

Split hand/split foot malformation, deafness, and mental retardation with a complex cytogenetic rearrangement involving 7q21.3

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Abstract

Split hand/split foot malformation (SHSF) has been described in several patients associated with cytogenetically visible rearrangements involving chromosome 7q. Characterisation of these patients has led to localisation of an autosomal dominant form of SHSF to 7q21-22; the locus has been designated SHFM1. We describe a patient with a complex, apparently balanced cytogenetic rearrangement, including a translocation breakpoint at 7q21.3 near the DSS1 gene. In addition to ectrodactyly of all four limbs, the patient has congenital deafness, submucous cleft palate, microcephaly, and mental retardation. This patient represents an additional case of syndromic ectrodactyly related to the SHFM1 gene region, which may be responsible for both syndromic and non-syndromic ectrodactyly.

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Key words: split hand/split foot; human chromosome 7q; translocation; congenital deafness.

Split hand/split foot deformity (SHSF), or ectrodactyly, is the result of maldevelopment of the central rays of the limb buds and can occur as an isolated defect or as a part of a variety of syndromes.^{1,2} Both the non-syndromic and syndromic ectrodactylies may be sporadic or inherited as an autosomal dominant trait or rarely as an autosomal recessive or X linked recessive trait.^{3,4} Most patients reported had normal karyotypes. In some patients, however, either syndromic or non-syndromic ectrodactyly has been described in association with cytogenetic abnormalities involving chromosome 7q.⁵⁻²⁰ These findings have led to the localisation of a locus for an autosomal dominant form of SHSF to 7q21-q22, designated SHFM1 (MIM 183600).⁴ Based on linkage studies, at least one additional autosomal locus, designated SHFM3, exists.^{21,22}

We describe a patient with syndromic ectrodactyly associated with a complex cytogenetic rearrangement involving the 7q21.3 region and the molecular characterisation of the rearrangement.

Case report

The patient, a 54 year old male, had healthy, non-consanguineous parents. There is no fam-

ily history of limb malformations, mental retardation, cleft palate, or hearing loss. The pregnancy and delivery were normal. Immediately after birth, the child was found to have malformations in all four limbs. Developmental milestones were delayed and he walked at 3 years. The patient was found to be deaf at the age of 6 months and he never learned to speak. First psychological tests were performed at 10 years of age, and he was found to be severely mentally retarded (IQ 30). He has been permanently institutionalised since the age of 42.

On clinical examination, the patient was found to be a mentally retarded, deaf-mute man with an outgoing character. He was able to communicate with gestures. He had a peculiar facial appearance with microcephaly, triangular face, downward slanting palpebral fissures, small ears with poorly developed folds, and a prominent lower jaw with prognathism (fig 1). He had a submucous cleft palate and split hand/split foot anomaly in all four limbs. There was bilateral upper limb ectrodactyly with absent second and third rays on the left and absent second ray and missing third finger on the right. Bilateral split foot anomaly was observed in the lower limbs (fig 1). The skin was normal and the body hair distribution was masculine. There were no signs of heart, lung, or abdominal organ dysfunction, and the urogenital organs were normal, including normal intravenous urography results. On electric response audiometry, no responses at 90 dB and 100 dB could be obtained.

Cytogenetic studies

Karyotype analysis by trypsin-Giemsa banding was performed on phytohaemagglutinin stimulated lymphocyte cultures. G banding analysis showed a complex karyotype: 46,XY, inv(1)(q21q32),t(4;7)(q31.1;q21.3), inv(11)(p15.1q23) (fig 2). This interpretation was suggested by the cytogenetic study and was supported by chromosome painting and in situ hybridisation results. The mechanism of the inversions and translocations in this patient remains undetermined. When this patient was first studied in 1976, his father had already died; his mother, brother, and sister had normal karyotypes (A de la Chapelle, personal communication).

