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Autosomal dominant frontometaphyseal dysplasia: Delineation of the clinical phenotype

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Frontometaphyseal dysplasia (FMD) is caused by gain-of-function mutations in the X-linked gene *FLNA* in approximately 50% of patients. Recently we characterized an autosomal dominant form of FMD (AD-FMD) caused by mutations in *MAP3K7*, which accounts for the condition in the majority of patients who lack a *FLNA* mutation. We previously also described a patient with a de novo variant in *TAB2*, which we hypothesized was causative of another form of AD-FMD. In this study, a cohort of 20 individuals with AD-FMD is clinically evaluated. This cohort consists of 15 individuals with the recently described, recurrent mutation (c.1454C>T) in *MAP3K7*, as well as three individuals with missense mutations that result in substitutions in the N-terminal kinase domain of TGFβ-activated kinase 1 (TAK1), encoded by *MAP3K7*. Additionally, two individuals

have missense variants in the gene *TAB2*, which encodes a protein with a close functional relationship to TAK1, TAK1-associated binding protein 2 (TAB2). Although the X-linked and autosomal dominant forms of FMD are very similar, there are distinctions to be made between the two conditions. Individuals with AD-FMD have characteristic facial features, and are more likely to be deaf, have scoliosis and cervical fusions, and have a cleft palate. Furthermore, there are features only found in AD-FMD in our review of the literature including valgus deformity of the feet and predisposition to keloid scarring. Finally, intellectual disability is present in a small number of subjects with AD-FMD but has not been described in association with X-linked FMD.

KEYWORDS

Frontometaphyseal dysplasia, keloid, locus heterogeneity, scoliosis, TAB2, TAK1

1 | INTRODUCTION

Frontometaphyseal dysplasia (FMD) is a sclerosing skeletal dysplasia clinically characterized by prominent supraorbital ridges, sclerosis of the skull, and dense, undermodelled cortices of the long bones and phalanges. A range of extraskeletal manifestations, such as progressive joint contractures, genitourinary tract defects, laryngeal stenosis, and hearing loss, significantly impact the health and wellbeing of affected individuals over their lifetime (Fitzsimmons, Fitzsimmons, Barrow, & Gilbert, 1982; Morava, Illes, Weisenbach, Karteszi, & Kosztolanyi, 2003; Robertson et al., 2006). Furthermore, some individuals have a predisposition to develop keloid scars which can be disfiguring and debilitating (Basart et al., 2015; Wade et al., 2016). To date, little data is available on the phenotype of individuals with FMD, especially those living into their fourth decade and beyond.

FMD exhibits locus heterogeneity. A proportion of individuals have gain-of-function mutations in *FLNA*, which encodes the actin binding protein, filamin A (Robertson et al., 2003). Due to the X-chromosomal location of *FLNA*, the presentation of FMD is more severe in males and milder in females. Nevertheless there is considerable variation in the presentation in both sexes, which in the instances of females may be related to the degree of skewing of X-inactivation (Robertson, 2007; Robertson et al., 2006). X-linked (XL)-FMD is allelic to a spectrum of phenotypically related skeletal dysplasias, the otopalatodigital spectrum disorders (OPDSDs), which are also caused by gain-of-function mutations in *FLNA* (Robertson et al., 2003). Mutations in *FLNA* which lead to FMD and the OPDSDs tend to be missense or, small, in-frame deletions which are found in specific domains of the protein (Robertson, 2007; Robertson et al., 2003).

Approximately 50% of FMD patients do not have their condition explained by mutations in *FLNA* (Basart et al., 2015; Robertson et al., 2006). We have recently characterized mutations in *MAP3K7*, encoding TGFβ-activated kinase 1 (TAK1), that are causative of an autosomal dominant type of FMD. Consequently we suggested that FMD caused by mutations in *FLNA* be referred to as FMD1 and, that caused by mutations in *MAP3K7* be referred to as FMD2 (Wade et al., 2016). We also described a single individual with a de novo mutation in *TAB2*, encoding TAK1-associated binding protein 2 (TAB2), which we predicted would most likely represent a third locus for the disorder (Wade et al., 2016). We hypothesized that this missense mutation would be causative of the disease because of the close functional relationship between TAK1 and TAB2 (Besse et al., 2007; Wade et al., 2016). Evidence from knockout mouse models (Greenblatt et al., 2013; Qi et al., 2014; Sanjo et al., 2003) as well as from in vitro work (Wade et al., 2016) suggests that mutations in *MAP3K7* and *TAB2* also produce the FMD phenotype through a gain-of-function mechanism.

The most common form of autosomal dominant (AD)-FMD is caused by a recurrent *MAP3K7* mutation, c.1454C>T (GenBank: NM_003188.3), that predicts a substitution in TAK1, p.Pro485Leu (Wade et al., 2016). This mutation results in a FMD phenotype which is remarkably similar to that exhibited by the single patient with the *TAB2* de novo variant. As well as the recurrent C-terminal substitution, variants in the N-terminal kinase domain of TAK1 also confer an FMD phenotype, albeit with a milder presentation.

Here we describe the clinical presentation of AD-FMD attributed to mutations in *MAP3K7* and *TAB2*. The presentation of AD-FMD is distinct from FMD caused by mutations in *FLNA*, however the phenotypes are similar enough to suggest that the mechanism of disease is related to the same biochemical process.

