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Localization of a gene for oculodentodigital syndrome to human chromosome 6q22–q24

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Oculodentodigital syndrome (ODD) is a congenital, autosomal dominant disorder which affects the development of the face, eyes, limbs and dentition. Spastic paraparesis is thought to be an occasional manifestation of the disorder. Type III syndactyly, which occurs as part of ODD, has also been reported to occur as an isolated entity. In the current investigation, a total genome search for the location of the ODD locus was instigated and linkage to polymorphic markers located on chromosome 6q established (pairwise Z_{max} = 9.37; θ = 0.001). Analysis of a large family with type III syndactyly, but atypical facial features, further suggested that isolated type III syndactyly is also located in this same region of the genome.

INTRODUCTION

Oculodentodigital syndrome (ODD; McKusick number 164200) is a congenital disorder which affects the development of the face, eyes, limbs and dentition. The disorder is inherited in an autosomal dominant fashion and displays high penetrance but variable expression (1). In addition, a high rate of *de novo* mutations is observed (2). Facially, affected patients exhibit a narrow nose with hypoplastic alae nasi and thin, anteverted nostrils; short palpebral fissures and bilateral microcornea often with anomalies of the iris (3,4). Secondary glaucoma occurs in a number of patients (5). Bilateral complete syndactyly of the fourth and fifth fingers (type III syndactyly) is the characteristic digital malformation. The third finger may also occasionally be involved and associated camptodactyly is a common finding (6). In addition, there is generalized hypoplasia of the enamel (6,7). Less common features include thin, sparse hair and conductive deafness secondary to recurrent otitis media. A number of authors have reported spastic paraparesis or lower limb weakness in association with ODD in both sporadic and familial cases (6–10). In two of these reports, magnetic resonance imaging demonstrated an underlying leukodystrophy and it has, therefore, been proposed that the definition of ODD be widened to include these features (9,10).

Interestingly, type III syndactyly has been reported to occur as an isolated entity in several autosomal dominant pedigrees and it is uncertain whether the two conditions are separate genetic entities or part of the same disease spectrum (11–14). In this regard, Brueton *et al.* (15) have reported a family who, while not exhibiting the ocular or dental anomalies associated with ODD, did have a facial appearance that appeared to bridge the gap between the two conditions. It therefore seems possible that the two conditions are either part of a contiguous gene syndrome or are allelic disorders. Nevertheless, the mutated gene(s) underlying ODD and type III syndactyly is not known. In order to identify the genetic location of the ODD/type III syndactyly gene(s), we have undertaken genetic linkage analysis in six families with a history of ODD, one of which is the atypical family reported by Brueton *et al.* (15). The results of this analysis indicated that the ODD/type III syndactyly locus is located at chromosome 6q22–q24.

RESULTS

The pedigrees of the families used in the current study are illustrated in Figure 1. Families 2 and 3 have been described previously (15,16). Family 1 exhibited bilateral complete 4–5 syndactyly of the fingers, with the additional involvement of the third digit in four members, narrow nose with hypoplastic alae nasi, small corneas and short palpebral fissures. Family 4 had complete syndactyly of fingers 3–4–5 in the child and 4–5 in the father, with additional 4–5 toe syndactyly. They also had a narrow

