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Familial Syndromic Esophageal Atresia Maps to 2p23-p24

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Summary

Esophageal atresia (EA) is a common life-threatening congenital anomaly that occurs in 1/3,000 newborns. Little is known of the genetic factors that underlie EA. Oculodigitoesophageoduodenal (ODED) syndrome (also known as “Feingold syndrome”) is a rare autosomal dominant disorder with digital abnormalities, microcephaly, short palpebral fissures, mild learning disability, and esophageal/duodenal atresia. We studied four pedigrees, including a three-generation Dutch family with 11 affected members. Linkage analysis was initially aimed at chromosomal regions harboring candidate genes for this disorder. Twelve different genomic regions covering 15 candidate genes (~15% of the genome) were excluded from involvement in the ODED syndrome. A subsequent nondirective mapping approach revealed evidence for linkage between the syndrome and marker D2S390 (maximum LOD score 4.51 at recombination fraction 0). A submicroscopic deletion in a fourth family with ODED provided independent confirmation of this genetic localization and narrowed the critical region to 7.3 cM in the 2p23-p24 region. These results show that haploinsufficiency for a gene or genes in 2p23-p24 is associated with syndromic EA.

Introduction

Esophageal atresia (EA) is a common life-threatening congenital condition. EA occurs in ~1/3,000 newborns (David and O’Callaghan 1975; Szendrey et al. 1985). EA is frequently associated with other congenital anomalies. Of these, the most common are other gastrointestinal atresias or stenoses, anomalies of the urinary tract, and heart defects (Kimble et al. 1997). This combination of features is often referred to as the “VATER association” (MIM 192350). In some cases, EA is associated with chromosomal abnormalities, such as deletions of 22q11 (Digilio et al. 1999), trisomy 18, and trisomy 21 (Beasley et al. 1997). A recent compilation of data on chromosomal deletions failed to identify any region that is specifically associated with EA (Brewer et al. 1998). Nonsyndromic EA is considered to be a multifactorial trait whose pathogenesis and causation are ill defined. The recurrence of EA in some families (van Staey et al. 1984) suggests a contribution of genetic factors. In addition, several families with dominantly inherited forms of syndromic EA have been reported. To identify a gene involved in EA, we are studying families with the autosomal dominant oculodigitoesophageoduodenal (ODED) syndrome (MIM 164280). This syndrome has been described under the following names: microcephaly-oculo-digito-esophageal-duodenal (MODED) syndrome, microcephaly mesobrachyphalangy and tracheoesophageal fistula (MMT) syndrome, and Feingold syndrome. The principal features of ODED syndrome are clinodactyly of the 2d and 5th fingers; toe syndactyly, typically of the 4th and 5th toes; microcephaly; short palpebral fissures; and esophageal/duodenal atresia (Feingold 1975; König et al. 1990; Brunner and Winter 1991; Courten et al. 1997; Feingold et al. 1997; Frydman et al. 1997; Innis et al. 1997). EA or duodenal atresia is present in ~33% of patients with ODED, whereas minor digital abnormalities are present in all
(Brunner and Winter 1991). We conducted a linkage study of ODED syndrome in a large Dutch family with 11 affected members, as well as in three other small families. We first excluded several chromosomal regions containing candidate genes. We then started a genome-wide scan on the remaining parts of the genome that were not covered by our candidate genes. Our results clearly indicate the presence of the ODED-syndrome gene in the p23-p24 region of human chromosome 2.

Subjects

The four families with syndromic EA that were analyzed in this study all showed autosomal dominant inheritance of the ODED-syndrome phenotype, including toe syndactyly, microcephaly, and esophageal and/or duodenal atresia (for pedigrees, see figs. 1 and 2). Family A was described by Brunner and Winter (1991); family B was described by Innis et al. (1997); and family C was described by Frydman et al. (1997). Family D is an unreported family whose records were contributed by R. Hennekam. Four additional isolated patients and small families with ODED syndrome (König et al. 1990; Courten et al. 1997; H.K. and J.T., unpublished data) were examined for mutations of the human SIX2 gene. In these small families, as well as in the isolated patients, the core features of ODED syndrome—namely, microcephaly, limb abnormalities, and EA or duodenal atresia—were present.

