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ORIGINAL ARTICLE

Autosomal recessive monilethrix: Novel variants of the *DSG4* gene in three Chinese families

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Abstract

Background: Monilethrix is a rare hereditary hair loss disorder characterized by hair fragility and beaded hair shaft alterations. Monilethrix is classically inherited in an autosomal dominant (AD) fashion caused by variants in the hair keratin genes *KRT81*, *KRT83,* or *KRT86*. Interestingly, an autosomal recessive (AR) form of monilethrix with variants in *DSG4* gene has also been reported in recent years.

Objective: To identify causative variants in Chinese patients with autosomal recessive (AR) form of monilethrix.

Methods: Three families with AR form of monilethrix were observed and sequence variant analysis of *DSG4* was performed by polymerase chain reaction (PCR), quantitative real-time PCR, and DNA sequencing.

Results: All the patients had sparse, fragile hair involving the scalp, eyebrows, and eyelashes with keratotic follicular papules and pruritus since birth. Atypical-beaded hairs and broken hair shaft fragments were identified in all the patients under dermoscopy. Heterozygous variants c.837del and c. 2389C > T, a homozygous splice site variant c.2355 + 1G > A, and a homozygous 48,644 bp large deletion variant g.31381440_31430084del in the *DSG4* gene were identified and verified in the families.

Conclusion: This report provided further evidence for the phenotypic spectrum and clinical features of, and the expanded variant database of AR form of monilethrix.

Cheng Zhou and Pei Wang contributed equally to this work.

KEYWORDS
autosomal recessive, *DSG4*, hypotrichosis, monilethrix, variant

1 | INTRODUCTION

Monilethrix (OMIM 158000), also known as beaded hair, is a rare hereditary hair loss disorder. It is characterized by fragility, dryness, and sparseness of scalp hair, with a beaded or moniliform appearance as a result of a periodic decrease in the diameter of the hair. The hair is susceptible to fracture at the delicate narrower internodal regions, leading to short hair and hair loss. Regions other than the scalp may be affected and various additional ectodermal anomalies may occur. The disease is often associated with keratosis pilaris-like papules on the extensor surfaces, occipital scalp, and nape.

Monilethrix classically is inherited in an autosomal dominant (AD) fashion, and is usually caused by variants in the *KRT81*, *KRT83*, and *KRT86* genes. Interestingly, an autosomal recessive (AR) form of monilethrix (OMIM 607903), also known as monilethrix-like congenital hypotrichosis or hypotrichosis 6, has been reported in recent years. The autosomal recessive monilethrix is caused by variants in *DSG4* gene, which encodes desmoglein 4 (DSG4) (Schaffer et al., 2006; Zlotogorski et al., 2006). This is the same causative gene previously reported as localized autosomal recessive hypotrichosis (LAH1) (Kljuic et al., 2003). It is suggested that autosomal recessive monilethrix and LAH1 should be regarded as a spectrum disorder due to their overlapping clinical and genetic findings.

DSG4 is expressed in the keratinizing zone of the hair shaft cortex, where hair keratins K81, K83, and K86 are also predominantly expressed (Shimomura et al., 2006). The defect of DSG4, K81, K83, or K86 leads to a periodic dysfunction of the hair matrix and monilethrix appearance. To date, however, only a few cases with *DSG4* gene sequence variants have been identified, and thus precise clinical features resulting from *DSG4* variants remain to be elucidated.

In this study, we report three Chinese patients with autosomal recessive monilethrix and respective novel pathogenic variants, and summarize the clinical features of autosomal recessive monilethrix.

2 | METHODS

2.1 | Subjects

2.1.1 | Case 1

A 11-year-old Chinese boy (patient 1) of non-consanguineous parents had normal scalp without hair at birth. Within the first few months of life he developed sparse, brittle, lusterless, and short scalp hair, eyebrows, and eyelashes (Figure 1a,b). There were numerous pruritic keratotic follicular papules with erythema on the scalp and nape of the neck (Figure 1e). The hair beading was scarce and was not captured under light microscopy or scanning electron microscopy. No other abnormalities were identified except enamel hypoplasia (Figure 1f). Histopathologic examination of the scalp was performed when the patient was 4 years old and showed hyperkeratosis at the follicular orifice with keratin plugging and several transections of "vellus hairs" (Figure 2c). He was misdiagnosed as trichostasis spinulosa for several years. Fortunately, his hair loss gradually improved with age. At a follow-up appointed at age 11, monilethrix-like beaded hairs and fragmented hairs were visualized via dermoscopy.

