Novel autosomal dominant mandibulofacial dysostosis with ptosis: clinical description and exclusion of TCOF1

P Hedera, H V Toriello, E M Petty

**Background:** Treacher Collins syndrome (TCS), the most common type of mandibulofacial dysostosis (MFD), is genetically homogeneous. Other types of MFD are less common and, of these, only the Bauru type of MFD has an autosomal dominant (AD) mode of inheritance established. Here we report clinical features of a kindred with a unique AD MFD with the exclusion of linkage to the TCS locus (TCOF1) on chromosome 5q31-q32.

**Methods:** Six affected family members underwent a complete medical genetics physical examination and two affected subjects had skeletal survey. All available medical records were reviewed. Linkage analysis using the markers spanning the TCOF1 locus was performed. One typically affected family member had a high resolution karyotype.

**Results:** Affected subjects had significant craniofacial abnormalities without any significant acral changes and thus had a phenotype consistent with a MFD variant. Distinctive features included hypoplasia of the zygomatic complex, micrognathia with malocclusion, auricular abnormalities with conductive hearing loss, and ptosis. Significantly negative two point lod scores were obtained for markers spanning the TCOF1 locus, excluding the possibility that the disease in our kindred is allelic with TCS. High resolution karyotype was normal.

**Conclusions:** We report a kindred with a novel type of MFD that is not linked to the TCOF1 locus and is also clinically distinct from other types of AD MFD. Identification of additional families will facilitate identification of the gene causing this type of AD MFD and further characterisation of the clinical phenotype.
in males and females and they are affected with similar frequency. Two instances of male to male transmission (IV.6 to V.3 and V.4) exclude X linked inheritance. Review of an old family photograph (not shown) of II.9 together with his seven sibs and parents showed severe, bilateral ptosis and a small jaw at approximately 30 years of age. The appearance of other family members was unremarkable. He was the youngest of nine children and paternal and maternal ages are unknown. Even though non-paternity cannot be excluded, this is suggestive of a new mutation event in this subject.

Phenotype analysis
Table 1 summarises the phenotypic features of six examined subjects. Every affected subject had downward slanting palpebral fissures and bilateral congenital ptosis. Surgical correction was indicated in V.1 and IV.5; their phase could not be determined because DNA from subjects III.1 and III.2 was not available. Affected offspring V.1, V.2, V.3, and V.4 inherited all three chromosomes from their affected fathers, excluding linkage to chromosome 5q31-32.

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>IV.1</th>
<th>IV.5</th>
<th>V.1</th>
<th>V.3</th>
<th>V.4</th>
<th>V.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ptosis</td>
<td>+</td>
<td>Bilateral, mild</td>
<td>+</td>
<td>Bilateral, severe (surgery)</td>
<td>+</td>
<td>Bilateral, severe (surgery)</td>
</tr>
<tr>
<td>Downward slanting palpebral fissures</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Malar hypoplasia</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Micrognathia</td>
<td>Severe, required tracheostomy</td>
<td>Mild, no surgery</td>
<td>Mild, no surgery</td>
<td>Moderate, required surgery</td>
<td>Moderate, required surgery</td>
<td>Moderate, required surgery</td>
</tr>
<tr>
<td>Malocclusion</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Malformation of auricle</td>
<td>Right rudimentary tag and EAC atresia</td>
<td>Left ear normal with EAC stenosis</td>
<td>Left ear normal with EAC stenosis</td>
<td>Right rudimentary tag and EAC atresia</td>
<td>Left ear normal with EAC stenosis</td>
<td>Both ears unremarkable, Bilateral stenosis of EAC</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>+</td>
<td>Bilateral conductive hearing loss</td>
<td>Left ear conductive hearing loss</td>
<td>Left ear normal hearing</td>
<td>Right ear conductive hearing loss</td>
<td>Bilateral conductive hearing loss</td>
</tr>
</tbody>
</table>

EAC=external auditory canal.
cupped ear. All four subjects with unilateral anotia had signs of contralateral EAC stenosis and conductive hearing loss. The other two subjects (V.4 and V.5) had unremarkable auricles; however, symmetrical bilateral EAC stenosis and conductive hearing loss were also present in both subjects without anotia. Small, cupped ears without unilateral anotia and severe hearing loss were reported for II.9 and III.2.

None of the affected subjects had microphthalmia, epibulbar lipodermoid, upper or lower lid colobomas, partial absence of the lower eyelashes, propagation of hair onto the cheeks, or macrostomia. We did not observe unilateral hypoplasia of the facial muscles in affected subjects with facial asymmetry.

Clinical examination of the skeletal system did not show any abnormalities in IV.1, IV.5, or V.1. No vertebral anomalies were present on x-rays obtained in two affected subjects, V.3 and V.4, and the rest of their skeletal surveys were also normal. V.5 had nail hypoplasia on both fifth toes and mild scoliosis, to the left, of the thoracic spine. Both of her brothers, V.3 and V.4, had mild camptodactyly of the fourth and fifth fingers on both hands and increased laxity of the distal interphalangeal joints of all fingers. All three also had mild soft tissue syndactyly of the fingers and a sandal gap between toes 1 and 2. There was hallux valgus of the big toe in all three and V.3 and V.4 also had a short distal phalanx of the big toe. V.3 also had mild pectus carinatum.

A review of the past medical history of affected family members did not show any associated medical problems that were present in every affected subject. All affected family members had normal psychomotor development and normal intelligence with the exception of subject V.4 who had delayed speech acquisition and started to talk at the age of 7 years. However, at the same age he was diagnosed with severe hearing loss that had not been suspected previously. He was also diagnosed with learning disabilities but graduated from high school.

