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ORIGINAL ARTICLE

A novel *FAM83H* variant causes familial amelogenesis imperfecta with incomplete penetrance

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Abstract

Background: Amelogenesis imperfecta (AI) is known to be a monogenic genetic disease caused by a variety of genes demonstrating a wide spectrum of penetrance. *FAM83H* is reported to be involved in AI: however, whether *FAM83H* causes AI with incomplete penetrance is unclear.

Methods: Whole-exome sequencing was performed on two patients with AI, and putative disease-related variants were validated by Sanger sequencing. Bioinformatic and in vitro functional analyses were performed to functionally characterize the identified disease-causing variants.

Results: We identified a novel heterozygous nonsense variant of *FAM83H* (NM_198488: c.1975G > T, p.Glu659Ter); in vitro functional analysis showed that this mutant produced mislocalized proteins and was deleterious. Surprisingly, the clinical manifestations of each of the six individuals carrying this variant were different, with one carrier appearing to be completely asymptomatic for AI.

Conclusion: Our findings expand the variant spectrum for *FAM83H* and the phenotypic spectrum for *FAM83H*-associated AI and suggest that *FAM83H*-mediated AI exhibits incomplete penetrance.

KEYWORDS
amelogenesis imperfecta, *FAM83H* variant, hypocalcification, incomplete penetrance

Rui-Qi Bai and Wen-Bin He equal contribution to this study.

1 | INTRODUCTION

Amelogenesis imperfecta (AI) refers to abnormal enamel production during tooth development. AI, a group of hereditary diseases without systemic symptoms, is associated with a global incidence of between 1 in 14,000 and 1 in 700 (Bäckman & Holm, 1986). Clinically, there are four types of AI (Witkop, 1988; Nusier et al., 2004): hypoplastic AI, hypocalcified AI, hypomaturation AI, and complex AI; the major manifestations include the quality and extent of enamel defects in the affected individual. Enamel defects affect not only esthetic appearance, but also normal tooth function. Therefore, it is important to identify the cause of AI and ensure appropriate measures to reduce its incidence.

AI is reported to be a single-gene genetic disorder (Gadhia et al., 2012; Wright, Carrion, & Morris, 2015) and is associated with mutations in more than 10 different genes (Hart et al., 2004; Kim, 2005; Kim et al., 2005; Lu et al., 2018; Poulter et al., 2014; Wang et al., 2015), including *FAM83H* (MIM *611927), which is associated with an autosomal dominant inheritance pattern. Approximately 20 inactivating mutations have been identified (Wang et al., 2021). Here, we investigated the case of four generations of a Chinese family diagnosed with AI using whole-exome sequencing (WES), Sanger sequencing and in vitro analysis. Our evaluations identified a novel nonsense mutation in *FAM83H* (c.1975G>T, p.Glu659Ter) which is likely to be the genetic etiology of AI in these patients. More importantly, we observed, for the first time, an incomplete penetrance in the *FAM83H* mutation that causes AI.

2 | MATERIALS AND METHODS

2.1 | Editorial policies and ethical considerations

This study was approved by the Ethics Committee of the Xiangya Stomatological Hospital of Central South University. The study participants or their guardians provided written informed consent.

2.2 | Subjects

A Chinese family with AI was recruited for this genetic study. Peripheral blood samples were obtained from all participants. Clinical examinations were performed on the five participants, and additional x-ray examinations were performed on the proband and her mother to characterize their dental phenotype. Moreover, all the participants were enquired about systemic diseases, tetracycline treatment, fluoride consumption, and any other information that might affect their tooth development process. Additionally, the patients were clinically assessed for skin, hair, nail, and bone development to exclude syndromic enamel hypoplasia

2.3 | WES, variant filtering, and Sanger sequencing

The gDNA of the proband and her mother was subjected to WES according to the protocol described earlier (Aittomäki et al., 1995; He et al., 2018). Whole exomes were captured using an xGen Exome Research Panel v2 0.0 (Integrated DNA Technologies, Coralville, Iowa, USA), and then sequencing was performed using a DNBSEQ-T7 sequencing platform (MGI, Shenzhen, Guangdong, China). The WES data were analyzed using the Genome Analysis Toolkit (GATK) and data analysis involved removing adaptors, mapping WES raw reads to a reference human genome sequence (NCBI GRCh37, reference genome Hg19) using the Burrows–Wheeler Aligner, eliminating PCR duplicates, and sorting sequences using Picard (http://broadinstitute.github.io/picard/). Variant identification was performed using the GATK package according to the recommended best practices, including base recalibration of variant calls using HaplotypeCaller, and recalibration of variant quality score and annotation using ANNOVAR software

We set the inclusion criteria for all candidate variants as follows: (a) absent or occurring at a frequency of less than 0.01 in any of the following databases: 1000 Genomes Variant Database, Genome Aggregation Database (gnomAD), or NHLBI-GO Exome Sequencing Project; (b) coexisting in the proband and her mother were prioritized; (c) predicted to be deleterious, and (d) relating to the clinical phenotype.

