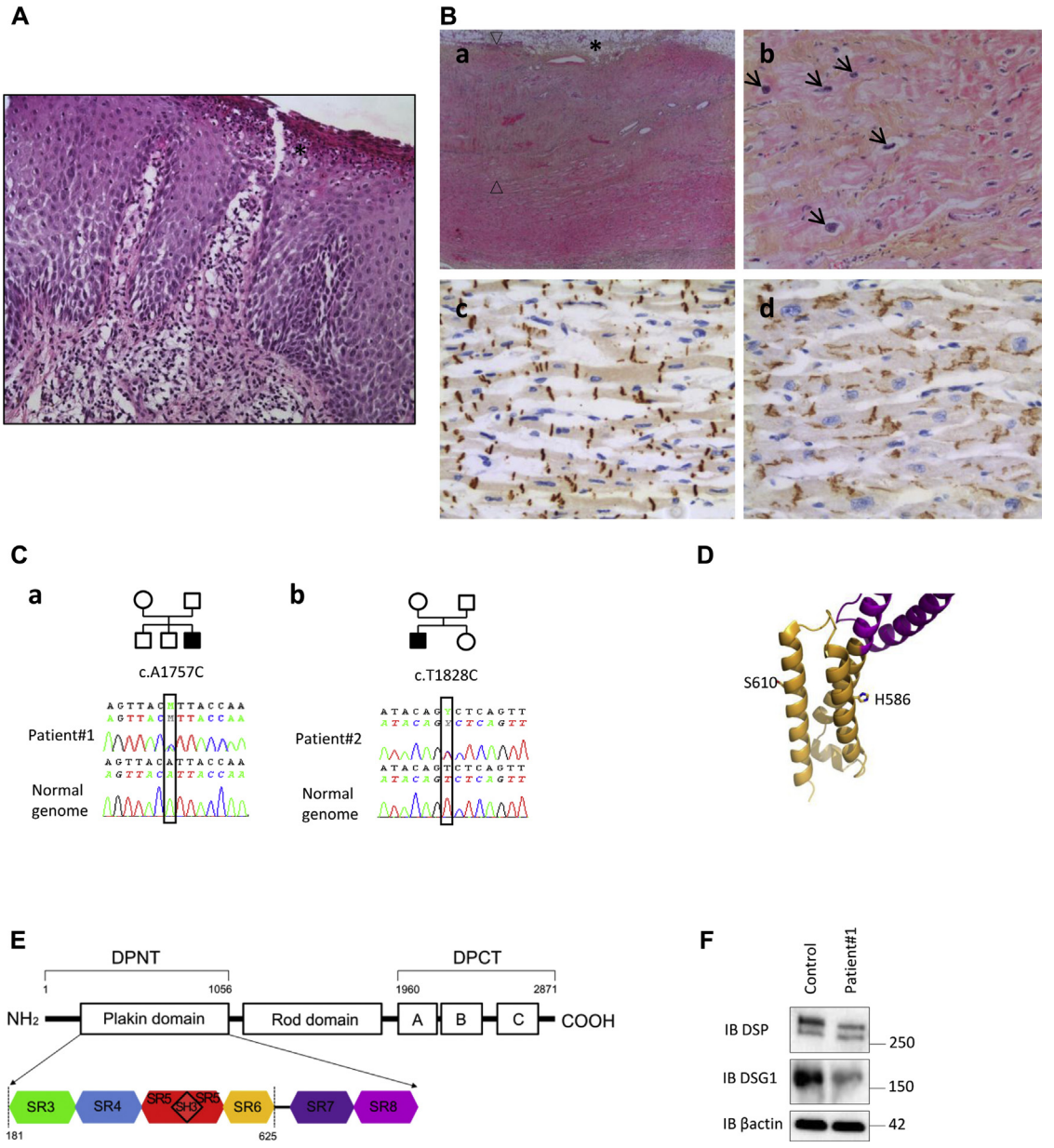

FIG E1. Histopathologic and molecular features of patients 1 and 2. **A,** Histopathology of a skin biopsy specimen (patient 2) revealed acanthosis, acantholysis (lower part of the epidermis), inflammatory infiltrate (lymphocytes and histiocytes) in the dermis, and a pustula with neutrophils (*asterisk*; ×200 magnification for the *inset* of Fig E1, *A* and *B*, *b*). **B,** Histopathology of heart explants (left ventricle, patient 2) showing fatty infiltration (epicardium, *asterisk*) and major fibrous infiltration (subepicardium, *arrows*, *a*; ×25 magnification for Fig E1, *B*, *a*). Presence of dystrophic nuclei in the cardiomyocytes is shown (fibrotic areas, *arrows*, *b*). Immunohistochemical comparison of DSP expression in heart sections shows a strong and regular pattern of reactivity in the intercalated discs (control, *c*) compared with the lower and abnormally distributed pattern (patient 2, *d*). **C,** Pedigrees and sequence electropherograms of patients 1 *(a)* and 2 *(b)*. **D,** Locations of H586 and S610 residues within DSP's SR6 domain (orange) at the surface of straight α-helices. The SR5 domain is shown in magenta. **E,** DSP protein consists of 3 major regions with the indicated amino acid boundaries. Close-up view of the plakin domain within the DSP N-terminal domain *(DPNT)*, with colored regions representing the 4 spectrin repeats found in the crystal structure of DSP (residues 181-625). The figure was used with permission from Choi et al.[E3] **F,** Immunoblots of DSP and DSG1 in keratinocytes from patient 1 and a control subject.

