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Combination of palmoplantar keratoderma and hair shaft anomalies, the warning signal of severe arrhythmogenic cardiomyopathy: a systematic review on genetic desmosomal diseases

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ABSTRACT

Inherited desmosomal diseases are characterised by skin and/or cardiac features. Dermatological features might be a clue in the determination of the underlying life-threatening cardiac disease. This article aims to propose a dermatological algorithm for the diagnosis of desmosomal diseases after a systematic review of published articles. Palmoplantar keratoderma (PPK), hair shaft anomalies and skin fragility are the major features in the 458 patients analysed. Isolated PPK or isolated hair shaft anomalies are associated with a desmosomal disease limited to skin. The combination of PPK and hair shaft anomalies was recorded in 161 patients, and this association is at high risk of cardiac disease (129/161, 80.1%). Skin features had led to cardiac monitoring in only 2.3% of those patients. We delineated three major phenotypes: the PPK–hair shaft anomalies–non-fragile skin subtype (77%), always associated with cardiac involvement; the PPK–hair shaft anomalies–skin fragility–normal cardiac function subtype (19.9%), frequently associated with *PKP1* mutations; the PPK–hair shaft anomalies–skin fragility–cardiac involvement subtype (3.1%), always due to *DSP* mutations. Three mutation hotspots in *DSP* and *JUP* account for 90.8% of the patients with cardiac involvement. The combination of PPK and hair shaft anomalies justifies long-term cardiac monitoring.

INTRODUCTION

Desmosomes are intercellular junctions providing strong adhesion between cells by anchoring intermediate filaments to the plasma membrane. They are abundant in the heart and epidermis. Desmosomes play an important role in maintaining the integrity of these tissues and in signal transduction pathways.[1 2] The desmosomal complex scaffolding includes armadillo proteins plakoglobin (PG) and plakophilins (PKP, isoforms 1 and 2), cadherins desmocollin (DSC, isoforms 1–3) and desmoglein (DSG, isoforms 1–4), and plakins desmoplakin (DSP).[3] Corneodesmosin (CDSN), a component of corneodesmosome, is involved in the cohesion of corneocytes. All these proteins are present in the epidermis while five participate in the cardiomyocyte desmosomes: PKP2, DSP, PG, DSC2 and DSG2.

Since the first identification of *PKP1* mutation, several cases of desmosomal genodermatoses have been reported.[4] Autosomal dominant or recessive mutations in one of the genes encoding for a desmosomal protein may cause dermatological and/or cardiac abnormalities.[5 6]

Disease severity is related to cardiac involvement corresponding to an arrhythmogenic cardiomyopathy. Arrhythmogenic cardiomyopathy is a progressive genetic cardiomyopathy characterised by myocyte degeneration followed by a fatty and fibrous replacement of the ventricular myocardium. Depending on the more involved ventricle, three arrhythmogenic cardiomyopathy subtypes are described: classic right dominant, left dominant and biventricular. The first clinical presentation of each of these subtypes is an episode of arrhythmia.[7]

Dermatological features are a clue for the clinical and molecular diagnosis of desmosomal diseases. They justify cardiac investigations and follow-up. Palmoplantar keratoderma (PPK) is easily recognisable while skin fragility, and hair and nail anomalies might be hardly perceptible.[8]

We conducted a systematic review of the published data in order to propose a clinical and molecular algorithm for the diagnosis of desmosomal diseases with dermatological features.

MATERIALS AND METHODS

A systematic MEDLINE search, using Medical Subject Heading terms, covered 1995 through March 2015. The following terms were used in association with 'mutations': 'plakoglobin'; 'Naxos disease', 'plakophilin', 'desmoplakin'; 'desmoglein'; 'desmocollin'; 'corneodesmosin'. Full text articles were systematically read. References quoted in the articles were checked. Articles were retained based on the following criteria: (1) at least one identified mutation in the following genes: *JUP* (junctional plakoglobin), *PKP1*, *PKP2*, *DSP*, *DSG1* to *4*, *DSC1–3* and *CDSN*; (2) description of the cutaneous phenotype. Articles focusing on extracutaneous manifestations and/or cardiac involvement only were excluded. Redundant articles were excluded (figure 1). Data were extracted from each article and recorded in standardised form focusing on gender, age, dermatological, cardiac and other manifestations. Family history, mutation(s), mode of inheritance, ethnic background, epidemiological and clinical data were recorded. All the available pictures were carefully analysed in order to improve the description of dermatological manifestations. Sequence variations were checked and actualised using ENSEMBL software.