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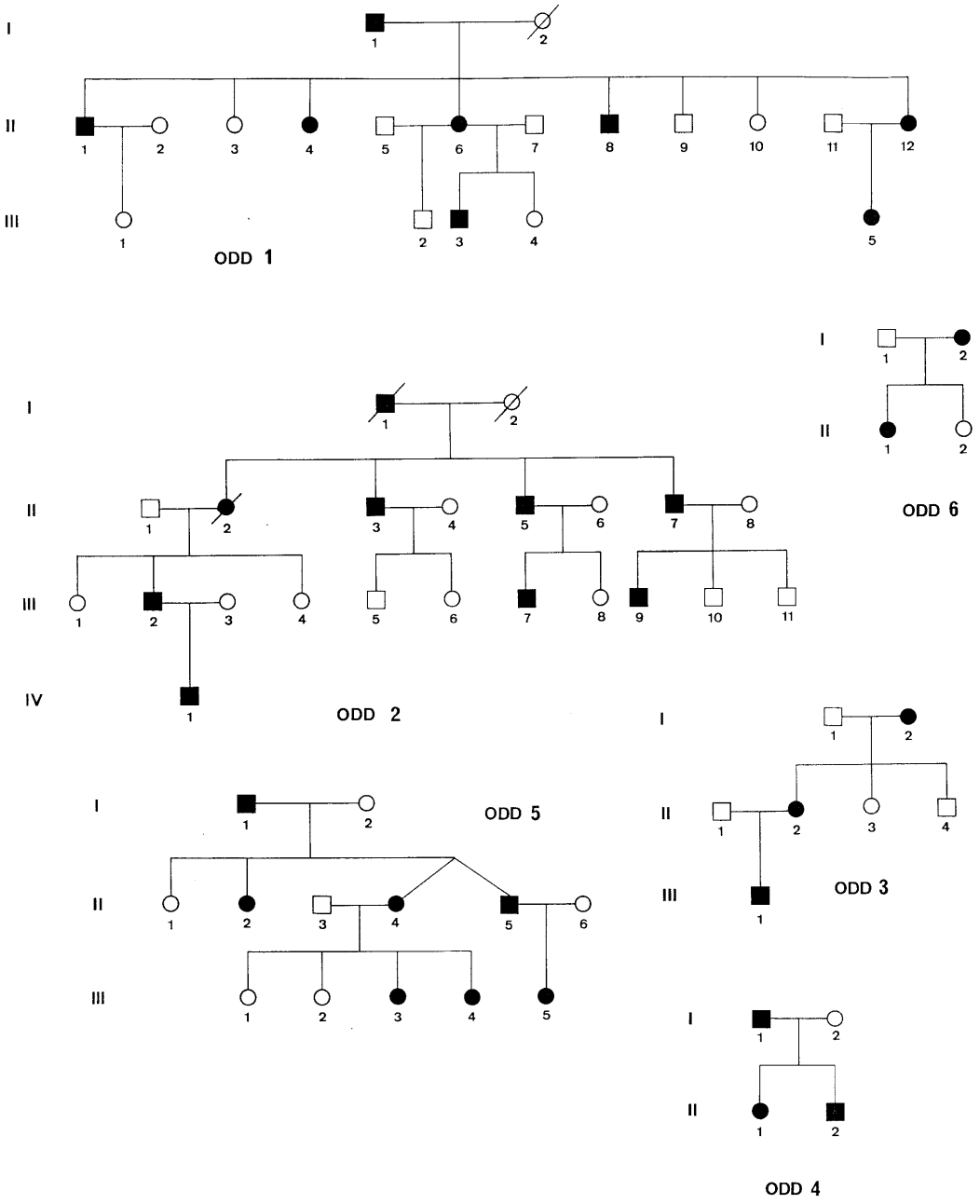

Figure 1. Pedigrees of the families used in the current investigation. Solid symbols represent affected and open symbols unaffected individuals, respectively.

nose with hypoplastic alae nasi. In family 5, four individuals exhibited 4–5 syndactyly of the fingers, three of whom also had microphthalmia and oligodontia, while the fourth individual had additional 3–4 syndactyly of the toes. Three other individuals exhibited 3–4 toe syndactyly, but without anomalies of the fingers, one of whom also had glaucoma. Family 6 had 4–5 syndactyly of the fingers, with additional 2–3 syndactyly of the left hand, thin hair, dental anomalies and hypoplastic alae nasi. In addition, both affected individuals had neurological symptoms similar to those described previously (6–10).

In the absence of a focusing cytogenetic abnormality or strong candidate gene, a genome-wide search for the location of the ODD locus was instigated using short tandem repeat polymorphisms (STRPs). No evidence of linkage was detected with 25 STRPs from chromosomes 3, 14, 16 and 17 (data not shown), but highly significant evidence of linkage between ODD and markers from chromosome 6q22–q24 was demonstrated (Table 1). The strongest support for positive linkage was provided by D6S435 which yielded a maximum pairwise LOD score of 9.37 at recombination fraction of 0.001, after the clinical status of individual III.8 of family 2 had been re-evaluated (see below). There was also no evidence for recombination between D6SS287, D6S267, D6S262, D6S457, D6S472 or D6S292 and ODD, whereas D6S474 and D6S310 produced positive, but non-significant, LOD scores (Table 1). Examination of the recombinant individuals revealed by pairwise linkage analysis indicated that the ODD locus resides in the D6S474–D6S292 interval (Table 2) which is a region of approximately 28 cM (17).

