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CASE REPORT

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Congenital diaphragmatic hernia in a case of Cat eye syndrome

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Key Clinical Message

Our findings extend the phenotypic spectrum of Cat eye syndrome, a disorder with wide clinical variability. The potentially life-threatening complications of congenital diaphragmatic hernia should be considered in genetic counseling and prenatal diagnostic.

KEYWORDS

22q11.2, case report, Cat eye syndrome, congenital diaphragmatic hernia, supernumerary bisatellited marker chromosome

1 | INTRODUCTION

Cat eye syndrome (CES) is a rare congenital malformation syndrome characterized by various findings, with an estimated prevalence of 1 in 50 000-150 000 live births.[1] Approximately 40% of CES patients present the classical CES triad of iris colobomas, anorectal malformations, and pre-auricular anomalies.[1] Colobomas in CES can also involve the choroid and/or the retina. Further documented disorders include congenital heart defects; renal malformations such as unilateral absence, unilateral or bilateral hypoplasia, and cystic dysplasia; intrahepatic or extrahepatic biliary atresia; and malrotation of the gut. Furthermore, craniofacial dysmorphic features, such as high forehead, down-slanted palpebral fissures, microphthalmia, epicanthus, micro-retrognathism, large low-inserted ears, and microtia with atresia of the external auditory canal, are all reported.[2,3] Mild-to-moderate mental retardation is reported in approximately 30% of cases, with no apparent phenotypic difference found between mentally retarded and mentally normal CES patients.[1] There is a significant phenotypic variability with the condition, ranging from patients with almost normal phenotypes to those with severe abnormalities, including life-threatening congenital malformations.[1,4-6] Some rare manifestations have also been reported, including anatomical asplenia,[7] hemifacial microsomia,[8] and Müllerian agenesis.[9]

The genetic basis and mode of inheritance of CES was first described by Schachenmann et al[10] in 1965. CES is characterized by the presence of an extra bisatellited marker chromosome, resulting in partial tetrasomy of euchromatic material from 22pter to 22q11.[1] The typical CES chromosomes are formed from breakpoints within band 22q11. The most common breakpoint interval is a region that corresponds to the proximal breakpoint interval in the 22q11 deletion syndrome (DiGeorge/velocardiofacial syndrome). The small (type I) CES chromosomes are symmetrical, with both breakpoints located within the proximal interval, and the larger (type II) CES chromosomes are either asymmetrical, with one breakpoint located in each of the 2 intervals, or symmetrical, with both breakpoints located in the distal interval, which result in

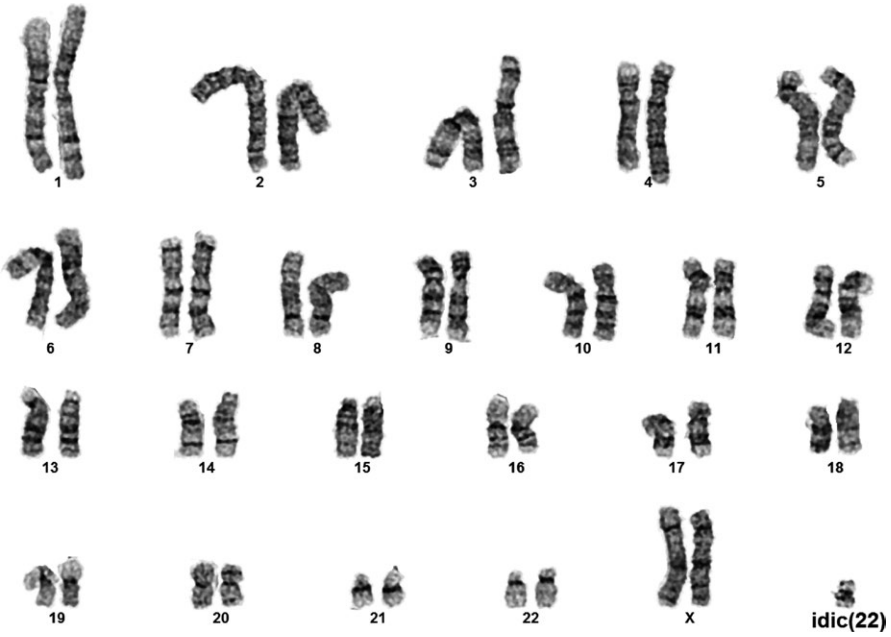


FIGURE 1 Giemsa banding of lymphocytes of the mother, with extra chromosome idic(22)

