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Case Report

Maternally Derived Complex Small Supernumerary Marker Chromosome 22 Associated with Cat-Eye Syndrome Like Features

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Abstract

Cat-eye syndrome (CES) is a rare genetic disease first reported in 1965. The estimated prevalence of CES is 1:50,000 to 1:150,000, and it is typically associated with an inverted duplicated small supernumerary marker chromosome (sSMC) derived from chromosome 22. The specific chromosomal band involved in CES causing partial tetrasomy is 22q11.21, where

chromosomal rearrangements occur due to the presence of low-copy repeats (LCR22). The phenotype of CES is extremely diverse, ranging from normal to multiple abnormalities including intellectual disabilities and dysmorphic features. To our knowledge, over 340 patients with CES have been reported to date. This study reports a patient displaying a duplication of chromosome 22pter-22q12 involving band 22q11.21 where the CES critical region is located, and 18pter to 18p11. The propositus is a three-year-old girl, born to an unrelated and healthy couple. She was referred for facial dysmorphism and psychomotor delay. Banding cytogenetic analysis revealed an sSMC resulting from abnormal 3:1 segregation of the maternal balanced translocation t(18;22). Furthermore, the origin of the sSMC was confirmed by fluorescence in situ hybridization technique. The current study emphasized the importance of molecular cytogenetic techniques such as FISH in apprehending chromosomal abnormality. In addition, it shows that partial trisomy 22q11.2 to 22q12 may lead to CES-like symptoms.

Keywords
Cat-eye syndrome; small supernumerary marker chromosome (sSMC); maternal translocation (18;22); banding and molecular cytogenetics

1. Introduction

Iris coloboma, anal atresia, and preauricular tags and pits are established diagnostic criteria for CES [1, 2]. Additionally, malformations of the heart and great vessels, abnormalities of the kidneys and the urinary tract, cleft palate, and mental retardation are frequently associated with the syndrome [3]; according to Jedraszak et al. (2024) [4], the actual leading symptoms of CES are indeed cardiac anomalies, intellectual disability, ocular motility defects, abdominal malformations, ophthalmologic malformations, and genitourinary tract defects.

The most common cytogenetic anomaly associated with CES is a bisatellite and dicentric small supernumerary marker chromosome (sSMC), cytogenetically designated as inv dup(22) (q11.21) [5]. Furthermore, CES-like phenotypes may result from other chromosomal abnormalities, including 22q11.2 interstitial duplications or unbalanced translocations caused by abnormal meiotic segregation in one of the parents [6]. The site-specific reciprocal translocation t(11;22) (q23;q11) is the most frequent non-Robertsonian constitutional translocation in humans. Meiotic nondisjunction events in carriers of the t(11;22) translocation can then lead to offspring with der(22) syndrome [7]. However, these patients with Emanuel syndrome are more severely affected than CES patients due to partial trisomy of 11q23 to 11qter material.

We report on the clinical and cytogenetic findings in a case associated with CES features. To our knowledge, this is the first such case resulting from a maternal balanced translocation 46,XX,t(18;22) (p11;q12).

2. Case Presentation

2.1 Patient's Medical History

A 3-year-old girl, the second of two siblings (Figure 1), was referred for facial dysmorphism and psychomotor delay. The baby girl was born after a well-monitored pregnancy and delivery with no reports of neonatal distress. However, the patient experienced neonatal hypotonia and upon examination, she presented microcephaly with a small forehead, hypertelorism, a flattened nasal base, a long philtrum, microstomia, and micrognathia. In addition, she had psychomotor retardation, with no ability to stand at the age of 3 years, although she could sit with support. She also had convergent strabismus and myopia, wore corrective glasses, and her ophthalmic examination revealed a chorio-retinal coloboma and bilateral microphthalmia. The patient also had chronic constipation and was under clinical observation for gastroesophageal reflux.