2 | MATERIALS AND METHODS

2.1 | Patient ascertainment

Patients were recruited based on clinician-initiated referral and consented under approved protocols MEC/08/08/094 and 13/STH/56 (Health and Disability Ethics Committee, New Zealand). The diagnosis of FMD was confirmed based on published clinical and radiological criteria (Robertson et al., 2006). *FLNA* mutations were sought using Sanger sequencing to examine the exons and exon-intron boundaries of that gene. Copy number variants of *FLNA* were excluded by use of a customized multiplex ligation-dependent probe amplification (MLPA) probeset. Cases

with a firm clinical diagnosis of FMD and no detectable mutation in the exons or intron exon boundaries of *FLNA* formed a cohort of 20 individuals. Thirteen individuals have been clinically reported before (Table 1) (Basart et al., 2015; Morava et al., 2003; Robertson et al., 2006). Nineteen individuals (all except individual 09) were described as part of a biochemical study of AD-FMD (Wade et al., 2016). We are including all known instances of AD-FMD here for a clarity.

2.2 | Mutation discovery

Previously we utilized whole exome sequencing and targeted Sanger sequencing (Wade et al., 2016) to undertake mutation discovery on 19 participants. Subsequently a sample from individual 09 (Table 1) was subjected to exome sequencing using the Illumina HiSeq (BGI-Europe, Denmark) platform after enrichment of the exome with the Agilent SureSelectXT Human All Exon 50 Mb capture kit. After read alignment with BWA and variant calling with GATK, variants were annotated by the Genetics Department of the Radboud UMC using an in-house analytical pipeline. Candidate variants were confirmed with Sanger sequencing.

3 | RESULTS

3.1 | Craniofacial findings

The 20 subjects with FMD described here all manifested the three mandatory diagnostic facial features of FMD; prominent supraorbital ridges, downslanting palpebral fissures, and hypertelorism (Robertson et al., 2006) (Figure 1, Table 1). A broad nasal bridge was a ubiquitous finding (20/20). Despite manifesting similar facial characteristics as seen in XL-FMD, patients with the recurrent C-terminal substitution in TAK1 (p.Pro485Leu), have coarser facial features than those individuals with XL-FMD (Figure 1). However those individuals with mutations in the 5′ region of *MAP3K7*, which encodes the kinase domain of TAK1 (patients 07, 19, and 20; Table 1 and Supplementary Table S1) manifest notably milder facial features (Figure 1, Table 1). Micrognathia, a mandatory diagnostic feature of XL-FMD, was only present in 16/20 (80%) of the individuals with *TAB2* and *MAP3K7* mutations (Table 1). Other features which may set AD-FMD apart from XL-FMD include the lack of bias toward affected males and the presence of hearing loss, which can be conductive, sensorineural or mixed. Some kind of deafness is observed in 6/8 (75%) males and

TABLE 1 Clinical and radiological findings in AD-FMD

			Clinical findings																			Radiological findings							
Individual	Sex	Age (years)	Prominent supraorbital ridges	Hypertelorism	Downslanting palpebral fissures	Broad nasal bridge	Full cheeks	Micrognathia	Intellectual disability	Keloid	Subglottal stenosis	Hydronephrosis	Urethral stenosis	Cleft palate/bifid uvula*	Hearing loss	Scoliosis	Ulnar deviation of the hands	Long fingers	Distal phalangeal hypoplasia thumb	Valgus deformity of the feet	Structural heart defect	Cervical vertebral fusion	Skull base sclerosis	Under-modelled phalanges, metacarpals and metatarsals	Undermodelled metaphyses/diaphyses	Digital and wrist contractures	Elbow contractures/ dislocated radial head	Broad thumbs/fingers	Protein substitution
01*	M	57	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	TAK1 Pro485Leu
02	M	9	+	+	+	+	+	+	+	-	+	U	-	+	+	+	-	+	+	U	-	+[1]	+	+	+	+	+	+	TAK1 Pro485Leu
03	M	52	+	+	+	+	-	-	+	-	U	+	+	-	+	+	+	+	U	+	U	-	+	U	U	+	+	+	TAK1 Pro485Leu
04	M	D	+	+	+	+	U	-	-	-	U	U	U	U	+	+	+	+	+	-	U	+	+	+	+	+	+	+	TAK1 Pro485Leu
05*	M	26	+	+	+	+	+	+	-	+	-	U	-	-	+	+	+	+	-	+	+	-	+	+	+	+	+	+	TAK1 Pro485Leu
06*	M	29	+	+	+	+	U	+	+	-	-	U	-	-	U	+	U	U	U	U	U	-	+	+	+	+	+	+	TAK1 Pro485Leu
07	M	15	+	+	+	+	-	-	-	-	-	-	-	-	-	-	+	+	-	-	-	+	-	+	-	+	+	-	TAK1 Gly168Arg
08†	M	U	+	+	+	+	-	+	-	+	+	U	-	-	+	+	+	+	+	-	-	+	+	+	+	+	+	+	TAK1 Pro485Leu
09	M	24	+	+	+	+	-	+	-	-	-	+	+	-	-	+	+	+	-	+	-	-	-	+	U	+	+	+	TAB2 Gln540Arg
10*	F	U	+	+	+	+	+	+	-	+	-	-	na	+	+	-	-	+	+	U	+	+	+	+	+	+	+	+	TAK1 Pro485Leu
11†	F	26	+	+	+	+	+	+	-	+	-	-	na	+	+	+	+	+	+	+	+[2]	+	+	+	+	+	+	+	TAK1 Pro485Leu
12†	F	29	+	+	+	+	+	-	-	+	+	-	na	-	+	+	+	+	-	+	-	+	+	+	+	+	+	+	TAK1 Pro485Leu
13	F	7	+	+	+	+	+	+	-	-	+	-	na	+	+	-	-	+	-	+	-	+	+	+	+	+	+	+	TAK1 Pro485Leu
14†	F	19	+	+	+	+	+	+	-	+	+	-	na	+	+	+	+	+	-	+	-	-	+	+	+	+	+	+	TAK1 Pro485Leu
15	F	13	+	+	+	+	+	+	-	+	U	+	na	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	TAK1 Pro485Leu
16†	F	8	+	+	+	+	+	+	-	+	-	-	na	+	+	-	+	+	+	U	+	-	+	+	+	+	+	+	TAK1 Pro485Leu
17*†	F	D	+	+	+	+	+	+	-	+	-	+	na	-	+	+	-	+	-	-	-[2]	+	-	+	+	+	+	+	TAK1 Pro485Leu
18*	F	18	+	+	+	+	+	+	-	-	-	-	na	-	+	+	+	+	-	-	-	+	-	+	+	+	+	-	TAB2 Glu569Lys
19*†	F	U	+	+	+	+	+	+	-	-	U	-	na	-	+	+	U	U	U	U	U	-	-	+	-	-	U	U	TAK1 Glu70Gln
20*‡	F	34	+	+	+	+	+	+	-	-	-	-	na	-	+	+	-	+	+	-	-	U	+	+	+	+	+	+	TAK1 Val100Glu