Chromosome painting by chromosome in situ suppression (CISS) hybridisation was performed using chromosome 1, 4, 7, and 11

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Figure 1 (Above) Facial features of the patient. Note triangular facies, microcephaly, prognathism, and small, malformed ears. (Below) Split hand/split foot deformity is present in all four limbs.

specific library probes (LA01NS01 code 57738, LL04NS02 code 57745, LA07NS01 code 57722, LL11NS01 code 57704; ATCC).

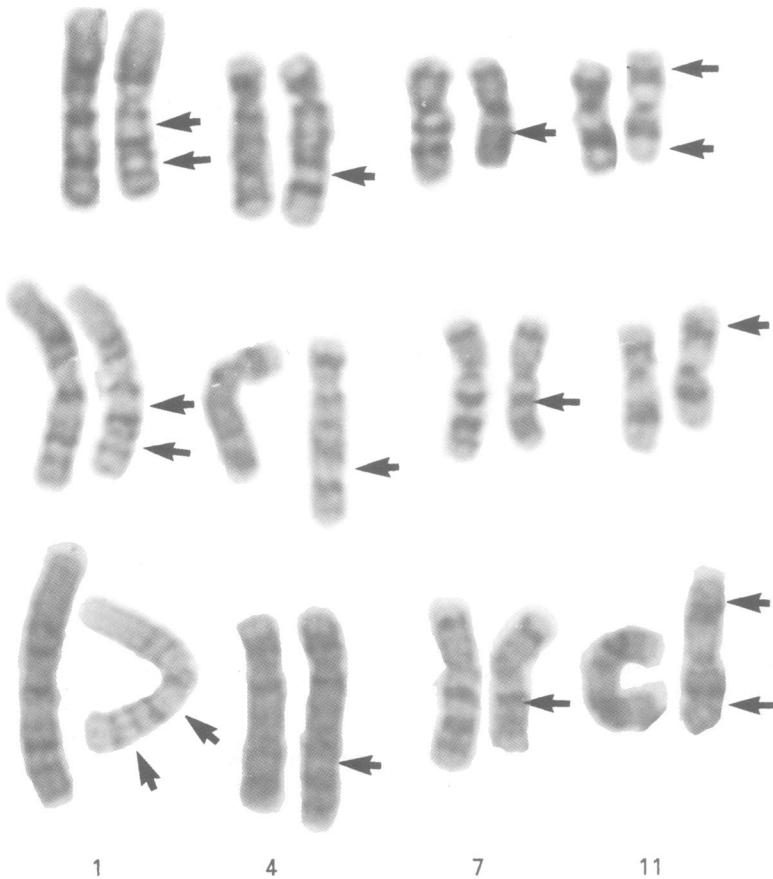


Figure 2 Partial karyotypes from three metaphase mitoses. Arrows indicate chromosomal breakpoints. The cytogenetic interpretation is 46,XY,inv(4)(q21q32),t(4;7)(q31.1;q21.3),inv(11)(p15.1q23).

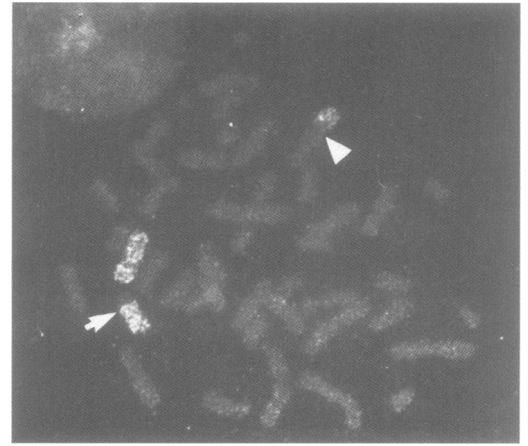


Figure 3 Chromosome painting with chromosome 7 specific whole chromosome suppressed library. Translocation between chromosomes 4 and 7 is confirmed using this paint and a paint for chromosome 4. No other chromosomes show hybridisation. Triangle indicates der(7) and arrow der(4).

