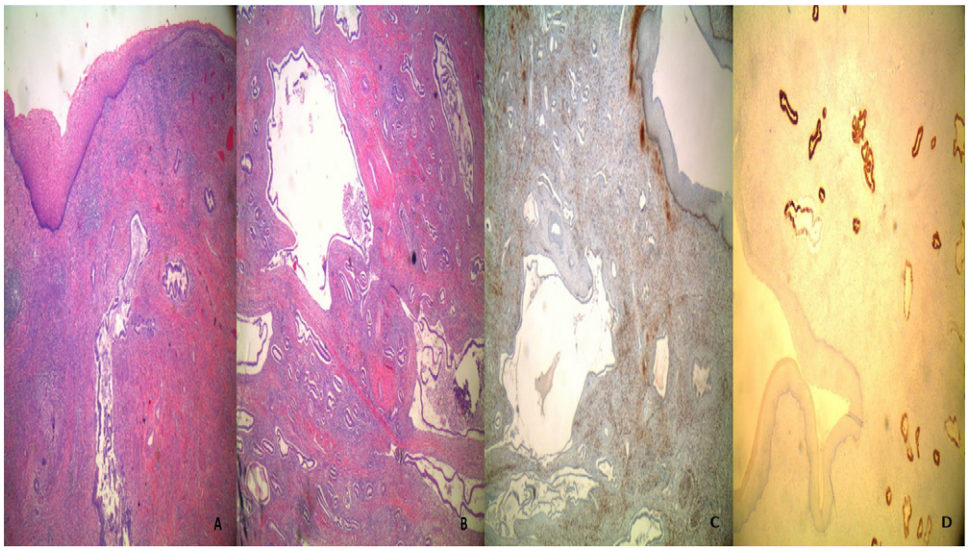

Fig. 1. A–D: A. High view of the adenocarcinoma that resemble the gastric adenocarcinoma, this particular field highlight a lymphovascular invasion; B. It is possibile to notice the infiltrative pattern of the adenocarcinoma gastric-type. The glands are composed by cells with high clear cytoplasm and distinct borders; C. Immunohistochemical analysis: negativity for the estrogen and progesterone receptors that are commonly negative in this type of cervix adenocarcinoma; positive controls stated by the fibroblasts in the stroma; D. Immunohistochemical analysis: positivity for MUC6.

nabothian cysts. This uncommon entity needs a particular attention for its aggressive behavior and because it is not HPV related. Screening methods for cancer control for the usual endocervical type like HPV DNA testing are ineffective and this may result in a probable delay in diagnosis and a worse prognosis. It would be really interesting to evaluate the role of nabothian cysts in the pathogenesis of this particular tumor.

Declaration of interest statement

The authors declare that they have no conflicts of interest and nothing to disclose.

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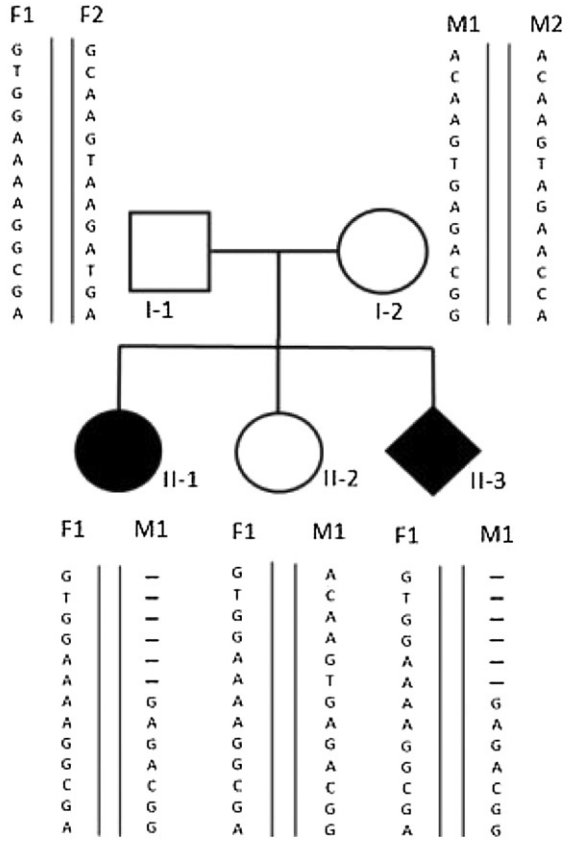
Apparent germline mosaicism for a 15q11-q13 deletion causing recurrent Angelman syndrome in a Chinese family

