

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.

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

Age	Case 1 9 years	Case 2 4 weeks	Case 3 3 years	Case 4 24 years	Case 5 ^e 3 years	Case 6 2 weeks	Case 7 12 years
Family history	Adopted; biologic mother with history of palate surgery and heart murmur with holes, no heart surgery; twin sister normal	Normal older sister healthy parents with FISH	Younger brother has 22q11.2 deletion	She is the mother of Case 3. Parents: FISH normal.	Healthy parents, not tested with FISH	Normal parents, not tested with FISH	Parents: FISH normal
Height, weight, head circumference	All around 25th centile	25–50th centile	Less than 5th centile	Normal	Weight: 10th centile Height: <-3 SD Head: -4 SD	10–15th centile	25–50th centile
Facial features	Broad nasal root	No dysmorphism	Broad nasal bridge; upward slanting eyes	Strabismus, prominent nasal bridge	Broad nasal bridge; small palpebral fissures	Prominent nose, left preauricular pit	Small palpebral fissures
Palate Cleft/VPI ^a	Immobile soft palate	Cleft of soft palate	Submucous cleft palate	VPI	Cleft palate	Too young to know about VPI	Cleft of soft palate
DAOM hypoplasia ^b	Right sided	Left sided	Right sided	Right sided	Left sided	Right sided	Left sided
Heart	Tetralogy of Fallot, had surgery	VSD, ^c death at 4 months, hypertrophic cardiomyopathy	Left pulmonary artery stenosis	None; functional murmur	Vascular ring; right aortic arch	Right aortic arch, truncus, arteriosus type II	Tetralogy of Fallot
Fingers	Long and thin	Normal	Long and thin	Long and thin	Normal	Normal	Long and thin
Genitalia	1 Testis absent	Normal	Normal	Normal	Normal	Normal	Normal
IQ	Mild developmental delay	Died young	Slow, particularly language	Borderline mental retardation	Mild delay	Too young	Learning disability
Hearing	Mild conductive loss	Died young	Normal	Mild loss	Mild loss	Normal	Normal
Immunoglobulins CBC	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Karyotype ^d	46,XY	46,XY of blood and amniocytes	46,XY	46,XX	46,XX,del(22)(q11.2)	46,XX,del(22)(q11.2)	46,XY,del(22)(q11.2)
Calcium/parathyroid	Normal	Absent parathyroid at autopsy	Normal	Normal	Low in neonatal period	Has hypoparathyroidism	Normal

^aVPI, velopalatal insufficiency.

^bDAOM: Depressor Anguli Oris Muscle.

^cVSD, ventricular septal defect.

^dAll showed deletion (22)(q11.2)(D22S75-) by FISH.

^eHas an intracranial Rathke's pouch cyst.

