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Cat eye syndrome: Clinical, cytogenetics and familial findings in a large cohort of 43 patients highlighting the importance of congenital heart disease and inherited cases

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[Correction added after first online publication on 13 December 2023. Author name changed from 'Caroline Rooryck-Thambo' to 'Caroline Rooryck'.]

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Abstract

Cat Eye Syndrome (CES) is a rare genetic disease caused by the presence of a small supernumerary marker chromosome derived from chromosome 22, which results in a partial tetrasomy of 22p-22q11.21. CES is classically defined by association of iris coloboma, anal atresia, and preauricular tags or pits, with high clinical and genetic heterogeneity. We conducted an international retrospective study of patients carrying genomic gain in the 22q11.21 chromosomal region upstream from LCR22-A identified using FISH, MLPA, and/or array-CGH. We report a cohort of 43 CES cases. We highlight that the clinical triad represents no more than 50% of cases. However, only 16% of CES patients presented with the three signs of the triad and 9% not present

Guillaume Jedraszak and Florence Jobic contributed equally to this work.

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any of these three signs. We also highlight the importance of other impairments: cardiac anomalies are one of the major signs of CES (51% of cases), and high frequency of intellectual disability (47%). Ocular motility defects (45%), abdominal malformations (44%), ophthalmologic malformations (35%), and genitourinary tract defects (32%) are other frequent clinical features. We observed that sSMC is the most frequent chromosomal anomaly (91%) and we highlight the high prevalence of mosaic cases (40%) and the unexpectedly high prevalence of parental transmission of sSMC (23%). Most often, the transmitting parent has mild or absent features and carries the mosaic marker at a very low rate (<10%). These data allow us to better delineate the clinical phenotype associated with CES, which must be taken into account in the cytogenetic testing for this syndrome. These findings draw attention to the need for genetic counseling and the risk of recurrence.

KEYWORDS

array-CGH, 22q11.2 region, cat eye syndrome, congenital heart disease, eye anomalies, familial disease, FISH, heart defect, mosaicism, parental transmission, small supernumerary marker chromosome (sSMC)

1 | INTRODUCTION

Cat eye syndrome (CES) (OMIM 115470) is a rare genetic disease whose prevalence is estimated to be between one in 50,000 and one in 150,000 live births (Berends et al., 2001).

The “classical triad” of CES typically associates iris coloboma, anal atresia, and preauricular tags or pits (Schachenmann et al., 1965; Berends et al., 2001; Rosias et al., 2001). All the studies published on this syndrome have highlighted the high clinical variability. CES patients can also feature congenital kidney abnormalities, congenital cardiac defects, intellectual disability (ID), and/or growth delay, highlighting the importance of phenotype variability (Berends et al., 2001; Rosias et al., 2001).

Most patients diagnosed with CES carry an extra small supernumerary bisatellited marker chromosome (sSMC) derived from chromosome 22. The presence of sSMC derived from chromosome 22, which results in a partial tetrasomy of the 22p-22q11.21 region, was the first reported molecular basis of CES. It has been proved that this sSMC involved at least the proximal 22q11.2, between the centromere and the LCR22-A region. This region is named Cat Eye Syndrome Critical Region (CESCR) (Mears et al., 1995). Two types of sSMC have been described, depending on the size and the breakpoint site. Type 1 sSMC only includes the CESCR, and type 2 sSMC, reported in only a few cases of CES, includes both the CESCR and the DiGeorge syndrome critical region (McTaggart et al., 1998). To date, sSMC remains the most frequent cytogenetic anomaly observed in CES (Berends et al., 2001; Rosias et al., 2001). However, in the last 10 years, due to progress in molecular cytogenetic techniques, other molecular anomalies have been described. These anomalies include intrachromosomal duplication of CESCR, intrachromosomal triplication of CESCR, and a ring of chromosome 22 (Karcaaltincaba et al., 2010; Knijnenburg et al., 2012; Rosias et al., 2001). Despite this progress, the genetic etiology of some clinically defined/convincing CES patients remains unknown.

To our knowledge, over 300 patients with CES have been reported to date. In 2001, the two of the largest literature reviews of CES patients were published simultaneously (Berends et al., 2001; Rosias et al., 2001). These two studies curiously led to significantly different results regarding the number of patients and their clinical presentation.

