Desmoglein 4 Mutation Underlies Autosomal Recessive Keratosis Pilaris Atrophicans

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Keratosis pilaris atrophicans (KPA) is a group of hair follicle disorders that share features of follicular keratinization abnormality. KPA has long been suspected to have a strong underlying genetic background, but this has not been thoroughly elucidated. This study investigated the genetics of 2 patients who presented in early infancy with clinical manifestations reminiscent of keratosis pilaris atrophicans faciei/ulerythema ophryogenes. Following DNA extraction from leukocytes from these 2 patients and their family members, whole exome sequencing was performed, which identified a previously unreported homozygous variant in *Desmoglein 4* c.129DelAACA. This mutation is predicted to cause a frameshift and introduce a premature stop codon (p. Thr43fs40*) in the 2 patients. This report helps explain the genetic background underlying KPA and opens the way for further investigation regarding the role of *Desmoglein 4* in other hair diseases.

CASE REPORT

KPA is a group of hair follicle disorders that share features of follicular keratinization abnormality and atrophy, which includes keratosis pilaris atrophicans faciei (KPAF, ulerythema ophryogenes), atrophoderma vermiculatum, and keratosis follicularis spinulosa decalvans (KFSD) (1). KPAF is characterized by early onset (in infancy) of keratotic follicular papules of the facial area, leading to follicular atrophy of the lateral eyebrows and keratosis pilaris over the trunk and extremities (2). KFSD is more severe with more extensive distribution of follicular papules, scarring alopecia, and extrafollicular involvement (keratitis and keratoderma) (3). Patients with atrophoderma vermiculatum present in childhood with pitted atrophic depression in a honeycomb pattern (4). Individuals affected by this family of diseases may manifest overlapping features (4).

Overall, the genetic background underlying KPA has not yet been fully elucidated. Although most cases are sporadic, several familial cases were reported consistent with autosomal dominant or X-linked inheritance. Mutations in the membrane-bound transcription factor protease site 2 gene (MBTPS2) were found to cause X-linked KFSD (3). Recessive inheritance was recently reported in patients manifesting with KFSD-atrophoderma vermiculatum overlap (4), which was suggested, after whole exome sequencing, to be caused by homozygous mutation in LRP-1, encoding LDL-related protein 1. KPAF is reportedly inherited in an autosomal dominant pattern. It is associated with RASopathies and with cases of 18p monosomy (2); however, no underlying gene has been found. We report here, for the first time, a homozygous mutation in desmoglein 4 (*DSG4*) underlying AR KPAF. A 10-year-old Muslim-Arab girl (patient 1, **Fig. 1**a, individual III-2, family A) from the north of Israel presented in the early months of life with localized hypotrichosis over the eyebrows and eyelashes. No other abnormalities were present, including sweating, teeth, nails, palms or soles. Her family medical history disclosed a similar phenotype in her grandmother. Thorough examination of the skin revealed hypotrichosis of the eyebrows (more prominent on the lateral third) accompanied by follicular papules and focal atrophy, as well as hypotrichosis of the lower eyelids (**Fig. 2**a). Widespread keratotic follicular papules were observed over the face, scalp and extremities, accompanied by skin xerosis. Scalp hair appeared normal, with mild diminution in the frontal area (Fig. 2a). Her hair was neither fragile nor pluckable. Biopsy of a keratotic papule revealed hair follicles with widened infundibulum. Patient 2 (Fig. 1a, individual I-2, family B) is a 2.5-year-old Muslim-Arab boy, born to second-degree family relatives, with a birth onset of partial hypotrichosis over the eyebrows, which deteriorated over the early years of life. Physical examination revealed localized hypotrichosis over the eyebrows and lower lids, accompanied by generalized follicular keratotic papules over the face, scalp, trunk and extremities. His scalp hair was dense (Fig. 2b). Microscopy of hair from both patients did not reveal any changes in the hair shaft. Following consent from the guardians, DNA was extracted from leukocytes of patients and family members (Fig. 1a). The DNA sample of patient 2 was analysed using whole exome sequencing. Following filtering for homozygous variants in genes expressed in hair follicles, considering the probable autosomal recessive (AR) inheritance, 4 variants were found, including a novel variant in *DSG4* c.126-129DelAACA (Fig. 1b), which is predicted to cause a frameshift and premature termination in the pro-peptide domain of *DSG4*