1 or 2 additional copies of the DiGeorge critical region.[11] Of note is the fact that the penetrance and clinical symptoms do not correlate with the amount of the supernumerary euchromatic material. The additional chromosome 22 usually arises de novo from one of the parents. For the offspring of a carrier, the risk of inheriting the marker chromosome is around 50%.[12]

Congenital diaphragmatic hernia (CDH) represents a spectrum of rare developmental defects of the diaphragm. The condition results in an upward displacement of the abdominal organs into the thorax. Additional disorders that can occur with CDH include pulmonary hypoplasia, patent ductus arteriosus, patent foramen ovale, and intestinal malrotation.[13] CES in association with CDH has not been previously reported; but investigations revealed that segment 22q11 is a good candidate for CDH in trisomic condition.[14]

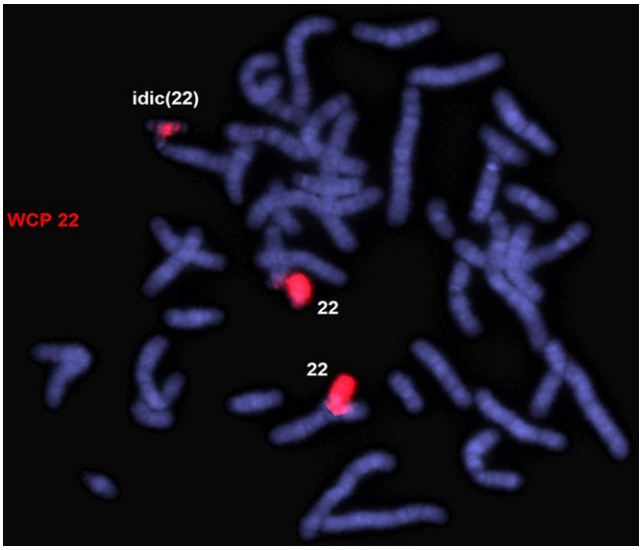


FIGURE 2 Fluorescence in situ hybridization with whole chromosome paint of chromosome 22 (WCP22, Cytocell)

2 | CLINICAL REPORT

The male index patient was the third child of nonconsanguineous parents (mother 34 years old, father 44 years old). The father had no reported health problems. The mother showed the following facial dysmorphic features: facial asymmetry, mild hypertelorism, and down-slanted small palpebral fissures and no other organic disorders or malformations. She was diagnosed by chromosomal analysis with maternal de novo isodicentric chromosome 22 and a mild form of CES at the age of 7. In a repeated chromosomal study, all analyzed lymphoid cells showed the supernumerary bisatellited marker chromosome 22q (Figure 1). Fluorescence in situ hybridization with a whole chromosome paint of chromosome 22 and specific probes the karyotype was determined to be 47,XX,+mar.ish idic(22)(11.2)(wcp22+,TUPLE1−) (Figures 2 and 3). Subsequent multiplex ligation-dependent probe amplification revealed tetrasomy of all 5 CES-relevant probes. The symmetrical small CES chromosome (type I) involved tetrasomy of 22pter-22q11.2 including approximately 1.05 Mb of euchomatin in 22q11.1-q11.21.

The present pregnancy was her fourth, with a history of 2 apparently healthy newborns, and one early miscarriage. It was complicated by gestational diabetes, which was diagnosed by screening at 26 weeks of gestation and managed

by diet. Genetic testing was not performed with any of the previous pregnancies. Indications for referral to our hospital were polycystic dysplastic kidneys, initially raising the possibility of fetal polycystic kidney disease. Chromosomal analysis from the amniotic cell culture of the present pregnancy, performed at 17 weeks of gestation, revealed inheritance of the supernumerary bisatellited marker chromosome 22q. At 25 weeks, the mother presented for a second opinion ultrasound at our prenatal unit. The fetus was of normal growth, with slightly increased amniotic fluid, but exhibited a variety of anomalies: hypertelorism, bilateral preauricular skin tags, a perimembranous outlet ventricular septal defect (2.5 mm in diameter), unilateral multicystic dysplastic kidney, dilated bowel loops with enterolithiasis suggestive of anal atresia with fistula of the urinary tract, and right-sided CDH with intrathoracic liver and bowel with an observed-to-expected lung to head ratio of 80%.

