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Dermatological manifestations in cardiofaciocutaneous syndrome: a prospective multicentric study of 45 mutation-positive patients*

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Summary

Background Data on dermatological manifestations of cardiofaciocutaneous syndrome (CFCS) remain heterogeneous and almost without expert dermatological classification.
Objectives To describe the dermatological manifestations of CFCS; to compare them with the literature findings; to assess those discriminating CFCS from other RASopathies, including Noonan syndrome (NS) and Costello syndrome (CS); and to test for dermatological phenotype–genotype correlations.
Methods We performed a 4-year, large, prospective, multicentric, collaborative dermatological and genetic study.
Results Forty-five patients were enrolled. Hair abnormalities were ubiquitous, including scarcity or absence of eyebrows and wavy or curly hair in 73% and 69% of patients, respectively. Keratosis pilaris (KP), ulerythema ophryogenes (UO), palmoplantar hyperkeratosis (PPHK) and multiple melanocytic naevi (MMN; over 50 naevi) were noted in 82%, 44%, 27% and 29% of patients, respectively. Scarcity or absence of eyebrows, association of UO and PPHK, diffuse KP and MMN best differentiated CFCS from NS and CS. Oral acitretin may be highly beneficial for therapeutic management of PPHK, whereas treatment of UO by topical sirolimus 1% failed. No significant dermatological phenotype–genotype correlation was determined.

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Conclusions A thorough knowledge of CFCS skin manifestations would help in making a positive diagnosis and differentiating CFCS from CS and NS.

What's already known about this topic?

- Data on dermatological manifestations of cardiofaciocutaneous syndrome (CFCS) remain heterogeneous and almost without expert dermatological input.
- Dermatological findings remain essential to diagnose CFCS and to differentiate it from other RASopathies that it resembles phenotypically, specifically Noonan syndrome (NS) and Costello syndrome (CS).

What does this study add?

- Scarcity or absence of eyebrows, association of ulerythema ophryogenes and palmoplantar keratoderma, diffuse keratosis pilaris and multiple melanocytic naevi appeared pertinent manifestations in assisting the positive diagnosis of CFCS and differentiating it from CS and NS.
- Oral acitretin could be highly beneficial for therapeutic management of PPHK.
- No significant dermatological phenotype–genotype correlation in the presence or absence of *BRAF* mutation could be determined.

Cardiofaciocutaneous syndrome (CFCS) is a RASopathy, a type of human genetic syndrome. It is caused by germline activating mutations in genes of the Ras–mitogen-activated protein kinase (MAPK) pathway: *BRAF*, *MAP2K1*, *MAP2K2* and *KRAS*.[1,2] Since their discovery,[3,4] which helped to define better the CFCS phenotype among the RASopathies, the overview data on dermatological manifestations (Table S1; see Supporting Information) have remained heterogeneous, with several limitations. These include: (i) data compilation of case reports,[2,5,6] (ii) data collection based on surveys[7] and (iii) almost complete absence of dermatological expertise.[3,8–15]

In this French multicentric and prospective collaborative dermatological, paediatric and genetic study, we prospectively defined the dermatological manifestations of mutation-proven CFCS in children and adults and compared them with the findings in the literature. Our secondary objectives were to assess the key signs that discriminate CFCS from other RASopathies, including Noonan syndrome (NS) and Costello syndrome (CS), and to test for a dermatological phenotype–genotype correlation based on the presence of *BRAF* mutation.

Patients and methods

We prospectively enrolled children and adults (age > 18 years) with CFCS seen in French departments of medical genetics, dermatology and paediatric dermatology [i.e. Bordeaux, Marseille, Montpellier, Nancy, Nice, Paris (Necker Hospital and Robert-Debré Hospital), Rennes, Saint-Pierre (South Reunion) and Toulouse] between March 2013 and December 2017 and at two workshops organized by the French Costello and CFC Association in 2015 and 2017 in Bordeaux.

