Identification of the Gene for Oral-Facial-Digital Type I Syndrome

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Oral-facial-digital type 1 syndrome (OFD1 [MIM 311200]) is transmitted as an X-linked dominant condition with lethality in males and is characterized by malformations of the face, oral cavity, and digits, and by a highly variable expressivity even within the same family. Malformation of the brain and polycystic kidneys are commonly associated with this disorder. The locus for OFD1 was mapped by linkage analysis to a 12-Mb interval, flanked by markers DXS85 and DXS7105 in the Xp22 region. To identify the gene responsible for this syndrome, we analyzed several transcripts mapping to the region and found mutations in *OFD1* (formerly named "*Cxorf5/71-7a*"), encoding a protein containing coiled-coil α-helical domains. Seven patients with OFD1, including three with familial and four with sporadic cases, were analyzed. Analysis of the familial cases revealed a missense mutation, a 19-bp deletion, and a single base-pair deletion leading to a frameshift. In the sporadic cases, we found a missense (de novo), a nonsense, a splice, and a frameshift mutation. RNA in situ studies on mouse embryo tissue sections show that *Ofd1* is developmentally regulated and is expressed in all tissues affected in OFD1 syndrome. The involvement of *OFD1* in oral-facial-digital type I syndrome demonstrates an important role of this gene in human development.

Introduction

Oral-facial-digital syndromes (OFDS) are a heterogeneous group of developmental disorders of which at least nine different forms have been described (Toriello 1993). Oral-facial-digital type 1 (OFD1 [MIM 311200]) syndrome was first reported in 1954 by Papillon-League and Psaume (1954) and was further defined in 1962 by Gorlin and Psaume (1962). This syndrome is transmitted as an X-linked dominant condition with lethality in males (Doege et al. 1964; Wettke-Schafer and Kantner 1983) and is characterized by malformations of the face, oral cavity, and digits. Dysmorphic features affecting the head include facial asymmetry, hypertelorism, micrognathia, broadened nasal ridge, and facial milia. Oral cavity lesions reported for this syndrome are median pseudoclefting of the upper lip (45%), clefts of the palate (>80%) and tongue (30%), and oral frenulae. Thickened

alveolar ridges and abnormal dentition, including absent lateral incisors, are additional characteristics of OFD1. The digital abnormalities, which affect the hands (50%–70%) more often than the feet (25%), include syndactyly, brachydactyly, clinodactyly, and, more rarely, pre- or postaxial polydactyly. The CNS may also be involved in as many as 40% of cases. Involvement of the CNS includes mental retardation, hydrocephalus, cerebellar anomalies, porencephaly, and agenesis of the corpus callosum (Towfighi et al. 1985; Connacher et al. 1987). In recent years, with the introduction of high-resolution renal ultrasound scanning, it has become evident that polycystic kidney disease is commonly associated with OFD1 (Connacher et al. 1987; Donnai et al. 1987; Scolari et al. 1997), with reports of patients in whom the renal involvement completely dominates the clinical course of the disease (Coll et al. 1997; Feather et al. 1997a).

These clinical features overlap with those reported in the other nine forms of OFDS (Toriello 1993), although among these, OFD1 can be easily distinguished, because of its X-linked dominant inheritance pattern and because of the polycystic kidney disease, which seems to be specific to type 1. The locus of OFD1 was first mapped by linkage analysis to a 19.8-cM interval, flanked by crossovers with markers DXS996 and DXS7105 in the Xp22 region (Feather et al. 1997b).

More recently, the interval was narrowed by Gedeon et al., to a 12-Mb interval of the same region (1999).

Patients, Material, and Methods

Patients

We screened, by direct sequencing, genomic DNA from three familial and four sporadic cases. Although there is overlap with other oral-facial-digital syndromes, the phenotype of OFD1 is highly specific (Toriello 1993), and all patients included in this study were diagnosed with OFD1. In particular, the familial cases were selected on the basis of the X-linked inheritance and/or because of the presence of polycystic kidneys. A summary of the clinical features is given in table 1. An example of the digit anomalies and an ultrasound scan displaying the polycystic lesions reported for this syndrome are provided in figure 1.