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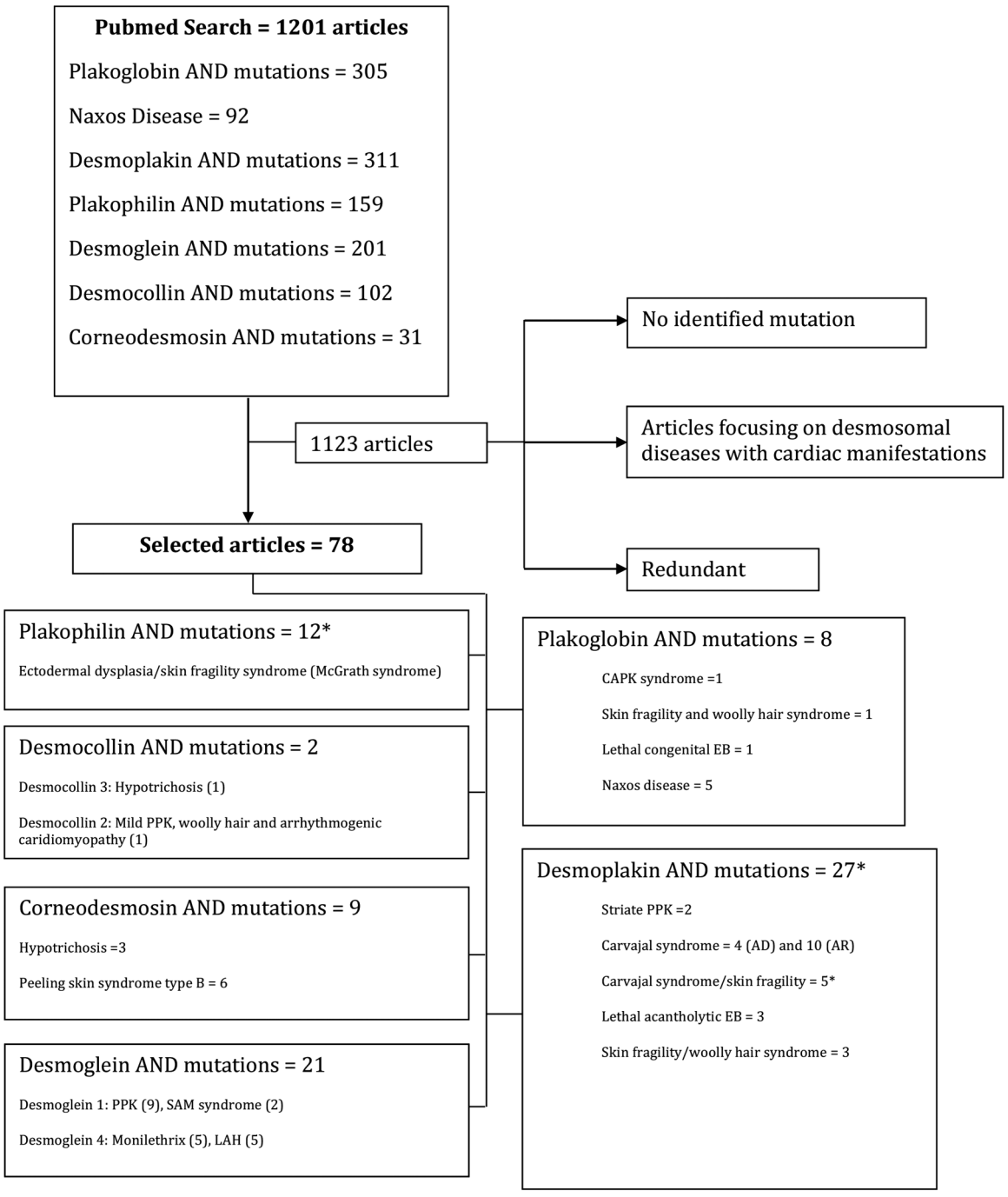

Figure 1 Desmosomal diseases: flow chart of the articles' selection process. *Reference 31 focuses on both *PKP1* and *DSP* genes mutations. AD, autosomal dominant; AR, autosomal recessive; CAPK, cardiomyopathy, alopecia and PPK; EB, epidermolysis bullosa; LAH, localised autosomal recessive hypotrichosis; PPK, palmoplantar keratoderma; SAM, skin dermatitis, multiple allergies, metabolic wasting.

RESULTS

A total of 78 articles were retained. They reported 458 patients carrying at least one mutation in one of the epidermal desmosomal genes. For one family, the total of affected members was not specified.[9] Among the 458 patients, 161 had the combination of PPK and hair shaft anomalies (ie, woolly and/or sparse and/or short hair or congenital atrichia). Among those 161, 129 had cardiac involvement, including 63 patients (48.8%) who experienced clinical manifestations, that is, syncope, stroke, heart failure, arrhythmias or sudden death, before cardiac disease diagnosis. For three patients only (2.3%), the initial detection of dermatological features had led to cardiac explorations. For the 63 remaining patients, the information was not available. Results were gathered according to the disease-causing gene (see online supplementary tables S1–S6).

JUP mutations

Within the 305 'plakoglobin mutations' and 92 'Naxos disease' references, eight were retained (see online supplementary table S1). They correspond to 82 patients, all carrying a recessive *JUP* mutation. Male-to-female ratio was 1.07 for the 68.3% of patients for whom the information was available. Among them, 74 patients carry the Naxos homozygous deletion (c.2157del2, exon 14).[10–14] The Naxos phenotype is

characterised by diffuse PPK, woolly hair and classic right dominant arrhythmogenic cardiomyopathy in all reported patients. Two Turkish related patients carried a homozygous missense mutation (c.794G>A, exon 4).[15] Their phenotype was close to Naxos syndrome and characterised by the association of cardiomyopathy (classic right dominant arrhythmogenic cardiomyopathy), alopecia (atrichia) and PPK (CAPK syndrome). In patients with Naxos and CAPK syndromes, symptomatic cardiac involvement started during the second decade (13–43 years).[12–15]

Five patients, aged 6 months to 14 years, presented with the association of skin fragility, woolly hair, diffuse PPK and normal cardiac function. For them, the repeated cardiac monitoring (echocardiography and 12-lead ECG) was reported as normal at the time of publication. Two different homozygous mutations were found: c.71C>A (exon 2) and c.468G>A (exon 3).[16] In patients with *JUP* mutation, the woolly hair appears from birth, whereas PPK develops later after the first year of life.

