Received: 20 July 2016 | Revised: 14 January 2017 | Accepted: 23 January 2017

DOI: 10.1002/ajmg.a.38179

CLINICAL REPORT

WILEY AMERICAN JOURNAL OF medical genetics PART A

Oral-facial-digital syndrome type 1 in males: Congenital heart defects are included in its phenotypic spectrum

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Oral-facial-digital syndrome type 1 (OFD1; OMIM# 311200) is an X-linked dominant ciliopathy caused by mutations in the OFD1 gene. This condition is characterized by facial anomalies and abnormalities of oral tissues, digits, brain, and kidneys. Almost all affected patients are female, as OFD1 is presumed to be lethal in males, mostly in the first or second trimester of pregnancy. Live born males with OFD1 are a rare occurrence, with only five reported patients to date. In four patients the presence of a congenital heart defect (CHD) was observed. Here, we report an affected male fetus with a hemizygous de novo mutation in OFD1 (c.2101C>T; p.(Gln701*)). Ultrasound examination demonstrated severe hydrocephalus, a hypoplastic cerebellum and a hypoplastic left ventricle of the heart. The pregnancy was terminated at 16 weeks of gestation because of poor prognosis. Post-mortem examination of the fetus confirmed severe hypoplasia of the left ventricle of the heart. We emphasize that CHDs should be included in the phenotypic spectrum of OFD1 in males. This justifies molecular analysis of OFD1 when CHD is encountered prenatally in combination with one or more phenotypic features previously described in the OFD1 gene alteration spectrum. The underlying pathogenesis of CHD in OFD1 (and other ciliopathies) probably involves dysfunction of the primary cilia regarding coordination of left-right signalling during early heart development. Whether these CHDs wholly or partly result from defective left right signalling, in which different types of cilia are known to play a critical role, remains a topic of research.

KEYWORDS
congenital heart defect, congenital heart disease, hypoplastic left heart syndrome, OFD type 1, oral-facial-digital syndrome type 1

1 | INTRODUCTION

Oral-facial-digital syndrome type 1 (OFD1; OMIM# 311200) was initially reported in 1954 by Papillon-Leage and Psaume (1954) and further defined by Gorlin and Psaume in (1962). This syndrome is transmitted as an X-linked dominant condition with predominant lethality in male embryos, which usually occurs during the first and second trimester of pregnancy (Doege, Thuline, Priest, Norby, & Bryant, 1964; Macca and Franco, 2009; Wettke-Schäfer and Kantner, 1983). OFD1 has an estimated incidence of 1:50,000 live births (Wahrman, Berant, Jacobs, Aviad, & Ben-Hur, 1966). It is caused by mutations in the *OFD1* gene (OMIM# 300170) (Ferrante et al., 2001) which encodes for a centrosomal protein located at the basal body of the primary cilia (Franco and Thauvin-Robinet, 2016; Romio et al., 2003, 2004; Singla, Romaguera-Ros, Garcia-Verdugo, & Reiter, 2010). Functional studies have demonstrated that OFD1 has a crucial role in the formation of the primary cilia and that OFD1 should therefore be considered a ciliopathy (Macca and Franco, 2009; Toriello, 2009). The current clinical spectrum of OFD1 includes

TABLE 1 Phenotypic overview table of all reported male patients with OFD1 and congenital heart defects