2.1.2 | Case 2

A 26-year-old Chinese male (patient 2) from non-consanguineous family developed sparse, short, and fragile scalp hairs with hair loss since infancy. All body hairs of the eye brows, eye lashes, axillary, and pubic regions were involved (Figure 1c). There were numerous keratotic follicular papules with surrounding erythema on the scalp. No other abnormalities were identified. Since no prominent beaded hair was noticed by light microscopy at that time, the patient had been misdiagnosed as alopecia areata and was treated accordingly for some time. During subsequent follow-up consultations, broken hairs and hairs with irregular atypical beads were identified under dermoscopy.

2.1.3 | Case 3

A 11-year-old boy (patient 3), the first child of unaffected, non-consanguineous Chinese parent, was born with numerous erythematous keratotic follicular papules without scalp hair (Figure 1d). His younger brother had normal hair. Scalp hair that was sparse, short, coarse, and straight began growing at age of 8. His eyebrows began growing at the age of 10 years. The pruritic erythematous keratotic follicular papules increased in number, gradually involving the areas of his eye brows, trunk, and extremities. His teeth, nails, stature, and intelligence were normal.

No typical beaded hairs were found under light microscopy or scanning electron microscopy. Scanning electron microscopy revealed that the hair cuticle was irregularly

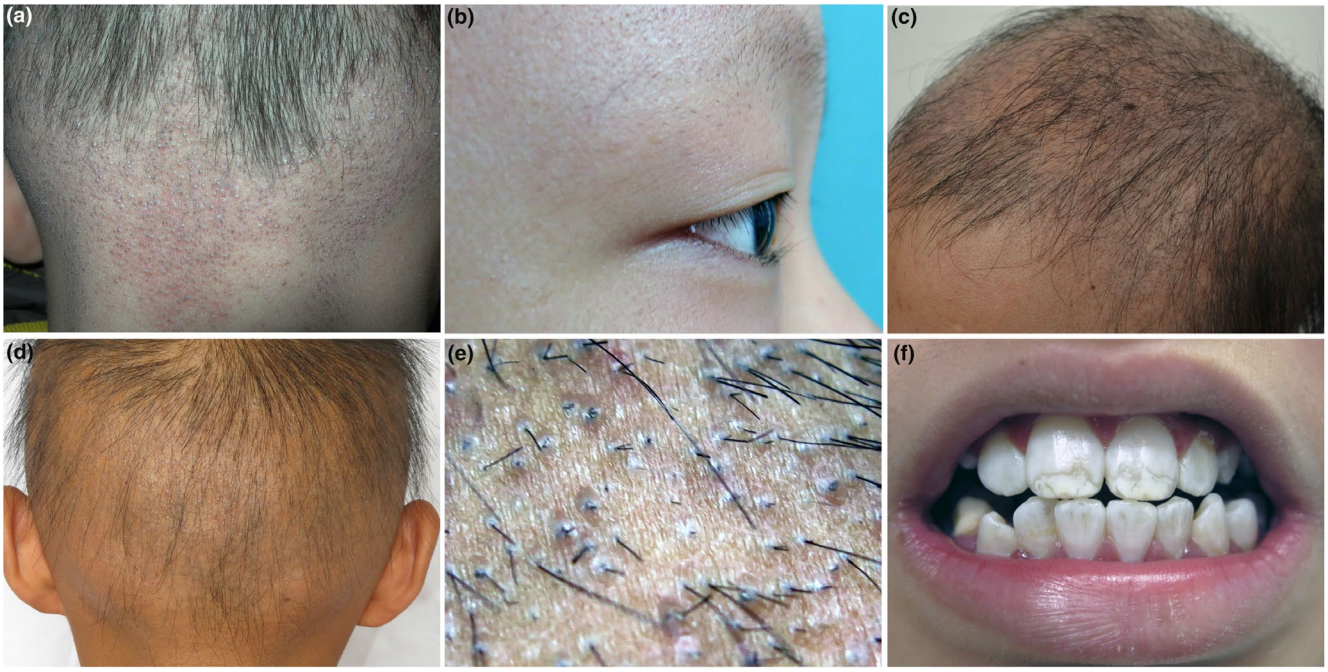

FIGURE 1 Clinical appearance of the patients. The scalp hair is sparse with diffuse keratotic follicular papules with erythema in (a) patient 1, (c) patient 2, and (d) patient 3. (b) Eyebrows and eyelashes involvement of patient 1. (e) Higher magnification showing fragile and broken scalp hairs with keratotic follicular papules and perifollicular erythema. (f) Enamel hypoplasia in patient 1