The family with nonsyndromic EA (fig. 3) lacked all other ODED-syndrome characteristics (specifically, microcephaly, short palpebral fissures, and limb abnormalities) and was evaluated by L.C.P.G.

Material and Methods

Materials from Patients

After informed consent was obtained, venous blood samples were collected from affected and unaffected family members. The DNA used in this study was isolated from peripheral blood lymphocytes of patients and relatives, as described elsewhere (Miller et al. 1988).

Microsatellite PCR and Data Analysis

Polymorphic markers used were derived mainly from the Généthon genetic map (Dib et al. 1996). PCR reactions were performed in a 12-μl volume containing 50 ng of DNA; 30 ng of each primer; 200 μM dATP, dGTP, and dTTP; 2.4 μM dCTP; 0.6 μCi α[32P]-dCTP; 10 mM Tris-HCl pH 9.0; 50 mM KCl; 1.5 mM MgCl2; 0.1% Triton-X100; and 0.3 U of Taq DNA polymerase (GIBCO-BRL Life Technologies). After initial denaturation at 94°C for 5 min, 35 cycles of amplification at 94°C for 1 min, at 55°C for 2 min, and at 72°C for 1 min, and a final extension at 72°C for 6 min were performed in a 96-well thermal cycler (M.J. Research). Amplified products were electrophoresed in 6.6% denaturing polyacrylamide gels and were visualized by autoradiography on Kodak X-OMAT films.

Linkage calculations were performed, by use of the LINKAGE package (version 5.03), on the basis of autosomal dominant inheritance, with full penetrance for the families with ODED syndrome and with incomplete penetrance (50%) for the family with nonsyndromic EA. The frequency of the mutant allele was set at .00001. Penetrance was set at 100% for the families with ODED, in accordance with other estimates (Brunner and Winter 1991). All patients with ODED have, at least, microcephaly and limb abnormalities. As for the setting of penetrance to 50% in the family with nonsyndromic EA, this was deduced from the pedigree, and it is in agreement with the penetrance of intestinal atresia in ODED syndrome.

DNA Sequence Analysis

Exon 1 of the SIX2 gene was amplified from genomic DNA, with the use of overlapping primers designed to amplify the six domain from the N terminus of the gene (Six2D + Six2B) and the homeobox domain (Six2A + Six2B). The primer sequences were as follows: Six2A, GCG TGC TCA AGG CCA AGG CCG TGG; Six2B, CCT GTC GCG CTG CCG CCG GTT CT; and Six2D, GCC ACC ATG TCC ATG TTG CC. PCR reactions were performed in a 50-μl volume containing 100 ng of DNA, 5 μM of each primer, 0.2 mM of each dNTP, 1.5 mM of MgCl2, 1 × PCR buffer (200 mM Tris-HCl pH 8.4, and 500 mM KCl) (GIBCO-BRL Life Technologies), and 1 U of Taq DNA polymerase (GIBCO-BRL Life Technologies). After initial denaturation at 94°C for 2 min, 35 cycles of amplification at 94°C for 30 s, at 70°C for 1 min, and at 72°C for 1 min, and a final extension at 72°C of 6 min were performed in a PE 480 DNA thermal cycler (PE Biosystems). Products were sequenced with use of the Big Dye Terminator Cycle Sequencing Ready Reaction Kit mix and were analyzed with a semiautomated sequencer, Applied Biosystems model 377 (ABI/PE Biosystems).

