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RESEARCH ARTICLE

Ptosis as a unique hallmark for autosomal recessive *WNT1*-associated osteogenesis imperfecta

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Osteogenesis imperfecta (OI) is a heritable connective tissue disorder, mainly characterized by bone fragility and low bone mass. Defects in the type I procollagen-encoding genes account for the majority of OI, but increasingly more rare autosomal recessive (AR) forms are being identified, which are caused by defects in genes involved in collagen metabolism, bone mineralization, or osteoblast differentiation. Bi-allelic mutations in *WNT1* have been associated with a rare form of AR OI, characterized by severe osteoporosis, vertebral compression, scoliosis, fractures, short stature, and variable neurological problems. Heterozygous *WNT1* mutations have been linked to autosomal dominant early-onset osteoporosis. In this study, we describe the clinical and molecular findings in 10 new patients with AR *WNT1*-related OI. Thorough revision of the clinical symptoms of these 10 novel patients and previously published AR *WNT1* OI cases highlight ptosis as a unique hallmark in the diagnosis of this OI subtype.

KEYWORDS

collagen, osteogenesis imperfecta, ptosis, *WNT1*

1 | INTRODUCTION

Osteogenesis imperfecta (OI) is a heritable connective tissue disorder that is mainly characterized by bone fragility with multiple fractures and variable short stature. Extraskeletal manifestations include blue sclerae, dentinogenesis imperfecta, hearing impairment, easy bruising, and joint hypermobility. The phenotypic spectrum of OI ranges from mild forms with only few fractures, to severe and even perinatal lethal forms (Forlino & Marini, 2016; Kang, Aryal, & Marini, 2017; Marini et al., 2017). The majority of OI cases are inherited in an autosomal dominant (AD) manner and are caused by heterozygous mutations in either *COL1A1* or *COL1A2*, the genes encoding the major fibrillar type I (pro)collagen (Kang et al., 2017). With the exception of *IFITM5* (AD inheritance, function in bone mineralization), mutations in non-collagen genes are associated with autosomal recessive (AR) forms of OI, which are nowadays categorized based on the cellular pathways in which their molecular functions are executed: involvement in bone mineralization (*SERPINF1*), collagen modification (*CRTAP*, *P3H1*, and *PPIB*), collagen processing and cross-linking (*SERPINH1*, *FKBP10*, *PLOD2*, and *BMP1*), and osteoblast differentiation and function (*SP7*, *TMEM38B*, *WNT1*, *CREB3L1*, and *SPARC*; Forlino & Marini, 2016; Kang

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et al., 2017; Marini et al., 2017). Recently, this last class was further expanded with a report of an X-linked form of OI caused by mutations in *MBTPS2* (Lindert et al., 2016; Marini et al., 2017).

The *WNT1* gene (Wingless-type MMTV integration site family, member 1) encodes the secreted signaling protein WNT1, which belongs to the family of proteins that regulate many aspects of cell growth, differentiation, function, and death. One of the pathways activated by Wnts is signaling through the canonical Wnt/β-catenin pathway, which results in an increased bone mass through a number of mechanisms, including stimulation of preosteoblast replication, induction of osteoblastogenesis, and inhibition of osteoblast and osteocyte apoptosis (Aken et al., 2016; Joeng et al., 2017; Krishnan, Bryant, & MacDougald, 2006).

Homozygous and compound heterozygous mutations in *WNT1* have been identified in a series of patients displaying moderate to severe AR forms of OI (compatible with OI type III or IV according to the Sillence classification; Aldinger et al., 2016; Fahiminiya et al., 2013; Faqeih, Shaheen, & Alkuraya, 2013; Keupp et al., 2013; Kuptanon et al., 2018; Laine et al., 2013; Lu et al., 2018; Pyott et al., 2013; Umair et al., 2017; Won et al., 2017). This type of OI is currently classified as OI type XV (Forlino & Marini, 2016; Kang et al., 2017; Marini et al., 2017; Sillence, Senn, & Danks, 1979). In addition, heterozygous *WNT1*-mutations have been shown to result in nonsyndromic AD early-onset osteoporosis (Laine et al., 2013).