Dear Editors,

Angelman syndrome (AS) is a genetic and neurological disorder characterized by severe developmental delay and learning disabilities, speech impairment, ataxia, tremulousness with jerky movements of limbs and a happy, sociable disposition. This disorder affects males and females in equal numbers with a prevalence of approximately 1 in 12,000–20,000 live births. The etiology is the loss of function of the imprinted UBE3A gene in 15q11-q13. The four known mechanisms include chromosome deletions, genetic imprinting errors, mutations in the UBE3A gene, and paternal uniparental disomy (UPD) [1]. By far, the most common cause of AS is the interstitial 15q11-q13 deletion, which occurs in about 80 percent of cases. Almost all of 15q11-q13 deletions arise de novo, being present in affected patients, but not in their parents nor in healthy siblings. Here, we report a family

with AS caused by a 6.1-Mb deletion of 15q11.2-q13.1, in which two siblings were affected, providing evidence of germline mosaicism.

The 2.5-year-old female patient was born to clinically normal parents, a 27-year-old mother and 28-year-old father. She has a 4-year-old healthy sister. The diagnosis of AS in the patient was based on the following characteristics. Facial features included microcephaly with a wide mouth and protruded tongue. She had a happy disposition with paroxysms of laughter. A marked neuro-developmental delay with severely impaired communication and lack of any recognizable speech was noted. She could sit, but could not walk independently. Chromosomal microarray analysis (CMA) using a CytoScan 750 K array (Affymetrix Inc, Santa Clara, CA) revealed a 6.1-Mb 15q11.2-q13.1 deletion or arr[hg19]15q11.2q13.1



(A)

Chr position	Gene	I-1		I-2		II-1		II-2		II-3	
		F1	F2	M1	M2	F1	M1	F1	M1	F1	M1
15:26806064	GABRB3	G	G	A	A	G	-	G	A	G	-
15:27017536	GABRB3	T	C	C	C	T	-	T	C	T	-
15:28197037	OCA2	G	A	A	A	G	-	G	A	G	-
15:28235773	OCA2	G	A	A	A	G	-	G	A	G	-
15:28414665	HERC2	A	G	G	G	A	-	A	G	A	-
15:28482209	HERC2	A	T	T	T	A	-	A	T	A	-
15:29368221	APBA2	A	A	G	A	A	G	A	G	A	G
15:31197564	FAN1	A	A	A	G	A	A	A	A	A	A
15:31294654	TRPM1	G	G	G	A	G	G	G	G	G	G
15:33905410	RYR3	G	A	A	A	G	A	G	A	G	A
15:34157444	RYR3	C	T	C	C	C	C	C	C	C	C
15:34634324	NOP10	G	G	G	C	G	G	G	G	G	G
15:38591785	SPRED1	A	A	G	A	A	G	A	G	A	G

CNV region: chr15: 23006221-28566579

(B)

Fig. 1. Family pedigree and results of SNP typing of chromosome 15. (A) The two affected subjects had the same maternal haplotypes, as did their unaffected sibling, which is compatible with germline mosaicism for a deletion in 15q11.2-q13.1; (B) Chromosomal positions and genes in which the SNPs locate.

(22,770,421–28,928,730)×1 consistent with the diagnosis of AS or Prader-Willi syndrome. The deletion was not detected in the parents following analysis of DNA extracted from peripheral blood by CMA. The parents were counseled at the time that a third pregnancy was planned, and prenatal diagnosis was not requested.

One year later, the woman came again at her first trimester of gestation. A normal NT (1.2 mm) was measured at 12 weeks with a negative combined first-trimester screening result. However, the mother worried about the pregnancy because of having given birth to an affected child. She required an invasive procedure for prenatal diagnosis. Unexpectedly, CMA of chorionic villi revealed again the familial deletion. The pregnancy was terminated by the parents' request. Mosaicism was then considered in the mother. The maternal germline mosaicism was confirmed by the haplotype analysis of chromosome 15 in this family (Fig. 1).

