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Case Report

Prenatal diagnosis and molecular cytogenetic characterization of partial dup(18q)/del(18p) due to a paternal pericentric inversion 18 in a fetus with multiple anomalies

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ABSTRACT

Objective: We present prenatal diagnosis of rec(18)dup(18q)inv(18)(p11.2q21.2)pat owing to paternal pericentric inversion in a fetus.**Case report:** A 37-year-old woman was diagnosed with multiple anomalies on a prenatal ultrasound scan at 17 weeks and 5 days of gestation. She underwent amniocentesis at 20 weeks and 2 days. Conventional karyotyping of amniocyte showed 46, XX, der(18). She was thus referred for genetic counseling; cytogenetic analysis revealed a 46, XY karyotype, inv(18)(p11.2q21.2), of the father. Therefore, based on the results of the father, the fetal karyotype was defined as 46, XX, rec(18)dup(18q)inv(18)(p11.2q21.2)pat. Array comparative genomic hybridization of amniocytes to obtain specific information showed a 3-Mb deletion of 18p11.31p11.32 (136227_3100353)x1 and a 23.7-Mb duplication of 18q21.31-q23 (54222717_77957375) × 3.**Conclusion:** Maternal serum screening produces normal results for 18p-/18q+ syndrome, but it can be diagnosed by fluorescent *in situ* hybridization, quantitative-fluorescent polymerase chain reaction, or array comparative genomic hybridization test by observing abnormal findings on ultrasound.© 2019 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

Inversion of chromosome 18 in one of the parents can lead to partial trisomy and monosomy of short-arm and long-arm terminal regions, respectively, in their offspring. This is called as partial 18p-/18q+ recombination syndrome, which can appear with variable clinical features from mild to severe including developmental delay, various degrees of intellectual disability, facial dysmorphisms, and hand and feet anomalies [1,2]. This disease not only has a devastating impact on the patient's family but also on society. Although the severity depends on the inversion length, it

can also be influenced by the mutation site [3]. Some genetic material near the inversion breakpoints could be either lost or gained, and these chromosomal rearrangements could translate into diverse clinical manifestations [1]. Based on the presence of a centromere, two types of chromosome inversion exist: pericentric and paracentric.

To date, there have been 16 publications (20 cases) regarding parental pericentric inversion caused by chromosome 18 recombination, of which only three cases were diagnosed before birth [1–7]. Clinical features of chromosome 18 recombination found during prenatal diagnosis include holoprosencephaly (HPE) and congenital cystic adenomatoid malformation of the lung [4–6].

Therefore, we present the first case of prenatal diagnosis using chromosomal microarray findings for rec(18)dup(18q)inv(18)(p11.2q21.2)pat karyotype accompanied with multiple anomalies including fetal hydronephrosis caused by a paternal chromosome 18 pericentric inversion. Based on the literature, we also discuss a summary of the phenotypes that can be seen in 18p-/18q+ syndrome.

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Case presentation

A 37-year-old woman, gravida 2, para 0, spontaneous abortion 1, was transferred to our institution owing to abnormal findings in her ultrasound scan at 17 weeks and 5 days of gestation. Her husband was aged 43 years. The couple's first pregnancy terminated in a spontaneous abortion on approximately the 15th gestational week. Their family history for congenital malformations was unremarkable. During that pregnancy, she had undergone integrated maternal serum screening testing for trisomy 18, trisomy 21, neural tube defects, and fragile X syndrome at 11 weeks and 2 days as well as at 17 weeks and 5 days of gestation, and all associated results were normal (Table 1). However, ultrasonography performed at 17 weeks and 5 days of gestation revealed that both kidneys had hydronephrosis, which is characterized by renal pelvis dilatation (right: 6.8 mm, left: 7.6 mm) and calyceal dilatation. We also confirmed the presence of two choroid plexus cysts (CPCs) (7 × 5 mm, 11 × 5 mm). On performing follow-up ultrasonography at 20 weeks and 2 days of gestation, we noted that the extent of hydronephrosis had increased (right: 7 mm, left: 9 mm) and CPCs were still present (4 × 2 mm, 5.1 × 4 mm). Thus, she underwent amniocentesis on the same day. The next day, only the quantitative results of fluorescent polymerase chain reaction was confirmed, and were found to be normal; hence, we decided to follow-up after 2 weeks. At 22 weeks and 5 days of gestation, conventional amniocyte cytogenetic analysis revealed a karyotype of 46, der(18) (Fig. 1). In addition, we also suspected ventricular septal defect (VSD) (perimembranous type), clenched hand, hypertelorism, and increased hydronephrosis (right: 7.7 mm, left: 11 mm) after performing ultrasonography (Fig. 2). The patient was referred for genetic counseling; cytogenetic analysis of the parents revealed a karyotype of 46, XY, inv(18)(p11.2q21.2) of the father (Fig. 3) and a karyotype of 46, XX of the mother. Therefore, based on the father's results of fluorescent *in situ* hybridization test, the fetal karyotype was defined as 46, XX, rec(18)dup(18q)inv(18)(p11.2q21.2)pat and further confirmed the occurrence of inversion and a recombinant chromosome 18 (Fig. 4). The pregnancy was terminated, and a female fetus (640 g weight) was delivered at 23 weeks and 3 days of gestation. The postnatal fetal manifestation was hypertelorism, and additionally, a clenched hand was visible (Fig. 5). Since then,