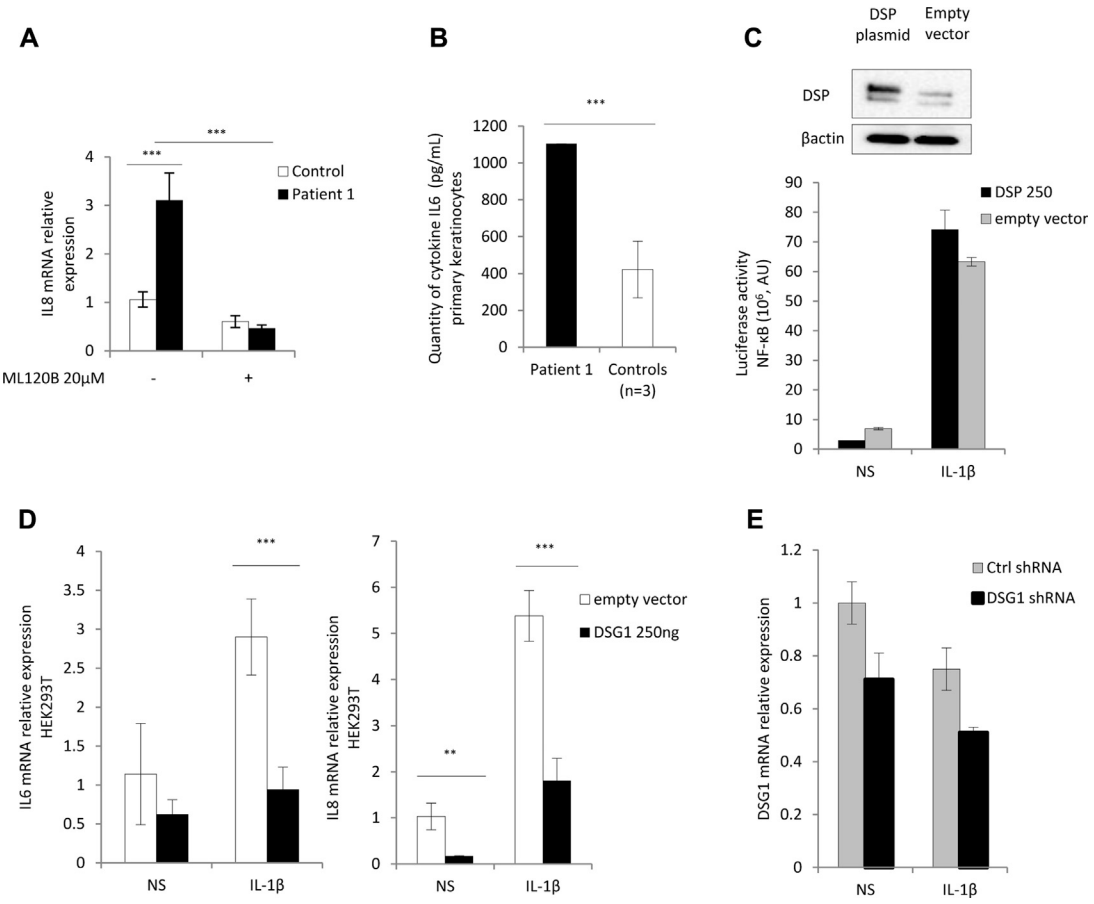

FIG E2. DSG1 inhibits NF-κB–mediated epithelial inflammation. **A,** Relative mRNA expression of *IL8* analyzed by using quantitative RT-PCR in primary keratinocytes from patient 1 and a healthy control subject after inhibition of IKKβ by ML120B. **B,** *IL6* production by keratinocytes from patient 1 and control subjects (n = 3). **C,** NF-κB luciferase reporter assay in HEK293T cells transfected with 250 ng of DSP. *Inset*, Western blot analysis of DSP expression in HEK293T cells transfected with 250 ng of DSP. **D,** *IL6* and *IL8* mRNA relative expression in HEK293T cells transfected with DSG1 (250 ng) and stimulated with IL-1β. **E,** *DSG1* mRNA relative expression in control keratinocytes infected with lentivirus expressing shDSG1 and stimulated or not with IL-1β. *AU*, Arbitrary units; *NS*, nonstimulated. $^{**}P < .01$ and $^{***}P < .001$.

