MICA and NKG2D variants as risk factors in spondyloarthritis: a case–control study

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Received: 25 June 2018 / Revised: 22 July 2018 / Accepted: 24 July 2018 / Published online: 4 September 2018
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Abstract
The major histocompatibility complex class I polypeptide-related sequence A (MICA) glycoprotein mediates the activation of the natural killer group 2D receptor (NKG2D) expressed on NK and CD8+ T cells. A methionine or valine at position 129 in exon 3 results in strong (MICA129 met) or weak (MICA129 val) binding to NKG2D. The MICA A5.1 allele causes a premature stop codon. Various NKG2D polymorphisms are associated with low (NKC3 C/C and NKC4 C/C) or high (NKC3 G/G and NKC4 T/T) levels of NK cell cytotoxic activity. In 162 patients with spondyloarthritis (115 with ankylosing spondylitis, 46 with psoriatic arthritis and 1 with reactive arthritis) compared to 124 healthy controls, MICA-129 with methionine allele was more frequent in patients with spondyloarthritis (odds ratio (OR) (95% confidence interval) = 4.84 (2.75–8.67)), whereas MICA-129 val/val, MICA A5.1 and NKC3 C/C variants were less frequent (OR = 0.20 (0.11–0.37), 0.15 (0.06–0.36) and 0.24 (0.13–0.44), respectively). After adjustment for HLA-B*27 status, only NKC3 C/C remained linked to spondyloarthritis (adjusted OR = 0.14 (0.06–0.33)). Homozygosity for MICA A5.1 is linked to ankylosing spondylitis, and NKC3 C/C and MICA-129 val/val to psoriatic arthritis. MICA and NKC3 polymorphisms (related to a low NK cell cytotoxic activity) constituted a genetic association with spondyloarthritis.

Introduction
Spondyloarthritis (SpA) refers to a group of chronic inflammatory diseases with a number of similar features, including axial manifestations (such as sacroiliitis or spondylitis), peripheral manifestations (such as arthritis, enthesitis and dactylitis) and extra-articular manifestations (such as psoriasis, uveitis and inflammatory bowel disease (IBD)) [1]. Ankylosing spondylitis (AS) and psoriatic arthritis (PsA) are the two most prevalent SpA diseases. In young adults, AS and PsA cause irreversible tissue damage and worsen the quality of life [2]. The prevalence of SpA is 0.43% in France, with a sex ratio of 1 [3]. The presence of the well-known genetic marker HLA-B*27 allele in patients with symptoms increases the risk of developing SpA (risk ratio (95% confidence interval (CI)) = 39 (17–86)), and is one of the Assessment of Spondyloarthritis International Society (ASAS) criteria for diagnosis of this disease [4]. In the general population, the HLA-B*27 allele is found in 1 to 5% of symptom-free individuals. However, this allele accounts for only 20 to 40% of the genetic susceptibility to SpA, suggesting that other genes are significantly involved in the physiopathology of these diseases [5].

On chromosome 6, the gene closest to the HLA-B locus is major histocompatibility complex class I chain A related (MICA). It codes for a cell stress-inducible glycoprotein [6] that mediates the activation of natural killer group 2D receptor (NKG2D) expression and the associated pro-inflammatory pathway [7–9]. Exons 2–4 of MICA
best of our knowledge, NKG2D receptor polymorphisms
MICA
between SpA and
high level [12].
whereas
are associated with a low level of NK cell cytotoxicity,
repeat microsatellite polymorphisms. Moreover, the
cytoplasmic domain) [11].
of truncated transmembrane MICA protein (i.e., lacking the
creates a premature stop codon and results in the production
A5.1
allele has an additional G nucleotide insertion, which
natural killer (NK) cells, CD8
cytotoxic activity. In particular,
to be closely associated with differences in the level of
Eight single-nucleotide polymorphisms (SNPs) are known
computerized tomography,
CT
and
rheumatoid arthritis) but not yet in SpA [18].
The primary objective of this study was to determine
whether MICA and NKG2D polymorphisms (linked to the
cytotoxic activity of NK cells) are associated with a pre-
disposition to SpA (i.e., AS or PsA) and the clinical and
radiological features of the disease.