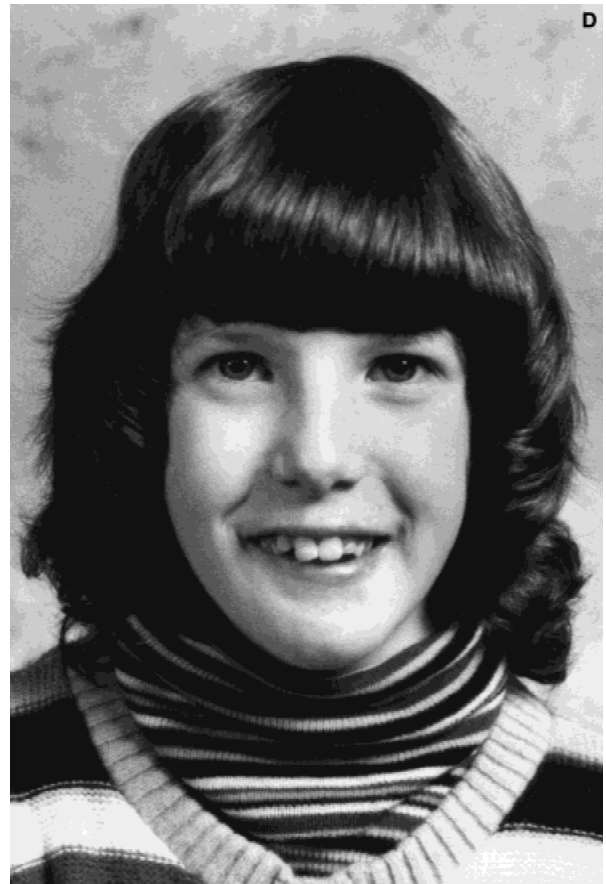
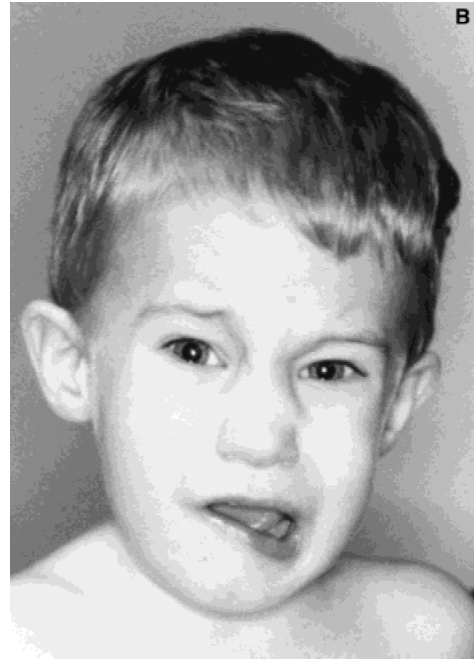


Fig. 1. **A:** Case 2, left HDAOM, cleft of soft palate. **B:** Case 3, right HDAOM. **C:** Case 4, mother of Case 3, strabismus, right HDAOM. **D:** Case 4, at a younger age, right HDAOM, more noticeable.