	Tsurusaki et al. (2013)	Tsurusaki et al. (2013)	Tsurusaki et al. (2013)	Goodship et al. (1991)	Present case (2017)
Male patient with OFD1	**1: II-4, family 1**	**2: III-1, family 1**	**3: III-5 family 1**	**4: family 2**	**5: family 3**
Molecular diagnosis (OFD1)	no	no	c.2388+1G>C; p.?	no	c.2101C>T; p.(Gln701*)
Cardiac features	ASD, PDA	AVSD	HLHS	AVSD	HLHS
Oral	Cleft soft palate	Cleft palate	Cleft soft palate	Cleft soft palate	Cleft palate
Facial	Hypertelorism, short palp. fissures, depressed nasal bridge, pseudocleft upper lip, low set ears	Hypertelorism, epicanthal folds, short palp. fissures, low set ears, cleft lip	Hypertelorism, dysplastic ears, small cleft lip	Hypertelorism, pseudocleft upper lip	Hypertelorism, broad and bifid nasal tip, cleft lip, micro-/retrognathia, simple low set ears
Digital	Postaxial polydactyly of the left hand, wide halluces	Postaxial polydactyly of both hands, preaxial polydactyly of both feet		Postaxial polydactyly of both hands, bifid halluces, bifid right fifth toe	Postaxial polydactyly of both hands, postaxial polydactyly of left foot, deviated broad hallux of both feet
Other	Micropthalmia/microcornea, retinal detachment, hypoplastic gyri, bilateral hydroureters, micropenis, left cryptorchidism	Micropthalmia, optic disc and pupillary membrane coloboma, hydrocephalus, agenesis of corpus callosum and cerebral vermis	Hydrocephalus with Dandy-Walker malformation, agenesis of cerebellar vermis, enlargement of fourth ventricle, anomalous positioning of esophagus	Hydrocephalus, absent corpus callosum	Hydrocephalus, cerebellar hypoplasia, dilatation of some renal tubules

ASD, atrial septal defect; AVSD, atrioventricular septal defect; HLHS, hypoplastic left heart syndrome; PDA, patent ductus arteriosus.

abnormalities of the oral cavity, digits, brain, and kidneys combined with facial dysmorphisms as described by Toriello and Franco (2002), Franco and Thauvin-Robinet (2016), and Prattichizzo et al., (2008). However, these extensive reviews do not mention congenital heart defects (CHD) in either male or female patients as a characteristic feature of OFD1. To date, only five liveborn male patients have been reported in the literature. Interestingly, in four of them CHDs were described: atrial septal defect (ASD), atrioventricular septal defect (AVSD), and hypoplastic left heart syndrome (HLHS) (Table 1) (Gillerot, Heimann, Fourneau, Verellen-Dumoulin, & Van Maldergem, 1993; Goodship, Platt, Smith, & Burn, 1991; Tsurusaki et al., 2013). All died within the first 14 days of life. In a cohort of female patients with OFD1, CHDs were reported in 16% (4/25) (Bisschoff et al., 2013). CHDs have been described in a review of different types of OFD syndromes, but not in OFD1 (Digilio et al., 1999). Here, we report on a male fetus with genetically confirmed OFD1 and HLHS. Based on the combination of clinical data of previously reported male and female patients with OFD1, we emphasize that CHDs should be included in the phenotypic spectrum of OFD1. This is especially important when multiple malformations are observed prenatally and the suspicion of OFD1 is raised.

2 | CLINICAL REPORT

The mother (35 years of age, G3P0) of the proband was referred to our outpatient clinic for genetic counselling. She and the child's father were non-consanguineous and healthy. The first two pregnancies had resulted in spontaneous abortions for which no cause was known. At 13 + 5 weeks the patient was referred because of suspected hydrocephalus following a routine ultrasound screening. The hydrocephalus was confirmed and a chorionic villus biopsy was performed. Array-CGH (chorionic villus sample) demonstrated a normal male profile (arr(1–22)×2,(XY)×1). The ultrasound scan was repeated at 15 + 3 weeks of gestation. Multiple abnormalities were observed including severe hydrocephaly (OFC>3SD), cerebellar hypoplasia, apparently widely spaced eyes and asymmetry of the cardiac ventricles which was suspicious for HLHS (Figure 1). The presence of bilateral polydactyly of the hands could not be excluded. The pregnancy was terminated at 16 + 1 weeks of gestation because of poor prognosis. Post-mortem examination was performed. The birth weight of the proband was 113.6 g (+0.5 SD) and the crown-rump length was 18.2 cm (+0.5 SD). Dysmorphic craniofacial features included a large anterior fontanel, widely spaced eyes, broad, and bifid nasal tip, cleft lip and palate, microretrognathia, and simple apparently low set ears (Figure 2). No abnormalities of the tongue were observed. Additional physical features included postaxial polydactyly of both hands, postaxial polydactyly of the left foot and deviated broad hallux of both feet (Figure 2).

