

ELECTRONIC LETTER

Partial trisomy of chromosome 22 resulting from an interstitial duplication of 22q11.2 in a child with typical cat eye syndrome

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Cat eye syndrome (CES) is a rare malformation syndrome with a variable pattern of congenital anomalies. The characteristic features of CES include ocular coloboma, preauricular pits or tags, anal anomalies, and congenital heart and renal malformations. Furthermore, CES may be associated with other craniofacial malformations, skeletal anomalies, and, in some cases, with mental retardation.^{1,2} In almost all cases CES is associated with the cytogenetic finding of a supernumerary marker chromosome consisting of duplicated material of chromosome 22. The marker is usually bisatellite and dicentric (idic(22)(pter→q11.2::q11.2→pter)) and thus results in tetrasomy of the p arm and a part of 22q11.2.^{1,3}

Cytogenetically detectable intrachromosomal direct or inverted duplications are rare and can arise with equal frequency by rearrangement between sister chromatids or non-sister chromatids both on the maternal or paternal chromosome.⁴ The proximal part of the long arm of chromosome 22 (22q11.2) has been recognised as a hot spot for chromosomal rearrangements and contains both the cat eye and the DiGeorge critical region (for reviews see Kotzot *et al*⁵ and Edelmann *et al*⁶). Multiple congenital malformations showing overlap with CES can arise from familial translocation t(11;22) in the der(22) syndrome,^{7,8} and, in rare cases, from interstitial duplication of proximal 22q.⁹⁻¹¹ However, none of these patients described so far with interstitial duplications of 22q showed the full CES phenotype including all major clinical features. We report here a patient with an interstitial inverted duplication of 22q11.2 and typical features of cat eye syndrome including coloboma, preauricular anomalies, heart defect, renal anomalies, and anal atresia.

Key points

- Cat eye syndrome (CES) is a rare malformation syndrome with characteristic major features.
- CES is usually associated with a supernumerary bisatellite marker chromosome containing material of chromosome 22 (idic(22)(pter→q11.2::q11.2→pter)), which results in partial tetrasomy 22.
- We report here the first case of a typical CES phenotype caused by an interstitial inverted duplication of 22q11.2. The patient shows all the major features (coloboma, preauricular anomalies, heart defect, renal anomalies, and anal atresia), and many minor features.
- This case shows that partial trisomy of proximal 22q11.2 is quite sufficient to cause classical cat eye syndrome. We suggest that a cytogenetic analysis for cat eye syndrome should always include a careful evaluation for structural anomalies affecting the proximal part of 22q.

CLINICAL FINDINGS

The boy was referred for clinical genetic diagnostics at the age of 3.5 weeks. He was born at term after an uneventful pregnancy; the parents were healthy and unrelated and birth weight was 3650 g, length 54 cm, and head circumference 36.5 cm. Postnatally, he developed a transient cyanosis and was admitted to our neonatal intensive care unit for evaluation of a heart defect and anal atresia. Dymorphological examination showed characteristic craniofacial features including low set, posteriorly rotated ears, bilateral preauricular pits, hypertelorism, downward slanting palpebral fissures, bilateral ptosis of the eyelids, and bilateral iris colobomata. The nose was short and beaked with a flattened nasal bridge and depressed nasal tip. Further findings were a long philtrum, thin lips, highly arched palate, and micro/retrognathia (fig 1A, B). Organ involvement included a combined heart defect (large secundum atrial septal defect, medium sized pressure reducing muscular perimembranous ventricular septal defect, and tricuspid valve dysplasia with tricuspid regurgitation grade II), kidney anomalies (bilateral dilated renal pelvis), congenital left inguinal hernia, and anal atresia. The cardiac defects did not cause congestive heart failure, thus treatment (preferably interventional device closure) has been postponed until the child reaches a body weight of at least 12 kg. The tricuspid valve function improved spontaneously. The child underwent surgical treatment for the hernia and anal atresia.

Detailed ophthalmological examination was performed at the age of 8.5 months and at 13 months, respectively, and disclosed bilateral microphthalmus (left>right) and bilateral anterior and posterior colobomata of the iris and choroid, and subluxated lenses inferiorly. In both eyes the optic nerve head and macula were not visible in the depth of the coloboma (fig 1 C and D). A persistent choroidal artery was found in the left eye. Further findings were intermittent strabismus (esotropia), apparent restriction of eye movements (abduction deficit), and high hyperopia (≥ 13 dp). Owing to bilateral ptosis, severe chin raising was observed.