We designed and validated specific PCR primers for targeting the variants of the *FAM83H* gene (NM_198488). The primers are listed in Table S1.

2.4 | Plasmid constructs

The cDNA of the wild-type (WT) FAM83H gene was cloned into pcDNA3.1-3xFlag, as described previously (Aittomäki et al., 1995), generating 3xFlag, and then human FAM83H (3xFlag-FAM83H-WT). The c.1975G>T mutation was introduced into the 3xFlag-FAM83H-WT plasmid vector using a MutExpress II Fast Mutagenesis Kit V2 (Vazyme). Sequencing of all the expression constructs was performed to determine the

presence of the desired mutations and to exclude PCR-induced mutations.

2.5 | Cell culture and transient transfection

Chinese hamster ovary (CHO) cells were seeded in a 12-well plate at a density of 2.5 × 105 cells and grown to 70–80% confluence under standard conditions in complete media (DMEM/F12, Gibco; 10% FBS; 37°C; 5% CO_2). According to the manufacturer's instructions, expression vectors containing different receptors (WT or mutated) were transiently transfected into CHO cells using Lipofectamine® 3000 (Thermo Fisher Scientific). Empty vector (without FAM83H) was also transfected into CHO cells as a negative control

2.6 | Western blot analysis

Western blot analysis was performed as previously reported (He et al., 2021). Briefly, cells were harvested 48 hr of post-transfection and homogenized using RIPA lysis buffer (Beyotime Biotechnology) supplemented with a protease inhibitor cocktail (Thermo Fisher Scientific). Proteins extracted from the transfected cells were blotted onto a polyvinylidene difluoride membrane and incubated overnight at 4°C with anti-FLAG antibody (1:1000 dilution, Abways). The subsequent morning, the membrane was incubated with secondary antibodies (goat anti-rabbit IgG; 1:5000 dilution; Abcam). Finally, the blots were developed using an ECL western blotting kit (Pierce Biotechnology). Cells transfected with an empty vector (without *FAM83H*) served as the negative control.

2.7 | Immunofluorescence analysis

Immunofluorescence analysis was performed as previously reported (He et al., 2021), and transfected CHO cells were grown on coverslips with anti-FLAG (1:800 dilution) primary antibodies. All fluorescent images were captured using a confocal microscope (Olympus FV1000).

2.8 | Real-time RT-PCR analysis

Real-time RT-PCR was employed to quantify the expression level of *FAM83H* in CHO cells using a LightCycler480 (Roche). After 48 hr of transfection, total RNA was extracted from the CHO cells and then reverse-transcribed to cDNA using Thermo Scientific RevertAid RT kit. The cDNA was used as a template in the real-time RT-PCR, which was performed according to the manufacturer's instructions using FastStart Universal SYBR® Green Master Mix (Roche). The primers, as listed in Table S1, were designed using Primer3.

2.9 | Statistical analyses

We repeated the experiment three times. The Student *t* test was used for statistical analysis, and SPSS software (version 19.0; SPSS) was used for one-way analysis of variance.

3 | RESULTS

3.1 | Clinical features

We investigated 33 members of a four-generation Chinese family with six active cases of AI (Figure 1a).

The proband (III-15), a 16-year-old girl, who never had dental treatment in another hospital, was admitted to the Xiangya Stomatological Hospital of the Central South University due to irregular tooth alignment and shape. Her teeth were crowded, with rough, yellow surfaces and a very small amount of enamel visible in the neck of some teeth. Periodontitis and caries were also evident, and panorama imaging confirmed these observations. The patient claims that her teeth presented normally when they first erupted (Figure 1b).

The proband's mother (II-7), who was 51 years old, had yellow teeth with relatively smooth surfaces, although some of her teeth had a light black appearance, which is likely the result of hyperpigmentation. Her teeth were significantly worn, and the clinical crowns were shortened. Teeth 15, 16, 25, 26, 35, 46, and 47 had almost no crown, and there was no tooth 36 (Figure 1b).