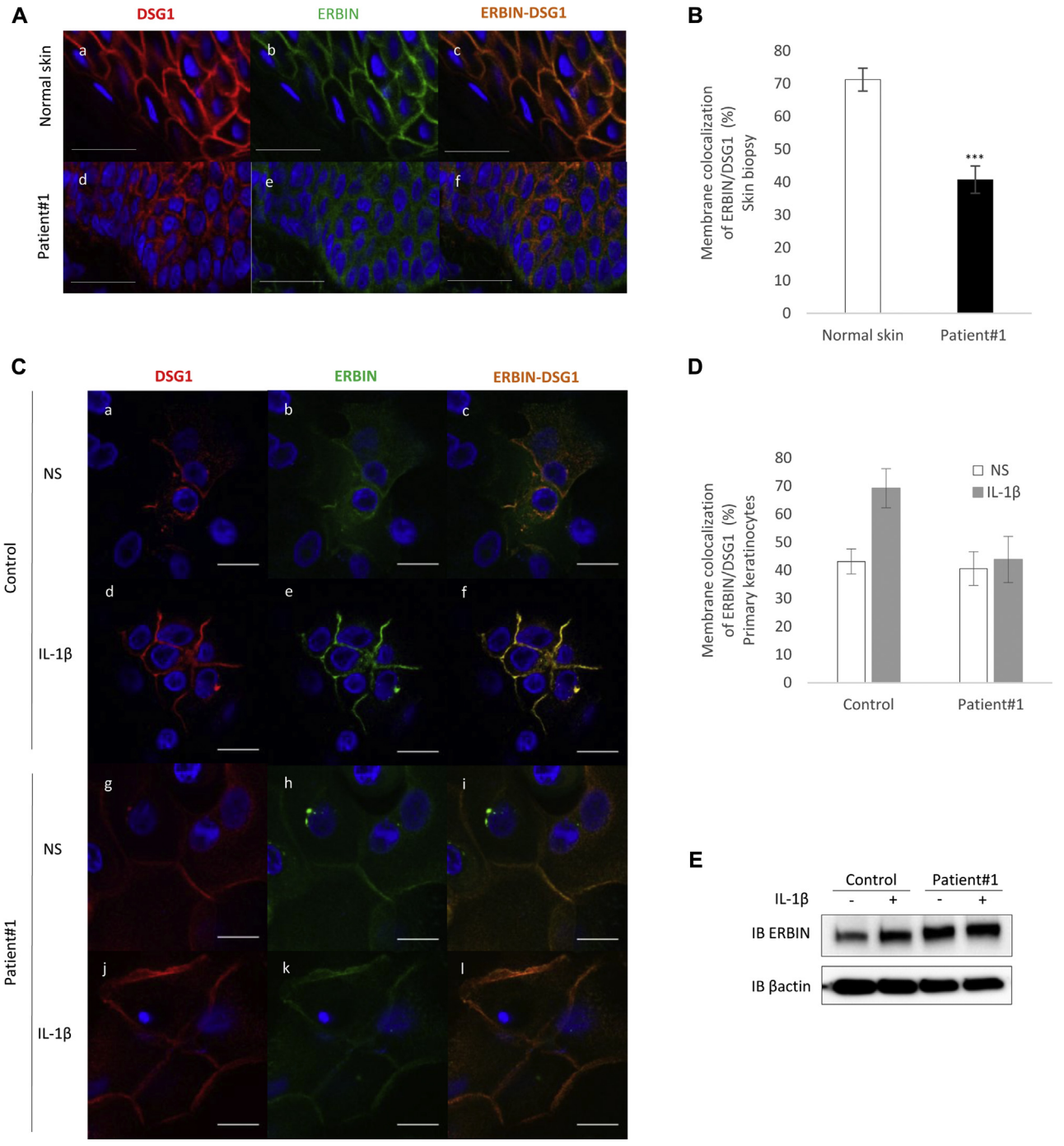

FIG E3. Expression and subcellular localization of ERBIN in the keratinocytes of patient 1. **A,** Immunofluorescence analysis of skin sections from a healthy control subject *(a-c)* and from patient 1 *(d-f)* showing a reduction in DSG1 (in *red*) and ERBIN (in *green*) staining at the plasma membrane of patient 1's keratinocytes. The 2 proteins accumulated in the cytoplasm of patient 1's keratinocytes. *Scale bar* = 20 μm. Data are representative of 3 independent experiments. **B,** Quantification of ERBIN/DSG1 colocalization at the plasma membranes in skin keratinocytes from a healthy control subject and patient 1. **C,** Immunofluorescence analysis of primary keratinocytes from a healthy control subject *(a-f)* and patient 1 *(g-l)*. Note the increase in DSG1 (in *red*) and ERBIN (in *green*) staining at the plasma membrane of control keratinocytes *(d-f)* after stimulation with IL-1β. This increase was absent in patient 1's keratinocytes *(j-l)*. *Scale bar* = 20 μm. Data are representative of 2 independent experiments (controls, n = 3). **D,** Quantification of ERBIN/DSG1 colocalization at the plasma membrane of primary keratinocytes. **E,** Immunoblotting of ERBIN in keratinocytes from patient 1 and a healthy control subject. Primary keratinocytes were either stimulated with IL-1β or not stimulated *(NS)*. Data are shown as means ± SDs. ***$P < .001$.