The probes were labelled with biotin-11-dUTP (Sigma Chemical Co, St Louis, MO) and detected using fluorescein labelled avidin (FITC).²³ Chromosome painting was consistent with the results of G banding analysis and did not suggest the presence of a complicated three or four way translocation between chromosomes 1, 4, 7, and 11 (fig 3).

The location of the translocation breakpoint at 7q was refined earlier with fluorescence in situ hybridisation (FISH) analysis using YAC DNA probes mapped to the region.²⁴ Three YAC probes from the region (HSC7E578, HSC7E1131, and HSC7E571) were shown by FISH to cross the breakpoint in this patient (patient T6 in reference 24). These findings mapped the breakpoint to the same minimal critical region for SHFM1 as observed in several other patients with both syndromic and non-syndromic ectrodactyly.

To refine the breakpoint further, a cosmid probe, cos177c8, which was isolated by probing with a new gene DSS1 (Deleted in Split hand/Split foot 1, cloned from the SHFM1 critical region²⁵) was used in FISH. The cosmid was

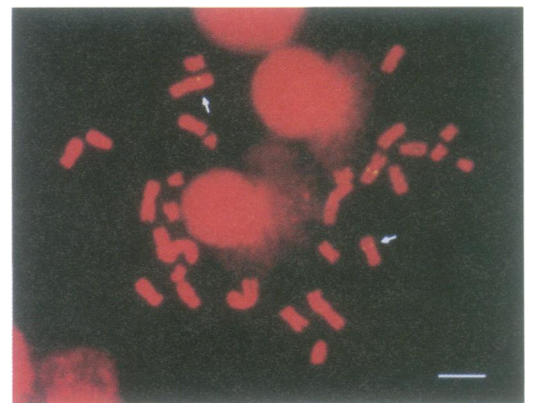


Figure 4 FISH analysis of the patient's chromosomes with the cos177c8 probe. Signal is seen on three chromosomes, the normal chromosome 7, der(7), and der(4), indicating that the cosmid spans the translocation breakpoint. Arrows indicate der(4) (top left) and der(7) chromosomes. Size bar = 5 μm.

Ectrodactyly associated with 7q2 rearrangements

Ref	Deleted segment	Ectrodactyly		Additional findings
		Hands	Feet	
<i>Unbalanced rearrangements (deletions, insertions)</i>				
5	q11-q21 or 22	—	Bilateral	Microcephaly, low set ears, retrognathia, mental retardation
6	q11.2-q22.1	Right	Bilateral	Microcephaly, cleft palate, severe mental retardation
7	q11.23-q22	Right	Bilateral	Microcephaly, malformed ears, ocular malformations, severe mental retardation
8	q21.3-q31.3	Right	Bilaterally absent legs	Microcephaly, malformed ears, congenital hearing loss, ASD, corpus callosum agenesis, developmental delay
9	q21.3-q22	Left	Bilateral	Microcephaly, genitourinary anomalies, growth delay
10	q21.3	Bilateral	Bilateral	Malformed ears, hypertelorism, speech delay
16	q21.12-q22.1	—	Bilateral	Microcephaly, coloboma, short stature, seizures, mental retardation
17	q21.12-q21.3	Bilateral	Bilateral	Malformed ear, submucous cleft palate, enamel defects, micrognathia, short stature, mild mental retardation
18	q21.2-q22.1	—	Bilateral	Microcephaly, malformed ears, skin pigmentation abnormalities, developmental delay
19	q11.23-q22	Right	Bilateral	Microcephaly, malformed ears, seizures, severe mental retardation
15	q22 (ins)	Bilateral	—	Situs inversus
<i>Apparently balanced rearrangements (translocations, inversions)</i>				
11	q21.2	Bilateral	Bilateral	Small, low set ears, hypertelorism
12	q22.1	Bilateral	Bilateral	Cleft lip/palate, fused incisors, sparse hair, bilateral accessory nipples
13	q22	Right	Bilateral	Bifid uvula
14	q22.1	Right	—	Hearing loss
14	q22.1	Bilateral	Right	Hearing loss
16	q21.3	Bilateral	Bilateral	Mild speech delay
20	q21.3	Bilateral	Bilateral	Right arm arteriovenous malformation
Our case	q21.3	Bilateral	Bilateral	Microcephaly, small malformed ears, hearing loss, submucous cleft palate, severe mental retardation

