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PHENOTYPIC VARIABILITY OF THE CAT EYE SYNDROME. CASE REPORT AND REVIEW OF THE LITERATURE

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Summary: *Phenotypic variability of the cat eye syndrome. Case report and review of the literature:* We present a male infant with preauricular skin tags and pits, downslanting palpebral fissures, hypertelorism, ectopic anus, hypospadias, and hypoplastic left heart syndrome. The clinical features in our patient show phenotypic overlap with the cat eye syndrome, as illustrated by the review of 105 reported cases. Cytogenetic analysis revealed a supernumerary marker chromosome, which was identified by microdissection and fluorescence in situ hybridization as an isodicentric chromosome 22(pter → q11.2: :q11.2 → pter). It was proved with probes specific for the cat eye syndrome critical region that this region was present in quadruplicate in the proposi-tus. We conclude that CES is characterized by large phenotypic variability, ranging from near normal to severe malformations, as reflected in the neurodevelopmental outcome. Preauricular skin tags and/or pits are the most consistent features, and suggest the presence of a supernumerary bisatellited marker chromosome 22 derived from duplication of the CES critical region.

Key-words: Cat eye syndrome – Fluorescence in situ hybridization – Microdissection – Supernumerary marker chromosome 22.

INTRODUCTION

Cat eye syndrome (CES; OMIM # 115470) is a rare disorder characterized by a variable phenotype with ocular colobomata, downslanting palpebral fissures, hypertelorism, preauricular skin tags and/or pits, micrognathia, cardiac defects, anal atresia and urogenital anomalies. Mental retardation is usually mild or borderline. No feature is consistently present. CES results from duplication of part of the proximal long arm of chromosome 22 (13). The most common form of this duplication is a supernumerary dicentric bisatellited chromosome, described as idic chromosome 22(pter → q11.2::q11.2 → pter). We report on a newborn with a CES phenotype in which a supernumerary marker chromosome 22 was found.

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MATERIALS AND METHODS

1. CASE REPORT

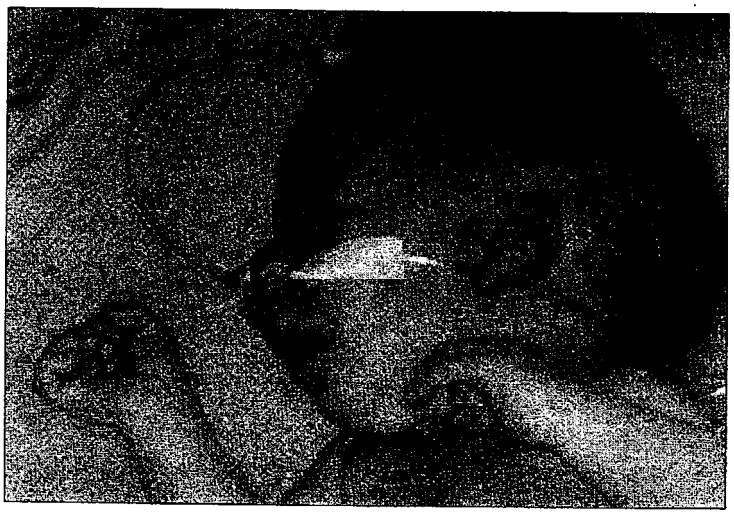
The male proband was born in cephalic presentation at a gestational age of 40 weeks as the second child of healthy unrelated parents. Pater-

nal age was 30 and maternal age 29 years. The pregnancy was complicated by oligohydramnios. Apgar scores after 1 and 5 minutes were 6 and 6 respectively.

Birthweight was 2600 g (3rd centile), length 44.5 cm (<3rd centile), occipitofrontal circumference 34.8 cm (2nd-50th centile).

Physical examination showed a central cyanosis and intermittent tachypnea. At neurological examination there was axial hypotonia and absence of suckling reflex. The following dysmorphic features were noted (Fig. 1): large anterior fontanel and diastasis of the cranial sutures, prominent occiput, high forehead with a small haemangioma, downslanting palpebral fissures, long eyelashes, hypertelorism (inner canthal distance 2.5 cm and outer canthal distance 7 cm) (both > +2 standard deviations), bilateral preauricular skin tags and pits with a normal position of the ears, prominent philtrum with a thin upperlip, micrognathia and webbed-neck. Furthermore, a mono-arterial umbilical cord, a glandular hypospadias, a deep sacral dimple and an ectopic ventrally displaced anus were seen. Radiological and ophthalmological examinations, as well as abdominal ultrasound were normal. Cerebral ultrasound showed asymmetrical lateral ventricles (left > right). Echocardiography demonstrated a hypoplastic left heart syndrome: mitral valve stenosis, hypoplasia of the left ventricle, hypoplasia of the ascending aorta and aortic arch, and a patent ductus arteriosus with right to left shunting. Furthermore, two atrial septal defects type II, enlargement of the right atrium and ventricle with severe tricuspid insufficiency and pulmonary hypertension were detected.