Fluorescence In Situ Hybridization (FISH)

Four DNA probes were applied in our experiments; all were derived from the WC2.2 YAC contig of the Whitehead Institute for Biomedical Research/MIT Center for Genome Research. To identify chromosome 2, a chromosome paint for 2q was used. FISH procedures were applied as described elsewhere (Suijkerbuijk et al. 1992). In brief, the probes were labeled with biotin-14-dATP (GIBCO-BRL Life Technologies) while paint 2q was labeled with digoxigenin-11-dUTP (Boehringer), by
Figure 1  Pedigrees used in the DNA-marker studies. Segregation of chromosome 2 markers is seen in the three-generation Dutch family with ODED syndrome (family A). The blackened bar indicates the haplotype that segregates with the disease. Affected patients III:5 and III:7 show recombination at markers D2S352 and D2S131, respectively. Pedigrees of the two smaller families with ODED syndrome (families B and C) confirm linkage to the 2p23-p24 region. A recombination at D2S390 in individual II:3 (family C) defines the proximal border of the linkage interval.
Figure 2  CA-repeat analysis of the microdeletion in 2p23-p24 in family D with ODED syndrome. In this family, the genotypes in the affected mother and daughter are inconsistent with Mendelian inheritance for the markers between D2S2199 and D2S320. In the affected daughter, these markers show only the father’s allele and not the allele that is present in the mother. The mother is also hemizygous for these markers. Note that marker D2S2267 is either homozygous or hemizygous in individual II:1.

Cloning and Mapping of Human SIX2

An 884-bp-long human SIX2 cDNA fragment containing the ATG and TAG codons was obtained by reverse-transcriptase (RT)-PCR, with the use of primers derived from the mouse Six2 gene sequence and of total RNA prepared, by means of the guanidinium thiocyanate method (Chomczynski and Sacchi 1987), from 31-wk-old human embryonic eyes. RT was performed with the use of oligo-(dT) as a primer and with Moloney murine leukemia virus RT. Confirmation that the sequence obtained was indeed human SIX2 was obtained by the comparison of its predicted amino acid sequence with the sequences of the human SIX1 and the mouse Six1 and Six2 genes. Mapping of the human SIX2 gene was performed with the Stanford Human Genome Center G3 Radiation Hybrid Panel (Research Genetics), by means of primers derived from the intronic sequences of the SIX2 gene.