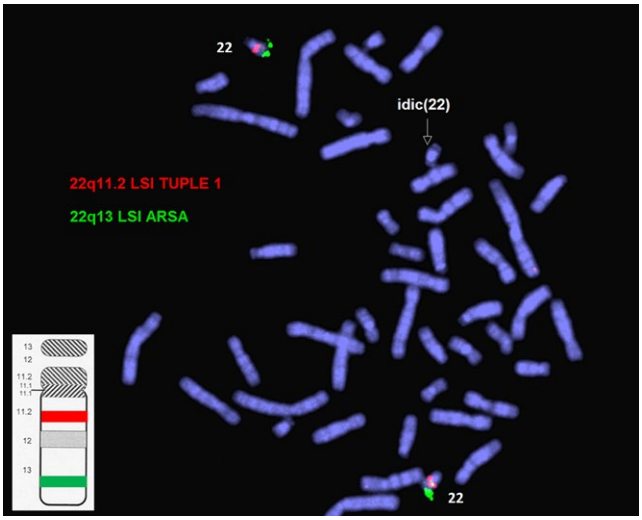
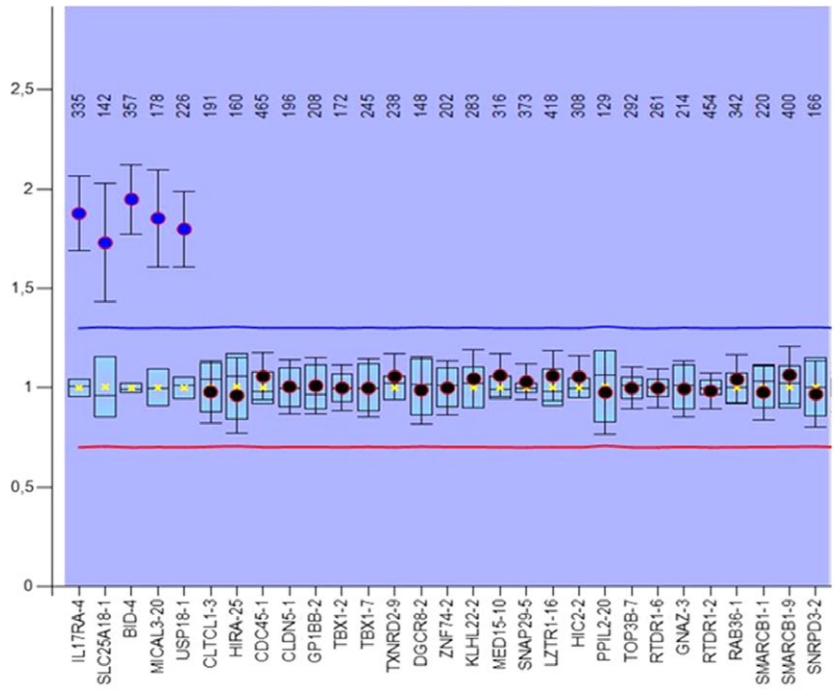


FIGURE 3 Fluorescence in situ hybridization with 22q11.2 LSI (Locus-Specific Identifier) TUPLE 1 from DiGeorge/velocardiofacial syndrome critical region and 22q13 LSI ARSA (Arylsulfatase A) probes designed to hybridize to the ARSA gene (Abott-Vysis, LSI Table1). Positive signal for both probes on both chromosomes 22. The FISH probe for the DiGeorge critical region (TUPLE 1), localized to 22q11.2, exhibited no signal on the marker chromosome (arrow)

Complementary magnetic resonance imaging at 33 weeks of gestation confirmed the diagnosis of right-sided CDH with herniation of parts of the small intestine, the stomach, and the liver into the thorax (Figure 5). The measured fetal body volume was 1401 mL and the lung volume 51.5 mL, with an observed-to-expected total fetal lung volume of about 30%. With respect to the various malformations and after interdisciplinary counseling, we refrained from tracheal occlusion and favored expectative management. The mother was transferred to another hospital before birth to facilitate the possibility of providing, if indicated, extracorporeal membrane oxygenation for pulmonary failure, due to the presence of pulmonary hypoplasia.

