Genetic Susceptibility Factors in a Cohort of 38 Patients with SAPHO Syndrome: A Study of *PSTPIP2, NOD2,* and *LPIN2* Genes

MARGARITA HURTADO-NEDELEC, SYLVIE CHOLLET-MARTIN, DIANA CHAPETON, JEAN-PIERRE HUGOT, GILLES HAYEM, and BÉNÉDICTE GÉRARD

ABSTRACT*. *Objective. The SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, and osteitis) is a rare disorder that mainly affects bone and skin. Chronic multifocal osteitis is the main diagnostic feature. Genetic studies of HLA genes have shown no role for these class II antigens, whereas studies of 2 mouse models (*cmo* and *Lupo*) point to a role of the *PSTPIP2* gene. We analyzed the *PSTPIP2* gene in patients with SAPHO syndrome.

***Methods*.** In a cohort of 38 patients with SAPHO we analyzed *PSTPIP2* and 2 other candidate genes, *NOD2/CARD15* (Crohn's disease occurs in about 10% of SAPHO patients), and *LPIN2* (clinical similarities of SAPHO with Majeed syndrome).

Results. Rare variants of the 3 genes observed in patients with SAPHO were not specific or were not found more frequently compared to controls, suggesting no major pathogenetic role of these genes in the SAPHO syndrome.

Conclusion. We found no association between *PSTPIP2*, *NOD2*, and *LPIN2* variants and the SAPHO syndrome. (First Release Dec 23 2009; J Rheumatol 2010;37:401–9; doi:10.3899/jrheum.090456)

Key Indexing Terms:

SAPHO SYNDROME | GENE POLYMORPHISM | *PSTPIP2*
POLYMORPHONUCLEAR NEUTROPHILS | *NOD2* | *LPIN2*

The SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, and osteitis) is a rare disorder that mainly affects bone and skin, with multifocal osteitis as the main diagnostic feature. The broad spectrum of clinical features in the SAPHO syndrome, and their highly varied combinations, raise diagnostic difficulties, especially in patients with only bone lesions[1-3]. This results in a probable underestimation of the frequency of the disease. Several factors have been implicated in the development of the SAPHO syndrome, such as *Propionibacterium acnes* infection[4-8] and impaired immune responses, but the etiopathogenesis is still largely unknown. Despite the pathological characteristics that the SAPHO syndrome shares with some spondyloarthropathies, such as axial skeleton involvement, skin lesions, and inflammatory bowel disease (IBD)[9-11], some authors underline the absence of certain typical features of spondyloarthropathies, such as a strong association with HLA-B27, familial segregation, male predominance, and typical radiographic lesions[12].

We recently reported strong humoral and cellular proinflammatory responses in a group of 29 patients with SAPHO syndrome, as shown by high interleukin 8 (IL-8) and IL-18 plasma levels and hyperproduction of the 2 cytokines by purified polymorphonuclear neutrophils (PMN) *ex vivo*. *P. acnes*-specific PMN deactivation was also observed[11]. We and others have found that anti-tumor necrosis factor-α therapies (infliximab and etanercept) can be beneficial in patients with refractory SAPHO syndrome[11,13-16].

Genetic factors have been implicated in SAPHO syndrome, based on familial clustering[17-19]. However, genetic studies of class II HLA antigens revealed no role for HLA-B27, HLA-Cw6, or HLA-DR[9,10,20].

The recent description of mutated genes in 2 mouse models, *cmo* (chronic multifocal osteomyelitis, *p.Leu98Pro*)[21] and *Lupo* (macrophage infiltration, paw osteolysis, and ear necrosis, *p.Ile282Asn*)[22], that share some manifestations

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with the human SAPHO syndrome has provided new insights into the molecular basis of the SAPHO syndrome. These 2 models involve nonsynonymous homozygous mutations in the proline serine threonine phosphatase interacting protein 2 gene (*pstpip2*). Moreover, low levels of *pstpip2* have been linked to abnormal macrophage functions, suggesting that *pstpip2* mutations might be related to the bone destruction and skin inflammation observed in cmo and Lupo mice[22,23].

SAPHO-related human diseases point to other possible candidate genes. Majeed syndrome is an autoinflammatory bone disease that shares with SAPHO syndrome features of chronic recurrent multifocal osteitis and inflammatory dermatosis[23,24]. Recently, LPIN2 mutations have been implicated in this disease[25,26]; lipin 2 catalyzes the transformation of phosphatidic acid (PA) into diacylglycerol. As the intracellular PA concentration regulates the mTOR (mammalian target of rapamycin), cell cycle, and RANKL (receptor activator of nuclear factor-κB) pathway[27], a lipin 2 abnormality might account for the altered bone proliferation observed in Majeed syndrome.

Because of the high prevalence (10%) of chronic IBD in patients with SAPHO[10,28-30] we also studied the main gene involved in Crohn's disease (CD), *NOD2/CARD15*. NOD2 is an intracellular receptor of muramyl dipeptide (MDP), which is the minimal common component in the peptidoglycans of Gram-negative and Gram-positive bacteria; this molecule is thus thought to serve as a general sign of bacterial infection[31,32]. *NOD2* gene mutations lead to intestinal tolerance breakdown, and this might result in increased microbial translocation and a strong inflammatory response in the gut of patients with IBD[33,34]. Interestingly, *in vitro* studies have shown that NOD2-activating agonists can induce IL-8 production by monocytes and dendritic cells[35].

