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PHENOTYPIC VARIABILITY OF CAT-EYE SYNDROME

BY M.J.W. BERENDS[1], G. TAN-SINDHUNATA[2], B. LEEGTE[1] AND A.J. VAN ESSEN[1]

Summary: *Phenotypic variability of cat-eye syndrome:* Cat-Eye syndrome (CES) is a disorder with a variable pattern of multiple congenital anomalies of which coloboma of the iris and anal atresia are the best known. CES is cytogenetically characterised by the presence of an extra bisatellited marker chromosome, which represents an inverted dicentric duplication of a part of chromosome 22 (inv dup(22)).

We report on three CES-patients who carry an inv dup(22) diagnosed with FISH studies. They show remarkable phenotypic variability. The cause of this variability is unknown. Furthermore, we review clinical features of 71 reported patients. Only 41% of the CES-patients have the combination of iris coloboma, anal anomalies and pre-auricular anomalies. Therefore, almost 60% of the CES-patients are hard to recognize by their phenotype alone. Mild to moderate mental retardation was found in 32% (16/50) of the cases. Mental retardation occurs more frequently in male CES-patients. There is no apparent phenotypic difference between mentally retarded and mentally normal CES-patients.

Key-words: Cat-Eye syndrome – CES-phenotype – phenotypic variability – inv dup(22).

INTRODUCTION

The Cat-Eye Syndrome (CES) may present as a clinically recognizable pattern of congenital abnormalities. Colobomas, anal anomalies, pre-auricular anomalies, defects of heart and kidneys and mild to moderate mental retardation are important features (43). The name «Cat Eye» was introduced because the iris colobomas resemble the pupil shape of cats. In 1965 an extra bisatellited marker chromosome was described in patients with a CES-phenotype (42). In 1981 Schinzel *et al.* concluded that the marker chromosome is an inverted dicentric duplication of a part of chromosome 22 (inv dup(22)(pter→q11::q11→pter)) (43). The presence of the inv dup(22) in mosaic form in some patients (9, 13, 15, 33, 38, 39, 46, 48) is probably due to early loss of the marker during postzygotic divisions (15). The risk for CES-patients of having a child with the inv dup(22) should be close to 50%. This percentage would be lower in patients with the inv dup(22) in mosaic form. However, there are no data available on recurrence risks for sibs of a CES-patient. Even when the parents have normal chromosomes, a small recurrence risk could remain, because germline mosaicism can not be excluded. The parental origin of the de novo inv dup(22) has been determined in five cases and in all of them the origin was maternal (14, 27, 46, 47).

The phenotypic variability in CES-patients varies from a normal phenotype to patients with severe congenital abnormalities (43).

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Because of this variability CES may resemble other disorders like (partial) trisomy 22, the oculo-auriculo-vertebral syndrome, the VATER-association and the CHARGE-association. In the present paper we give a new survey of the frequency of the most frequently occuring clinical features of CES-patients. We calculate how many patients fulfill the classical CES-trias of colobomas, anal anomalies and pre-auricular anomalies and we attempt to determine how many patients show mental retardation.

PATIENTS AND METHODS

PATIENTS

Patient 1 was born at term after an uneventful pregnancy. Her father was 36 years old and her mother 31 years old. Her parents are second cousins. Her two sisters are healthy. Her birthweight was 3250 g (P75). Anal atresia, bilateral colobomas and pre-auricular appendices were noted (Fig. 1a and b). At 9 years a sigmoid resection was performed because of chronical constipation and a megacolon. Pathological examination showed ganglion cells in the sigmoid, a muscular hypertrophy and a dilatation of the lower third of the sigmoid. Because of persistent constipation, low activity of the pelvic muscles, and a dolichosigmoid a hemicolectomy was performed at age 29. She also had recurrent urinary tract infections because of bilateral vesicoureteral reflux. Further urological examination revealed lateralised ostia of the ureters which required reimplantation of the ureters. Because of frequent headaches a CT-scan and a EEG were made. The scan showed no abnormalities, the

Figure 1a:
Patient 1. Note the bilateral coloboma and strabismus divergens of the right eye.