U, unknown; na, not applicable; D, deceased; presented previously in *(Robertson et al., 2006).
All individuals, except for 09, were described in (Wade et al., 2016). Where possible, individuals have been clinically re-evaluated therefore this table is this most up-to-date phenotypic spectrum.
Protein substitution. see Supplementary Table SI for full mutation information.
+Present.
−Absent.
†Described in (Basart et al., 2015).
‡Described in (Morava et al., 2003).
[1]Cervical spinal cord compression.
[2]Aortic dilatation.

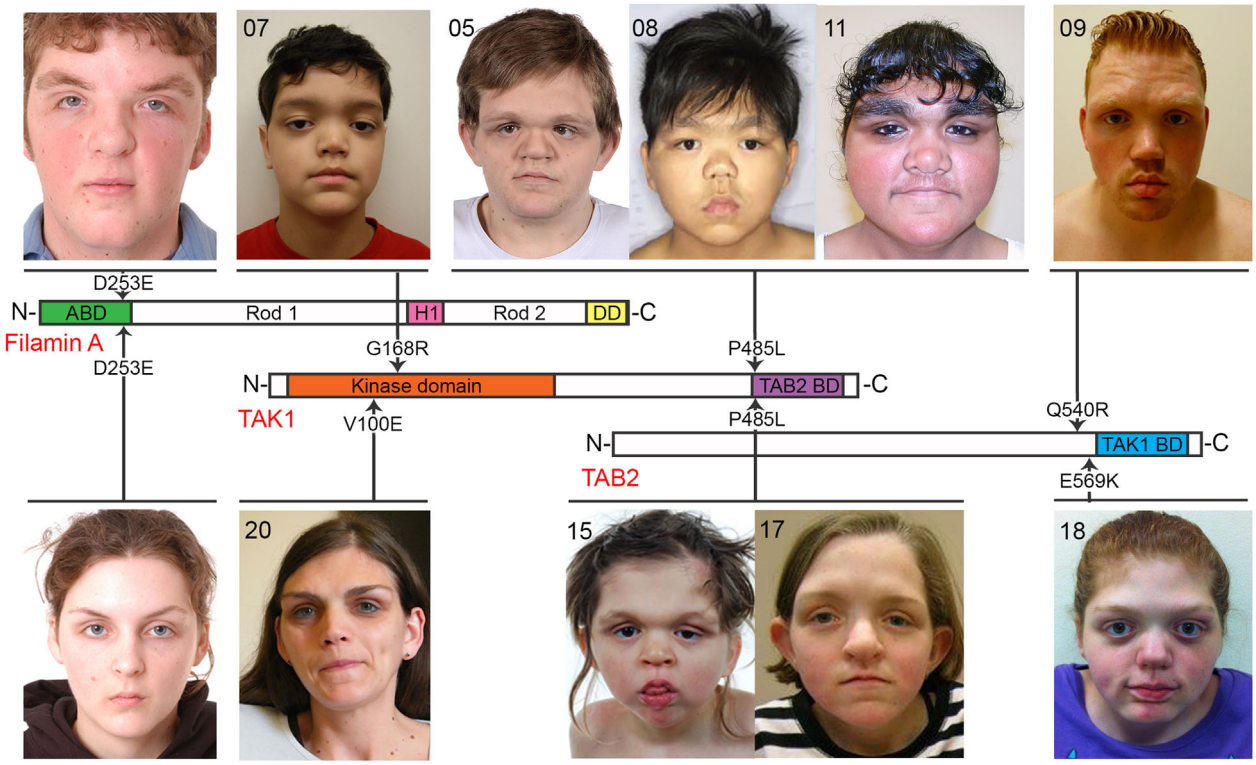

FIGURE 1 Facial characteristics of AD-FMD compared to XL-FMD. All types of FMD are characterized by prominent supraorbital ridges, downslanting palpebral fissures, hypertelorism, and a small chin. Those individuals with TAK1 substitutions in the N-terminal kinase domain have milder features, but still display the defining supraorbital ridges. Those individuals with the most common substitution found in this cohort with AD-FMD (p.Pro485Leu), located in the coiled-coil domain responsible for TAB2 binding (TAB2 BD) have coarse facial features with a small chin, broad nasal bridge and full cheeks. Individuals with substitutions in TAB2, both of which have been found slightly upstream of the coiled-coil domain responsible for TAK1 binding TAK1 BD, have facial features remarkably similar to individuals with the p.Pro485Leu TAK1 substitution. Two individuals with FMD and mutations in *FLNA* are shown for comparison. Patient numbers from this cohort are shown in the top left of each image. Individuals 05, 08, 15, 18, and 20 have been described before (Basart et al., 2015; Morava et al., 2003; Wade et al., 2016), as have the siblings with *FLNA* mutations (Robertson et al., 2006) but are reproduced here for comparison. [Color figure can be viewed at wileyonlinelibrary.com]

11/11(100%) females in this cohort compared to 67% of males and 27% of females with XL-FMD (Robertson et al., 2006) (Table 1). Cleft palate or a bifid uvula is more common in AD-FMD, occurring in 6/19 (32%) patients presented here compared to 5% of XL-FMD patients (Robertson et al., 2006) (Table 1). Radiological findings in the skull in those with AD-FMD were indistinguishable from those seen in XL-FMD for the majority of individuals, the exception being two individuals (07 and 19) with the milder presentation of AD-FMD due to substitutions in the kinase domain of TAK1: p.Gly168Arg (*MAP3K7* c.502G>C) and p.Glu70Gln (*MAP3K7* c.208G>C), who lacked skull-base sclerosis (Table 1 and Supplementary Table S1).