In the present study, we report 10 patients from 8 families in whom we identified homozygous *WNT1* mutations and provide a comprehensive overview of all AR *WNT1* OI cases that have been reported until now. The patients presented in this study have moderate to severe OI, with the unique and striking clinical observation that they all have uni or bilateral ptosis.

2 | MATERIALS AND METHODS

2.1 | Family ascertainment

For eight families, 10 patients (all children) were available. Eight patients originated from six Indian families (hereupon referred to as PI-1, PI-2, PI-3, PII, PIII, PIV, PV, and PVI), two patients originated from two Turkish families (hereupon referred to as PVII and PVIII). Written and signed informed consent was obtained from the parents of the patients. Genomic DNA (gDNA) from patients, (healthy) siblings, or parents was isolated from blood according to the standard procedures (QIAamp DNA Blood Mini Kit, Qiagen).

2.2 | Molecular analyses

Prior to sequencing, gDNA for PI-1, PI-2, PI-3, PII, PIII, PIV, PV, PVI, and PVII was PCR amplified for all known OI genes, encompassing the coding and flanking 5′ and 3′ untranslated regions. Subsequent sequencing was performed using next generation sequencing (MiSeq platform—Illumina). For PVIII, whole exome sequencing (HiSeq platform—Illumina) was applied after excluding the presence of a (likely) pathogenic variant in *COL1A1* and *COL1A2*. Confirmational Sanger sequencing was performed for all 10 patients, siblings and parents (when available; ABI 3730XL DNA Analyzer, Life Technologies Foster City, CA, USA).

Nucleotide numbering of variants reflects cDNA numbering, with +1 corresponding to the A of the ATG translation initiation codon in the *WNT1* reference sequence (NM_005430.3). Amino acid residues are numbered from the first methionine residue of the protein reference sequence (NP_005421.1). Variant nomenclature follows the HGVS guidelines (http://www.hgvs.org/mutnomen), and variant classification was done using the Alamut Visual software and according to the ACMG standards and guidelines (Richards et al., 2015). All variants were checked and submitted to the OI Variant Database (http://www.le.ac.uk/ge/collagen/).

3 | RESULTS

3.1 | Clinical phenotype

This study includes eight patients (five females and three males) from six Indian families, and two male patients from two Turkish families. PI-1 and PI-2 are siblings and PI-3 is remotely related to PI-1 and PI-2 (Pedigree, Supporting Information Figure S1). Parental consanguinity was reported for six patients (6/10, 60%). Clinical details of affected individuals are summarized in Table 1. All Indian families were from the same region from south India. Ages at diagnosis ranged from 11 months to 11 years. The skeletal presentation of all subjects was (very) severe and similar to OI type III. The age at which the first fracture occurred ranged from in utero to 6 months. The most common skeletal features included severe osteopenia (10/10, present in 100% of the patients), thin cortices of long bones (10/10, 100%), wavy long bones (9/10, 90%), (severe) bowing of upper (8/10, 80%) and lower (8/9, 88.9%) extremities (to the extent that height measurement was not possible in the majority of them), and nonunion of fractures (5/10, 50%). Vertebral compression was common (3/7, 42.9%), with "codfish" thoracic and lumbar vertebrae. Four subjects developed severe scoliosis (4/8, 50%). All patients had gross delay in motor development due to frequent fractures and severe deformities.

Radiological examination revealed popcorn appearance of the epiphyses of long bones in three older subjects (PI-1, PI-2, and PIV; 3/8, 37.5%). Response to bisphosphonates, which was administered to all patients, was minimal, with some reduction in the frequency of fractures, but none achieved independent walking.

None of our patients had blue sclerae and two patients presented with hearing impairment (2/9, 22.2%) or dentinogenesis imperfecta (2/10, 20%), respectively. A unique and striking facial feature was the presence of congenital ptosis in all 10 patients (10/10, 100%; bilateral in eight subjects and unilateral in two subject), which is accompanied by high arched eyebrows (highlighted in Figure 1).