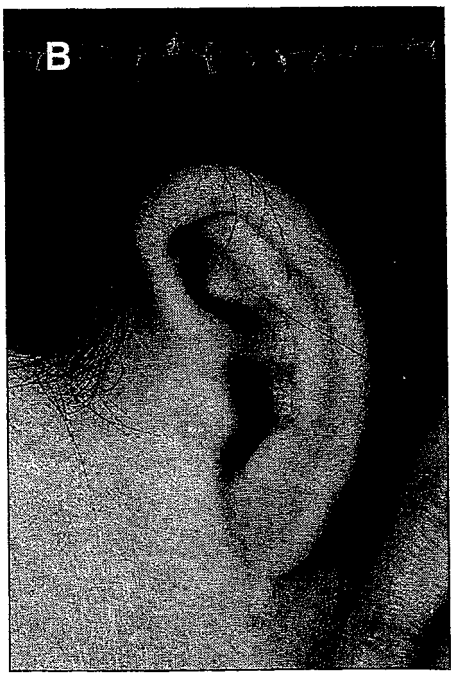

Figure 1b:
Patient 1. Note the pre-auricular tag.

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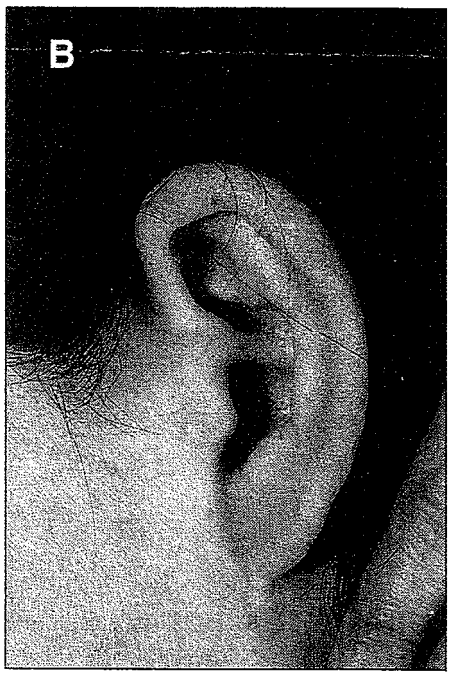

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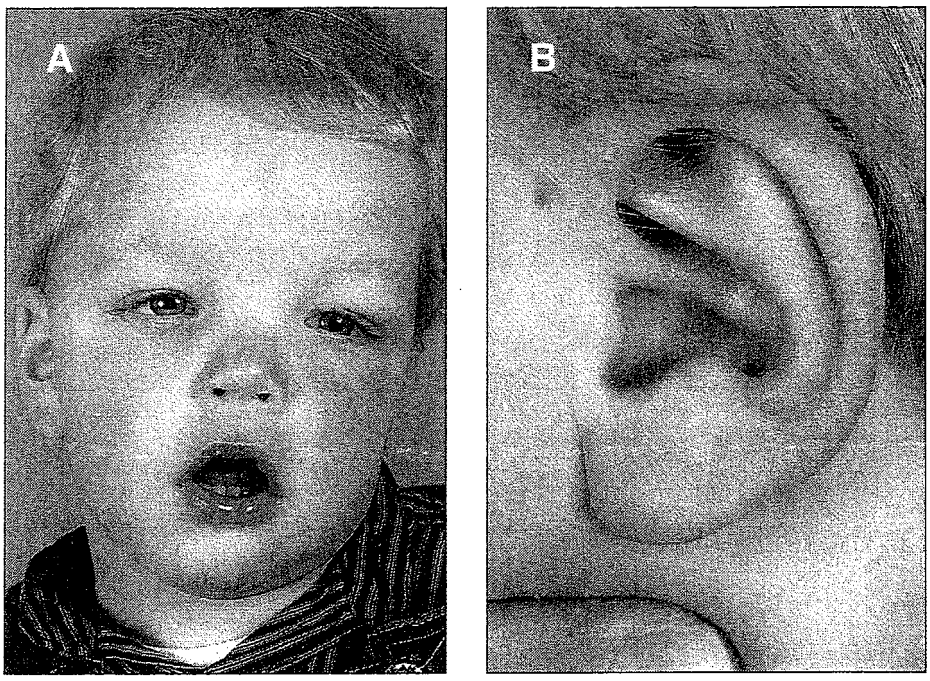


Figure 2a:
Patient 2. Note the antimongoloid palpebral fissures and the bilateral epicanthus.

Figure 2b:
Patient 2. Note the pre-auricular pit.

thalmia, bilateral pre-auricular pits, anal atresia combined with a perineal fistula and reduced vision of the right eye. She now attends a regular secondary school.

