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Single-nucleotide polymorphisms *p53 G72C* and *Mdm2 T309G* in patients with psoriasis, psoriatic arthritis, and SAPHO syndrome

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Abstract Psoriasis (Ps), psoriatic arthritis (PsA), and SAPHO syndrome are diseases of unknown etiology that share common clinical features; however, family studies support the hypothesis of a genetic background for each of these diseases. To study the two common single-nucleotide polymorphisms (SNP) in the murine-double-minute-2- (*Mdm2*) and *p53* genes in patients with Ps, PsA, and SAPHO syndrome. Genomic DNA was obtained from 187 patients with Ps, 50 with PsA, and 36 with SAPHO as well as 478 healthy controls. *Mdm2*-gene SNP *T309G* and *p53*-gene SNP *G72C* genotypes were determined by the polymerase chain reaction. Genotype and allele frequencies were analyzed with χ^2 -tests. Among the patients with Ps and PsA, no differences in allele or genotype frequencies of the *p53*-gene SNP *G72C* and *Mdm2*-gene SNP *T309G* were detected. However, in the SAPHO patients group, the frequencies of the *Mdm2* SNP309 G allele and the genotype SNP 309 GG were significantly increased compared with

the controls (G allele: 51.4 vs. 38.7%, $P = 0.034$; genotype GG: 36.1 vs. 14.2%, $P = 0.002$). In addition, the frequencies of the *p53* SNP72 C allele and the genotype SNP 72 CC were also increased in the SAPHO patients cohort (C allele: 36.1 vs. 25.6%, $P = 0.05$; genotype CC: 16.7 vs. 6.3%, $P = 0.05$). SAPHO syndrome may be linked to an imbalance between MDM2 and p53 regulation with a “weak” p53-response associated with the *Mdm2* SNP 309 G allele. In contrast, the p53 network does not seem to play a major role in pathogenesis of Ps or PsA.

Keywords Polymorphism · p53 · Mdm2 · Psoriasis · Arthritis · SAPHO

Introduction

The histopathological features of the skin in patients with psoriasis (Ps) are characterized by elevated proliferation and inflammatory activity. Overexpression and functional mutations of *p53* have been noted in cutaneous lesions of Ps [1]. Moreover, altered *p53* expression levels were detected in synovial tissues of joints from patients with psoriatic arthritis [2]. SAPHO syndrome is defined inter alia by singular or multiple localized proliferation and inflammation of the bone, with the leading symptoms being hyperostosis and osteitis [3, 4]. The tumor suppressor protein p53 and its most important negative regulator, Mdm2, are positioned in the center of a pathway that eliminates damaged cells through apoptosis [5]. Mdm2 is an ubiquitin ligase that binds p53 and blocks its function as a transcription factor. Moreover, recent in vitro and in vivo studies have indicated that p53 is one of the most important negative regulators of the proinflammatory transcription factor NF κ B [6]. Functional SNPs were detected in both

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genes. *Mdm2* SNP *T309G* is located in the promoter/enhancer region of the *mdm2* gene intron 1 and affects the binding of the transcription factor SP1. The *G* allele has been documented to cause higher Mdm2 levels and consequently, less functional p53 in stressed cells. On the other hand, p53 binds to the promoter of *mdm2*, and activates its expression. The balance between MDM2 and p53 regulates the expression of downstream genes, and depends on the protein level and functional activity of both molecules [7]. The *p53* gene SNP *G72C* gives rise to either an arginine or a proline at amino acid position 72 in the proline-rich domain (PRD) of p53 and thereby affects the structure of p53 and influences its functional activity. p53 72 Arg has been reported to induce apoptosis much more efficiently than p53 72 Pro [8]. Here we have conducted a case control study to evaluate whether *p53* SNP *G72C* and/or *Mdm2* SNP309 might be associated with Ps, PsA, and SAPHO syndrome.

