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SHORT COMMUNICATION

A Japanese case of oto-palato-digital syndrome type II: an apparent lack of phenotype–genotype correlation

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Abstract We report the case of a 12 year-old boy with oto-palato-digital syndrome type II (OPD II). He had various anomalies at birth, including bilateral cataracts, bilateral glaucoma, bilateral severe hearing impairment, congenital heart defect, umbilical herniation, bowed extremities and constrictions of various joints. These clinical features and whole body X-ray findings were compatible with OPD II. However, his ocular disorders such as congenital cataract and glaucoma, and congenital heart defect have never been associated with OPD II as far as we know. His chromosomal analysis revealed normal karyotype, 46,XY. Analysis of the filamin A gene using a standard PCR-direct sequencing method determined a C586T (Arg196Trp) missense mutation in exon 3. Interestingly, the same C586T mutation was reported previously in a patient with OPD I (mild form). Thus, phenotype–genotype correlation of OPD is lacking in those patients. Further clinical and genetic studies are needed to clarify the relationship between phenotypes and genotypes, or to identify other factor(s) that influence the clinical features of this syndrome.

Keywords Oto-palato-digital syndrome type II · OPDII · Filamin A gene · *FLNA* · Genotype–phenotype correlation

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Introduction

Oto-palato-digital (OPD) syndrome is characterized by hearing impairment, cleft palate, deformities of extremities and characteristic facies including frontal bossing, marked micrognathia, hypertelorism and downslant palpebral fissures. OPD syndrome is classified into two types according to clinical severity: the mild form OPD I (OMIM: 311300), and the severe form OPD II (OMIM: 304120; Taybi 1962; Dudding et al. 1967; Fitch et al. 1976, 1983; Brewster et al. 1985). Furthermore, several patients have been reported to have overlapping clinical features among OPD I and II, Larsen syndrome, atelosteogenesis I and II, boomerang dysplasia, the lethal male Melnick-Needles syndrome, and acro-coxo-melic dysplasia (Plauchu et al. 1984; Blanchet et al. 1993; Nishimura et al. 1997; Robertson et al. 1997; Verloes et al. 2000).

The causative gene of OPD syndrome has been mapped to Xq28 (Biancalana et al. 1991; Hoo et al. 1991; Hoar et al. 1992). Robertson et al. (2003) demonstrated that OPD II is caused by mutations in the coding region of the filamin A gene (*FLNA*; OMIM: 300017). *FLNA* is a gene encoding an actin-binding

protein, and mutations in this gene have been detected in patients with Melnick-Needles syndrome or frontometaphyseal dysplasia in addition to OPD I and OPD II. However, it is not clear why mutations in the same gene results in different clinical entities (Robertson et al. 2003; Robertson 2005). Here, we report on a 12-year-old boy with severe OPD II manifestations whose mutation in *FLNA* was identical to that of an OPD I patient.

Case report

The patient is a 12-year-old Japanese boy. He was born as the first child of nonconsanguineous healthy parents at 41 weeks and 2 days of gestation, with weight and length of 3,068 g (–0.3 SD) and 50.0 cm (+0.3 SD), respectively. His eyes exhibited pseudoexophthalmos and were always closed. He also had a widow's peak, micrognathia, small mouth, short neck, heart murmur, narrow chest, umbilical herniation, bowed extremities, and contractures of bilateral elbow, wrist, shoulder, hip, knee, and ankle joints (Fig. 1a–i). Ophthalmological examinations revealed bilateral cataracts and bilateral glaucoma, for which he has undergone ophthalmologic surgery several times. His left eye was removed and replaced with an artificial eyeball. He is blind in the right eye despite corneal transplantation. Various clinical examinations revealed cleft palate, bilateral severe hearing impairment (no response to 90 dB bilaterally), congenital heart defects such as dilatation of Valsalva sinus, atrial septal defect (ASD), dilatation of the aortic valve, and thickness of the mitral valve as seen in neonatal Marfan syndrome. His skeletal radiographic findings were as follows: large cranium relative to the face, large orbita, Wormian bones, flat pituitary sella, vertical clivus with unusual projection in its dorsal aspect, tall occipital condyles and hypoplastic mandible; kyphoscoliosis, tall vertebrae, spina bifida and bifid spinous processes in cervical spine, long curved clavicles and curved deformity of ribs; bowing deformity with undertubulation of long tubular bones, posterior dislocation of the radius at the elbows, short ulna, pseudo-epiphysis of second metacarpal bones and enlarged distal phalanges in his extremities; flat foot and enlarged distal phalanges of the hands and feet; and small iliac wings with flat acatebular roof in his pelvis (Fig. 1j–l). Most of the aforementioned clinical and radiological features were compatible with OPD II. However, congenital cataracts and glaucoma as well as congenital heart defects such as dilatation of Valsalva sinus, ASD, dilatation of the aortic valve and thickness of the mitral valve have never been reported to be associated with OPD II. He also suffered complications because of respiratory failure due to deformed chest and adenoid hyperplasia, urinary tract stenosis, apnea attacks and poor weight gain. Because of skeletal anomalies, hearing loss, and near total blindness, precise assessment of his mental development has been difficult. His present general