CYTOGENETIC ANALYSIS

For cytogenetic analysis of our three patients GPG (G-bands by pancreatin using Giemsa) banded chromosomes were obtained from peripheral lymphocytes using standard cytogenetic techniques with ethidium bromide treatment before harvesting. Additional CBG-banding and silver staining was done. Fluorescence in situ hybridization (FISH) was carried out according to routine protocols and performed on metaphase spreads of all three patients, using a whole chromosome 22 paint, a centromere probe (p22/1:2.1) (29) and a home-made probe for human ribosomal DNA (personal communication K. Kok). Routine chromosome analysis has been performed in peripheral blood lymphocytes of the parents.

CLINICAL DATA FROM LITERATURE

We traced reports on patients with a CES-phenotype and an extra bisatellited marker chromosome.

All reported clinical symptoms were collected. In the phenotype analysis we also included our three patients. A distinction was made

EEG was diffusely irregular. The psychomotor development was normal. She attended the domestic science school. She worked as a geriatric helper.

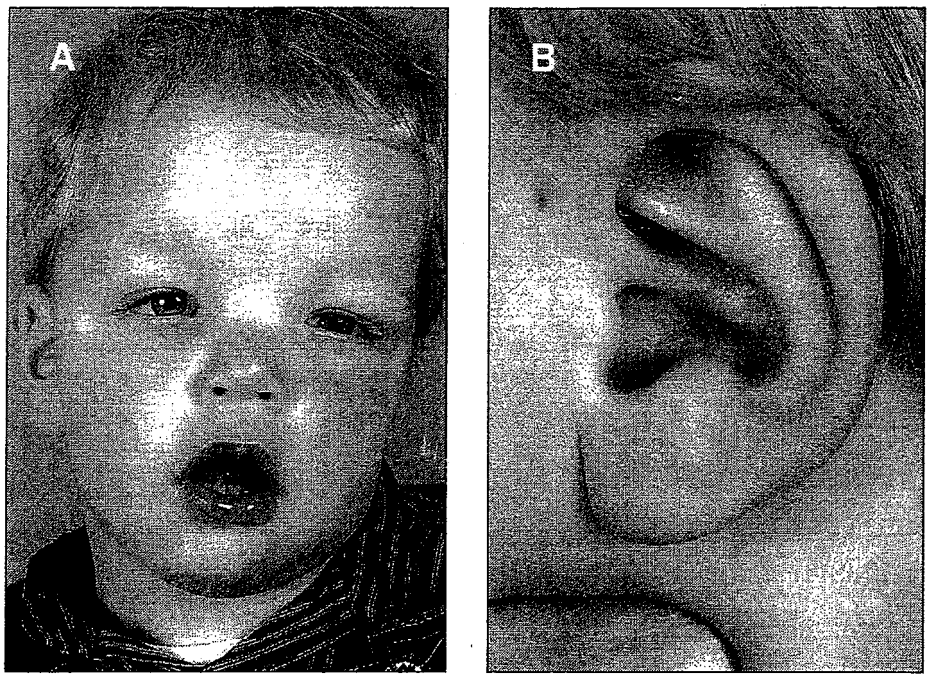
Physical examination in our department at the age of 30 years showed a height of 1.70 meter (P90), head circumference 54 cm (P25), inner canthal distance 3.5 cm (P75-P97). Furthermore, she had an asymmetric facies, a widow's peak, bilateral colobomas of the irides, strabismus divergens of the right eye, a long narrow nose, a short philtrum with hypertrichosis, dentures (because of serious caries), small ears with attached ear-lobes and, at the right side, a pre-auricular pit and scars where preauricular tags have been removed and, at the left side, also a preauricular tag. She had a colostomy and thoracolumbar scoliosis.

Patient 2 was born in 1992 after an uneventful pregnancy of 41.5 weeks. His father was 32 years old, his mother, G8P7A1, was 36 years old. Brothers and sisters are healthy. The birth weight was 3600 g (P50-P75). Postnatally he suffered from convulsions, apnoea's and cyanosis. EEG showed irritative dysfunctions. MRI of the brain showed underdevelopment of the corpus callosum. Left-sided hydronephrosis and hydro-ureter developed because of partial distal obstruction of the left ureter. A supracardial anomalous pulmonary venous return was surgically corrected. A butterfly-vertebra at Th7 was noticed on the chest X-ray. He had bilateral alternating intermittent divergent strabism and restricted abduction. Bilateral glue ears caused conductive hearing loss. Colobomas and anal abnormalities were not present. At the age of one year a developmental delay of three to four months was recorded. He walked at the age of 22 months and his speech ability developed slowly.