Mutation Analysis

Primers and conditions used for mutation analysis are available at the TIGEM website. PCRs were performed, by means of the Gentra systems Capture Column Kit, on genomic DNA extracted from peripheral blood leukocytes. Using the ABI Prism Big Dye Terminator Cycle Sequencing Kit (PE Biosystems) and an ABI 377 automated DNA sequencer, we checked PCR products on agarose gel and then sequenced them on both strands. When necessary, PCR amplification products were cloned, by means of the TOPO TA cloning kit supplied by Invitrogen, to separate the mutant and wild-type alleles. Ninety normal X chromosomes from white individuals were analyzed by SSCP for exons 3, 11, and 13, as described (Orita et al. 1989), whereas the same number of chromosomes were analyzed for exon 16 by denaturing high-performance liquid chromatography, using the Wave DNA fragment analysis system (Transgenomic, Inc.), according to the manufacturer's instructions. Mutation description follows standard nomenclature (Antonarakis 1998). All the patients and controls used in this study were white, and ethical approval was obtained by the universities and research institutes involved in this study.

In Situ Hybridization Studies

RNA in situ studies were performed on mouse tissue sections at E10.5, E12.5, E14.5, and E16.5, by means of radioactive in situ hybridization, according to published protocols (Rugarli et al. 1993). The sense strand of the same fragment did not reveal any detectable signal above the background level (data not shown).

Results

A systematic mutation analysis of genes located in Xp22 in seven female patients with OFD1 was done. Six candidate genes (*MSL3L*1, *MAEG*, *RAB 9*, *STK9*, *M1D1*, and *pirin*) were selected on the basis of their known functions and/or expression patterns and were excluded by mutation analysis (B. Franco, unpublished data; Prakash et al. 1999; Buchner et al. 2000). We then decided to analyze *Cxorf5* (alias 71-7a) (GenBank accession numbers Y15164 and Y16355), one of the first transcripts to be assigned to the X chromosome (Kunkel et al. 1983) and included in the OFD1 critical region (de Conciliis et al. 1998). Characterization of the cDNA clones revealed the existence of two alternative transcripts—namely, *Cxorf5*-1 and *Cxorf5*-2, which are differentiated by the use of an alternative 3′ splice site. The *Cxorf5*-1 transcript is predicted to encode a 1011–amino acid protein with a molecular mass of 116 kDA, whereas *Cxorf5*-2 encodes a predicted protein of 367 amino acids, containing the first 351 residues of the Cxorf5-1 protein and an alternative C-terminal region of 16 amino acids (de Conciliis et al. 1998). Searches of nonredundant DNA and databases with the BLAST algorithm, using both the Cxorf5-1 and the Cxorf5-2, predicted proteins; queries did not reveal significant homology with previously characterized genes and proteins except for the presence of coiled-coil domains (data not shown; de Conciliis et al. 1998). Using genomic sequences available in public databases (GenBank accession number AC003037), we designed primers for PCR amplification of all 23 coding exons, including splice junctions. *Cxorf5* was reported to have related loci on both Yq11.22 (Cyorf1) and 5p13 (C5orf1) regions (de Conciliis et al. 1998). Cyorf1 represents a pseudogene (de Conciliis et al. 1998). Concerning C5orf1, Blastn searches of the htgs and gss databases, using the *Cxorf5* sequence as query, reveals a genomic sequence corresponding to the C5orf1 locus (AC025449). This sequence is colinear with most of the coding region of the *Cxorf5* transcript and does not contain introns (data not shown). On the basis of these results, primers were designed in order to specifically amplify the X chromosome transcript.

Mutation Studies

The patients included in this study were analyzed for the 23 coding exons of the *Cxorf5* gene. Mutations were identified in all the patients, and a summary of the results is reported in table 2. Among the familial cases, we identified a missense mutation and two intragenic deletions. In family 1, a 1303 A→C transversion, which changed a polar amino acid (serine) to a basic amino acid (arginine) at codon 434 (S434R), was identified (table 2).