Delayed cognitive development was observed in four subjects (4/10, 40%), speech delay was significant in two subjects. Behavioral abnormalities, including the use of abusive language, were reported for PI-2 and PIV. Brain images were available for only one patient PVIII, who showed severe brain anomalies at age 1.5 years (Figure 1v).

TABLE 1 Detailed overview of molecular, clinical, and radiographic findings of the AR WNT1 OI patients included in this study

Case	PI–1	PI–2	PI–3	PII	PIII	PIV	PV	PVI	PVII	PVIII	All	All earlier reported (Supporting information Table S1)
Sex	Female	Male	Female	Female	Female	Male	Male	Female	Male	Male	/	/
Ethnicity	Indian	Indian	Indian	Indian	Indian	Indian	Indian	Indian	Turkish	Turkish	/	/
Age at diagnosis	8 y	11 y	11 m	2.5 y	3.25 y	7 y	6 y	3 y	5 y	1.5 y	4.8 y	/
Consanguinity	–	–	+	–	–	+	+	+	+	+	6/10 (60%)	22/38 (57.9%)
Alive	–	+	+	+	+	+	+	+	+	–	8/10 (80%)	/
Phylogenic relationship	Sib of PI-2	Sib of PI-1	Relative of PI-1 and P1-2	?	?	?	?	?	?	?	/	/
WNT1-molecular results												
Inheritance	AR	AR	AR	AR	AR	AR	AR	AR	AR	AR	/	/
cDNA change	c.506dupG	c.506dupG	c.506dupG	c.506dupG	c.506dupG	c.255delG	c.685_689del	c.859delC	c.859dupC	c.859dupC	/	/
Protein change	p.(Cys170Leufs*)	p.(Cys170Leufs*)	p.(Cys170Leufs*)	p.(Cys170Leufs*)	p.(Cys170Leufs*)	p.(Leu86Cysfs*)	p.(Val229Hisfs*)	p.(His287Thrfs*)	p.(His287Profs*)	p.(His287Profs*)	/	/
Variant classification (ACMG)[12]	Class 5	Class 5	Class 5	Class 5	Class 5	Class 4	Class 4	Class 4	Class 4	Class 4	/	/
gnomAD	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent	/	/
OI variant database	Already reported	Already reported	Already reported	Already reported	Already reported	Absent	Absent	Absent	Already reported	Already reported	/	/
Parents	Mother het Father het	Mother het Father het	Mother het	Mother het Father het	?	Mother het Father het (mosaic)	Mother het Father het	?	–	Mother het Father het	/	/
Height, weight, and head circumference												
Height (cm)	NMP	NMP	75	81	74	NMP	NMP	NMP	91	71	/	/
Weight (kg)	?	?	9	8.75	8.25	17	18	11.3	13.8	6.0	/	/
Head circumference (cm)	52	49	43.5	45	47.5	48	47	46	48	41.5	/	/
Clinical phenotype												
Dentinogenesis imperfecta	–	–	–	–	–	–	–	–	+	+	2/10 (20%)	2/32 (6.3%)
Blue sclerae	–	–	–	–	–	–	–	–	–	–	0/10 (0%)	9/33 (27.3%)
Hearing impairment	–	–	–	–	+	–	++	–	–	?	2/9 (22.2%)	/
Ptosis	Bilateral	Bilateral	Bilateral	Bilateral	Bilateral	Unilateral	Bilateral	Unilateral	Bilateral	Bilateral	10/10 (100%)	12/18 (66.7%)
Neurological/brain abnormalities	?	?	?	?	?	?	?	?	?	Severe anomalies (see Figure 1)	1/1 (100%)	6/11 (54.5%)
Speech	Normal	Sentences	Not attained	Sentences	Single words	Sentences	Speaks fluently	Sentences	Sentences	Not attained	/	/
Delayed cognitive development	–	+	–	–	+	+	–	–	–	+	4/10 (40%)	11/28 (39.3%)
Maximum motor milestone achieved	Sits when made to sit	Sits when made to sit	Sits when made to sit	Sits without support	Sits with support	Sits by himself	Sits with support	Sits with support	Sits by himself	Sits by himself	/	/
Scoliosis	+	+	–	–	?	–	+	?	–	+	4/8 (50%)	/
Hypermobility of joints	+	+	–	+	–	+	–	–	–	–	4/10 (40%)	5/16 (31.3%)
Fracture history and therapy												
Age of 1st fracture	3 m	4 d	6 m	In utero	11 d	6 m	9 d	10 d	10 d	1 w	/	/
Number of fractures	>50	>50	4	3	Multiple	Multiple	Multiple	Multiple	Multiple	Multiple	/	/

