Jaffe–Campanacci syndrome, revisited: detailed clinical and molecular analyses determine whether patients have neurofibromatosis type 1, coincidental manifestations, or a distinct disorder

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Purpose: “Jaffe–Campanacci syndrome” describes the complex of multiple nonossifying fibromas of the long bones, mandibular giant cell lesions, and café-au-lait macules in individuals without neurofibromas. We sought to determine whether Jaffe–Campanacci syndrome is a distinct genetic entity or a variant of neurofibromatosis type 1.

Methods: We performed germline *NF1*, *SPRED1*, and *GNAS1* (exon 8) mutation testing on patients with Jaffe–Campanacci syndrome or Jaffe–Campanacci syndrome–related features. We also performed somatic *NF1* mutation testing on nonossifying fibromas and giant cell lesions.

Results: Pathogenic germline *NF1* mutations were identified in 13 of 14 patients with multiple café-au-lait macules and multiple nonossifying fibromas or giant cell lesions (“classical” Jaffe–Campanacci syndrome); all 13 also fulfilled the National Institutes of Health

diagnostic criteria for neurofibromatosis type 1. Somatic *NF1* mutations were detected in two giant cell lesions but not in two nonossifying fibromas. No *SPRED1* or *GNAS1* (exon 8) mutations were detected in the seven *NF1*-negative patients with Jaffe–Campanacci syndrome, nonossifying fibromas, or giant cell lesions.

Conclusion: In this study, the majority of patients with café-au-lait macules and nonossifying fibromas or giant cell lesions harbored a pathogenic germline *NF1* mutation, suggesting that many Jaffe–Campanacci syndrome cases may actually have neurofibromatosis type 1. We provide the first proof of specific somatic second-hit mutations affecting *NF1* in two giant cell lesions from two unrelated patients, establishing these as neurofibromatosis type 1–associated tumors.

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Key Words: café-au-lait macule; giant cell lesion; Jaffe–Campanacci syndrome; neurofibromatosis type 1; nonossifying fibroma

INTRODUCTION

The term “Jaffe–Campanacci syndrome” (JCS) was coined in 1982 to describe the complex of multiple nonossifying fibromas (NOFs) of the long bones, giant cell granulomas of the jaw, and café-au-lait macules (CALMs) in individuals without neurofibromas; additional variable features included intellectual

disability, precocious puberty, congenital blindness, and kyphoscoliosis.^{1–3} The possibility that JCS is a form of neurofibromatosis type 1 (NF1), an autosomal-dominant disorder with CALMs and deregulated tissue growth, has been suggested⁴ but never resolved. Nonossifying fibromas are common benign bone lesions typically observed in the second decade of life and

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are predominantly found in the lower extremities. Most are asymptomatic and regress spontaneously. Giant cell granulomas of the jaw are benign bone lesions observed in the second and third decade of life and are predominantly located in the mandible. They are not inflammatory in nature and are more appropriately termed aggressive (or nonaggressive) “giant cell lesions” based on established clinical and radiographic criteria.^{5,6} The lesions are most commonly solitary but may be multiple.⁷ Only 18 cases of JCS have been published in the English literature, including four cases in which an initial diagnosis of NF1 was overturned in favor of JCS (see **Supplementary Table S1** online). Multiple bilateral NOFs of the long bones are a consistent feature in JCS, whereas CALMs have been present in most, but not all, reported individuals. Relatively few jaw lesions have been identified. Extraskelatal abnormalities, when present, are not consistent. Reports of JCS have appeared primarily in the orthopedic, radiology, and pathology literature. In most reports of JCS, a diagnosis of NF1 has been considered but was usually dismissed because of the absence of neurofibromas, a hallmark of NF1. However, 16 out of 18 individuals reported with JCS were younger than 18 years of age, and hence, they may not yet have developed neurofibromas (see **Supplementary Table S1** online), which typically appear in early adolescence. It is not uncommon to see adolescents and young adults harboring a known germline *NF1* mutation without any neurofibromas.⁸ There has even been one specific in-frame deletion found (c.2970_2972delAAT) that is associated with a milder phenotype lacking dermal neurofibromas.⁹ Many of the JCS accounts lack documentation of slit-lamp (Lisch nodules) and skin (café-au-lait macules, freckling) examinations, evaluation of family history, or consideration of the consensus criteria for the diagnosis of NF1, even for reports published after 1988 when the National Institutes of Health (NIH) criteria were established.¹⁰ To date, no consensus criteria exist to diagnose JCS, and *NF1* genetic testing was pursued in only one⁴ of the previously published case reports. All cases were sporadic.