3.2 | Limb and digit manifestations

Contractures of the fingers, wrists, and elbows are an important diagnostic feature of both XL-FMD and AD-FMD. In this AD-FMD cohort, 19/20 had digital (Figure 2a,c) and wrist contractures and 19/19 had either a contracture of the elbow joint or a dislocated radial head (Table 1). Ulna deviation of the hands, which is a mandatory diagnostic criterion of XL-FMD, was seen in 13/18 in this cohort (Table 1). There are other notable differences in the hands and feet of AD-FMD patients; the fingers and thumbs are long (as they also are in XL-FMD; Figure 2a,b, Table 1) but the spatulate finger and thumb tips seen in XL-FMD are not as prevalent. Additionally a valgus deformity of the feet was seen in 8/15 subjects (Table 1), a sign not previously associated with XL-FMD. Radiologically, undermodeling of the phalanges is a distinct finding (Figures 2b,d). The long bones can be slightly bowed, with dense cortices. Furthermore the femur and tibia display abnormal modeling of the diaphysis and metaphysis giving the appearance of an Erlenmeyer-flask (Figure 2e, Table 1).

3.3 | Other radiological characteristics

Other radiological features which may help distinguish XL-FMD from AD-FMD include scoliosis, present in 16/20 (80%) with AD-FMD (Figure 3a, Table 1) denoting it as more prevalent in AD-FMD than in the X-linked condition (56% of males and 18% of females (Robertson et al., 2006)), an observation not previously noted in studies of *FLNA* mutation-negative FMD (Morava et al., 2003; Robertson et al., 2006). Another radiological finding which may be more prevalent in AD-FMD is the presence of cervical vertebral fusions, seen in 12/19 (63%) individuals in this cohort (Figure 3b, Table 1). Cervical fusions are only seen in 33% of *FLNA*-mutation positive males, and have never been reported in *FLNA* mutation-positive females (Robertson et al., 2006).