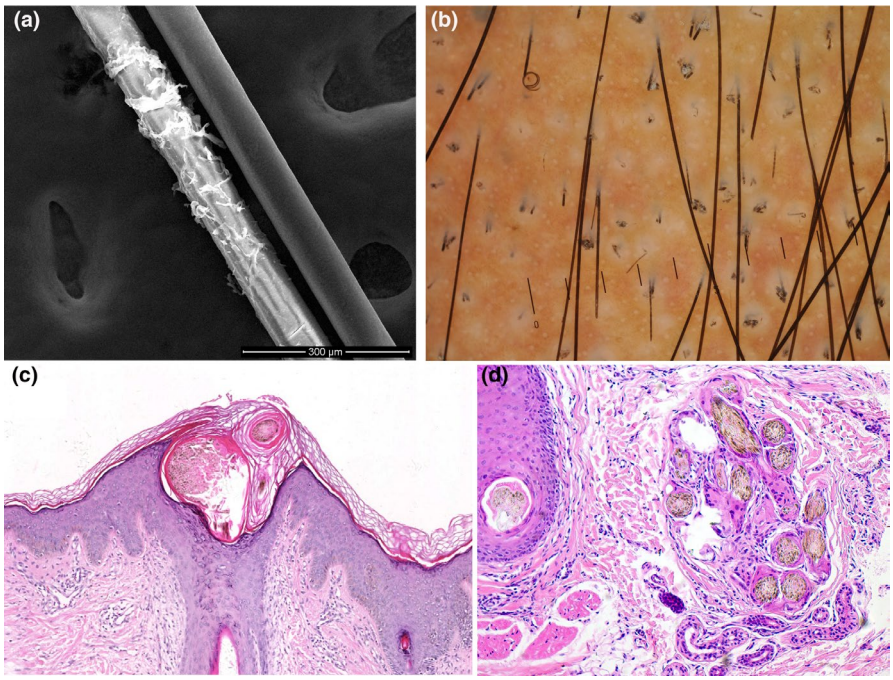

FIGURE 2 Scanning electron microscopy, dermoscopy, and histopathology examination of the patients. (a) Beading changes were not found in shedding hairs in patient 3 under scanning electron microscopy, but irregularly arranged and detached hair cuticle with longitudinal grooves were revealed in a few hairs. (b) Dermoscopy examination showed multiple black dots, broken hairs, and irregular atypical beads (patient 3). Histopathology examination of scalp skin showed (c) hyperkeratosis at the follicular orifice with keratin plugging and several transections of "vellus hairs" (patient 1), and (d) small hair shaft fragments with foreign body giant cell reaction (patient 3)

arranged and detached with longitudinal grooves in a few examined hairs (Figure 2a). Multiple black dots, broken hairs, and irregular atypical beads were identified under dermoscopy (Figure 2b). Histopathological examination of the affected scalp showed hyperkeratosis and acanthosis at the follicular orifice with plugging and several

transections of curled ingrown vellus-like hair shaft fragments. A fair number of small hair shaft fragments with foreign body giant cell reaction were found in the dermis around the distorted hair follicles (Figure 2d).

2.2 | Variant analysis of the *DSG4* gene

Blood samples were obtained from the patients and their parents following written informed consent. After genomic DNA was extracted, the encoding exons with flanking intron regions of the *DSG4* (transcript variant 2, RefSeq NM_177986), as well as *KRT81*, *KRT83*, and *KRT86* genes were amplified by polymerase chain reactions (PCR) using standard conditions with primer pairs and PCR conditions as described previously (Shimomura et al., 2006; van Steensel et al., 2005). PCR reactions were prepared to a final volume of 50 μl with the following conditions: (1) amplification for *DSG4* gene: 94°C for 5 min, followed by 35 cycles of 94°C for 30 s, 57°C for 45 s, 72°C for 45 s, and final extension at 72°C for 10 min; (2) amplification for *KRT81*, *KRT83*, *KRT86* genes: 94°C for 1.5 min, followed by 35 cycles of 94°C for 30 s, 62°C for 30 s, 72°C for 60 s, and final extension at 72°C for 10 min. The amplified PCR products were purified and directly sequenced in an ABI 3700 automated DNA sequencer (Applied Biosystems, USA). Sequence comparisons and analysis were performed with Chromas software (version 2.33).