Physical examination at the age of 18 months showed a head circumference 49.5 cm (P90), inner canthal distance 3 cm (P90-P97), outer canthal distance 8.5 cm (>P97), a dolichocephal skull, frontal bossing, antimongoloid palbebral fissures, bilateral epicanthus, a high and wide nasal bridge, bilateral pre-auricular pits, low-set ears, highly arched palate, retrognathia, and webbing of the neck (Fig. 2a and b). The right side of the face was slightly hypoplastic. He had a presacral dimple, phimosis and an unpalpable left testis.

Patient 3 was born in 1982 after a pregnancy complicated by polyhydramnion. Her father was 33 years old, her mother 32 years old. Mother was G5P4A1, the brothers and sisters were healthy.

The birth weight was 3800 g (P97), the height 54.4 cm (>P97), the skull circumference 36.5 cm (>P97), inner canthal distance was 2.6 cm (P90-P97), outer canthal distance 7.3 cm (P90-P97). In the post-natal period she developed cyanosis because of an atrial septal defect, anomalous pulmonary venous return, and a small left atrium and ventricle. She was hypotonic and she had bilateral ocular colobomas of the iris extending from the iris to the papilla nervi optici, bilateral micropli-



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between CES-patients with a cytogenetically and/or molecularly well-documented inv dup(22) and patients with poorly described markers. This last category of patients was essentially diagnosed before 1980 when banding was not well-developed.

In familial cases only those persons who had features that would justify chromosomal analysis were included.

RESULTS

The results of the cytogenetic analysis of patients and their parents are shown in table I.

Table I.

	patient 1	patient 2	patient 3
G-banding (14 metaphases)	47,XX + inv dup(22)(q11)	47,XX + inv dup(22)(q11)	46,XX/47,XX + inv dup(22)(q11) lymphocytes 21% [11/3] fibroblasts 90% [3/26]
CBG-banding	2 centromeres	unclear	2 centromeres
NOR-staining	signals at both sides	no signals	signal at one side
chromosome 22 bank	signal on whole marker	signal on whole marker	signal on whole marker
probe p22/1 :2.1	2 signals on marker	2 signals on marker	2 signals on marker
probe	2 signals on marker	not done	2 signals on marker
routine chromosome analysis parents	normal	normal	normal

In the literature we traced reports on 34 female and 30 male CES-patients. Their age varied from 0-42 years. In 10 cases the sex was not reported. In 12 patients the inv dup(22) was present in mosaic form varying from 20% to 97% mosaicism of the marker in lymphocyte cultures. In two patients fibroblasts were also examined and mosaicism was found.

In table II the frequency of clinical features that occurred in more than 10% of the 74 CES-patients is presented. Of the CES-patients 41% had the combination of coloboma, anal anomalies and pre-auricular anomalies. Colobomas and anal anomalies (stenosis or atresia) were present in 45%. Of the 54 (73%) patients with anal anomalies, at least 40 (75%) had anal atresia, 7 (13%) had anal stenosis and 28 (52%) patients had a fistula in the urogenital and/or intestinal region. Heart

Table II:
Frequency of clinical features in 74 CES-patients with an inv dup(22). (1, 2, 4-16, 18-25, 27, 28, 32, 33, 35, 37-39, 41, 43, 45-53).