(Continues)

TABLE 1 (Continued)

Case	PI–1	PI–2	PI–3	PII	PIII	PIV	PV	PVI	PVII	PVIII	All	All earlier reported (Supporting information Table S1)
Effect of bisphosphonate therapy	No further fractures	3 fractures in last 3 y	No further follow up	5 fractures	Fractures reduced in frequency	2 fractures in last 3 y	Fractures reduced in frequency	Fractures reduced in frequency	Very low effect of therapy	Very low effect of therapy	/	/
ALP (IU/L)	319.4	197.6	?	345.7	?	?	?	?	520	368	/	/
Radiological features												
Thin cortices of long bones	+	+	+	+	+	+	+	+	+	+	10/10 (100%)	/
Wavy long bones	++	++	–	+	+	++	+	+	+	+	9/10 (90%)	/
Thin skull	?	?	?	+	+	+	?	?	?	?	3/3 (100%)	/
Wormian bones	+	?	?	+	+	+	?	?	?	?	4/4 (100%)	/
Bowing of upper limbs	+	+	–	+	+	+	+	–	+	+	8/10 (80%)	/
Bowing of lower limbs	+	+	–	+	+	+	?	+	+	+	8/9 (88.9%)	/
Vertebral compression fractures	++	++	–	–	–	++	–	?	?	?	3/7 (42.9%)	27/33 (81.8%)
Nonunion	+	–	–	–	+	+	–	–	+	+	5/10 (50%)	/
Thin fibula	+	+	–	+	+	+	+	–	+	+	8/10 (80%)	/
Popcorn appearance of epiphysis	+	+	–	–	–	+	–	–	?	?	3/8 (37.5%)	/
Delayed bone age	+	+	+	+	?	+	+	?	?	?	6/6 (100%)	/
Osteopenia	++	++	+	+	+	++	+	+	+	+	10/10 (100%)	8/8 (100%)

Note. AR = autosomal recessive; + = present; – = absent; ? = no information; d = days; w = weeks; m = months; y = years; het = heterozygote; NMP = no measurement possible; gnomAD = genome aggregation database (http://gnomad.broadinstitute.org).

