



## Case Report

## First-trimester cystic hygroma and neurodevelopmental disorders: The association to remember

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## ABSTRACT

**Objective:** We present two prenatal cases of first-trimester cystic hygroma who are later found to suffer from rare genetic syndromes.**Case report:** Both of the two pregnant women were showed to have fetal cystic hygroma on ultrasound at the first trimester. Fetal microarray result was normal. Follow-up sonographic examinations showed no structural anomalies. The two pregnancies continued uncomplicatedly to term. However, the two infants developed early neurodevelopmental syndrome within two years of age. Exome sequencing confirmed that one child had Mental retardation, autosomal dominant 23 (MRD23) with a c.646delC (p.Q216Sfs\*35) variant in *SETD5* gene, and the other child had Smith-Magenis syndrome with a c.3103dupC (Q1035Pfs\*31) variant in *RAI1* gene.**Conclusion:** Clinicians have to be vigilant when counseling the patient whose fetus has a first-trimester cystic hygroma even with a normal array result and normal sonographic scans. Although they are rare, monogenetic syndromes are possible outcomes.© 2020 Taiwan Association of Obstetrics & Gynecology. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## Introduction

Cystic hygroma (CH) is a congenital malformation of the lymphatic system, characterized by the development of distended fluid-filled spaces, typically affecting the fetal neck. It can occur as an isolated finding or in association with other defects as part of a syndrome. Since the widespread introduction of first-trimester nuchal translucency (NT) measurement for Down screening, the prenatal diagnosis of CH is becoming more frequent. Indeed, the differential diagnosis between CH and increased NT is based on that features that suggest a CH are large size with multiple septae, while increased NT tends to be smaller and more likely to be confined to the nuchal region between the occiput and upper spine [1]. CH may result from environmental factors, genetic factors, or unknown factors. Chromosomal abnormalities, mainly Turner syndrome, are found in about 50% of cases [2]. Like in cases with increased NT, genetic syndromes are also occasionally reported in those with CH [3]. The most common are Noonan syndrome, Multiple-Pterygium syndrome, Fryns syndrome and Neu-Laxova syndrome. In this

study, two rare genetic syndromes are first reported in patients with first-trimester CH.

## Case presentation

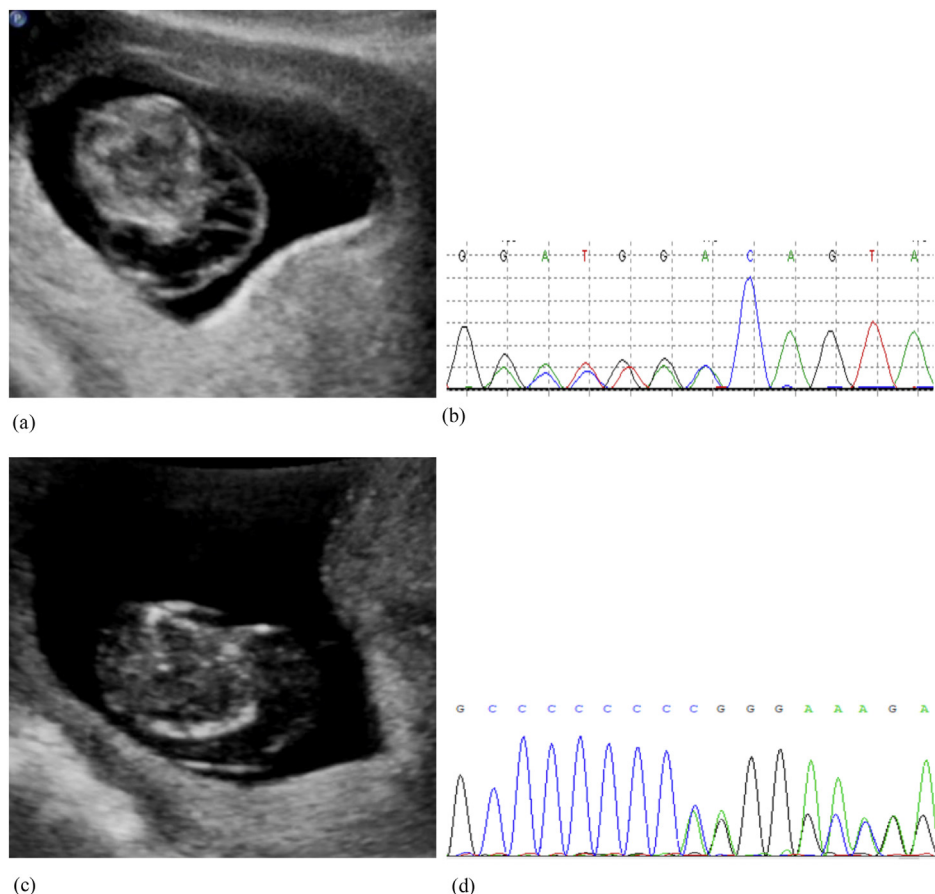
A 31-year-old G2P1 woman was referred at 12 weeks of gestation for further assessment with fetal cystic hygroma (Fig. 1a). She had a healthy daughter. At this referral, chorionic villus sampling (CVS) was performed after a detailed genetic counseling. Microarray analysis of placental DNA gave a normal report. A level 2 ultrasound at 20 weeks showed no obvious structural malformations except a thickened nuchal fold. Fetal echocardiography showed a normal heart. The pregnancy continued uneventfully to full term. A male infant weighting 3.3 kg was delivered vaginally with Apgar scores of 8 and 10 after 1 and 5 min, respectively. The boy had a triangular face, an abnormally shaped nose, a long philtrum, and mild micrognathia. Neurodevelopmental delay was noted in his growth. He was able to sit unsupported at 10 months, and walk unassisted at 16 months. He only spoke a single word, and his behavior was clearly within the spectrum of intellectual disability. His physical growth was not retarded.

