The aetiology of the cat eye syndrome reconsidered

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SUMMARY The cat eye syndrome (CES), usually ascribed to the presence of a deleted supernumerary 22 chromosome, is characterised by a typical clinical picture including anal atresia, ocular coloboma, preauricular tags and sinuses, congenital heart defects, urinary tract anomalies, and mental and physical retardation. An analysis of published reports revealed that of the 57 reported cases, only 21 showed the complete form, and 11 had a normal karyotype.

Several observations question the existence of a trisomy 22: (1) the absence of any report in living subjects of trisomy 22 arising from an inherited Robertsonian translocation; (2) the recurrent abortions in carriers of Robertsonian translocations involving chromosome 22; and (3) the existence of a syndrome, showing the same clinical features as trisomy 22, which is irrefutably dependent on a trisomy of the distal region of the 11 long arm.

On the basis of a comparison of the clinical features in full trisomy 13, partial 13 trisomies, 13 rings, 13 deletions, and CES the small marker present in this syndrome is considered to be a chromosome 13 with an interstitial deletion.

An attempt to map this chromosome has been made.

One century ago, Haab1 described the clinical association of ocular coloboma and anal atresia. In 1965 Schachenmann et al2 were the first to find a supernumerary acrocentric chromosome in three subjects with these malformations.

The term 'cat eye', derived from the particular appearance that the vertical iridochoroidal coloboma gives to these patients, was introduced by Gerald et al.3

The syndrome is usually ascribed to the presence of a small submetacentric or acrocentric chromosome, but there are several case reports in which no chromosomal abnormality is apparent.4-8

Although cytogenetic investigations have not provided precise information, because of the small size of the supernumerary element, a 22q—chromosome is believed to be involved. Therefore, the syndrome would depend on a partial 22 trisomy.

A recent examination of three patients with cat eye syndrome (CES) and an accurate analysis of the previously reported cases5-40 (table 1a, b, 2a, b) enabled us to make some observations about the clinical and cytogenetic picture of this syndrome.

Case reports

CASE 1

This was a newborn male infant, born after 40 weeks' gestation, the first child of a 30-year-old mother and 33-year-old father. The delivery was normal; birthweight 3000 g, head circumference 33 cm, length 55 cm. The following anomalies were observed: sloping forehead, prominent occiput, large fontanelles, widely patent cranial sutures, epicanthal folds, hypertelorism, antimongoloid slanting eyes, depressed nasal bridge, prominent nose, increased philtrum length, malformed ears, bilateral preauricular skin tags and sinuses (fig 1A), high arched palate, narrow chest, widely spaced nipples, and small scrotum with neither testicle palpable in the sac or in the inguinal canal. Anal atresia was noted at 48 hours after birth and was surgically resolved on the third day. The baby showed failure to thrive and was admitted to hospital for salmonellosis and infection of the urinary tract. He died 50 days after birth. Necropsy showed the following additional abnormalities: micropolygyria of the frontal lobes, intestinal malrotation (fig 1B), megacolon, megarueter on right side, and abdominal testes. The death of
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### TABLE 1a  
Cat eye syndrome: patients with abnormal karyotype

<table>
<thead>
<tr>
<th>Case No</th>
<th>Authors</th>
<th>Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ballesta et al.</td>
<td>M</td>
</tr>
<tr>
<td>2</td>
<td>Case 2</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Bass et al.</td>
<td>F</td>
</tr>
<tr>
<td>4</td>
<td>Case 3</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Levy et al.</td>
<td>F</td>
</tr>
<tr>
<td>6</td>
<td>Case 4</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Boffinger and Soukup</td>
<td>F</td>
</tr>
<tr>
<td>8</td>
<td><em>Buhler et al</em></td>
<td>M</td>
</tr>
<tr>
<td>9</td>
<td>Case III.1</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td><em>Same</em></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Case II.3</td>
<td></td>
</tr>
</tbody>
</table>

- Same cases in Sebestyen and Méhes
- Same cases in Freedom and Gerald
- Same case in Buhler
- Same case in Noël
- Same case in Thomas
- Same cases in Emanuel et al.