The eutrophic boy (birth weight 2.745 g, birth length 49.5 cm and head circumference 35 cm) was born by primary Caesarean section at 37 + 6 weeks of gestation and



D [nt]	Gene-Exon	Chr.band	hg18 loc.
335	IL17RA-4	22q11.1	22-015,959666
142	SLC25A18-1	22q11.21	22-016,423313
357	BID-4	22q11.21	22-016,606684
178	MICAL3-20	22q11.21	22-016,704656
226	USP18-1	22q11.21	22-017,012924
191	CLTCL1-3	22q11.21	22-017,621597
160	HIRA-25	22q11.21	22-017,699015
465	CDC45-1	22q11.21	22-017,847478
196	CLDN5-1	22q11.21	22-017,891318
208	GP1BB-2	22q11.21	22-018,091521
172	TBX1-2	22q11.21	22-018,127111
245	TBX1-7	22q11.21	22-018,133286
238	TXNRD2-9	22q11.21	22-018,266225
148	DGCR8-2	22q11.21	22-018,453612
202	ZNF74-2	22q11.21	22-019,079428
283	KLHL22-2	22q11.21	22-019,173307
316	MED15-10	22q11.21	22-019,266745
373	SNAP29-5	22q11.21	22-019,572014
418	LZTR1-16	22q11.21	22-019,679191
308	HIC2-2	22q11.21	22-020,129442
129	PPIL2-20	22q11.21	22-020,379682
292	TOP3B-7	22q11.22	22-020,652996
261	RTDR1-6	22q11.22	22-021,734047
214	GNAZ-3	22q11.22	22-021,795392
454	RTDR1-2	22q11.22	22-021,812539
342	RAB36-1	22q11.22	22-021,817561
220	SMARCB1-1	22q11.23	22-022,459370
400	SMARCB1-9	22q11.23	22-022,506362
166	SNRPD3-2	22q11.23	22-023,283701

FIGURE 4 Multiplex ligation-dependent probe amplification (MLPA, MRC-Holland) with microdeletions-/microduplications-probe Set P250-B2, 29 loci of 22q11, including 5 probes in the CES critical region 22q11.2. The analysis revealed tetrasomy of all 5 CES-relevant probes (Ratio: 1.73-1.95, normal range: 0.7-1.3) without additional copies of the DiGeorge critical region leading to type I CES chromosome

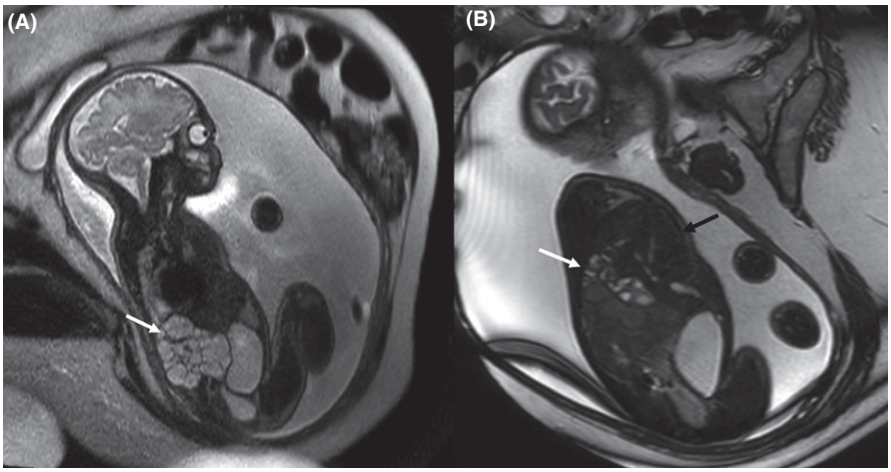


FIGURE 5 Magnetic resonance imaging at 33 weeks of gestation, sagittal views of the fetus. A, Left polycystic dysplastic kidney (arrow). B, Right-sided CDH with herniation of parts of the small intestine (white arrow) and the liver (black arrow) into the thorax

immediately intubated and ventilated. Postnatally, and in addition to the prenatal findings, the boy presented downslanting palpebral fissures and preauricular pits. Due to severe lung hypoplasia and pulmonary hypertension, the boy died on his second day of life.

