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ORIGINAL ARTICLE

Distinct impacts of bi-allelic *WNT10A* mutations on the permanent and primary dentitions in odonto-onycho-dermal dysplasia

Miao Yu[1*] | Yang Liu[1*] | Haochen Liu[1] | Sing-Wai Wong[2] | Huiying He[1] | Xiaoxia Zhang[1] | Yue Wang[1] | Dong Han[1] | Hailan Feng[1]

[1]Department of Prosthodontics, Peking University School and Hospital of Stomatology & National Clinical Research Center for Oral Diseases & National Engineering Laboratory for Digital and Material Technology of Stomatology & Beijing Key Laboratory of Digital Stomatology, Beijing, PR China

[2]Department of Periodontology, School of Dentistry, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

Correspondence
Dong Han, Department Prosthodontics, Peking University School and Hospital of Stomatology, 22 Zhongguancun South Avenue, Haidian District, Beijing 100081, PR China.
Email: donghan@bjmu.edu.cn

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Abstract

Odonto-onycho-dermal dysplasia (OODD) is a rare autosomal recessive syndrome characterized by multiple ectodermal abnormalities. Mutations of the wingless-type MMTV integration site family member 10A (*WNT10A*) gene have been associated with OODD. To date, only 11 OODD-associated *WNT10A* mutations have been reported. In this report, we Characterized the clinical manifestations with focusing on dental phenotypes in four unrelated OODD patients. By Sanger sequencing, we identified five novel mutations in the *WNT10A* gene, including two homozygous nonsense mutations c.1176C>A (p.Cys392*) and c.742C>T (p.Arg248*), one homozygous frame-shift mutation c.898-899delAT (p.Ile300Profs*126), and a compound heterozygous mutation c.826T>A (p.Cys276Ser) and c.949delG (p.Ala317Hisfs*121). Our findings confirmed that bi-allelic mutations of *WNT10A* were responsible for OODD and greatly expanded the mutation spectrum of OODD. For the first time, we demonstrated that bi-allelic *WNT10A* mutations could lead to anodontia of permanent teeth, which enhanced the phenotypic spectrum of *WNT10A* mutations. Interestingly, we found that bi-allelic mutations in the *WNT10A* gene preferentially affect the permanent dentition rather the primary dentition, suggesting that the molecular mechanisms regulated by WNT10A in the development of permanent teeth and deciduous teeth might be different.

KEYWORDS

anodontia, mutation, odonto-onycho-dermal dysplasia, tooth agenesis, WNT10A

1 | INTRODUCTION

Odonto-onycho-dermal dysplasia (OODD; OMIM #257980) is a rare autosomal recessive inherited type of ectodermal dysplasia that was first described in 1983 in two Lebanese families (Fadhil, Ghabra, Deeb, & Der Kaloustian, 1983). This disorder is characterized by a series of core clinical features including sparse hair, tooth agenesis, onycho-dysplasia, hyperkeratosis of the palms and soles, hyperhidrosis and hypohidrosis of the skin, and atrophic patches on the face (Adams, 2007; Arnold, Merkx, & Steijlen, 1995). In addition, smoothness of the tongue due to a reduction in fungiform and filiform papillae has also been reported (Adaimy et al., 2007; Megarbane et al., 2004). However, the dental phenotype, which is marked by peg-shaped incisors, enamel hypoplasia, a reduction in tooth number and widely spaced teeth, is the most notable clinical manifestation among OODD patients (Zirbel, Ruttum, Post, & Esterly, 1995).

The human *WNT10A* gene (wingless-type MMTV integration site family member 10A, OMIM *606268) contains four exons, spans approximately 13.4 kb, and is located at chromosome 2q35 (Bohring et al., 2009). The encoded WNT10A protein is a member in the Wnt ligand family, which activates the canonical Wnt/β-catenin signaling pathway (Coudreuse & Korswagen, 2007; Kroigard, Clemmensen, Gjorup, Hertz, & Bygum, 2016). The Wnt pathway is evolutionarily conserved and plays an essential role in ectodermal organogenesis

*These authors contributed equally to this work.

processes in the nervous system, skeleton, skin, and hair follicle (Nawaz et al., 2009; Tardieu et al., 2017; Wang & Shackleford, 1996). Moreover, Wnt10a was found to be expressed in the dental epithelium and the enamel knot, as well as in the mesenchymal preodontoblast layer during tooth development (Dassule & McMahon, 1998; He et al., 2013), suggesting that it may be involved in regulating odontoblast differentiation, and thus it is required for dentinogenesis and tooth morphogenesis (Liu, Han, Wang, & Feng, 2013; Yamashiro et al., 2007).