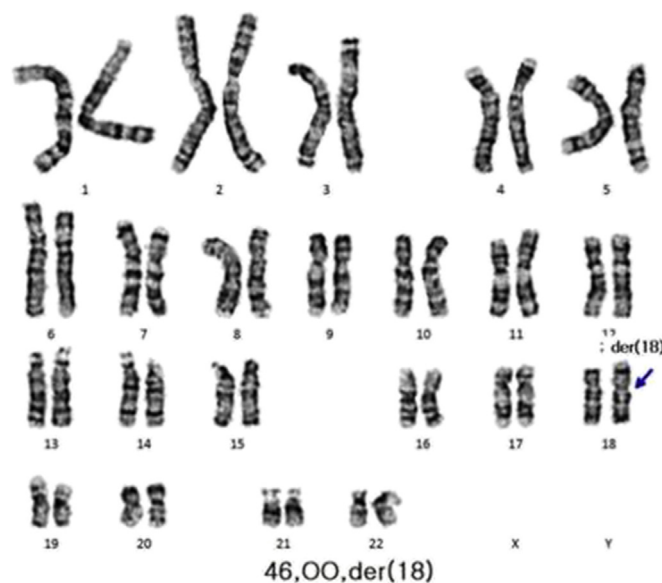


Fig. 1. A karyotype of 46, OO, der(18) in the amniocyte.

additional array comparative genomic hybridization of amniocytes to obtain specific information showed a 3-Mb deletion of 18p11.32p11.31 (136227_3100353)x1 including 14 Online Mendelian Inheritance in Man (OMIM®) genes and a 23.7-Mb duplication of 18q21.31q23 (54222717_77957375) × 3 including 19 OMIM® genes (Fig. 6) (Table 2).

Discussion

A chromosomal inversion is a 180° rotation of the fragment containing the genetic material comprising the two breakpoints and its reinsertion into the same chromosome. This fragment can be classified into two types, pericentric and paracentric, depending on whether the centromere is included or not, and it appears in 0.7% and 0.5%, respectively, in the general population [8]. Owing to chromosomal inversions in parents, the offspring may either have trisomy or monosomy. If one of the parents has chromosome inversion similar to this case, the probability of the offspring carrying a recombinant chromosome is approximately 5% [8]. However, even if recombination occurs, it may not be expressed clinically, and even when expressed, clinical manifestation may range from mild to severe symptoms. This phenomenon can be influenced by the location of the inversion which directly involves or is located near the associated genetic material as well as by the segment length [1,3].

If inversion occurs on chromosome 18, then a so-called 18p-/18q+ syndrome can occur; furthermore, the presentation of its clinical symptoms may be consistent with that of Edwards' syndrome, which is associated with trisomy 18. Many studies have reported the incidence of 18p-/18q+ syndrome, but its clinical features have not yet been clearly identified. Thus, we decided to summarize the features of each 18p deletion and 18q duplication. Hasi et al. reviewed the most common features associated with centromeric 18p deletions and their frequency: hypotonia/mixed-tone abnormalities (84%), neonatal complications (71%), magnetic resonance imaging anomalies (66%), recurrent otitis media (61%), heart defects (56%), ptosis (55%), refractive errors (52%), strabismus (42%), pectus excavatum (29%), hearing loss (23%), isolated growth hormone deficiency (23%), scoliosis/kyphosis (19%), pes planus

Table 1

Results of maternal serum screening tests in this case.