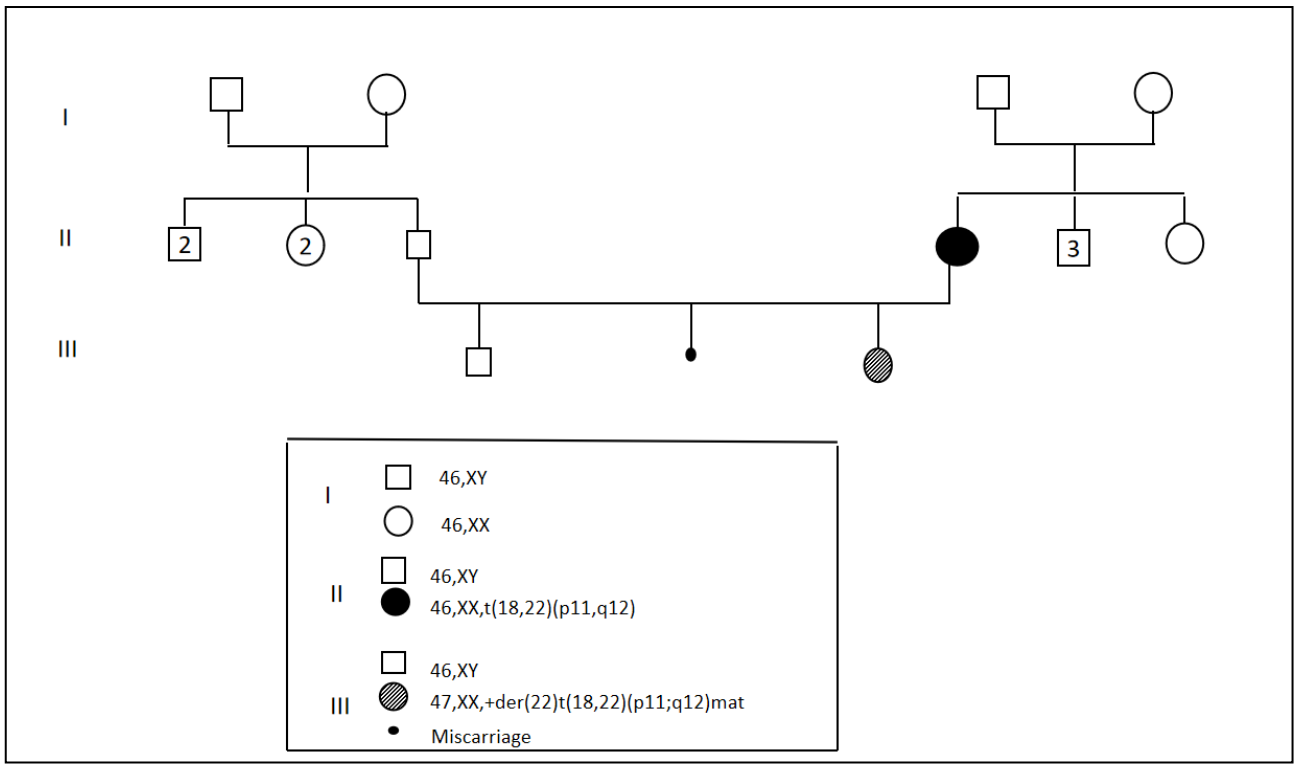

Figure 1 The pedigree of the family.

2.2 Banding and Molecular Cytogenetics

The patient's parents gave informed consent for this study, which was performed in accordance with the Declaration of Helsinki protocols and approved by the local institutional review boards. Venous blood (3 to 5 ml) acquired in a heparinized tube was taken from the patient and her parents for cytogenetic and molecular cytogenetic studies. Chromosomal analysis was performed by R-banding at the resolution level of 400 bands according to standard methods; 15 metaphases were karyotyped, and the total number and structure of chromosomes were determined. Subsequently, a fluorescence in situ hybridization (FISH) assay was performed on metaphase and interphase cells from the patient and her mother. Probes included whole chromosome painting (WCP) for chromosome 22, Tuple1/ARSA in 22q11.2, subtelomeric probe for chromosome 18pter

(subtel18pter or D18S552) (Abbott/Vysis, Germany), the homemade probe midi54 specific for acrocentric short arms, and the bacterial artificial chromosome probe from BACPAC Chori (USA) RP11-81B3 located in 22q11.21. Chromosomes were counterstained with 4',6-diamidino-2-phenylindole (DAPI).

2.3 Statement of Ethics

Study approval statement: The pre-analytic and post-analytic steps described in this work were performed for patients by the Department of Medical Genetics of the National Institute of Health as medical services in agreement with the tenets of the Declaration of Helsinki.

All ethical issues of the National Institute of Health in Rabat, Morocco, where the Department of Medical Genetics, is in charge of an Intramural Advisory Committee.

Consent to publish statement: The patient's parents gave written informed consent to publish the details of their medical care and any accompanying images.