This work was approved by the clinical research department of the university hospital of the principal investigators (D.B., C.P. and D.G.), the Consultative Committee for the Processing of Health Research Data (CCTIRS; 12.750) and the National Commission on Informatics and Liberty (CNIL; 913041). Consent was obtained from all individuals.

Inclusion and evaluation criteria

Eligible patients were consecutively included if they had a clinically confirmed diagnosis of CFCS evaluated by clinical geneticists and the presence of a pathogenic mutation in *BRAF*, *MAP2K1*, *MAP2K2* or *KRAS*. For each patient, demographic information, medical history and dermatological manifestations were documented prospectively on a standardized pro forma.

The data were collected during consultation with an experienced dermatologist and then classified following an exhaustive literature review: (i) melanocytic naevi (MN) > 2 mm in diameter, in order to avoid confusion with freckles or lentigines, with appraisal of the number of naevi and palmar and/or plantar locations; (ii) hair abnormalities including temporal alopecia, scarcity of global scalp hair (excluding isolated temporal alopecia), wavy or curly hair considered pathological only when absent among first-degree relatives, and scarcity or absence of eyebrows and eyelashes; (iii) keratinization disorders including keratosis pilaris (KP) with appraisal of location (face, upper and lower limbs, generalized), ulerythema ophryogenes (UO) defined by chronic keratotic follicular papules with perifollicular erythema, associated with scarring and/or atrophy and/or alopecia, palmar and/or plantar hyperkeratosis (PPHK), acanthosis nigricans, ichthyosis and papillomas (small wart-like lesions); (iv) pigmentary disorders including café-au-lait macules, hypochromic macules and multiple lentigines (> 100); (v) connective tissue disorders including hyperelastic skin and acral excess skin; (vi)

lymphoedema; (vii) nail abnormalities including dystrophy and slow-growing nails; (viii) hyperhidrosis, whatever the location; and (ix) other unclassifiable cutaneous manifestations including easy bruising, history of infantile haemangioma and history of atopic dermatitis, all determined by questioning the parents and examining the child's health record.

After obtaining patient and/or parental agreement, nonstandardized photographs of the dermatological lesions were taken during the visit and reviewed by the principal investigators.

Gene screening

Genomic DNA was obtained from peripheral leucocytes using standard procedures. Genotyping was performed by bidirectional Sanger sequencing of exons and their flanking intron–exon boundaries, as previously described.[10] Direct sequencing of polymerase chain reaction products was performed using the Big Dye Terminator Cycle Sequencing Ready Reaction Kit (ABI, Foster City, CA, U.S.A.). Reaction products were run on an automated capillary sequencer (ABI 3130 Genetic Analyzer, ABI). Sequences were aligned using Seqscape® analysis software (ABI) and compared with reference sequences for genomic DNA and mRNA. Mutations were named according to the National Center for Biotechnology Information reference transcript sequence with the following GenBank accession numbers: *BRAF* NM_004333, *MAP2K1* NM_002755, *MAP2K2* NM_030662 and *KRAS* NM_033360 (isoform a) or NM_004985 (isoform b). A previous report of single-nucleotide variants was verified by consulting the Ensembl genome browser (https://www.ensembl.org). The pathogenicity of amino acid variants was interpreted according to the international expert consensus previously reported.[16]

Statistics

Statistical analysis was done using SAS version 7.13 (SAS Inc., Cary, NC, U.S.A.) and R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria). The characteristics of patients with CFCS with positive *BRAF* mutations and negative *BRAF* mutations were compared using the χ^2-test or Fisher's exact for categorical variables and Student's t-test or the Wilcoxon Mann–Whitney test for continuous variables. The results were adjusted with the Benjamini–Hochberg procedure and P-values ≤ 0.05 were considered significant.