From day 10 on progressive congestive heart failure was observed. The infant died on the 17th day of life. Permission for autopsy was not given.



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2. REVIEW OF LITERATU

The MEDLINE on-line dat through December 1999 to fi eye syndrome and/or supernu entry for cat eye syndrome at (OMIM) database was chec exclusively in a non-current l mation of studies was doubl reported.

3. CYTOGENETIC EXAM

Chromosomes were prep using the synchronization m with only minor modification ment of the chromosomes w microdissection routinely f suspensions stored at -20°C on 45 x 64 mm coverslips. Th in 98% ethanol at -20°C. Mi chromosome and degenerate reaction (DOP-PCR) were p DOP-PCR product was label (BioNick TM labeling syst hybridization (FISH) was pe minor modifications (8). FIS mid S9, locus D22S9) and N mid, personal communicatic of Lichter *et al.* (12). Analy microscope and photograph colour slide film.

RESULTS

1. REVIEW OF LITERA

Table I shows the gene complete list of references clinical findings as (a) majo Mears *et al.* (16), and as (b 10% of the CES patient po rodevelopmental outcome. of CES patients.

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2. REVIEW OF LITERATURE

The MEDLINE on-line database was searched for the period 1966 through December 1999 to find all papers indexed for the subject cat eye syndrome and/or supernumerary marker chromosome 22, and the entry for cat eye syndrome at the Online Mendelian Inheritance in Man (OMIM) database was checked (OMIM # 115470). Papers written exclusively in a non-current language were excluded (n=3). The summation of studies was double-checked to avoid duplication of cases reported.

3. CYTOGENETIC EXAMINATION

Chromosomes were prepared from peripheral blood lymphocytes using the synchronization method of Dutrillaux and Viegas-Pequignot with only minor modifications (3). GTG-banding was obtained by treatment of the chromosomes with trypsin and staining with Giemsa. For microdissection routinely fixed (methanol: acetic acid 3:1) cell suspensions stored at -20°C were used to prepare metaphase spreads on 45 x 64 mm coverslips. The slides were rinced with water and stored in 98% ethanol at -20°C. Microdissection of five copies of the marker chromosome and degenerate oligonucleotide primed-polymerase chain reaction (DOP-PCR) were performed as described previously (5). The DOP-PCR product was labeled by nick-translation with biotin-14-dATP (BioNick TM labeling system [Gibco BRL]). Fluorescence in situ hybridization (FISH) was performed following the protocol of Guan with minor modifications (8). FISH with CES-specific probes N107D6 (cosmid S9, locus D22S9) and N41A6 (cosmid H32, locus D22S43) (McDermid, personal communication) was performed according to the protocol of Lichter *et al.* (12). Analysis was carried out using a Zeiss Axiophot microscope and photographs were taken with Scotch chrome 640 ASA colour slide film.

RESULTS

1. REVIEW OF LITERATURE

Table I shows the general characteristics of 105 CES patients. A complete list of references is available on request. We categorized all clinical findings as (a) major features (Table II) based on the findings of Mears *et al.* (16), and as (b) minor features (Table III) present in at least 10% of the CES patient population. Table IV shows the associated neurodevelopmental outcome. Table V shows age and cause of early death of CES patients.

sex ratio: male / female / not reported	46 / 57 / 2
birthweight	2910 gram (1420 - 4430)
gestational age	40 weeks (33 - 43)
paternal age	34 years (21 - 50)
maternal age	31 years (19 - 44)

figures shown as median and (range)

Table I: General characteristics of 105 cat eye syndrome patients.

2. CYTOGENETIC EXAMINATION

Analysis of GTG-banded metaphase chromosomes revealed that the patient had an extra small marker chromosome (Fig. 2A) in all the 25 cells examined. This marker was isodicentric, NOR-positive at both sides (indicating to be a bisatellited marker chromosome) and DA/DAPI negative (ruling out the involvement of chromosome 15 short arms). Micro-FISH demonstrated that the marker chromosome derived from chromosome 22 (Fig. 2B), which was confirmed by a chromosome 22 specific paint (Fig. 2C). Furthermore, with both CES-specific probes N41A6 and N107D6, two FISH signals were present on the marker chromosome (Fig. 3). The karyotype of the patient is 47, XY, idic(22) (pter → q11.2::q11.22 → pter). Both parents had a normal karyotype.