An autopsy was performed which confirmed previous ultrasonographic findings regarding the internal organs including the presence of hydrocephaly, the small and hypoplastic cerebellum and the severe hypoplasia of the left cardiac ventricle. No other cardiac anomalies were observed. Histologic examination of the kidneys demonstrated dilatation of some renal tubules which suggested the presence of

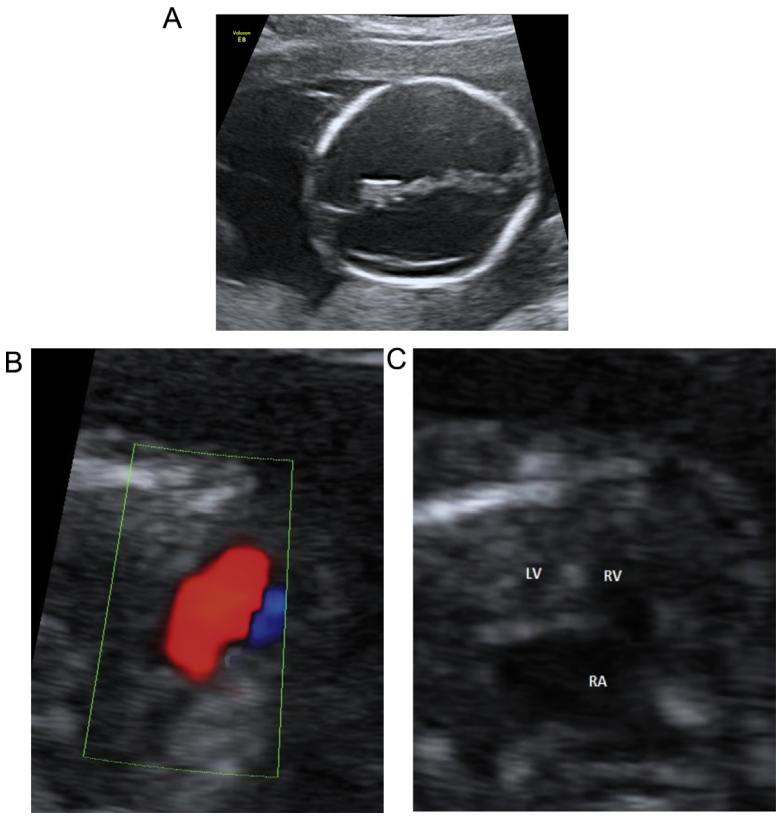

FIGURE 1 Ultrasonography of the fetal brain and the heart at a gestational age of 15 weeks and 3 days. Images illustrate (A) severe hydrocephalus and (B–C) hypoplasia of the left ventricle of the heart [Color figure can be viewed at wileyonlinelibrary.com]

