dental defects including cleft lip and palate, dental hypoplasia, midfacial hypoplasia, craniosynostosis, and retrognathia/micrognathia.[6] However, craniofacial defects have been reported only in primary ciliopathy

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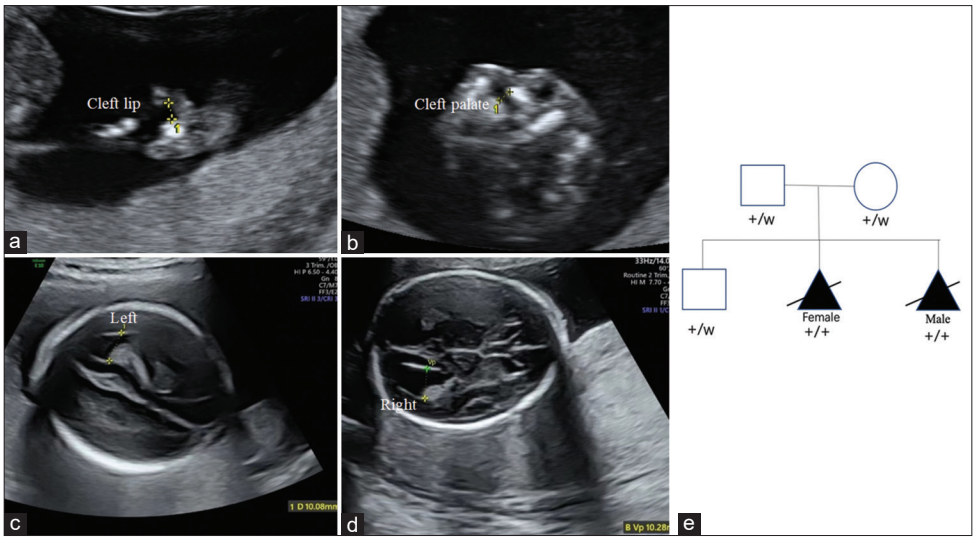

Figure 1: Two fetuses with orofacial cleft and ventriculomegaly, respectively, caused by a *RSPH4A* variant in a family. Prenatal ultrasound showing cleft lip and palate (a and b) in one fetus at 16 weeks, and mild ventriculomegaly (c and d) in another fetus at 22 weeks. Family pedigree (e) showing the variant c.1774_1775del in a homozygous state in the two aborted fetuses, and a heterozygous state in the parents and the healthy son. +: Mutant allele, w: Wild allele

patients. We first observed a case of cleft lip and palate associated with a motile ciliopathy. Our findings expanded the phenotypic spectrum related to *RSPH4A* ciliopathy. Prenatal detection of ventriculomegaly should raise the suspicion for multisystem ciliopathies and warrant subsequent advanced genetic testing.

Ethics statement

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and its amendments. The authors certify that they have obtained all appropriate patient consent form. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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