Results

Forty-seven patients were recruited, although two patients with clinically diagnosed CFCS but no identified pathogenic mutation of causative genes were excluded. Three patients were described previously.[17] Pertinent characteristics of the 45 patients are summarized in Table 1 (further details in Tables S2 and S3; see Supporting Information). The patients were all white, mostly male (56%) and had a median age at consultation of 8 years

Table 1 Baseline characteristics and dermatological manifestations of the 45 mutation-positive patients and clinical characteristics associated with presence of *BRAF* mutation (univariate analysis)

	Total	*BRAF* mutation	*MAP2K1* or *MAP2K2* mutation	P-value[a]	Corrected P-value[b]
Baseline characteristics					
Sex ratio (n female, male)	0.8 (20, 25)	0.52 (12, 23)	4 (8, 2)	0.01	0.49
Age at consultation (years), median (range)	8 (2–24)	8 (2–24)	6.5 (2–19)	–	
Mutated gene					
BRAF	78 (35/45)	–	–	–	
MAP2K1	16 (7/45)	–	–	–	
MAP2K2	7 (3/45)	–	–	–	
Dermatological manifestations					
Melanocytic naevi (> 10)	93 (42/45)	91 (32/35)	100 (10/10)	1.0	1.0
Hair abnormalities	89 (40/45)	97 (34/35)	60 (6/10)	0.006	0.17
Keratinization disorders	84 (38/45)	83 (29/35)	90 (9/10)	1	1.0
Pigmentary disorders	36 (16/45)	43 (15/35)	10 (1/10)	0.071	0.49
Connective tissue disorders	36 (16/45)	40 (14/35)	20 (2/10)	0.29	0.60
Hyperhidrosis	34 (15/44)[d]	35 (12/34)	30 (3/10)	1.0	1.0
Nail abnormalities[c]	24 (11/45)	26 (9/35)	20 (2/10)	1.0	1.0
Lymphoedema	7 (3/45)	3 (1/35)	20 (2/10)	0.12	0.49
Other cutaneous manifestations					
Easy bruising	13 (6/45)	17 (6/35)	0 (0/10)	0.16[e]	0.49
Infantile haemangioma (history of)	13 (6/45)	17 (6/35)	0 (0/10)	0.16[e]	0.49
Atopic dermatitis (history of)	7 (3/45)	6 (2/35)	10 (1/10)	0.54	0.92
Xanthogranuloma	2 (1/45)	–	–	–	

Values are the percentage (n/N) unless stated otherwise. [a]Fisher's exact test was used to compare categorical variables. [b]Benjamini and Hochberg correction for multiple testing. [c]Nail dystrophy in 18% (eight of 45, mostly koilonychia) and slow nail growth in 11% (five of 45). [d]For one patient, data were not available. [e]The χ^2-test was used to compare categorical variables.

(range 2–24). Mutations in *BRAF*, *MAP2K1* and *MAP2K2* were identified in 78%, 16% and 7% of patients, respectively.

Hair abnormalities

Scarcity or absence of eyebrows and wavy or curly hair (Fig. 1a) were present in 73% and 69% of patients, respectively. Temporal alopecia, scarcity of global scalp hair and scarcity of eyelashes occurred respectively in 59%, 49% and 47%. The parents or patients reported slow-growing scalp hair, frequently not requiring haircuts, in 58% (data not shown).

Keratinization disorders

KP was present in 82% of patients and was located on the face, arms or legs or was generalized (Fig. 1b) in 73%, 67%, 60% and 24% of patients, respectively. UO was observed in 44%, with eyebrow, cheek and helix involvement. Two girls, 7 and 11 years old, complained of severe aesthetic discomfort linked to alopecia and redness of the eyebrows. A trial treatment with topical sirolimus 1% cream (for preparation details, see Malissen *et al.*)[18] twice daily to the eyebrow area was proposed, with assessment every 3 months for 1 year. Progressive mild regrowth of vellus hair (two cases) with rare sparse terminal hair (one case) was noted after 6 months of treatment, while erythema and follicular papules remained unchanged (Fig. 2). No further benefit was observed after an additional 6 months. No serious adverse events related to topical sirolimus were observed.