Clinical features	total (n=74)*	well-defined marker (n=45)*	mosaicism (n=12)*
Pre-auricular anomalies	60/74 (81%)	39/45 (87%)	10/12 (83%)
Total anal anomalies	54/74 (73%)	30/45 (67%)	10/12 (83%)
Coloboma	40/73 (55%)	20/44 (46%)	7/12 (58%)
Total cardiovasc. anom.	37/74 (50%)	21/45 (47%)	6/12 (50%)
Downslant fissures	34/73 (47%)	19/44 (47%)	3/12 (25%)
Visual disability	8/19 (42%)	4/ 8 (42%)	2/ 4 (50%)
Hypertelorism	28/73 (38%)	14/44 (38%)	5/12 (42%)
Mental retardation	16/50 (32%)	9/32 (28%)	2/10 (20%)
Total kidney anomalies	22/72 (31%)	13/43 (30%)	4/12 (33%)
Total skeletal anomalies	21/73 (29%)	11/44 (25%)	2/12 (17%)
Retrognathia	20/54 (27%)	15/45 (33%)	0/12
Epicanthus	19/74 (26%)	11/45 (24%)	1/12 (8%)
Strabismus	16/64 (25%)	8/35 (23%)	2/ 9 (22%)
Cryptorchidism	6/31 (24%)	3/16 (19%)	1/ 6 (11%)
Microphthalmia	10/54 (19%)	5/35 (14%)	2/ 9 (22%)
Low-set ears	14/73 (19%)	11/44 (25%)	1/12 (8%)
Hearing loss	9/54 (17%)	3/33 (9%)	2/ 8 (25%)
Ear deformities	12/72 (17%)	6/43 (14%)	1/12 (8%)
Short stature	9/62 (15%)	3/35 (9%)	2/10 (20%)
Flattened nasal bridge	9/64 (14%)	4/35 (11%)	1/ 9 (11%)
Cleft palate	10/72 (14%)	6/43 (14%)	1/12 (8%)
Hypotonia	9/64 (14%)	4/36 (11%)	2/10 (20%)

* The denominator for some anomalies is lower, because not in all described patients the information needed was available.

defects were reported in 37 (50%) patients, of which 16 (43%) had a total anomalous pulmonary venous return and 3 (8%) patients had a tetralogy of Fallot. Other, incidentally reported heart anomalies were atrial septal defect, hypoplasia of the mitral valve, atrium or ventricle, monoventricle and persistence of the left superior vena cava. There were 22 (31%) patients who had kidney anomalies of which 11 (50%) unilateral agenesis and 13 (60%) hydronephrosis (at least one had both). Hypoplastic bladder, stenosis of the pyeloureteral junction, absence of a renal artery, cystic dysplastic kidney, hypertrophy of a kidney and doubling of the pelvis and ureter were also described. There were 10 (14%) patients with a cleft palate and 10 (14%) with a highly

arched palate. Skeletal anomalies like scoliosis or kyphosis, funnel chest, dislocated hips, anomalies of the shape of the skull, short clavicle and shortness of extremities were reported in 21 (29%) patients. Caudal regression was described once (22). Motor development was described in 38 patients and motor retardation was present in 19 of them (50%). Neurological anomalies such as cerebellar ataxia, micropolygyria of the frontal lobes, hyperextensibility and both cerebral and cerebellar atrophy were incidentally noticed.

Data on the mental development of 50 patients are shown in table III. Sixteen patients (32%) were mildly to moderately retarded. The results of the IQ-tests were converted if possible according to the DSM IV criteria.

Table IV shows the clinical features in patients with normal or borderline intelligence versus patients with mild or moderate mental retardation.

	sex unknown (n=9)	female (n=23)	male (n=18)
Normal (IQ ≥ 85)	3	15	6
Borderline (71 ≤ IQ ≤ 84)	3	6	2
Mild (50 ≤ IQ ≤ 70)	2	2	5
Moderate (IQ<50)	1	1	5

Table III: Mental development of the CES patients, including our three patients (n=50)

DISCUSSION

The phenotypic variability of CES makes it hard to define clinical criteria for this disorder. Only 41% of the CES-patients have the classical combination of iris coloboma, anal anomalies and pre-auricular anomalies. A pre-auricular tag or pit is the most consistent feature in CES (Table II). Therefore many CES-patients can not be identified as having CES by their phenotype alone. Until now the presence of the inv dup(22) is the most valuable diagnostic criterion.

Our three patients demonstrated the phenotypic variability in CES. Patient 1 had colobomas, anal atresia, kidney anomalies and a low normal development. Patient 2 had no coloboma and no anal anomaly, but he had a psychomotor retardation. Patient 3 had a characteristic presentation with colobomas, anal atresia and a heart defect although she had the inv dup(22) in mosaic form (low-grade in lymphocytes (21%), high-grade in fibroblasts (90%)). She was not mentally retarded. Of the 12 patients with the inv dup(22) in mosaic form, 9 patients had a mosaicism of more than 80% in lymphocytes. These 9 patients all had anal problems while only one of the three other patients (21 to 68%

Table IV:
Frequency of clinical features in patients with normal intelligence vs. with mental retardation (MR).