2.3 | Screening for the large deletion variants in case 3

The PCR amplifications only produced amplification of exon 1 of *DSG4*. Exons 2 to 16 could not be successfully amplified. No variants were identified in the exon 1 of patient 3 after sequencing. Normal amplification products were found in his parents and brother. We assumed that large deletions spanning the whole *DSG4* gene in patient 3 might exist. In order to verify this assumption, quantitative real-time PCR (qPCR) was performed in the patient and his unaffected parents and brother. Three primer sets for qPCR analysis were designed by using the Primer Premier 5.0 software (Premier Biosoft International, CA), which contained primers targeted to exon 5 and exon 16 of *DSG4* gene in the suspicious deleted region as well as normal internal control β-actin. The qPCR was performed in a total volume of 20 μl with the following conditions: 95°C for 4 min, and 40 cycles of 95°C 15 s/60°C 15 s/72°C 20s. The relative copy number (RCN) was determined by relative quantification, which was calculated using 2 e(-ΔΔCt) method, with the patient's brother as the calibrator. Melt curve analysis was performed to confirm amplification specificity. The experiments was repeated four times. The result of qPCR showed no exon 5 and exon 16 products in the patient and a half relative quantity (RQ) value in unaffected parents with respect to the patient's brother. This confirmed the whole *DSG4* gene, except exon 1, was completely deleted. Subsequently, a series of PCR reactions were performed with three pairs of primers targeted at the sequence about 1×10^7 bp, 5×10^7 bp, and 10×10^7 bp downstream of *DSG4* and, fortunately, normal production was successfully obtained with all the three pairs of primers. Thus the 5′ break point might locate in intron 1 of *DSG4* and the 3′ break point might locate between exon 16 and 1×10^7 bp downstream of *DSG4*. Then 8 pairs of primers that evenly distributed in these break points harboring regions (pairs 1 to 4 in intron 1 and pairs 5 to 8 after exon 16) were used for further narrowing down the possibilities. Finally, the forward primer of pair 2 and the reverse primer of pair 7 were utilized for final amplification and sequencing to detect the break points.

3 | RESULTS

3.1 | Identification and verification of variants in the *DSG4* gene

Disease-associated gene variants in the *DSG4* gene were found in all the three cases, and no variant in the *KRT81*, *KRT83*, nor *KRT86* was identified.

3.1.1 | Case 1

We identified compound heterozygous variants in patient 1. One heterozygous variant was a deletion variant, c.837del, in the exon 8 of the *DSG4* gene. It resulted in a frameshift and a premature termination codon (PTC) at 4 aa residues downstream of the variant (p.Glu280Argfs*4). The second heterozygous variant was a nonsense variant c. 2389C > T (p.Arg797*) in the exon 16 of the *DSG4* gene. Screening the parents revealed that the heterozygous variants c.837del and c. 2389C > T were inherited from his father and mother, respectively (Figure 3a). Both of the two variants were absent in 50 normal controls.

3.1.2 | Case 2

A homozygous donor splice site variant in intron 15 of *DSG4*, c.2355 + 1G > A, was identified in the patient 2 (Figure 3b). Genetic analysis revealed the parents were unaffected heterozygous variant carriers. The variant was not found in 50 normal controls.