Patients and methods

We recruited 186 patients with Ps, 50 with PsA, and 36 with SAPHO syndrome from the outpatient departments of Rheumatology and Dermatology of Saarland University Medical School, Homburg/Saar, Germany, and from the Department of Rheumatology, University Medical School Hannover, Germany. Blood donors from the Institute for Transfusion Medicine, University of Saarland Medical School, served as healthy controls ($n = 478$). Patients and controls were of central European Caucasian ethnicity. The ethics committees of the medical association of the Saarland, Germany, approved the study, and all study participants gave written informed consent. All patients fulfilled the diagnostic criteria for Ps, PsA or SAPHO syndrome [3, 9]. The patient's characteristics are outlined in Table 1. Ps- or SAPHO Patients with axial disease and spondylitis were excluded in order to avoid including patients with spondylitis ankylosans (and Bechterew's disease). The SNP genotyping was performed as previously reported [10]. The statistical analysis was performed by data analysis using SPSS statistical software. The differences in genotype and allele frequencies between patients and controls were analyzed using χ^2 -tests for 2×3 tables and 2×2 tables,

respectively. Differences in allele frequencies were quantified by odds ratios (OR) and 95% CI.

Results

The allele and genotype frequencies are shown in Table 2. The analysis of both the allele and genotype frequencies of *p53* SNP *G72C* and *Mdm2* SNP *T309G* revealed no differences between the patients with Ps or PsA, and the healthy controls, respectively. A subgroup analysis according to gender also failed to show differences (data not shown). In contrast, the *Mdm2* SNP *T309G* allele frequencies among SAPHO patients differed significantly from the allele frequencies among the controls, with the minor *G* allele being more frequent in SAPHO patients (51.4 vs. 38.7%, OR 0.60, CI 95% 0.37–0.97, $P = 0.034$). In addition, the frequencies of the *Mdm2* genotype *GG* were significantly higher in the patient group compared to the controls (36.1 vs. 14.2%, $P = 0.002$). Analysis of the *p53* SNP *G72C* revealed that among SAPHO patients the frequencies for the minor C-allele as well as for the genotype *CC* was increased compared to the controls, albeit with weak significance ($P = 0.052$, 0.054, respectively). The Hardy–Weinberg equilibrium was tested for genotype distribution among the SAPHO patients and healthy controls outlined in Table 3. A significant difference was found in the distribution of the *Mdm2* SNP 309 genotype between the study population and the calculated values: 12/11/8 versus 8.5/18/9.5 for TT/GT/GG genotype, respectively ($P = 0.020$).

Discussion

To our knowledge this is the first study that indicates an association between the susceptibility for SAPHO syndrome and *Mdm2* SNP *T309G*. For psoriasis and psoriatic arthritis no association was detected, in accordance with a recent study in PsA patients [11]. Despite many clinical similarities between Ps, PsA and SAPHO, several clear hints at different genetic determinants have recently emerged. For example, large studies point to distinct genetic backgrounds for PsA and Ps [12]. Furthermore, PsA exhibits a much greater heritability among first-degree

Table 1 Clinical characteristics of patients and healthy controls

	Controls $n = 478$	Ps $n = 186$	PsA $n = 50$	SAPHO $n = 36$
Median (range, years)	37 (18–65)	45 (18–72)	45 (18–73)	43 (18–63)
Gender female (%)	37	39	41	43
<i>HLA B27</i> pos (%)	ND	18	21	12

Ps psoriasis, PsA psoriatic arthritis, ND not determined

Table 2 Allelic and genotype frequencies of the SNP *p53 G72C* and SNP *Mdm2 T309G* in patients and healthy controls