To better delineate the clinical, familial, and cytogenetics findings associated with CES, we present results of an international collaborative retrospective study of 43 patients with a confirmed genomic gain of CESCR.

To better delineate the clinical, familial, and cytogenetics findings associated with CES, we retrospectively collected the medical history of a cohort of 43 CES patients with a confirmed cytogenetics diagnosis of CES. We specifically focused our attention on the symptoms of the classical clinical triad and the other recurrent anomalies. With the arrival of recent cytogenetic techniques, particularly array-CGH, we tried to find genotype–phenotype correlations. In cases where data were available, we also examined familial histories of the patients.

2 | PATIENTS AND METHOD

In order to identify as many CES patients as possible, we conducted an international collaborative project involving French networks (AChroPuce and the French Clinical Geneticist society—AFGC), and the sSMC database (<https://cs-tl.de/DB/CA/sSMC/0-Start.html>). For this, an email was sent to all the colleagues belonging to this mailing list, explaining the objectives of the study. We have added to this email a datasheet to ensure relative consistency of data collection on phenotype and genotype (Supplementary Data). Patients were included only if colleagues returned the datasheet. For each explored feature, colleagues can answer “Yes,” “No,” or “Not Determined.” For patients whose answer was “not determined” for a sign, we decided

to not include the patient in the calculation of the frequency of this sign.

Patients were included in cases in which genomic gain of CESC (22q11.21, upstream of LCR22-A) was proven by cytogenetics, fluorescence in situ hybridization (FISH), multiplex ligation-dependent probe amplification (MLPA), and/or array-CGH) and where clinical data was available. Patients were excluded when they have other pathogenic chromosomal anomalies.

Exclusion criteria were lack of clinical information (less than 50% of items filled) and/or lack of genetic confirmation of CESC involvement with a molecular method (FISH, MLPA, array-CGH) if primary diagnosis was made by karyotyping.

Informed consent was obtained for genetic tests. Cytogenetics and molecular investigations were performed by reference centers.

3 | RESULTS

Sixty-three observations of CES patients were collected. Among them, five were excluded for lack of clinical information, five were excluded because cytogenetic anomalies did not meet the strict definition of CES (der22, partial 22q trisomy, atypical array-CGH). Ten prenatal cases that ended in abortion were excluded for the clinical study because postnatal phenotyping could not be performed, so 43 observations met the inclusion criteria. Results are reported in Table 1. Cytogenetics data analyses were performed on all 53 cases, including prenatal cases, as there was sufficient data to discuss type or inheritance of the chromosomal anomaly.

1. Clinical data: analysis of 43 cases

TABLE 1 Frequency of signs of the classical triad.

	Number of patients	Frequency (%)
Preauricular anomalies	35/43	81
Preauricular pits	28	65
Preauricular tags	21	49
Ear malformation	10	23
Hearing loss	12	28
Abdominal malformations	19/43	44
Anal atresia or imperforate anus	16	37
Associated fistula	9	21
Other anal anomalies	3	7
Other abdominal malformations	6	14
Ophthalmologic anomalies	15/43	35
Iris coloboma	14	33
Other colobomas	9	21
Other visual disability	3	7

3.1 | Symptoms of the classical triad (Tables 2 and 3)

Ear anomalies are the main clinical feature observed in our cohort (81% of patients). Preauricular pits were more common than preauricular tags, although they were often associated (43% of patients with ear anomalies). We also noted 10 patients with more severe ear malformation and 12 with associated hearing loss. Among patients with hearing loss, only four had associated ear malformation.

The two signs of the clinical triad were present in less than half of the cases: rectal anomalies (including anal atresia or imperforate anus with or without associated fistula) were noted in 44% of cases and coloboma was present in 35% of cases.

Digestive anomalies were present in 44% of the patients. Anal atresia/imperforate anus was the most common sign, seen in 16 patients (37%). In 9 patients (21%), a fistula was associated. Other ano-rectal anomalies were present in 3 cases (7%) and consisted in anal ante-position and anal stenosis. Other abdominal anomalies were seen in 6 patients and comprised megarectum, bile duct cyst, biliary atresia, intestinal malrotation, constipation, and gastroesophageal reflux.

TABLE 2 Association of the triad's signs in CES patients.