Mosaicism in AS most often occurs in imprinting defects that do not involve deletions of the imprinting center. Individuals with AS who are imprinting-type mosaics can have relatively higher developmental ability. Maternal germline mosaicism of a UBE3A mutation has also been found [2]. However, germline mosaicism of a deletion in AS has never been reported. Germline mosaicism is a rare but important phenomenon which most of the time occurs in autosomal dominant and X-linked recessive disorders, including osteogenesis imperfecta, neurofibromatosis type I and Duchenne muscular dystrophy [3]. To our knowledge the present case is the first documentation of germline mosaicism for an interstitial 15q11-q13 deletion. This has important implications for genetic counseling. For apparently an isolated case of AS where the mother has been fully investigated, including molecular analysis of genomic DNA directly extracted from peripheral blood leukocytes, and appears unaffected, she is still at risk of another affected child. Indeed, germline mosaicism for other pathogenic microdeletions has also been described in literature [4,5]. The potential for recurrence in future pregnancies should be explained in families with microdeletion syndromes.

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Fetal phenotypes of congenital disorder of glycosylation: A case presentation

Dear Editors,

Congenital disorders of glycosylation (CDG) are a rapidly growing and genetically and clinically heterogeneous family caused by impaired synthesis of glycoconjugates [1]. Affected individuals have multi-systemic manifestations, mainly profound neurological deficiencies, growth failure, facial dysmorphisms, and a wide range of multiorgan symptoms. Currently, all reported CDG cases are child patients. We here first present a prenatal case of CDG due to a *de novo* variant in the X-linked gene *SLC35A2*.

A 40-year-old G4P0A3 woman was referred at 12 weeks of gestation for Down screening. She had three first-trimester miscarriages. Both partner had a normal karyotype. A NT of 1.6 mm with a CRL of 62 mm was demonstrated. Down screening using maternal cell-free DNA screening test was normal. The ultrasound at 17 weeks showed shortened femur length. The anomaly scan at 21 weeks showed retarded growth of both upper and lower limbs with no other abnormality. Genetic amniocentesis showed a 46, XY male and a normal chromosomal microarray. Scoliosis and polyhydramnios were noted at 25 weeks with a normal glucose tolerance test and a normal fetal echocardiogram (Fig. 1). The pregnancy continued to 34 weeks when an emergency caesarean section was performed after reporting reduced fetal movements.

A male infant was delivered with a birth weight of 1.88 kg and length of 43 cm. At birth, resuscitation was required and the boy was transferred to NICU for further management. Physical examination showed coarse facies, broad nasal bridge, thick lips, short stature, mild scoliosis and muscular hypotonia. Unfortunately, the boy developed multiple organ failure and died at the day 3 after birth. The patient's blood sample was sent for investigation of underlying etiology. Whole-exome sequencing (WES) of the patient/parent trio revealed a hemizygous *de novo* c.1A > G (p.M1?) variant in *SLC35A2* associated with CDG in the patient; this was confirmed by Sanger sequencing of the patient and both parents (Fig. 1).

SLC35A2, located on chromosome Xp11.23, encodes the UDP-galactose translocator (UGT), a transmembrane protein important for the supply of nucleotide sugars for various glycosylation pathways. SLC35A2-CDG constituted approximately 7% of all type II CDG [2]. It is inherited with an X-linked dominant pattern. Therefore, the majority of patients reported thus far are females, and only three male patients with mosaic for *SLC35A2* pathogenic variants have been reported [3,4]. It is likely that the presence of a functional SLC35A2 allele is required for survival. Our case is the fourth male patient. Although both WES and Sanger sequencing results showed a non-mosaic pattern, a low-level mosaic wild-type SLC35A2 allele might be present in other tissues.

The c.1A > G, a translation initiation codon (ATG) variant, has been reported in a female patient [4]. Another *de novo SLC35A2* initiation codon variant, c.3 G > A (p.Met1?), was also detected in a female patient [3]. Furthermore, initiation codon (ATG) variants have been clearly associated with other genetic disorders. Therefore, we interpret c.1 A > G to be the disease-causing variant in our patient.

SLC35A2-CDG has never been reported in prenatal cases. As the main characteristics of this disorder are developmental delay, seizures, and ataxia, it is impossible to demonstrate these neurological signs on prenatal sonography. However, there are