Monogenic Syndromes: The Need for Clinical Vigilance in Fetuses with Pierre Robin Sequence in the Era of Noninvasive Prenatal Screening

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Dear Editor,

Osteopathia striata with cranial sclerosis (OSCS) is caused by variants in the *AMER1* gene and is inherited in an X-linked dominant pattern. Traditionally, OSCS is considered to be a skeletal dysplasia and remains in the nosology and classification of skeletal disorders. Most recent publications, however, have described other multisystem findings, including abnormal neurodevelopmental presentations in OSCS patients.[1,2] The diagnosis of OSCS is established in a patient with characteristic features and a heterozygous or hemizygous variant in AMER1 identified by molecular genetic testing. Almost all cases were diagnosed postnatally. We report here the first prenatal case of OSCS with an *AMER1* variant detected by fetal exome analysis.

A 28-year-old G2P1 woman had a normal first-trimester scan at 12 weeks of gestation with a nuchal translucency (NT) measurement of 1.0 mm. The genome-wide noninvasive prenatal screening was negative. Both nonconsanguineous partners were healthy, and they had a healthy son. The second-trimester ultrasound at 22 weeks showed normal fetal biometry and amniotic fluid volume but abnormal morphology with bilateral borderline ventriculomegaly (10 mm/10.4 mm), Pierre Robin sequence (cleft palate, glossoptosis, and micrognathia) and small ears [Figure 1]. After genetic counseling, amniocentesis was offered. Considering the negative cell-free DNA screening, which indicates a low risk for chromosomal abnormalities, exome analysis was used as a first-tier test. This approach identified a heterozygous *de novo* frameshift variant c. 372del, p.(Cys125fs) of *AMER1* in the fetus. A loss of function or haploinsufficiency of *AMER1* is associated with OSCS. This variant was classified as likely pathogenic according to the American College of Medical Genetics and Genomics guidelines. The parents elected for termination of pregnancy at 25 weeks following genetic counseling. Postnatal physical examination revealed macrocephaly, dysmorphic facial features (frontal bossing, hypertelorism, and micrognathia), cleft palate, glossoptosis, and small and low-set ears. The parents declined full postmortem or X-ray imaging.

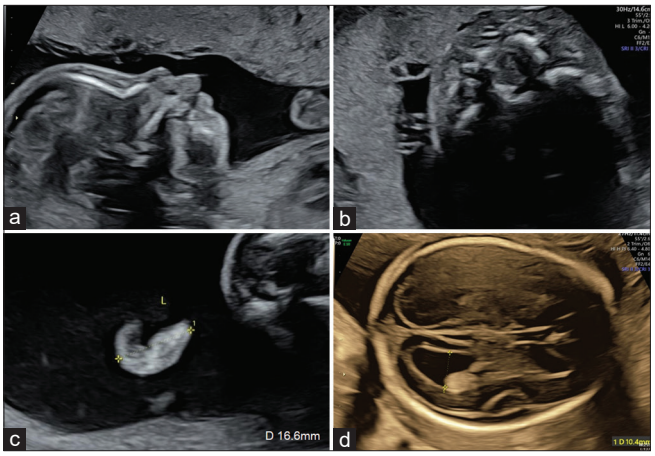

Figure 1: Scan images showing (a) micrognathia and glossoptosis; (b) cleft palate; (c) small ear; and (d) borderline ventriculomegaly

The prenatal diagnosis of OSCS caused by a *de novo* variant is challenging in the absence of a family history suggesting the diagnosis because fetal clinical presentation is highly variable. Heikoop *et al*.[3] reported the phenotypic spectrum of 12 patients with OSCS, aged 5 months–38 years, and 8 had

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medical records regarding prenatal sonographic findings. The prenatal features include polyhydramnios, ventriculomegaly, Pierre Robin sequence, short long bones, macrocephaly, and limb abnormalities. All patients were confirmed by the detection of *AMER1* variants. Our case is the first one in which a genetic diagnosis of OSCS was made *in utero*. This is important for the prenatal consultation in the present family. Even with triad malformation, Pierre Robin sequence itself has good outcomes.[4] However, females with OSCS often had additional presentations of macrocephaly, distinctive facial features, mild learning disabilities, sclerosis of the long bones and skull, and longitudinal striations of the long bones, pelvis, and scapulae.[5] When this information was adequately communicated to the parents by a fetal medicine team, they opted for pregnancy termination.

Various genetic and cytogenetic associations have been made with Pierre Robin sequence. With the routine use of NT screening and the widespread use of genome-wide cell-free DNA testing in the early gestation, the risk of fetal chromosomal abnormality in late pregnancy is very low, even with structural anomalies.[6] In this situation, exome can be considered a first-tier test in the prenatal diagnosis of structural anomalies. The identification of a monogenic variant in a fetus would establish the correct diagnosis and be a key part of genetic counseling.

Declaration of patient consent

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 identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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