DISCUSSION

1. CLINICAL REVIEW OF THE LITERATURE

The association of iridochoroidal coloboma, left renal hypoplasia and anal atresia was first described in 1878 by Haab in a three day old child who died from rectal rupture (10). In 1965 Schachenmann *et al.* (17) associated colobomata of the iris and anal atresia with a small extra marker chromosome. Gerald *et al.*(7) introduced the trivial name «cat's eye syndrome», derived from the particular appearance of these patients due to the vertical iridochoroidal coloboma. Many cases showing incomplete expression of the syndrome were reported. In 1995 Mears *et al.* (16) reported on a CES patient, originally described by El-Shanti *et al.* (4), with an unusual supernumerary dicentric double-ring chromosome 22 (dic r(22)). The dic r(22) was smaller than the typical CES chromosome (18), and still resulted in expression of characteristic features (i.e. ocular coloboma, preauricular skin tags and/or pits, micrognathia, cleft palate, anal atresia, urogenital malformation and congenital heart defect). When comparing the findings of Mears *et al.* (16) with those of others (9, 11, 18), we conclude that the major clinical features of the CES consist of (a) preauricular skin tags and/or pits, (b) anorectal malformation, (c) urogenital malformation, (d) ocular coloboma and (e) congenital heart defect.

MAJOR FEATURES
Preauricular skin tags and/
Anorectal malformations – anal atresia or imperfora – anal stenosis – anorectal atresia – ectopic anus – associated rectal fistulas
Urogenital malformations – male external genital ma – renal agenesia – hydro(uretero)nephrosis – vesicoureteral reflux – female in/external genita – dysplasia or polycystic k – bladder defects – renal cystic malformatio – ectopic/horseshoe kidne
Ocular coloboma
Congenital heart defect – VSD – TAPVC – ASD – Tetralogy of Fallot – PDA – aortic malformation – PS – TA – hypoplastic left heart sy

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VSD: ventricular septal defe
TAPVC: total anomalous pulr
ASD: atrial septal defect
PDA: patent ductus arteriosi
PS: pulmonary stenosis
TA: tricuspid atresia

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MAJOR FEATURES	Review	propositus
Preauricular skin tags and/or pits	78 / 90	yes
Anorectal malformations	71 / 88	yes
– anal atresia or imperforate anus	61	
– anal stenosis	6	
– anorectal atresia	3	
– ectopic anus	1	yes
– associated rectal fistulas	36	
Urogenital malformations	55 / 77	yes
– male external genital malformation	18	yes
– renal agenesia	18	
– hydro(uretero)nephrosis	13	
– vesicoureteral reflux	13	
– female in/external genital malformation	7	
– dysplasia or polycystic kidney	5	
– bladder defects	4	
– renal cystic malformation	2	
– ectopic/horseshoe kidney	2	
Ocular coloboma	54 / 88	no
Congenital heart defect	50 / 80	yes
– VSD	18	
TAPVC	15	
– ASD	15	yes
– Tetralogy of Fallot	7	
– PDA	7	yes
– aortic malformation	5	
– PS	5	
– TA	3	
– hypoplastic left heart syndrome	2	yes

figures shown as positive / informative.

VSD: ventricular septal defect
TAPVC: total anomalous pulmonary venous connection
ASD: atrial septal defect
PDA: patent ductus arteriosus
PS: pulmonary stenosis
TA: tricuspid atresia

Table II:
Major clinical features of 105 cat eye syndrome patients, compared to the propositus.

The reporting of CES patients may have been biased, since a number of mildly affected patients probably never have been detected. The major and minor clinical features of 105 CES patients described in literature, are summarized in table II and III respectively. Each of the associated major features are relatively common and none are necessarily present in every instance of the CES. Preauricular skin tags and/or pits are the most consistent features, which is in agreement with former reports (9, 18). Only nine patients showed all the major clinical features of the CES. The phenotypic variability, ranging from near normal to severe malformations, is reflected in the neurodevelopmental outcome and early death as shown in table IV and V respectively.

MINOR FEATURES	Review	propositus
Downslanting palpebral fissures	48 / 70	yes
Hypertelorism	48 / 69	yes
Orthopedic malformations	46 / 63	no
– arm or hand deformity	20	
– leg or foot deformity	14	
– scoliosis or chest deformity	13	
– vertebral anomaly	13	
– congenital dislocation of the hip	8	
– rib or sternal anomaly	8	
Low set or dysplastic ears	42 / 61	no
Abdominal malformations	33 / 48	no
– umbilical hernia	8	
– malrotation of the gut	8	
– Hirschsprung or megacolon	6	
– biliary atresia or choledochal cyst	4	
– volvulus	2	
– Meckel diverticulum	2	
Short stature	32 / 64	no
Ocular motility defect	32 / 42	no
Epicanthic folds	29 / 45	no
Micrognathia	27 / 48	yes
Microphthalmia	23 / 59	no
Microcephaly	15 / 57	no
Cleft palate or absent uvula	15 / 48	no

Table III: Minor clinical features of 105 cat eye syndrome patients, compared to the propositus.

figures shown as positive / informative.