3 | DISCUSSION

The reason for the significant phenotypic variability in CES, ranging from almost normal phenotype to severe abnormalities including life-threatening congenital malformations, is still not understood. This broad phenotypic variation is well illustrated in this familiar case of CES. The case supports the use of adequate prenatal diagnostic for carriers of small supernumerary marker chromosome to allow for intrauterine detection of, in particular, acute life-threatening congenital malformations, in order to ensure proper postnatal treatment of an affected newborn. Apart from CDH, all the clinical features of the patient, including polycystic dysplastic kidneys, anal atresia, downslanting palpebral fissures, hypertelorism, a membranous type of ventricular septal defect, and preauricular skin pits and tags, are well-described symptoms of CES. In the literature, some rare manifestations have also been reported, such as anatomical asplenia, hemifacial macrosomia, and Müllerian agenesis.[7-9] The patient described here, to our knowledge, represents the first patient diagnosed so far with both CES and CDH.

With a birth prevalence of 1 in 3000-4000, CDH is much more frequently occurring than CES.[15] The diaphragm develops during the 4th-8th week of gestation, and the hernia is thought to occur when any of the structures making up the diaphragm fails to fuse. Posterior lateral hernias (Bodaleck) account for >95% of neonatal diagnoses with only about 20% occurring on the right side.[16] In approximately 60% of patients, CDH occurs as an isolated malformation; 40% of patients have additional malformations as part of a chromosomal aneuploidy, monogenic syndromes, or a constellation of anomalies that do not have an identifiable genetic basis. Conventional karyotyping identifies chromosomal anomalies in about 6.3% of CDH patients.[15] Of late, various monogenetic causes and smaller microduplication/deletions have been identified. However, the aetiology of CDH is still unknown in most patients.[13]

Unolt et al[17] published a report investigating the association between CDH and 22q11.2 deletion syndrome, with a prevalence of CDH in this cohort of 0.8%, which is greater than in the general population (0.025%). Analysis of both the genomic sequence for the 22q11 interval and the orthologous regions in the mouse has identified 14 putative genes that are shared between CES and der(22) syndrome.[18] Autosomal duplications have been less commonly associated with CDH than autosomal deletions, but hernias have been seen in patients with tetrasomy 21, trisomy 22, and trisomy 9. Complete and partial trisomy 22 have been reported with CDH, pulmonary hypoplasia, agenesis of the corpus callosum, facial dysmorphism, and nail hypoplasia.[19] Borys and Taxy[20] described the first case of unbalanced translocation of chromosomes 11 and 22 47,XY, +der(22)t(11:22) (q23.3:q11.2)) presenting with CDH and anal atresia; both malformations are shared in our case. Additional evidence for the importance of trisomy 22q in some cases of CDH comes from further documented patients with CDH and the unbalanced products of a recurrent chromosome translocation resulting in partial trisomy of 22q and partial monosomy of chromosome 11q.[19] The diaphragmatic defects associated with this abnormality have been attributed primarily to duplication of material from chromosome 22. This was based on several reports of diaphragmatic hernia in individuals with trisomy 22, and the existence of only 2 reports of CDH associated with partial duplication of 11q due to translocation (11;12) and (11;13).[21]

Thus, perhaps there is a more complex gene dosage effect with the 22q11.2 region of deletion, trisomy and tetrasomy being a hot spot for CDH.

4 | CONCLUSION

In light of the patient described here and the broad phenotypic variability of CES in general, we suggest an association

between CES and CDH; coincidence, however, cannot be excluded. At this point, the potentially life-threatening complication of congenital diaphragmatic hernia should be considered in genetic counseling and prenatal diagnostic. Furthermore, this finding may lead to the identification of an additional locus for diaphragmatic hernia in the general population.

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CONFLICT OF INTEREST

None declared.

AUTHORSHIP

EAA: first author, responsible for writing and reviewing the manuscript and literature review. All other authors have equal contribution in preparing and editing the text of this manuscript: its concept, form, and figures.

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