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Split hand/split foot malformation associated with sensorineural deafness, inner and middle ear malformation, hypodontia, congenital vertical talus, and deletion of eight microsatellite markers in 7q21.1-q21.3

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EDITOR—The split hand/split foot malformation (SHFM, MIM 183600) is a central reduction defect of the hands and feet and occurs both as an isolated malformation and as part of several syndromes including the EEC syndrome (MIM 129900). We report on a 2 year old boy with SHFM associated with features of ectodermal hypoplasia, a submucous cleft palate, congenital vertical talus, malformations of the middle ear, profound sensorineural hearing loss resulting from Mondini dysplasia, and a de novo deletion of the paternal chromosome 7q21.1-q21.3. This patient with syndromic SHFM represents a case of atypical EEC syndrome, but also displays abnormalities previously not associated with SHFM or EEC syndrome.

The classical features of the autosomal dominant inherited EEC syndrome are ectrodactyly, ectodermal dysplasia, and clefting of the lip/palate. In most patients, there are additional anomalies typically affecting the urogenital and lacrimal systems.^{1,2} Some patients also have dysmorphic facies, a tendency to infectious disease, endocrine disorders, and mental retardation. This phenotypic variability has become increasingly apparent over the last 15 years^{3,4} and numerous related and overlapping syndromes have been delineated by many investigators.⁵ In an attempt to clarify classification, major and minor criteria for the diagnosis of EEC syndrome have been elaborated.^{3,4}

Dominant inheritance of EEC has been documented in several large multigenerational

Figure 1 The proband aged 18 months. (A, B) Note facial dysmorphism (see text). (C) He cannot stand unsupported.

Figure 2 Right foot of the patient. (A) Ectrodactyly (split foot malformation) with apparent absence of the 2nd toe and syndactyly of toes 3 to 5. (B) Radiograph showing syndactyly of the first and second metatarsals and absence of the second phalanges and malformation of the third to fifth phalanges. (C) Ectrodactyly and pes planovalgus (severe talus verticalis deformity).

families.⁶ At least 15 patients have been reported to have cytogenetic abnormalities of chromosome 7q21.2-7q22.1, including nine patients with interstitial deletions.⁷⁻⁹ In addition, mutations in the gene encoding the trans-activation factor p63 on chromosome 3q27 have been identified in familial and sporadic cases of EEC syndrome.¹⁰ A third locus was mapped to chromosome 19q,¹¹ further delineating the genetic heterogeneity of this syndrome. The reason for the phenotypic heterogeneity in EEC syndrome patients with 7q abnormalities is unclear but may relate to the size of the deletion.

Case report

Our patient is the fifth child of healthy, consanguineous, fourth cousin, Austrian parents. The father and the mother were 41 and 36 years, respectively, at the time of his birth. His four sibs are healthy. He was born after an uneventful pregnancy in the 41st week of gestation and weighed 2840 g (10th centile), was 48 cm long (10th centile), and had a head circumference of 31.5 cm (10th centile). Ectrodactyly of the right foot was noted and transient evoked otoacoustic emission screening indicated hearing impairment. Further examinations were at first declined by the mother. At 15 months of

Figure 3 Inner ear of the patient. A 3D reconstruction of a coronal MRI scan shows Mondini type malformation on both sides. (A) Right ear: overall dilated and plump structures of the inner ear. asc denotes the anterior semicircular canal, va the vestibular aqueduct with saccule and utricle, and co the cochlea showing a reduced number of coils. (B) Left ear: a large endolymphatic sac is shown (es). (C) Schema of the normal inner ear. 1. Anterior semicircular canal. 2. Membranous ampulla (MA) of the anterior semicircular canal. 3. MA of the lateral semicircular canal. 4. Saccule. 5. Cochlear canal. 6. Helicotrema. 7. Lateral semicircular canal. 8. Posterior semicircular canal. 9. MA of the posterior semicircular canal. 10. Vestibular window. 11. Cochlear window. 12. Scala vestibuli. 13. Scala tympani. 14. Utricule.