Mental development	
– normal or borderline normal	30 / 68
– mild to moderate retardation	33 / 68
– severe retardation	5 / 68
Neurological findings	62 / 68
– ocular motility disorders	32
– dysregulation of muscular tonus	17
– other visual handicap	16
– hearing impairment	11
– ventricular dilatation	4
– abnormal slow EEG	4
– seizures	4
– spasticity	3
– cerebral or cerebellar atrophy	2
– hyperactive behaviour	2
– ataxia	2
– facial nerve palsy	2

Table IV: Neurodevelopmental outcome of 105 cat eye syndrome patients.

figures shown as positive / informative

Age of early death (*)
Cause of early death (**
– sepsis / bronchopneu
– heart failure
– liverfailure / biliary a
– unknown
– failure to thrive
– respiratory distress
– renal failure and bror
– asphyxia
– postoperative compli
– rectal rupture

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2. MOLECULAR LITERATURE

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Age of early death (*)	90 days (15 minutes - 41 months)
Cause of early death (**)	
– sepsis / bronchopneumonia	4/21
– heart failure	4/21
– liverfailure / biliary atresia	3/21
– unknown	3/21
– failure to thrive	2/21
– respiratory distress	1/21
– renal failure and bronchopneumonia	1/21
– asphyxia	1/21
– postoperative complication	1/21
– rectal rupture	1/21

(*) figures shown as median and (range).
(**) figures shown as number / total number.

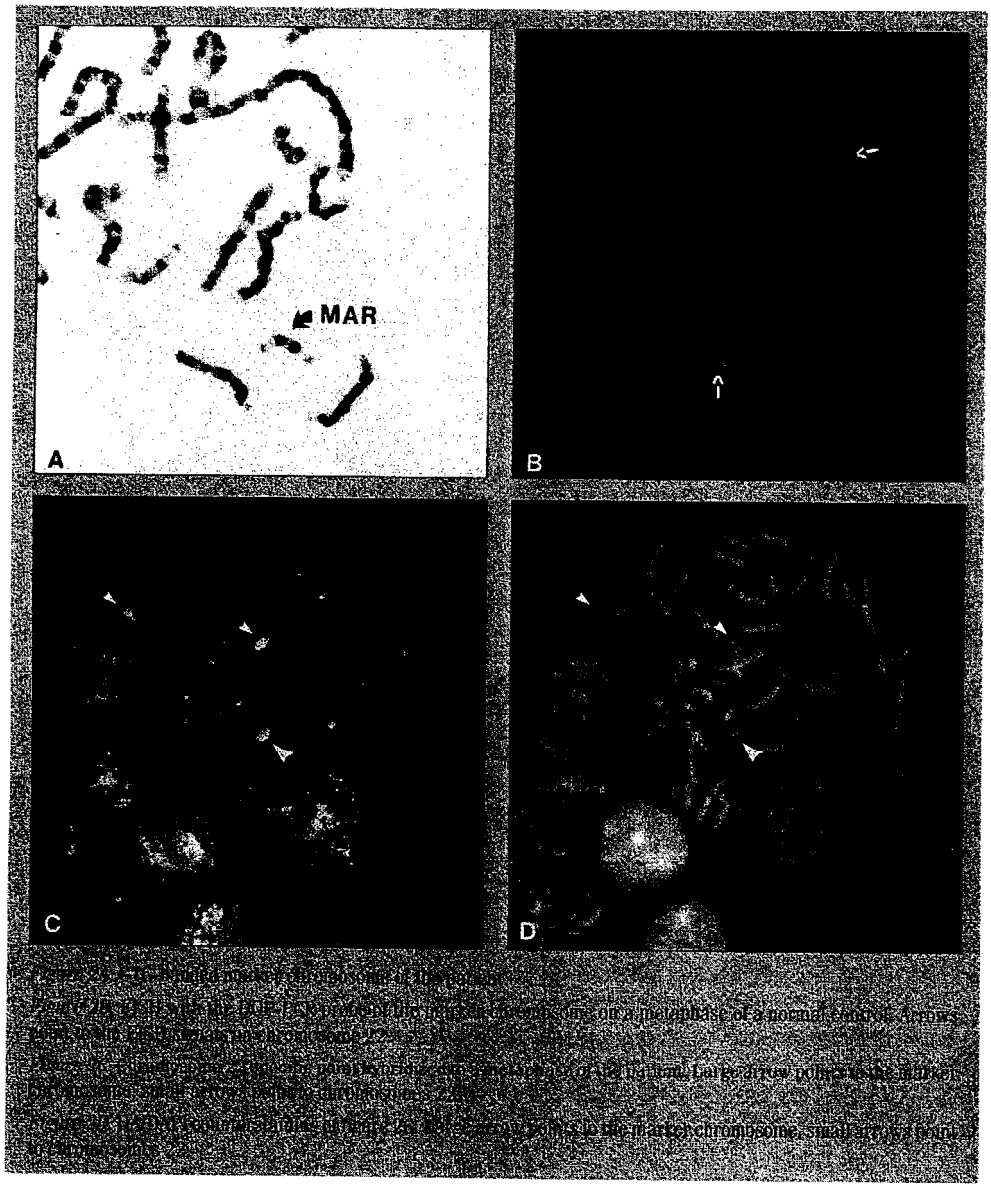
Table V:
Early death of CES patients.