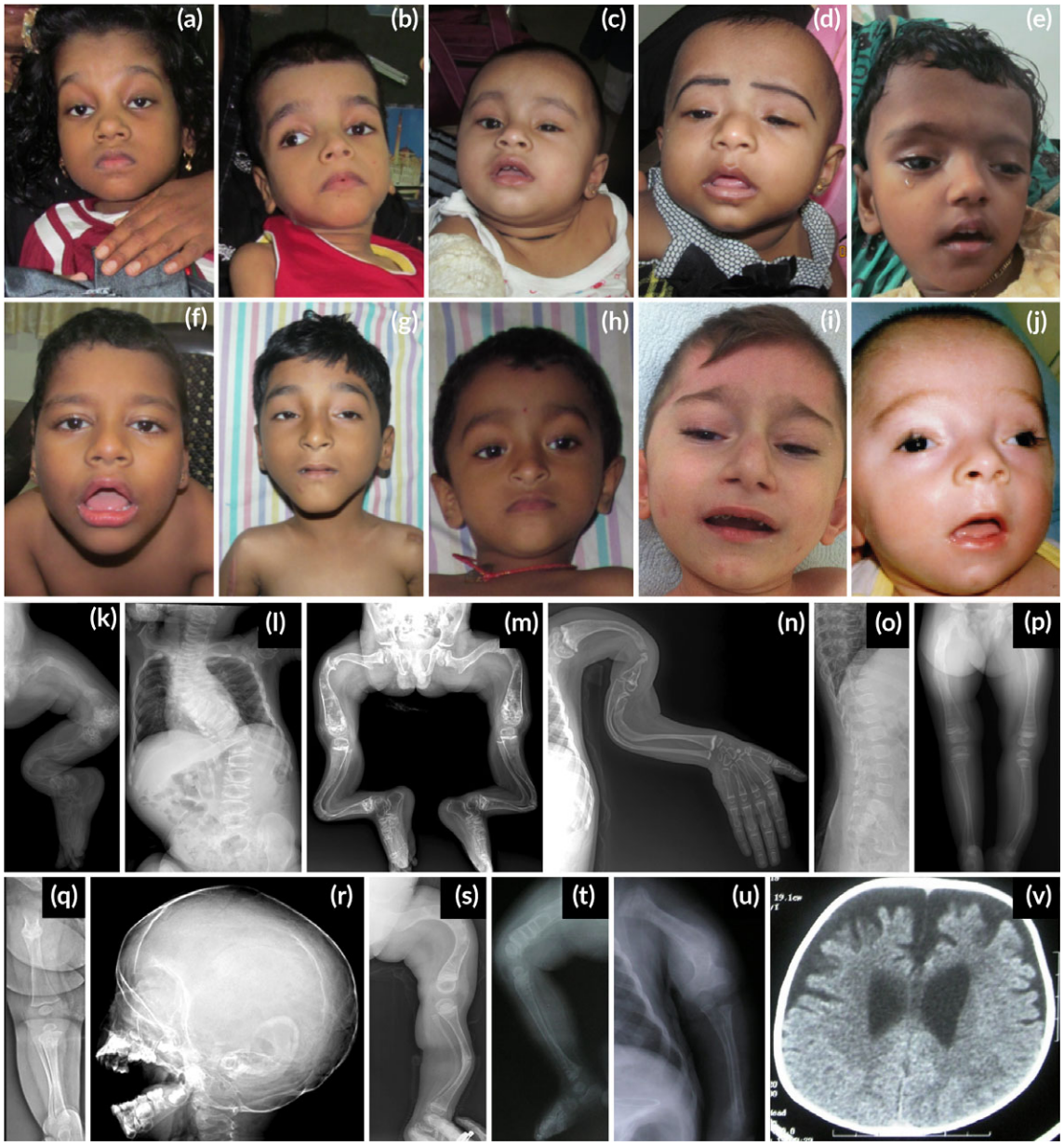

FIGURE 1 Clinical spectrum of autosomal recessive *WNT1*-associated osteogenesis imperfecta. Clinical pictures of all patients [PI-1 (a), PI-2 (b), PI-3 (c), PII (d), PIII (e), PIV (f), PV (g), PVI (h), PVII (i), and PVIII (j)] highlight ptosis—accompanied by high arched eyebrows—and some patients [PIII (e) and PIV (f)] present with hypotonia of the facial muscles. Radiographs of PI-1 at age 8 years (k: extreme deformity and popcorn appearance of the epiphyses of the lower femur and upper tibia), PI-2 at age 9 years (l: severe scoliosis, vertebral compression, and "codfish" appearance of thoracic and lumbar vertebrae; m: wavy long bones of lower limbs with thin cortices, nonunion of both femora with pseudo joint formation on the right femur, bilateral popcorn appearance of distal femoral epiphyses; n: severely deformed osteoporotic long bones of left upper limb which present with retarded bone age, a wavy thin cortex and nonunion of the humerus with pseudo joint formation), PI-3 at age 11 months (o: wedging of the spine at T5-T7), PII at age 16 months (p: long bones of lower limbs showing osteoporosis, curvature, and callus formation of the right femur and impact of bisphosphonate therapy; q: early stage wavy fibulae and callus formation of the right upper femur following a fracture in utero), PIII at age 3 years (r: severe thinning of the calvarium and presence of Wormian bones of the skull), PVII at age 5 years (s: curved long bones of the left femur, tibia, and fibula), and PVIII at age 1.5 years (t and u: osteoporotic bones of the right lower limb and fracture healing of the left humerus, respectively; v: MRI image of the brain showing ventriculomegaly, cortical atrophy, and an increased subarachnoid space and sulcus depth, respectively) [Color figure can be viewed at wileyonlinelibrary.com]