We investigated whether SAPHO syndrome is associated with *PSTPIP2*, *LPIN2*, or *NOD2* polymorphism in 38 French patients.

MATERIALS AND METHODS

Patients and phenotyping. The study population consisted of consecutive patients attending the Rheumatology Department, Bichat teaching hospital, Paris, France. We studied 38 patients with the SAPHO syndrome (36 unrelated patients and 2 affected siblings of 2 families) who had typical osteoarticular involvement (with at least one site of condensing and/or hypertrophic osteitis) and who met the diagnostic criteria proposed by Benhamou, *et al*[36]. A standardized questionnaire was completed for each patient, which included the date of birth, gender, family history, geographic origin, age at onset, age at diagnosis, smoking habits (smoker/ex-smoker or non-smoker), the number and location of bone lesions, the number of involved joints (peripheral and/or axial), skin lesions (acne, palmoplantar pustulosis, psoriasis vulgaris), and intestinal involvement (CD and/or ulcerative colitis). Patients with associated inflammatory diseases such as IBD and pyoderma gangrenosum were excluded. The patients all had rheumatic disease, with at least one osteoarticular inflammatory site, identified by physical examination and/or magnetic resonance imaging. Specific treatments included nonsteroidal antiinflammatory drugs, prednisone, and/or methotrexate. No patient was receiving biological therapies. Patients were informed of the purpose of the study and gave their written informed consent. All the procedures were conducted in accord with our institutional ethical guidelines.

As a control group, 162 unaffected and unrelated west European Caucasians were screened for the polymorphisms found in the patients. These subjects were recruited from CEPH (Centre d'Étude du Polymorphisme Humain), which maintains a database for genetic markers that have been typed in the CEPH reference family resource for linkage mapping[37,38].

Genetic analysis. Genomic DNA was isolated from peripheral blood leukocytes by using the QIAamp DNA Blood Midi kit (QIAGEN GmbH, Hilden, Germany) following manufacturer's recommendations.

Coding sequences and intron-exon junctions of *PSTPIP2* (GenBank NM_024430), *LPIN2* (GenBank NM_014646), and *NOD2* (GenBank AF_178930) were direct sequenced.

Polymerase chain reaction (PCR) and sequencing conditions for *PSTPIP2*, *NOD2*, and *LPIN2* are available on request. Primers are described in Table 1. Purified PCR amplification products were sequenced using the BigDye Terminator Cycle Sequencing Kit v.1.1 (Applied Biosystems, Foster City, CA, USA) according to manufacturer's instructions, and were resolved on an ABI 3100 automated sequencer (Applied Biosystems). Sequence data were aligned with SeqScape 2.0 software and compared to the published sequences of *PSTPIP2*, *LPIN2*, and *NOD2*.

Statistical analysis. Chi-square test was used for case-control association analysis. The Mann-Whitney test and ANOVA, respectively, were used to compare qualitative and quantitative variables between groups. The threshold of statistical significance was set at $p < 0.05$. Correlations between clinical or biological variables and presence of one or several variants were sought using the Spearman coefficient or Mann-Whitney test.

RESULTS

Clinical description of patients. We investigated 38 patients (30 female, 8 male) with SAPHO syndrome. The syndrome was sporadic in 34 cases and familial in 4 cases (2 families). Mean age at onset was 31.3 ± 2.3 years (range 12–65). Osteitis was unifocal in 17 patients (44.7%) and multifocal in 21 patients (55.26%). The mean number ± SEM of bone lesions was 1.9 ± 0.3 (range 1–8), and the mean number of involved joints [anterior chest wall (ACW), pelvis, or distal joints] was 1.9 ± 0.3 (range 1–5). Skin lesions were present in 34 (89%) patients and consisted of palmoplantar pustulosis in 19 cases (50%), severe acne in 8 cases (21%), and psoriasis vulgaris in 20 cases (52.6%). Thirteen patients (34%) had 2 concomitant skin lesions (Appendix 1). No patient had detectable rheumatoid factor, anti-citrullinated cyclic peptide antibodies, antinuclear antibodies, or anti-extractable nuclear antigen antibodies, as described[11], in spite of elevated autoantibody frequency observed in other forms of inflammatory rheumatism[39,40]. No patient had CD.

Genetic analysis. Twenty-six variants of *PSTPIP2*, *NOD2*, and *LPIN2* were found in the 38 patients (Table 2), 4 of which were new. The frequency of variants was studied in 162 controls if the relevant data were not available in the dbSNP database (http://www.ncbi.nlm.nih.gov/SNP/snpLocus.html).

1. *PSTPIP2 variants*. The *PSTPIP2* gene has different alternative splicings (exon 1, exon 2, exon 10, exon 11), as described[41] and/or in databases (Figure 1). The ΔE2 and

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Table 1. Primers used for PSTPIP2, LPIN2, and NOD2 gene analysis.