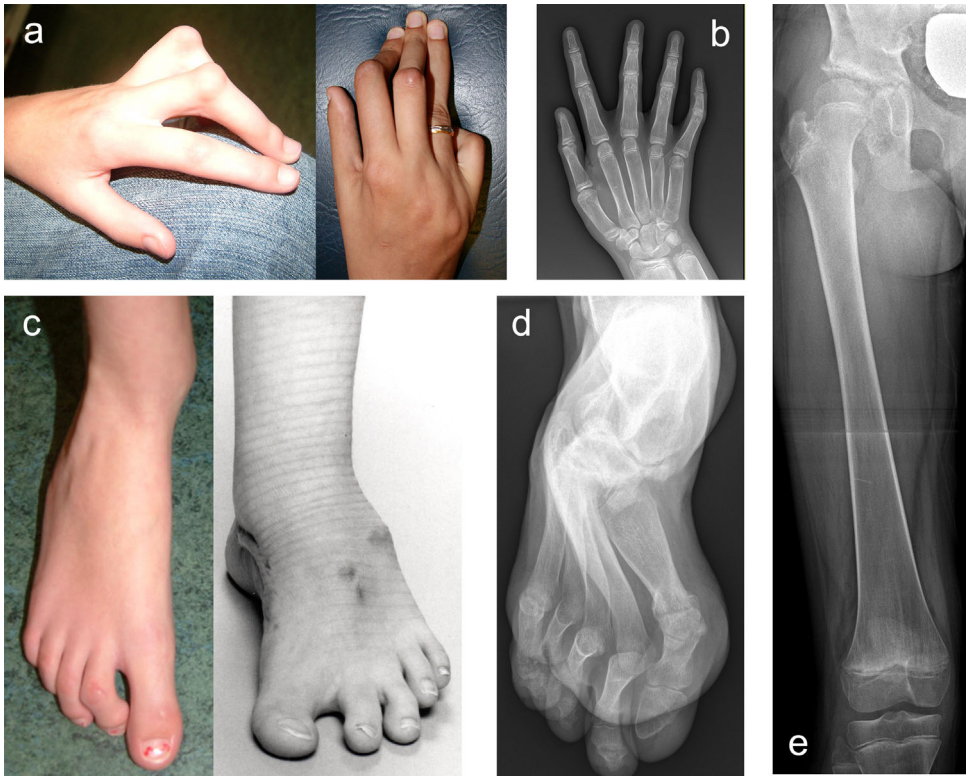

FIGURE 2 Digital and limb findings in AD-FMD. (a) Contractures of the digits are a common finding in AD-FMD, along with long fingers and ulna deviation of the hands (individuals 14 and 11). (b) The phalanges of the hands are undermodelled (individual 08). (c) Contractures of the toes are also present (individuals 14 and 05). (d) The phalanges of the feet are also undermodeled, and valgus deformity of the foot was found in 7 individuals in this cohort (individual 05). (e) The long bones are typically flared at the metaphysis with thick cortices (individual 08). [Color figure can be viewed at wileyonlinelibrary.com]

Notably one individual with a *MAP3K7* mutation developed a cervical spine myelopathy secondary to cervical vertebral anomalies.

3.4 | Non-skeletal findings

The extraskeletal manifestations of FMD result in significant morbidity and are often the cause of early mortality. Individuals with AD-FMD manifest many of the same extraskeletal malformations as the patients with XL-FMD without the bias toward an increased prevalence in males. Subglottic stenosis or congenital stridor was seen in 6/16 (38%) individuals studied here (Table 1) compared to 11% of males and 9% of females with XL-FMD (Robertson et al., 2006). Genitourinary tract defects, usually in the form of urethral obstruction, were seen in 3/8 (38%) of the male patients described here (Table 1) and have previously been reported in 22% of males with XL-FMD. There are no previous reports of such defects in females with XL-FMD (Robertson et al., 2006), however 2/11 (18%) female patients in this cohort have some form of genitourinary tract defect (Table 1). Structural heart defects which are sometimes present in XL-FMD males (22%) were found in 2/6 (33%) males and 4/10 (40%) females with AD-FMD. A small number of patients with dilation of the aorta, that was slowly progressive in one instance, were noted (Table 1). Finally, and significantly, intellectual disability was observed in 3/20 individuals with AD-FMD (Table 1) but has never been previously associated with FMD of any description (Robertson et al., 2006). Intellectual disability is only seen in the individuals with the TAK1 p.Pro485Leu substitution, and a further individual with intellectual disability has been reported with this substitution in another study (Martinez et al., 2016).

3.5 | Predisposition to keloid scarring

Keloid scar formation is not a reported manifestation of XL-FMD but has been connected with another *FLNA*-associated phenotype, which manifests with cardiac and kidney malformations and joint contractures (Atwal et al., 2015; Lah et al., 2015). Individuals with the skeletal manifestations of FMD, together with an increased tendency to form keloid scars generally do not have a mutation in *FLNA* (Basart et al., 2015; Wade et al., 2016). In the AD-FMD cohort studied here 10/20 patients have some form of keloid scarring (Table 1) and this finding is more prevalent in females (7/10). The severity of the scarring varies considerably between individuals with one individual developing florid keloid after relatively trivial procedures such as venepuncture (Basart et al., 2015).

3.6 | Genotype-phenotype correlation in AD-FMD

The most common FMD-causing mutation found in *MAP3K7* Leads to the substitution p.Pro485Leu, and was observed in 15/20 (75%) individuals in this cohort. The other three mutations found in *MAP3K7*