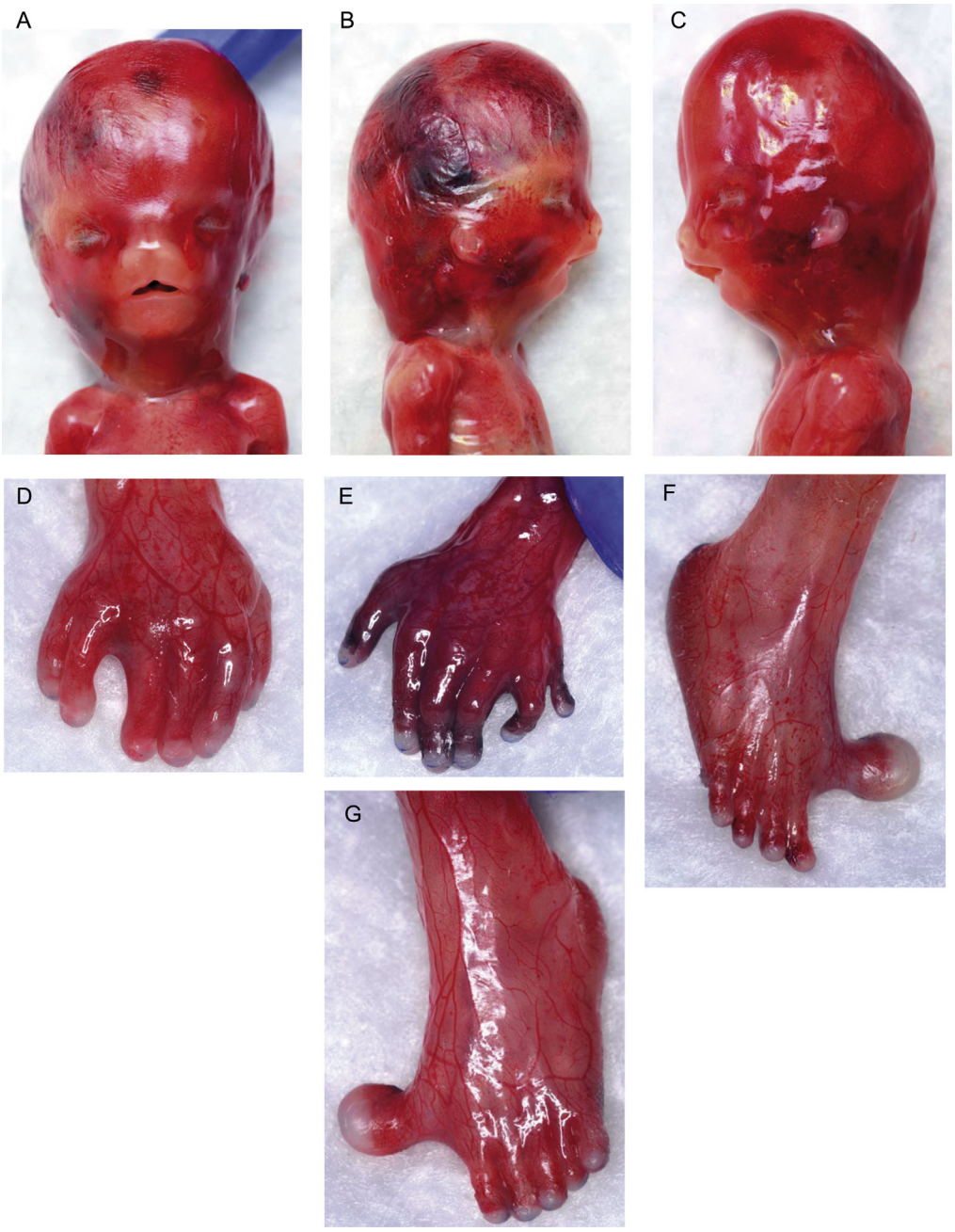

FIGURE 2 Post-mortem images of the fetus at a gestational age of 16 weeks and 1 day. (A) Overview picture. (A–C) Facial dysmorphisms including large anterior fontanel, hypertelorism, bifid nasal tip, cleft lip, and palate, micro-/retrognathia, and simple low set ears. (D–G) Postaxial polydactyly of both right and left hand, postaxial polydactyly of left foot, deviated large hallux of both right and left foot [Color figure can be viewed at wileyonlinelibrary.com]

multicystic anomalies (Supplementary information S1). No cysts were present in liver or pancreas.

Because of the two early miscarriages, karyotyping was also performed in both the father and the mother of the proband. Both had a normal karyotype.

3 | MATERIALS AND METHODS

A full description of this section is available online (Supplementary information S2).