Screened Exon	Forward Primer	Reverse Primer	Size of PCR Product, bp
PSTPIP2			
1	CGG CTT CCC TGC GCG AGT GTG GAAC	CTG AGC CCC GCG ATC CGC TGTC	196
2	AGC TTC CCA CCT CTT TTG TCT	AGG AAA TTG TTC CTT GTC TGTG	281
3	AGG GAG GGT CAT TGT GTC TTA AC	TTC AAC CTC CTG GTA ACT CTG TC	242
4	AAG ATA TGG GCA GAG AGA AGC AT	AAA ACA CAC CTT TGA CGA CAG AC	305
5	TGA TGT TGA TTT TA CCA CTT ACT CC	AGG TCA TGA TTA CAT GAT GGT GG	338
6	CTT AAC CCT CAA GAT AAG CTG GT	TAT GTT CAT ACA CAG CAC AGG AT	231
7	ACT AAT CAG ACG GCC CTG TCC	AAG GAA GAT ATT TCC AGG GGT TT	325
8	CTT TTC AAT CTG TTT TGC CTG TG	CTT TCT CAG GGA CAC ATT TAG GA	206
9	GAC CAG CCT GTG GGT GTA TCT GCG AGC CAC	CTG AGC AGC TTC CTG TTA CAC	457
10	TTT CTT AAG TCA CAG CTA GCC AAA	GGC AAA GTG AAC CAA TCA ATA TC	267
11	CCG CCT CAA ACC CAT GTT TTT AAG	AGG AGG GTC TTC TTA CGT CAG GGT	352
12	GGG GTG GGG AGT GTT ATT TAC	CAG CCT TAT TAA GCA GAT GCA GT	310
13	TTT GCT TTA GGT GAG CTT TCT TG	AGG TTC AAA CAA TTC TTG TGG CT	374
14	ATC TGT AAG TGA AAT GCC CTGG	AGG TTC AAA GGC TTC AAT AGC AC	223
15	TGC ACC CTT ATT CTT GTT GAAT	CAA AGT CTT CAT TGC TGA CAT AAC	193
LPIN2			
2	TGA AAT CTG GCA TAC AAG TGAG	GCG ATT TAT TCA TAG AGG ATG ACTT	412
3	TTC TAG GAA CCT CAA AAC TAT GCT AA	TTG CCA ACA ACA GTC CTC TGTA	328
4	CAG TGG GAC TTT CTT GCC TTTA	CCA AAC CTC ACA CTG TGT ATCC	542
5	CCC CTC TTC ATT TTG ATT GTTT	ATT CAG TTC CTT GGC TGT GTG	331
6	TTT AAT CTG TCA GGC TCA GCAA	ATT GCC TCC TTT ACT TAT GGGC	283
7	AAT GAA CAC ATT GCC AGC TTAG	CCA TCA CGT TAT GTG GAA CACT	509
8	CCC TAT TCA AAT CCT GCT TGTC	GGA CAC CAT CAT CTT GTT CCTT	313
9	CCC CAG AGA ACC ATG CAG TA	ATA TCC TGA AAT GGC TAC ACGG	356
10	TGA TTT TAG CCT TCA ATT TCT GC	ATG ACA AGT TTT ATA AGAA GGA ACA CT	299
11	CCT GAT TCC CTC CCC TCT CT	TGA ATA GTA CCC AGT TCA GAA ATA TG	240
12	TTC AGG CTA GCA TAG AAG GTA GG	AAA TTC CTG TGC CTG ACA AAA	254
13	TTC TTT CCT AGA GAG GGC TGCT	AAC AAG CTG CCA AAA TCA ACTT	253
14	TCT TGA TCC TAA ATG AAA AGC TCTC	ACA GAA GAG GAT GTG CAT CAAA	298
15	CGA GAC ACC AGT TGT TCT GTA AA	GAA CTC CCC ACC ACA CAC TG	314
16	GGC AGC TGA TAG TCA ACC AAA T	GGA CTG AAG ACT TAC ACC ATT GTTC	255
17	AAA GAA AGA AAA GTG TGG GGT TT	CAA CAT CTG ACT TCT GTT CCCA	343
18	GAA GAA ATT GGG TGG TTG TGAG	GGC TAC ACC CCA CGA AGT ACA	285
19	TGT CTG TGC AGT GCT TCT GG	AAA AGG ACA GGG TCT GTC TGTC	274
20	TGA GTG ACA GCT TCA CAG CC	CTG GTA TCT GAG GTC AGC AGAA	320
NOD2			
1	CTC ACC AGT CCT GTG CCA CT	AAG GAT GAA AGA AGG CTG AGG	220
2	GCT AGA ACC ATG GCC AAC TC	AGT TAC CCC ACA GGC TGA CTT	678
3	CAG TAA TCA GTA AGC CTT CCC AC	TTA ACC ATG GAT CTG CAC TGA CT	241
4-1	GTT AGG TCC CGT CTT CAC CAT	GTG AAC CTG AAC TTG AAC TCG TC	578
4-2	CTC TCT GTG CGG ACT CTA CTC TT	CTT GGG AAG CTG AGT CTG GG	574
4-3	CTT CTC ATG GAT GGT GTC CAA	CTT CTC AGA TGT CTG GCA CTCA	634
4-4	GCT CAG ACA CCT CTT CAA TTG TG	CAC ACT TAG CCT TGA TGG TGCT	647
5/6	ACT TCA GGG ATG AAT GAA AGT CT	TCA GAC TGA CTC AGG AAT GGG	547
7	ACAGACGGCCCTCCTTTTCT	CTA AAT CCT CAA AAG TCC CAA GC	309
8	GGA GGA GGA CTG TTA GTT CAT GTC	GCT CCT CCC TCT TCA CCT GAT	224
9	GAA TTT TGC CCT CCA TAG GTT AG	AGG GGA TCA ACA GAG ATT GTGA	222
10	GCA TGT GAG TTC ATC ATC TTCC	CAG AAA TGC CCC TTC CAA AG	214
11	TCA GTA GAC TGG CTA ACT CCT GC	GAT CCT CAA AAT TCT GCC ATTC	280
12	GTT TGA AAG CCC TGC TCT AAT	CAC ATG TCA CCC AGC CTC TG	213

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Table 2. Gene variants observed in 38 patients with the SAPHO syndrome and in 162 healthy controls.