	Number of patients	Frequency (%)
3 SIGNS	7/43	16
2 SIGNS	17/43	40
Abdominal malformation + coloboma	0	0
Preauricular anomalies + coloboma	6	14
Preauricular anomalies + abdominal malformation	11	26
1 SIGN	15/43	35
Abdominal malformation	2	5
Coloboma	1	2
Preauricular anomalies	12	28
0 SIGN	4/43	9

TABLE 3 Frequency of other signs in CES patients (patients were taking into account only if answer was "Yes" or "No" in the clinical part of the datasheet).

	Number of patients	Frequency (%)
Heart anomalies	20/39	51
Intellectual disability	15/32	47
Ocular motility defect	14/31	45
Genitourinary anomalies	12/38	32
Cerebral malformation	7/29	24
Growth retardation	8/34	24
Hormone deficiency	5/23	22

Ophthalmological symptoms were the least frequent of the triad, only present in 15 patients (35%). Iris coloboma was observed in 14 patients (33%). Other types of coloboma were associated in 9 patients (21%).

Association of symptoms of the classical triad is summarized Table 3. Only seven patients (16%) had the association of 3 symptoms of the classical triad (Table 2). Seventeen patients (40%) exhibited 2 signs of the triad, and 15 patients (35%) had only one. Interestingly, 4 patients (9%) had no signs of the triad. When two signs were present, the most common association was preauricular anomalies with a digestive malformation (11 patients; 26%). The association between pre-auricular anomalies and coloboma was less frequent (6 patients; 14%). The association between digestive anomalies and coloboma was never encountered. Only one patient had coloboma without auricular and anal anomalies.

3.2 | Other signs

Among all the signs observed in our cohort (Table 3), the second most frequent was heart anomaly, which was noted in 51% of cases. Heart anomalies include atrial septal defect (18% of cases), total anomalous pulmonary venous return (23% of cases), and ventricular septal defect (10% of cases). Genitourinary anomalies are extremely variable: the most frequent is VUR (8% of cases), and we also noted sporadic features such as renal duplication, renal dysplasia, and urethral stenosis.

ID was noted in 14 patients (47%), it was mostly mild ID (73%). One case had moderate ID with an IQ at 69, and two cases presented with severe ID. In our cohort, 7 patients had cerebral malformation, such as mild ventricular dilation in 2 cases, thin corpus callosum in 2 cases, thin ante pituitary in 2 cases, and ectopic post pituitary in 3 cases. Growth retardation was present in 8 cases. In 5 cases growth retardation was associated with growth hormone deficiency. Fourteen patients had an ocular motility defect, which was Duane syndrome in 6 cases and strabismus in 8 cases.

2. Cytogenetic data: analysis of 53 cases

The presence of a dicentric sSMC derived from chromosome 22 was the most frequent cytogenetic anomaly observed in our cohort (49/53 cases—92%). In the 4 additional cases, the cytogenetic anomaly consisted of triplication of the CESC region (8%) (Table 4).

When sSMC was the molecular basis of the disease, it was found in a homogenous state in 60% of cases and in a mosaic state in 40% of cases (Table 4). Mosaic ranges from 4% to 93%, and in one case,

we observed a difference between lymphocyte rate (20%) and amniotic fluid rate (60%). In the majority of inherited cases, parent's phenotype was not available.

Cytogenetic anomaly was de novo in 51% of cases (27/53 cases) and inherited in 23% of cases (12/53 cases). In 26% of cases (14/53), information was not available. When parental analysis was available, that is, in 39/53 cases, sSMC was described as de novo in two-thirds of cases and inherited in one-third of cases. Parental analysis was performed by karyotyping for 11 cases, by karyotyping, and FISH for 7 cases, and information was not available for the 9 last cases. When the sSMC was inherited, the transmitting parent carried the sSMC in mosaic state in two-thirds of cases and in all cells in one-third of cases. Transmission over three generations has been found once.

4 | DISCUSSION

CES is a rare chromosomal disease historically characterized by a triad of signs (preauricular anomalies, anal malformations, and iris coloboma) potentially associated with a wide range of congenital anomalies. We report clinical and cytogenetic data from 43 CES cases, the largest series described to date. This work is the first to report a large cohort of CES patients without a literature review, allowing us to better delineate the phenotype and genotype of CES to improve follow-up and genetic counseling of these patients and their families.