*Integrated screening test			
Date of 1st collection	Maternal weight	53.1 kg	
	GA (by USG)	11 weeks and 2 days	
	PAPP-A	2.13mIU/ml (0.716 MoM)	
	NT	1.05 mm (1.021 MoM)	
	free-hCG	39.0 ng/ml (0.706 MoM)	
Date of 2nd collection	Maternal weight	55.1 kg	
	GA (by USG)	17weeks and 5 days	
	AFP	31.2 IU/ml (0.800 MoM))	
	hCG	40.3 IU/ml (1.075 MoM)	
	uE3	1.9 ng/ml (1.306 MoM))	
	Inhibin-A	158.3 pg/ml (0.860 MoM)	
Down syndrome	Low risk	1:7500 (reference value = 1:270)	
Edward syndrome	Low risk	1:36,000 (reference value = 1:100)	
Neural tube defect	Low risk	0.800 MoM (reference value = 2.5 MoM)	
*Fragile X syndrome screening test			
CGG repeat sequence in FMR1 gene on Xq27.3 chromosome		normal	

GA = gestational age; USG = ultrasonography; PAPP-A = pregnancy-associated plasama protein A; NT = nuchal translucency; hCG = human chorionic gonadotropin; uE3 = estradiol.

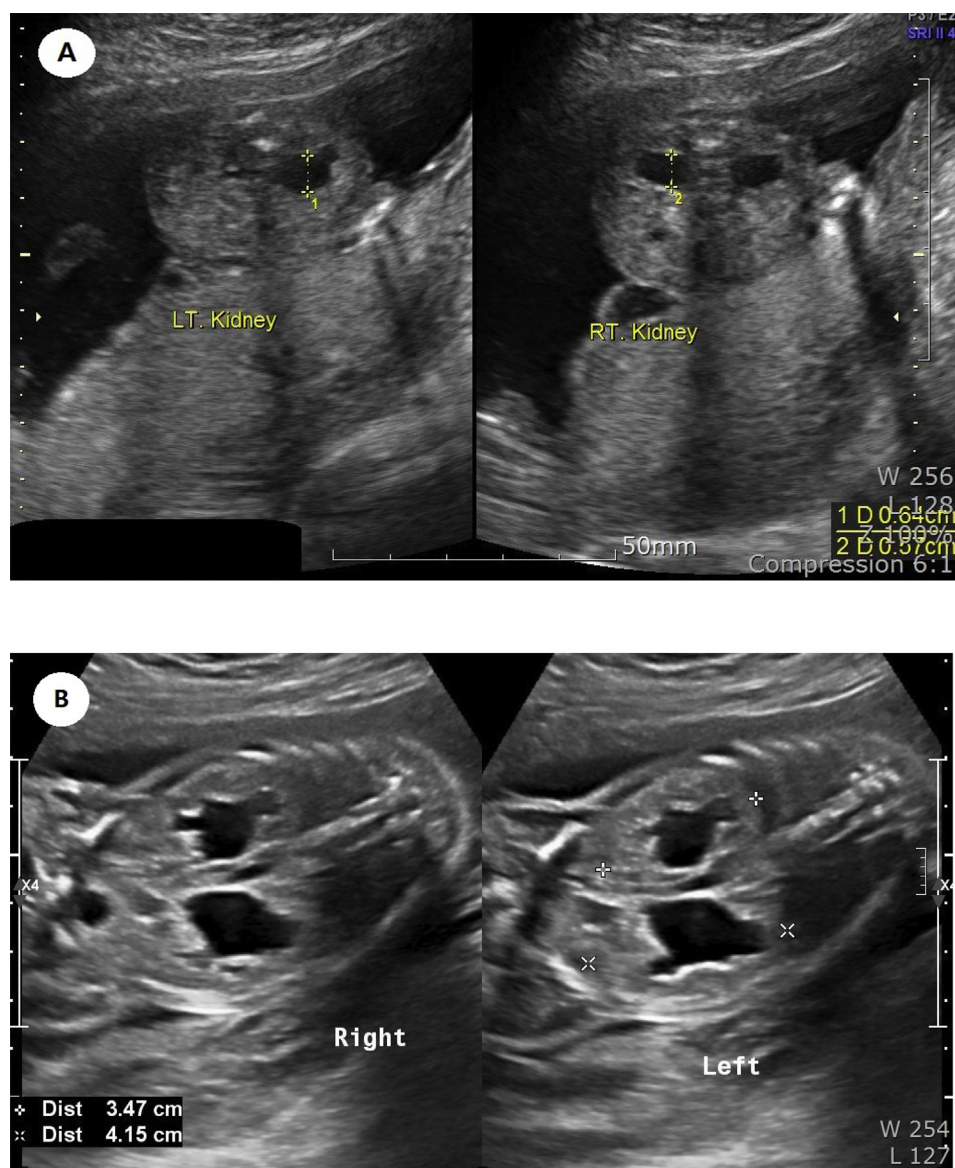


Fig. 2. Prenatal ultrasonographic findings of hydronephrosis were **A** at 17 weeks and 6 days and **B** at 22 weeks and 5 days.

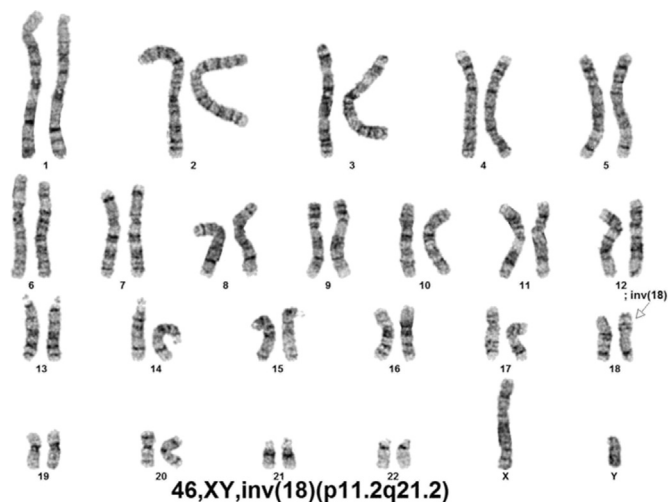


Fig. 3. A karyotype of 46,XY,inv(18)(p11.2q21.2) of the father.

(19%), cryptorchidism (14%), panhypopituitarism or hypopituitarism (13%), seizures (13%), immunoglobulin deficiency (IgA, IgG, or IgM) (13%), holoprosencephaly or HPE microform (13%), autoimmune disorder (10%), sacral agenesis (6%), optic nerve hypoplasia (6%), congenital cataracts (6%), and myelomeningocele (3%) [9]. On the other hand, the phenotype of 18q duplication is similar to that of Edwards' syndrome, although it varies depending on the region that has been duplicated; the following phenotypes are usually noted in 18q duplication: (1) craniofacial deformities (prominent occiput, dolichocephaly, low-set ears, short palpebral fissure, narrow oral opening, micrognathia, narrow palatal arch, narrow bifrontal diameter, and redundant skin at the back of the neck), (2) musculoskeletal deformities (clenched fist with overriding fingers (4th finger overlapped by the 3rd and 5th fingers), rocker-bottom feet, hypoplastic skeletal muscles, underdeveloped thumbs, small fingernails, underdeveloped thumbs, short sternum, small nipples, clubbed feet), (3) cardiac abnormalities (septal defects (specifically ventricular septal defects), ductus arteriosus, and polyvalvular disease), (4) abdominal abnormalities (umbilical hernia, inguinal