The association between the *WNT10A* mutation and OODD was first identified by Adaimy et al. (2007). Subsequently, mutations in the *WNT10A* gene were also found in another autosomal recessive form of ectodermal dysplasia, Schöpf–Schulz–Passarge syndrome (SSPS; OMIM #224750) (Bohring et al., 2009; Petrof, Fong, Lai-Cheong, Cockayne, & McGrath, 2011). Although SSPS shares many common clinical symptoms with OODD, such as hypodontia, skin and nail dysplasia, and smooth tongue, the presence of eyelid cysts is a unique feature in SSPS (Kantaputra & Sripathomsawat, 2011; Mues et al., 2014). In addition to the abovementioned autosomal recessive disorders, recent studies indicated a high prevalence of heterozygous *WNT10A* mutations in patients with non-syndromic tooth agenesis (Kantaputra, Kaewgahya, & Kantaputra, 2014; Plaisancie et al., 2013; Song et al., 2014; van den Boogaard et al., 2012). Therefore, the disease phenotypes caused by *WNT10A* mutations are exclusively restricted in ectodermal-derived organs.

In this study, we identified five novel *WNT10A* mutations in four unrelated individuals who were clinically diagnosed with OODD. We performed detailed phenotypic characterization (including the intra- and extra- oral manifestations and ectodermal symptoms) of these patients, by which we analyzed and summarized the distinct impacts of bi-allelic *WNT10A* mutations on the primary and permanent dentitions.

2 | MATERIALS AND METHODS

2.1 | Editorial policies and ethical considerations

The human study protocols were approved by the institutional review board of Peking University. The patient's assent and parental informed consent for each patient (as they were under 18 years old) for DNA analysis and reproduction of the photographs were obtained.

2.2 | Participants

Four individuals were referred to the Department of Prosthodontics at Peking University Hospital of Stomatology because of their retention of primary teeth and missing of permanent teeth. Panoramic radiographs were taken to assess the number and pattern of missing teeth. The third permanent molars were excluded in this study because they are frequently absent in the general population. The patients were also examined for clinical symptoms in the skin, hair, nails, and intra-oral region.

2.3 | DNA extraction and mutational analysis

Genomic DNA of all patients, their family members, and normal controls was isolated from peripheral blood lymphocytes as previously described (Wong et al., 2014). All exons of the *WNT10A* gene (NM_025216.2), including the intron-exon boundaries, were amplified by polymerase chain reaction (PCR) using specific primers (primer sequences can be made available upon request). The amplified PCR products were purified and sent to Tsingke Biological Technology Co. (Beijing, China) for Sanger sequencing. Chromatograms were aligned and compared to the reference sequence of the human *WNT10A* gene using the "BLAST" program to detect sequence variants. For the confirmation of a frame-shift mutation, PCR products were cloned into pGEM-T Easy Vectors (Tiangen, Beijing, China), and this was followed by sequencing of TA clones. All variants identified in our study have been submitted to the ClinVar database (https://submit.ncbi.nlm.nih.gov/clinvar/).

2.4 | Conservation analysis

Amino acid sequence alignment analysis of the WNT10A protein (NP_079492.2) in multiple species was carried out using ClustalX 2.1. The affected amino acids in the WNT10A protein across nine different vertebrate species were obtained from ENSEMBL.

TABLE 1 Overview of the clinical features of the patients in this study

Clinical features	#9–12 II 1	#E6 II 1	#14–43 II 1	#20–34 II 1
Gender, age (years)	Male, 17	Male, 16	Female, 9	Female, 14
Consanguineous parents	+	+	–	+
Permanent dentition				
Missing number	28	28	28	28
Deciduous dentition				
Severe attrition	+	+	+	+
Taurodontism	–	–	+	+
Peg-shaped teeth	+	+	+	+
Enamel hypoplasia	–	+	+	+
Microdontia	+	+	+	+
Number of missing teeth	4	2	2	5
Hair				
Sparse scalp	–	–	+	–
Sparse eyebrows	+	–	+	–
Skin				
Dystrophic nails	+	+	+	+
Palmar hyperkeratosis	+	+	+	–
Plantar hyperkeratosis	+	+	+	–
Hypohidrosis	–	–	+	+
Hyperhidrosis	–	–	–	–
Dry skin	+, DE	+	+	+, E
Erythematous astrophic patches on the face	–	+	–	–

+ = present; – = absent; E = eczema; DE = dry eyes.