There are many accounts in the English literature that describe an association between NF1 and multiple NOFs, the first dating to 1948 (see **Supplementary Table S2** online). To our knowledge, only one study has reported a germline mutation in *NF1* in patients with NOFs.⁴ In the English literature, there are eight case reports in seven publications of NF1 patients with either solitary or multifocal giant cell lesions of the jaw (see **Supplementary Table S3** online); in many of these reports, no imaging of the long bones was performed or reported (see **Supplementary Table S3** online). Three of these studies found an *NF1* mutation in blood and/or in the giant cell lesion or in the giant cell lesion-like lesion: (i) a case study of an 11-year-old girl carrying the *NF1* splice mutation c.4268A>G with a giant cell lesion of the nasal bridge (but no evidence of biallelic inactivation of *NF1* in the lesion, although only exon 24 of the *NF1* gene was sequenced)¹¹; (ii) a case study of a 10-year-old boy with cherubism secondary to multiple mandibular cysts with osteoclast-like giant cells and a splice mutation (IVS37+1G>A, exon 37) in *NF1* in DNA from peripheral blood lymphocytes (jaw lesion DNA not sequenced),¹² and (iii) a case study of a 7-year-old girl with NF1 and a recurrent

giant cell lesion of her right mandible that demonstrated loss of heterozygosity for *NF1* in the lesion.¹³ This latter case was the first with evidence of biallelic inactivation of *NF1* in a giant cell lesion. Finally, there are three case reports of individuals diagnosed with NF1 (but who lack *NF1* genetic testing) with *both* long bone and jaw lesions (see **Supplementary Table S4** online).

Both Jaffe and Campanacci considered the likelihood that JCS is a form of neurofibromatosis.^{2,3} Solitary NOFs are common, and the incidence of multiple NOFs may be underestimated,¹⁴ raising the possibility of a simple coincidental presence of NOF in NF1 patients. Colby and Saul (2003)⁴ reported a case series of four individuals meeting consensus criteria for the diagnosis of NF1¹⁰ who could, however, equally legitimately have been diagnosed with JCS. A partial deletion, not further specified, of *NF1* was identified in one subject (patient CS4); the other three subjects had not undergone genetic testing at the time of the paper's publication.⁴ To clarify the relationship of NOF, giant cell lesions, and JCS with NF1, we performed an extensive literature review, pursued further *NF1* mutation analysis in previously published cases,⁴ reviewed all patients with solitary or multiple NOFs and/or giant cell lesions referred to the Center for Human Genetics at University Hospitals Leuven, and reviewed all patients referred for comprehensive *NF1* testing to the Medical Genomics Laboratory at the University of Alabama Birmingham (UAB), due to the presence of at least one NOF and/or a suspected diagnosis of JCS. Given some similarities in pigment and bony abnormalities in NF1 and McCune–Albright syndrome, in individuals with negative *NF1* mutation testing with JCS and/or NOF, we also performed sequencing of exon 8 of *GNAS*.¹⁵ Since Legius syndrome is only recently described and prominently features pigment abnormalities, we also performed *SPRED1* sequencing.¹⁶

MATERIALS AND METHODS

NF1 mutation analysis in patients described by Colby and Saul

For patients 1–3, comprehensive cDNA-based sequencing of *NF1* was performed as previously described.¹⁷

Cell culture of NOFs and giant cell lesions and *NF1* mutation detection

Surgically excised NOFs or giant cell lesions were digested at 37 °C overnight with collagenase (160 U/ml) and dispase (0.8 U/ml). Cells were grown to confluency in Dulbecco's Modified Eagle Medium (Gibco, catalog no. 11995-065); Nutrient Mixture F-12 (Gibco, catalog no. 11765-054) + 10% fetal bovine serum (Atlanta Biologicals, catalog no. S11150) + penicillin + streptomycin (Gibco, catalog no. 15070-063) and harvested. *NF1* mutation detection was performed essentially as previously reported.¹⁷

Retrospective review of patient samples with suspected JCS and/or NOF referred for *NF1* testing to UAB Medical Genomics Laboratory

A phenotypic checklist (<http://www.genetics.uab.edu/medgenomics>), completed by the referring physician, accompanies each sample referred for comprehensive clinical *NF1*

testing to the UAB Medical Genomics Laboratory. Search for genotype–phenotype correlations using a Microsoft Access database containing deidentified phenotypic and mutation data was performed using JCS-related descriptors, including “non-ossifying fibroma” (solitary or multiple), “giant cell granuloma” of the mandible (solitary or multiple), and the label “Jaffe–Campanacci syndrome.” Referring physicians were recontacted to confirm the accuracy of the previously submitted information as well as to obtain updated phenotypic information about the tested individuals, if available since the time genetic testing was performed. All *NF1* mutation–negative patients (except for KUL-22) with JCS and/or NOF also underwent comprehensive *SPRED1* genetic testing, as previously described.^{8,18} In addition, direct sequencing of *GNAS1* exon 8 was performed after amplification using two pairs of primers: 8-1f: 5′-ggactctgagccctcttcc-3′, 8-1r: 5′-ggactgggtgaatgtcaag-3′ and 8-2f: 5′-gagcgatcaggtgtgcaaaa-3′, 8-2r: 5′-cagagggtggtgaatg-3′. In addition, clinical and genetic data on five individuals diagnosed with JCS at the Center for Human Genetics from the University Hospitals Leuven (KUL) was reviewed and included. Descriptions of patients UAB/NIH-9¹⁹ and KUL-14²⁰ have been previously reported. This work was performed under the auspices of the institutional review boards of the respective participating institutions.

