

## SHORT COMMUNICATION

# Prenatal diagnosis of complete trisomy 19q

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This communication presents the first case of complete trisomy 19q, prenatally detected by ultrasound investigation.

Real-time high-resolution ultrasound examination was performed at 19 weeks of gestation. After termination of the pregnancy, autopsy investigation was done. GTG-banding, fluorescence *in situ* hybridization m-(FISH) analysis, and FISH analysis with a 19q subtelomeric specific probe were used for identification of the fetal karyotype. Sonographic examination revealed an enlarged cisterna magna, cerebellar hypoplasia and aplasia of the inferior part of the vermis, combined and bilateral kidney malformations, significant nuchal fold, absence of fetal nasal bones, and intracardial calcifications. Autopsy confirmed ultrasound findings, but also revealed situs viscerum inversus of the lungs. Fetal karyotype was defined as: 46,XY,der(21)t(19;21)(q11;p13)mat. Our ultrasound and autopsy findings will certainly contribute to better knowledge of phenotype characterization of this rare chromosomal disorder. Copyright © 2007 John Wiley & Sons, Ltd.

KEY WORDS: trisomy 19; prenatal diagnosis; multiple malformations

## INTRODUCTION

Unbalanced karyotypes due to reciprocal translocation or rearrangement of 19q chromosome are a rare aneuploidy. To our knowledge, only ten cases with no concomitant monosomy have been reported so far. All of them were, in fact, partial trisomies that resulted from unbalanced translocation, familiar or *de novo*, or from pure duplication (Lange and Alfi, 1976; Rivas *et al.*, 1985; Boyd *et al.*, 1992; Valerio *et al.*, 1993; Cotter *et al.*, 1997; Bhat *et al.*, 2000; Tercanli *et al.*, 2000; Qorri *et al.*, 2002; Rombout *et al.*, 2004). Some authors have stated that it could be a recognizable syndrome (Lange and Alfi, 1976; Rivas *et al.*, 1985; Bhat *et al.*, 2000; Tercanli *et al.*, 2000; Rombout *et al.*, 2004) associated with the phenotype that usually includes low birth weight, growth and psychomotor retardation, short neck with redundant skin fold, microcephaly, facial dysmorphism (flat nasal bridge, small nose, short philtrum, down turned mouth, abnormal ears), clinodactyly, heart malformations, and anomalies of the genitourinary tract and/or gastrointestinal system (Rombout *et al.*, 2004).

Moreover, only three of the reported cases were prenatally diagnosed. They arose *de novo* owing to a duplication in two cases (Cotter *et al.*, 1997; Tercanli *et al.*, 2000) and to a translocation involving chromosome 22 (Rombout *et al.*, 2004) in the third case. We present another prenatally diagnosed case of trisomy 19q, resulting from maternal translocation (19;21)(q11;p13). In contrast to other reported cases, this is the first report of complete trisomy of 19q chromosome.

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## CASE REPORT

A 25-year-old primigravida was referred to routine ultrasound examination at 19 weeks of gestation. The woman and her husband were healthy, non-consanguineous, and had no family history of congenital malformations. Real-time sonography revealed multiple malformations and because of extremely poor prognosis, the parents decided, after counselling, to terminate the pregnancy.

### Ultrasound findings

The fetal biometry agreed with 19 weeks of gestation (biparietal diameter (BPD) 4.4 mm, femur 2.6 mm, abdominal circumference 16.5 mm). Fetal heart rate was normal (145 bpm). Placenta was anterior and amniotic fluid volume was normal. All three umbilical cord vessels were present. However, we found a number of fetal structural abnormalities: increased nuchal fold (13 mm), absence of nasal bones, dilated cisterna magna, agenesis of the inferior part of the cerebellar vermis (keyhole sign), cerebellar hypoplasia (transverse cerebellar diameter (TCD) 16 mm), partially multi-cystic and hydronephrotic left kidney (grade IV) with dilated ureter and mild hydronephrosis of the right kidney (Figures 1 and 2), and intracardial calcifications (two in the left ventricle). Fetal movements were decreased. Umbilical artery velocimetry was normal. RI: 0.71.