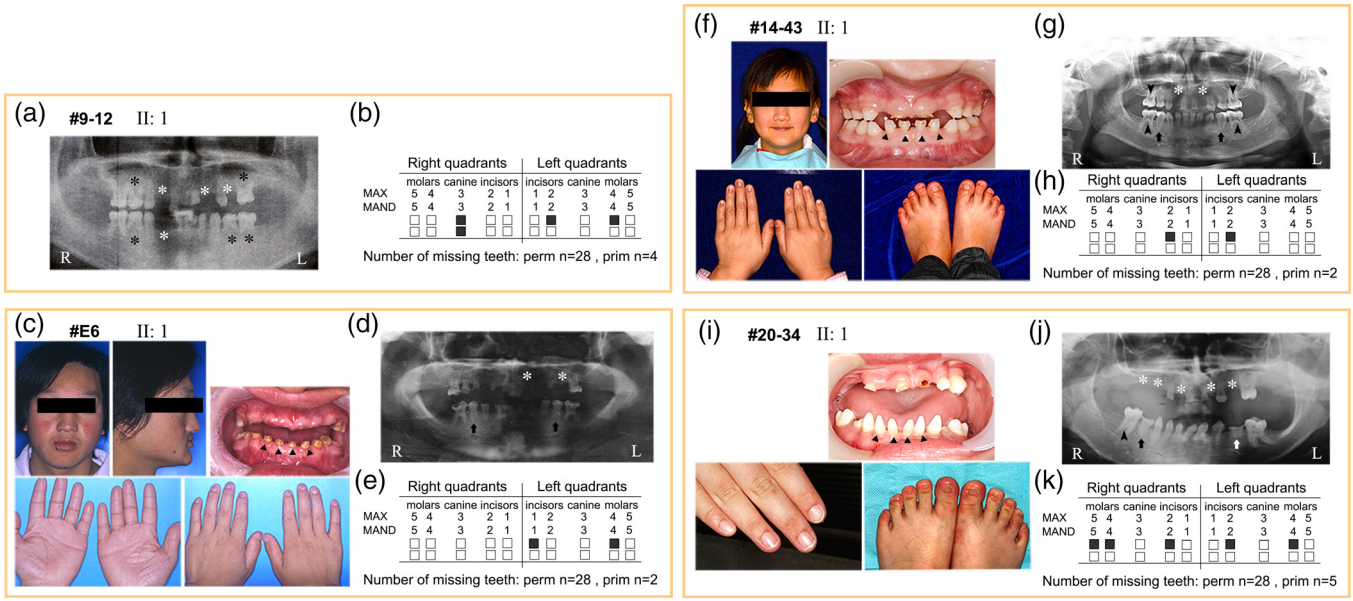

FIGURE 1 Clinical photographs and panoramic radiographs of patients with OODD. Panoramic radiographs of patient #9–12 II1 (a), patient #E6 II1 (d), patient #14–43 II1 (g), and patient #20–34 II1 (j) showing the pathological findings of their dentitions. Congenitally missed teeth are indicated by a white asterisk; teeth with taurodontism, with a black arrowhead; single-rooted teeth, with a black arrow; short-rooted teeth, with a black asterisk; root fusion, with a white arrow. (c, f, and i) Facial and intra-oral photos (upper panel) of each patient. Peg-shaped teeth are indicated with triangles. Photographs of the feet and hands (lower panel) show dysgenesis of the nails and the skin of palms and soles. (b, e, h, and k) Schematic presentation of congenitally missing deciduous teeth in the four OODD patients. The missing teeth are labeled with solid squares. "Max" indicates maxillary; "Mand," mandibular; "perm," permanent dentition; "prim," primary dentition; and "*n*," number [Color figure can be viewed at wileyonlinelibrary.com]

2.5 | *In silico* predictions of *WNT10A* mutants

Commonly used web-based algorithms (SIFT, http://sift.jcvi.org/, PolyPhen-2, http://genetics.bwh.harvard.edu/pph2/ and MutationTaster, http://www.mutationtaster.org/) were performed for potential pathogenic prediction of *WNT10A* mutations.