PPHK was present in 27% of patients. Bilateral and symmetrical plantar involvement was constant, characterized by painful, thick, yellow-to-orange, patchy keratotic plaques prominent in pressure areas. Due to functional limitations in walking and based on our past experience in using retinoids for the treatment of hereditary PPHK, two female patients, 11 and 19 years old, were treated with oral acitretin 0.3–0.4 mg kg^{-1} per day. Marked reduction in the thickness and pain of the plantar callosities was observed after 6 months of treatment (Fig. 3a, b), with routine care reduced to daily application of emollient. Good long-term clinical and biological tolerance was noted, including regular blood haematological, hepatic and lipid monitoring.

Melanocytic naevi

Multiple melanocytic naevi (MMN), defined as > 50 MN, were noted in 29% of patients, with a median age at consultation of 14 years (range 7–23). By age group, MMN were

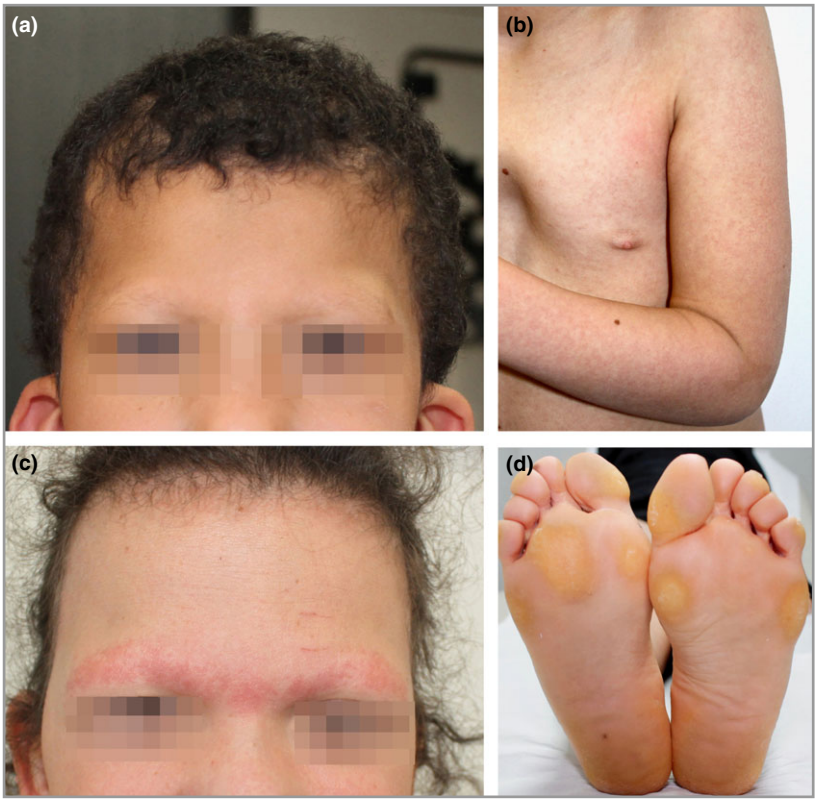

Fig 1. Cardiofaciocutaneous syndrome and characteristic dermatological abnormalities. (a) Curly hair, temporal alopecia and scarcity of eyebrows in an 8-year-old boy with *BRAF* mutation. (b) Diffuse keratosis pilaris of the upper limb and chest of a 7-year-old girl with *BRAF* mutation. (c) Ulerythema ophryogenes in an 11-year-old girl with *BRAF* mutation: multiple pinpoint translucent follicular papules overlying a horizontal band of erythema of the brow line and the root of the nose with absence of eyebrows. Slight involvement of the frontal scalp hairline is also present. (d) The same patient as (c): patchy yellow–orange keratotic plaques prominent in areas of pressure.