Results

To uncover the genetic basis of ODED, we started our mapping efforts by focusing on chromosomal regions containing candidate genes. Candidate genes were selected on the basis of gene-expression patterns, the effect of knockout mutations in mice, and the physiological role of the corresponding proteins. We selected a total of 15 candidate genes on the basis of their prominent expression in developing esophagus and limb (e.g., PAX9; see Peters et al. 1997), on the basis of occurrence of EA in a knockout animal (e.g., Hoxc4; see Boulet et al. 1996), or because mutations in these genes caused
other forms of intestinal atresias (e.g., ITGa6; see Pulkkinen et al. 1997). Genes encoding proteins involved in retinoic-acid metabolism—such as CRABP, RAR, and RXR—were considered candidates because of their role in apoptotic processes in early development (Båvik et al. 1997; Brickell et al. 1997; Dickman et al. 1997). We also tested genomic regions in which deletions are associated with limb abnormalities that match those of ODED syndrome (13q14-qter and 2q24-q31) (Brunner and Winter 1991; Boles et al. 1995). In total, 12 different regions of the genome were selected. These loci were tested with markers at intervals of 5–10 cM in family A shown in figure 1. No linkage was detected, which allowed us to exclude ~15% of the genome. We then started a genomewide linkage analysis in family A, to cover those areas not excluded by our candidate gene-directed screening. Linkage was almost immediately detected with marker D2S170 (maximum LOD score \( Z_{\text{max}} = 3.91 \) at recombination fraction \( \theta = 0 \)) from the 2p23-p24 region. Positive LOD scores were also found with markers D2S390, D2S149, D2S352, and D2S168 (table 1). Linkage was then confirmed for the two smaller families (families B and C) (fig. 1). Families A–C together gave \( Z_{\text{max}} = 4.51 \) at \( \theta = 0 \) for D2S390 (table 1). These cumulative two-point linkage results were confirmed by multipoint linkage analysis that showed the presence of association with the disease, between markers D2S131 and D2S390, with \( Z_{\text{max}} = 5.1 \) at marker D2S144. Haplotype analysis in family A (fig. 1) showed a recombination event between the disorder and marker D2S131 in affected individual III:7, which demarcates the distal border of the linkage interval. Recombination at marker D2S352 in an affected male (individual III:5) established the proximal border of the region. Haplotype analysis of the two other small families with ODED syndrome showed a recombination event between markers D2S170 and D2S144 in an unaffected sibling (individual II:2) in family C. With the assumption of complete penetrance, this crossover event restricts the linkage area to 18 cM between D2S170 and D2S131. The haplotype of family C also showed a recombination within the minimal linkage region at marker D2S170 in II:3 (fig. 1). In family D, initial analysis showed that the chromosome 2 marker alleles in the affected mother and daughter are inconsistent with Mendelian inheritance for marker D2S149 (fig. 2). Alternative primers were designed for marker D2S149. Identical results were obtained, indicating that this apparently null allele could not be explained by a polymorphism in the primer sequences. Absence of a maternally inherited allele in individual II:1 was also detected for markers D2S2267, D2S149, D2S2295, D2S2346, D2S2155, and D2S332. The mother and the daughter each carried only a single allele for these markers. These data are consistent with the presence of a microdeletion of 2p23-p24, inherited by an affected daughter from her affected mother (fig. 2). The microdeletion was confirmed by in situ hybridization, by use of YACs 953G11, 916C7, and 875B11 (fig. 3 and data not shown). Each of these YACs gave only a single hybridization signal. We also tested these YACs for the presence of markers used in the marker study: D2S2346 was present in YAC 953G11; D2S312 gave signal in YAC 916C7 and in YAC 875B11. Other markers used in this study that have been reported to be present in these YACs (Whitehead Institute for Biomedical Research/MIT Center for Genome Research) are markers D2S2155 and D2S332, which are present in YAC 953G11, and marker D2S2346, which is present in YAC 916C7.

For markers D2S2199 and D2S320, two alleles were present in the affected child as well as in the mother. Therefore, these markers are outside the deletion, on either side (fig. 2). Marker D2S2267 showed only a single allele in the affected daughter. Whether this represents homozygosity or hemizygosity cannot yet be determined.

### Table 1

Combined Maximum LOD Scores for Families A–C with ODED Syndrome

<table>
<thead>
<tr>
<th>Interval (cM)</th>
<th>Marker</th>
<th>( Z_{\text{max}} )</th>
<th>( \theta )</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.7</td>
<td>D2S168</td>
<td>1.614</td>
<td>.143</td>
</tr>
<tr>
<td>.0</td>
<td>D2S2200</td>
<td>2.047</td>
<td>.108</td>
</tr>
<tr>
<td>2.9</td>
<td>D2S131</td>
<td>3.393</td>
<td>.050</td>
</tr>
<tr>
<td>12.3</td>
<td>D2S149</td>
<td>3.608</td>
<td>.001</td>
</tr>
<tr>
<td>2.7</td>
<td>D2S144</td>
<td>3.007</td>
<td>.001</td>
</tr>
<tr>
<td>.7</td>
<td>D2S170</td>
<td>2.891</td>
<td>.064</td>
</tr>
<tr>
<td>6.4</td>
<td>D2S390</td>
<td>4.510</td>
<td>.001</td>
</tr>
<tr>
<td></td>
<td>D2S352</td>
<td>2.342</td>
<td>.106</td>
</tr>
</tbody>
</table>

\* Between marker indicated and that on line below.
Figure 4  Pedigree of family E with nonsyndromic familial EA. Marker D2S149 segregates with the nonsyndromic form of familial EA. A recombination in individual IV-1 excludes markers proximal to D2S144.

determined. The combined data from the linkage analysis in families A–C and the microdeletion in family D are consistent with a localization of the ODED-syndrome gene in 2p23-p24, between markers D2S2199 and D2S320.