Clinical features	normal (n=34)	MR (n=16)
Pre-auricular anomalies	30/34 (88%)	11/16 (69%)
Total anal anomalies	28/34 (82%)	9/16 (56%)
Coloboma	20/34 (59%)	8/16 (50%)
Total cardiovasc. anom.	13/34 (38%)	8/16 (50%)
Downslant fissures	14/34 (41%)	9/16 (56%)
Visual disability	8/12 (67%)	0/5
Hypertelorism	13/34 (38%)	5/16 (13%)
Total kidney anomalies	10/33 (30%)	2/15 (13%)
Total skeletal anomalies	8/33 (24%)	5/16 (31%)
Retrognathia	6/34 (18%)	5/16 (31%)
Epicanthus	8/34 (24%)	5/16 (31%)
Strabismus	10/28 (36%)	4/13 (31%)
Cryptorchidism	0/8	1/10 (10%)
Microphthalmia	7/28 (25%)	2/13 (15%)
Low-set ears	5/33 (15%)	2/16 (13%)
Hearing loss	6/29 (21%)	3/13 (23%)
Ear deformities	4/33 (12%)	2/16 (13%)
Short stature	4/27 (15%)	4/13 (31%)
Flattened nasal bridge	2/28 (7%)	1/12 (8%)
Cleft palate	2/33 (6%)	2/16 (13%)
Hypotonia	6/28 (2%)	1/14 (7%)

mosaic) had anal atresia. However, there does not seem to be a clear-cut correlation between the phenotype and the degree of mosaicism (data not shown).

All in all there are no clear-cut differences between the patients with and without a well-identified marker or the patients with and without the marker in mosaic form. In the familial cases, however, we noted that the relatives with the inv dup(22) in mosaic (especially low grade) seem to have a milder phenotype than the non-mosaic relatives (15, 43, 48). On the other hand, two family members described by Lüleci *et al.* (25) had a normal phenotype and the inv dup(22) in all lymphocytes examined. This is difficult to understand.

The calculated frequencies of symptoms are probably too high because CES-patients with a normal or slightly abnormal phenotype are likely to be underreported (25, 43, 48, 52). These CES-carriers can only be detected when another relative with CES has a more severe phenotype and is therefore cytogenetically analysed. In this light, the observed prevalence of the inv dup(22) of 1:50.000-150.000 in Northeastern Switzerland is probably an underestimation (31). To analyse in this study a homogenous population of seriously affected CES-patients, we excluded the (slightly) normal family members with an inv dup(22), even though this creates a clinical picture with a poorer prognosis for CES-patients.

Total anomalous pulmonary venous return (TAPVR) and tetralogy of Fallot (TOF) are considered as two of the most frequently occurring cardiac defect in CES (respectively 35% and 20% of the cardiac anomalies) (17). TOF, however, is a frequently occurring cardiac anomaly (about 5-7% of the congenital cardial anomalies), whereas the relative frequency of TAPVR is 1-2% (36). In our study 16 (21%) CES-patients had TAPVR and only 3 (4%) had TOF. We conclude therefore, that TOF, in contrast with TAPVR, is not one of the important features in CES.

In 50 reported patients with a known mental development 16 (32%) were retarded. This is in agreement with Schinzel *et al.* (43). Of the males 10/18 (56%) and of the females 3/23 (13%) were retarded. Although both groups are small, statistical analysis revealed that mental retardation seems to occur significantly more frequently in males ($p=0.015$). Sofar, different phenotypes for CES according to sex were not reported. Borderline retardation occurred in 11 patients (22%). Of the 12 patients with a mosaic inv dup(22) 2 were retarded. The severity of mental retardation seemed not to be related to the frequency of other congenital anomalies or presence of mosaicism.

The origin of the phenotypic variability is still unknown, despite the efforts to restrict the CES-critical region (CESCR). To date, the CESCR extends from the centromere to locus D22S57 (about 1.9 Mb) and seems to be proximally localized on the area deleted in the velo-cardio-facial syndrome or DiGeorge syndrome (30, 34). The ATP6E gene, coding for a protein in a proton pump, is the only gene currently localized in this region (3). The duplication of the CES-region is not necessarily symmetrical (33). The size of the duplicated fragment does not seem to be associated with the phenotype. Some patients have a duplication of the CESCR in 22q11, without an inv dup (22, 26, 40, 44). These patients are trisomic for the CESCR. The frequency of their anomalies, however, seem to be the same for cases with the CESCR in fourfold.

Unfortunately, many questions still exist about the phenotypic variability and the genetic background of CES. A good specification of CES-patients and their relatives remains necessary. Hopefully new molecular insight will help to understand the variability in CES.

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