The last female patient presented with lethal congenital generalised epidermolysis bullosa and complete absence of scalp hair at birth. She died at 12 days of life, and carried a homozygous nonsense mutation (c.1615C>T; exon 9).[17]

DSP mutations

Among the 311 'desmoplakin mutations' references, 27 were retained (see online supplementary table S2). A total of 93 patients carrying either an autosomal dominant or recessive mutation in *DSP* were found. Male-to-female ratio was 0.96 for the 96.8% of patients for whom the information was available.

Two autosomal dominant (39 cases) and four autosomal recessive (54 cases) cutaneous syndromes were described. Two large families with a striate PPK, characterised by linear and focal hyperkeratosis of the palms and soles, were reported. The three patients of the first family carried a heterozygous splice site mutation (c.939+1G>A, intron 7), while the 27 patients of the second family carried the heterozygous nonsense mutation (p.Q331X, exon 8).[18 19]

The first autosomal recessive syndrome related to *DSP* mutations is known as Carvajal syndrome. Thirty-seven patients carrying either a homozygous or a compound heterozygous mutation in *DSP* were identified. All the mutations were located in exon 23 or 24, except for one compound heterozygous patient who carried mutations in exons 9 and 16.[20–29] The Carvajal phenotype is similar to Naxos disease: striate or focal PPK, woolly ± sparse hair and arrhythmogenic cardiomyopathy involving more frequently the left ventricle (left dominant arrhythmogenic cardiomyopathy).[7] The median age of the first cardiac manifestation was 8 years (3–35). One 6-year-old boy had normal cardiac ultrasound at the time of publication.[29]

Nine patients presented with PPK, woolly and/or sparse hair, left dominant arrhythmogenic cardiomyopathy associated with oligodontia for eight and leukonychia or nail dystrophy in four of them. All of them carried a heterozygous *DSP* mutation in exon 13 (one mutation) or 14 (three mutations). The median age of the first cardiac symptom was 12 years (7–14).[30–33]

Three additional autosomal recessive syndromes, related to *DSP* mutations sharing the skin fragility feature, were reported in a total of 17 patients: (1) five patients carrying heterozygous compound mutations, with at least one of the mutation located in exon 23 or 24, presented with the combination of Carvajal syndrome, skin fragility ± ectodermal dysplasia features. Four of the five patients presented with nail dystrophy. The first cardiac symptom occurred early at the median age of 35 months (1–14 years). Blisters or erosions occurred spontaneously or after very mild trauma.[34–38] (2) Eight patients presented with skin fragility associated with woolly hair. All the patients had nail dystrophy. Cardiac function was normal. At the time of publication, one 4½-year-old boy had normal cardiac monitoring, including ECG and echocardiography.[39] One 14-year-old female patient with her four relatives, aged 3–16 years, had normal clinical cardiac examination at the time of publication, but three of them refused cardiac monitoring.[40] For the two other patients, age and type of cardiac exploration were not specified.[41] In patients with *DSP* mutation, the woolly hair appears from birth, whereas PPK develops after the first year of life. (3) The four last compound heterozygous patients died during their first month of life. They presented with lethal acantholytic epidermolysis bullosa, associated with alopecia and anonychia. Ultrasound showed cardiac hypocontractility in one patient only. For these three autosomal recessive syndromes, skin fragility was noticed at birth, or soon after, except for one patient for whom skin fragility started at 2 years.[42–44]

PKP1 mutations

Among the 159 'plakophilin mutations' references, 12 were retained (see online supplementary table S3). Nineteen patients carrying a homozygous or a heterozygous compound mutation were published. Male-to-female ratio was 1.83 for the 88.9% of patients for whom the information was available.

The corresponding McGrath syndrome, or ectodermal dysplasia/skin fragility syndrome, is characterised by the association of skin fragility, sparse and short hair, PPK and nail dystrophy. Cheilitis and/or perioral fissuring or redness, reported in at least 11 patients, are considered as a discriminative clinical feature. Cardiac function is normal. Five patients (26.3%) presented with reduced sweating and six with normal sweating. Information was not available for the last eight patients. Skin fragility started at birth or soon after, except for one patient for whom it started at 18 years.[4 35 45–54]

DSG1 and *DSG4* mutations

Among the 201 'desmoglein mutations' references, 21 were retained. Eleven articles correspond to *DSG1* and 10 to *DSG4* mutation (see online supplementary table S4).