Table 1

Clinical Features of Patients with OFD1 Who Were Included in the Study

Family (Case[a])	Anomalies					
	Oral	Facial[b]	Hand/Foot	Cerebral	Kidney	Miscellaneous[b]
1 (F)	Hamartomas, dental anomalies, cleft tongue, highly arched palate	Skin milia, dolichocephaly, down-slanting palpebral fissures	...	Suprasellar expansive lesion, mild mental retardation	...	Alopecia, coarse hair
3 (F)	Cleft palate, frenula, lingual hamartomas	Alar hypoplasia	Polydactyly, short second right toe	Cysts of cerebral hemisphere	Polycystic	...
4 (F)	Cleft palate/upper lip	Facial asymmetry	Clinodactyly, syndactyly	Moderate mental retardation, mild cerebral atrophy	Polycystic	Alopecia, dry hair, liver/pancreatic cysts
6 (S)	Frenula, cleft gums, lingual hamartomas	Skin milia	Syndactyly	...	...	...
10 (S)	Cleft lip/palate	NA	Syndactyly	...	...	NA
27 (S)	Cleft palate, dental anomalies, tongue-tied	Skin milia	...	Learning difficulties	Polycystic	...
28 (S)	Cleft palate/upper lip, dental anomalies	Skin milia	Brachydactyly, clinodactyly	Learning difficulties	...	Patchy alopecia

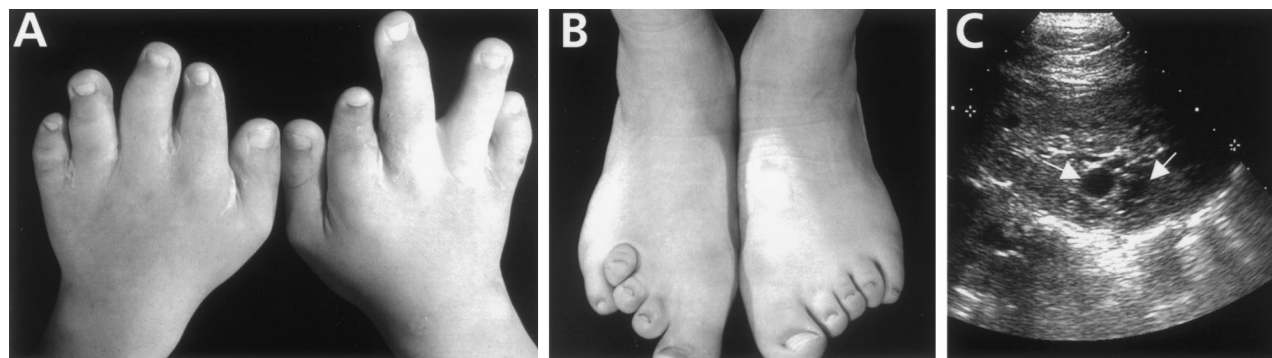[a] F = familial; S = sporadic.
[b] NA = not available.

Figure 1   *A* and *B*, Upper- and lower-digit abnormalities in a 12-year-old girl with OFD1. Note brachydactyly and syndactyly. *C*, Ultrasound scan of kidney of the same individual who is depicted in *A* and *B*. She had chronic renal excretory failure and polycystic kidneys: note the cysts (*white arrows*), up to 1 cm in diameter, located in the parenchyma of the organ.

DNA from the affected mother and grandmother was analyzed, and the same mutation was recognized, although the father's DNA displayed a normal pattern (data not shown). In family 3 (Odent et al. 1998), a deletion of a G at nucleotide 312, leading to a frameshift, was identified (table 2). This deletion was confirmed after cloning and analysis of the two distinct alleles. The same mutation was also identified in DNA extracted from an affected female fetus aborted after a 5-wk-old pregnancy from the family described elsewhere (data not shown).

Sequence analysis of family 4 (Scolari et al. 1997) revealed an abnormal pattern, and the study of the two separate alleles identified a deletion of 19 bp in exon 3, leading to a frameshift (fig. 2). This family was studied by SSCP, and although the same abnormal shift was observed in the affected daughter and mother, the father and the unaffected son and daughter displayed a normal pattern. These results were confirmed by sequence analysis and demonstrate that, in this family, the mutation segregates with the disease.

Among the sporadic cases, we identified one missense, one nonsense, one splice, and one frameshift mutation

(table 2). In family 6, a 121 C→T transition creates a termination codon TGA (R41X) in exon 3. DNA samples from this patient's parents were not available for molecular studies. In family 10, a deletion of eight bases, followed by an insertion of eight bases, causes the substitution of three amino acids: basic, acid, and acid (KDD), respectively, with another three amino acids: hydrophobic, polar, and polar (FSY) (fig. 3). We analyzed DNA samples from both parents by direct sequencing, and no abnormalities were found, which demonstrates that this is a de novo mutation. In family 27, a 312 + 2 deletion of six bases (taaagt) was identified, 312 + 2del(6), and similar mutations have been shown to disrupt splicing. A deletion of a G at base 1757, resulting in a frameshift, was identified in family 28 (table 2). For both of these latter mutations, maternal DNA was analyzed and revealed a normal pattern; the father's DNA was not available for the study. Thus, since OFD1 is an X-linked dominant male lethal condition, these can be considered de novo mutations. None of the mutations found in patients with OFD1 were identified in 90 normal X chromosomes, which were analyzed for exons 3, 11, 13, and 16.