Variant			SAPHO, n = 78 (%)	Controls, n = 324 (%)	dbSNP Database, %
PSTPIP2					
c.248–20 T>C	Intron 4	rs688547	7 (9)	29 (9)	7
c.516+7 A>G	Intron 7	NDS	8 (10)	43 (13)	NA
c.663 T>C; p.Cys221Cys	Exon 10	NDS	2 (3)	10 (3)	
c.964 A>G; p.Asn322Asp (variant ΔE11, c.867 A>G, p.Pro289Pro)	Exon 14 (Exon14)	rs2276199	7 (9)	43 (13)	NA
c.1005+26 G>T; (variant ΔE11, c.934 G>T, p.Gly322Cys)	3'UTR (Exon 14)	rs58786055	7 (9)	43 (13)	NA
c.1005+45 T>C	3'UTR	rs57589400	7 (9)	42 (12)	
LPIN2			n = 78 (%)	n = 324 (%)	
c.288+63 G>A	Intron 3	rs7226624	35 (45)	ND	NA
c.1168+44 T>C	Intron 7	rs3826637	26 (33)	ND	31
c.991 G>T; p.Ala331Ser	Exon 7	NDS	1 (1)	0 (0)	1 hit, Infevers*
c.1456+29 A>G	Intron 9	rs16944068	4 (5)	ND	NA
c.1793+27 C>G	Intron 13	NDS	1 (1)	ND	
c.1938+14 G>A	Intron 14	NDS	1 (1)	ND	
c.1801 G>A; p.Glu601Lys	Exon 14	NDS	1 (1)	0 (0)	1 hit, Infevers*
c.2223 C>T; p.Ala741Ala	Exon 17	rs17555442	2 (2)	ND	2
c.2546+51 T>A	Intron 19	rs3737514	9 (11)	ND	8
NOD2/CARD15			n = 78 (%)	n = 206 (%)†	
c.74–25 G>T	Intron 1	rs2076753	18 (23)	68 (33)	37
c.534 C>G; p.Ser178Ser	Exon 2	rs2067085	33 (42)	79 (38)	41
c.802 C>T; p.Pro268Ser	Exon 4	rs2066842 SNP5	20 (26)	57 (28)	31
c.1377 C>T; p.Arg459Arg	Exon 4	rs2066843, SNP6	20 (26)	59 (29)	31
c.1761 C>T; p.Arg587Arg	Exon 4	rs1861579, SNP7	29 (37)	83 (40)	37
c.1833 C>T; p.Ala611Ala	Exon 4	rs61736932	2 (3)	5 (2)	NA
c.2050 C>T; p.Arg684Trp	Exon 4	rs5743276	1 (1)	0	NA
c.2104 C>T; p.Arg702Trp	Exon 4	rs5743277 SNP8	3 (4)	9 (4)	NA
c.2264 C>T; p.Ala755Val	Exon 4	rs61747625	1 (1)	0	NA
c.2863 G>A; p.Val955lle	Exon 9	rs5743291	4 (5)	21 (10)	10
c.3095 G>A; p.Gly1032Asp	Exon 12	New	1 (1)	0	—

* According to Infevers database: http://fmf.igh.cnrs.fr/ISSAID/infevers. † According to Lesage, *et al*[43] and Moll, *et al*[13]. n : allele number; NA: not available; ND: not done; NDS: not described.

