Letter to the Editor

Seven New Cases of Cayler Cardiofacial Syndrome With Chromosome 22q11.2 Deletion, Including a Familial Case

To the Editor:

Cayler cardiofacial syndrome comprises congenital unilateral hypoplasia of the depressor anguli oris muscle (HDAOM) and congenital heart defects [Cayler, 1969]. Hypoplasia of this muscle leads to failure of one corner of the mouth to move downward and outward while crying or grimacing and hence, is described as “asymmetric crying face.” Asymmetric facial expression is most noticeable in young babies and with age it becomes less distinct. The cause of Cayler syndrome is heterogeneous: It may be an autosomal dominant trait, occurring sporadically, or it can be seen in chromosome 22q11.2 deletions. Our clinical geneticist (E.V.B.) diagnosed 24 patients with 22q11.2 deletions in the last 2.5 years and found seven of them to have Cayler syndrome (29%). Their clinical findings are summarized in Table I. Six of the seven patients are shown in Figure 1. There was no correlation between the type of heart defect and the side of the HDAOM. All except one (who is too young to evaluate) had either a cleft palate or velopharyngeal incompetence, and six had a conotruncal cardiac malformation. The mother (Case 4) of Case 3 has normal cardiac structure on echocardiogram. Cases 3, 4, and 5 were erroneously suspected to have traumatic facial nerve paralysis neonatally. The HDAOM in Case 7 was barely noticeable at age 12 years but he had been evaluated at 18 months of age when the diagnosis of Cayler syndrome was made.

Fluorescent in situ hybridization (FISH) studies were performed to determine the size and extent of the deletion in the affected mother (Case 4) and one of her sons (Case 3). Both individuals have an approximately 1.5-Mb deletion within the DiGeorge syndrome region and share similar proximal and distal deletion boundaries. The size of the deletion does not appear to differ from the common deletion seen in most patients with the 22q11.2 deletion syndrome.

Giannotti et al. first reported Cayler syndrome in 5 of their 15 patients (33%) with chromosome 22q11.2 deletions [Giannotti et al., 1994]. However, in a large series of 558 patients with an interstitial deletion of chromosome 22q11.2 from 23 European centers, only 11 patients (2%) with unilateral HDAOM were reported [Ryan et al., 1997]. The frequency of Cayler cardiofacial syndrome (29%) among our patients with 22q11.2 deletion is comparable to that reported by Giannotti et al. (33%). Our Case 4 and the two patients reported by Stewart and Clayton Smith [1997] have HDAOM without a congenital heart defect. Cases of asymmetric crying face resulting from unilateral HDAOM with or without other defects showing autosomal dominant inheritance have been reported [Papadatos et al., 1974; Miller and Hall, 1979; Singhi et al., 1980; Silengo et al., 1986]. However, these reports predate the application of FISH to detect microdeletions of chromosomes. Therefore, the prevalence of 22q11.2 deletions in Cayler syndrome or in patients with only HDAOM is unknown. We think that this is the first report of autosomal dominant transmission of unilateral HDAOM due to 22q11.2 deletion. The face of the crying baby or child usually shows the asymmetric facies. However, HDAOM may not be noticeable in adults. Diagnoses in our Cases 4 and 7 were made based on their photographs taken during infancy. Therefore we recommend that infant photographs be examined. Our observations provide additional evidence that unilateral HDAOM is part of the spectrum of syndromes associated with 22q11.2 deletion, namely the velocardiofacial syndrome and DiGeorge syndrome. We recommend investigations for 22q11.2 deletion in all cases of unilateral HDAOM.