RESULTS

NF1 mutation analysis in patients described by Colby and Saul

An *NF1* mutation was found in each of the four individuals reported by Colby and Saul⁴ (**Table 1**): a minor lesion mutation in patients CS1–CS3 and a deletion in patient CS4. The deletion in patient CS4 spanned 1.4Mb indicative of a type 1 microdeletion.²¹

Thirteen of fourteen individuals with “classical” (multiple CALMs and multiple NOFs or giant cell lesions) JCS harbored pathogenic mutations in *NF1*

Table 1 lists, in addition to the four patients described by Colby and Saul⁴ (2003), 10 individuals with suspected JCS referred to UAB or KUL. Only individual UAB-19 did not harbor a mutation in *NF1*. If the definition of JCS is restricted to include patients with CALMs and NOFs or giant cell lesions and no neurofibromas (CS1, CS2, and UAB-19), as defined in the original reports,^{1,2} two of the three patients (CS1 and CS2) harbor a pathogenic mutation in *NF1*. We were not able to evaluate UAB-19 for *NF1* mosaicism, which seems a likely diagnosis.

A second group of patients (UAB-12, KUL-14, and KUL-15 in **Table 2**) who did not have classical JCS but had CALMs and a single NOF of a long bone or a giant cell lesion of the jaw also met diagnostic criteria for *NF1*. In this group, all three (100%) had a pathogenic mutation in *NF1*. In summary, all patients (16/16) who met *NF1* diagnostic criteria also harbored a pathogenic mutation in *NF1*. Five of the 16 patients (31%) with an *NF1* mutation and at least one NOF or giant cell lesion had

a history of pathologic fracture, in some cases requiring multiple orthopedic procedures. In the group with an *NF1* mutation, we observed a male:female ratio of 11:5 with an age range of 2 months to 43 years at the time of *NF1* genetic testing. Seven of the 16 individuals (42.7%) carried truncating *NF1* mutations, five had splicing mutations (31.2%), two had a multiexon *NF1* deletion (12.5%), one a total *NF1* gene deletion (6.6%), and one (6.6%) a missense *NF1* mutation. The distribution of mutations spanned the length of the *NF1* gene.

Table 2 lists the nine individuals with NOFs of the long bones or giant cell lesions of the jaws. As noted above, three (UAB-12, KUL-14, and KUL-15) harbored pathogenic mutations in *NF1*. The remainder had one or two NOFs (patients UAB-16, UAB-17, UAB-18, and KUL-22), a single giant cell lesion and one NOF (patient UAB-21) or multiple lytic lesions but no CALMs (patient UAB-20). Of the six patients (**Table 2**) without an *NF1* mutation, we observed a male:female ratio of 2:4 with an age range of 9–15 years at last follow-up. Two of the six patients (33%) had a history of a pathological fracture. Short clinical descriptions of these six individuals are provided in the **Supplementary Data** online.

Cell culture of NOFs and giant cell lesions and *NF1* mutation detection

Somatic *NF1* mutations were detected in two giant cell lesions (patients KUL-14 and KUL-15; **Table 1**) but not in two NOFs (patient KUL-13; **Table 1** and patient KUL-22; **Table 2**). However, it is possible that none of the *NF1* two-hit cells in the NOFs enriched in tissue culture and were therefore undetectable.

DISCUSSION

JCS is a controversial entity⁴ that features CALMs, NOFs, and/or giant cell lesions and a significant overlap with the *NF1* phenotype. The majority of patients with a JCS diagnosis have been published in the orthopedic, radiography, or pathology literature (see **Supplementary Table S1** online). *NF1* genetic testing has been reported in only one case of JCS.⁴

We found germline *NF1* mutations in 13 of 14 patients with multiple NOFs and multiple CALMs, a group that could be considered to have “classical” JCS (**Table 1**). If the diagnosis of JCS is further constricted to include only those with multiple CALMs, multiple NOFs, and an *absence* of neurofibromas, as has been advocated,^{1,2} two of the three (patients 1 and 2) harbored pathogenic *NF1* mutations. The third individual (UAB-19) may be mosaic for *NF1*, although this was not tested. A second group of three (patients UAB-12, KUL-14, and KUL-15) with a single NOF of a long bone or a giant cell lesion of the jaw met *NF1* diagnostic criteria but were not considered to have “classical” JCS; all three patients had *NF1* pathogenic mutations. The finding of multiple, bilateral NOFs in an individual with a germline *NF1* mutation suggests that the NOFs arise secondary to *biallelic* inactivation of *NF1*, as predicted by the Knudson hypothesis, and as previously demonstrated in a number of *NF1*-related tumors and CALMs.²² However, we did