TABLE E1. Main clinical characteristics of reported patients with SAM syndrome caused by recessive mutation in the *DSG1* gene

Disease	Total patients	Past familial history	Dermatologic symptoms	Features of ectodermal dysplasia				Allergic details	Cardiac involvement	*DSG1* mutation
				Hair	Teeth	Nails	Sweating			
SAM syndrome	Two sisters	Diffuse plantar keratoderma (mother)	PPK, skin fragility, congenital ichthyosiform erythroderma	Sparse	NS	NS	NS	Severe food allergies, increased total IgE levels, eosinophilic esophagitis (1 patient)	No (1)/muscular ventricular-septal defects (1)	c.49-1G>A (homozygous)[E4]
	Two sisters	Focal palmar keratoderma (father)	Congenital erythroderma	Sparse	NS	NS	NS	Multiple food allergies, increased total IgE levels	No	c.1861delG (homozygous)[E4]
	1 (F)	Focal plantar keratoderma (mother)	PPK, atopic dermatitis since the first month of life with severe generalized flares of dermatitis	Curly	No	No	NS	Multiple allergies, increased total IgE levels	No	c.2659C>T, p.R887*, exon 15 (homozygous)[E5]
	Two half brothers	Mild PPK (mother)	PPK, skin erosions, psoriasiform and eczematous erythroderma in the first few months of life	No	No	No	No (1)/NS (1)	Multiple allergies, increased total IgE levels	No	c.2614delA (p.Ile872Serfs*10), exon 15 (homozygous)[E6]
	Two brothers and sisters	PPK (both parents)	PPK, skin erosions, congenital erythroderma	Curly and hard	No	No (1)/"affected nails" w/o precision (1)	NS	Isolated increased total IgE levels for the boy	No	c.1892-1delG/ p.Gly631Glnfs*8, exon 14 (homozygous)[E7]
	1 (F)	PPK (father)	PPK, transient erythematous patches	Curly	No	No	No	Slight increased total IgE levels, no clinical manifestation of allergy	No	c.811_812delAC, (p.Q271Vfs*20), exon 7 + c.2100+4A>G, IVS14+4A>G, intron 14[E8]

These 10 patients do not seem to have ectodermal dysplasia, even when they presented with ectodermal dysplasia features.
F, Female; *NS*, not specified; *PPK*, palmoplantar keratoderma; *w/o*, without.

TABLE E2. Main clinical characteristics of reported patients with SAM syndrome caused by a dominant mutation in the *DSP* gene

Disease	Total patients	Past familial history	Dermatologic symptoms	Features of ectodermal dysplasia				Allergic details	Cardiac involvement	*DSP* mutation
				Hair	Teeth	Nails	Sweating			
SAMEC syndrome	1 (M)	NS	Diffuse PPK, erythroderma from the first week of life with superficial pustulosis	Yes, hypotrichosis	Yes, hypodontia	Yes, nail dystrophy	NS	Multiple food allergies, increased total IgE levels	Normal at 6 y (clinical examination and ultrasonography)	c.1757A>C (p.His586Pro-, exon 14 (heterozygous)[E9]
	1 (M)	NS	PPK, erythrokeratodermia	Yes, sparse hair at birth, scalp hair was absent afterward	Yes, enamel defect, no hypodontia on primary teeth (but died at 3 y)	Yes, nail dystrophy	NS	No clinical manifestation of allergy, normal level of total IgE	Yes, marked left atrial and ventricular dilation and right ventricular dilation with an ejection fraction of 20%; patient died of heart failure at 3 y	Q616P, exon 14 (heterozygous)[E10]
	1 (M)		PPK, erythrokeratodermia	Yes, sparse eyebrows, eyelashes, and scalp hair	Yes, hypodontia, enamel defects	Yes, nail dystrophy	NS	No clinical manifestation of allergy, normal level of total IgE	Yes, pronounced left ventricular dilation and right atrial dilation	H618P, exon 14 (heterozygous)[E10]
	1 (F)		PPK, erythrokeratodermia	Yes, sparse eyebrows, eyelashes, and scalp hair	Yes, hypodontia	Yes, nail dystrophy	NS	No clinical manifestation of allergy, normal level of total IgE	Yes, a moderately dilated left ventricle with low normal systolic function	L622P, exon 14 (heterozygous)[E10]

These 4 patients have ectodermal dysplasia.

F, Female; *M*, male; *NS*, not specified; *PPK*, palmoplantar keratoderma.