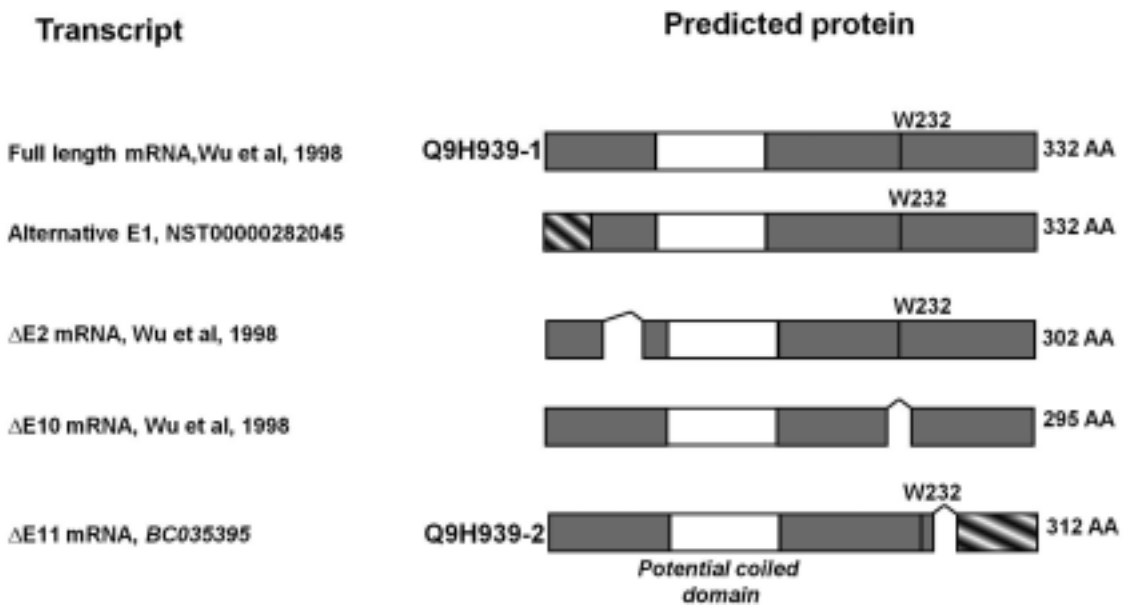

Figure 1. PSTPIP2 transcripts and predicted proteins. Alternative segments are represented by a shaded box and potential coiled domains by a white box.

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ΔE10 isoforms are in-frame, whereas the ΔE11 isoform encodes a different COOH-terminal part, starting at amino acid 246. ΔE11 (BC035395, protein Q9H939-2) has been reported in databases but has not been confirmed at the protein level. ΔE10 lacks the tryptophan 206 that is believed to be essential for PEST-type PTP binding.

All the coding sequences of *PSTPIP2* were analyzed and plotted on the full-length cDNA (NM_024430). Among the 6 sequence variations, 2 were intronic (c.248 –20 T>C, c.516+7 A>G), one was synonymous (c.663 T>C, p.Cys221Cys), one was nonsynonymous (c.964 A>G, p.Asn322Asp), and 2 were located in the 3' untranslated region (c.1005+26 G>T and c.1005+45 T>C). The c.1005+26 G>T may induce a nonconservative substitution of the last amino acid of the ΔE11 isoform (c.934 G>T, p.Gly312Cys). Five variants were linked to a common haplotype (haplotype H: c.248C-c.516G-c.964G-c.1005+26T-c.1005+46C). This haplotype was found to be heterozygous in 5 patients and homozygous in one patient. Its frequency in our SAPHO patient population was 9% (7/76). One patient had the c.663 T>C, p.Cys221Cys allele in the heterozygous state, and the remaining 31 patients were wt/wt. As all but one of these single-nucleotide polymorphisms (SNP) (c.663 T>C, p.Cys221Cys) were reported in dbSNP, but with no frequency information, the 162 controls were screened for these variants. We observed a similar allele frequency for all SNP (see Table 2). In particular, haplotype H showed a frequency of 13% (43/324) in controls, which was not significantly different from the frequency in SAPHO patients (chi-square test = 0.928).

2. LPIN2 variants. Among the 2 heterozygous sequence variations, 6 affected intronic regions of the *LPIN2* gene (c.288+63 G>A, c.1168 T>C, c.1456+29 A>G, c.1793+27 C>G, c.1938+14 G>A, and c.2546+51 T>A) and one was a synonymous substitution (c.2223 C>T, p.Ala741Ala). All but 2 had been described (c.1793+27 C>G and c.1938+14 G>A). These 2 intronic variants were not predicted to be deleterious, based on splice site prediction software (http://www.fruitfly.org/seq_tools/splice.html and http://genome.cbs.dtu.dk/services/NetGene2; accessed 5 November 2009) and were not screened for in controls. Finally, 2 heterozygous nonsynonymous substitutions were found in SAPHO patients (p.Ala331Ser and p.Glu601Lys; Table 2). These 2 variants were not described in dbSNP and were not found by direct sequencing in any of the 162 controls. However, they were mentioned in the "infevers" database (autoinflammatory mutation online registry), in 2 patients with psoriasis[42]. These 2 mutations do not affect the same region as the putative nonsynonymous mutation described in Majeed syndrome (p.Ser734Leu)[25,26] and were not predicted to be deleterious by the various prediction programs (Appendix 2). However, those substitutions affected residues conserved through evolution. The 2 SAPHO patients with these 2 variants also had psoriasis.

3. NOD2 variants. A total of 11 variants were found in 38 patients. Ten had been described[43], and the new variant was p.Gly1032Asp. The frequencies of the NOD2 variants are reported in Table 3. Variants of the NH_2-terminal part of the protein showed a frequency similar to that found in the SNP database (c.74 –25 G>T, c.534 C>G, c.802 C>T, c.1377 C>T). They are all located within the CARD and NBD domains of NOD2 (Figure 2). The SNP showed a high frequency (between 23% and 42%), and most of the SAPHO patients and controls had at least one variant in the heterozygous state. The second part of the NOD2 protein bore fewer variations (frequency below 4%), except for p.Val955Ile (10%). This latter variant has been considered neutral[43]. Six rare variants were observed in the SAPHO patients: one (p.Ala611Ala) was synonymous (considered a neutral variant in previous studies) and 5 were nonsynonymous (p.Arg684Trp, p.Arg702Trp, p.Ala755Val, p.Val955Ile, p.Gly1032Asp). One variant (p.Arg702Trp, SNP8) has been linked to CD (DCM, disease-causing mutation)[44], and 2 others have been potentially linked to CD (p.Arg684Trp and p.Ala755Val)[43]. Finally, one patient had a new variant (p.Gly1032Asp), in the heterozygous state, which affected the COOH-terminal part of the NOD2/CARD15 protein. Only one of them affected a conserved amino acid (p.Ala755Val) (Appendix 2). Protein impact prediction software clearly identified p.Arg702Trp and p.Arg684Trp as probably deleterious. The rare variant p.Gly1032Asp identified here does not affect a conserved residue and was not predicted to be deleterious.