Examination of the family-specific LOD scores generated for the locus D6S435 revealed LOD scores in excess of 3 for both families 1 (typical ODD) and 2 (type III syndactyly) (Table 3), indicating that ODD/type III syndactyly are linked to markers in the same region of the human genome.

Interestingly, individual III.8 of family 2 was initially diagnosed as being clinically normal on the basis that she did not exhibit the type III syndactyly which is typical of affected members of this family (15). On the basis of this diagnosis, this individual appeared to exhibit recombination between the ODD locus and all of the chromosome 6 STRP markers typed. Re-examination of this individual revealed that she had facial features of ODD with a thin nose and hypoplastic alae nasi; she was therefore considered to be affected, despite the absence of type III syndactyly (Fig. 2) and was coded as such for linkage analysis.

One of the families examined in the current study exhibited neurological features in addition to classical signs of ODD. As this is only a very small family it is not possible to assess whether this family shows independent evidence of linkage to the same region of the genome. Given the current findings, it will be interesting to assess whether any of the larger families that have been reported with similar features are also linked to STRPs from 6q (10). This seems to be likely given that families with a history of ODD and spastic paraparesis have been reported in which some of the individuals presenting with classical features of ODD did not manifest neurological problems (6,23). Further support for the hypothesis that families with a history of ODD together with spastic paraparesis are linked to 6q22–q24 is provided by a family with a history of both hereditary spastic paraplegia and type III syndactyly (24).

Table 1. Pairwise LOD scores for ODD

LOD score at a recombination fraction of:									
Locus	0.00	0.05	0.10	0.15	0.20	0.30	0.40	Z_{max}	θ
D6S278	–9.07	2.25	2.63	2.56	2.29	1.47	0.56	2.64	0.112
D6S474	–1.06	7.19	6.62	5.88	5.06	3.26	1.36	7.31	0.026
D6S266	5.56	5.68	5.25	4.69	4.06	2.64	1.13	5.78	0.023
D6S287	4.55	4.07	3.58	3.07	2.55	1.49	0.52	4.55	0.001
D6S267	4.87	4.39	3.89	3.37	2.83	1.69	0.61	4.87	0.001
D6S262	5.42	4.89	4.35	3.78	3.19	1.97	0.77	5.42	0.001
D6S435	9.37	8.51	7.61	6.67	5.69	3.62	1.50	9.37	0.001
D6S457	4.89	4.45	3.99	3.51	3.01	1.96	0.86	4.89	0.001
D6S472	4.34	3.92	3.48	3.03	2.56	1.59	0.66	4.34	0.001
D6S292	6.13	5.49	4.83	4.14	3.44	2.03	0.74	6.13	0.001
D6S310	–5.39	1.19	1.53	1.53	1.37	0.85	0.28	1.55	0.122

Table 2. Analysis of individuals showing recombination between chromosome 6q STRPs and the ODD locus

Individual	Family 1	Family 2	Family 3	Family 3	Family 3	Family 5
	II.9	III.1	II.4	II.3	III.1	III.3
Phenotype	Unaffected	Unaffected	Unaffected	Unaffected	Affected	Affected
D6S278	R	–	R	NR	–	R
D6S474	NR	NR	NR	NR	NR	R
D6S266	NR	NR	NR	NR	NR	–
D6S287	–	–	–	–	NR	NR
D6S267	–	–	NR	NR	–	NR
D6S262	NR	NR	NR	NR	NR	–
D6S435	NR	NR	NR	NR	NR	NR
D6S457	–	NR	NR	NR	NR	–
D6S472	–	NR	NR	NR	NR	–
D6S292	NR	–	NR	NR	NR	NR
D6S310	NR	R	NR	R	R	–

R, recombinant individual; NR, non-recombinant individual; –, uninformative or partially informative meiosis.