3.2 | Molecular results

Five different homozygous disease-causing *WNT1* variants were detected (Table 1 and Figure 2). Sequencing of parental DNA confirmed the bi-allelic inheritance, and molecular screening of (healthy) siblings revealed that they are heterozygous carriers of the familial mutation (data not shown). We identified the earlier reported homozygous duplications c.506dupG (p.(Cys170Leufs*)) in patients PI-1, PI-2, PI-3, PII, and PIII, and c.859dupC (p.(His287Profs*)) in patients PVII and PVIII (Keupp et al., 2013; Pyott et al., 2013). In three other patients (PIV, PV, and PVI), molecular analysis revealed novel homozygous deletions c.255delG (p.(Leu86Cysfs*)), c.685_689del (p.(Val229Hisfs*)), and c.859delC (p.(His287Thrfs*)), respectively. None

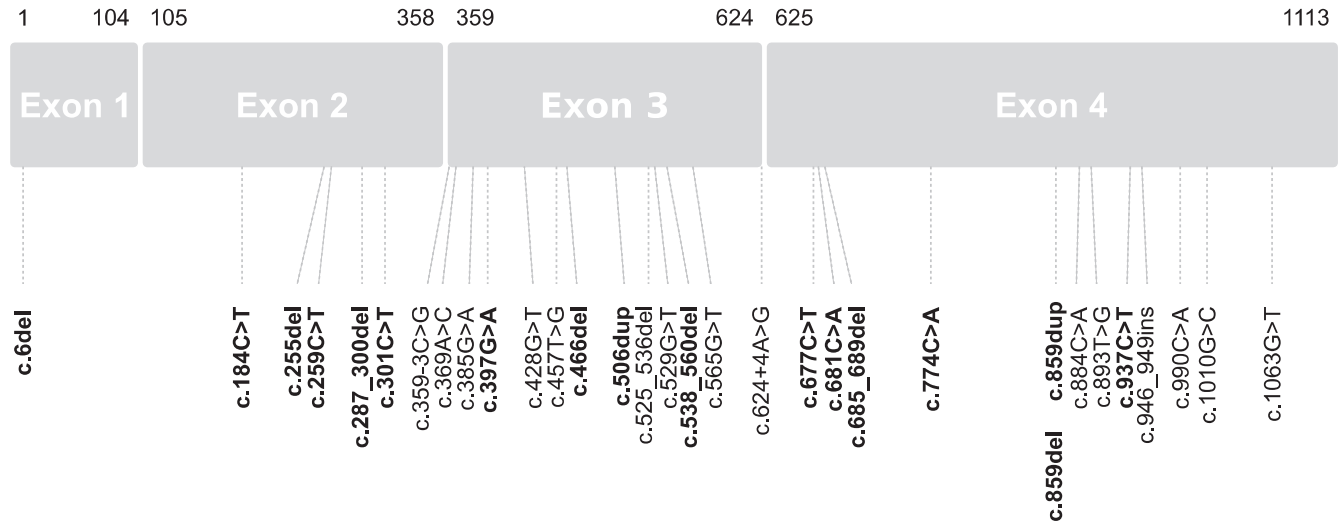

FIGURE 2 Schematic overview of all AR *WNT1* (likely) pathogenic variants. (Likely) pathogenic variants linked to ptosis are highlighted in bold, nucleotide numbers on top correspond to the start and end sites of each exon, respectively

of these deletions were previously reported and were absent from population databases.

