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 (DSG4) underlying KPA. The study report explains 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 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 KPAF. A 10-year-old Muslim-Arab girl (patient 1, Fig. 1a, 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. 2a). 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.126-129delAACG (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.126-129delAACG mutation in the desmoglein 4 (DSG4) gene. The same mutation was found in patient 1. Individuals II-1, III-2 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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case represents previously reported heterogeneity in microscopic MT changes (7). One could argue that this choice, accompanied by keratotic follicular papules and no microscopic changes of MT (6) or AR MT, which suggests 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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REFERENCES