DNA extracted from the peripheral blood of the proband and his parents was analyzed with whole exome sequencing. This detected a loss of function variant in the *SETD5* gene: NM\_001080517:

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**Fig. 1.** The prenatal ultrasound and genomic sequencing data of the two fetuses. (a) Cystic hygroma at 12 weeks in the fetus with MRD23; (b) Sanger sequencing showing a c.646delC variant in *SETD5*. (c) Cystic hygroma at 12 weeks in the fetus with Smith-Magenis syndrome; (d) Sanger sequencing showing a c.3103dupC variant in *RAI1*.

c.646delC (p.Q216Sfs\*35), confirmed by Sanger sequencing (Fig. 1b). This variant was not detected in the parents, suggesting a de novo event in the proband. This novel variant was not previously listed in the literature and was also not listed in the dbSNP, 1000 Genomes and gnomAD databases as well as the in-house database.

The second case is a 27-year-old G1P0 woman, who was also referred at the 12 weeks of gestation for further investigation with a fetal CH (Fig. 1c). Following an extensive genetic counseling, CVS was performed to search for etiology. Chromosome analysis using microarray reported a normal result. The routine organ scan and fetal echocardiography showed no structural or cardiac anomalies. The pregnancy continued uncomplicatedly to 41 weeks' gestation. A female infant weighing 3.5 kg was delivered vaginally with Apgar scores of 9 and 10 after 1 and 5 min, respectively. She had distinctive craniofacial features with a broad square-shaped face, prominent forehead, up-slanting palpebral fissure, broad nasal bridge, deep set eyes and tented mouth. She was admitted to neonatal intensive care unit on day 2 of life for feeding difficulty. Some developmental milestones were normal, but she was significantly delayed in language development. At 2 years of age, there was no speech, and had persistent sleeping difficulty since birth. Trio-based exome sequencing of the family detected a de novo frameshift variant in the *RAI1* gene: NM\_030665.3:c.3103dupC (Q1035Pfs\*31) (Fig. 1d), a known variant causing Smith-Magenis syndrome [4].

## Discussion

Genetic evidences suggest that *SETD5* malfunction contributes to Mental retardation, autosomal dominant 23 (MRD23) (OMIM

615761), a disorder characterized by significantly below average general intellectual functioning and facial dysmorphism. Kuechler et al. found that *SETD5* loss-of-function variants demonstrate a prevalence of 0.7% in unexplained intellectual disability patients [5]. Fernandes et al. proposed that variants on the *SETD5* gene result in a new syndromic condition in males, which leads to autism spectrum disorders-related intellectual disability and dysmorphic features [6]. However, there has been no study that reports the prenatal period of this disease. Our case is the first one in which we found a first-trimester fetal CH is associated with a pathogenic *SETD5* variant.