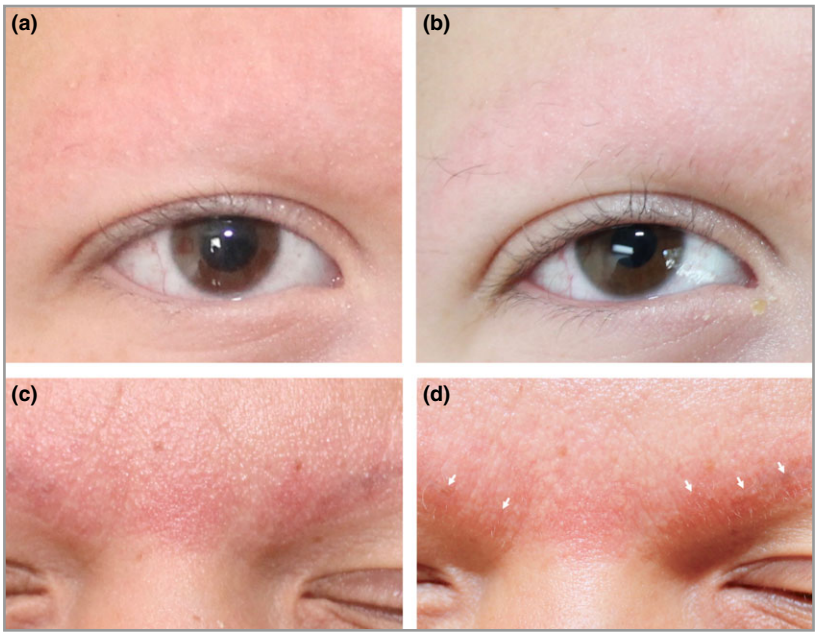

Fig 2. Relative failure of topical sirolimus 1% to treat ulerythema ophryogenes. (a) Initial condition of a 7-year-old girl with *BRAF* mutation and (c) an 11-year-old girl with *BRAF* mutation. (b, d) After 6 months of topical sirolimus 1% cream applied twice daily, slight growth in vellus hair with rare sparse terminal hair was noted, whereas erythema and follicular papules remained unchanged.