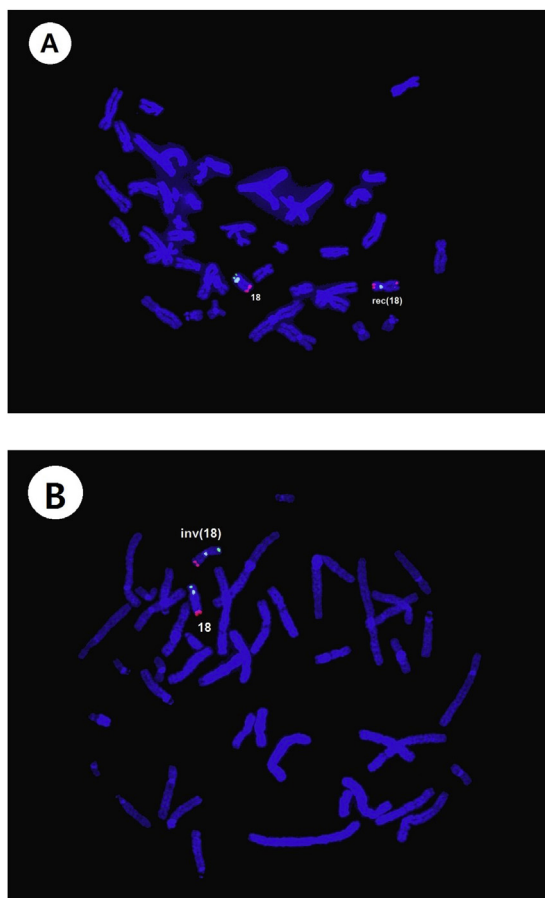


Fig. 4. Fluorescence *in situ* hybridization study of amniocytes using the following probes: Television 18p SpectrumGreen (SG) for the short arm CEP 18 (D18Z1), SpectrumAqua for the centromere, and Television 18q SpectrumOrange (SO) for the long arm. **A** shows an amniocyte with one aqua signal, two red signals, and two green signals on chromosome 18 as well as one aqua signal, four red signals, and no green signal on recombinant chromosome 18. **B** shows the father's peripheral blood cell, and the green and red signals on chromosome 18 show different sites of the inversion.



Fig. 5. Hypertelorism and right clenched hand of the fetus at birth.

hernia, and diastasis rectus abdominis), and (5) nervous system abnormalities (mental retardation, hypertonia, decreased response to sounds, and seizures) [10]. It is known that 2% of the inversions exhibiting the Edwards' syndrome phenotype are arise from duplication in the long arm of chromosome 18 (18q+) [11]. Hence, it is assumed that information on only the long arm phenotype is available on OMIM® database for the gene associated with this case (Table 2). Based on this, we were expecting similar symptoms when an individual is affected by a mutation at the same location on the long arm of chromosome 18. However, the findings of Boghosian-Sell et al. who investigated the partial duplication of 18q21.31q23 which was the same region as that affected in our case, were consistent with those observed in our case, i.e., 18q+ did not present with hydronephrosis, VSD, CPCs, clenched hand, and hypertelorism [11]. This may be due to the difference in duplicated chromosome length. Vigi et al. reported a female child, similar to our case, who had genitourinary malformations including hydronephrosis owing to the karyotype 46, XX, rec(18)inv(18)(p11q21), attributable to the maternal carrier. They showed that its length was approximately 60% of the total chromosomal length and has a relatively high risk of recombination [12]. Additionally, the inversion phenomenon may also be associated with a short arm that is not yet apparent.

To our knowledge, this is the first case diagnosed in the prenatal period of 18p-/18q+ syndrome with multiple anomalies including hydronephrosis. Of course, there are limitations associated with rec(18) detection during prenatal diagnosis, in terms of understanding the related functional abnormalities; however, its diagnosis can have important implications in genetic function mapping based on the detection of related structural anomalies. This article highlights that maternal serum screening test for confirming aneuploidy will require an additional ultrasound screening. Especially, during the 2nd/3rd trimester, abnormal phenotypes including intrauterine growth retardation, polyhydramnios, brachycephaly, narrow frontal cranium, CPC, overlapping of the 3rd and 4th fingers with the 2nd and 5th fingers, congenital heart defects, omphalocele, and a single umbilical artery can indicate 18p-/18q+ syndrome such as the Edwards' syndrome [10]. In case of such abnormal sonographic findings, a chromosomal confirmation test should be performed. Additionally, information obtained prenatally by performing preimplantation genetic diagnosis in the future pregnancy will facilitate the avoidance of a painful repetition of fetal loss.