4 | RESULTS

Exome sequencing of DNA from the proband and both parents (trio approach) was performed. The data analysis was restricted to the candidate genes *OFD1* (OMIM# 300170), *KIF7* (OMIM# 611254), and *HYLS1* (OMIM# 610693) demonstrated a hemizygous truncating mutation in *OFD1*: c.2101C>T; p.(Gln701*) in the proband. The mother of the proband did not carry this mutation. Therefore, the mutation was most likely *de novo* in the proband. This novel variant was not present in the Human Gene Mutation Database (HGMD Version 2014.2) nor in the ExAC database (http://exac.broadinstitute.org).

Since this is a truncating mutation it is considered to be pathogenic. No abnormalities were found in *KIF7* and *HYLS1*.

Additionally, *NOTCH1* (OMIM# 190198) was analyzed to exclude genomic variations which could contribute to the cardiac phenotype (HLHS) of the proband. No mutations were found.

5 | DISCUSSION

In this report we describe a male fetus with OFD1 and HLHS. A hemizygous pathogenic mutation in *OFD1* (c.2101C>T; p.(Gln701*)) was demonstrated by exome sequencing in the proband. Only five live born male patients with OFD1 have been previously reported in the literature (Table 1) (Goodship et al., 1991; Tsurusaki et al., 2013). Four of the five patients had CHDs (ASD, AVSD, HLHS). We propose therefore that CHDs should be included in the phenotypic spectrum of OFD1 in males, although the number of reported male patients presently remains small. Interestingly, CHDs (common atrium, ASD, VSD, and myxomatous changes of the mitral and tricuspid valve) were also reported in several females with OFD1 (Bisschoff et al., 2013; Su, Wang, Lian, & Lin, 2008). Besides OFD1, *OFD1* mutations are also associated with Type 2 Simpson-Golabi-Behmel syndrome (SGBS2; OMIM# 300209) and X-linked Joubert syndrome (JBTS10; OMIM# 300804) indicating the phenotypic variability of the *OFD1* spectrum (Budny et al., 2006; Coene et al., 2009; Field et al., 2012; Wentzensen et al., 2016). Although one patient with JBTS10 and a CHD was previously described (Field et al., 2012), none of the other reported male patients with SGBS2 or JBTS10 have had CHDs.