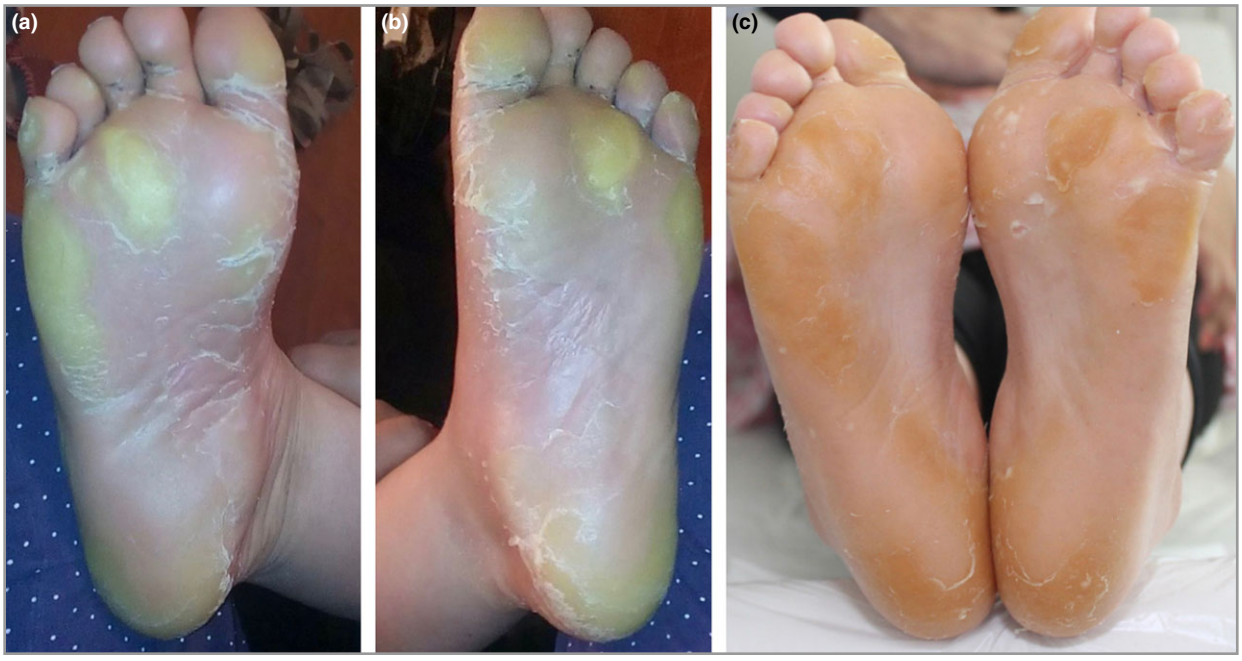

Fig 3. Successful treatment of plantar keratoderma by oral acitretin. (a, b) Initial lesions with thick and yellow patchy plaques associated with fissures, prominent in areas of pressure in a 19-year-old woman with *BRAF* mutation. (c) After 6 months of oral acitretin at a dosage of about 0.4 mg kg^{-1} per day, marked regression of thickness of plantar callosities.

observed in 7% of children (0–9 years), 67% of adolescents (10–17 years) and 60% of adults. MN were distributed over the entire body (Fig. 4a), without predilection for photoexposed areas (data not shown). Palmar and/or plantar MN (PPMN) were noted in 44% of patients, with multiple MN in 65% and a mean of 3.6 PPMN (range 1–10) per patient (Fig. 4b, c). MN were mostly acquired, common, pigmented and smaller than 6 mm and had the same clinical pattern in each patient. No family history of MMN or melanoma was identified.

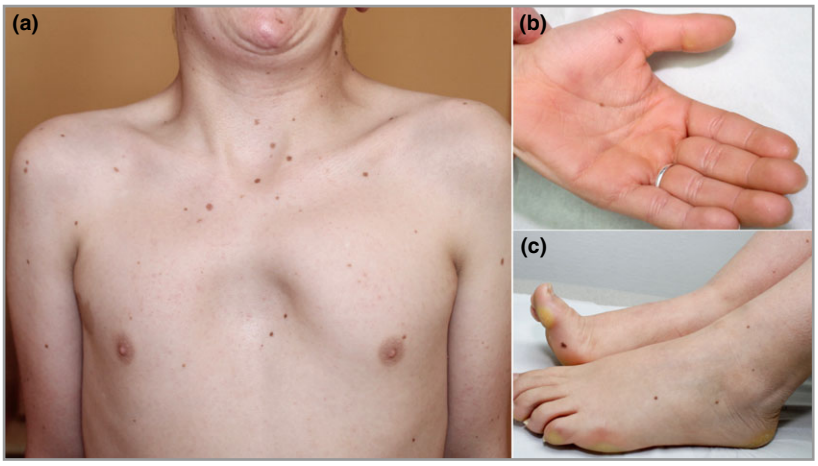

Fig 4. Cardiofaciocutaneous syndrome and melanocytic naevi. (a) Multiple melanocytic naevi widely distributed on the chest of a 14-year-old boy with *BRAF* mutation. (b, c). Acral melanocytic naevi present on the palmar area of a 16-year-old girl with *BRAF* mutation and on the feet of an 11-year-old girl with *BRAF* mutation.

Additional cutaneous features

All relevant data regarding other cutaneous features are summarized in Table 1 and Table S3 (see Supporting Information).

Dermatological phenotype–genotype correlation

The pertinent characteristics of the patients with and without *BRAF* mutations are shown in Table 1 and Table S3 (see Supporting Information). Patients with *BRAF* mutations had significantly more hair abnormalities than those with *MAP2K1* or *MAP2K2* mutations (97% vs. 60%, $P < 0.006$) in univariate analysis, but no individual type of hair abnormality was significantly discriminating.