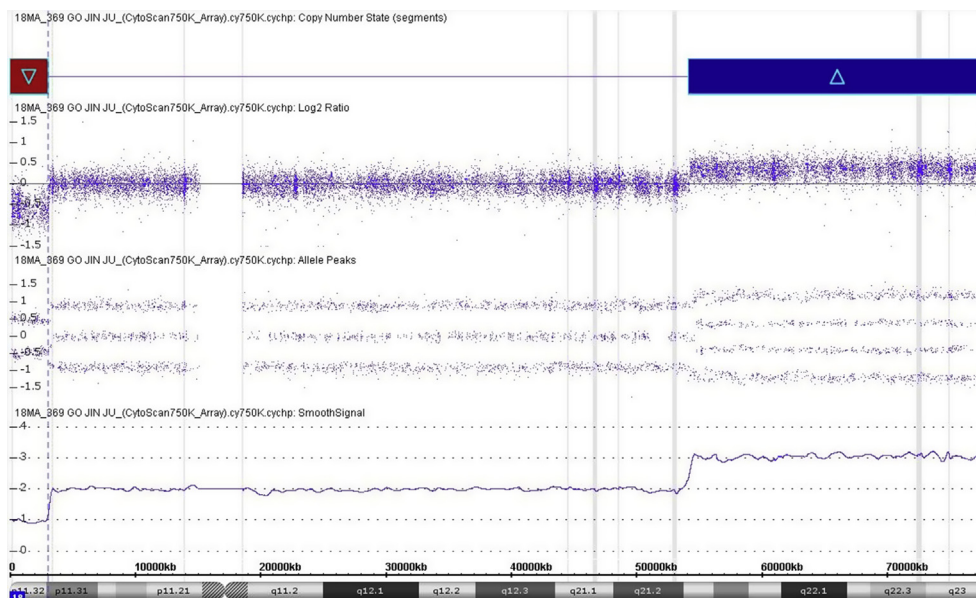


Fig. 6. Array comparative genomic hybridization of amniocytes using Affymetrix Cytoscan 750K array protocols (Affymetrix®, Santa Clara, CA, USA) and Genome Build: Hg19 shows a deletion of 18p11.32p11.31 (136227_3100353)x1 and a duplication of 18q21.31q23 (54222717_77957375) × 3. At the top line, red and blue boxes signal loss and gain of chromosomal material, respectively.

Table 2

Information from the Online Mendelian Inheritance in Man^a database for the gene of interest in this case.

Gene	Cytogenetic location	Phenotype	Inheritance
ATP8B1	18q21.31	cholestasis, benign recurrent intrahepatic cholestasis, intrahepatic, of pregnancy cholestasis, progressive familial intrahepatic	AR AD AR
BCL2	18q21.33	leukemia/hymphoma, B-cell	not reported
CCBE1	18q21.32	Hennekam lymphangiectasia-lymphedema syndrome 1	AR
CTDP1	18q23	congenital cataracts, facial dysmorphism, and neuropathy	AR
CYB5A	18q22.3	methemoglobinemia and ambiguous genitalia	AR
FECH	18q21.31	protoporphyrria, erythropoietic, autosomal recessive	AR
KDSR	18q21.33	erythrokeratoderma variabilis et progressiva 4	AR
LMAN1	18q21.32	combined factor V and VIII deficiency	AR
MALT1	18q21.32	immunodeficiency	AR
MC4R	18q21.32	obesity, autosomal dominant	AD, Mu, AR
NEDD4L	18q21.31	periventricular nodular heterotopia	AD
PIGN	18q21.33	multiple congenital anomalies-hypotonia-seizures syndrome	AR
RAX	18q21.32	microphthalmia, isolated	AR
RTTN	18q22.2	microcephaly, short stature, and polymicrogyria with seizures	AR
SERPINB7	18q21.33	palmo-plantar keratoderma, Nagashima type	AR
SERPINB8	18q22.1	peeling skin syndrome	AR
TNFRSF11A	18q21.33	osteolysis, familial expansile osteopetrosis, autosomal recessive {Paget disease of bone 2, early-onset}	AD AD AR
TSHZ1	18q22.3	aural atresia, congenital	AD
TXNL4A	18q	Burn-McKeown syndrome	AR
ADCYAP1	18p11.32	not reported	not reported
CETN1	18p11.32	not reported	not reported
CLUL1	18p11.32	not reported	not reported
COLEC12	18p11.32	not reported	not reported
EMILIN2	18p11.32	not reported	not reported
ENOSF1	18p11.32	not reported	not reported
LPIN2	18p11.31	not reported	not reported
MYOM1	18p11.31	not reported	not reported
SMCHD1	18p11.32	not reported	not reported
THOC1	18p11.32	not reported	not reported
TYMS	18p11.32	not reported	not reported
USP14	18p11.32	not reported	not reported
YES1	18p11.32	not reported	not reported

^a <https://www.omim.org/>.

Conflict of interest

None.

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