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Research Letter

Pregnancy with *de novo* 9q34.3 microdeletion and Kleefstra syndrome in the fetus may be associated with an abnormal maternal serum screening result

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A 32-year-old, primigravid woman underwent amniocentesis in the second trimester due to an abnormal maternal serum screening result of a Down syndrome risk of 1/44 calculated from a level of 0.78 multiples of the median (MoM) of α-fetoprotein (AFP), a level of 3.05 MoM of free β-human chorionic gonadotrophin (β-hCG), a level of 2.66 MoM of inhibin A, and a level of 0.98 MoM of unconjugated estriol (E3) at 15 weeks of gestation. Amniocentesis revealed a karyotype of 46,XY. Prenatal ultrasound findings were unremarkable, and the pregnancy was uneventful. A male baby was delivered smoothly at term with a body weight of 3674 g and a body length of 49 cm. The infant postnatally manifested characteristic facial appearance of Kleefstra syndrome, intellectual disability, and developmental delay. Array comparative genomic hybridization (aCGH) analysis of the peripheral blood revealed an 8.08-kb 9q34.3 microdeletion or arr 9q34.3 (140,687,823–140,695.906)×1 encompassing an OMIM gene of *EHMT1* consistent with the diagnosis of Kleefstra syndrome.

The present case had an 8.08-kb 9q34.3 microdeletion encompassing the *EHMT1* gene and manifested characteristic Kleefstra syndrome and 9q subtelomeric deletion syndrome. Kleefstra syndrome (OMIM 610253) is caused by haploinsufficiency or heterozygous mutations of the *EHMT1* gene (OMIM 607001) and is characterized by distinct facial dysmorphism of arched eyebrows, midface hypoplasia, upturned nares, full everted lower lip, cupid bowed upper lip and prognathia, congenital heart defects (primarily ventricular septal defect and atrial septal defect) in half of the affected patients, intellectual disability, developmental delay and childhood hypotonia, and minor features of genitourinary defects, seizures, and behavior problems [1–7].

We previously reported prenatal diagnosis of 9q34.3 microdeletion with Kleefstra syndrome and 3q26.31-q29 duplication in a fetus with abnormal first-trimester maternal serum screening result at 12 weeks of gestation: an elevated level of 4.04 MoM of maternal serum free β-hCG, a level of 1.069 MoM of maternal serum pregnancy-associated plasma protein-A (PAPP-A), a Down syndrome risk of 1/8 and a trisomy 18 risk of 1/136 [8]. We additionally also reported prenatal diagnosis of mosaic ring chromosome 9 or r(9)(p24q34.3) in a pregnancy with an abnormal second-trimester maternal serum screening result at 15 weeks of gestation: a level of 0.63 MoM of maternal serum AFP, a level of 1.15 MoM of maternal serum free β-hCG level, and a Down syndrome risk of 1/57 [9]. The present case provides additional evidence that pregnancy with 9q34.3 microdeletion and Kleefstra syndrome in the fetus may be associated with an abnormal maternal serum screening result but without abnormal fetal sonographic findings. The aCGH analysis has the advantage of detecting microdeletion syndromes in the fetuses with a normal karyotype by conventional cytogenetic analysis [10,11]. In this regard, the Kleefstra syndrome may be detected by prenatal application of aCGH in addition to conventional cytogenetic analysis in the pregnancy with an abnormal

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maternal serum screening result. We suggest an application of aCGH on uncultured amniocytes at prenatal diagnosis of microdeletion syndrome in the following pregnancies if necessary.

Conflicts of interest

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

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