3. Results

Karyotype analysis revealed the presence of an sSMC in all metaphases examined in the patient: 47,XX,+mar (Figure 2). The father's karyotype appeared normal, whereas the mother showed a balanced translocation involving chromosomes 18 and 22, identified as 46,XX,t(18;22)(p11;q12) (Figure 3) according to the ISCN (International System for Human Cytogenomic Nomenclature) (ISCN, 2020).

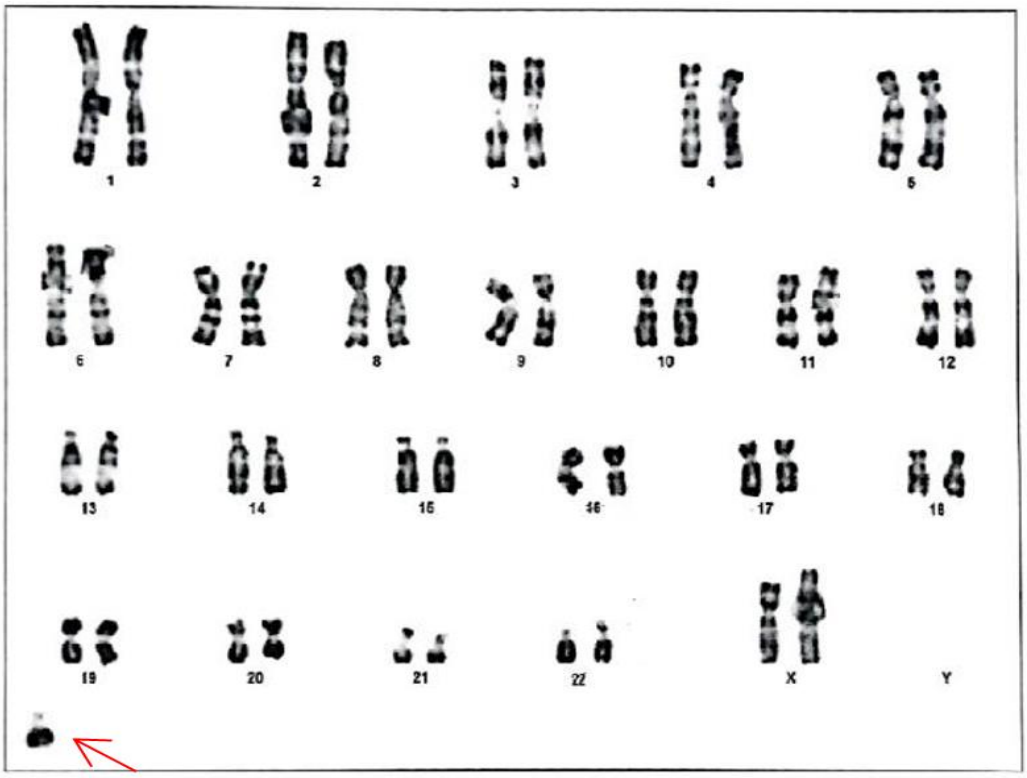

Figure 2 The patient's karyotype (R-banding technique) shows the small supernumerary marker chromosome (arrow).