3 | RESULTS

3.1 | General clinical findings

The four referred patients exhibited variabilities in disease severity of OODD. Because they did not have eyelid cysts, a distinguishing clinical feature of SSPS, we diagnosed the patients with OODD. The clinical and radiographic information are summarized in Table 1 and Figure 1. In addition, the pedigrees of the four families of the probands and their identified mutations are displayed in Figure 2.

Patient #9–12 II1: This patient was a 17-year-old boy who was the only child in a consanguineous family. The patient had normal scalp hair but had sparse eyebrow hair. He also had hyperkeratotic palms, soles and dystrophic toenails, and fingernails. Although the patient complained of dry eyes, his sweat glands were unaffected (clinical images were not available).

Patient #E6 II1: This patient was a 16-year-old boy who presented with dystrophic nails, dry skin, palmar and plantar keratoderma. Notably, the patient had localized erythematous atrophic patches on his face, which is uncommon in OODD. He had normal body hair and defected heat intolerance (Figure 1(c)). Similarly, the patient was from a consanguineous family, but his parents did not have any obvious phenotypic abnormalities.

Patient #14–43 II1: This patient was from a non-consanguineous family and was 9 years old at the time of examination. She exhibited a typical ectodermal dysplasia with sparse body hair, hypohidrosis, dry skin, and nail dystrophy. She also had keratodermas in her palms and soles (Figure 1(f)). Although her parents were affected with mild tooth agenesis, they had no other signs of OODD.

Patient #20–34 II1: This patient was a 14-year-old girl, who was the only affected individual in a consanguineous family. Physical examination revealed that she had dry skin, hypohidrosis, curly hair and dystrophic nails (Figure 1(i)). Furthermore, her mother noted that the patient had a periodical atopic dermatitis on her leg. Both her mother and her younger brother are unaffected with OODD. Her father, however, had some conical-shaped teeth.

3.2 | Dental clinical findings

Dental abnormalities were the most common pathological findings in OODD patients and thus they can be regarded as a key feature of OODD. However, the dental phenotypic can be frequently variable among affected patients. By dental and radiographic examinations, we found that OODD patients exhibited a wide spectrum of tooth anomalies including retention, taurodontism, enamel hypoplasia and sever attrition of primary teeth, and agenesis of both deciduous and permanent teeth. All of patients' dental clinical findings were shown in Table 1 and Figure 1, and are described below:

Patient #9–12 II1: This patient missed four deciduous teeth (52, 62, 64, and 82), but strikingly, he was afflicted with anodontia of

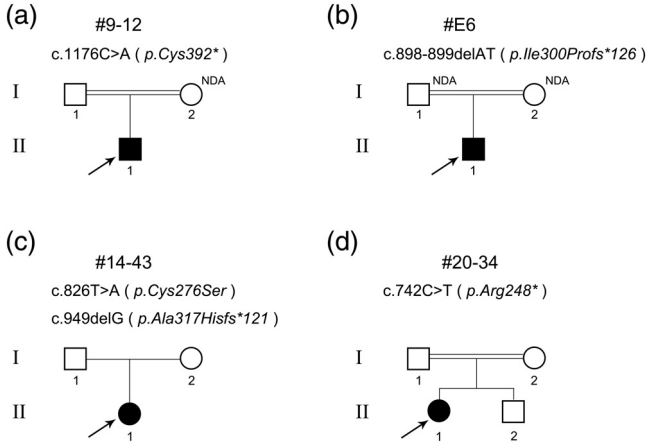

FIGURE 2 Family pedigrees of the four OODD patients in this study. Squares and circles filled in black represent individuals with OODD. Arrows indicate the proband on each family; Available *WNT10A* genetic sequencing results of family members are provided. "NDA" means that the DNA sample was not available

permanent dentition (complete absence of permanent teeth, missing tooth *n* = 28; Figure 1a,b). The patient's primary canines and the mandibular primary incisors were peg-shaped, and the severe attrition on retained maxillary primary incisors. In addition, localized microdontia of the maxillary primary incisors were observed. The enamel of his deciduous teeth was normal. The panoramic radiograph revealed that patient's permanent tooth germs were completely absent and that the deciduous molars (54, 65, 74, 75, and 84) showed extensively short roots. (Figure 1b).

Patient #E6 II1: Similar to the patient #9–12 II1, although this patient had a mild deciduous tooth agenesis (missing tooth number = 2), all of his permanent teeth were congenitally missing (*n* = 28; Figure 1d,e). Intra-oral examination revealed his primary dentitions were in an abnormal dark yellow color, suggesting that the patient had generalized enamel hypoplasia. Both the maxillary and mandibular deciduous incisors were small, in peg-shaped and widely spaced. Furthermore, the maxillary anterior teeth showed crown fracture and the mandibular teeth showed attrition (Figure 1c). The panoramic radiograph revealed the congenital absence of all the permanent tooth germs, the two mandibular first deciduous molars appeared to be single rooted (Figure 1d).