Figure 2  (A) Subject V.5 with prominent, bilateral ptosis and downward slanting palpebral fissures. (B) Subject V.4 with bilateral ptosis, malar hypoplasia, and malocclusion. (C) Subject V.3 with mild facial asymmetry on the left and malocclusion. (D) Subject V.3 with unilateral anotia with a rudimentary ear and micrognathia. Note the absence of the lateral propagation of hair onto the cheeks.
analysed markers spanning the loci linked to the genes associated with colobomas, and asymmetrical facial and auricular abnormalities. None of these patients had severe ptosis as was seen in the acrofacial dysostoses.

**DISCUSSION**

We report one kindred with six affected subjects who had bilateral ptosis, downward slanting palpebral fissures, various degrees of malar hypoplasia and micrognathia, conductive hearing loss, and unilateral anotia in four affected subjects. Three affected subjects had minimal limb abnormalities (nail hypoplasia on both fifth toes and mild camptodactyly of the fourth and fifth fingers bilaterally); however, these skeletal anomalies are trivial when compared with the clinical spectrum seen in the acrofacial dysostoses. Moreover, three other examined affected subjects did not have signs of any limb abnormalities and we propose that the phenotype of this family is consistent with MFD.

Facial asymmetry with hemifacial microsomia and asymmetrical hypoplasia of the mandible and external ear, together with epibulbar dermoid, colobomas of the upper lid, and vertebral anomalies are cardinal features of oculoauriculo-vertebral dysplasia (Goldenhar syndrome, OMIM 164210). The majority of cases are sporadic but several examples of vertical transmission support an AD mode of inheritance.

Even though some degree of asymmetrical involvement was a constant feature in affected patients from the present pedigree, we did not detect any asymmetry of the mouth or epibulbar dermoids. Moreover, two subjects had a radiographical examination of the spine and no hemivertebral, vertebral hypoplasia, or block vertebral anomalies were present, thus excluding the diagnosis of oculoauriculo-vertebral dysplasia.

The mode of inheritance in this pedigree is consistent with an AD mode of inheritance. The most common type of AD MFD is TCS. Even though bilateral ptosis, absence of lower lid colobomas, and asymmetrical facial and auricular abnormalities did not suggest the diagnosis of TCS, we genotyped markers linked to the TCOF1 locus to exclude conclusively the possibility of an atypical manifestation of a variant form of TCS in the family. We obtained significantly negative two point lod scores (<−2), thus excluding linkage to chromosome 5q31-q34 (fig 1).

**REFERENCES**

8 Ballestazzi P, Baetenman MA, Mattei MG, Mattei JF. Franceschetti syndrome in a child with a de novo balanced translocation (5;13)(q13;p11) and significant decrease of hexosaminidase B. Hum Genet 1985;64:305-8.
If you have a burning desire to respond to a paper published in Journal of Medical Genetics, why not make use of our “rapid response” option? Log on to our website (www.jmedgenet.com), find the paper that interests you, and send your response via email by clicking on the “eLetters” option in the box at the top right hand corner. Providing it isn’t libellous or obscene, it will be posted within seven days. You can retrieve it by clicking on “read eLetters” on our homepage. The editors will decide as before whether to publish it in a future paper issue as well.

From errant enzymes to colon cancers

The suggestion that some colorectal cancers (CRCs) develop by a methylation pathway has been given support by a genetic study of 500 patients in Australia. The findings support the view that key enzymes in the metabolism of folate and methyl groups, which affect DNA methylation, influence predisposition to CRCs, particularly sporadic (non-familial) cancers with microsatellite instability (MSI).

The researchers hypothesised that genetic polymorphisms in enzymes of folate metabolism—methylenetetrahydrofolate reductase (MTHFR) and cystathionine beta-synthase (CBS)—would respectively predispose to or protect against MSI+ CRCs, owing to their effects on enzyme activity.

Comparison of the frequency of polymorphic genotypes in patients with MSI+ and MSI− CRCs and in controls confirmed the hypothesis. The MTHFR TT genotype—which results in a 30% drop in enzyme activity—was significantly associated with CRC, but in patients aged ≥70 years, compared with age matched controls (12% v 7%). It also correlated with increased age at diagnosis of proximal tumours (median age 74 v 67 years) and was found almost twice as commonly in MSI+ as in MSI− tumours (16% v 9%). The CBS844ins68 genotype—which increases activity in reducing plasma homocysteine—was less common in proximal tumours than in controls (4% v 10%).

The study was performed in 500 patients with CRC: 75 cancers were MSI+ and 426 were MSI− cancers of the proximal (203) or distal (233) colon. The controls were 1207 healthy subjects from the Western Australian population. A subgroup of 155 of the controls was typed for the CBS polymorphism.

Novel autosomal dominant mandibulofacial dysostosis with ptosis: clinical description and exclusion of *TCOF1*

P Hedera, H V Toriello and E M Petty

doi: 10.1136/jmg.39.7.484

Updated information and services can be found at:
http://jmg.bmj.com/content/39/7/484

These include:

**References**

This article cites 15 articles, 1 of which you can access for free at:
http://jmg.bmj.com/content/39/7/484#BIBL

**Email alerting service**

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Topic Collections**

Articles on similar topics can be found in the following collections

- Calcium and bone (307)
- Genetic screening / counselling (886)
- Clinical genetics (256)

**Notes**

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/