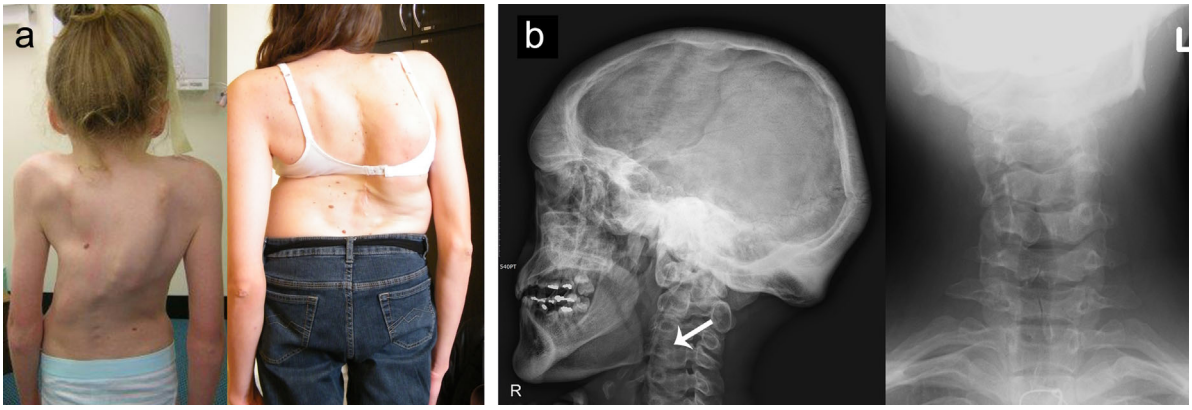

FIGURE 3 Scoliosis and cervical vertebral fusions are more common in AD-FMD. (a) Scoliosis, which can be severe, was found in 15 individuals in this cohort (individuals 18 and 20). (b) Cervical vertebrate fusions are also a fairly common finding, affecting 10 individuals in this cohort (individuals 08 and 10). [Color figure can be viewed at wileyonlinelibrary.com]

predict substitutions in the N-terminal kinase domain of TAK1 (Supplementary Table S1) (Wade et al., 2016). In one case the mutation was de novo, in the other two unrelated cases the mutation was transmitted from the affected mother (Wade et al., 2016). Substitutions in the kinase domain lead to a notably milder presentation than the recurrent mutation (Figure 4, Table 1). The three individuals with kinase domain substitutions have less dramatic undermodeling of the phalanges, minimal splaying of the metaphyses and can lack skull base sclerosis (Figure 4, Table 1). None of these three individuals have developed keloid.

FMD has overlapping features with the recently described dominant condition cardiospondylocarpofacial syndrome (CSCF) which is associated with missense mutations, or small deletions, affecting the N-terminal region of TAK1 (Le Goff et al., 2016). These include facial characteristics such as hypertelorism and full cheeks, as well as deafness, cervical fusions, and cardiac defects (Le Goff et al., 2016); however clear clinical distinctions can be made between the two conditions. CSCF is characterized by brachydactyly, short extremities and joint laxity (Le Goff et al., 2016), in direct contrast to the FMD phenotype which, in contradistinction, exhibits arachnodactyly and joint contractures (Table 1). Furthermore the three patients with kinase domain substitutions have the characteristic prominent brow ridges which are absent in individuals with CSCF.

3.7 | Individuals with mutations in *TAB2*

Here we describe two individuals with TAB2 substitutions p.Gln540Arg (*TAB2* c.1619A>G; NM_ NM_015093.5) and p.Glu569Lys

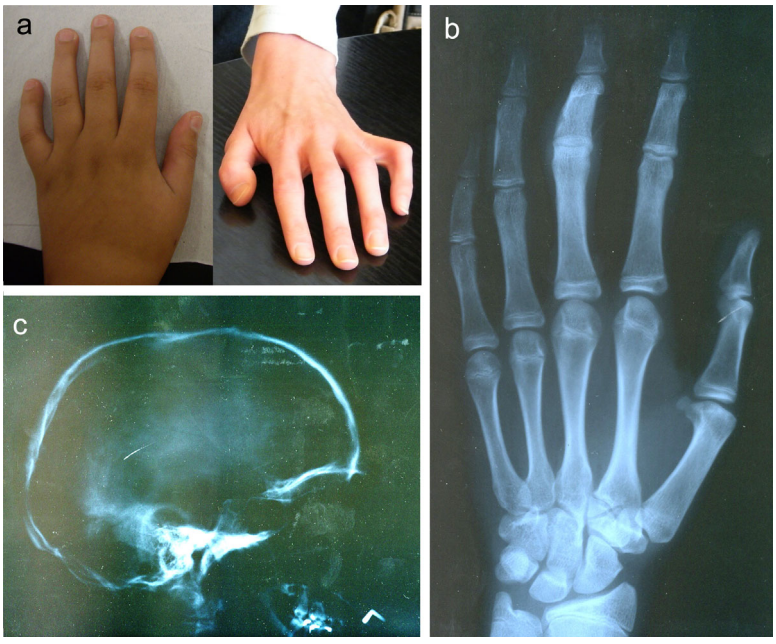

FIGURE 4 Characteristics of kinase domain TAK1 AD-FMD. (a) Individuals with substitutions in the kinase domain of TAK1 have a notably milder phenotype with fewer contractures of the digits, however the fingers can still be long (individuals 07 and 20). (b) Radiographs show much less undermodeling of the phalanges in these individuals (individual 19). (c) The skull is also less sclerotic in patients with kinase domain substitutions (patient 19). [Color figure can be viewed at wileyonlinelibrary.com]

(*TAB2* c.1705G>A), caused by variants in the same exon of *TAB2*. The p.Gln540Arg variant is newly described, not present in the Exome Aggregation Consortium (ExAC) database and the affected residue is phylogenetically conserved (Supplementary Figure S1). Variant effect prediction software predicted the p.Gln540Arg substitution as pathogenic: SIFT score of 0 (damaging), PolyPhen2 score of 0.954 (probably damaging), and predicted to be disease causing by MutationTaster. Both of the described variants in *TAB2* had arisen de novo. The subject with this variant has a remarkably similar presentation to the original female we described with a *TAB2* mutation (Figure 1), and both resemble the individuals with the recurrent *MAP3K7* mutation more than those subjects with kinase domain substitutions in TAK1 (Figure 1). Neither subject with a *TAB2* variant has keloid scars.