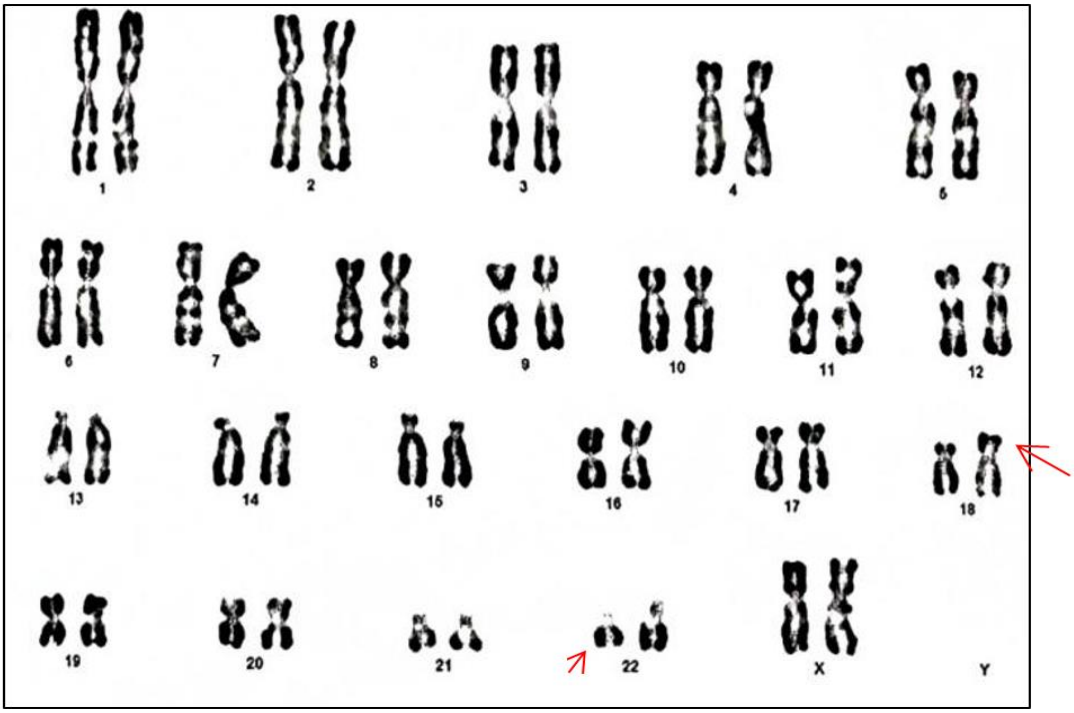

Figure 3 The karyotype (R-banding technique) of the patient's mother, showing the balanced translocation (arrow).

FISH analysis in the mother revealed translocation of a portion of chromosome 22 to another chromosome, according to inverted DAPI banding chromosome 18, consistent with karyotype findings (Figure 4). Additional interphase FISH experiments in the patient confirmed trisomy of the chromosome 22 region (22pter to 22q12), with three copies of TUPLE1 (22q11.2) (Figure 5). The patient was thus diagnosed with trisomy of chromosome 22 (22pter to 22q12) and of chromosome 18 (18pter to 18p11.2), with a final result der(22) t(18;22) (p11.2?3;q12) (midi54+,wcp22+,RP11-81B3+,TUPLE1+,ARSA-,D18S552+) mat in the patient (Figure 6).

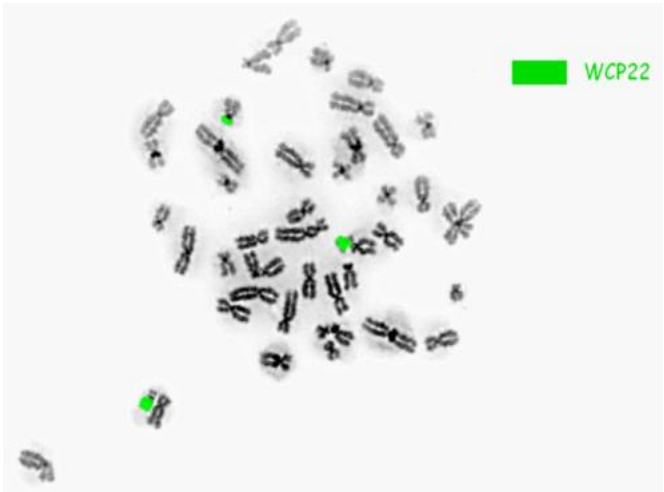

Figure 4 FISH analysis in cells of the mother reveals a chromosome 22 segment translocated onto chromosome 18, consistent with karyotype t(18;22).