Smith-Magenis syndrome is characterized by distinctive physical features, developmental delay, cognitive impairment, and behavioral abnormalities [7]. The diagnosis of Smith-Magenis syndrome is based on clinical findings and being confirmed by detection of deletion or variants of *RAI1* on 17p11.2 region. Several prenatal cases have been described. Thomas et al. reported a 17-week fetus with multiple fetal anomalies (a complex cardiac anomaly, brachycephaly and significant shortening of long bones) confirmed to have 17p11.2 deletion by fluorescent in situ hybridization [8]. Zhou et al. reported monozygotic twin fetuses presenting with discordant phenotypes (ventricular septal defect and stenosis of the main pulmonary artery in one twin, and fetal growth retardation in other twin) at 28 weeks. Both twins had the same 3.7-Mb deletion in the 17p11.2 region identified by microarray [9]. Lei et al. reported two fetuses with increased NT at first trimester in two families [10]. One fetus had mild lateral ventriculomegaly, tricuspid regurgitation, and right aortic arch with left ductus arteriosus with a de novo 4.79-Mb

deletion at 17p11.2. The other fetus had pulmonary stenosis and a ventricular septal defect with a de novo 3.68-Mb deletion at 17p11.2. Our case is the first prenatal one of Smith-Magenis syndrome with a *RAI1*-truncating variant without 17p11.2 deletion. Only first-trimester CH was observed in our case. The possible modifier genes other than *RAI1* within 17p11.2 might affect the phenotype.

However, due to the rarity of these monogenetic syndromes, our findings cannot be used as a strong evidence of association of the two entities. Although CH is a common sonographic feature in early pregnancy, no studies have been found to show the prevalence of mental disorders in children with prenatal CH. We believe that with the increasing application of exon sequencing in pediatric patients, more similar cases will be revealed. Our case reports show that one has to be vigilant when counselling the patient whose fetus has a first-trimester CH with a normal array result. Exome sequencing may serve as a reserve approach for those women who have already undertaken a risky diagnostic procedure because of a first-trimester CH. It will be especially cost-effective in the genetic testing of genetically heterogeneous prenatal features like CH or increased NT.

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## Declaration of competing interest

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

## References

- [1] Scholl J, Durfee SM, Russell MA, Heard AJ, Iyer C, Alammari R, et al. First-trimester cystic hygroma: relationship of nuchal translucency thickness and outcomes. *Obstet Gynecol* 2012;120:551–9.
- [2] Malone FD, Ball RH, Nyberg DA, Comstock CH, Saade GR, Berkowitz RL, et al., FASTER Trial Research Consortium. First-trimester septated cystic hygroma: prevalence, natural history, and pediatric outcome. *Obstet Gynecol* 2005;106:288–94.
- [3] Copel J, D'Alton ME, Feltovich H. *Obstetric imaging: fetal diagnosis and care*. Philadelphia: Elsevier; 2018. p. 331. 2nd Edition.
- [4] Dubourg C, Bonnet-Brilhault F, Toutain A, Mignot C, Jacquette A, Dieux A, et al. Identification of nine new *RAI1*-truncating mutations in Smith-Magenis syndrome patients without 17p11.2 deletions. *Mol Syndromol* 2014;5:57–64.
- [5] Kuechler A, Zink AM, Wieland T, Lüdecke HJ, Cremer K, Salviati L, et al. Loss-of-function variants of *SETD5* cause intellectual disability and the core phenotype of microdeletion 3p25.3 syndrome. *Eur J Hum Genet* 2015;23:753–60.
- [6] Fernandes IR, Cruz ACP, Ferrasa A, Phan D, Herai RH, Muotri AR. Genetic variations on *SETD5* underlying autistic conditions. *Dev Neurobiol* 2018;78:500–18.
- [7] Shayota BJ, Elsea SH. Behavior and sleep disturbance in Smith-Magenis syndrome. *Curr Opin Psychiatr* 2019;32:73–8.
- [8] Thomas DG, Jacques SM, Flore LA, Feldman B, Evans MI, Qureshi F. Prenatal diagnosis of Smith-Magenis syndrome (del 17p11.2). *Fetal Diagn Ther* 2000;15(6):335–7.
- [9] Zhou Y, Xie Y, Zhu Y, Wu J, Shang M, Chen B, et al. Smith-Magenis syndrome in monozygotic twin fetuses presenting with discordant phenotypes and uteroplacental insufficiency. *Mol Med Rep* 2016;13:347–52.
- [10] Lei TY, Li R, Fu F, Wan JH, Zhang YL, Jing XY, et al. Prenatal diagnosis of Smith-Magenis syndrome in two fetuses with increased nuchal translucency, mild lateral ventriculomegaly, and congenital heart defects. *Taiwan J Obstet Gynecol* 2016;55:886–90.