Periodontitis and abrasion were noted in the teeth of the proband's aunt (II-1), but no enamel defects (Figure 1b). However, she was diagnosed with breast cancer at the age of 53. The teeth of the proband's father (II-8) and one cousin (III-3) were all fine, whereas another cousin had her teeth repaired a few years ago, despite an enamel defect (III-2).

3.2 | Identification of the *FAM83H* variant

The original WES was collected at an average depth of ~120.00-fold, indicating that the sequencing was of high quality. The WES data are shown in Table S2, and our evaluations identified a heterozygous nonsense variant of *FAM83H* (NM_198488: c.1975G>T, p.Glu659Ter) in both

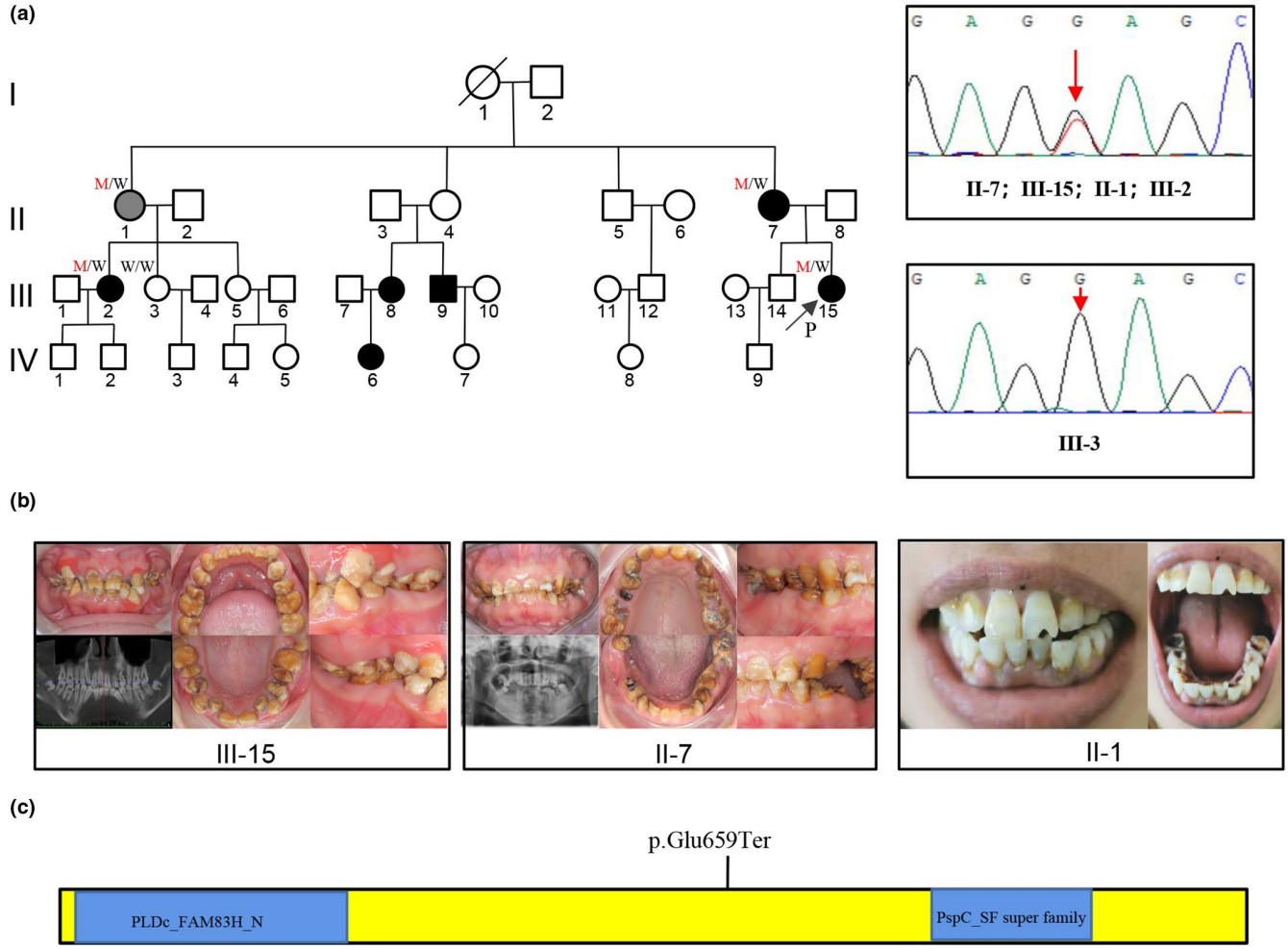

FIGURE 1 Pedigree and clinical manifestations. (a) The pedigree of the family with enamel defects. Males are marked as squares and females as circles. Affected members are indicated with filled symbols; unaffected relatives are indicated by open symbols. Family members affected by enamel defects have solid black symbols; The symbols filled with gray color indicate individuals affected by breast cancer. Arrows and "P" indicate the proband. Sanger sequencing confirmed that the proband, proband's mother, another patient (III-2), and her mother (II-1) carried the c.1975G>T in *FAM83H*. The proband's father and cousin (III-3) were free of this variant. (b) Intraoral photographs and panorama of infected members represented by the proband and his mother showed that the family had a typical clinical phenotype of hypocalcified AI. Other members, such as the proband's aunt, had no enamel defect. (c) The *FAM83H* protein consists of 1179 amino acids, including two main domains. The variant discovered in this study is shown at the top of the Figure. M and W indicate the mutation and wild type, respectively