Patient #14–43 II1: This patient presented only two congenitally missing deciduous teeth (52 and 62), whereas her permanent dentition was completely absent (missing tooth *n* = 28) (Figure 1g,h). Intra-oral examinations demonstrated that all the mandibular deciduous incisors were either peg-shaped or microdontia. The primary dentition was affected with generalized enamel hypoplasia, which led to crown fracture of the upper central deciduous incisors and attrition of the lower anterior teeth (Figure 1f). This patient also had a very thin alveolar crest in edentulous areas. The panoramic radiograph revealed no permanent tooth germs. Notably, all of her primary molars exhibited taurodontism. Her mandibular first molars had only one root comparing the healthy control teeth having two roots, suggesting an impairment of tooth root development (Figure 1g).

Patient #20–34 II1: This patient presented with a widely spaced primary dentition with the congenital absence of five deciduous teeth (52, 54, 55, 62, and 64) and the complete absence of permanent teeth (*n* = 28; Figure 1j,k). Peg-shaped or microdontia of primary mandibular teeth were found. This patient also had enamel hypoplasia of primary teeth, resulting in coronal fractures in mandibular first molars and the attrition of the maxillary anterior teeth (Figure 1i). The panoramic radiograph revealed that the permanent tooth germs were completely absent, the primary mandibular teeth had multiple root developmental anomalies, including a single rooted right first molar, taurodontism of the right second molar, and root fusion of the left first molar (Figure 1j).

3.3 | Genetic analysis

Since *WNT10A* gene mutations have been linked to OODD, we sequenced all exons of this gene for the mutational detection in the four patients. We identified two novel homozygous nonsense mutations in (patient #9–12 II1, Figure 2a and patient #20–34 II1, Figure 2d), one novel homozygous frame-shift mutation (patient #E6 II1, Figure 2b), and one novel compound heterozygous mutation (patient #14–43 II1, Figure 2c). These mutations were not seen in healthy controls (*n* = 200). An overview of these mutations, amino acid changes and possible impacts is presented in Table 2, Figure 3 and Supporting Information Table.

3.4 | Conservation analysis

Finally, we presented the distribution of novel *WNT10A* gene mutations identified in the four OODD patients of this study in the schematic human *WNT10A* gene structure (Figure 4a). These five mutations (highlighted in red) were located in exon 3 and exon 4. Comparison of the sequence of the human wild-type WNT10A protein to orthologs from a variety of animals showed that the human Cys276 residue is highly conserved across species during evolution (Figure 4b).

4 | DISCUSSION

In this study, we reported four unrelated OODD cases in which five novel mutations in the *WNT10A* gene were identified. Pedigree

TABLE 2 Overview of the *WNT10A* mutations detected in the patients in this study

Mutational results	#9–12 II 1	#E6 II 1	#14–43 II 1	#20–34 II 1
Nucleotide substitution (first allele)[a]	c.1176C>A	c.898-899delAT	c.826T>A	c.742C>T
Nucleotide substitution (second allele)[a]	c.1176C>A	c.898-899delAT	c.949delG	c.742C>T
Amino acid substitutions[b]	p.Cys392* p.Cys392*	p.Ile300Profs*126 p.Ile300Profs*126	p.Cys276Ser p.Ala317Hisfs*121	p.Arg248* p.Arg248*

[a] According to NCBI reference sequence: NM_025216.2.
[b] According to NCBI reference sequence: NP_079492.2.