Ninety-three patients had a heterozygous or homozygous mutation in *DSG1*. Male-to-female ratio was 0.96 for 94.6% of the patients for whom the information was available. *DSG1* mutations are associated with autosomal dominant striate PPK and with autosomal recessive skin dermatitis, multiple allergies and metabolic wasting syndrome, or SAM syndrome. Eighty-six patients presented with isolated PPK; among them, 69 had striate PPK, and four had diffuse PPK. Information was not available for the 13 remaining patients. Seventeen different heterozygous mutations were reported.[55–63] Seven patients belonging to three unrelated families carry three different homozygous *DSG1* mutations. They presented with the association of congenital erythroderma, hypotrichosis or curly hair, striate PPK (for at least three of them), severe food allergy, high level of IgE and recurrent infections with severe metabolic wasting (for six of them). One patient presented with ventricular septal defect. The six remaining patients had no cardiac manifestation.[64 65]

Sixty-six patients had a recessive mutation in *DSG4*. Male-to-female ratio was 1.03 for 98.5% of the patients for whom the information was available. Two phenotypes are associated with recessive *DSG4* mutations: localised autosomal recessive hypotrichosis (LAH)[66–70] and monilethrix.[71–75] In LAH, hypotrichosis affects the hair of the scalp, trunk and extremities, and spares facial, pubic and axillary regions. An in-frame intragenic homozygous deletion (Ex5_8del) was reported in 34 of the 41 patients

with LAH. Two other homozygous mutations were identified (c.GG384–385TT and c.87delG). Monilethrix, reported in 25 patients, is characterised by periodic beaded hair shafts and pronounced hair fragility leading to hair loss. In these two diseases, manifestations started at birth or during the first month of life.

DSC2 and *DSC3* mutations

Among the 102 'desmocollin mutations', two articles, corresponding to six patients, were retained (see online supplementary table S5). While recessive mutations in *DSC2* are known to cause isolated arrhythmogenic cardiomyopathy, two related patients presented with the combination of left cardiac involvement, woolly hair and mild PPK. Both carry a *DSC2* homozygous mutation (c.1841delG, exon 12).[76] Hypotrichosis, the only phenotype related to *DSC3* mutations, is reported in four patients of the same Afghan family. They carry a homozygous mutation (c.2129T>G, exon 14). They presented with sparse and fragile whole body hair.[77]

CDSN mutations

Within the 31 'corneodesmosin mutations' references, nine were retained (see online supplementary table S6). Mutations in *CDSN* are associated with hypotrichosis simplex of the scalp (HSS) and peeling skin syndrome type B (PSS). At least, 99 patients carried a mutation in *CDSN*. The total of affected relatives was not specified for one Danish family with HSS.[9] Male-to-female ratio was 1.28 for 97% of the patients for which the information was available.

HSS is characterised by diffuse progressive scalp hair loss from childhood to adulthood. So far, more than 88 patients belonging to five HSS families have been reported. Four different heterozygous mutations in the exon 2 were identified.[9 78 79] PSS is characterised by an inflammatory lifelong peeling of the stratum corneum on the whole body. Eleven patients with PSS were reported. The inflammatory exfoliation started at birth or during the first week of life (nine patients) or at 3 years (one patient). Information was not available for the last patient. To date, food allergies and a high level of IgE are reported. Six different homozygous mutations in exon 2 of *CDSN* were identified.[80–85]

DISCUSSION

Skin fragility, hair shaft anomalies and PPK are the main dermatological features of cutaneous desmosomal diseases. We propose a flow chart to detect the patient at risk of sudden death due to cardiac involvement and a strategy of gene sequencing (figure 2).