the proband and her mother (Table S3). Sanger sequencing showed that another patient (III-2) and her mother who was unaffected by AI (II-1) also carried this variant. Additionally, the proband's father and cousin (III-3) did not carry this variant (Figure 1a).

3.3 | Effects of *FAM83H* variant on protein expression

Western blot analysis showed that the expression of the mutant *FAM83H* protein was higher than that of the WT protein (Figure 2a). However, real-time RT-PCR analysis showed that the mRNA expression of *FAM83H* was significantly reduced in cells transfected with the mutant *FAM83H* plasmid compared to that in cells transfected with the WT *FAM83H* plasmid (Figure 2b). Immunofluorescence analysis showed that the subcellular localization of the WT and mutant *FAM83H* were also different (Figure 2c). WT *FAM83H* was localized to the cytoplasm in a diffuse manner, whereas the mutant *FAM83H* was primarily localized within the nucleus. Cells transfected with the empty vector displayed scattered signal across the whole cell.

4 | DISCUSSION

FAM83H is located on chromosome 8q24.3, and this locus has been shown to house ~20 pathogenic mutations, with

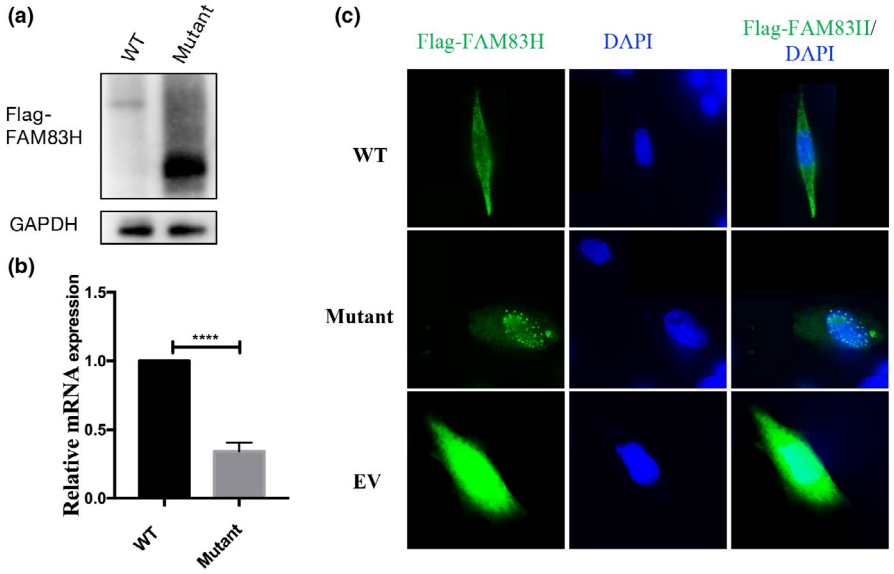

FIGURE 2 Functional studies of the mutated variant in vitro. (a) Western blot analysis showed that the expression of the mutant *FAM83H* protein in cells transfected with the mutant *FAM83H* plasmid was higher than that of the wild-type protein in cells transfected with the wild-type *FAM83H* plasmid. (b) Real-time RT-PCR analysis showed that the mRNA expression of *FAM83H* in cells transfected with the mutant *FAM83H* plasmid was significantly reduced compared with that in cells transfected with the wild-type *FAM83H* plasmid. (c) Immunofluorescence analysis showed that wild-type *FAM83H* was localized in the cytoplasm in a diffuse manner, whereas the mutant *FAM83H* was primarily localized in the nucleus. Cells transfected with the empty vector displayed a scattered signal throughout the cell. WT and EV indicate the wild type and empty vector, respectively