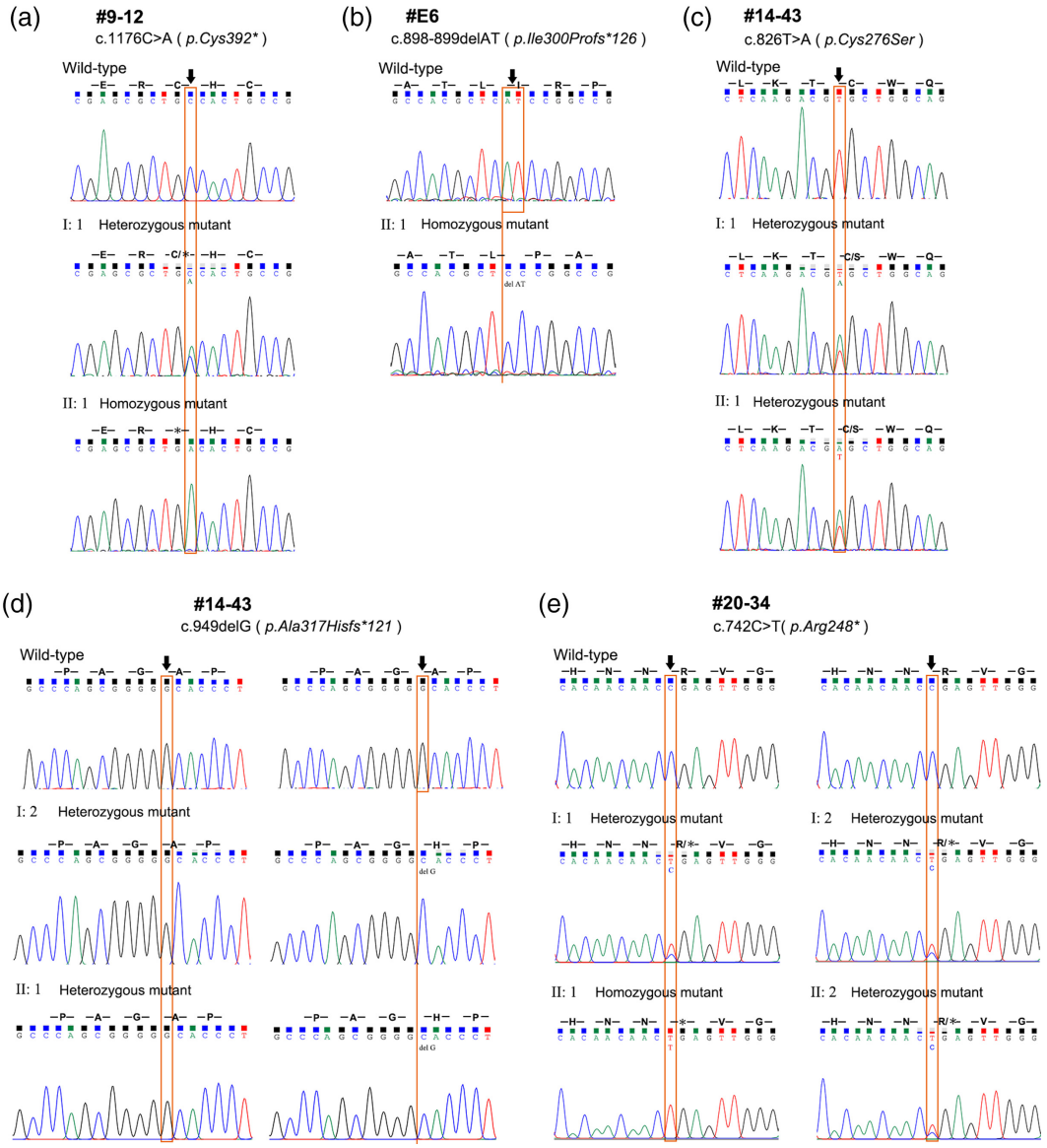

FIGURE 3 Five novel *WNT10A* mutations detected in the patients with OODD. (a) DNA sequence chromatograms showing the nonsense mutation c.1176C>A (p.Cys392*) in Family #9–12. The patient has consanguineous parents: while the unaffected father carried the same heterozygous WNT10A mutation (Figure 3a), his mother was not available for the study. (b) DNA sequence chromatograms showing the frame-shift mutation c.898-899delAT (p.Ile300Profs*126) in family #E6. Although his parents were consanguineous, the paternal DNA sample was not available. Therefore, the origin of the mutant allele is unknown. (c,d) DNA sequence chromatograms for Family #14–43 showing the missense mutation c.826T>A (p.Cys276Ser), inherited from the father, and the frame-shift mutation c.949delG (p.Ala317Hisfs*121), inherited from the mother. (e) DNA sequence chromatograms showing the nonsense mutation c.742C>T (p.Arg248*) in Family #20–34. This patient is an offspring of consanguineous parents. Both her parents and her younger brother are heterozygous carriers of this nonsense mutation, but they did not exhibit any observable symptoms of OODD. Solid arrows indicate nucleotide mutations [Color figure can be viewed at wileyonlinelibrary.com]

analysis by visual inspection and genetic screening results suggested that the OODD trail is autosomal recessive in four affected individuals. These four patients all exhibited classical OODD features, including agenesis of permanent and primary teeth, nail dysplasia, palmoplantar keratodermas, dry skin, and abnormal hair. Interestingly, two affected patients had atypical OODD clinical manifestations in skin such as erythematous patches on the face and atopic dermatitis on the legs. Based on their clinical findings, a diagnosis of OODD was made for these patients.