The propositus shows phenotypic overlap with the CES: i.e. four major and three minor features. His clinical picture was dominated by the congenital cardiac malformation, which was the lifelimiting factor. To our knowledge he is the second CES patient ever reported to have an ectopic anus, and the third one to have a hypoplastic left heart syndrome.

2. MOLECULAR AND CYTOGENETICAL REVIEW OF THE LITERATURE

The association of an extra, metacentric and satellited chromosome, smaller than a group G (21-22) chromosome with the CES was first described in 1965 by Schachenmann *et al.* (17). Although Buhler *et al.* (1) reported familial partial trisomy 22 with CES phenotype in 1972, nosological discussions continued, because of both the phenotypic variability, and the speculation on the origin of the extra small chromosome. In 1981 the association between CES and trisomy or tetrasomy of 22pter → q11 was reported by Schinzel *et al.* (18). CES features might also result from the formation of transient or unstable dic r(22) during early fetal development, which subsequently are lost from most cells (6). The minimal common duplication required to produce features of CES, or the CES critical region, is defined by the dic r(22) patient (16): breaking between proximal locus ATP6E and distal locus D22S57, and covering approximately 2 Mb of 22q11.2 (14). At present, the making of direct correlations between the extent of duplicated chromosome 22 material and the severity of the CES still remains difficult (2, 15).

We conclude that CES is characterized by large phenotypic variability, ranging from near normal to severe malformations, as reflected in the neurodevelopmental outcome. Preauricular skin tags and/or pits are the most consistent features, and suggest the presence of a supernumerary bisatellited marker chromosome 22 derived from duplication of the CES critical region.



ACKNOWLEDGMENTS

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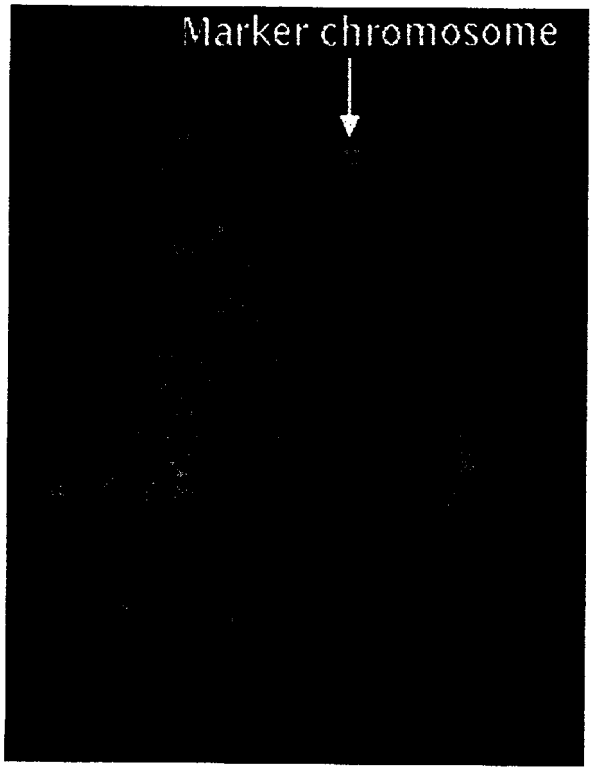

Figure 3:
FISH with probe N41A6, showing a fluorescent signal on both chromosomes 22 and two fluorescent signals on the marker chromosome 22.

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