It is currently unknown whether ODED syndrome is due to a mutation in a single gene or whether it might represent a contiguous-gene syndrome. Our finding of a small submicroscopic deletion in family D is consistent with both hypotheses. We decided to explore the hypothesis of a contiguous-gene syndrome by examining a family with nonsyndromic EA, for linkage to 2p23-p24. Interestingly, haplotype analysis in this small family with nonsyndromic EA (fig. 4) is also consistent with an assignment to 2p23-p24. However, the small size of this family precludes more-definitive conclusions, and the LOD score is only 0.35.

We identified the SIX2 gene as a possible candidate, on the basis of homology mapping. The SIX2 gene is a member of the expanding family of homologues of the Drosophila sine oculis gene (Oliver et al. 1995). SIX2 maps on mouse chromosome 17, between Lhcgr (luteinizing hormone/choriogonadotropin receptor) and Sos1, both of which map to 2p21-p22 in humans. This suggests that the human SIX2 gene might also map to this region. The pattern of mRNA expression during embryogenesis of SIX2 in the mouse is strikingly similar to what might be expected for the ODED-syndrome gene. SIX2 has prominent expression in the esophagus, pyloric region, hindbrain, and interdigital mesenchyme (Oliver et al. 1995). We used primers to amplify 546 bp of the human SIX2 cDNA sequence containing the Six and homeobox domains (fig. 5). The analysis failed to identify any abnormalities in a panel of eight unrelated patients with ODED syndrome. Mapping of the human SIX2 gene was performed with the Stanford Human Genome Center G3 Radiation Hybrid Panel (Research Genetics), by use of primers derived from the intronic sequences of the SIX2 gene. The statistical evaluation of the results confirmed the predicted location for SIX2 and placed it on chromosome 2, 20 cM from sequence-tagged-site marker SHGC-11647 (LOD score 5.76), within the 5.2-cM interval defined by
twice.

The SIX domain is underlined; and the homeobox domain is underlined in italic lowercase type; start and stop codons are in boldface type; and Génèthon markers D2S119 and D2S288. This is outside Figure 5.

Figure 5 Human SIX2 partial cDNA sequence. Primers used are in italic lowercase type; start and stop codons are in boldface type; and the SIX domain is underlined; and the homeobox domain is underlined twice.

We report the assignment of a gene for the autosomal dominant syndrome of EA, syndactyly, and microcephaly (ODED or Feingold syndrome) to the short arm of chromosome 2. Significant evidence for linkage was obtained in a large Dutch kindred. Analysis of two smaller kindreds confirmed the original assignment and narrowed the interval to a 18.3-cM region between markers D2S131 and D2S170.

In a smaller family, an apparently null allele for markers D2S2267, D2S149, D2S2295, D2S2346, D2S2155, and D2S332 was inherited by an affected daughter from her affected mother. These findings are best explained by a microdeletion in 2p23-p24. This interpretation was supported by FISH analysis, which indicated the presence of a single copy of probes from 2p23-2p24. The combined data from the linkage analysis and from the microdeletion suggest that the critical region for the ODED-syndrome gene lies in a 7.3-cM region between markers D2S2199 and D2S320 (fig. 6).

The SIX2 gene appeared to be a strong candidate, on the basis of its expression pattern during mouse development (Oliver et al. 1995) and its localization in a mouse chromosome 17 region that is syntenic to human 2p21-p22. However, the lack of mutations in SIX and homeobox domains of SIX2 in eight unrelated families with ODED syndrome and the subsequent localization of SIX2 outside the ODED-syndrome critical interval, by means of radiation-hybrid mapping, excluded SIX2 as the ODED-syndrome gene.