### TABLE 1b  
Cat eye syndrome: patients with normal karyotype

<table>
<thead>
<tr>
<th>Case No</th>
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</tr>
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<tr>
<td>1</td>
<td>Franklin and Parslow</td>
<td>Case 1</td>
</tr>
<tr>
<td>2</td>
<td>Taft et al.</td>
<td>Case 2</td>
</tr>
<tr>
<td>3</td>
<td>Tailermite et al.</td>
<td>F</td>
</tr>
<tr>
<td>4</td>
<td>Toomey et al.</td>
<td>M</td>
</tr>
<tr>
<td>5</td>
<td>Weber et al.</td>
<td>F</td>
</tr>
<tr>
<td>6</td>
<td>Weleber et al.</td>
<td>F</td>
</tr>
<tr>
<td>7</td>
<td>Zackai et al.</td>
<td>Case 1</td>
</tr>
<tr>
<td>8</td>
<td>Zellweger et al.</td>
<td>Case 2</td>
</tr>
<tr>
<td>9</td>
<td>Zellweger et al.</td>
<td>Case 4</td>
</tr>
<tr>
<td>10</td>
<td>Our case 2</td>
<td>M</td>
</tr>
<tr>
<td>11</td>
<td>Our case 3</td>
<td>M</td>
</tr>
</tbody>
</table>

The patient was attributed to diffuse infection of the urinary tract and to salmonella septicaemia.

The family history was unremarkable, with the exception of a maternal cousin who died a few days after birth of biliary atresia. Both the parents were in good health and the mother had bilateral preauricular pits.

### Genetic studies

Sex chromatin was negative. Cytogenetic studies on peripheral blood showed a modal number of 47 chromosomes with one extra chromosome smaller than a G chromosome. It appeared to have satellites on one end and to participate in satellite association. The identification of this supernumerary chromosome was impossible even using G, Q, and C banding (fig 2). Blood and serum groups were normal. The karyotype of both parents was normal.

### CASE 2

The patient was the first child of healthy unrelated parents. At the birth the father was 28 years old and the mother 21 years old. Delivery was normal; birth weight 3100 g, length 54 cm, head circumference 31.9 cm. During the first weeks the baby suffered from respiratory distress, cyanosis, constant feeding problems, and failure to gain weight. Multiple congenital malformations were noted including sloping forehead, frontal asymmetry, antimongoloid slanting of eyes, bilateral coloboma of iris and choroid (fig 1C), right palpebral ptosis, prominent nose, macrostomia, micrognathia, low set ears, hypertelorism, short neck with low posterior hairline,
TABLE 2 Clinical findings

|                | 1  | 2  | 3  | 4  | 5  | 6  | 7  | 8  | 9  | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 |
|----------------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| Psychosomatic retardation | +  | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ |
| Genital malformations     | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| Urinary tract anomalies   | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| Kidney malformations      | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| Cardiovascular anomalies  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| Foot malformations        | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| Hand malformations        | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| Other skeletal anomalies   | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| Limited hip abduction     | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| Vertebral malformations   | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| Preauricular pits/tags/sinuses | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| Low set malformed ears    | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| Cleft lip or palate       | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| Micrognathia              | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| Microcephaly              | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| Prosis                   | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| Downward slanting eyes    | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| Epicanthus                | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| Strabismus                | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| Hypertelorism             | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| Microphthalmia            | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| Coloboma                  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| Anal atresia or stenosis  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |

FIG 1 Case 1, ear malformations (A), intestinal malrotation (B); case 2, ocular coloboma (C), genital malformations (D).

widely spaced nipples, umbilical hernia, right cryptorchidism, incurved penis (fig 1D), and hypospadias. Anal stenosis was suspected because of persistent constipation and thread-like stools. Renal malformations were suspected because of the persistent high azotaemia.

There was no familial history of congenital malformations.

**Genetic studies**

Buccal smears were negative for sex chromatin. Cytogenetic investigation on peripheral blood showed...
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a modal number of 46 chromosomes. G, C, and Q banding techniques did not reveal any structural anomalies. Normal karyotypes were found in blood cultures of both parents.

CASE 3
This was a newborn male infant born after 42 weeks' gestation by caesarian section. He was the first child of a 26-year-old mother and 35-year-old father. Birthweight was 3250 g, head circumference was 34 cm, and length was 50 cm. He had the following malformations: sloping forehead, hypertelorism, downward slanting eyes, epicanthal folds, bilateral iris coloboma, flattened nose, elongated philtrum, preauricular tags, radial dysplasia, vertebral malformations, ventricular septal defect, single umbilical artery, low set ears, narrow chest, small scrotum, and bilateral cryptorchidism. Anorectal atresia was noted 24 hours after birth and was immediately resolved surgically. Two days after birth the patient...
developed respiratory distress and died on the third day. Unfortunately no pictures were taken.