Discussion

The epidemiological characteristics of CFCS, including balanced sex ratio, predominance of *BRAF* mutation and almost constant presence of dermatological manifestations, were broadly similar to those described in previous series.[3,7–15]

We found a lower frequency of hair abnormalities (89%) than the 100% in previous studies,[3,5,11,15] possibly because we did not take into account subjective assessments like 'thin', 'brittle' or 'dry' hair[5,11,15] or wavy or curly hair when it was seen in familial first-degree relatives. Scarcity or absence of eyebrows and wavy or curly hair were the most common hair abnormalities, present respectively in 73% and 69% of patients, which are within the ranges of 53–100% and 59–96% reported in previous studies.[2,5–11,13,15] Wavy or curly hair is also common in CS and NS with *SOS1* or *SOS2* mutations, with frequencies respectively ranging from 82% to 96%[17,19] and 69% to 80%.[20–22]

Given the potentially significant changes in hair characteristics in later childhood and adolescence in RASopathies,[23,24] wavy or curly hair discriminates poorly between CFCS, CS and NS. Likewise, scarcity or absence of eyebrows is reported in NS with *SOS1* and *SOS2* mutations with frequencies ranging from 77% to 83%,[20–22] and therefore does not appear to discriminate between CFCS and NS. Yet scarcity or absence of eyebrows was reported in about 9% of patients with CS,[17,19] with thick eyebrows being considered a common feature,[19] and it may therefore be useful in distinguishing CFCS from CS.

PPHK and UO are classic manifestations of CFCS[1,6] and could be helpful in discriminating it from other RASopathies. PPHK is unusual in all genotypic forms of NS[23–27] and is present in 45–76% of patients with CS,[17,19] whereas UO is common in *SOS1*- or *SOS2*-mutated NS, with frequencies ranging from 33% to 67%,[20–22] and has not been reported to date in CS.[17,19] Thus, in the context of RASopathies, the UO–PPHK association may be highly indicative of clinical CFCS diagnosis and relevant in distinguishing it from CS or NS. This association was present in 20% of our patients, but in only 11% of the children. It is therefore of limited value for diagnosis in childhood, a period when the challenge of clinical diagnosis of RASopathies is most arduous.[28–30]

We observed KP in 82% of patients, an overall higher frequency than the 11–73% range observed in genetic studies of CFCS,[2,6–8,11–13,15] but close to that of a large paediatric dermatological study.[9] Mild-to-moderate KP is not unusual in children and adolescents in the general population (2–26%),[31–34] those with CS (9–33%)[17,19] and those with *SOS1*-mutated NS (up to 50%).[29] However, generalized KP involvement, present in about one-quarter of our cases of CFCS, is usually not mentioned in large series of patients with CS[17,19,35] or NS[23–27] and therefore could provide a valuable clinical orientation sign for CFCS.

The rate of UO was significantly lower than in the main dermatological study, 44% vs. 90%,[9] a difference possibly due to our restrictive definition of UO and our data collection

method based on systematic clinical examination. UO treatment remains a challenge[35–37] and no treatment for eyebrow alopecia has been reported to date. The therapeutic rationales for using topical sirolimus, an inhibitor of the phosphatidylinositol-3-kinase–mammalian target of rapamycin (mTOR) pathway in UO, are the role of the mTOR pathway in reducing keratinocyte proliferation[38,39] and regulating the hair cycle,[40] its anti-inflammatory properties[41] and its cross-talk with the Ras–extracellular signal-regulated kinase–MAPK pathway.[42] In our study, the lack of substantial improvement in the redness and keratotic components of UO suggests that topical sirolimus 1% is not useful for this indication.

We found PPHK in 27% of patients, which is consistent with the published range of 13–36%.[2,6,9–11,15] Severe forms of plantar hyperkeratosis can lead to functional limitations in walking, and topical treatment can be particularly time consuming and only modestly effective. Although oral treatment with retinoids has been effective in some forms of hereditary PPHK[43] and in one case of CS-associated PPHK,[44] this is the first report to our knowledge of the use of acitretin for treating CFCS-associated PPHK. After 6 months of oral acitretin treatment, marked regression of pain and hyperkeratosis was obtained. Although few patients were treated, these results suggest that oral acitretin may be a useful and well-tolerated treatment for the PPHK of CFCS.