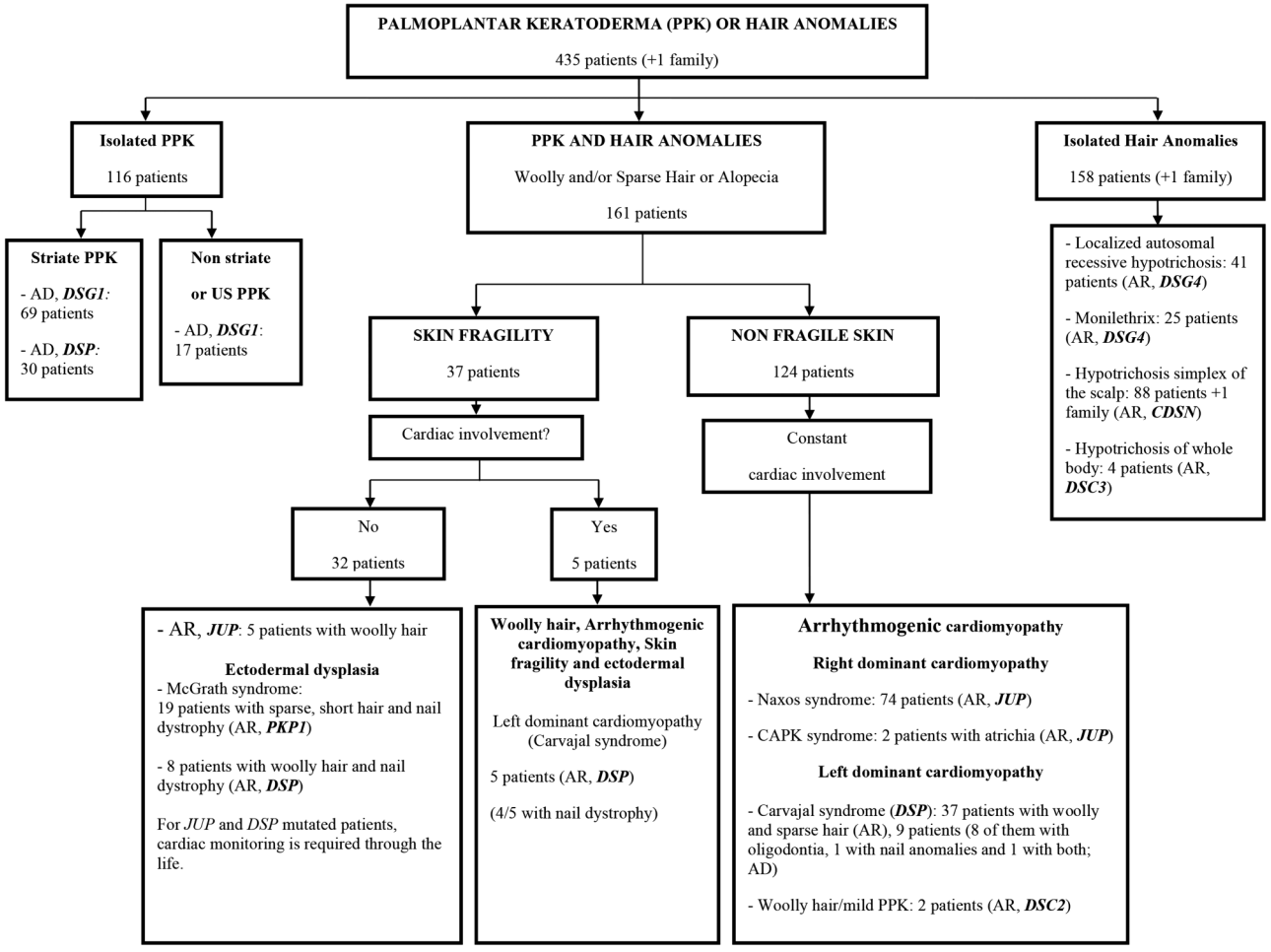

Figure 2 Desmosomal diseases with cutaneous features: clinical and molecular diagnosis flow chart. Desmosomal diseases were classified according to the three commonly associated dermatological manifestations: palmoplantar keratoderma (PPK), hair shaft anomalies and skin fragility, when reported PPK occurred after 1 year of age. PSS (11 patients, AR, *CDSN*) and SAM syndrome (7 patients, AR, *DSG1*) were not included because their main symptoms are inflammatory skin exfoliation and erythroderma, respectively. Neither was lethal acantholytic epidermolysis bullosa (1 patient, AR, *JUP*; 4 patients, AR, *DSP*) as patients died during their first month of life. Therefore, their main manifestations were congenital epidermolysis bullosa and ectodermal dysplasia features (hair, nail and dental anomalies). AD, autosomal dominant; AR, autosomal recessive; CAPK, cardiomyopathy, alopecia and PPK; CDSN, corneodesomsin; DSC, desmocollin; DSG, desmoglein; DSP, desmoplakin; JUP, junctional plakoglobin; PKP1, plakophilin 1; PSS, peeling skin syndrome; SAM, skin dermatitis, multiple allergies, metabolic wasting; US, unspecified.

While isolated PPK or isolated hair shaft anomalies are associated with a desmosomal disease limited to skin, their combination is associated with classic right dominant (*JUP* mutations) or left dominant (*DSP* and *DSC2* mutations) arrhythmogenic cardiomyopathy in 80.1% (129) of the 161 reported patients with such association (PPK–hair shaft anomalies). In all the 129 reported patients, dermatological features occurred before cardiac manifestations, that is, hair shaft anomalies since birth and PPK after 1 year. For the earliest case, cardiac involvement is reported during the first year of life. Interestingly, the detection of skin features led to cardiac disease diagnosis by systematic monitoring in only 2.3% of the patients with PPK–hair shaft anomalies.[33 37] Therefore, regular cardiac monitoring is mandatory in all patients presenting with PPK–hair shaft anomalies, even in the absence of clinical cardiac manifestations. Importantly, 11.8% (19) of the remaining patients with PPK–hair shaft anomalies carried mutations in *PKP1*, which is not expressed in the cardiac desmosome. Finally, only 8.1% (13) patients with PPK–hair shaft anomalies, due to a recessive mutation in *JUP* (5) or *DSP* (8), were reported with normal cardiac function. Considering their median age at the time of publication (4 years (6 months to 17 years)), late cardiac involvement is not excluded.[16 39–41]

The clinical diagnosis of the third dermatological feature, known as 'skin fragility', might be challenging. The skin fragility spectrum ranges from easy recognisable blisters to superficial linear erosions accompanying scratching. Taking skin fragility into account, three major clinical subtypes might be individualised:

- The PPK–hair shaft anomalies–non-fragile skin subtype, reported in 77% (124/161) of the patients, was always associated with arrhythmogenic cardiomyopathy. Recessive mutations of *JUP*, *DSP* and *DSC2* were found in all but nine patients (7.3%) who carried a heterozygous mutation of *DSP*.
- The PPK–hair shaft anomalies–skin fragility–cardiac involvement subtype is reported in 3.1% (5/161) of the patients or 13.5% (5/37) of the patients with skin fragility. For them, homozygous or compound heterozygous mutations of *DSP* were always identified.
- The PPK–hair shaft anomalies–skin fragility–normal cardiac function subtype, reported in 19.9% (32/161) of the patients, might be divided into patients carrying recessive *PKP1* mutations and patients carrying recessive *JUP* or *DSP* mutations. For the former, considering PKP1 tissue expression, cardiac follow-up is not required. For the latter, additional data are mandatory in order to exclude late cardiac involvement during adulthood.