4 | DISCUSSION

We have previously shown that FMD is a genetically heterogeneous disorder caused by mutations in *FLNA* (Robertson et al., 2003), *MAP3K7* and *TAB2* (Wade et al., 2016). Here we present the clinical phenotype of patients with mutations in these recently characterized AD-FMD loci. This cohort of patients with AD-FMD can be divided into three categories: those with the recurrent C-terminal substitution in TAK1 (p.Pro485Leu) which confers the most severe of the three phenotypes, those with substitutions in the TAK1 kinase domain which result in a milder presentation, and finally those patients with mutations that predict substitutions in the TAK1 interacting protein, TAB2. Previously we described a single individual with a typical AD-FMD phenotype and a de novo missense variant in *TAB2* (Wade et al., 2016). We hypothesized that the resulting substitution (p.Glu569Lys) would eventually be shown to constitute the basis for her AD-FMD phenotype and that *TAB2* would represent a third FMD locus. Here we present a second individual with a mutation in *TAB2*, in the same exon as the originally described variant. The presence of a novel missense mutation in *TAB2*, which confers a similar phenotype to that associated with the p.Glu569Lys substitution, is solid evidence that this gene represents a third FMD locus and a second cause of AD-FMD.

Despite considerable phenotypic overlap with XL-FMD which suggests that the two conditions are caused by disruption of the same biochemical pathway, distinctions can be made which may aid diagnosis. Clearly the inheritance pattern and presentation of females in the pedigree can indicate the likelihood or otherwise that X-linked inheritance of the trait might apply. Additionally, to our knowledge there are no instances of inheritance of the recurrent *MAP3K7* mutation (c.1454C>T, TAK1 p.Pro485Leu), although two of the singular *MAP3K7* mutations (c.208G>C, TAK1 p.Glu70Gln and c.299T>A, TAK1 p.Val100Glu) have been vertically transmitted from a clinically affected parent.

A common finding in all forms of FMD is undermodeling of the phalanges reflecting that an X-ray of the hands is often the most convenient, diagnostic radiograph to perform on these individuals. Individuals with an FMD skeletal phenotype together with any of the following: keloid, scoliosis, cervical fusions, cleft lip or palate, or intellectual disability, and in females, deafness, should be screened for mutations in exon 16 of *MAP3K7* initially. If the condition is dominantly inherited, and if the craniofacial manifestations are reminiscent of FMD but the radiographs are unremarkable, the 5′ end of *MAP3K7* should be examined for pathogenic variants. Another phenotype is associated with missense mutations in this region of the *MAP3K7* gene. CSCF is caused by small deletions and missense mutations in *MAP3K7* (Le Goff et al., 2016) and is characterized by short stature, brachydactyly, cardiac septal defects and deafness. It is worth noting that the individuals described here often have scoliosis and contractures which sets the diagnosis of AD-FMD apart from CSCF (Le Goff et al., 2016). Therefore, as is the case with *FLNA*, mutations in *MAP3K7* can give rise to an allelic spectrum of disorders.

X-linked-FMD belongs to a spectrum of bone sclerosing conditions, the OPDSDs which includes, listed here in order of increasing phenotypic severity, otopalatodigital syndrome type 1 (OPD1), FMD, OPD2, Melnick-Needles syndrome (MNS), and terminal osseous dysplasia (TOD) (Robertson, 2007). The presentation of the five disorders is distinct in males (Melnick & Needles, 1966; Robertson, 2007). However the severity varies considerably in females, and OPD1, FMD, and OPD2 share overlapping features which can make correct diagnosis difficult (Naudion et al., 2015; Robertson, 2007). The AD form of FMD presents with a more recognisable FMD phenotype in females, the most remarkable feature being supraorbital hyperostosis. There is little to set *MAP3K7* c.1454C>T (TAK1, p.Pro485Leu) mutation positive AD-FMD apart from *TAB2* mutation positive AD-FMD, however it appears mutations in *TAB2*, both of which are restricted to exon 5, are comparatively rarely encountered. Missense, presumed loss-of-function mutations in *TAB2* have previously been associated with congenital heart defects (Thienpont et al., 2010). The two individuals we have presented here with *TAB2* mutations do not have a described cardiac defect. This disparity in phenotype could be explained by the location of the mutations with those conferring a loss-of-function found in the second coding exon of the *TAB2* (GenBank: NM_015093.5) and more N-terminal in the TAB2 protein (p.Pro208Ser and p.Gln230Lys). These variants have the same phenotypic outcome as large deletions which encompass the TAB2 locus (Thienpont et al., 2010). In contrast the mutations that cause AD-FMD are located in the third coding exon, resulting in substitutions that are more C-terminal in the protein (p.Gln540Arg and p.Glu569Lys). The number of individuals with *TAB2* mutations presented here is small and therefore it is not possible to be certain that *TAB2* mutations leading to AD-FMD are not associated with heart defects also.