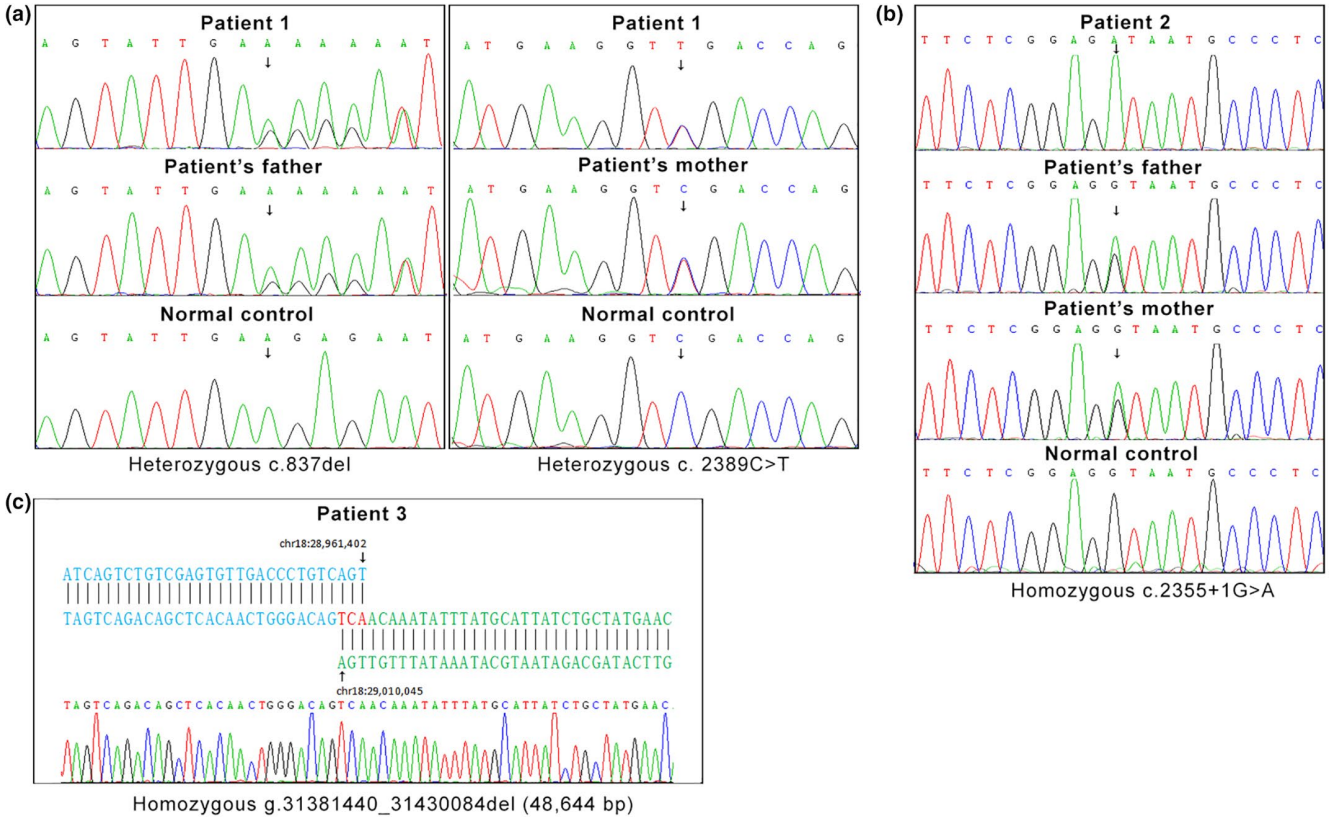

FIGURE 3 Identification of variants in the *DSG4* gene. (a) in patient 1, the compound heterozygous variants c.837del and c. 2389C > T were inherited from the patient's father and mother, respectively. (b) in patient 2, homozygous donor splice site variant c.2355 + 1G > a was identified. (c) Homozygous 48,644 bp large deletion variant g.31381440_31430084del was found in patient 3

3.1.3 | Case 3

Using a pair of primers, including forward primer 5′-CGAAGCAAATCTCACCTCTA-3′ in intron 1 of *DSG4* and reverse primer 5′-ACTGACCTTTACTGTCTCCA-3′ in downstream intergene region of *DSG4*, the deletion breakpoints harboring fragment was successfully PCR-amplified with the case 3 patient's template DNA (for PCR cycles, annealing temperature was 58°C and extension time was 4.5 min). Sequencing of the fragment revealed the 5′ and 3′ breakpoints with a homozygous 48,644 bp large deletion variant, NC_000018.10: g.31381440_31430084del, staring in intron 1 of *DSG4* and spanning to the downstream intergene region between *DSG4* and *DSG3* (Figure 3c). The variant was similarly not found in 50 normal controls.

4 | DISCUSSION

The clinical diagnosis of AR form of monilethrix is still a great challenge. The clinical manifestations can mimic other congenital or acquired hair loss disorders. Case 1, despite findings on scalp biopsy, was misdiagnosed as trichostasis spinulosa. Case 2 was misdiagnosed as alopecia areata because of the sparse scalp hair with broken hairs. Although a positive consanguineous family history is helpful in the diagnosis, 18 of the 30 reported cases (Table 1) were sporadic, originating from non-consanguineous families, as with the three cases in this study.

The classic morphologic alteration of monilethrix is regular beading of the hair shaft. This alteration is thought to be the most valuable diagnostic finding in monilethrix. The elliptical nodes of AD form of monilethrix, which are 0.7–1 mm apart, are separated by tapered internodes lacking a medulla. Although this typical moniliform hairs can be identified by light microscopy or scanning electron microscope, there is usually only a small proportion of small hairs that are affected, increasing the likelihood of false negatives (Wang et al., 2015). In the AR form of monilethrix, only atypical-beaded changes could be identified in a few short and thin hairs. Most long and thick terminal hairs obtained by pulling, plucking, or cutting appear normal (Shimomura et al., 2006; Zlotogorski et al., 2006).