The family history was unremarkable.

Genetic studies
The sex chromatin was negative. Chromosome analysis performed on peripheral blood cells of the patient and his parents revealed normal karyotypes.

Discussion

Clinical Spectrum
The clinical spectrum of this anomaly is fairly wide as shown by several cases in which the extra chromosome was transmitted directly from a phenotypically normal parent to a son with the cat eye syndrome.\(^1\)\(^2\)\(^3\)\(^7\)\(^8\)\(^9\)\(^10\) The typical malformations include anular atresia, usually associated with a rectoperineal or rectovaginal fistula, ocular coloboma, downward slanting eyes, microphthalmia, hypertelorism, strabismus, epicanthus, preauricular tags, sinuses or fistulas, congenital heart defects, particularly septal defects, urinary tract abnormalities, skeletal anomalies, and, frequently, mental and physical retardation.

Diagnostic Criteria
Initially, the combination of coloboma and anal atresia was the essential requisite for the diagnosis of CES. Subsequently the criteria became less restrictive, and thereafter several cases of the incomplete syndrome were reported.

According to Hsu and Hirshhorn\(^6\) the diagnosis of cat eye syndrome (CES) should be made according to the following minimal clinical criteria:

1. a combination of the two major features, namely coloboma and anal atresia, with or without other associated abnormalities;
2. a combination of one major feature, coloboma or anal atresia, plus at least one of the most frequent associated specific anomalies, for example, preauricular skin tags or sinuses or renal anomalies;
3. a combination of one major feature plus two less frequent features, such as antimongoloid slanting eyes, skeletal anomalies, congenital heart disease, and other eye defects;
4. a combination of five or more minor specific features.

In the light of criteria 2 and 3 we have included in tables 1 and 2 several cases of full trisomy 22 described as trisomy 22 syndrome.\(^10\)\(^15\)\(^16\)\(^37\)\(^38\)\(^44\)\(^48\) However, based on criterion 4, all the cases of trisomy 22 syndrome could be included.

Cytogenetics of Cases with Abnormal Karyotype
Of 57 subjects with clinical features of CES, 46 had a karyotype with an extra marker chromosome of variable morphology and of variable length, that is, similar to or shorter than a 22.

As previously mentioned, the simplest explanation for the origin of the abnormal chromosome is that of a partial deletion of chromosome 22, but the involvement of this chromosome has never been well documented.

Observations Which Question the Existence of Trisomy 22 in Living Subjects
The following observations question the existence of trisomy 22.

1. Living subjects with 22 trisomy arising from an inherited Robertsonian translocation have never been reported.
2. The carriers of a Robertsonian translocation involving a chromosome 22, which is an extremely rare event,\(^6\)\(^7\)\(^8\) frequently have recurrent abortions.
3. A syndrome dependent on trisomy of the distal region of the long arm of chromosome 11\(^7\)\(^8\)\(^9\) is characterised by the same features as trisomy 22, namely craniofacial dysmorphia, broad nose, long philtrum, micrognathia, malformed low set ears with preauricular pits or tags, cleft palate, cardiac malformations, etc.

Observations Which Question the Existence of Partial Trisomy 22
Doubts about the existence of partial trisomy 22 are underlined by the following considerations.

1. If the extra chromosome gives rise to partial trisomy for a chromosome 22, the affected persons would be expected to have some clinical features similar to the recognised full trisomy syndrome carriers, who obviously should present more marked consequences of the genome alterations. Instead one finds a more severe phenotypic picture in the cat eye syndrome than in the trisomy 22 syndrome.
2. If the CES is the phenotypic expression of partial 22 trisomy, the affected patients should have a shorter chromosome 22 than normal. Instead, there are subjects with an extra chromosome of the same length as a 22 who exhibit the cat eye syndrome\(^10\)\(^15\)\(^36\)\(^39\)\(^43\)\(^45\) and subjects with supernumerary deleted chromosome who have the trisomy 22 syndrome.\(^8\)\(^8\)
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TABLE 3  Comparison of some features in full 13 trisomy*, in partial 13 trisomies†, and in cat eye syndrome