4. Rare NOD2 variants. Five SAPHO patients had rare NOD2 variants (p.Arg684Trp, p.Ala755Val, p.Gly1032Asp) and/or a DCM (p.Arg702Trp) in the heterozygous state (Table 3). Four patients had one variant, and one patient had 2 variants (p.Arg702Trp and p.Ala755Val); DNA from these subjects' parents was not available to confirm that variants affected both alleles of the *NOD2* gene. The frequency of rare variants and DCM in the SAPHO population was not significantly different from reported frequencies in healthy controls (6/76 = 8% vs 21/206 = 10%)[43,44]. The numbers of rare variants and NOD2 DCM did not differ significantly between our SAPHO and CD patients and controls studied by Lesage, *et al* (chi-square = 0.96; Table 3).

Familial studies. Three genes were analyzed in 4 patients from 2 pedigrees (Family 1, P1, P2, P3, and Family 2, P4; Figure 3). Both families were Sephardic Jews from North Africa. No specificities were found in terms of bone or skin lesions.

In family 1 the 3 SAPHO patients were siblings. Their parents had no clinical signs. The 2 affected girls (P1 and P2) had SAPHO syndrome, and P1 also had psoriatic arthri-

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Table 3. Proportions of patients with 0, 1, 2, or 3 disease-causing mutations (DCM) or rare *NOD2* variants in this study and in previous Crohn's disease studies.

	DCM or Rare *NOD2* Variant.			
	0	1	2	3
Controls, n = 103 (%)	82 (80)	21 (20)	0 (0)	0 (0)
Crohn's disease, n = 458* (%)	229 (51)	145 (31)	81 (17)	3 (1)
SAPHO, n = 38 (%)	33 (86)	4 (13)	1 (3)	0 (0)

* Reported by Lesage, *et al*, 2002[43]

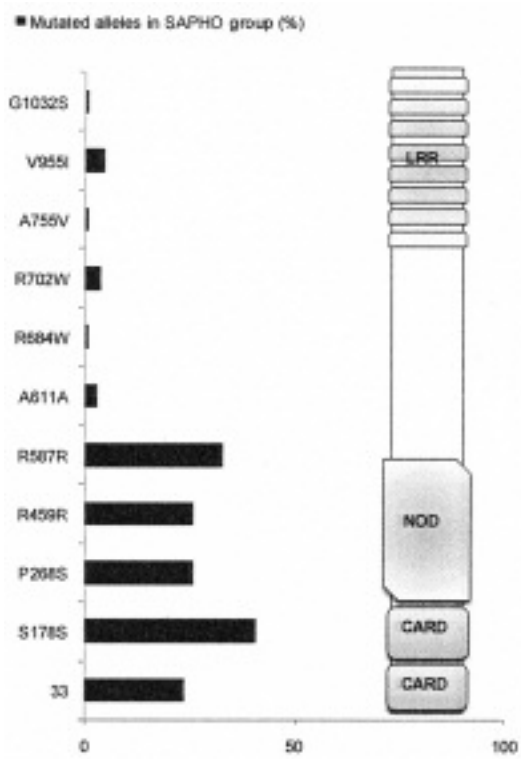

Figure 2. Distribution of the variants along the NOD2 protein sequence and percentage of mutated alleles observed among the 38 patients with the SAPHO syndrome.

tis. Their brother, P3, had SAPHO syndrome and psoriasis. Another brother had ulcerative colitis but not SAPHO syndrome. Age at onset and clinical characteristics of these patients are reported in Table 4. No rare variants of *NOD2*, *PSTPIP2*, or *LPIN2* were found in P1, P2, and P3.

In family 2 the patient (P4) had a sister with the SAPHO syndrome and a brother with CD. The parents were free of SAPHO signs. DNA from the affected sister was not available. Patient P4 had a typical form of SAPHO syndrome, with no clinical signs of CD. Disease was moderate, and onset occurred at age 27 years. No rare variants were detected in P4, including *NOD2* DCM.

DISCUSSION

SAPHO syndrome is an uncommon form of inflammatory spondyloarthritis of unknown cause. Susceptibility genes may be involved, as rare familial clusters have been reported. Because previous studies showed no HLA gene involvement[10,20], we chose to undertake an association study with 3 candidate genes: (1) *PSTPIP2* gene involved in murine autoinflammatory bone disorders similar to those seen in the human SAPHO syndrome; (2) the *LPIN2* gene involved in Majeed syndrome (autosomal recessive inheritance), which is also close to the SAPHO syndrome; and (3) the *NOD2* gene associated with CD.