4 | DISCUSSION

We present 10 patients from eight independent families, with a severe form of OI in whom homozygous *WNT1* mutations were identified. The skeletal phenotype in our patient cohort is highly similar to the phenotype of previously reported patients with bi-allelic *WNT1* mutations (43 patients from 29 independent families—see Supporting Information Table S1). Clinical hallmarks include short stature and severe osteoporosis with fractures starting in infancy. Few patients, including PII in the current study, presented with fractures in utero, but most patients developed fractures within the first weeks or months of life. Early-onset involvement of the spine, with severe vertebral compression fractures and sometimes scoliosis is another consistent feature. Bluish sclerae were not observed in our patient cohort, but have been noted in a few patients with bi-allelic-*WNT1* mutations (9/34, 26.5%; Supporting Information Table S1). Hearing and tooth development are usually not impaired (Aldinger et al., 2016; Fahiminiya et al., 2013; Faqeih et al., 2013; Keupp et al., 2013; Kuptanon et al., 2018; Laine et al., 2013; Lu et al., 2018; Pyott et al., 2013; Umair et al., 2017; Won et al., 2017).

A striking and unique clinical observation in our patient cohort is the presence of congenital ptosis, as illustrated in Figure 1. All patients presented here had either unilateral (2/10) or bilateral (8/10) ptosis, and review of the literature revealed that 12 patients were noted to have ptosis (eight unilateral, two bilateral; 12/18, 66.7%), 6 presented without ptosis and for 25 patients ptosis was not described (Supporting Information Table S1). The cause of ptosis is currently unknown. It has been noted that some patients with bi-allelic *WNT1* mutations have neurological/brain abnormalities (6/11, 54.5%), including abnormalities of the midbrain and/or cerebellum, and/or severe developmental/intellectual delay (11/28, 39.3%; Aldinger et al., 2016; Fahiminiya et al., 2013; Faqeih et al., 2013; Keupp et al., 2013; Kuptanon et al., 2018; Laine et al., 2013; Lu et al., 2018; Pyott et al., 2013; Umair et al., 2017; Won et al., 2017). Brain images for our cohort were available for only one patient (PVIII, presenting with severe brain anomalies, Figure 1v) and four patients had a significant delay in cognitive development (4/10, 40%). In addition to this, a combined literature search for all the unreported (our cohort, n = 10) and earlier reported AR *WNT1* patients (n = 43; Table 1 and Supporting Information Table S1) shows that ptosis is present in all patients suffering from developmental or intellectual delay and/or neurological/brain abnormalities, and that ptosis has never been described to be present in patients where those features were absent. As such, it is possible that the ptosis observed in this patient cohort is due to abnormal brain and/or nerve development, leading to dysfunction of the muscles that elevate the eyelid, however, further studies are needed to evaluate this hypothesis. Earlier studies in mice revealed *Wnt1* as a key molecule in the development of specific regions of the central nervous system (McMahon & Bradley, 1990). McMahon and Bradley (1990) reported severe abnormalities of the midbrain and the cerebellum in late-gestational homozygous *Wnt1* null mice, and demise of the newborn pups within the first 24 hr of life. At the time, no skeletal abnormalities were reported in these mice. After the identification of homozygous and heterozygous *WNT1* mutations in humans with severe OI and early-onset osteoporosis respectively, studies in the nonlethal swaying mouse ($Wnt1^{sw/sw}$ mice, carrying a spontaneous single nucleotide deletion in the *Wnt1* gene) revealed major features of OI. These features include severe bone fragility, fractures, reduced bone strength, and altered levels of mineral and collagen in the bone matrix (Joeng et al., 2014). To further investigate the role of *WNT1* in bone formation, late-osteoblast-specific and osteocyte-specific *WNT1* loss- and gain-of-function mouse models were generated (Joeng et al., 2017), which emphasized the regulatory role of *WNT1* in osteoblast functioning.

In summary, the present study of 10 novel patients with *WNT1*-associated AR OI brings the total number of patients with OI type XV to 53, and further extends both the phenotypic and genotypic spectrum of this condition. Besides the clinical hallmarks of early onset

fracture risk, early involvement of the spine and neurological/brain abnormalities, our observations highlight that uni or bilateral ptosis (22/28, 78.6%) is a unique characteristic of this condition, which can serve as a clinical clue to the underlying molecular diagnosis.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

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

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