Table 1 Individuals with JCS (multiple café au lait spots and multiple nonossifying fibromas or giant cell lesions). Only patients CS1, CS2, and UAB-19 lack neurofibromas and thus have JCS as described in the original clinical reports (refs. 1 and 2). All these patients except UAB-19 meet the clinical diagnostic criteria for NF1, and all the patients except UAB-19 were found to have pathogenic *NF1* mutations

Patient number	Reference	Age at time of phenotypic report (years)	Gender	Fulfill NIH criteria	≥6 CALMs	≥2 neurofibromas or ≥1 axillary and/or inguinal freckling	Optic glioma	Lisch nodules	≥2 Lisch nodules	Distinct bony lesion (other than NOF)	First degree relative with clinical NF1	Original diagnosis	Additional phenotypic information	NOF/giant cell lesion location	History of pathologic fracture?	<i>NF1</i> mutation	Type of mutation	Exon
CS1 ^a	Colby and Saul ⁴ (2003); Patient 1	16 (reported)	Female	Yes	+	–	+	+	?	?	+	?	+	?	?	+	+	IVS 22
CS2 ^a	Colby and Saul ⁴ (2003); Patient 2	18 (reported)	Male	Yes	+	–	+	+	?	?	+	?	+	?	+	+	+	3
CS3 ^a	Colby and Saul ⁴ (2003); Patient 3	13 (reported)	Male	Yes	+	+	+	+	?	?	+	?	+	?	+	+	+	38
CS4 ^a	Colby and Saul ⁴ 27 (tested) (2003); Patient 4	19 (reported); Male	Male	Yes	+	+	+	+	?	?	+	?	+	?	+	+	+	All
KUL-5	This report	25	Male	Yes	+	+	?	?	?	?	?	?	+	?	+	+	+	46

+, present; –, absent; ?, unknown; CALM, café-au-lait macule; JCS, Jaffe–Campanacci syndrome; NOF, nonossifying fibroma; NIH, National Institutes of Health.

^aDNA samples from patients CS1–4 underwent copy-number analysis using the Affymetrix (Santa Clara, CA) Genome-wide Human SNP 6.0 Array (1.8 M probes) according to the manufacturer's instructions. Patient CS2 carried a loss of approximately 30 kb (chr 20: 20,585,029–20,614,841; build 36.3) on chromosome band 20p11.23. This region includes *RALGAP2* (C20orf74), a small GTPase that regulates a variety of cellular processes by opposing the effect of guanine nucleotide exchange factors. Because additional validation or parental testing of this deletion could not be performed, the significance of this copy-number change remains unknown. No deletions or duplications of known or potential significance were detected by microarray analysis in patients CS1 and CS3.

Table 1 Continued on next page

Table 1 Continued

Patient num-ber	Refer-ence	Age at time of phenotypic report (years)	Gender	Fulfill NIH criteria	≥6 CALMs	≥2 neurofi-bromas or ≥1 plexi-form neurofi-broma	Axillary and/or inguinal freck-ling	Optic glioma	≥2 Lisch nod-ules	Distinctive bony lesion (other than NOF)	First de-gree rela-tive with NF1 diagnosis	Additional phenotypic information	NOF/giant cell lesion location	History of patho-logic fracture?	NF1 mutation	Type of mutation	Exon
UAB-6	This report	17.5	Female	Yes	+	+	+	?	?	?	?	No additional details	Bilateral distal femora and proximal tibia, right distal fibula and left proximal fibula—large NOF in distal metaphyseal region and posterior cortex of both femurs. Multiple large lesions in the proximal tibial metaphyseal regions. Smaller lesions in the proximal left fibular metaphysis and distal right fibular metaphysis. The smaller lesions seem to be cortical and most have resolved with age with sclerotic borders indicating a healing/normalization process	No	c.5839C>T; p.Arg1947*	Truncating—nonsense	40 (31)

+, present; −, absent; ?, unknown; CALM, café-au-lait macule; JCS, Jaffe–Campanacci syndrome; NOF, nonossifying fibroma; NIH, National Institutes of Health.
*DNA samples from patients CS1–4 underwent copy-number analysis using the Affymetrix (Santa Clara, CA) Genome-wide Human SNP 6.0 Array (1.8 M probes) according to the manufacturer's instructions. Patient CS2 carried a loss of approximately 30 kb (chr 20: 20,585,029–20,614,841; build 36.3) on chromosome band 20p11.23. This region includes *RALGAP2* (C20orf74), a small GTPase that regulates a variety of cellular processes by opposing the effect of guanine nucleotide exchange factors. Because additional validation or parental testing of this deletion could not be performed, the significance of this copy-number change remains unknown. No deletions or duplications of known or potential significance were detected by microarray analysis in patients CS1 and CS3.