PSTPIP2 was involved in the *cmo* and *Lupo* mouse models[21,22], which share some features of human SAPHO syndrome. Bone lesions in *cmo* mice resemble those observed in SAPHO syndrome, with both acute and chronic inflammatory processes, abnormal bone resorption, and deformities. The main difference with the SAPHO syndrome is the location of the lesions: long bones (limbs and clavicles) are affected by the inflammatory process in 75% of SAPHO patients but are spared in *cmo* mice[10,11,24]. In addition, skin lesions in *cmo* mice are seen only in the ears, also affecting the cartilage, while palmoplantar pustulosis and severe acne are the most common inflammatory skin disorders in the syndrome[10,23]. Gastrointestinal inflammation (CD or ulcerative colitis) has also been reported in patients with the SAPHO syndrome[10,25-27] but not in *cmo* mice[21]. The *Lupo* mouse model has a phenotype primarily affecting the distal appendages, with edematous and swollen toes that, in advanced stages, can adhere together and become osteolytic with localized necrosis. Such features are never observed in SAPHO patients. Analysis of the *PSTPIP2* coding sequence revealed no specific variants in the 38 SAPHO patients studied, thus confirming results obtained in 10 SAPHO patients[45]. A rare common haplotype, with a potential nonsynonymous substitution of an alternatively spliced form (ΔE11 isoform), had the same frequency in our patients as in our healthy controls. Thus, to date, no human diseases have been linked to an abnormal PSTPIP2 protein (also known as macrophage actin-associated tyrosine phosphorylated protein, MAYP).

We also studied *LPIN2*, as it is involved in Majeed syndrome, a condition that shares with SAPHO syndrome the presence of chronic recurrent multifocal osteomyelitis. However, dyserythropoietic anemia and neutrophilic dermatosis are not seen in SAPHO syndrome[25,26]. SNP of the *LPIN2* gene were similarly frequent in the patients and con-

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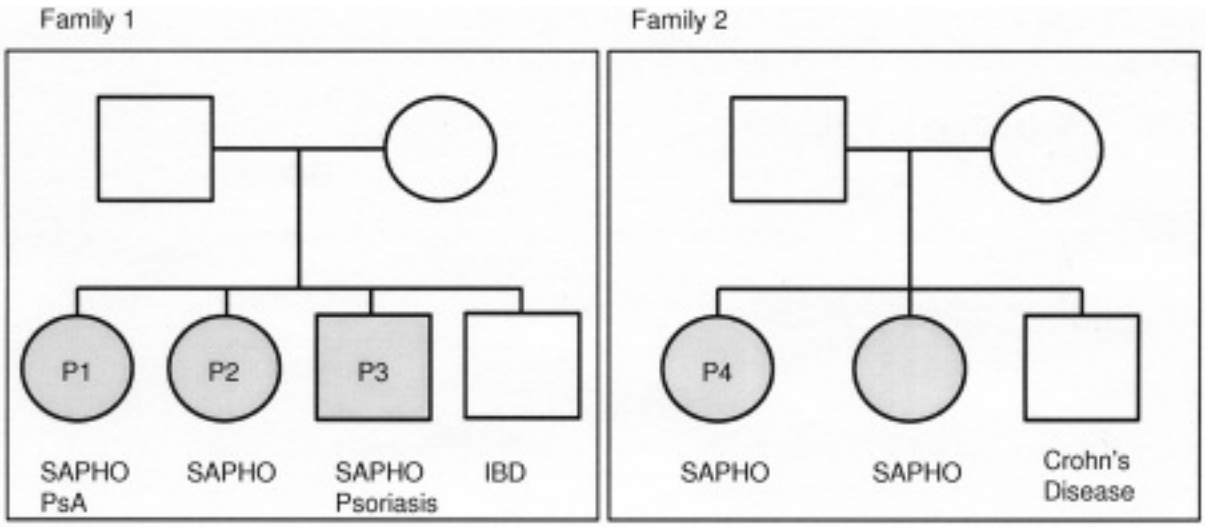

Figure 3. Pedigree of the 2 SAPHO syndrome families.

Table 4. Familial cases of the SAPHO syndrome. Ethnicity: all Sephardic Jews from North Africa.

	Family 1			Family 2
	P1	P2	P3	P4
Bone lesions				
ACW	Yes	Yes	Yes (2)	Yes
Vertebrae	Yes	No	No	No
Pelvis	No	No	Yes	No
Distal bones	No	No	No	No
Mandible	No	No	No	No
Total bone foci	2	1	3	1
Articular lesions				
Anterior chest pain	Yes (2)	Yes	Yes	No
Pelvis	—	No	Yes	No
Distal joints	—	No	—	No
Total articular lesions	2	1	2	0

trols[42]. *LPIN2* haplotype analysis was not possible in our study because the parents' DNA was not available. Nevertheless, we found 2 rare variants (p.Ala331Ser and p.Glu601Lys) in the heterozygous state in 2 SAPHO patients with psoriasis, an association observed in almost 50% of SAPHO patients. These 2 variants are listed in the "infevers" database[42]; they affect residues conserved through evolution but were not predicted to have a deleterious effect on protein function. The "infevers" database currently lists 5 rare *LPIN2* variants found in patients with psoriasis (p.Ala331Ser, P348Leu, Lys387Glu, Leu504Phe, Glu601Lys). Moreover, the *LPIN2* locus had been weakly associated to psoriasis susceptibility locus, PSORS10[46]. This suggests that *LPIN2* may account for the psoriasis component of SAPHO in these 2 patients. However, the role of *LPIN2* in the inflammatory phenotype of the Majeed syndrome and in psoriasis is still unclear. Lipin 2 has a putative role in fat metabolism and mitosis and, more interestingly, it may control inflammation following oxidative stress[47]. This latter property could be of particular importance in SAPHO syndrome, as we have observed PMN hyperactivation in this setting[11].

Finally, we also studied the *NOD2* gene, as it is involved in CD (present in 10% of SAPHO patients), as well as in chronic recurrent osteomyelitis, a childhood form of the SAPHO syndrome[48]. However, rare variants and described DCM were not found in excess relative to the controls.