Re-evaluation at the age of 8.5 months and 12 months showed good progress and only moderate developmental delay. Gross impairment of hearing could be excluded. Exact determination of visual acuity was impossible but was considered to be low.

Owing to the typical findings of iris coloboma, heart defect, and anal atresia in combination with further malformations in the clinical genetic-dymorphological analysis, cat eye syndrome was suspected.

Abbreviations: CES, cat eye syndrome; FISH, fluorescence in situ hybridisation; ARSA, arylsulphatase A

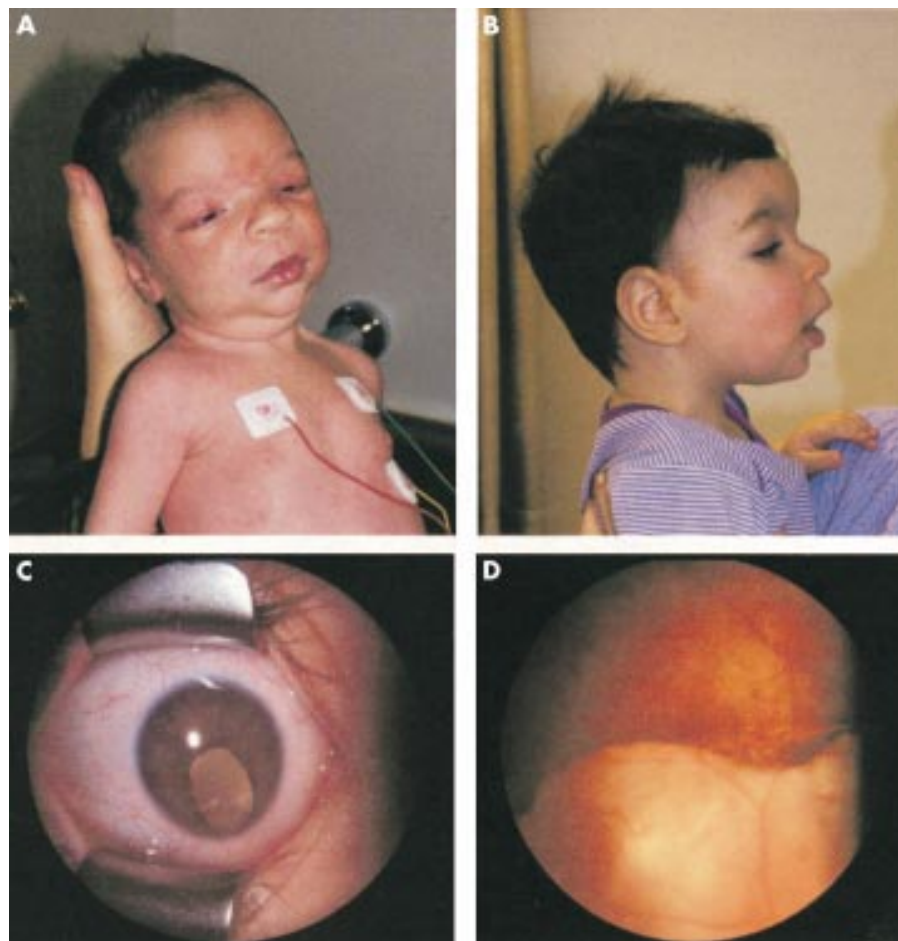


Figure 1 Boy with cat eye syndrome (A) at the age of 3 weeks and (B) at the age of 8 months. Ophthalmological examination at the age of 13 months: (C) the anterior segment, here in the right eye (in miosis) showing inferior nasal iris coloboma. (D) Funduscopy of the left eye. Retinal and uveal coloboma, optic nerve head, and macula are not visible in the depth of the coloboma.

CYTOGENETIC ANALYSIS

Cytogenetic analysis on cultured blood lymphocytes was performed according to standard protocols. Trypsin-Leishman G banded (GTL) metaphases (15) were interpreted at a resolution level of 450 bands and disclosed no numerical aberration, but a structural anomaly 46,XY,add(22)(q11.2) of one chromosome 22 (fig 2A). Fluorescence in situ hybridisation (FISH) on metaphase spreads with probes for the DiGeorge critical region (D22S553, D22S942) as well as control probes for a more distal region on 22q13.3 (arylsulphatase A, LSI, ARSA, all from Vysis, Downers Grove, USA) repeatedly showed only one signal on each chromatid of chromosome 22 (data not shown).