Table 1 Continued on next page

Table 1 Continued

Patient number	Reference	Age at time of phenotypic report (years)	Gender	Fulfill NIH NF1 criteria	≥6 CALMs	≥1 neurofibromas	Axillary freckling	Optic glioma	≥2 Lisch nodules	Distinctive bony lesion (other than NOF)	First degree relative with NF1	Additional phenotypic information	NOF/giant cell lesion location	History of pathologic fracture?	NF1 mutation	Type of mutation	Exon
UAB-7	This report	18	Male	Yes	+	+	+	?	?	?	?	Learning disability; suspected positive family history but family lost for follow-up	Bilateral lower limbs, location not specified	No	Deletion exon 28—exon 49	Multiexon deletion	37–58 (28–49)
UAB-8	This report	10	Male	Yes	+	+	+	?	?	?	–	Hyperactivity and learning disability	Likely multiple, location not specified	No	c.4184C>A, p.Pro1395His	Missense	32(24)
UAB/NIH-9	Hau <i>et al.</i> 15 (2002)	15 (reported); 25 (tested)	Male	Yes	+	+	+	?	+	?	?	Asymptomatic spinal neurofibromas and learning disability	Bilateral distal femora, proximal left tibia and fibula, and proximal right tibia	Yes	c.1318C>T, p.Arg440*	Truncating—nonsense	12(10a)
UAB-10	This report	19	Male	Yes	+	+	+	+	?	?	?	Plexiform neurofibroma of left leg with hypertrichosis, dural ectasia, irregularities of skull bone and chest wall, learning disability	Multiple NOF bilateral distal femurs and proximal right tibia	No	Deletion exons 9(7)—end	Multiexon deletion	9(7)—end
UAB-11	This report	22	Female	Yes	+	+	+	?	?	?	+	No additional details	Multiple NOF bilateral in upper and lower extremities; bilateral femur and humerus, left fibula; right fibula and tibia	No	1261-1G>T, 1261_1284del	Splice mutation, in frame, skip 24nt	12(10a)

+, present; –, absent; ?, unknown; CALM, café-au-lait macule; JCS, Jaffe–Campanacci syndrome; NOF, nonossifying fibroma; NIH, National Institutes of Health.

^aDNA samples from patients CS1–4 underwent copy-number analysis using the Affymetrix (Santa Clara, CA) Genome-wide Human SNP 6.0 Array (1.8 M probes) according to the manufacturer's instructions. Patient CS2 carried a loss of approximately 30 kb (chr 20: 20,585,029–20,614,841; build 36.3) on chromosome band 20p11.23. This region includes *RALGAP2* (C20orf74), a small GTPase that regulates a variety of cellular processes by opposing the effect of guanine nucleotide exchange factors. Because additional validation or parental testing of this deletion could not be performed, the significance of this copy-number change remains unknown. No deletions or duplications of known or potential significance were detected by microarray analysis in patients CS1 and CS3.

Table 1 Continued on next page

Table 1 Continued

Patient number	Reference	Age at time of phenotypic report (years)	Gender	Fulfill NIH NF1 criteria	≥6 CALMs	Neurofibromas or ≥1 plexiform neurofibroma	Axillary and/or inguinal freckling	Optic glioma	≥2 Lisch nodules	Distinctive bony lesion (other than NOF)	First degree relative with clinical NF1	Additional phenotypic information	NOF/giant cell lesion location	History of pathologic fracture?	NF1 mutation	Type of mutation	Exon
KUL-13	This report	15	Male	Yes	+	+	+	?	?	?	–	Plexiform neurofibroma of the left hemifacial region, learning difficulties	NOF in bilateral femora	Yes	c.6365-3C>G (germline mutation); no somatic mutation in culture of NOF	Splicing, insertion of 2 nucleotides at the beginning of exon 34	Intron 33
UAB-19	This report	6	Female	No	<6	–	–	–	–	–	–	Hemihyperplasia isolated to the right lower extremity and a hyperpigmented patch over the posterior base of the neck with hazy, irregular margins, but respecting the midline. The patient has normal IQ, attention-deficit disorder and behavioral difficulties, with parental concerns that the child may evolve into a diagnosis of bipolar illness	"Innumerable bone lesions on right leg"	No	Negative	–	–
UAB-23	This report	17	Female	Yes	+	+	+	?	?	?	+	>6 CALMs, bilateral axillary and inguinal freckling, 2–6 cutaneous neurofibromas, juvenile xanthogranulomata, internal plexiform neurofibromas (both hands), learning disabilities. Affected father required bone grafting in the past. Also family history of Addison's disease	Multiple NOFs both legs, cortically based lesions within the distal femurs and proximal right tibial metaphyses	No	c.1721G>A	Splicing, skipping exon 11	(Exon 11 skipped)