Two additional severe diseases are associated with desmosomal gene mutations. Lethal epidermolysis bullosa, reported in five patients, associates epidermal detachment to ectodermal dysplasia features. The major concerns are early medical care requiring neonatal intensive care unit and positive diagnosis. Erythroderma seems to be constant in the seven patients with SAM syndrome.

Dominant or recessive mutations of *JUP* or *DSP* were identified in 87% (140) of the 161 patients with PPK–hair shaft anomalies. The ratio reached 98.4% (127/129) in case of cardiac involvement. In this group, the Naxos deletion (c.2157del2, exon 14) accounts for 97.4% (74/76) of the patients with *JUP*. Mutations in the long exons 23 and/or 24 accounted for 83.5% of the patients with *DSP* with PPK–hair shaft anomalies. These three mutation hotspots, accounting for 90.8%, of PPK–hair shaft anomalies with cardiac involvement cases might be sequenced first in this situation. Cardiac involvement occurring during the first 5 years of life suggested recessive *DSP* mutations. In case of normal cardiac function, identification of a recessive *PKP1* mutation leads to stoppage of cardiac monitoring. Identification of a recessive mutation of *JUP* or *DSP* justifies cardiac monitoring throughout life.

Oligodontia and onychodystrophy were reported in at least 24.8% (40/161) of patients with PPK–hair shaft anomalies. With hair shaft anomalies, they represented the major features of ectodermal dysplasias. Unfortunately, nail, tooth and sweating anomalies were not detailed. Additional data might help to refine the phenotype-to-genotype correlation and to classify desmosomal skin disorders in the group of ectodermal dysplasias.

Finally, considering this extensive review of publications on desmosomal diseases, the combination of PPK and hair shaft anomalies justify long-term cardiac monitoring. This monitoring might be stopped in the situation of the identification of *PKP1* gene mutation only.

Contributors SH-R designed the work. LP collected the data. SH-R and LP analysed the data and wrote the manuscript. CB participated in the critical revision of the manuscript for important intellectual content. All the authors agreed with the integrity of any part of the work.

Competing interests None declared.

Provenance and peer review Commissioned; externally peer reviewed.

Data sharing statement All the data we collected were reported in the original article or in the online supplementary data section. We are available to answer any question.

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Table S1: Desmosomal disorders related to *JUP* mutation(s)

Disease	Dermatological symptoms				Cardiac involvement	Mode of inheritance	Mutation	Location	Total of patients	Total of families	Origin
	PPK	Hair	Skin fragility	Others ectodermal features							
Naxos syndrome	+	woolly +/- sparse	-	-	ARVC	recessive	c.2157del2	Exon 14	74	NA	Greek / Turkish [1–5]
CAPK syndrome	+	atrichia	-	-	ARVC	recessive	c.794G>A/ p.R265H	Exon 4	2	1	Turkish [6]
Skin fragility + PPK + Woolly hair	+	woolly + sparse	+	-	no	recessive	c.71C>A/ p.S24X	Exon 2	3	1	Argentine [7]
							c.468G>A	Exon 3	2	1	Kuwaiti [7]
Lethal congenital epidermolysis bullosa	-	alopecia	+	onycholysis	no	recessive	c.1615C>T/ p.Q539X	Exon 9	1	1	German [8]

Sequences variations of *JUP* are referenced in the transcript GENEBANK accession NM_002230.

Table S2: Desmosomal disorders related to *DSP* mutation(s)

Disease	Dermatological symptoms				Cardiac involve-ment	Mode of inheritance	Mutation	Location	Total of patients	Total of families	Origin
	PPK	Hair	Skin fragility	Others ectodermal features							
Striate PPK	+	-	-	-	no	dominant	c.939+1G>A	Intron 7	3	1	NA [9]
							c.C991T/p.Q331X*	Exon 8	27	1	NA [10]
Autosomal dominant Carvajal Syndrome	+	woolly and/or sparse	-	oligodontia	yes	dominant	c.1691C>T/p.T564I	Exon 13	3	2	NA [11,12]
				oligodontia			30bp insertion	Exon 14	2	1	NA [13]
				oligodontia leuconychia			c.1790C>T/p.S597L	Exon 14	3	1	NA [14]
				nail dystrophy			c.1748T>C/p.L583P	Exon 14	1	1	Caucasian [12]
Autosomal recessive Caravajal Syndrome	+	woolly and/or sparse	-	-	yes	recessive	c.7901delG	Exon 24	12	3	Ecuadorian [15]
							c.3799C>T/p.R1267X	Exon 23	1	1	Turkish [16]
							c.6166G>C/p.G2056R	Exon 24	1	1	Danish [17]
							c.3901C>T/p.Q1301X	Exon 23	1	1	Indian [18]
							c.5208_5209delAG/ p.G1737TfsX7	Exon 24	2	1	NA [19]
							c.7780delT /p.S2594PfsX8	Exon 24	1	1	Turkish [20]
							c.7567delAAGA/p.K2523fsX37 c.6577G>A/p.E2193K	Exon 24 Exon 24	1	1	NA [21]