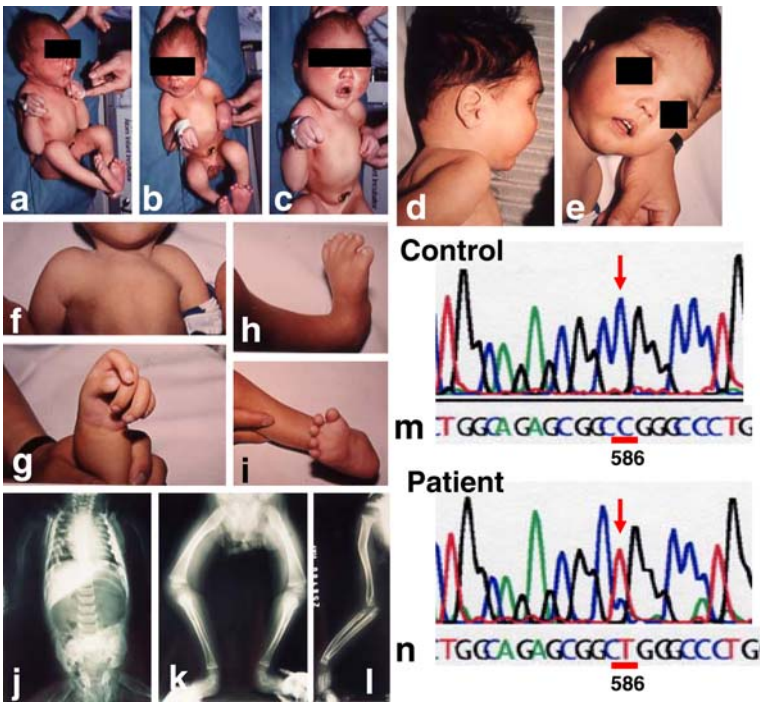

Fig. 1 **a–c** Pictures of our patient at neonatal stage. **d–i** Pictures of our patient at 7 years old. **j–l** Bone X-ray films of our patient at 7 years old. **m**, **n** Sequence data from the filamin A gene (*FLNA*) of a control (**m**) and the patient (**n**). *Arrows* indicate the discordant base pair

condition at 12 years old are as follows: his weight, length and head circumference are 14.0 kg (–3.3 SD), 105.0 cm (–5.9 SD) and 53.0 cm (–0.6 SD), respectively. He cannot sit, stand up, or move by himself. He can drink only nutritional formula by himself and never takes a solid meal; however, his swallowing function is not defective. Therefore, his dietary problems may reflect psychological problems. He also has sleeping disorder. He has keen olfactory and tactile sensations. He has social smile but cannot speak: his only way to express his complaint is to cry.

Molecular and cytogenetic studies

Chromosomal analysis revealed normal karyotype, 46,XY in our patient. Sequence analysis of the*FLNA* gene was performed according to a previously reported method (Robertson et al. 2003), and revealed a missense C to T mutation at position 588, resulting in an Arg196Trp change in the filamin A protein.

Discussion

OPD II syndrome is a potentially lethal skeletal dysplasia with X-linked recessive inheritance, and has various clinical spectrums ranging from relatively mild to severe, depending on the kinds of complications the patient has. The cardinal clinical manifestations of OPD II are characteristic facial features, multiple skeletal abnormalities, hearing impairment, and palate abnormality. Our patient had various malformations compatible with OPD II, and not associated with other disorders caused by *FLNA* gene mutations such as OPD I and Melnick-Needles syndrome. However, his ocular disorders—congenital cataract and glaucoma—as well as the congenital heart defect have never been associated with OPD II as far as we know. Interestingly, his congenital heart defects—dilatation of bothValsalva sinus and aortic valve—are usually seen in Marfan syndrome. On the other hand, glaucoma, tetralogy of Fallot and ASD have been reported in Melnick-Needles syndrome patients (Donnenfeld et al. 1987; Neou et al. 1996). Thus, our patient can be categorized as having OPD II, but his clinical features are relatively severe and unique in that he had additional unusual complications.

Genetic studies on *FLNA* gene mutations have been reported in OPD syndrome (Robertson et al. 2003; Robertson 2005). *FLNA* mutations can result in loss-of-function or alterations in filamin A function (Robertson 2005). The former was seen in bilateral periventricular nodular heterotopia (PVNH) (OMIM: 300049) (Fox et al. 1998), and the latter has been reported in OPD-spectrum disorders such as OPD I, OPD II, frontometaphyseal dysplasia and Melnick-Needles syndrome. Genotype–phenotype correlation is relatively clear between Melnick-Needles syndrome and OPD II, but is not always so between OPD I and OPD II. Mutations have been detected in the actin-binding domain of filamin A in both OPD I and II patients (Robertson 2005). Our patient has a missense mutation, 586C to T leading to an Arg196Trp substitution in filamin A. Two other patients have previously been reported to have a mutation at the same position in *FLNA* as our patient. One patient had C586T, exactly the same mutation as our patient; however, his phenotype was quite different from that of our patient. He only had abnormal digits and cleft palate, but not short stature or bowed bones, and therefore was diagnosed OPD I (Robertson et al. 2003). Another patient had a 586C to G mutation, leading to an Arg196Gly substitution in filamin A (Robertson et al. 2003). Andre et al. (1981) originally reported that the family of the patient had had four other cases of OPD II, all of which were severe, with the patients dying at 21 days to 3.5 months after birth. Thus, the phenotype–genotype correlation was not apparent in the three OPD patients with a mutation at 586C in *FLNA*: the identical mutation (C586T) can give rise to two distinct phenotypes, OPD I and OPD II. Furthermore, a family with both OPD I and II patients has been reported (Horn et al. 1995).

Phenotype–genotype correlation is apparent between OPD-spectrum disorders and PVNH: OPD-spectrum disorders are phenotypically distinct from PVNH, and such differences are due to alteration vs loss-of-function in filamin A function, respectively (Robertson et al. 2003). However, OPD I and II are phenotypically very different, despite the fact that they result from similar or even identical mutations in *FLNA*. It is possible that an additional factor(s) plays a role in the pathogenesis of OPD-spectrum disorders. Further study will be needed to clarify the molecular mechanisms of OPD-spectrum disorders.

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