The ODED linkage region contains the locus for syndecan-1 precursor (SYND1), which is a possible positional candidate gene. The syndecans are a family of cell-surface heparan sulfate proteoglycans that interact with adhesion molecules, growth factors, and a variety of other molecules. SYND1 is thought to function as a receptor for extracellular-matrix components and growth factors that are differentially expressed during development (David et al. 1993). Synd1 is strongly expressed in esophageal, facial, and digital mesenchyme in mouse embryos (Mitsiadis et al. 1995). Fine mapping of the SIX2 gene will be required in order to establish whether the gene is contained within the deletion area in family D.

Study of knockout mice may help to unravel the pathways that are involved in normal esophageal development. Several such targeted mutations have been reported to be associated with EA, but none of these genes map to the ODED-syndrome critical region. EA is present in mice mutants carrying nonfunctional alleles of Hoxc4 (Boulet and Capecchi 1996) and in mice that have a homozygous null mutation for the Gli2 gene (Mo toyama et al. 1998). The human Gli2 gene is located in 2q14, which is well outside the ODED-syndrome region identified here. Similarly, the occurrence of EA in mice that have a homozygous null mutation of the sonic hedgehog (Shh) gene (Litingtung et al. 1998) does not provide a likely explanation for EA in humans. The SHH gene is located on chromosome 7q36 in humans, and mutations are specifically associated with holoprosencephaly (Roessler et al. 1996).

Like many other structural malformations in humans, isolated EA is probably a multifactorial disorder. A number of familial cases have been identified (Casteels et al. 1993), but the actual recurrence risk is only ~1% in sporadic cases (van Staey et al. 1984). Because ODED syndrome carries a 30% risk of EA and/or duodenal atresia and because ODED syndrome is probably still underdiagnosed, it is possible that most cases of familial EA are in fact due to this syndrome. We have already identified four families with ODED syndrome from the Netherlands alone, indicating that the syndrome may not be extremely rare. Also, the microcephaly associated with the syndrome is mild and is associated with minimal learning disability or even normal intelligence (Brunner and Winter 1991; Feingold et al. 1997; Kawame et al. 1997). Some cases lack the distinctive toe syndactyly (Feingold et al. 1997) and may easily be misdiagnosed as nonsyndromic EA. Our finding of a microdeletion in 2p23-p24 in family D raises the possibility that ODED syndrome could represent a contiguous-gene syndrome. In this regard, it is of interest that the results of haplotype analysis conducted on a small family with nonsyndromic familial EA are consistent with a causative gene in 2p23-p24 (fig. 4). Families with autosomal dominant microcephaly (Rossi et al. 1987) and families with autosomal...
Figure 6  Comparison of linkage intervals for families A–C with ODED syndrome, the microdeletion in family D (the diagonally barred area indicates possible reduction of the deleted area; see text), and the cosegregating haplotype in nonsyndromic family E. In family E, the linkage interval continues more distally. Distances (in cM) between each marker and the next are indicated and are computed on the basis of average distances on the Généthon map for chromosome 2 (Dib et al. 1996).

dominant EA (Pletcher et al. 1991) but without other ODED-syndrome characteristics have been reported. If such families are also consistent with linkage to 2p23-p24, this would strengthen the hypothesis that ODED syndrome is in fact a microdeletion syndrome.

The best name for the syndrome studied here remains to be found. In view of the expanding phenotype, which now includes deafness and kidney anomalies in some cases, we suggest that the term “Feingold syndrome” be used, in preference to the acronyms “ODED,” “MODED,” or “MMT.”

In conclusion, haploinsufficiency of a gene or genes in 2p23-p24 causes syndromic EA (Feingold or ODED syndrome). Cloning of the ODED-syndrome gene should shed light on a significant proportion of inherited EA.

Acknowledgments

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Electronic-Database Information

Accession numbers and URLs for data in this article are as follows:

Généthon, http://www.genethon.fr/
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for VATER association [MIM 192350] and ODED syndrome [MIM 164280])
Stanford Human Genome Center, http://www-shgc.stanford.edu/
Whitehead Institute for Biomedical Research/MIT Center for Genome Research, http://www-genome.wi.mit.edu/

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