<table>
<thead>
<tr>
<th></th>
<th>Complete 13 trisomy</th>
<th>Distal trisomy</th>
<th>Proximal trisomy</th>
<th>CES with marker</th>
<th>CES without marker</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Mental retardation</td>
<td>26/26 (100)</td>
<td>30/30 (100)</td>
<td>7/9 (78)</td>
<td>29/36 (80)</td>
<td>6/11 (55)</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>16/25 (64)</td>
<td>13/30 (43)</td>
<td>3/7 (43)</td>
<td>18/39 (46)</td>
<td>4/11 (36)</td>
</tr>
<tr>
<td>Low set malformed ears</td>
<td>20/25 (80)</td>
<td>22/28 (79)</td>
<td>3/7 (43)</td>
<td>43/46 (93)</td>
<td>9/11 (82)</td>
</tr>
<tr>
<td>Cleft lip or palate</td>
<td>30/40 (75)</td>
<td>7/30 (23)</td>
<td>2/9 (22)</td>
<td>12/46 (26)</td>
<td>3/11 (27)</td>
</tr>
<tr>
<td>Hypertelorism</td>
<td>24/26 (92)</td>
<td>7/30 (23)</td>
<td>3/6 (50)</td>
<td>23/45 (51)</td>
<td>4/11 (36)</td>
</tr>
<tr>
<td>Epicanthus</td>
<td>14/25 (56)</td>
<td>8/30 (27)</td>
<td>2/6 (33)</td>
<td>12/45 (27)</td>
<td>4/11 (36)</td>
</tr>
<tr>
<td>Coloboma</td>
<td>17/37 (46)</td>
<td>3/30 (10)</td>
<td>1/9 (11)</td>
<td>26/46 (57)</td>
<td>11/11 (100)</td>
</tr>
<tr>
<td>Microphthalmia</td>
<td>19/25 (76)</td>
<td>6/30 (20)</td>
<td>1/9 (11)</td>
<td>8/45 (20)</td>
<td>3/11 (27)</td>
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<tr>
<td>Cardiovascular anomalies</td>
<td>19/26 (73)</td>
<td>5/27 (19)</td>
<td>2/8 (25)</td>
<td>25/46 (54)</td>
<td>6/11 (55)</td>
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<tr>
<td>Genital malformations</td>
<td>21/32 (66)</td>
<td>8/27 (30)</td>
<td>2/9 (22)</td>
<td>7/44 (16)</td>
<td>3/11 (27)</td>
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<tr>
<td>Kidney malformations</td>
<td>13/32 (41)</td>
<td>9/27 (33)</td>
<td>0/6 (0)</td>
<td>9/46 (20)</td>
<td>2/11 (18)</td>
</tr>
<tr>
<td>Inguinal/umbilical hernia</td>
<td>10/25 (40)</td>
<td>9/27 (33)</td>
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<td>2/46 (4)</td>
<td>1/11 (9)</td>
</tr>
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<td>15/21 (71)</td>
<td>18/30 (60)</td>
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<td>0/46 (0)</td>
<td>0/11 (0)</td>
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<td>Polydaactyly</td>
<td>19/25 (76)</td>
<td>19/30 (63)</td>
<td>0/9 (0)</td>
<td>0/46 (0)</td>
<td>0/11 (0)</td>
</tr>
<tr>
<td>Simian crease</td>
<td>16/25 (64)</td>
<td>11/19 (58)</td>
<td>2/9 (22)</td>
<td>4/21 (19)</td>
<td>3/7 (43)</td>
</tr>
<tr>
<td>Distal r triradius</td>
<td>14/20 (70)</td>
<td>4/12 (33)</td>
<td>4/8 (50)</td>
<td>5/21 (24)</td>
<td>0/7 (0)</td>
</tr>
<tr>
<td>Anal atresia or stenosis</td>
<td>0/37 (0)</td>
<td>1/30 (3)</td>
<td>0/9 (0)</td>
<td>33/46 (72)</td>
<td>6/11 (55)</td>
</tr>
<tr>
<td>Sex (F : M)</td>
<td>35 : 29</td>
<td>18 : 12</td>
<td>4 : 4</td>
<td>31 : 15</td>
<td>5 : 2</td>
</tr>
<tr>
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<td>31-6</td>
<td>26-2</td>
<td>26-5</td>
<td>30-3</td>
<td>27-0</td>
</tr>
<tr>
<td>Paternal age</td>
<td>31-9</td>
<td>30-3</td>
<td>29-6</td>
<td>32-9</td>
<td>31-5</td>
</tr>
<tr>
<td>Gestational age</td>
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<td>39-7</td>
<td>39-8</td>
<td>40-0</td>
<td>41-0</td>
</tr>
<tr>
<td>Birthweight (g)</td>
<td>2610</td>
<td>3263</td>
<td>2926</td>
<td>2917</td>
<td>2691</td>
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</table>