Figure 4 Cytogenetic and molecular findings. (A) High resolution cytogenetic analysis of both chromosomes 7 of the patient. The deletion is indicated by the arrow. (B) Preliminary analysis of microsatellite markers from chromosome 7q in the family of the patient. The deleted interval spans at least 8.9 cM on the paternal chromosome flanked by microsatellite markers D7S2443 and D7S2480. Data regarding microsatellite mapping are compiled from Dib et al.¹³ and Crackower et al.¹⁴ The arrow indicates the position of the gene mutated in Pendred syndrome.

age, he was referred to the hospital because of failure to thrive (weight 7200 g, below the 3rd centile; length 70 cm, below the 3rd centile; head circumference 43 cm, below the 3rd centile). Physical examination showed arched eyebrows, a small triangular nose with a depressed nasal bridge, and ears with overfolded helices and attached earlobes (fig 1). He also had hypertelorism, a large biparietal diameter, hypopigmented retina, micrognathia, a submucous cleft palate, carious primary teeth and hypodontia, sparse, light hair, pale skin, cryptorchidism, and bilateral severe congenital vertical talus, in addition to the previously noted ectrodactyly of the right foot (fig 2). CT and MRI scans showed Mondini dysplasia of the inner ear (fig 3) and cochlear implanting showed fixation of the ossicular chain. Audiometric examinations were consistent with these findings and showed conductive and profound sensorineural hearing loss. Laboratory investigations showed partial deficiency of growth hormone secretion. Mental and psychomotor developmental delay was noted.

On GTG banding, we observed an interstitial deletion of chromosome 7 confined to the interval q21.1-q21.3 (fig 4A); parental karyotypes were normal. To delineate this deletion further, we used 21 chromosome 7q microsatellite markers to reconstruct parental and

patient haplotypes and found that for the eight markers flanked by D7S2443 and D7S2480, the patient had a deletion of the paternal allele (fig 4B). Two markers within the interval (D7S2410 and D7S527) were uninformative, as were two flanking markers (D7S524 and D7S1796). These data define a deletion of 8.9 to 17 cM, which includes the critical interval of <1 Mb on 7q21.3 previously associated with either SHFM or EEC syndrome.^{7,9,13}

Discussion

Extensive investigations have not been able to support any of several hypotheses to connect the chromosomal aberrations with the occurrence and varying characteristics of syndromic SHFM.^{13,15} Given the rare occurrence of cytogenetic abnormalities in persons with syndromic and non-syndromic SHFM, the fact that the deletion we report includes the critical region previously described in patients with SHFM emphasises the importance of this chromosome 7 interval in the pathogenesis of SHFM/syndromic SHFM. Furthermore, we believe that the range of phenotypic findings in SHFM patients with aberrations of chromosome 7q favours a contiguous gene syndrome as the underlying cause.

In our patient, the inner ear malformation (fig 3) was recognised as Mondini dysplasia, an

association that has not previously been reported with either SHFM or a chromosome 7 aberration. Mondini dysplasia is characterised by bony and membranous anomalies of the inner ear exhibiting a wide range of morphological and functional abnormalities. Typically, the cochlea is flat, the cochlear duct is short, the auditory and vestibular sense organs and nerves are immature, the vestibule is large, the semicircular canals are wide, small, or missing, and the endolymphatic sac is dilated. The anomaly can be unilateral or bilateral and occurs in isolation or in association with anomalies in other organs.¹⁶ Familial examples of Mondini dysplasia generally represent examples of Pendred syndrome, an autosomal recessive disorder in which congenital sensorineural hearing impairment and goitre cosegregate.

Because Pendred syndrome is caused by mutations in *PDS*, a gene that maps to chromosome 7q31, the simultaneous occurrence of atypical EEC syndrome and Pendred syndrome in our patient seemed an attractive possibility to explain the rare combination of physical findings. Although molecular analysis in our patient appears to place the distal breakpoint of the deletion about 9 cM centromeric to *PDS*, we cannot exclude a more complex chromosomal rearrangement. Assuming that the paternal copy of *PDS* could have been deleted, we completed a mutation screen for maternally inherited *PDS* allele variants. We were unable to identify any mutations by SSCP and direct sequencing as described previously¹⁷ and therefore could not establish a causal connection between the observed Mondini dysplasia and the chromosomal aberration. We also excluded an independent cause of the sensorineural hearing impairment, by sequencing the coding region and exon 1 of *GJB2*.¹⁸ Mutations in this gene are the most common cause of autosomal recessive non-syndromic deafness.