CHDs occur in 19–75 of every 1,000 live births, whereas the incidence is even higher among fetuses that do not survive to term (Bruneau, 2008). CHDs are commonly observed in many ciliopathy syndromes including different types of OFD syndromes (33–100%) (Digilio et al., 1999; Karp et al., 2012). The male fetus with OFD1 described in this report had a HLHS which can be classified as "left-sided obstruction defect": HLHS was also present in a male patients with OFD1 described previously (Tsurusaki et al., 2013). In three other male patients with OFD1 ASD and AVSD were described (Goodship et al., 1991; Tsurusaki et al., 2013). Several reports of patients with other OFD syndromes describe patients with left-sided cardiac obstructions, some of them in combination with AVSD (Balci, Onol, Eryilmaz, & Haytoglu, 1997; Digilio, Marino, Giannotti, & Dallapiccola, 1996; Gustavson, Kreuger, & Petersson, 1971; Iaccarino, Lonardo, Giugliano, & Della Bruna, 1985; Nevin & Thomas, 1989; Orstavik, Lindemann, Solberg, Foerster, & Sørland, 1992; Saari, Lovell, Yu, & Bellus, 2015; Váradi, Szabó, & Papp 1980). The exact mechanisms underlying CHD in OFD syndromes or other ciliopathies are currently unknown. Both nodal and primary cardiac cilia belong to the group of primary cilia and play a crucial role in early heart development (Koefoed, Veland, Pedersen, Larsen, & Christensen, 2014). Nodal cilia are a key player in the establishment of the embryonic left-right axis as they coordinate numerous embryonic signaling pathways (including the Hedgehog pathway) which are involved in cardiogenesis. Errors in left-right signaling can result in different kinds of CHDs arising from abnormal looping and remodeling of the primitive heart tube (Clement et al., 2009; Koefoed et al., 2014; Ramsdell, 2005; Slough, Cooney, & Brueckner, 2008). It seems likely that certain types of CHDs such as ASD, AVSD, VSD, tetralogy of Fallot, double outlet right ventricle, and transposition of the great arteries result from inadequate ciliary functioning. However, it remains unknown if a specific CHD in a ciliopathy results from nodal ciliary dysfunction or cardiac primary ciliary dysfunction. Proper expression of *OFD1* is required for formation of the primary cilia (Macca & Franco, 2009). Interestingly, knockout of *OFD1* in mice can cause cardiac laterality defects/disruption of left-right axis determination during early embryogenesis (Ferrante et al., 2006). Subsequently, it was demonstrated that cardiac laterality was completely randomized by disrupting *OFD1* during zebrafish embryogenesis (Ferrante et al., 2009). Both animal studies underline that *OFD1* has an important role in the coordination of early heart development. It seems that laterality defects due to a mutation in a gene involved in primary ciliary function (or ciliary function regulation), such as *OFD1*, can underlie certain types of CHDs in OFD-syndromes and ciliopathies. This concept was discussed previously by Digilio et al. (2012) who hypothesized that AVSDs in patients with Ellis-van Creveld (EVC) syndrome are an indicator of the underlying laterality defect due to ciliary dysfunction. This group also observed that the specific morphology of heart defects in EVC syndrome resembled the cardiac phenotype in patients with heterotaxy-syndromes, especially those with polysplenia (Digilio, Dallapiccola, & Marino, 2012). A significant clinical overlap between heterotaxy-syndromes and ciliopathies was further illustrated in a later report (Karp, Grosse-Wortmann, & Bowdin, 2012). In addition, it can be hypothesized that left-sided obstruction defects are not the direct result of laterality defects as these are established during cardiac morphogenesis and maturation in the post-gastrulational phase (Koefoed et al., 2014).

In conclusion, this report contributes to a further delineation of the phenotype associated with OFD1 in males. It seems that CHD is a component of the phenotypic spectrum in both male and female patients with OFD1 and that the underlying pathogenesis likely involves cilia dysfunction. However, whether these CHDs result from nodal or cardiac primary ciliary dysfunction (or both) remains to be determined. It should be noted that when a CHD in combination with phenotypic manifestations suggestive of OFD1 are observed prenatally that molecular analysis for *OFD1* mutations must be considered. Reports of additional males with OFD1 will contribute to more accurate descriptions of the cardiac phenotype.

ACKNOWLEDGMENTS

We are very grateful to the parents of the proband for their cooperation and permission regarding the publication of both clinical information and pictures of their child.

AUTHORS' CONTRIBUTIONS

All the authors contributed significantly to this research and preparation of the manuscript. AB, LL, NT and MM were involved in gathering and interpreting clinical data. MA was involved in

diagnostic studies and performing molecular analysis. AB, MA, RJO, EL, NT, AKK and MM were all involved in writing and editing the manuscript.

WEB RESOURCES

UCSC Genome Browser http://genome.ucsc.edu/
OMIM http://www.ncbi.nlm.nih.gov/
ExAC database (http://exac.broadinstitute.org)

CONFLICT OF INTEREST

None.

ETHICS APPROVAL

The genetic variation in the proband was found in a diagnostic setting. Therefore, no approval of an ethics committee was required. Publishing the photographs of this patient with signed consent of parents, is in line with the institutional guidelines of the AMC University hospital.

PROVENANCE AND PEER REVIEW

Not commissioned; externally peer reviewed.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Bouman A, Alders M, Oostra RJ, et al. Oral-facial-digital syndrome type 1 in males: Congenital heart defects are included in its phenotypic spectrum. *Am J Med Genet Part A*. 2017;173A:1383–1389. https://doi.org/10.1002/ajmg.a.38179