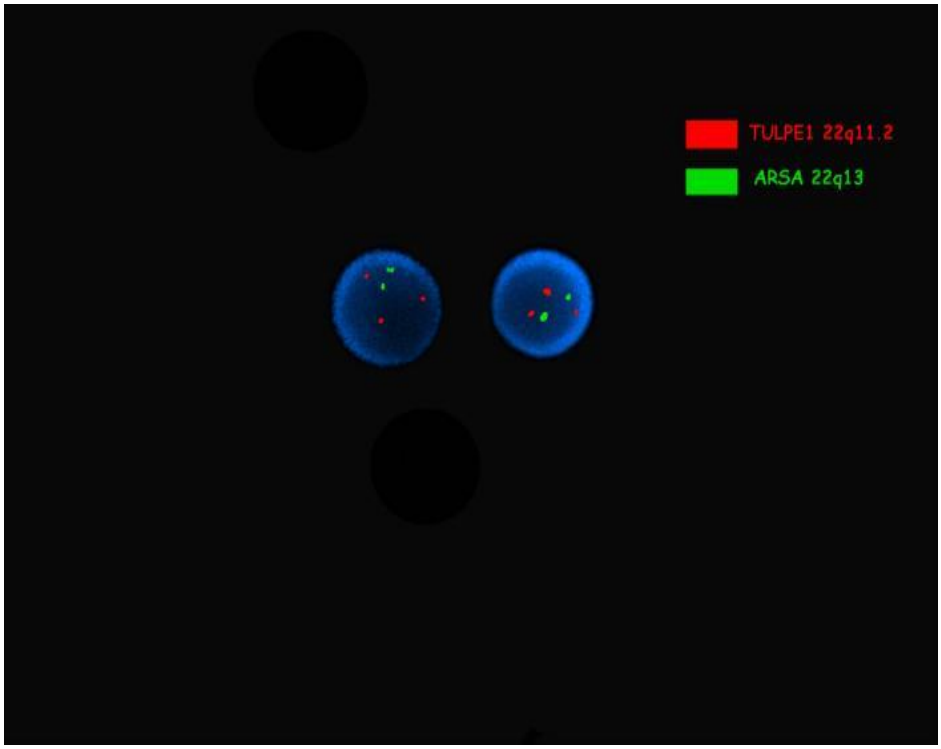

Figure 5 Interphase FISH analysis in the patient revealed three copies per cell of TUPL1 in 22q11.2 and 2 signals only for ARSA in 22q13.

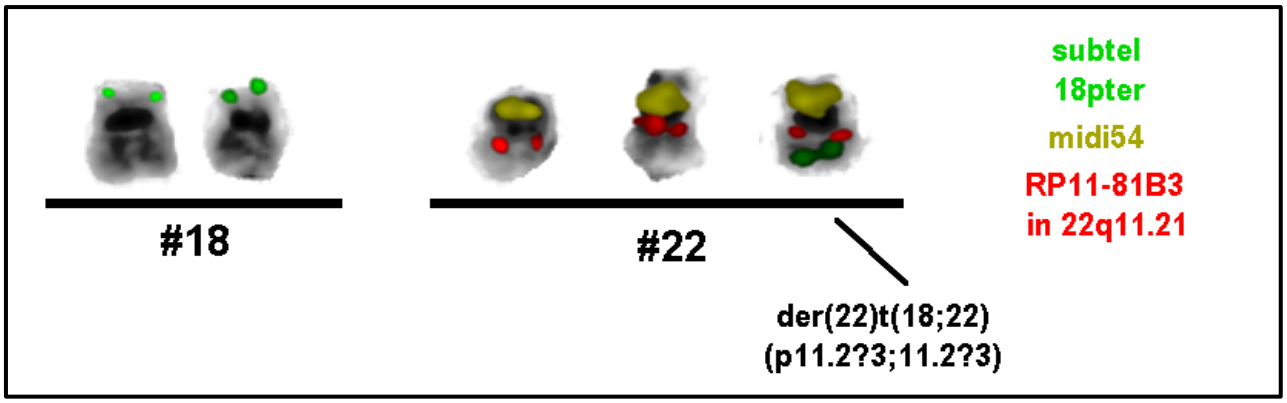

Figure 6 Molecular cytogenetics result of the patient on metaphases confirming the sSMC to be derived from material of chromosomes 18 and 22.

4. Discussion and Conclusion

Numerous translocations are reported between chromosome 22 and other chromosomes, with subband 22q11.2 being particularly prone to rearrangements. This susceptibility is attributed to a region containing eight chromosome-specific low-copy repeats [8]. The presence of these repeats within the region promotes non-allelic homologous recombination. Genetic variations within genes in the 22q11.21 region can affect various physiological functions, including those related to the eyes, heart, immune system, intelligence, and others [9].

Carriers of the balanced constitutional translocation are phenotypically healthy. Still, they risk having a progeny with supernumerary derivative chromosome der(22) due to 3:1 meiosis I missegregation, resulting in the production of a gamete with partial disomy for chromosome 22 [10].

CES associated with unbalanced translocations involving 22q11.2 have not been reported yet. The most commonly reported translocation involving chromosome 22 is translocation t(11;22) (p23;q11) [7]. Most classical CES cases are typically associated with a satellite sSMC 22, resulting in partial tetrasomy 22pter-22q11.21 [11].

Overall, there are 22 cases with complex sSMCs involving chromosome 22 (https://cs-tl.de/DB/CA/sSMC/22/d-uncl.html#2). As clinical data is rarely comprehensive, it is difficult to determine to what extent these cases might have resembled CES.