Table 2

Mutations in Patients with OFD1

Family (Case[a])	Location	Nucleotide Change[b]	Effect on Protein
1 (F)	Exon 13	1303A→C	S434R
3 (F)	Exon 3	312delG	Frameshift
4 (F)	Exon 3	294–312delTGGTTTGGCAAAAGAAAAG	Frameshift
6 (S)	Exon 3	121C→T	Nonsense mutation
10 (S)	Exon 11	1071–1078 del GAAGGATG / 1071–1078 ins TTTTTCCT	KDD 357–359del/FSY 357–359ins
27 (S)	Intron 4	312+2del (6)	Abnormal splicing
28 (S)	Exon 16	1757delG	Frameshift

    [a] F = familial; S = sporadic.
    [b] Mutation description is according to standard nomenclature, with the cDNA sequence of *OFD1* used as the reference and with the ATG translation-initiation codon numbered as +1.
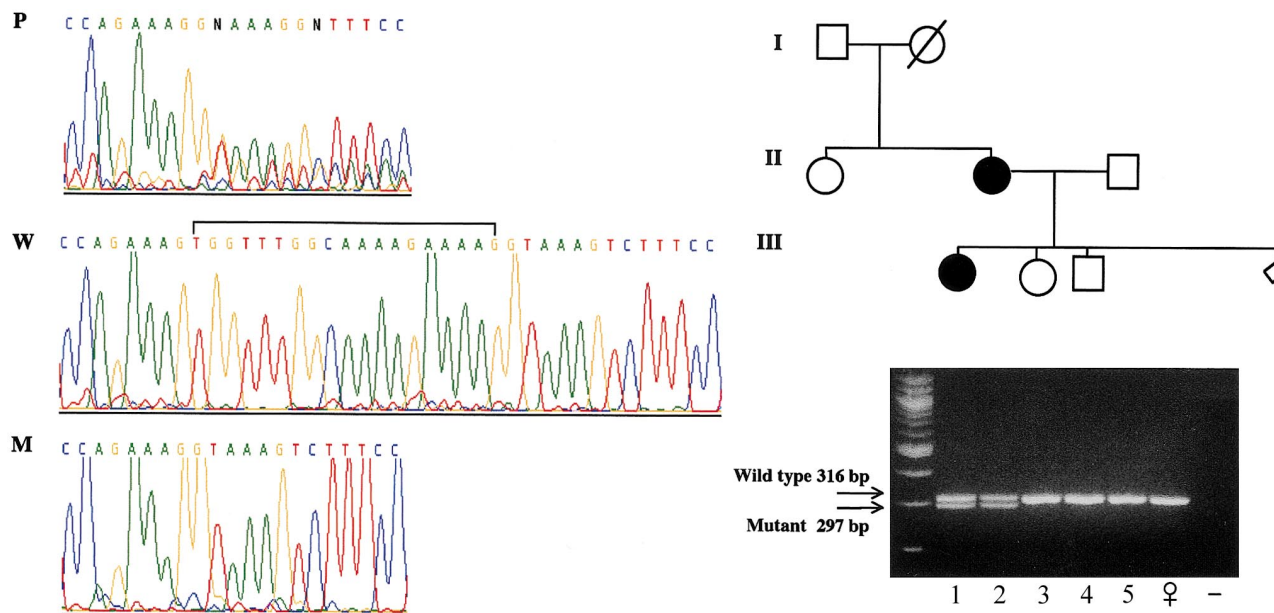
Figure 2 Analysis of family 4. *Left panel,* Sequencing chromatograms showing the genomic sequence of the affected individual (P) and of wild-type (W) and mutant (M) alleles. Note the presence of double peaks in the patient's DNA, downstream of the deletion due to the presence of both normal and out-of-frame alleles. In the wild-type allele, the 19-bp deletion is indicated by a horizontal bracket. Single alleles have been separated by cloning the PCR products. *Right panel,* Segregation of the 19-nucleotide deletion with the disease phenotype in family 4. After visualization of the PCR products on a 4% agarose gel, two different bands, corresponding to the wild-type (316-bp) and the mutant (297-bp) alleles, appear in the affected individuals (lanes 1 and 2), whereas only the wild-type band is visible in the unaffected individuals (lanes 3–5). In the next-to-last lane, a normal female control is depicted. In the last lane, the PCR-negative control (no DNA) is reported. The lozenge in the genealogical tree indicates an aborted fetus of unknown sex.