Altogether, we did not find a higher frequency of SNP in the 3 tested genes in the SAPHO syndrome versus healthy controls. Moreover, these genes were not specifically involved in familial cases of the SAPHO syndrome, as no rare variants were described in the 4 studied probands. Our findings therefore show no involvement of these 3 genes in the pathogenesis of SAPHO syndrome. However, this negative result could be due to limited statistical power, as only 38 SAPHO patients could be tested and as we focused on SNP in coding regions and exon/intron junctions.

Recent studies suggest that SAPHO syndrome could be related to PMN dysfunction. Ferguson, *et al*[49] recently reported a SAPHO-like family (a child and his mother) with subnormal PMN intracellular production of reactive oxygen species (ROS). We failed to detect such ROS underproduction with 2 other biological approaches (extracellular ROS assay and chemoluminescence) in 29 SAPHO patients[11]. Intracellular ROS production thus needs to be investigated in non-familial SAPHO patients to confirm its possible role. Another recent study showed a high level of IL-1ß production by whole-blood leukocytes in 9 children with a severe SAPHO-like phenotype due to mutations in the *IL1RN* gene encoding the IL-1-receptor antagonist[50]. Finally, we reported that *P. acnes* stimulated IL-8 release by PMN from SAPHO patients (6-fold vs controls), further supporting a role of PMN dysregulation in this disease[11]. Interestingly, in our present study, we also found that PMN from patients with at least one rare *PSTPIP2*, *NOD2*, or *LPIN2* variant

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had an intermediate capacity to release IL-8 on bacterial stimulation (3- to 4-fold increase, n = 9) compared with patients without rare variants (6-fold increase, n = 27, data not shown). Even if the 3 genes are not associated with SAPHO pathogenesis, they might influence the clinical course by modulating PMN IL-8 production on bacterial stimulation. Indeed, the 9 SAPHO patients with intermediate IL-8 production after bacterial stimulation had earlier clinical onset than patients with no rare variants (22.7 ± 2.8 yrs vs 34.8 ± 2.3 yrs, respectively), but the sample was too small for meaningful statistical analysis. This observation needs to be confirmed in a larger population in order to detect a potential link between rare *PSTPIP2*, *NOD2*, or *LPIN2* variant and PMN IL-8 production, and between IL-8 production and the clinical course of patients with SAPHO.

Appendix 1. Presence/absence (✓/✕) of skin lesions in patients with SAPHO syndrome.

Patient	Severe Acne	PPP	Psoriasis	Patient	Severe Acne	PPP	Psoriasis
1	✕	✓	✕	20	✓	✕	✓
2	✕	✓	✕	21	✕	✕	✕
3	✕	✓	✓	22	✕	✕	✓
4	✕	✕	✓	23	✕	✕	✕
5	✕	✓	✕	24	✕	✓	✓
6	✕	✓	✓	25	✕	✓	✕
7	✕	✓	✕	26	✕	✓	✓
8	✕	✕	✓	27	✕	✕	✓
9	✕	✓	✓	28	✕	✓	✓
10	✓	✕	✓	29	✓	✕	✕
11	✓	✕	✓	30	✕	✓	✕
12	✕	✓	✓	31	✓	✕	✕
13	✕	✓	✓	32	✕	✕	✓
14	✕	✓	✕	33	✕	✕	✓
15	✕	✕	✕	34	✕	✓	✓
16	✕	✕	✕	35	✓	✕	✕
17	✕	✓	✕	36	✕	✕	✓
18	✕	✓	✕	37	✓	✕	✕
19	✕	✓	✓	38	✓	✕	✕
				TOTAL (%)	8 (21)	19 (50)	20 (52.6)

PPP: Palmoplantar pustulosis

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Appendix 2. Main characteristics of the rare variants identified in patients with SAPHO syndrome.

Gene GI	Protein ID	Mutation	AA Conservation	Grantham Score[a]	SIFT[b]	Panter[b]	Panet[d]	Polyphen[e]
PSTPIP2 gi:48429065	Q9H939-2	G312C	No data	159	N.A.[f]	N.A.[f]	Pathological	Probably damaging
LPIN2 gi:2495724	Q92539	A331S	Conserved[g]	99	Non damaging	Non deleterious	Neutral	Benign
		E601K	Conserved[g]	56	Non damaging	Non deleterious	Neutral	Benign
NOD2 gi:20137973	Q9HC29	R684W	Non conserved[g]	101	Pathologic	Deleterious	Pathological	Probably damaging
		R702W	Non conserved[g]	101	Pathologic	Deleterious	Pathological	Probably damaging
		A755V	Conserved[g]	64	Non damaging	Deleterious	Neutral	Benign
		G1032D	Non conserved[g]	94	Non damaging	N.A.[f]	Pathological	Benign

a Considered as pathological if the Grantham score is > 100. http://www.genome.jp/dbget-bin/www_bget?aax2:GRAR740104
b http://sift.jcvi.org/ ; c http://www.pantherdb.org/tools/csnpScoreForm.jsp; d http://mmb2.pcb.ub.es:8080/PMut/;
e http://genetics.bwh.harvard.edu/pph/; f NA: not assessable;
g Blastp with *Pan troglodytes*, *Mus musculus* and *Rattus norvegicus* protein sequences

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