### Autopsy findings

Termination of pregnancy at 19 weeks' gestation revealed a male fetus, weighing 400 g, with crown/heel



Figure 1—A transverse scan of fetal head showing the cystic appearance of the fourth ventricle and cisterna magna. Cerebellar hemispheres due to hypoplasia of the inferior portion of the vermis are clearly separated. Nuchal skin is markedly edematous ( 8.5 mm)



Figure 2—A longitudinal sonographic scan of fetal abdomen demonstrating extremely enlarged intrarenal urinary collecting system of the left kidney

length 22 cm. External examination showed a flat nose, low-set ears, and a short neck with redundant skin fold.

On internal examination, the lungs appeared normal on gross inspection, but the left lung presented characteristics of the right lung and vice versa. No heart malformations were detected. Renal fusion of the upper poles produced the horseshoe kidney. The left kidney was enlarged, showing a marked dilatation of the renal pelvis, calyceal system, and ureter, blunting of renal papillae, and parenchymal thinning. Stenosis occurred at the vesicoureteric junction. The central nervous system showed moderate cystic dilatation of the fourth ventricle.

### Cytogenetic analysis

Cytogenetic analysis was performed by long-term cultures on fetal tissue. Unbalanced karyotype with additional chromosomal material on the short arm of



Figure 3—Mother's and fetal GTG-banded partial karyotype

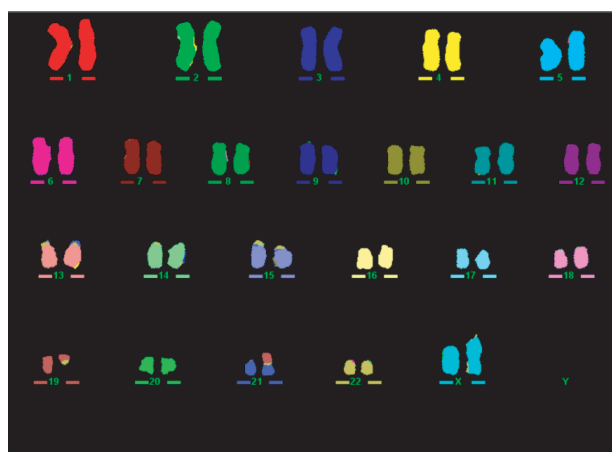


Figure 4—m-FISH performed on maternal metaphase chromosomes showing balanced translocation between a chromosome 19q and 21p

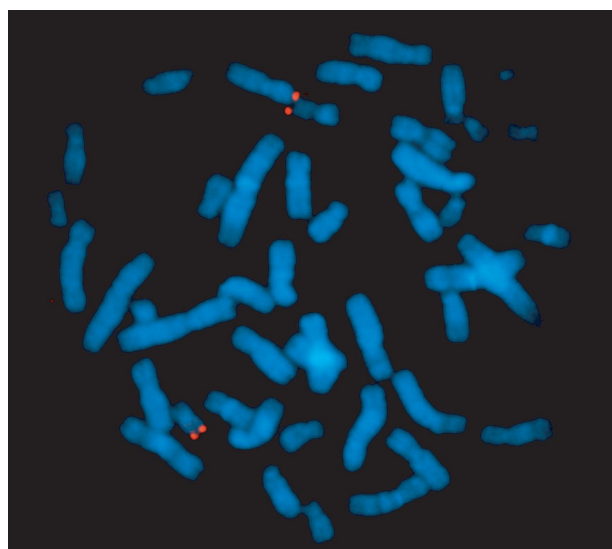


Figure 5—FISH with specific probe for telomere 19q performed on maternal metaphase chromosomes

chromosome 21 was detected (Figure 3). Chromosome analysis of the parents' lymphocytes (GTG-banding) showed a maternal balanced translocation between a chromosome 19q and 21p, 46,XX,t(19;21)(q11;p13). The father's karyotype was normal, 46,XY. In order to confirm translocation, m-FISH analysis was performed on maternal metaphase chromosomes (Figure 4). A subtelomeric specific probe for 19q (Visys) was further used for identification of the translocation (Figure 5).