After discovering the first *WNT10A* gene mutation (c.697G>T; p.Glu233*) in two Lebanese OODD families (Adaimy et al., 2007), about 30 cases of OODD and 11 mutations in *WNT10A* with these cases have been reported (Adaimy et al., 2007; Adams, 2007; Andl, Reddy, Gaddapara, & Millar, 2002; Bohring et al., 2009; Kroigard et al., 2016; Megarbane et al., 2004; Nawaz et al., 2009; Tardieu et al., 2017; van den Boogaard et al., 2012; Van Geel et al., 2010; Vink et al., 2014; Wedgeworth, Nagy, White, Pembroke, & McGrath, 2011). The eleven reported mutations comprise six nonsense mutations (p.Trp9*, p.Cys107*, p.Glu233*, p.Glu347*, p.Arg128*, and p.Cys376*), four missense mutations (p.Ala131Val, p.Gly213Ser, p.Phe228Ile, and p.Gly356Cys) and one frame-shift mutation (p.Glu52Glyfs*29). Among these mutations, p.Cys107X and p.Phe228Ile are the most frequent

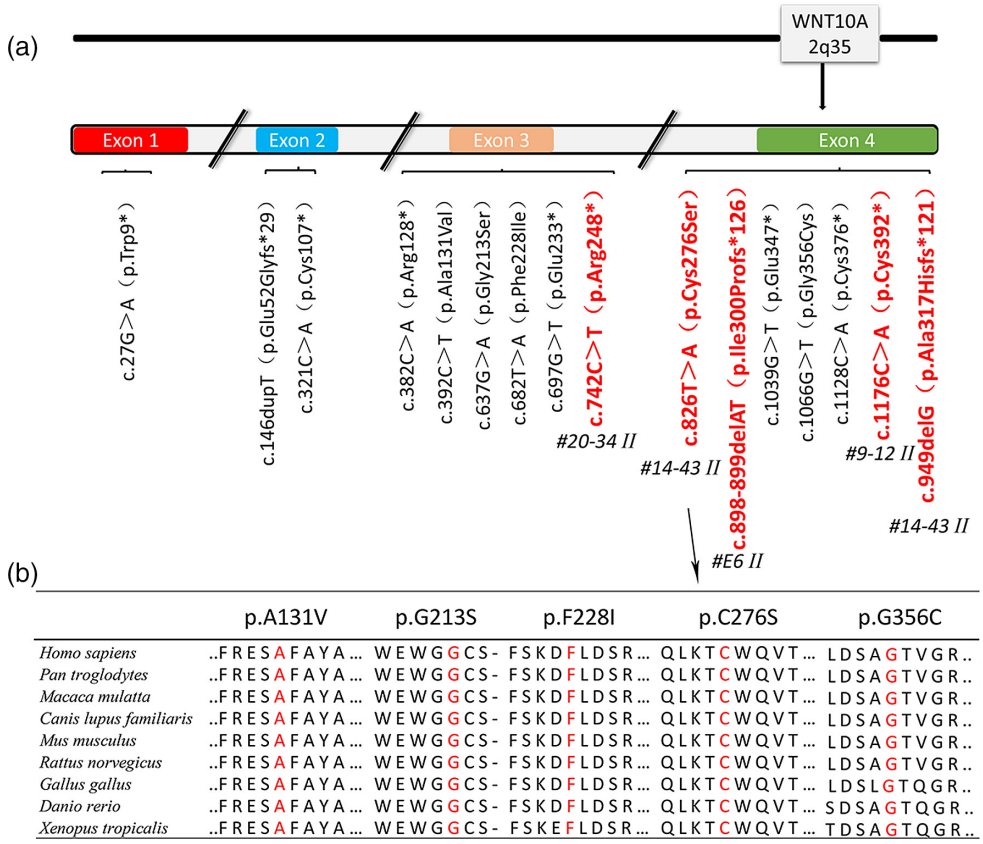

FIGURE 4 Location and conservation analysis of novel OODD-associated *WNT10A* mutations. (a) Distribution of mutations identified in OODD patients in the schematic diagram of the *WNT10A* gene. The five novel mutations identified in this study are highlighted in red. Reported mutation are labeled in black. (b) Conservation analysis of the affected amino acids of current and reported OODD-associated *WNT10A* mutations among 9 different vertebrate species. The amino acid residue 276 associated with the novel missense mutation (c.826T>A) is indicated by a black arrow [Color figure can be viewed at wileyonlinelibrary.com]