Expression Studies

Studies have shown that OFD1 is expressed in all adult tissues examined (pancreas, kidney, skeletal muscle, liver, lung, placenta, brain, and heart) (de Conciliis et al. 1998). To investigate the spatiotemporal expression of this transcript during development, a partial murine cDNA expressed-sequence tag (IMAGE 656917 was identified by BLAST analysis from the Expressed Sequence Tags database, was entirely sequenced, and was used for RNA in situ studies on mouse-embryo tissue sections at different developmental stages. The first site of expression was sharply and exclusively detected at 12.5 days of gestation in the genital ridges.

At later stages (E14.5 and E16.5), *Ofd1* expression is not only confined in the developing gonads, but high-to-moderate levels of expression are detected in various craniofacial structures and in the nervous system. In particular, *Ofd1* is highly expressed in the epithelium lining the oral and nasal cavities, including the tongue and the gum region, in the developing tooth buds, in the Rathke's pouch (primordium of the adenohypophysis), and in the vibrissae follicles (fig. 4a–f). The transcript is also highly represented in the following structures: the proliferative and postmitotic layers of the cerebral cortex and ganglionic eminences (anlage of the basal ganglia),

the neural retina, the inner ear, and the dorsal root ganglia. Postnatally, the expression in the CNS is diffuse to all the structures but has a higher level in the hippocampus and cerebellum (fig. 4g). Other organs expressing *Ofd1* at a lower level are the integumentary system, the lung, the thymus, and the kidney (fig. 4 and data not shown).

Discussion

On the basis of the results presented in this paper, we conclude that mutations in *Cxorf5* are the cause of OFD1 in the patients we analyzed, and we thus named the transcript *OFD1* (Human Gene Nomenclature Committee–approved gene symbol and gene name. Most (6/8) of the mutations identified so far lead to a premature truncation of the protein in its N-terminal region and are therefore predicted to act with a loss of function mechanism. However, due to interference with wild-type proteins in females, we cannot rule out the possibility that truncated OFD1 proteins act with a dominant-negative effect.

OFD1 is the first gene for an X-linked dominant male lethal disorder found to escape X inactivation (de Conciliis et al. 1998). Apparently, in affected females, one
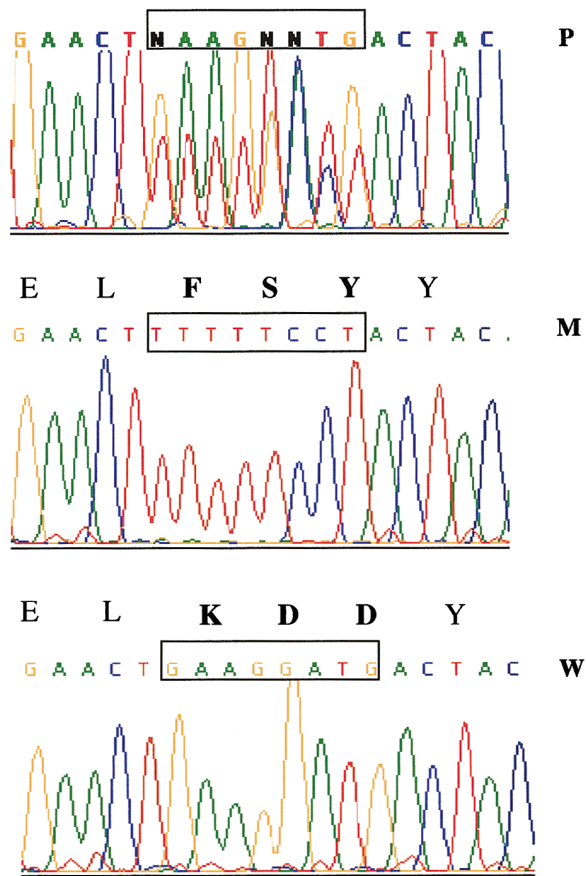
Figure 3 Mutation of *OFD1* in family 10. The DNA-sequence fluorogram of the patient's DNA for exon 11 displays eight double peaks that result from the presence of both the wild-type and the mutant alleles (*top*). After the PCR product was cloned, the wild-type allele (*bottom*) and the mutant allele (*middle*) were analyzed separately. The corresponding amino acid sequence is shown above the nucleotide sequence; the interchange of nine nucleotides results in a change of the three amino acids shown in boldface type.