The simultaneous occurrence of an inner ear malformation and SHFM has rarely been reported. Berndorfer¹⁹ noted absence of pinnae and lack of inner ears in one patient. Autosomal dominant ectrodactyly and deafness in a father and son were reported by Tolmie *et al.*²⁰ Both patients had CT verified cochlear abnormalities, which may have been consistent with Mondini dysplasia. There was no mention of any chromosomal anomaly. Moreover, sensorineural hearing impairment has rarely been reported in syndromic SHFM.²¹⁻²⁶ In two of these cases, however, an apparently balanced translocation involving chromosome 7q was found to cosegregate with the disease.^{25, 26}

Conductive hearing loss is observed in 14-44% of cases of EEC syndrome, most commonly reflecting Eustachian tube dysfunction in association with the palatal clefting,^{3, 4} although ossicular malformations have been described.²⁷

Of 10 patients with ectrodactyly in association with a deletion of 7q21-q22, microcephaly and general growth impairment have been reported in eight cases (80%^{7, 9}) compared to only 2% and 1%, respectively, in a survey of 230 patients with EEC syndrome.⁴ While adenohypophyseal

dysfunction in two sets of sibs has been reported in EEC syndrome,^{28, 29} partial growth hormone deficiency was identified in our patient as the aetiology of the growth retardation. However, growth retardation and microcephaly might also delineate a subtype of the EEC syndrome related to chromosomal aberrations involving chromosome 7q21-q22. We accordingly suggest initiating chromosomal and molecular investigations of this chromosomal region when growth retardation and microcephaly is present in patients with SHFM. Short stature, as well as low birth weight, abnormal skull shape, and ear malformations were common findings among patients with proximal/intermediate deletions or rearrangements of chromosome 7q, with and without SHFM.⁸

We believe that a specific pattern of facial anomalies characterises patients with aberrations of chromosome 7q21-q22. The facial phenotype consists of arched eyebrows, a small, triangular shaped nose with a depressed nasal bridge, abnormal ears with overfolded helices and attached earlobes, a large biparietal diameter, hypertelorism, and micrognathia. It was present in our patient and in at least six published case reports.^{9, 30-34}

The split foot malformation in our patient was right sided, as has been mostly observed in cases of unilateral involvement of either the upper or lower limbs.²⁶ The presence of bilateral congenital vertical talus could not be explained by aplasia of the anterior calcaneus with loss of talar support or by a spinal defect, though the split foot malformation complicates the anomaly of the talus. Bilateral congenital vertical talus is an otherwise rare disorder, and to our knowledge has not been reported in the EEC syndrome or in related conditions.

Our report suggests that patients with syndromic SHFM should be examined for the findings we describe, and that the molecular analysis should include karyotyping and complementary studies to establish whether the critical interval of <1 Mb on chromosome 7q21.1-q21.3 is deleted.

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A missense mutation in the *SEDL* gene results in delayed onset of X linked spondyloepiphyseal dysplasia in a large pedigree

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EDITOR—Spondyloepiphyseal dysplasia (SED) is a rare osteochondroplasia, characterised by disproportionate short stature with a short neck and trunk and barrel chest. The pelvis tends to be narrow and deep, the femoral neck short, and the femoral head flattened. Mild to moderate epiphyseal dysplasia of the large joints may also be seen. The latter may lead to premature secondary osteoarthritis with significant morbidity.¹ SED may occur sporadically; however, in many cases the family history indicates an inherited condition. In some of these pedigrees, the inheritance pattern seems autosomal dominant, while in others it is consistent with autosomal recessive or X linked recessive.²

Recently, mutations in the gene designated *SEDL*, located on Xp22, were identified as the cause of X linked spondyloepiphyseal dysplasia tarda in three families.³ We have previously described a large kindred of British descent

spanning four generations affected by SED.¹ Briefly, 14 males between the ages of 10 and 77 years were affected, with early adolescence development of progressive decline in growth rate accompanied by short stature, short trunk, and barrel chest. Although some of them had to limit their activities because of hip or back limitation of movement or pain, many continued with normal activity and were able to perform in the work place without impairment of function. There was no indication of other abnormalities previously reported in association with SED, such as mental retardation,² immune abnormalities and retinopathy,⁴ cardiac dysfunction,⁵ or hypogonadotrophic hypogonadism.⁶ The female carriers in this pedigree had normal height. Although some of the females suffered from occasional mild back or hip pain, it did not affect their daily activity, nor was there objective radiological evidence of spinal or joint involvement compatible with