homozygous mutations found in OODD patients. Additionally, the compound heterozygous mutation p.Cys107X/p.Phe228Ile has been repeatedly reported in OODD patients. In our study, all the five *WNT10A* mutations are novel and consist two nonsense mutations, two missense mutations, and one frame-shift mutation (Figure 4a).

Phenotypic analysis of *WNT10A* mutations demonstrate that while OODD probands carrying a homozygous mutation had severe ectodermal symptoms and anodontia of permanent dentitions, the heterozygous family members only showed mild hypodontia or no symptoms. These finding suggested that the impact of the homozygous *WNT10A* mutations in ectodermal organs is more severe than that of heterozygous mutations. Our study agrees with previous reports that mono-allelic mutations in *WNT10A* might lead to isolated tooth agenesis without any other ectodermal dysplasia features (Arzoo, Klar, Bergendal, Norderyd, & Dahl, 2014; Bohring et al., 2009; Tardieu et al., 2017).

Notably, all patients with a bi-allelic *WNT10A* mutation showed anodontia, the absence of all permanent teeth, in our study. To our best knowledge, this is the first study describing the anodontia of permanent dentitions in the OODD patients with a bi-allelic *WNT10A* mutation, while previous studies only showed severe hypodontia in OODD patients. We also scrutinized the primary tooth phenotype in these patients. Interestingly, agenesis of the primary teeth was very mild compared to the permanent teeth and the number of missing primary teeth ranged from 2 to 5. Retrospectively, bi-allelic *WNT10A* mutations often severely affect permanent dentition, whereas results in mild hypodontia of the primary teeth with morphological abnormalities (Bergendal, Norderyd, Zhou, Klar, & Dahl, 2016; Kantaputra, Kaewgahya, Jotikasthira, & Kantaputra, 2014). Therefore, bi-allelic *WNT10A* mutations may have a more deleterious effect on permanent dentition than primary dentition, suggesting that WNT10A is critical for permanent tooth development compared with deciduous teeth.

The clinical manifestations of the primary tooth anomaly in our OODD patients are microdontia/peg-shaped tooth, taurodontism, short root anomaly, root fusion, reduced root number, and enamel hypoplasia. Recent studies indicated that *Wnt10a* knockout mice had microdontia of the molars, misshapen roots with taurodontism (Tardieu et al., 2017; Yang et al., 2015; Xu et al., 2017). Obviously, the dental phenotypes of *Wnt10a* knockout mice, such as microdontia and root developmental anomalies, are identical to the primary dentition rather than the permanent dentition of bi-allelic *WNT10A* mutated patients, suggesting that the dentition of rodents is more analogous to the primary dentition of humans (Yang et al., 2015) and that the molecular mechanisms that regulate the development of primary and permanent teeth may be different. Therefore, understanding the developmental roles of WNT10A in diphyodont may provide opportunities to differentiate the molecular mechanisms that underlies the development of two sets of dentitions in humans. Because

rodents are monophyodont animals and only process a single set of dentitions, future studies should utilize diphyodont transgenic mammals, for example, miniture pig, to elucidate the role *WNT10A* in the development of diphyodont.

In conclusion, we present the general clinical manifestations, intra-oral findings and underlying genetic mutations in four unrelated patients with OODD. We report five novel *WNT10A* mutations, which further expand the spectrum of OODD-associated *WNT10A* mutations. Our study demonstrates that bi-allelic (compound heterozygous and homozygous) *WNT10A* mutations result a more severe overall phenotype compared to heterozygous *WNT10A* mutations. Based on genotype–phenotype correlation analysis, bi-allelic mutations of the *WNT10A* gene have a more deleterious effect on the permanent dentition than on the primary dentition. Given the molecular mechanisms that regulate the development of primary and permanent dentition may be different, further in-depth functional studies should be conducted to delineate the roles of WNT10A protein and effects of *WNT10A* mutation on diphyodont development.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

ORCID

Dong Han https://orcid.org/0000-0001-9625-3384

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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