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 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 homzygous mutation in desmoglein 4 (DSG4) underlying AR 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.126-129delAACA (Fig. 1b), which is predicted to cause a frameshift and premature termination in the pro-peptide domain of DSG4.
case represents previously reported heterogeneity in
chosis, accompanied by keratotic follicular papules and
presents with fragile, thin hair leading to scalp hypotri-
sic LAH6, with fragile hair leading to scalp hypotrichosis
mutation: KPA.
that c.126-129DelAACCA is a causative mutation, leading
association with
fact that other clinical diseases have been demonstrated
of cellular proliferation and differentiation (5). To date,
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
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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.

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