normal copy is not sufficient to protect from the disorder. It is conceivable to hypothesize that normal males who carry only one normal copy of *OFD1* may display a higher expression of the transcript on the single active X chromosome, but further studies are needed to compare, from a quantitative point of view, the level of expression of this transcript in both sexes. A similar mechanism has been reported for the Clc4 gene, which is X linked and subject to X inactivation in Mus spretus but autosomal in laboratory strains of mice (Rugarli et al. 1995). Quantitative analysis demonstrated that, compared with the single active X-linked locus, each autosomal locus has half the level of Clc4 expression (Adler et al. 1997). An alternative hypothesis is that *OFD1* undergoes X inactivation in the tissues affected in OFD1 syndrome at developmental stages when its function is necessary. Therefore, some tissues of affected females at certain stages during development may result in *OFD1* functional nullisomy, by inactivation of the normal X. Individual variation in the X-inactivation pattern of this gene may also explain the clinical variability observed in OFD1 syndrome. More detailed X-inactivation studies are needed to test this hypothesis.

Prior study had shown that OFD1 is ubiquitously expressed in adult tissues. Since the clinical features observed in this syndrome are suggestive of a developmental disorder, we decided to study the expression pattern of the *Ofd1* gene during development in mouse-embryo tissue sections.

Our studies showed a high-to-moderate level of expression in various craniofacial structures and in the nervous system, and lower levels of expression were also detected in the integumentary system, the lung, the thymus, and the kidney. These sites of expression correlate well with the tissues affected in patients with OFD1.

OFD1 is characterized by craniofacial anomalies, such as facial skin milia, alar hypoplasia (broadened nasal ridge), and facial asymmetry; oral anomalies include hamartomas, clefts of lip and palate, and dental abnormalities. Consistently, expression of *Ofd1* is detected in the olfactory and respiratory epithelium of the nasal cavities and nasopharynx, in several ectodermally derived structures of the mouth and palate (upper lips, the surface epithelium of the gum region of the mouth, and tooth primordia), and in the endoderm-derived surface epithelium of the tongue and oropharynx (fig. 4*a–f*). OFD1 is also characterized by an involvement of the CNS in as many as 40% of the cases with reports of mental retardation, seizures, and other neurological defects (Towfighi et al. 1985; Connacher et al. 1987). In the embryonic nervous system (E14.5 and E16.5), *Ofd1* expression is specifically detected in telencephalic primordia of the cerebral cortex and striatum, as well as in cranial and dorsal root ganglia (fig. 4*a–f*). In postnatal brain (P12.5), *Ofd1* transcript is detected in all structures, although with a specifically higher expression in the hippocampal region (fig. 4*f*). *Ofd1* is also expressed at lower levels in the lung, the thymus, the integumentary system (surface ectoderm and vibrissae follicles) and the kidney, which can be related to the alopecia and hair problems and with the kidney abnormalities reported for this syndrome (fig. 4*a–f* and data not shown).