most of these being nonsense or frameshift mutations located in exon 5. The novel mutation identified in our study was also found to be in exon 5, and western blot demonstrated that this mutation produced a truncated protein. Our evaluations also demonstrated that this mutation reduced the overall mRNA expression of this gene while increasing its protein expression, which might be explained by the fact that the mutant *FAM83H* proteins displayed an extended half-life and alterations in their degradation pathway, consistent with an earlier report (Zheng et al., 2021). Furthermore, the subcellular localization of mutant *FAM83H* was different from that of WT *FAM83H*, which might affect its normal function. Therefore, our data suggest that this novel mutation is both deleterious and disease-forming in this family.

It is well known that clinical heterogeneity is a common phenomenon in genetic disorders, such as VEXAS syndrome and DICER1 syndrome (Koster et al., 2021; Azzollini et al., 2021). Similarly, AI also demonstrates significant clinical heterogeneity (Crawford et al., 2007). Studies have shown that AI caused by *ENAM* mutations exhibits incomplete penetrance (Kim et al., 2005; Seymen et al., 2014). However, even though AI caused by other genes, including *FAM83H*, demonstrates phenotypic heterogeneity (Crawford et al., 2007), its incomplete penetrance has not been reported. Here, our proband's teeth were rough, whereas her mother's teeth, although darker, were relatively smooth, which suggests that the same *FAM83H* mutation may result in different levels of enamel defects, consistent with data from an earlier report(Kantaputra et al., 2016). We speculated that the different clinical manifestations in patients with the same *FAM83H* were the result of differences in the individual genetic background of each patient (Victoria et al., 2015). Furthermore, we found that the proband's aunt (II-1) carried the *FAM83H* mutation, but her tooth enamel was normal, which suggests that this *FAM83H* variant causes AI with incomplete penetrance. Therefore, our study is the first to report incomplete penetrance in AI caused by an *FAM83H* defect.

Although AI caused by *ENAM* mutation showed incomplete penetrance, the mechanism is still unclear. There might be various reasons for the incomplete penetrance, such as genotype quality, (epi) genetic modification, environmental impact, and mosaicism (Victoria et al., 2015; Sundell & Valentin, 1986; Shawky & Rabah, 2014; Raj et al., 2010; Gruber & Bogunovic, 2020). For instance, Mendelian susceptibility to mycobacterial disease is related to the degree of *IFNGR1* defect, that is, the quality of genotype, while different phenotypes of CVID-like disorders suggest the role of (epi) genetic modification in incomplete penetrance. Our discovery of this family provides a new clue for exploring the mechanism underlying incomplete penetrance of AI. However, the understanding the specific mechanism necessitates further investigation.

In clinical practice, we usually assume that individuals with normal phenotypes do not carry any disease-causing mutations for autosomal dominant disorders and therefore are not routinely evaluated by genetic testing. However, individuals with normal phenotypes may carry deleterious mutations associated with autosomal dominant disorders when these mutations demonstrate incomplete penetrance. These asymptomatic carriers still have a 50% risk of passing disease-causative mutations to their offspring. Therefore, it is also necessary to conduct genetic testing on normal individuals with a family history of autosomal dominant disorders.

It has been reported that the *FAM83* family of oncogenes are broadly involved in human cancers, including both breast cancer and glioma (Snijders et al., 2017). In our study, subject II-1 who carried the *FAM83H* mutation was diagnosed with breast cancer, providing new evidence that *FAM83H* may be associated with tumorigenesis.

In conclusion, we demonstrate the pathogenicity of our *FAM83H* mutation using in vitro functional evaluation. Additionally, we found that this mutation can produce a variety of phenotypes even in related individuals with the same mutation suggesting incomplete penetrance. Our results broaden the variant spectrum for *FAM83H* and the phenotypic spectrum for AI. We believe that further research into the pathogenesis of this disease will further our understanding of the clinical phenotypes of AI caused by *FAM83H* variants.

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CONFLICT OF INTEREST

The authors have declared no conflict of interest.

AUTHORS CONTRIBUTIONS

BR contributed to validation, resources, writing-original draft, and writing-review & editing. HW contributed to methodology, investigation, data curation, and formal analysis. PQ, SS, and YQ helped in providing basic information of patients, capturing photographs, and drawing blood. TY directed the conception and design of the study. WY and LB contributed to supervision and funding acquisition.

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SUPPORTING INFORMATION

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