According to the literature, more than half of all patients did not meet the three classical signs (Schachenmann et al., 1965; Berends et al., 2001; Rosias et al., 2001). Our study results confirm these data. The most common sign observed in our cohort was preauricular malformation (pits and/or tags). It was found in 81% of our patients, which is in line with the frequency observed in previous studies. In contrast, the two other features of the CES triad were less frequent than expected: digestive malformations were found in 44% of our patients, and iris coloboma was present in only 33% of our patients. Frequencies of the other features of our patients reinforce the idea of lack of diagnostic sensitivity of the classical triad. We observed that heart malformations (51%) are the second most commonly observed feature. We also observed that ID (47%) and ocular motricity defects (45%) were more frequent than iris coloboma. In total, iris coloboma, the sign that gives the syndrome its name, is only the sixth most frequent feature observed in our cohort. Only one of our CES patients presented with isolated coloboma. Considering these results, iris coloboma does not seem to be a critical sign of CES. Moreover, missing one or more of the three main clinical signs is not that rare in CES. The classical association between the three main signs has a lower

TABLE 4 Cytogenetic data from CES cohort.

	State		Type of anomaly		Inheritance		
	Homogeneous	Mosaicism	sSMC	Triplication of CESC	de novo	Inherited	Not available
Number of cases	32/53	21/53	49/53	4/53	27/53	12/53	14/53
Frequency (%)	60%	40%	92%	8%	51%	23%	26%

frequency than expected (16% of cases), and the association between two of the three main signs (40% of cases) is also less frequent than expected. Our study highlights the fact that it is important to consider CES diagnosis even if one or more signs of the triad are missing.

In addition, the extreme variability in range and severity of the associated features is confirmed and emphasized. The frequency of heart malformation—51% of cases, identical to the frequency observed in previous studies—is the second most frequent feature noted in our cohort and has to be considered as a major sign of CES. Most frequent heart malformations observed in our cohort (atrial septal defect and total anomalous pulmonary venous return) have previously been associated with CES (Gaspar et al., 2022; Williams et al., 2021). This frequency highlights the importance of anticipating these malformations in order to adjust the care and follow-up of the patient.

The frequency and severity of ID and the associated genetic counseling are important unanswered questions in CES. Previous studies have clearly proved that some CES patients show moderate to severe ID and some patients show no ID, regardless of the underlying molecular mechanism. Two large CES literature reviews estimate the frequency of ID in CES with a significant difference at 36% and 52% (Berends et al., 2001; Rosias et al., 2001). These two studies are also in discordance concerning ID severity: Rosias et al. found 7% of cases with severe ID and Berends et al. did not find any patients with severe ID. Our data—ID frequency at 47%—seems to place the ID frequency in the upper range of those previously estimated, and we note that 10% of our cases (3/32) presented with moderate to severe ID.

As described in the previous studies, ocular motricity defects are the most common ophthalmological impairment in CES. In our cohort, 45% of cases presented with Duane syndrome or strabismus. As reported before, there are some cases of intrafamilial recurrence of Duane retraction syndrome which cosegregate with a typical CES sSMC (Berends et al., 2001). These data (sporadic cases and familial recurrence in CES patients) lead us to highlight that CES is a potentially underestimated genetic cause of Duane retraction syndrome (Kekunnaya & Negalur, 2017).

Brain malformations are reported in sporadic CES cases but are not usually associated with CES (Jedraszak et al., 2015; Karcaaltincaba et al., 2010; Melo et al., 2013; Serra et al., 2022). We noted some brain malformation observed at an unexpected frequency, with 24% of CES patients in our cohort presenting with such malformations. The potential recurrence of hypothalamic–pituitary abnormalities that can be associated with different hormonal deficiencies (22% of cases), as already discussed in a previous study is notable (Jedraszak et al., 2015). Indeed, all the reported patients with this type of anomaly presented with growth retardation and growth hormone deficiency. In our cohort, we noted a growth hormone deficiency in 63% of patients with growth retardation. These observations lead us to conclude that it is important to screen for such brain anomalies (by MRI) to adjust clinical and biological follow-up of CES patients. It is also important to carry out a hormonal exploration to detect a potential deficiency that could be supplemented.