Multiplex-FISH (M-FISH hybridisation)¹² showed on both chromosomes 22 the typical hybridisation pattern and disclosed no interchromosomal exchanges on the derivative chromosome 22 (fig 2B). AkroM-FISH with a chromosome 22 specific painting probe, a chromosome 14/22 specific centromere probe, and an RNA probe resulted in the characteristic signals on both chromosomes 22 (data not shown). However, further analysis with centromere-near YAC probes (Cen-YAC iH05120 Cy3.5 and Cen-Yac 417h07 FITC) identified the structural anomaly on the derivative chromosome. The proximal YAC (Cen-YAC iH05120 Cy3.5, red) showed a broader hybridisation signal on the derivative chromosome compared to the normal chromosome 22 in all 10 analysed metaphases. For the distal YAC (Cen-Yac 417h07 FITC, green), two signals could be separated on the derivative chromosome in most cells (fig 2C, D). Overlaying of the two images showed that the

broadened red signal localised between the two green signals indicating an inverted duplication within chromosome band 22q11.2 (46,XY,inv dup(22)(q11.2)).

Cytogenetic analysis of blood lymphocytes from the parents by GTL banding disclosed in both cases a normal karyotype without structural anomalies of chromosome 22, thus pointing to a de novo origin of the inverted duplication in the index patient. Comparison of heteromorphisms in the short arm indicate that the duplication may have arisen on the maternal chromosome (data not shown).

DISCUSSION

To our knowledge this is the first case of CES exhibiting all the major symptoms of CES including kidney coloboma, preauricular anomalies, heart defect, kidney malformation, and anal atresia, which is caused by interstitial duplication of the CES critical region on 22q11.2, resulting in partial trisomy 22q11.2. To date reports on only four patients with interstitial duplications of chromosome 22 have been published.⁹⁻¹¹ Phenotypic overlap with CES was discussed in these cases, although none of these presented with a complete CES phenotype. Preauricular pits, heart defect, and urogenital malformation (unilateral absence of the kidney or bilateral dilated renal pelvis, respectively) were seen in two patients,^{10,11} whereas the patient described by Reiss *et al*⁹ presented with bilateral iris coloboma, preauricular malformations, microphthalmia, and facial anomalies, but no internal malformations. A fourth case with suspected interstitial duplication involving 22q11, mentioned by Knoll *et al*,¹⁰ was published by Taylor *et al*¹³ with several