+, present; –, absent; ?, unknown; CALM, café-au-lait macule; JCS, Jaffe–Campanacci syndrome; NOF, nonossifying fibroma; NIH, National Institutes of Health.
aDNA samples from patients CS1–4 underwent copy-number analysis using the Affymetrix (Santa Clara, CA) Genome-wide Human SNP 6.0 Array (1.8 M probes) according to the manufacturer's instructions. Patient CS2 carried a loss of approximately 30 kb (chr 20: 20,585,029–20,614,841; build 36.3) on chromosome band 20p11.23. This region includes RALGAP2 (C20orf74), a small GTPase that regulates a variety of cellular processes by opposing the effect of guanine nucleotide exchange factors. Because additional validation or parental testing of this deletion could not be performed, the significance of this copy-number change remains unknown. No deletions or duplications of known or potential significance were detected by microarray analysis in patients CS1 and CS3.

Table 2 Other individuals with nonossifying fibromas of the long bones or giant cell lesions of the jaws. KUL-22 was not tested for mutations in *SPRED1*

Patient number	Reference	Age at last follow-up (years)	≥2 Neuro-fibromas				Distinctive bony lesion (other than NOF)			First degree relative with NF1	Original clinical diagnosis	NOF location	History of pathologic fracture?	NF1, <i>SPRED1</i> , and <i>GNAS1</i> (exon 8) mutations
			Number of CALMs	plexiform or ≥1 neurofibroma	Axillary and/or inguinal freckling	Optic glioma	≥2 Lisch nodules	Distinctive bony lesion (other than NOF)	First degree relative with NF1					
UAB-12	Wimmer et al. ²⁵ (2011)	2 months	Male	Yes	NIH NF1 criteria	Fulfill	≥6	–	–	–	NF1	One NOF in proximal tibia and tibial dysplasia	No	NF1: 1721 + 5_1721 + 20dupinsAluSb1; (splice mutation—Alu insertion affecting exon 15 (11)
KUL-14	Legius et al. ²⁰ (1995)	18	Male	Yes	≥6	+	–	+	–	–	ECCL	Maxilla and mandible	No	NF1: c.5234C>G, p.S1745* (germline NF1 mutation); c.3916C>T, p.R1306* (somatic NF1 mutation of giant cell lesion culture); both germline and somatic variants are truncating nonsense mutations affecting exon 29 (germline) and exon 23.1 (somatic)
KUL-15	This report	43	Female	Yes	≥6	+	+	?	?	–	NF1	Recurring giant cell lesion of maxilla and mandible	No	NF1: c.4637dup, p.Phe1548Valfs*2 (germline NF1 mutation); c.781_812del32 (somatic NF1 mutation of giant cell lesion culture); both germline and somatic variants are truncating nonsense mutations affecting exon 27a (germline) and exon 6 (somatic)
UAB-16	This report	12	Male	No	5	–	–	–	–	Possible (mother with multiple CALMs)	NF1	One solitary lesion on femur (location not further specified)	No	Negative

+, present; –, absent; ?, unknown; CALM, café-au-lait macule; ECCL, encephalocraniocutaneous lipomatosis; JCS, Jaffe–Campanacci syndrome; NIH, National Institutes of Health; UAB, University of Alabama Birmingham.
KUL-14 met NF1 criteria at evaluation at the age of 18 years. At the age of 2 years, as reported, patient had lipomatous subcutaneous masses, hypotrophy of the left hemisphere with dilated left ventricle, and calcifications at left occipital area but did not meet NF1 diagnostic criteria.

Table 2 Continued on next page

Table 2 Continued

Patient number	Reference	Age at last follow-up (years)	Gender	Fulfill NIH NF1 criteria	≥2 Neuro-fibromas or ≥1			Optic ≥2 Lisch glioma nodules than NOF	Distinctive bony lesion (other than NOF)	First degree relative with NF1	Original clinical diagnosis	NOF location	History of pathologic fracture?	NF1, SPRED1, and GNAS1 (exon 8) mutations
					Number of CALMs	plexiform neurofibroma	Axillary and/or inguinal freckling							
UAB-17	This report	9	Male	No	1	–	–	–	–	–	Unknown	Fibular dysplasia and one NOF	No	Negative
UAB-18	This report	15	Female	No	<6	–	–	–	–	–	Multiple CALM only	Two lesions (location not further specified)	No	Negative
UAB-20	This report	14	Female	No	None (but some pigmentary dysplasia on neck and back)	–	Single axillary freckle	–	–	–	Single NF1 feature only	Multiple aggressive lesions in bilateral femora and tibia	Yes	Negative; no NF1 mutations in analysis of left femur tissue
UAB-21	This report	10	Female	No	None (multiple tiny nevi)	–	–	–	–	–	Single NF1 feature only	Right fibular lesion and right jaw lesion	No	Negative
KUL-22	This report	15	Female	No	2	–	–	–	–	–	McCune–Albright syndrome	Distal femur and proximal tibia	Yes	NF1 negative, GNAS1 negative on both normal tissue and NOF culture