Both XL-FMD and AD-FMD present with numerous morbidities. Qualitatively the skeletal phenotype progresses in early childhood but there is limited data available on how the condition progresses as affected individuals age. Since the finding that MAPK signaling underpins these phenotypes; evolving complications from progressive skeletal disease could be addressable with agents targeted to this pathway.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

REFERENCES

Atwal, P., Blease, S., Braxton, A., Graves, J., He, W., Person, R., … Hudgins, L. (2015). Novel X-linked syndrome of cardiac valvulopathy, keloid scarring, and reduced joint mobility due to filamin A substitution G1576R. *American Journal of Medical Genetics Part A*, *170A*, 891–895.

Basart, H., van de Kar, A., Adès, L., Cho, T.-J., Carter, E., Maas, S., … Hennekam, R. (2015). Frontometaphyseal dysplasia and keloid formation without *FLNA* mutations. *American Journal of Medical Genetics Part A*, *167*, 1215–1222.

Besse, A., Lamothe, B., Campos, A., Webster, W., Maddineni, U., Lin, S.-C., … Darnay, B. (2007). TAK1-dependent signaling requires functional interaction with TAB2/TAB3. *The Journal of Biological Chemistry*, *282*, 3918–3928.

Fitzsimmons, J., Fitzsimmons, E., Barrow, M., & Gilbert, G. (1982). Frontometaphyseal dysplasia. Further delineation of the clinical syndrome. *Clinical Genetics*, *22*, 195–205.

Greenblatt, M., Shim, J.-H., Zou, W., Sitara, D., Schweitzer, M., Hu, D., … Glimcher, L. (2013). The p38 MAPK pathway is essential for skeletogenesis and bone homeostasis in mice. *Journal of Clinical Investigation*, *120*, 2457–2473.

Lah, M., Niranjan, T., Srikanth, S., Holloway, L., Schwartz, C., Wang, T., & Weaver, D. (2015). A distinct X-linked syndrome involving joint contractures, keloids, large optic cup-to-disc ratio, and renal stones results from a filamin A (FLNA) mutation. *American Journal of Medical Genetics Part A*, *170A*, 881–890.

Le Goff, C., Rogers, C., Le Goff, W., Pinto, G., Bonnet, D., Chrabieh, M., … Cormier-Daire, V. (2016). Heterozygous mutations in *MAP3K7*, encoding TGF-β-activated kinase 1, cause cardiospondylocarpofacial syndrome. *American Journal of Human Genetics*, *99*, 407–413.

Martinez, F., Caro-Llopis, A., Rosello, M., Oltra, S., Mayo, S., Monfort, S., & Orellana, C. (2016). High diagnostic yield of syndromic intellectual disability by targeted next-generation sequencing. *Journal of Medical Genetics*, *54*, 87–92.

Melnick, J., & Needles, C. (1966). An undiagnosed bone dysplasia. A 2 family study of 4 generations and 3 generations. *American Journal of Roentgenology, Radium Therapy and Nuclear Medicine*, *97*, 39–48.

Morava, E., Illes, T., Weisenbach, J., Karteszi, J., & Kosztolanyi, G. (2003). Clinical and genetic heterogeneity in frontometaphyseal dysplasia: Severe progressive scoliosis in two families. *American Journal of Medical Genetics Part A*, *116*, 272–277.

Naudion, S., Moutton, S., Coupry, I., Sole, G., Deforges, J., Guerineau, E., … Fergelot, P. (2015). Fetal phenotypes in otopalatodigital spectrum disorders. *Clinical Genetics*, *89*, 371–377.

Qi, B., Cong, Q., Li, P., Ma, G., Guo, X., Yeh, J., … Li, B. (2014). Ablation of TAK1 in osteoclast progenitor leads to defects in skeletal growth and bone remodeling in mice. *Scientific Reports*, *4*(7158).

Robertson, S. (2007). Otopalatodigital syndrome spectrum disorders: Otopalatodigital syndrome types 1 and 2, frontometaphyseal dysplasia and Melnick-Needles syndrome. *European Journal of Human Genetics*, *15*, 3–9.

Robertson, S., Jenkins, Z., Morgan, T., Ades, L., Aftimos, S., Boute, O., … Krakow, D. (2006). Frontometaphyseal dysplasia: Mutations in FLNA and phenotypic diversity. *American Journal of Medical Genetics Part A*, *140A*, 1726–1736.

Robertson, S., Twigg, S., Sutherland-Smith, A., Biancalana, V., Gorlin, R., Horn, D., … group, O-sdcc (2003). Localized mutations in the gene encoding the cytoskeletal protein filamin A cause diverse malformations in humans. *Nature Genetics*, *33*, 487–491.

Sanjo, H., Takeda, K., Tsujimura, T., Ninomiya-Tsuji, J., Matsumoto, K., & Akira, S. (2003). TAB2 is essential for prevention of apoptosis in fetal liver but not for interleukin-1 signaling. *Molecular and Cellular Biology*, *23*, 1231–1238.

Thienpont, B., Zhang, L., Postma, A., Breckpot, J., Tranchevent, L., Van Loo, P., … Larsen, L. (2010). Haploinsufficiency of TAB2 causes congenital heart defects in humans. *American Journal of Human Genetics*, *86*, 839–849.

Wade, E., Daniel, P., Jenkins, Z., McInerney-Leo, A., Leo, P., Morgan, T., … Robertson, S. (2016). Mutations in *MAP3K7* that alter the activity of the TAK1 signaling complex cause frontometaphyseal dysplasia. *American Journal of Human Genetics*, *99*, 392–406.

SUPPORTING INFORMATION

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

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