Table 1—Ultrasound and autopsy findings in prenatally diagnosed cases of trisomy 19q

	Cotter <i>et al.</i>		Rombout <i>et al.</i>		Tercanli <i>et al.</i>		Present case	
	ultrasound	autopsy	ultrasound	autopsy (15 weeks)	ultrasound	autopsy	ultrasound	autopsy
Gestational age		10 weeks		12 weeks		20 + 4 weeks		19 weeks
Karyotype		46,XYdir dup(19)(q13.2;q13.4) <i>de novo</i>		46,XX,der(22)t(19;22)(q13.3;p13) <i>de novo</i>		46,XY,dup(19)(q13.1;qter) <i>de novo</i>		46,XY,der(21)(19;21)(q11;p13) mat
Findings	ultrasound	autopsy	ultrasound	autopsy (15 weeks)	ultrasound	autopsy	ultrasound	autopsy
General	cystic hygroma		abnormal nuchal translucency	short neck, microretrognathia, flat nose, low set ears, slightly enlarged interorbital space moderate dilatation of the lateral ventricles ventricular septal defect,atretic pulmonary artery, hypoplastic right heart	nuchal oedema, mild hydrops fetalis with ascites, oligohydramnion	enlarged abdomen	increased nuchal fold, absence of fetal nasal bone	short neck with redundant skin folds, flat nose, low set ears
Anomalies of central nervous system								
Heart malformations								
Anomalies of urinary tract								
Other anomalies								

On the basis of this result, the fetal karyotype was interpreted as: 46,XY,der(21)t(19;21)(q11;p13)mat.

## DISCUSSION

The present case is the first report of complete trisomy 19q, prenatally detected by a real-time high-resolution ultrasound investigation at 19 weeks of gestation. Sonographic examination revealed enlarged cisterna magna, cerebellar hypoplasia and aplasia of the inferior part of the vermis, combined and bilateral kidney malformations, significant nuchal fold and scalp edema, absence of fetal nasal bones, and intracardial calcifications (Table 1).

A comparison of all prenatally detected trisomies 19q indicates that the report of Tercanli *et al.* is the most comparable with our case, because of well-described second-trimester ultrasound findings and the fact that they described the largest trisomic segment of the long arm of chromosome 19, distal of 19q13.1 (Table 1). Urinary tract abnormalities were found in both cases. Observed multi-cystic dysplastic kidney disease could be associated with some changes of USF2 gene, located at the 19q13.1 band (Groenen *et al.*, 1996). Disruption of the USF2 gene may cause multi-cystic renal dysplasia with pelviureteric obstruction, and massive hydronephrosis. In contrast to other reported cases of trisomy 19q, we observed significant CNS anomalies (Table 1), which could be associated with Dandy–Walker complex, or more precisely, to the Dandy–Walker variant (Barkovich *et al.*, 1989). It is worth mentioning that similar brain anomalies have been reported in patients with fructin-related protein (FKRP) gene mutations, mapped to chromosome 19q13.3 (FKRP [OMIM 606596]; Brockington *et al.*, 2001). These gene mutations account for a wide spectrum of patients with congenital muscular dystrophy associated with brain malformations (Quijano-Roy *et al.*, 2006) including congenital muscular dystrophy type 1C (Louhichi *et al.*, 2004), muscle-eye-brain disease, and Walker–Warburg syndrome (Beltran-Valero de Bernabe *et al.*, 2004). In the present case, neither a real-time high-resolution ultrasound examination, as performed by a fetal echography specialist, nor fetal autopsy revealed any heart malformations. At present, the lack of heart anomaly seems an isolated finding since heart irregularities have been the most common anomalies associated with trisomy 19q (Lange and Alfi, 1976; Rivas *et al.*, 1985; Boyd *et al.*, 1992; Valerio *et al.*, 1993; Bhat *et al.*, 2000; Tercanli *et al.*, 2000; Rombout *et al.*, 2004).

Our autopsy findings also detected situs viscerum inversus of the lungs. Lung anomalies (bilobate right lung) were previously described only by Lange and Alfi (1976). They reported unbalanced translocation (19;22)(q13;p13) with the most severe clinical findings of all reported trisomies 19q, which could indicate the largest duplication. Since high-resolution banding was not available in 1976, the exact size of the trisomic segment was not established and we could not compare their results with ours.

According to the literature, trisomy 19q was reported as a recognizable syndrome (Jablonski, [www.nlm.nih.gov/mesh/jablonski/syndromes/syndrome198.html](http://www.nlm.nih.gov/mesh/jablonski/syndromes/syndrome198.html)).

However, phenotype variability associated with trisomy 19q still comprises a problem in syndromal characterization. The present case pointed out some new observations, for example, a possible association with Dandy–Walker variants and therefore raises questions about common clinical features of the mentioned syndrome. Our ultrasound and autopsy findings will certainly contribute to a better knowledge of phenotype characterization of this rare chromosomal disorder.

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