The clinical manifestations found in AR form of monilethrix are more severe than those found in AD form, with more extensive alopecia of the scalp, trunk, and

TABLE 1 Review of the autosomal recessive form of monilethrix and autosomal recessive hypotrichosis cases with DSG 4 variants in the literature

Diagnosis	Consanguinity[a]	Ethnic origin	Onset age	Sparse fragile hair			Hyperkeratotic papule	Beaded hair	Pruritus	DSG 4 variants		Reference
				Scalp	Eyebrow	Eyelash						
LAH	+/+	Pakistani	NA	+	+	−	+	−	NA	Ex5_8del	Homozygous	Kljuic et al. (2003)
LAH	+/+/+	Pakistani	1 week after birth	+	+	+	NA	NA	NA			Rafiq et al. (2004)
LAH	+	Pakistani	Since birth	+	+	+	+	NA	+			Moss et al. (2004)
LAH	+	Pakistani	1 week after birth	+	+	+	+[b]	−	NA			John et al. (2006)
LAH	+	Pakistani	Since birth	+	−/+[d]	−/+[d]	−	−	+	c.87delG	Homozygous	Wajid et al. (2007)
LAH	+	Iraqi	Since birth	+	+	+	+	−	+	p.Ala129Ser	Homozygous	Messenger et al. (2005)
LAH with monilethrix hair	−	Iraqi and Iranian	Since birth	+	+	+	+	+	+	p.Pro267Arg & IVS216 + 1G > T	Compound heterozygous	Schaffer et al. (2006)
ARM	+/+/−/−/−/−	Iraqi	Since birth	+	+	+	+	+	+	p.Pro267Arg	Homozygous	Zlotogorski et al. (2006)
ARM	−/−	Iraqi and Iranian	Since birth	+	+	+	+	+	+	p.Pro267Arg & IVS216 + 1G > T	Compound heterozygous	Zlotogorski et al. (2006)
ARM	−/−	Iraqi and Moroccan	Since birth	+	+	+	+	+	+	p.Pro267Arg & p.Arg289*	Compound heterozygous	Zlotogorski et al. (2006)
ARM	−	Iranian	Since birth	+	+	+	+	+	+	IVS216 + 1G > T & c.763delT	Compound heterozygous	Zlotogorski et al. (2006)
ARM	−	Iraqi and Iranian	Since birth	+	+	+	+	+	+	p.Pro267Arg & c.763delT	Compound heterozygous	Zlotogorski et al. (2006)
Monilethrix-like congenital hypotrichosis	−	Japanese	Since birth	+	+	−	+	+	NA	p.Ser192Pro & c.2039insT	Compound heterozygous	Shimomura et al. (2006)
ARM	−	Japanese	Since birth	+	+	+	+	+	NA	p.M208IfsX4 & p.Trp823*	Compound heterozygous	Farooq et al. (2011)
LAH with monilethrix	−	Chinese	Since birth	+	+	+	+	+	0	p.D323G	Homozygous	Wang et al. (2015)
LAH	+	Pakistani	Since birth	+	+	+	+	−/+[c]	NA	c.85-1_191del	Homozygous	Ullah et al. (2015)
ARM	−	Japanese	Since birth	+	+	+	+	+	NA	p.Asp707Ilefs*109	Homozygous	Kato et al. (2015)
ARM	−	Chinese	Since birth	+	+	+	+	+	+	c.837del & c. 2389C > T	Compound heterozygous	This study
ARM	−	Chinese	Since birth	+	+	+	+	+	+	c.2355 + 1G > A	Homozygous	This study
ARM	−	Chinese	Since birth	+	+	+	+	+	+	g.31381440_31430084del (48,644 bp deletion)	Homozygous	This study

Abbreviations: ARM, autosomal recessive form of monilethrix; LAH, autosomal recessive hypotrichosis; NA, not available or not mentioned in the reference.

[a]Each + or – represent a consanguineous or nonconsanguineous family in the reference.

[b]Not mentioned in text, but present in the clinical photo.

[c]One of the two families showed monilethrix-like hairs.

[d]The involvement of eyebrows and eyelashes varied among the patients in the reference.

limbs, and keratotic follicular papules involving the extremities and periumbilical region (Table 1) (Schaffer et al., 2006; Shimomura et al., 2006; Zlotogorski et al., 2006). Congenital scalp erosions and dry skin have also been reported in a family with the AR form (Farooq et al., 2011; Schaffer et al., 2006). As far as we known, the enamel hypoplasia in cases 1 and 3 of present study have not been reported previously.