biotinylated, hybridised to metaphase spreads prepared from Epstein-Barr virus transformed lymphoblasts derived from the patient, and detected with FITC-avidin.²⁶ This probe was found to cross the chromosome 7 breakpoint in the patient (fig 4), mapping the breakpoint in the immediate vicinity of DSS1.

Discussion

Before the present case, at least 18 cases with ectrodactyly associated with a visible cytogenetic abnormality involving band 7q2 have been described (table). The patients represent both syndromic and non-syndromic ectrodactyly, including one large family with a highly variable clinical picture and cases of both syndromic and non-syndromic ectrodactyly in the same pedigree.¹⁴ Clinical subtyping of the present case as well as other published cases in the spectrum of ectrodactyly associated syndromes is difficult. Several cases may be misleading because of the complex chromosome rearrangements found in different patients. Our patient's rearrangement involves a breakpoint in at least six chromosomal bands. Some of these breakpoints may disrupt genes with phenotypic consequences, others may be harmless. Furthermore, molecular deletions or duplications may have occurred in conjunction with rearrangements interpreted cytogenetically as simple translocations or inversions. Among the associated findings in our patient, mental retardation, microcephaly, and small, malformed ears are non-specific and commonly associated with many different chromosomal abnormalities, including those of chromosomes 1, 4, and 11. Although these findings were often encountered in other published cases of ectrodactyly associated with 7q rearrangements, especially 7q deletions, they may not be directly related to the disruption of the SHFM1 locus.

Deafness and oral clefting have been described in several patients with syndromic ectrodactyly and a cytogenetic abnormality at 7q21-q22. In addition to the present case, at least three other patients have been described who also had hearing loss, which appears to be congenital, sensorineural, and often severe.^{8,14} Hearing loss as well as cleft palate are features of ectrodactyly-ectodermal dysplasia-cleft palate (EEC) syndrome (MIM 129900), but our patient did not have findings consistent with ectodermal dysplasia. Only a few patients with ectrodactyly associated with a cytogenetic abnormality involving 7q21-22 were reported to have sparse hair or enamel hypoplasia.^{12,17} Deafness is also a part of the LADD (lacrimo-auriculo-dento-digital) syndrome (MIM 149730) as well as ectrodactyly-hearing loss syndrome (MIM 220600), and cleft palate is a part of the ECP (ectrodactyly-cleft palate) syndrome (MIM 129830). As all these syndromes show variable expressivity, the classification of a single case may be difficult on clinical grounds only.

Interestingly, patients with both non-syndromic and syndromic ectrodactyly with various additional abnormalities have been found to have cytogenetic rearrangements involving the same region at 7q21.3-q22.1. Further analysis of this region has mapped the breakpoints for chromosomal rearrangements to a common interval both in syndromic and non-syndromic patients.²⁴ In several patients with apparently balanced rearrangements, the translocation and inversion breakpoints have been mapped within a 700 kb interval in the SHFM1 critical region. Using three YAC probes, HSC7E578, HSC7E1131, and HSC7E571, the breakpoint was also mapped to the same region in the present patient. In this study, the cosmid probe cos177c8 was shown to cross the breakpoint to define its location more precisely. The role of the DSS1 gene contained in part in the same

cosmid probe is the subject of further study.²⁵

The developmental defects in patients with syndromic ectrodactyly associated with involvement of 7q range widely (table). This observation speaks for a common aetiological association between the simple split hand/split foot anomaly and abnormalities often seen in association with this condition. At least some of these birth defects may result from a defect in the SHSF gene itself or from a group of tightly clustered developmental genes at 7q21.3–q22.1.

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