+, present; –, absent; ?, unknown; CALM, café-au-lait macule; ECCL, encephalocraniocutaneous lipomatosis; JCS, Jaffe–Campanacci syndrome; NOF, nonossifying fibroma; NIH, National Institutes of Health; UAB, University of Alabama Birmingham.

KUL-14 met NF1 criteria at evaluation at the age of 18 years. At the age of 2 years, as reported, patient had lipomatous subcutaneous masses, hypotrophy of the left hemisphere with dilated left ventricle, and calcifications at left occipital area but did not meet NF1 diagnostic criteria.

Figure 1 Proposed algorithm to evaluate patients with multiple nonossifying fibromas (NOFs) and/or giant cell lesions and café-au-lait macules (CALMs). The appearance of diagnostic features of neurofibromatosis type 1 (NF1) are time dependent, and thus a child who does not meet diagnostic criteria should be periodically re-evaluated. JCS, Jaffe–Campanacci syndrome; NIH, National Institutes of Health.

Table 3 Disorders reported to be associated with multiple NOFs and giant cell lesions

Syndrome/condition	Associated gene	Multiple NOFs	Multiple giant cell lesions	Reference
Neurofibromatosis type 1	<i>NF1</i>	✓	✓	Multiple; see text
Noonan-like/multiple giant cell tumor syndrome	<i>PTPN11</i>		✓	36
Cherubism	<i>SH3BP2</i>		✓	37
Oculoectodermal syndrome		✓	✓	38
ECCL	<i>NF1</i>	✓		20,39
Ramon syndrome			✓	40
Schimmelpenning syndrome	<i>HRAS</i> and <i>KRAS</i> (postzygotic)		✓	41
Hyperparathyroidism	(Multiple)		✓	42

ECCL, encephalocraniocutaneous lipomatosis.

Noonan-like/multiple giant cell tumor syndrome may be a variant of Noonan syndrome since many reported patients have *PTPN11* mutations (de Lange *et al.*⁷). The association of giant cell lesions in Schimmelpenning syndrome is rare and may be coincidental (see ref. 43).

not find such a somatic *NF1* mutation in an NOF from patient 13, who harbored a germline *NF1* mutation. The detection rate of somatic *NF1* mutations in NF1-associated neurofibromas is high (~84%)²³; however, the detection rate of somatic *NF1* mutations in rarer NF1-associated tumors is unknown, but might be lower depending on the fraction of cells carrying a second hit in the NOF.²² As only one NOF was analyzed, no firm conclusions can be made at this point. However, we identified germline and somatic truncating *NF1* mutations in both giant cell lesions from patients KUL-14 and KUL-15, establishing definitive genetic proof that these are NF1-associated tumors.

This observation extends the previous finding of *NF1* loss of heterozygosity in a mandibular giant cell lesion in a female NF1 patient by Friedrich *et al.*¹³

The 16 patients with at least one NOF or giant cell lesion and who met NF1 diagnostic criteria harbored a pathogenic *NF1* mutation. These were distributed along the entire *NF1* gene: no mutational hotspots were identified.²⁴ Five nonsense, five splice-site, two multiexon deletions, two frameshift, one type 1 *NF1* gene microdeletion, and one missense mutation were detected. All variants except the but the missense mutation are expected to result in haploinsufficiency or absence of *NF1* and/or flanking

gene products. One splice-site mutation (patient UAB-12) was the result of a *de novo*, novel AluSb1 insertion, as recently described,²⁵ and would normally escape detection using exon-by-exon gDNA-based sequencing. There are only two well-documented examples of *NF1* genotype/phenotype correlation: a three base-pair deletion of one amino acid (c.2970_2972delAAT in exon 17) that is associated with an absence of neurofibromas⁹ and the microdeletions of the *NF1* gene (and a variable number of flanking genes) which are consistently associated with a more severe phenotype, including increased neurofibroma burden, learning disabilities, facial dysmorphism, and possible increased risk of malignant peripheral nerve sheath tumors.^{26,27} Given the wide spectrum of *NF1* mutation type observed in this study, there was no obvious genotype–phenotype correlation, although the total number of patients is small.