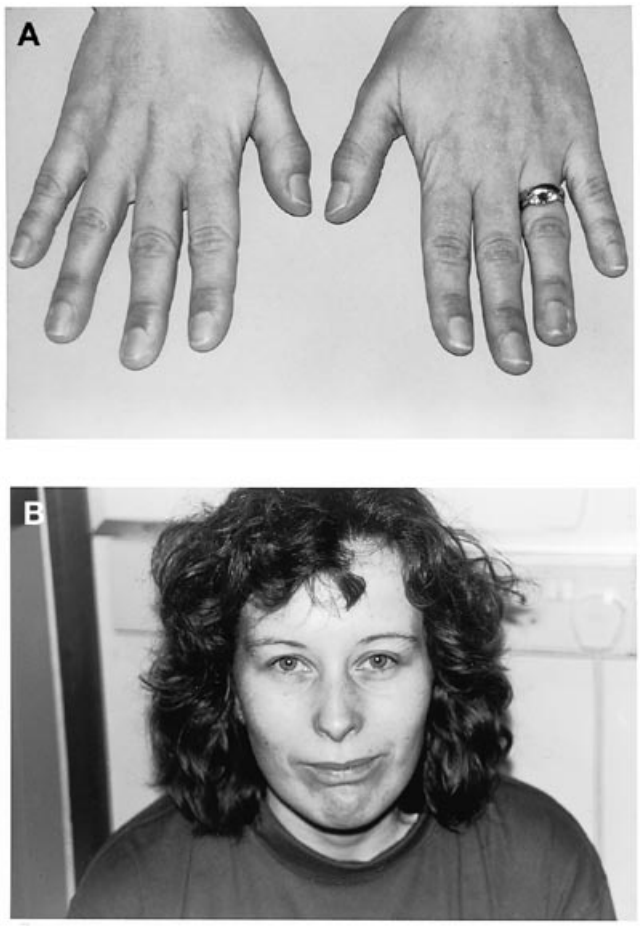

Figure 2. Photographs of individual III.8 from ODD family 2. (**A**) The hands do not show any evidence of type III syndactyly. (**B**) Facially, this person exhibits a thin nose with hypoplastic alae nasi.

Table 3. Results of the pairwise linkage analysis between ODD and D6S435 for each of the families used in the current study

Family number	Z_{max}
1	3.29
2	3.10
3	0.89
4	0.30
5	1.79
6	0.00

DISCUSSION

In the current investigation we have presented strong evidence that the ODD locus is located at chromosome 6q22–q24 in a 28 cM region defined by the markers D6S474, proximally, and D6S292, distally. Interestingly, examination of the two largest families indicates that both show independent evidence of linkage to this region of the genome (LOD score >3). While members of one of these families exhibit typical features of ODD, the second family manifested type III syndactyly with no ophthalmological, dental or other skeletal features commonly reported in ODD (15). A number of pedigrees have been reported in which type III syndactyly occurs separately from classical ODD (11–14); given the linkage findings reported in family two of this study, it seems highly likely that the gene, or genes, underlying ODD/type III syndactyly are located at 6q22–q24. It is not, however, clear from our study whether the conditions are part of a contiguous gene syndrome or are allelic disorders. Given the recent findings that Crouzon, Pfeiffer, Jackson-Weiss, Apert and Beare-Stevenson cutis gyrata syndrome all may result from mutations in FGFR2 (18–22), it is tempting to speculate that ODD and type III syndactyly are allelic disorders.

While strong evidence for linkage of ODD to chromosome 6q has been presented, the distribution of recombination events in the six families has only allowed us to assign the gene to a large genetic interval. This being the case, the map location will have to be substantially refined before a contig/transcript map of the region can be completed and the mutated gene identified. An alternative approach is to identify a candidate gene mapping to the region which could be tested for disease-specific mutations. Nevertheless, in order to expedite the identification of the mutated gene, we would welcome knowledge of additional families with a history of ODD, which might be used to refine the mapping of the gene.

MATERIALS AND METHODS

Families

The pedigrees of the families used in the current study are presented in Figure 1. In all cases the patients were examined by an experienced clinician. In total, 54 individuals were available for study, 29 of whom were diagnosed as being affected. Families 2 and 3 have been described previously (15,16). Brief clinical details of the remaining families are given above.

Segregation analysis

Oligonucleotides were purchased from Research Genetics or synthesized on an ABI 391 oligonucleotide synthesizer. Twenty-five short tandem repeat polymorphisms from chromosomes 3, 6, 14, 15 and 17 were PCR-amplified from the genomic DNA of the above patients as previously described (25). The alleles were scored independently by two investigators and the data coded for genetic linkage analysis. The ODD locus was modeled as an autosomal dominant, two-allele system. The gene frequency and the penetrance in heterozygotes were taken as 0.00001 and 0.99, respectively. Pairwise analysis was performed using the MLINK routine of the LINKAGE package (26). Maximum-likelihood estimates of sex-averaged recombination were calculated using ILINK. Significance was evaluated using the standard criterion (Z >3.0).

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