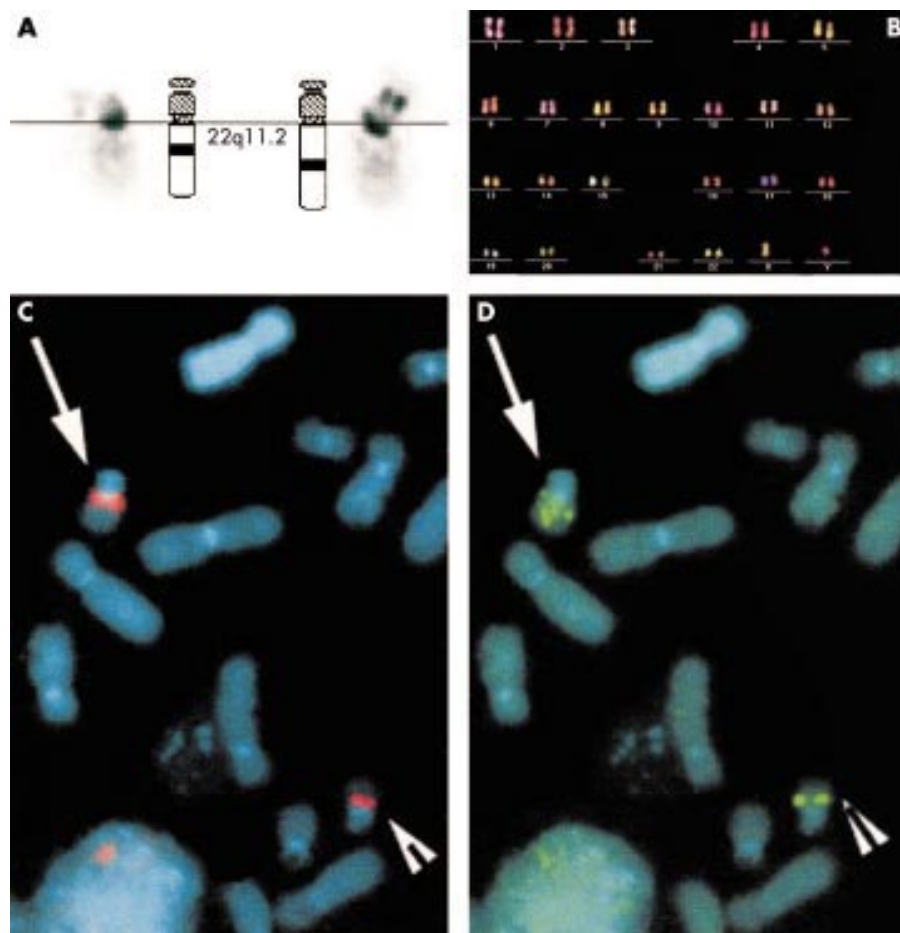


Figure 2 Cytogenetic analysis. GTL banded chromosomes 22 and ideograms. (A) Normal (left) and derivative (right) chromosome 22. (B) Karyogram based on the spectral signature of the M-FISH hybridisation. FISH analysis with two 22q11.2 band specific YAC probes. (C) The hybridisation signal of the proximal probe was consistently broader on the derivative compared to the normal chromosome 22. (D) The distal probe resulted in two signals on the derivative chromosome. The short arrows indicate the normal, the long arrows the derivative chromosome 22.

minor anomalies including microphthalmia and epicanthus, but no major symptoms of CES. Another patient with a similar duplication of the segment 22q11.2-q13.1 had preauricular pits, a highly arched palate, and bilateral hydronephrosis (table 1).¹⁴

Because of the published cases with interstitial duplications, it has been discussed that partial trisomy of the CES critical region on chromosome 22q11.2 may be associated with a partial CES phenotype, compared to partial tetrasomy 22q11.2 in cases of CES with an extra bisatellited marker chromosome 22. This suggestion is plausible as it assumes that a gene dosage effect of genes within the duplicated area is the cause of congenital malformation in CES. On the other hand, CES associated with a typical bisatellited marker shows a pronounced phenotypic variation (table 1). Only 41% of published patients with CES with a bisatellited marker chromosome 22 show the classical triad of iris coloboma, anal anomalies, and preauricular malformation,² and less than 10% of patients with CES present all major clinical signs of CES.¹⁵ Correlation of clinical severity has neither been found with the size of the marker chromosome nor with the extent of mosaicism in mosaic CES.⁶

Our findings indicate, however, that partial trisomy 22 as a result of interstitial duplication of 22q11.2 is sufficient to cause classical CES with all major and many minor features of the syndrome. Our data suggest thus that cytogenetic analysis for cat eye syndrome should always include a careful evaluation for structural anomalies affecting the proximal part of 22q.

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Table 1 Clinical symptoms of cat eye syndrome in this case and other published cases with an interstitial duplication of chromosome 22,^{9–11 13 14} compared to the frequency of the respective symptoms in cat eye cases associated with the typical marker chromosome as determined in two reviews^{2 15}

Clinical features	This case	Reiss <i>et al</i> ⁹	Knoll <i>et al</i> ¹⁰	Lindsay <i>et al</i> ¹¹	Taylor <i>et al</i> ¹³	Fujimoto and Lin ¹⁴	Behrends <i>et al</i> ²	Rosias <i>et al</i> ¹⁵
		Interstitial duplication (partial trisomy 22q)						Bisatellited marker chromosome (partial tetrasomy 22q)
Karyotype								
	inv dup (22q11.2)	dup(22q11.1 6q11.2)	dup(22q11.2 6q12)	dup(22q11 6q12)	dup(22q11 6q13)‡	dup(22q11.26q 13.1)	idic(22) (pter6q11.2::q11.26pter)	
Major anomalies:								
Preauricular anomalies	+	+	+	+	–	+	81%	86%
Ocular coloboma	+	+	–	–	–	–	55%	61%
Anal anomalies	+	–	–	–	–	–	73%	81%
Congenital heart defects	+	–	+	+	–	–	50%	63%
Urogenital malformations	+	–	+	+	–	+	31%*	71%
Minor anomalies:								
Downward slanting palpebral fissures	+	+	+	–	+	–	47%	68%
Microphthalmia	+	+	–	–	+	–	19%	39%
Hypertelorism	+	+	+	+	+	–	38%	70%
Low set ears	+	–	–	–	–	–	19%	69%†
Flattened nasal bridge	+	+	+	–	+	–	14%	NI
Strabismus	+	–	–	–	–	–	25%	NI
Micro/retrognathia	+	–	–	+	–	–	27%	56%
Epicanthic folds	–	–	+	–	+	–	26%	65%
Skeletal anomalies	–	–	–	–	–	–	29%	73%‡

*Only renal malformation; †low set or dysplastic; ‡skeletal or orthopaedic anomalies; NI, not indicated.

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