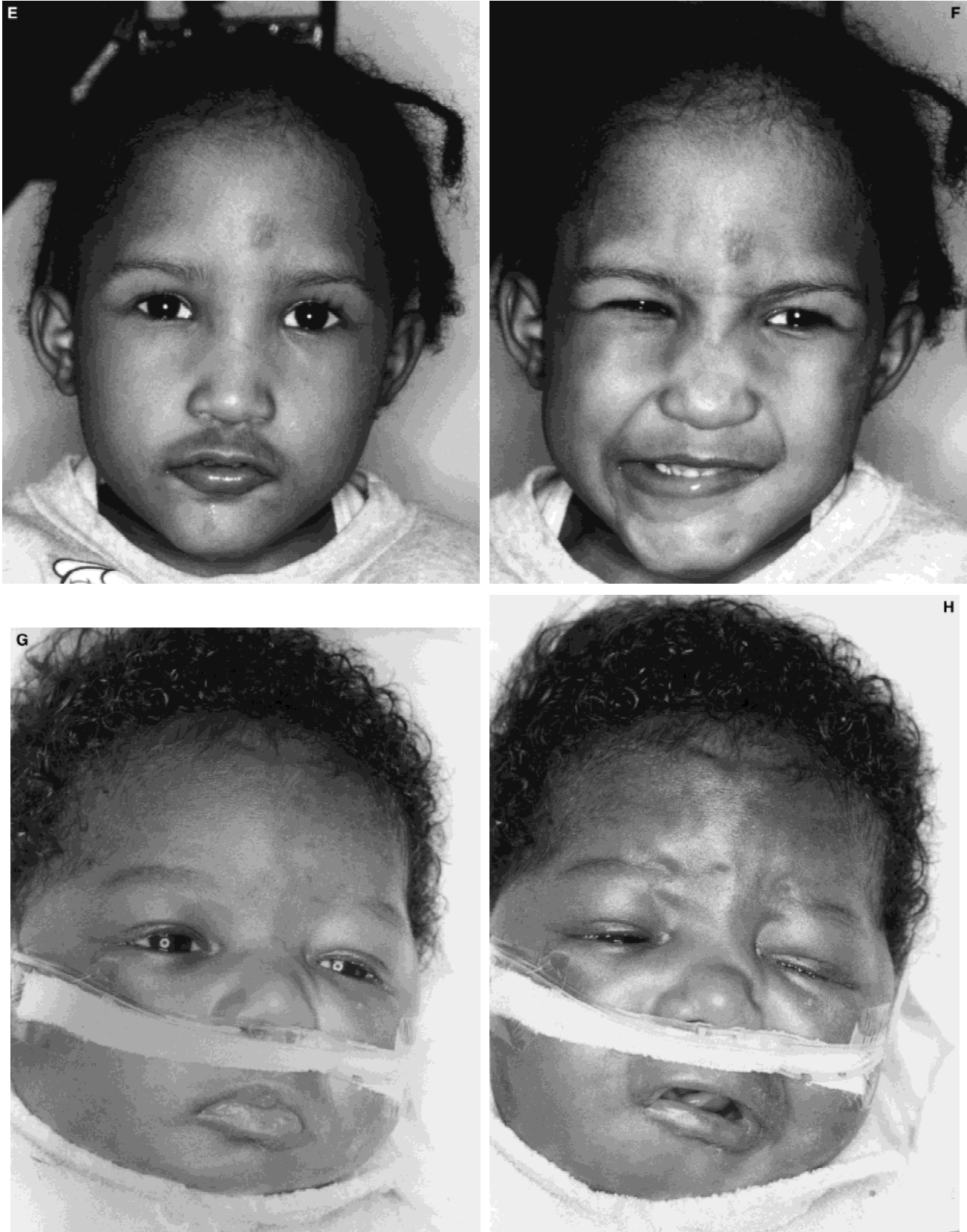


Fig. 1. *Continued*: **E**: Case 5, left HDAOM, not noticeable at rest. **F**: Case 5, asymmetric crying face. **G**: Case 6, right HDAOM, not noticeable at rest. **H**: Case 6, asymmetric crying face. Panels I-K on overleaf.

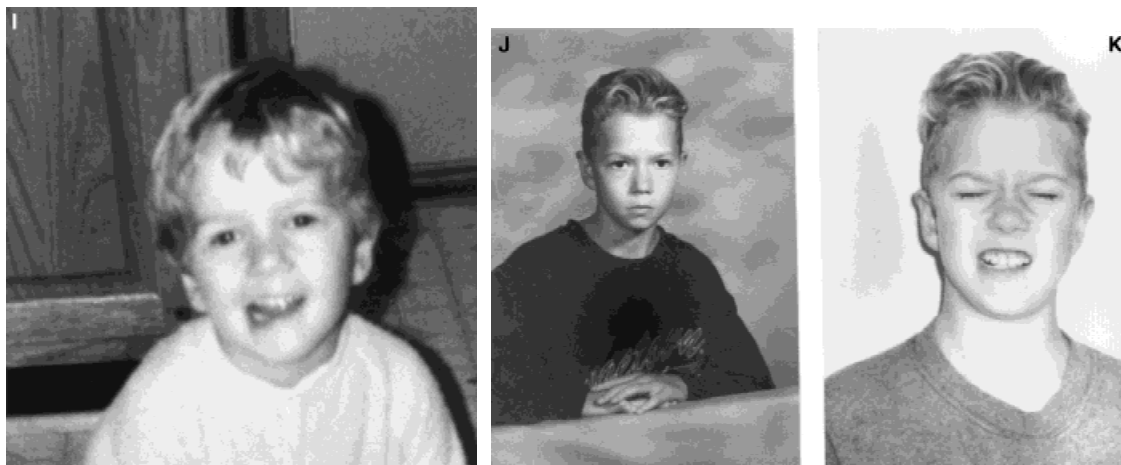


Fig. 1. Continued: **I:** Case 7, left HDAOM at age 2. **J,K:** Case 7, at age 12, asymmetric crying face barely noticeable.

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