AR form of monilethrix and LAH share some clinical and genetic findings (*DSG4* genetic variants). A major difference is monilethrix-like hairs changes could not be found in LAH. It is suggested that these diseases should be considered as a spectrum disorder. In our opinion, LAH cases should be evaluated carefully with dermoscopy, which is more sensitive than any other method in detecting monilethrix-like changes. A recent classification has placed them in to one new group of disorder, named hypotrichosis 6 (HYPT6, OMIM 607903), however, for better understanding of the clinical differential diagnosis of monilethrix spectrum, we still suggest to retain the name of "monilethrix, AR form".

Desmosomes are molecular complexes of cell adhesion proteins and linking proteins that attach the cell surface adhesion proteins to intracellular keratin cytoskeletal filaments. The cell adhesion proteins, desmogleins (DSGs), and desmocollins (DSCs), are members of the desmosomal cadherin family. In humans, coding genes for four DSG (*DSG1-DSG4*) and three DSC (*DSC1-DSC3*) have been identified on chromosome 18q12.2. They play a critical role in intercellular adhesion and keratinocyte differentiation. The human *DSG4* gene encodes DSG4, a new member of the cadherin superfamily. Structurally, DSG4 contains a signal (S) and preprotein (p) domain followed by 5 extracellular domains (EC1-4, EA), a transmembrane domain (TM), intracellular domains (Figure 4) (Whittock & Bower, 2003). *DSG4* is specifically expressed in the hair shaft cortex, cuticle, inner root sheath cuticle, and granular layer of the epidermis (Bazzi et al., 2006), where it constitutes part of the desmosome. The desmosome has an important role in cell-to-cell adhesion and signaling, and is crucial for proper hair follicle development and differentiation. Variants in the rat and mouse *DSG4* homolog cause the "lanceolate hair" phenotype, characterized by sparse, fragile broken hair shafts and follicular dystrophy.

To date, 30 families with nine different homozygous variants and eight different compound heterozygous variants have been reported in the *DSG4* gene (Table 1). Fourteen of these variants combinations, including the variants identified in our families, could lead to a monilethrix phenotype. Most of variants locate in the extracellular or intracellular domains (Figure 4).

In this study, compound heterozygous variants c.837del and c. 2389C > T were identified in patient 1. The variant c.837del in the *DSG4* gene was predicted to cause a frameshift and premature termination in the intracellular region (EC3) of the DSG4. It is theorized that the messenger RNA from the allele with the c.837del variant would be largely degraded by nonsense mediated messenger RNA decay. By contrast, the nonsense variant c. 2389C > T in the intracellular region of the DSG4 might escape from the nonsense mediated messenger RNA decay and generate a truncated protein with markedly reduced affinity to plakoglobin (Farooq et al., 2011). In patient 2, the homozygous c.2355 + 1G > A variant was predicted to cause skipping of one or more exons, followed by the activation of aberrant 5′(donor) splice sites (5'ss), 3′(acceptor) splice sites (3'ss) and retention of intron 15 in mRNA (Krawczak et al., 1992). The abnormal mRNA was postulated to be largely degraded by nonsense mediated messenger RNA decay. The 48,644 bp large deletion variant (g.31381440_31430084del) in patient 3, was identified as an entire gene deletion, except exon 1. This variant would be expected to cause a complete loss of function of *DSG4* and may serve as a future null model for better understanding the function of *DSG4*. Interestingly, the phenotype of patient 3 is not more severe compared to most other reported cases with different variants in *DSG4*. The patient did have a number of normal-looking hairs, which suggested the function of *DSG4* might be partly substituted by some other proteins.

To the best of our knowledge, all the four variants identified in this study have not been reported previously. The presence of these homozygous variants in nonconsanguineous families indicates that a possible founder effect in their predecessors is segregated to different subgroups within main ethnic groups in the locality. In all the three families, none of the six heterozygous variant carrier parents had any hair abnormality, suggesting that there was no dominant negative effect.

Identifying the variants involved in AR form of monilethrix cases can be challenging. A reason for this may be that most of the autosomal recessive monilethrix cases were sporadic without family history of consanguinity (18/30 families). Furthermore, large deletion variants are not uncommon in *DSG4* genes (9/30 families), which may not be discovered with the routinely used variant detection strategies. In this study, only with through utilizing qPCR and multi long-range PCR location strategy was the 48,644 bp large deletion variant in patient 3 finally identified.

There is no current cure for AR form of monilethrix. Improvement of the hair occurs with age and in females, during pregnancy, however, after delivery, the hair loss returns. Oral acitretin has been reported to have good clinical and cosmetic results in AD form of monilethrix, but no improvement was found in case 3 after oral acitretin treatment for 2 months.