Historically, sSMCs derived from chromosome 22 are considered to be the molecular basis responsible for CES, but other rare

anomalies are now known (Bélien et al., 2008; Karcaaltincaba et al., 2010; Knijnenburg et al., 2012; Rosias et al., 2001). There is no study that has explored the frequency of each molecular anomaly responsible for CES. Our study of 43 CES patients explored by a molecular technique confirms that type 1 sSMC is the main molecular basis of CES, as it is the cause of CES in 49/53 of our cases (92%). The 4 remaining cases showed an intrachromosomal triplication of the CESC, a chromosomal anomaly that could be missed by standard karyotyping. Even if an intrachromosomal gain of CESC is a rare event in our cohort. It seems important to consider array-CGH in the case of clinical suspicion of CES and in the absence of sSMC in the karyotype. This idea is reinforced by the absence of a phenotypic difference between CES and sSMC and CES with an intrachromosomal gain of CESC. Unfortunately, because most patients carry type 1 sSMC, our results do not allow us to define genotype–phenotype correlations. We hope that routine use of array-CGH will help to identify intrachromosomal triplication or other atypical gains in the CESC and help to define a better critical region implicated in the phenotype. To date, we can highlight that type 1 sSMC is the most common anomaly responsible for CES, and others being exceptions.

Previous studies have revealed that sSMC can be homogenous or in a mosaic state. It is not clear if mosaicism is associated with phenotypic variability (Berends et al., 2001; Rosias et al., 2001). Our study revealed an unexpectedly high frequency of patients with mosaicism for sSMC (40%). The mosaicism rate is highly variable and comprised between 4.5% and 93%. We did not find any link between the rate of mosaicism and severity of phenotype except for a very low mosaicism level (less than 5%) which could be associated with a milder phenotype. As previously reported, these cases of very low mosaicism levels are only observed during systematic family studies with FISH techniques (Kvarnung et al., 2012; Lüleci et al., 1989; Urioste et al., 1994). Somatic mosaicism is one of the major limitations to performing phenotype–genotype correlation (mosaicism rate of sSMC in different tissues in the same patient). Some previous studies have proved that the mosaicism rate can be very different between tissues in the same patient and have confirmed the existence of germinal mosaicism in CES (Kvarnung et al., 2012). Unfortunately, none of the patients reported in our study were explored in tissues other than blood. This limitation explains why we consider our data insufficient to highlight a possible genotype–phenotype correlation in cases of mosaicism in CES.

CES is reported in OMIM database as a de novo chromosomal syndrome (OMIM 115470). Although a few familial forms of CES have been reported and extensively studied, these forms seem to be exceptions (Berends et al., 2001; Kvarnung et al., 2012; Rosias et al., 2001; Urioste et al., 1994). We noted an unexpected rate of 23% of inherited cases in our cohort. We did not observe any sex bias in transmission, even though this had already been reported for sSMC transmission (Liehr, 2006). This rate could be higher if we consider that, in the 27 de novo cases (51%), about 20 of the parents' were only explored by conventional karyotyping which could possibly miss a low rate of sSMC mosaicism. We can also consider that, in the last 26% of cases no parental studies have been done. We suggest that a complete parental chromosomal investigation (karyotype and FISH)

should be performed for every case of de novo CES anomaly if the parents' phenotype appears to be normal. As reported before, in cases with a low rate of mosaicism in a parent, we recommend routinely proposing antenatal diagnosis because of the recurrence risk that cannot be estimated only by the rate of mosaicism in the blood (Kvarnung et al., 2012).

In conclusion, our study highlights some important points to consider in CES. First, the signs in the classical clinical triad are not the only features to consider in the diagnosis of CES, and the heart malformation should be considered to be a major feature. Second, we note the importance of some associated congenital anomalies that need more attention and follow-up (heart) or treatment (hormonal deficiency). Finally, we highlight the importance of performing appropriate cytogenetic analyses (FISH) to identify patients with a low percentage of sSMC mosaicism, and to perform prenatal diagnosis whatever the parental cytogenetic result. Such adapted cytogenetic analyses are also important to exclude parental transmission of sSMC, which is essential for genetic counseling on recurrence risk. Although we lack data to establish genotype–phenotype correlations, we hope that future studies will help to better understand the link between the presence of this sSMC and the CES phenotype.

AUTHOR CONTRIBUTIONS

Guillaume Jedraszak and Florence Jobic created the information sheet, collected the data, carried out the analysis, and wrote the manuscript, Gilles Morin and Thomas Liehr helped to diffuse the call for collaboration and critically reviewed the manuscript, Loïc Garçon critically reviewed the manuscript and gave support to help the co-first authors, other authors helped by providing data from their cases.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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