							c.7566_7567delAAinsC/ p.R2522SfsX39 c.7756C>T/ p.R2586X	Exon 24 Exon 24	1	1	NA [22]
							c.1067C>A/ p.T356K c.2131_2132delAG/ p.S711CfsX4	Exon 9 Exon 16	2	1	NA [22]
							c.7123G>C/p.G2375R	Exon 24	9	1	Israeli [23]
							c.3924delG/p. H1309TfsX1348	Exon 23	1	1	Palestinian [24]
							c.7111C>A, Q2371K	Exon 24	5	1	Palestinian [24]
Carvajal and skin fragility syndrome	+	woolly and/or sparse	+	-	yes	recessive	c.4336C>T/p.Q1446X c.2017C>T/p.Q673X	Exon 23 Exon 15	1	1	UK [25]
				nail dystrophy			c.4778_4790del13/p. L1593KfsX5 c.6310delA/p.T2104QfsX12	Exon 23 Exon 24	1	1	Swedish [26]
				nail dystrophy			c.4198C>T/R1400X c.6850C>T/R2284X	Exon 23 Exon 24	1	1	Dominican [27]
				teeth abnormalities nail dystrophy			c.6310delA/ p.T2104QfsX12 c.7964C>A/ p.A2655D	Exon 24 Exon 24	1	1	Finnish [28]
				nail dystrophy			c.2516del4/p.H839fsX23 c.3971del4/p.N1324f	Exon 18 Exon 23	1	1	Brazilian [29]

							sX23				
Skin fragility and woolly hair syndrome	+	woolly and/or sparse	+	nail dystrophy	no	recessive	c.2427T>A/p.C809X c.861G>T/p.N287K	Exon17 Exon 7	1	1	NA [30]
							c.1990C>T/p.Q664X c.7096C>T/p.R2366C	Exon 15 Exon 24	1	1	NA [30]
							c.7097G>A/ p.R2366H	Exon 24	5	1	Saudi Arabian [31]
							c.7096C>T/p.R2366C c.6721_6722delAT/p.I2241FfsX3	Exon 24 Exon 24	1	1	Caucasian [32]
Lethal acantholytic epidermolysis bullosa		alope -cia	+	anonychia	poor cardiac contracti -lity in one patient	recessive	c.5800C>T/p.R1934X ** c.6370delTT	Exon 24 Exon 24	1	1	Dutch [33]
							c.2874del5/p.L959MfsX5	Exon-In -tron 20	2	1	Yemeni [34]
							c.7248delT/p.F2416LfsX14	Exon 24	1	1	NA [35]

Sequences variations of *DSP* are referenced in the transcript GENEBANK accession NM_004415.
c.C991T/p.Q331X* : this mutation was published as c.C1323T/p.Q331X. The correspondence between c.C1323T and p.Q331X was not found in ENSEMBL software. Therefore, we renamed it with this new combination.
c.5800C>T/p.R1934X** : This mutation was published as c.C6079T/p.R1934X . The correspondence between c.C6079T and p.R1934T was not found in ENSEMBL software. Therefore, we renamed it with this new combination.

Table S3: McGrath Syndrome, *PKP1* identified mutations

Disease	Mode of inheritance	Mutation	Location	Total of patients	Origin
: Ectodermal Dysplasia/Skin fragility syndrome : - PPK - Skin fragility - Perioral lesions (at least 11 patients) - Sparse hair - Nail dystrophy - No cardiac involvement	recessive	c.203-1G>A c.213T>G/p.Y71X	Intron 1 Exon 2	1	Caucasian [36]
		c.203-1G>A	Intron 1	3	Arab [37]
		c.203-1G>T	Intron 1	2	Egyptian [38]
		c.847-2A>G	Intron 4	1	Arab [37]
		c.888delC	Exon 5	2	Turkish [39]
		c.897del5/p.P299fsX61	Exon 5	1	Iraqi [40]
		c.910C>T/p.Q304X c.1132ins28/PTC	Exon 5 Exon 6	1	British [41]
		c.1054+1G>T c.1835-2A>G	Intron 5 Intron 10	1	Chinese [42]
		c.1233+2A>T	Intron 6	1	French [43]
		c.1233-2A>G/p.R411SfsX51	Intron 6	1	Caucasian [44]
		IVS9+1G>A	Intron 9	1	Dutch [45]
		c.2014C>T / p.R672X	Exon 11	3	Brazilian [29]
		c.2021+1G>A	Intron 11	1	Japanese [46]

Sequences variations of *PKP1* are referenced in the transcript GENEBANK accession NM_001005337.