*Data from Warkany et al.52 and Taylor,66 †Data from Niebuhr,87

COMPARISON BETWEEN THE CAT EYE SYNDROME AND THE SYNDROMES ASSOCIATED WITH TRISOMY OF CHROMOSOME 13

On the basis of the clinical features, several authors52 26 29-32 have already suggested that the extra chromosome present in the CES may be a deleted 13; in fact, many clinical and pathological features usually associated with trisomy 13 are present in the cat eye syndrome (table 3).

Besides this, in some cases of CES52 the extra chromosome shows a bright centromere, a cytogenetic feature typical of chromosome 13.

We analysed all the malformation syndromes depending on numerical and structural aberrations of chromosome 13 and, according to criteria 2 and 3 of Hsu and Hirschhorn,65 we found striking similarities between the cat eye syndrome and the clinical pictures associated with some 13 ring chromosomes 56-64 and some partial 13 trisomies50-55 occurring in unbalanced translocations (table 1c, d, 2c, d).

Obviously the 13 rings and the partial 13 trisomies show the same clinical picture as the cat eye syndrome whenever they give rise to a duplication of the same regions present on the supernumerary chromosome in this syndrome. In deriving such a small extra chromosome from a 13, different portions of 13 may be involved in the constitution of the marker. This may account for the variability of the syndrome and make the identification of the marker impossible by banding (fig 3). Furthermore, since the marker chromosome could derive from a translocation between the long arm of a 13 and the short arm of another D or G chromosome, for example the 22, the presence of only some characteristics (fluorescent satellites, centromere, etc) of chromosome 22 cannot constitute sufficient criteria for the correct identification of the marker (fig 3c-e).

MAP OF CHROMOSOME 13

The clinical findings characteristic of partial trisomy of proximal and distal regions of chromosome 13 (table 3) have been delineated by Niebuhr.87 Recently attempts to map chromosome 13 on the basis of clinical features have been carried out.88 89

Obviously a perfect phenotype-karyotype correlation cannot be achieved, since the genetic material contained in a chromosomal band corresponds to several hundred genes. Furthermore the attempt to map a chromosome meets with several difficulties as stressed by Schutten et al.88 Nevertheless, we should attempt to localise the regions responsible for the cardinal signs of the CES and, at the same time, compare some of the clinical features of the partial trisomies with the clinical picture of the CES (fig 4).

For this comparison we must keep in mind that the proposed model (fig 3a, b) of chromosomal rearrangement which most frequently gives rise to the marker chromosome is an interstitial deletion involving the central region of the 13 long arm (bands q2→q33).
Ginevra Guanti

FIG 3  Schematic representation of possible rearrangements of chromosome 13. (a, b) Interstitial deletion which in b gives rise to a chromosome showing the same banding pattern as a 22. (c, d) 13/22 translocation giving rise to a marker chromosome with characteristics (centromere and/or satellites) of a 22. (e) Partial karyotype illustrating how a rearranged 13 chromosome resembles a 22 (G banding).

COMPARISON BETWEEN CES AND TRISOMIES OF PROXIMAL REGION OF LONG ARM OF CHROMOSOME 13
Psychosomatic retardation, microcephaly, low set ears, micrognathia, clinodactyly, microstomia, epicanthus, cleft palate, abnormal dermatoglyphs, increased r triradius, which are frequently described in trisomies of the proximal q region, are present in the CES too. The ocular coloboma frequent in the CES has been found once in trisomies of the proximal q region.63

The lack of coloboma in the other eight cases88 90–96 may be for the following reasons: (1) the trisomic region does not include the coloboma locus which, according to our map (fig 4), may be in the q13 region; (2) the trisomic region partially comprises the q13 region, excluding the coloboma locus; and (3) the locus is included in the trisomic region, but is silent. The latter could be accepted, if we consider that the coloboma is present in only about 50% of cases of complete trisomy 13.