ACKNOWLEDGMENTS

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## TABLE I. Summary of Cases With Asymmetric Crying Face and del(22)(q11.2) Detected by FISH

<table>
<thead>
<tr>
<th>Age</th>
<th>Case 1 9 years</th>
<th>Case 2 4 weeks</th>
<th>Case 3 3 years</th>
<th>Case 4 24 years</th>
<th>Case 5* 3 years</th>
<th>Case 6 2 weeks</th>
<th>Case 7 12 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history</td>
<td>Adopted; biologic mother with history of palate surgery and heart murmur with holes, no heart surgery; twin sister normal</td>
<td>Normal older sister healthy parents parents not tested with FISH</td>
<td>Younger brother has 22q11.2 deletion</td>
<td>She is the mother of Case 3. Parents: FISH normal</td>
<td>Healthy parents, not tested with FISH</td>
<td>Normal parents, not tested with FISH</td>
<td>Parents: FISH normal</td>
</tr>
<tr>
<td>Height, weight, head circumference</td>
<td>All around 25th centile</td>
<td>Less than 5th centile</td>
<td>Normal</td>
<td>Weight: 10th centile Height: ~3 SD Head: ~4 SD</td>
<td>Prominent nose, left preauricular pit Small palpebral fissures</td>
<td>10–15th centile</td>
<td>25–50th centile</td>
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<tr>
<td>Facial features</td>
<td>Broad nasal root</td>
<td>No dysmorphism</td>
<td>Broad nasal bridge; upward slanting eyes Strabismus, prominent nasal bridge</td>
<td>Strabismus, prominent nasal bridge</td>
<td>Prominent nose, left preauricular pit</td>
<td>Small palpebral fissures</td>
<td></td>
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<tr>
<td>Palate Cleft/API</td>
<td>Immobile soft palate</td>
<td>Cleft of soft palate</td>
<td>Submucous cleft palate</td>
<td>Submucous cleft palate VPI</td>
<td>Cleft palate</td>
<td>Too young to know about VPI</td>
<td>Cleft of soft palate</td>
</tr>
<tr>
<td>DAOM hypoplasia/Heart</td>
<td>Right sided</td>
<td>Left sided</td>
<td>Tetralogy of Fallot, had surgery</td>
<td>Left sided</td>
<td>Right sided</td>
<td>Right sided</td>
<td>Left sided Tetralogy of Fallot Type II</td>
</tr>
<tr>
<td>Fingers</td>
<td>Long and thin</td>
<td>Normal</td>
<td>Long and thin</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
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<td>Genitalia</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
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<td>IQ</td>
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<td>Normal</td>
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<tr>
<td>Hearing</td>
<td>Normal</td>
<td>Died young</td>
<td>Left pulmonary artery stenosis</td>
<td>Right sided</td>
<td>Vascular ring; right aortic arch</td>
<td>Too young</td>
<td>Learning disability</td>
</tr>
<tr>
<td>Immunoglobulins CBC</td>
<td>Normal</td>
<td>Died young</td>
<td>Left pulmonary artery stenosis</td>
<td>Right sided</td>
<td>Right sided</td>
<td>Right sided</td>
<td>Right sided</td>
</tr>
<tr>
<td>Karyotype</td>
<td>46,XY</td>
<td>46,XX</td>
<td>46,XX, del(22)(q11.2)</td>
<td>46,XX, del(22)(q11.2)</td>
<td>46,XY, del(22)(q11.2)</td>
<td>46,XY, del(22)(q11.2)</td>
<td>46,XY, del(22)(q11.2)</td>
</tr>
<tr>
<td>Calcium/parathyroid</td>
<td>Normal</td>
<td>Absent parathyroid at autopsy</td>
<td>Normal</td>
<td>Low in neonatal period</td>
<td>Has hypoparathyroidism</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

*aVPI, velopalatal insufficiency.
*bDAOM: Depressor Anguli Oris Muscle.
*cVSD, ventricular septal defect.
*dAll showed deletion (22q11.2)(D22S75−) by FISH.
*eHas an intracranial Rathke’s pouch cyst.
Fig. 1. A: Case 2, left HDAOM, cleft of soft palate. B: Case 3, right HDAOM. C: Case 4, mother of Case 3, strabismus, right HDAOM. D: Case 4, at a younger age, right HDAOM, more noticeable.
Fig. 1. **Continued:** E: Case 5, left HDAOM, not noticeable at rest. F: Case 5, asymmetric crying face. G: Case 6, right HDAOM, not noticeable at rest. H: Case 6, asymmetric crying face. Panels I–K on overleaf.
REFERENCES


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