Table S4: Desmosomal disorders related to *DSG1* and *DSG4* mutation(s)

Disease	Gene	Mode of inheritance	Mutation	Location	Total of patients	Origin
Isolated PPK	***Desmoglein 1***	dominant	IVS2-1G>A	Intron 2	6	Dutch [47]
			c.76C>T/p.R26X	Exon 2	11	Yemenite/pakistani [48–50]
			c.121insT/PTC	Exon 3	3	Libyan [51]
			IVS4-2A>G	Intron 4	11	Pakistani [50]
			c.395C>A/p.S132X	Exon 5	3	Iranian-Syrian [52]
			c.430A>T/p.R144X	Exon 5	4	Scottish [53]
			c.515C>T	Exon 5	10	Pakistani [50]
			c.C602T/p.Q201X	Exon 5	5	Jewish Sephardic [54]
			c.C655T/p.R219X	Exon 5	3	Jewish Ashkenazi [54]
			c.1079insC/PTC	Exon 9	1	NA [48]
			c.1095T>A/p.Y365X	Exon 9	1	NA [48]
			c.1189delA/PTC	Exon 9	1	NA [48]
			IVS9-3C>G	Intron 9	10	Pakistani [50]
			c.1399delA	Exon 10	3	Pakistani [50]
			c.1627delA/PTC	Exon 11	1	NA [48]
			c.1668-1G>T	Intron 11	11	Pakistani [55]

			c.1931delA /PTC	Exon 14	2	Jewish Ashkenazi [54]
SAM Syndrome : - Severe **S**kin dermatitis, - multiple **A**llergies - **M**etabolic wasting	*Desmoglein 1*	recessive	c.49-1G>A, in-frame skipping of exon 2	Exon 2	2	Arab [56]
			c.1861delG/ p.A612Qfs.X3	Exon 13	4	Arab [56]
			c.2659C>T/p.R887X	Exon 15	1	NA [57]
Localized Autosomal recessive Hypotrichosis (LAH Syndrome)	*Desmoglein 4*	recessive	c.Ex5_8del	Exon 5 to 8	34	Pakistani [58–60]
			c.GG384-385TT/p.A129S	Exon 5	1	Iraqi [61]
			c.87delG/PTC	Exon 3	6	Pakistani [62]
Monilethrix	*Desmoglein 4*	recessive	c.574T>C/p.S192P c.2039insT/PTC	Exon 6 Exon 13	1	Japanese [63]
			c.799C>G/ P267R	Exon 7	9	Iraqi [64]
			p.P267R p.R289X	Exon 7 Exon 8	3	Iraqi / Maroccan [64]
			c.216+1G>T p.P267R	Intron 3 Exon 7	6	Iraqi and Iranian [64,65]
			c.763delT c.216+1G>T	Exon 7 Intron 3	2	Iranian [64]
			p.P267R c.763delT	Exon 7 Exon 7	2	Iraqi and Iranian [64]

	c.624delG/p.M208lfsX4 c.2468G>A/ p.W823X	Exon 6 Exon 16	1	Japanese [66]
	c.2119delG/p.R707IfsX109	Exon 14	1	Japanese [67]

Sequences variations of *DSG1 and DSG4* are referenced in the transcript GENEBANK accession NM_001942 and NM_ 177986 respectively.

Table S5: Desmosomal genodermatoses induced by *DSC2* and *DSC3* mutation(s)

Disease	Gene	Mode of inheritance	Mutation	Location	Total of patients	Origin
- Woolly hair - Mild PPK - Left cardiac involvement	*Desmocollin 2*	recessive	c.1841delG/ p.S614fsX625	Exon 12	2	NA [68]
Hypotrichosis	*Desmocollin 3*	recessive	c.2129T>G/p.L710X	Exon 14	4	Afghan [69]

Sequences variations of *DSC2 and DSC3* are referenced in the transcript GENEBANK accession NM_024422 and NM_001941, respectively.

Table S6: Desmosomal disorders related to *CDSN* mutation(s)

Disease	Mode of inheritance	Mutation	Location	Total of patients	Total of families	Origin
Hypotrichosis Simplex of the Scalp (HSS)	dominant	p.Q215X	Exon 2	26 (Israeli family) + 17 (spanish family)	2	Spanish and Israeli [70]
		p.Q200X	Exon 2	US	1	Danish [70]
		p.Y239X*	Exon 2	42	1	Mexican [71]
		c.717C>G/p.Y239X*	Exon 2	3	1	Chinese [72]
Peeling Skin Syndrome type B (PSS)	recessive	c.164_167dup GCCT/ p.T57PfsX6	Exon 2	1	1	Ashkenazi Jewish [73]
		c.175A>T/p.K59X	Exon 2	4	1	German [74]
		c.424G>T/p.G142X	Exon 2	2	1	NA [75]
		c.746delG/ p.G249VfsX40	Exon 2	2	1	NA[76]
		A genomic deletion at the PSORS1 locus removing the entire *CDSN* gene		1	1	Japanese [77]
		A large homozygous deletion of 59,184bp extending from 40.6 kb upstream to 13.2 kb downstream of *CDSN*		1	1	Japanese [78]

Sequences variations of *CDSN* are referenced in the transcript GENEBANK accession NM_001264.
* These two mutations seem to be the similar.

Legend of the 6 supplemental tables :

- = absent, + = present, NA = Not Available, ARVC = Arrhythmogenic Right Ventricular Cardiomyopathy, *CDSN* = Corneodesmosin gene, *DSC2* = Desmocollin 2 gene, *DSC3* = Desmocollin 3 gene, *DSG1* = Desmoglein 1 gene, *DSG4* = Desmoglein 4 gene, *DSP* = Desmoplakin gene, *JUP* = Plakoglobin gene, *PKP1* = Plakophillin 1 gene, PPK = Palmoplantar Keratoderma, PTC = Premature Termination Codon

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