The trisomy of the region slightly distal (q14) would determine cardiac, renal, and genital malformations, anomalies rare in trisomies of the proximal q region and more frequent in the CES.

COMPARISON BETWEEN CES AND TRISOMIES OF DISTAL REGION OF LONG ARM OF CHROMOSOME 13
A comparison between partial trisomy of the distal q region90 91 94 95 96 99 112 and CES is more difficult, since most of the cases of the former include the
central region of the long arm (q2→q33) which is never present in the small marker in the CES.

This may account for the fact that polydactyly, syndactyly, and other hand and foot deformities, hernia, haemangioma, long incurved eyelashes, and bushy eyebrows, which are frequently observed in these partial trisomies, are almost always absent in the CES. Occular coloboma is mentioned by Crandall et al.\(^4\) (trisomy q12→qter), Wilson and Melnyk,\(^5\) and, unexpectedly, (trisomy q21→qter) by Stoll et al.\(^6\) Its absence in other cases\(^7\) may be attributed to the reasons mentioned above.

**Anal atresia in CES and in 13 rings and deletions**

The anal atresia frequently present in CES, but never described in complete or partial trisomies of chromosome 13, except the case reported by Giraud et al.\(^8\) has been observed in seven\(^9\) of 50 cases of 13 rings and in three\(^10\) of 21 cases, 70% of identified as chromosome 13,\(^11\) of 13q interstitial or terminal deletions.

As stressed by McClintock,\(^12\) terminal deletions are very rare events, since their formation, requiring the loss of the telomere, determines an unstable condition which can bring about elimination or further chromosomal change resulting from the fusion of chromatid ends.\(^13\) Therefore the idea that the anal atresia depends on a simple deficiency of the q terminal ends can be excluded.

The presence of the same anomaly in monosomic (rings and deletions) and trisomic (CES) conditions could be explained by postulating the presence of a (regulatory?) site on the distal region q33 or q34 which whenever involved in breakage may produce such a dominant mutation.

**CES with normal karyotype**

A normal karyotype was found in 11\(^1\) of 57 subjects with the CES (table 1b, 2b). These cases suggest that there may be a non-chromosomal basis for the syndrome, even in so called familial cases where the various features may be transmitted in an autosomal fashion.

If we admit the existence of a non-chromosomal basis, we can consider the association of CES with the extra chromosome to be fortuitous whenever an affected patient inherits the abnormal chromosome from a normal carrier parent.\(^14\) This hypothesis is not very convincing because, if in the latter cases the normal phenotype depends on a condition of mosaicism, the mosaicism also found in patients with CES remains unexplained.\(^15\)

Another possible explanation for the apparently normal karyotype may be the existence of a chromosomal aberration beyond the limits of our present techniques.

However, the possibility which must also be considered is that we are dealing with two different disorders resembling each other clinically.

**CES and VATER association**

A similar combination of defects occurring in CES is present in VATER association (a non-random combination of congenital malformations consisting of vertebral defects, anal atresia, cardiac malformations, tracheo-oesophageal fistula, oesophageal atresia, radial and renal dysplasia\(^16\) in such a way that some overlapping of the two forms exists (our case 3).\(^1\)

Most of the reported cases with the VATER association are sporadic. However, gene mutations could conceivably cause all these associated malformations. Several examples of dominant inheritance of some VATER traits are reported.\(^17\) It is of interest to
note that in the history of several carriers of CES (our case)\textsuperscript{4} \textsuperscript{21} \textsuperscript{29} \textsuperscript{31} \textsuperscript{47} there is familial occurrence of typical malformations.

From these observations two questions arise. Is there a correlation between CES and the familial occurrence of any particular malformations? Does there exist a relation between CES and VATER association?

In conclusion, from the cytogenetic point of view, we would like to postulate that the extra chromosome present in CES is essentially constituted of genetic material belonging to chromosome 13.

Since banding techniques proved to be inefficient in identifying the abnormal chromosome, another useful investigation would be to search for a gene dosage effect or an abnormal inheritance pattern in some gene markers for the genes mapped on these chromosomes. From the clinical point of view it is necessary to explain whether the incomplete forms reflect a reduced expressivity or the existence of one or more different entities.

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