Despite the recognized minimal critical within 22q11.2 being present generally at least in four copies required for the features of CES, phenotypic variability persists [9]. Less than 10% of reported cases of CES show all three classical major clinical features, which include iris coloboma, anal anomalies, and preauricular malformations. In comparison, only 41% had the classical triad of symptoms, as stated by Ko et al. (2010) [12]. Although congenital heart anomalies do not belong to the clinical presentation triad, they are present in about 50% of affected patients [4], with atrioventricular septal defect and total anomalous pulmonary venous return (TAPVR) being the most frequently identified [8]. In our case, the patient presents clinically with retinal choriocoloboma and anal atresia; however, preauricular tags, pits, and heart malformations were not detected. While Jedraszak et al. (2024) [4] reported that heart malformations are the second most common feature in CES patients, occurring in 51% of cases, our patient does not exhibit this characteristic. Additional features observed in our patient include moderate intellectual disability (ID), which is consistent with the established characteristics of CES. Furthermore, as described in previous studies [4], hypertelorism and digestive malformations are also evident in our patients.

Pure trisomy of the entire short arm of chromosome 18 (18p) is rare. The patients with this trisomy may exhibit non-specific facial features and mental development ranging from normal to moderate impairment. Some cases, like those described by Taylor et al. (1975) [13] and Takeda et al. (1989) [14], show no mental or physical anomalies, while others, like Moog et al. (1994) [15], report developmental delays and minor anomalies. Overall, 18p duplication is not associated with major malformations [16]. Barber (2005) [17] classified trisomy 18p as a euchromatic variant (EV) in chromosomal anomalies, noting that it generally lacks significant clinical repercussions, unlike trisomy 18q. Despite this, several genes mapped to 18p, such as *MC2R*, *TYMS*, and *LAMA1*, have unclear phenotypic impacts in trisomic patients [17]. However, partial tetrasomy of 18p leads practically always to severely impaired carriers [OMIM #614290].

Overall, we suggest that the phenotype of our patient may mainly result from the duplication of chromosome (22pter to 22q12), involving band 22q11.21, rather than partial trisomy of 18pter to 18p11.2?3. Determining the breakpoints on both chromosomes 18 and 22 through chromosomal microarray analysis would provide a more comprehensive understanding of the sSMC structure. However, due to a loss of communication with the family, we could not determine the translocation breakpoints, which constitutes a limitation of this study.

Our case adds another layer of clinical variability to the literature on CES; it is recognized for its phenotypic spectrum, ranging from normal to severe features (Table 1). However, the underlying reasons for this variation are still not fully understood.

Table 1 The significant variability in cat eye syndrome clinical features.

	Jedraszak et al. 2024 [4]		Karcaaltıncaba et al. 2010 [18]	Morales et al. 2007 [6]	Our case
	Number of patients	Frequency (%)			
Preauricular anomalies	**35/43**	81			
Preauricular pits	28	65	no		
Preauricular tags	21	49	yes	no	no
Ear malformation	10	23	yes		
Hearing loss	12	28	no		
Abdominal malformations	**19/43**	44			
Anal atresia or imperforate anus	16	37			yes
Associated fistula	9	21	no	no	no
Other anal anomalies	3	7			no
Other abdominal malformations	6	14			no
Ophthalmologic anomalies	**15/43**	35			
Iris coloboma	14	33	yes	no	yes
Other colobomas	9	21	no		
Other visual disability	3	7	no		
Heart anomalies	20/39	51	no	no	no
Intellectual disability	15/32	47	no	no	mild
Growth retardation	8/34	24	yes	no	yes

The rare occurrence of the triad anomalies (coloboma, anal anomalies, and preauricular anomalies) in only 41% of patients, together with the variability reported by Jedraszak et al. 2024, suggests a potential underdiagnosis of CES. The reporting of additional cases is essential to promote a fuller understanding of the syndrome and to improve diagnostic accuracy.

Familial translocations involving chromosome 22 are a significant concern because of their potential for increased recurrence rates within affected families. Genetic counseling is, therefore, essential for these families.

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Author Contributions

HB, ZE, SCE, FO, AS, LS, TL, AS and AN planned, performed the experiments, and wrote the manuscript. SCE, FO performed the clinical evaluation. SCE, FO, LS, AS, TL, AS and AN planned, performed the experiments, and revised the manuscript.

Competing Interests

The authors have no conflicts of interest to declare.

Data Availability Statement

All data generated or analyzed during this study are included in this article [and/or] its supplementary material files.

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