The six patients without *NF1*, *SPRED1*, or exon 8 of *GNAS1* mutations detected in the blood are a heterogeneous group and did not meet NF1 diagnostic criteria (Table 2). Patients UAB-16, UAB-17, UAB-18, UAB-21, and KUL-22 have two or fewer NOFs and/or giant cell lesions and fewer than six CALMs. Since a single NOF is common in the general population,²⁸ as is a single CALM,²⁹ it is plausible that some of the patients may have a coincidental cluster of minor abnormalities. Patient UAB-17 had fibular dysplasia, a rare but well-characterized abnormality.³⁰ The familial multiple CALMs without other features of NF1 in patient 16 is unexplained, despite mutation testing of *NF1* and *SPRED1*.¹⁶ Patients UAB-19 and UAB-20 feature a more severe phenotype with multiple lytic lesions or NOFs in one or more legs; however, only UAB-19 can be considered as “true” JCS given her multiple CALM. She may be mosaic for an *NF1* mutation. In patient UAB-20, it is unlikely that the bony lesions arose from *NF1* mosaicism because no *NF1* mutations were detected in cells cultured from the resected NOF of the left femur. Given the presence of so many aggressive lesions, an underlying genetic factor is presumed but unidentified. Multiple lytic foci of the mandible and femur in patients with a diagnosis of JCS have been reported previously (see **Supplementary Table S1** online), but no mutational data were available from these patients.

The high percentage of pathologic fractures in our cohort (patients CS1, CS2, KUL-5, UAB/NIH-9, and KUL-13) almost certainly reflects an ascertainment bias for bone cysts among the NF1 patients, and systematic screening in NF1 patients for presence of NOFs has been suggested.⁴ Such screening needs to be balanced with the risk of radiation exposure in the pediatric (increased risk of leukemia)³¹ and NF1 populations (possible increased risk of malignant peripheral nerve sheath tumor).³² However, it seems reasonable to have a lower threshold to image sites of persistent bony pain in individuals with NF1.

The JCS diagnosis requires an *absence* of neurofibromas and the *presence* multiple CALMs, the latter a classical hallmark of NF1. This is especially problematic in children because neurofibromas typically do not appear until adolescence, or later. In many of the reports describing JCS, insufficient or inadequate phenotypic data were provided, hampering evaluation of the appropriateness of the diagnosis. In addition, there is no feature

unique to JCS that must be *present* to distinguish it from other syndromes, including NF1. Axillary freckling, a specific finding in NF1, has also been reported in some patients with JCS.^{1,19} Since accurate diagnosis is essential to ensure appropriate medical management and genetic counseling, we recommend the clinical algorithm outlined in Figure 1 to be followed for patients presenting with multiple NOFs and/or giant cell lesions. The algorithm is derived from our data, which supports the hypothesis that JCS is frequently a manifestation of NF1.⁴ It also incorporates the hypothesis that a fraction of *NF1* mutation–negative patients with multiple NOFs may be mosaic for an *NF1* mutation. Formal consideration of a diagnosis of NF1 (and genetic testing, as needed) should prevent the “re-diagnosis” of JCS (from NF1) and its attendant confusion and avoid potentially missed screening opportunities (e.g., for optic pathway glioma in children). We recommend that the term “Jaffe–Campanacci syndrome” only be used for the likely small percentage of patients with multiple CALMs, multiple NOFs, and/or giant cell lesions who also lack a germline *NF1* mutation or who lack evidence of an other recognized, usually distinct and rare disorder associated with NOFs and giant cell lesions (Table 3). In these individuals, testing of melanocytes from multiple biopsies from CALMs for first and second hits in *NF1*, if available, is needed to exclude a diagnosis of mosaic NF1.^{33,34} It has been recognized recently that cherubism-associated giant cell lesions (and thus mutations in *SH3BP2*) result in loss of tankyrase-mediated destruction of adapter protein 3BP2 and thus stabilization and hyperactivation of SRC, SYK, and VAV pathways.³⁵ The association of giant cell lesions with mutations in *NF1* and *PTPN11* (Table 3), both members of the RAS signaling pathway, may provide additional insights to the pathogenesis of these tumors.

In conclusion, the majority of patients with CALMs and NOFs or giant cell lesions harbored a pathogenic germline *NF1* mutation, suggesting that many JCS cases may actually have NF1. In addition, we provide the first proof of specific somatic second-hit mutations affecting *NF1* in two giant cell lesions from two unrelated patients, establishing that these are NF1-associated tumors. The diagnosis of the JCS may apply to a small number of patients with multiple CALMs, multiple NOFs, and/or giant cell lesions who have undergone meticulous clinical evaluation to exclude other rare disorders associated with NOFs and giant cell lesions. In addition, comprehensive molecular analysis to exclude a germline *NF1* mutation and, when possible, testing to exclude mosaic NF1 should be performed.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at <http://www.nature.com/gim>

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DISCLOSURE

The authors declare no conflict of interest.

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