Our results highlight the relatively high frequency of MMN in CFCS, 29% whatever the age, in agreement with the only other study on this association.[9] This risk appeared to increase with age, particularly in adolescence, but not in adulthood, although definitive conclusions are limited by the young age and the low number of adult patients in our cohort. Although a strict comparison with the prevalence of MN in the general population is difficult due our data collection method, the percentage of patients with CFCS with MN was higher than expected in the general population of children. For example, in a population of 369 children in Catalonia, Spain, the median numbers of MN (≥ 2 mm) in children 4, 8 and 14 years old were 1, 5 and 10, respectively.[45] Likewise, in a study of 3127 Italian schoolchildren 13–14 years old, the median MN count (≥ 2 mm) was 11.[46] In our subgroup of children under 14 years, 59% and 21% had MN counts greater than 10 and 50, respectively. The percentage of patients with CFCS with MMN also appeared significantly higher than in patients with CS, as the latter frequency was evaluated at 4.3%[19] to 9%.[17]

No definite conclusion for NS can be drawn, as MMN in *RAF1*-mutated NS is reported in up to 35% of patients,[47] being more rare in *PTPN11*-mutated NS,[26] but without a precise definition of 'multiple'. We found palmar and/or plantar locations of MN in 44% of patients, a higher frequency than reported in the general population, including 19.5% of 221 healthy British patients aged 6 months to 19 years[48] and 19.4% of 180 children from Barcelona, Spain, aged 1–15 years.[49] Furthermore, multiple (more than two) palmar and/or plantar locations were noted in 65% of patients, markedly higher than the estimated 25% observed in a series of 195 healthy British participants.[48]

In this study, we detailed a wide range of dermatological findings after systematic examination. Some have been little studied and did not appear to be incidental. For example, hyperhidrosis and lymphoedema showed higher frequencies in our cohort than in children and adolescents in the general population, respectively 34% vs. 2%[50] and 7% vs. 0.001%.[51] These findings illustrate the overlap spectrum of cutaneous manifestations of RASopathies: hyperhidrosis is almost constant in CS[17] and lymphoedema is common in NS, affecting 20% of patients.[52] Other manifestations, including café-au-lait macules, history of infantile haemangioma or atopic dermatitis, nail dystrophy (mostly koilonychia) and ichthyosis, show an overall prevalence close to that observed in healthy children[17,19,31–33,53,54] and thus have very limited practical relevance for diagnosing CFCS.

Detailed data on the dermatological phenotype–genotype correlation in patients with CFCS are sparse,[8–13] and few studies have observed significant differences in skin manifestations according to *BRAF*, *MAP2K1*, *MAP2K2* or *KRAS* mutation.[8,10–12] *MAP2K1* and *MAP2K2* mutations appeared to be associated with a lower risk of curly and/or sparse hair,[13,55] while data for KP[9,13,55] and naevi[9,55] were contradictory. In our cohort, we found a trend for the association of lower risk of hair abnormalities in the subgroup of patients with *MAP2K1* or *MAP2K2* mutation vs. *BRAF* mutation, but no link to a specific abnormality including shape, growth or density of scalp hair.

The limitations of our study, especially the low number of patients, are due to the rarity of CFCS. The cohort may have been too small to allow definitive conclusions on phenotype–genotype correlations. Also, no patients with *KRAS* mutation were included, with this mutation being reported in < 1% of cases of CFCS.

In conclusion, scarcity or absence of eyebrows, association of UO and PPHK, diffuse KP and MMP appear to be pertinent manifestations in positively diagnosing CFCS and differentiating it from CS and NS. Oral acitretin may be highly beneficial for therapeutic management of PPHK. No significant dermatological phenotype–genotype correlation in the presence or absence of *BRAF* mutation could be determined.

Acknowledgments

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1 Epidemiological characteristics and frequency of dermatological manifestations in cardiofaciocutaneous syndrome reported in previous studies (> 10 patients).

Table S2 Details of the characteristics of the 45 patients with cardiofaciocutaneous syndrome.

Table S3 Baseline characteristics and dermatological manifestations of the 45 mutation-positive patients and clinical characteristics associated with the presence of *BRAF* mutation (univariate analysis).