	Controls <i>n</i> = 478 (100%)	Psoriasis <i>n</i> = 186 (100%)	<i>P</i> value ^a ; OR; CI	Psoriatic arthritis <i>n</i> = 50 (100%)	<i>P</i> value ^a ; OR; CI	SAPHO syndrome <i>n</i> = 36 (100%)	<i>P</i> value ^a ; OR; CI (power) ^b
<i>Allelic and genotype frequencies</i>							
<i>p53 SNP G72C</i> -alleles (rs1042522)							
G	711 (74.4)	278 (74.7)	0.893	80 (80)	0.217	46 (63.9)	0.052
C	245 (25.6)	94 (25.3)	1.01; 0.83–1.25	20 (20)	1.38; 0.83–2.30	26 (36.1)	0.61; 0.37–1.01; (49%)
<i>p53 SNP G72C</i> genotypes							
GG	263 (55.0)	103 (55.4)	0.984	31 (62.0)	0.388	16 (44.4)	0.054
GC	185 (38.7)	72 (38.7)		18 (36.0)		14 (38.9)	(60%)
CC	30 (6.3)	11 (5.9)		1 (2.0)		6 (16.7)	
<i>Mdm2 SNP T309G</i> alleles (rs2279744)							
T	586 (61.3)	226 (60.7)	0.840	58 (58)	0.497	35 (48.6)	0.034
G	370 (38.7)	146 (39.3)	0.99; 0.85–1.14	42 (42)	0.92; 0.72–1.16	37 (51.4)	0.60; 0.37–0.97 (61%)
<i>Mdm2 SNP T309G</i> alleles							
TT	176 (36.8)	71 (38.2)	0.641	19 (38.0)	0.326	12 (33.3)	0.002
TG	234 (49.0)	84 (45.2)		20 (40.0)		11 (30.6)	(91%)
GG	68 (14.2)	31 (16.6)		11 (22.0)		13 (36.1)	

CI confidence interval (95%), OR odds ratio, *Mdm2* murine-double-minute-2

^a χ^2 -tests for 2 × 3 tables and 2 × 2 tables, respectively

^b Power calculating according to χ^2 and effect size (PAWE)

Table 3 Hardy Weinberg equilibrium in SAPHO patients and controls

	Controls <i>n</i> = 478 (expected)	<i>P</i> value ^a ; variable allele frequency	SAPHO syndrome <i>n</i> = 36 (expected)	<i>P</i> value ^a variable allele frequency
<i>Genotype frequencies</i>				
<i>p53 SNP G72C</i>				
GG	263 (264.4)	0.738	16 (14.7)	0.346
GC	185 (182.2)	0.26	14 (16.6)	0.36
CC	30 (31.4)		6 (4.7)	
<i>Mdm2 SNP T309G</i>				
TT	176 (179.6)	0.487	12 (8.5)	0.020
TG	234 (226.8)	0.39	11 (18.0)	0.51
GG	68 (71.6)		13 (9.5)	

^a χ^2 -tests for 2 × 3 tables

relatives than does psoriasis [13]. For the rare SAPHO syndrome, only few family studies have been published. Dumolard et al. [14] has presented three siblings that fulfill the SAPHO criteria. One study examined the HLA status of all three disease entities. Whilst *HLA-Cw6* and *HLA B27* were associated with Ps and PsA, no association with SAPHO syndrome was observed [15]. The data presented here identify with *Mdm2 SNP T309G* for the first time a functional SNP in the p53 tumor suppressor pathway that may affect susceptibility to SAPHO syndrome. In addition, the *p53 SNP G72C* showed a trend for higher frequency of the minor allele in SAPHO patients. Both alleles (*Mdm2 SNP 309 G* and *p53 SNP 72 C*) have been linked to a “weak” p53 response by a large number of studies, with

the *Mdm2 G* allele producing more of the p53 antagonist Mdm2 and the p53 72 Pro form of wild-type p53 being a much less efficient apoptosis inducer [16, 17]. With regard to the balance between MDM2 and p53 regulating the expression of downstream genes our findings indicated that SAPHO may be favoured by a less efficient p53 response in one or several of the many cell types involved in the disease. Future studies on greater cohort sizes are needed to confirm and extent this finding.

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developed the statistical study design for this study and performed the statistical analysis. All authors were involved in the interpretation of the data. All authors read and approved the final manuscript.

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