Since OFD1 shares no sequence homologies—apart from the presence of coiled-coil domains—with other proteins having known functions either in mammals or in lower organisms, it is difficult at this point to predict its function. The presence of several coiled-coil domains suggests that OFD1 acts via a protein-protein interaction mechanism. Identification of OFD1 protein interactors may lead to the discovery of novel genes involved in mammalian development and possibly implicated in
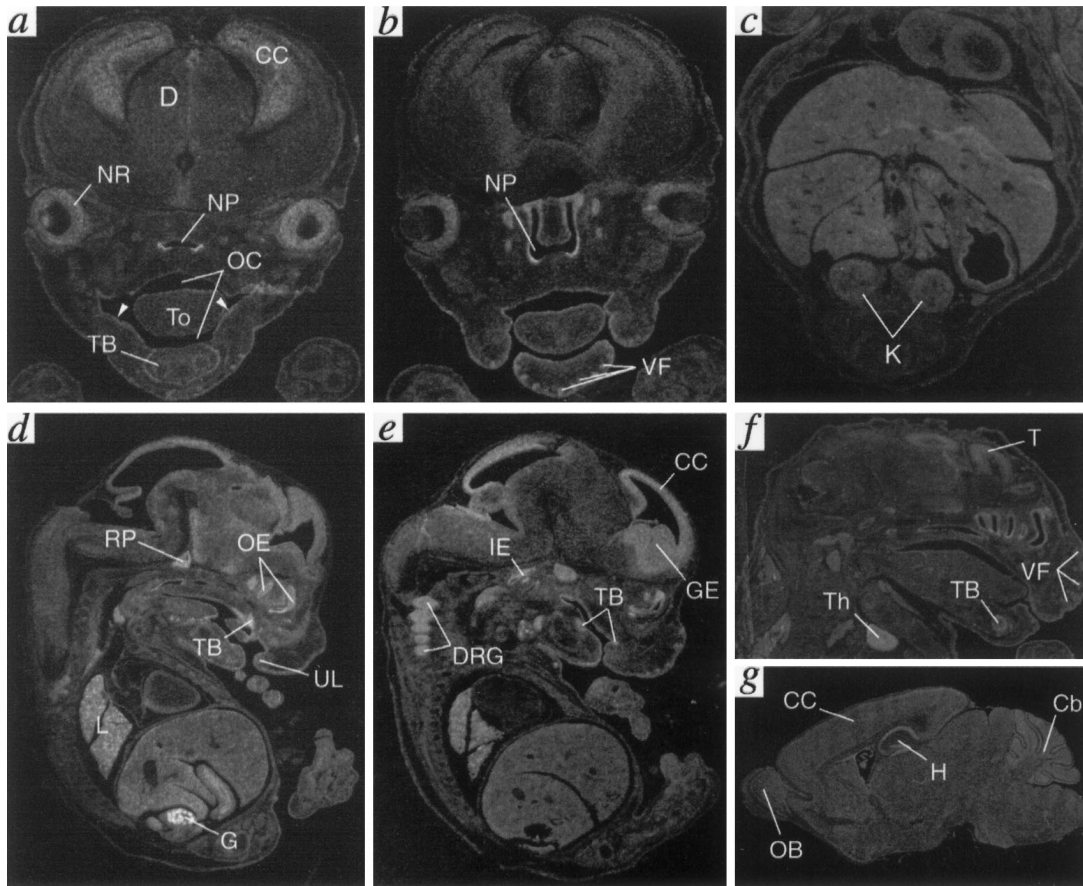
Figure 4   Expression analysis of *Ofd1,* revealed by in situ hybridization

other types of OFD syndromes. Furthermore, since OFD1 is often associated with polycystic kidney, it is intriguing to note that PKD1 and PKD2, the genes responsible for autosomal dominant polycystic kidney disease, physically interact through a coiled-coil domain (Qian et al. 1997).

The mouse mutant with X-linked dominant polydactyly (Xpl) maps to the region of the mouse X chromosome, where the murine counterpart of Ofd1 has been localized (Sweet and Lane 1980; de Conciliis et al. 1998). This mutant is characterized by urogenital malformations (hydroureter, hydronephrosis, and cystic or absent kidneys) and polydactyly (Sweet and Lane 1980), and may be considered the possible mouse model of OFD1. We are currently testing whether mutations in *Ofd1* may be responsible for the Xpl phenotype. If this is the case, the availability of a mouse model will allow functional studies toward the understanding of the pathogenesis of this syndrome.

In conclusion, the identification of the first gene involved in OFDS will be instrumental in the elucidation of the molecular mechanisms underlying this complex group of developmental disorders and may shed new light on the pathogenesis of polycystic kidney disease.

Electronic-Database Information

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

Expressed Sequence Tags database, http://www.ncbi.nlm.nih.gov/dbEST/index.html
GenBank Overview, http://www.ncbi.nlm.nih.gov/Genbank/

GenbankOverview.html (for *OFD1* locus [accession number AC003037], *OFD1* [accession numbers Y15164 and Y16355], and mouse EST [accession number AJ278702])

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for OFD1 [MIM 311200])

TIGEM, http://www.tigem.it/

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