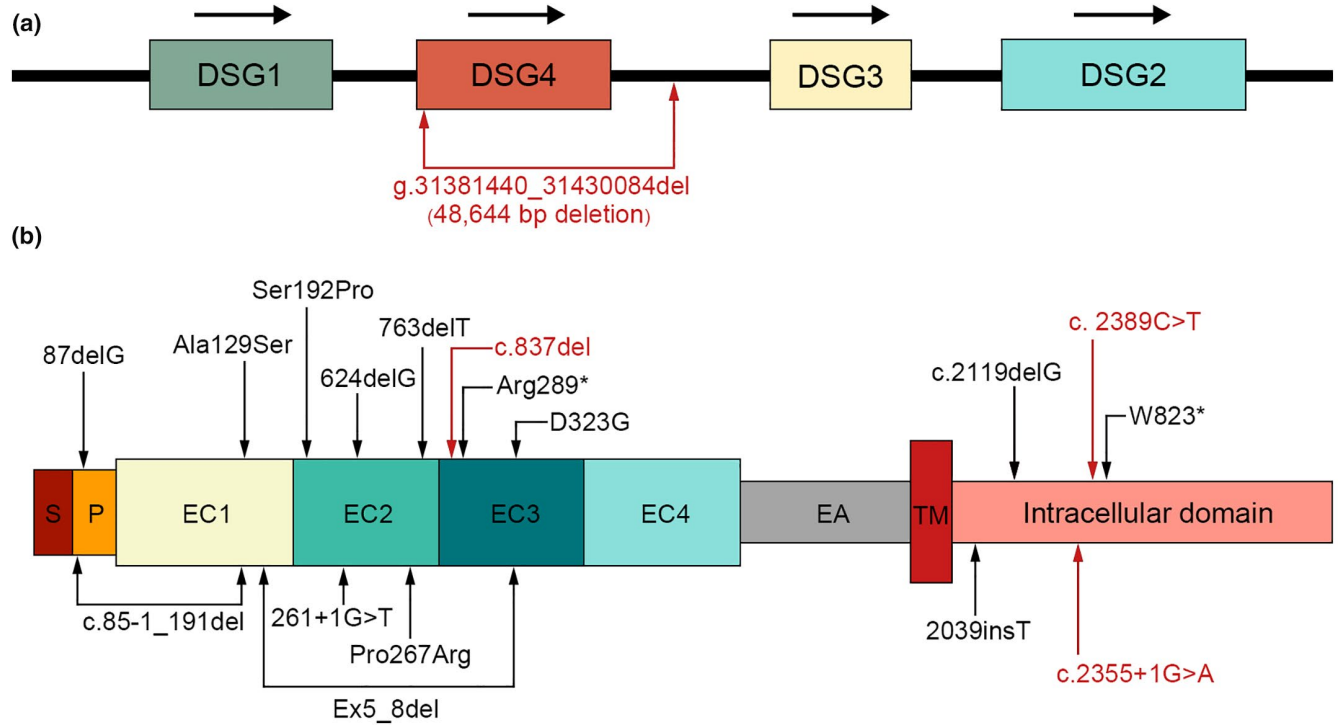

FIGURE 4 Schematic representation of the human DSGs arrangement on chromosome 18q12.2 (a) and *DSG4* structural and functional domains with the reported variants (b). S, signal domain; P, preprotein domain; EA, extracellular anchor domain; EC1-EC4 and EA, extracellular cadherin repeat domains; TM, transmembrane domain. The variants identified in the current study are shown in red

In this study, we have reported three cases of AR form of monilethrix and identified four novel variants in the *DSG4* gene, including a large deletion variant. These could provide further insight into the structure and function of the DSG4 protein and genotype–phenotype correlations.

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CONFLICT OF INTEREST

The authors have no conflict of interest.

AUTHOR CONTRIBUTIONS

Cheng Zhou designed the study, analyzed the research data and drafted the manuscript. Pei Wang, Jiacheng Li and Rongrong Wang participated in genetic studies and data analysis. Dingquan Yang, Wenjun Liao, Qing Guo, Guangdong Wen and Shuying Zheng collected and analysis the clinical data. Xue Zhang involved in the analysis of genetic research data. Jianzhong Zhang participated in its design and coordination of the study and edited the manuscript.

ETHICAL COMPLIANCE

The study was approved by the Ethics Committee of Peking University People's Hospital and informed written consent was obtained from all subjects.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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