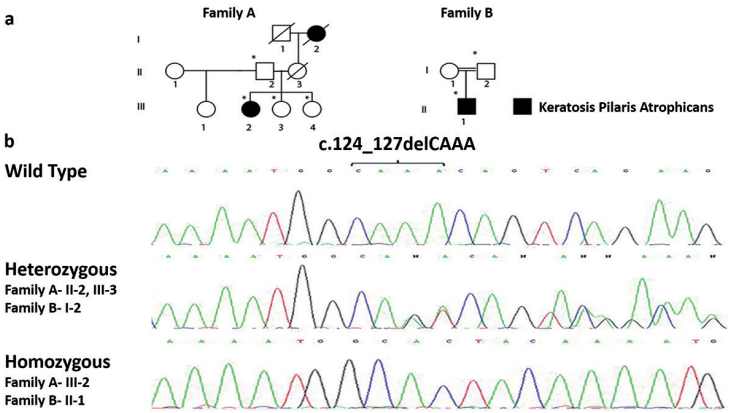

Fig. 1. Genetic analysis of families A and B. (a) Pedigrees of families A and B. Filled symbols denote patients affected by keratosis pilaris atrophicans (KPA). *Individuals whose DNA was analysed. (b) Molecular analysis. Whole exome sequencing revealed a homozygous c.126-129DelAACA mutation in the desmoglein 4 (*DSG4*) gene in patient 2. The same mutation was found in patient 1. Individuals II-2, III-3 of family A and individual I-1 of family B were found to be heterozygous carriers of the mutation. *DSG4* wildtype (WT) sequence is given for comparison (*upper panel*).

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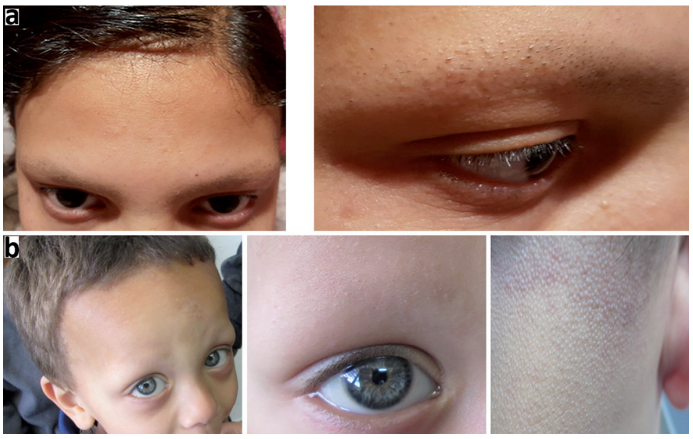

Fig. 2. Clinical manifestations of patients 1 and 2. (a) Patient 1 manifests hypotrichosis of eyebrows (lateral>medial) and eyelashes (*left*) and keratotic follicular papules over forehead and eyebrows, accompanied by follicular atrophy (*right*). (b) Patient 2 manifests normal scalp hair appearance, localized hypotrichosis over eyebrows and lower eyelashes, accompanied by keratotic follicular papules (*left* and *middle*), and keratotic follicular papules over the nape (*right*). Permission given to publish these photos.

(p. Thr43fs40*). This transcript will probably be degraded by nonsense mRNA decay. Patient 1 was found to harbour the same homozygous variant, which was verified by Sanger sequencing to co-segregate with the phenotype among members of both families (Fig. 1b). The variant was neither found in screening 107 DNA samples matched for ethnic origin, nor was it available in public databases, including GnomAD and ExAc. Despite the shared variant, the 2 families denied consanguinity.

DISCUSSION

DSG4 is a member of the desmosomal cadherin family that plays a crucial role in cell-cell adhesion. The protein family is comprised of other desmogleins (1–4) and desmocollins (1–3) (5). DSG4 is expressed specifically in hair follicle compartments including the hair shaft cortex, lower hair cuticle, and upper inner root sheath (IRS) cuticle, and is presumed to play a role in the balance of cellular proliferation and differentiation (5). To date, mutations in *DSG4* have been reported to cause 2 types of monogenic human diseases: AR localized hypotrichosis (AR LAH) (6) and AR monilethrix (AR MT) (7).

Considering the variant rarity, its segregation within families, the proven biological role of DSG4 protein and its presence in the hair follicle, the predicted premature termination of the protein caused by the variant, and the fact that other clinical diseases have been demonstrated associated with *DSG4* mutation (6), it may be concluded that c.126-129DelAACA is a causative mutation, leading to a new clinical phenotype of *DSG4* mutation: KPA.

DSG4 mutations were first thought to cause either classic LAH6, with fragile hair leading to scalp hypotrichosis and no microscopic changes of MT (6) or AR MT, which presents with fragile, thin hair leading to scalp hypotrichosis, accompanied by keratotic follicular papules and microscopic MT changes (7). One could argue that this case represents previously reported heterogeneity in LAH6 (8–10); however, in contrast to these previous reports, which reported fragile and sparse hair in all patients with different degrees of severity, the current report shows: (*i*) a consistent phenotype of hypotrichosis limited to the eyebrows and eyelashes in the 2 patients; (*ii*) hypotrichosis present only in areas with follicular hyperkeratosis; (*iii*) no scalp involvement over several years of serial examinations. We posit that the definition of *DSG4*-associated diseases should be expanded to include cases of AR KPA.

In summary, we report here, for the first time, an AR inherited KPA caused by mutation in *DSG4*, which contributes to the knowledge of the genetic background of KPA and opens the way for subsequent research regarding its pathogenesis.

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The authors have no conflicts of interest to declare.

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