Results

Demographic characteristics of the study groups

Patients with SpA (n = 162, mean (range) age at diagnosis
of SpA: 40 (9–72), 55% male) were compared with healthy
control participants (n = 90, 63.7% male) (Table 1). The
mean (range) disease duration was 8.6 (1–46) years. The
HLA-B*27 allele was observed in 99 patients (61%) and 4
controls (3.2%, p = 1.8 × 10^{-18}). At diagnosis, 80, 44, 23
and 11% of the patients presented with back pain, arthritis,
enthesitis and dactylitis respectively. All patients met ASAS
criteria. One hundred and thirty-one patients were ASAS-
positive axial SpA: 110 patients had structural damage or
sacroiliitis (SI X-ray, computed tomography (CT) scan or
magnetic resonance imaging (MRI)) and 21 patients were
HLA-B*27 positive associated with more than 2 others
symptoms. Thirty-one patients were only ASAS-positive
peripheral SpA. In 51 patients who had a SI X-ray, 21
patients (13%) met the modified New York (mNY) criteria.
Other patients had SI CT scan or MRI or did not have SI
explorations because they had only peripheral symptoms.
One hundred and fifteen patients (71%) had AS, 46 (28%)
had PsA and 1 patient had reactive arthritis.

Frequencies of MICA/NKG2D polymorphisms in the
SpA population

The overall observed frequencies of MICA/NKG2D
polymorphisms are listed in Table 2. The homozygote MICA
129 Val/Val was found to protect against the development
of SpA (odds ratio (OR) (95% CI) 0.20 (0.11–0.37)),
whereas the MICA 129 Met allele was more prevalent in
patients with SpA than in controls and thus constituted a
genetic association for SpA (OR 4.84 (2.75–8.67)).

Heterozygous and homozygous MICA A5.1 mutations
constituted a genetic association with SpA, with ORs of
0.56 (0.32–0.99) and 0.15 (0.06–0.36), respectively.

The NKC-3 C/C polymorphism was found to protect
against SpA (OR = 0.24 (0.13–0.44)), whereas the presence
of a G mutation in NKC3 constituted a genetic association
with SpA (OR = 4.12 (2.33–7.47)). After adjustment for
HLA-B*27 status, these polymorphisms remained
significantly associated with protection (OR_{adj} = 0.14 (0.06–
and disease risk ($OR_{adj} = 6.73$ (3.04–16.6)), respectively.

No significant associations between NKC4 polymorphisms and SpA were found.

All three protective markers (MICA 129 Val/Val, the MICA A5.1 mutation and the NKC3 C/C polymorphism) were found in 2 of the 160 patients with SpA (1%) and in 12 of the 90 controls (13%). This combination protected against SpA ($OR = 0.08$ (0.01–0.31); $p = 0.0001$).

In multivariate analysis, before adjustment for the HLA-B*27 status, heterozygous and homozygous MICA A5.1 mutations, the presence of a G mutation in NKC3 constituted a genetic association with SpA, with ORs of 0.60 (0.37–0.95), 0.20 (0.09–0.45) and 4.51 (2.35–8.93), respectively, whereas the NKC3 C/C polymorphism was
found to protect against SpA (OR = 0.22 (0.11–0.42)). No significant associations between NKC4 polymorphisms and SpA were found. Given that only NKC3 status was significant after HLA-B*27 adjustment, we did not perform a multivariate analysis.

**Frequencies of MICA/NKG2D polymorphisms in AS and PsA subgroups**

In patients with AS, the MICA 129 Val/Val polymorphism, homozygous MICA A5.1 mutation and the NKC3 C/C polymorphism protected against AS (OR = 0.19 (0.102–0.362), 0.11 (0.03–0.31) and 0.30 (0.16–0.56), respectively). After adjustment for HLA-B*27 status, only the homozygote MICA A5.1 mutation had still a genetic association (ORadj = 0.28 (0.067–0.96)).

In patients with PsA, MICA 129 Val/Val, the homozygous MICA A5.1 mutation and the NKC3 C/C polymorphism were protective (OR = 0.24 (0.10–0.55), 0.32 (0.08–1.02) and 0.11 (0.16–0.56), respectively). After adjustment for HLA-B*27 status, MICA 129 Val/Val and NKC3 C/C polymorphisms were still protective factors (ORadj = 0.33 (0.13–0.76) and 0.09 (0.02–0.28), respectively).

Any association was found between MICA 129 Met/Val, MICA A5.1, NKC3 C/G, NKC4 C/T polymorphisms and clinical data (Table 3). Indeed, these polymorphisms are not linked to uveitis, psoriasis, inflammatory bowel disease and sacroiliac joint damage in our cohort.

**Discussion**

Associations between MICA/NKG2D polymorphisms and several immune-mediated diseases have been reported previously. In particular, MICA polymorphisms are associated with inflammatory rheumatic diseases [19], Behçet’s disease [20], IBD1 [21], systemic lupus [22] and ankylosing spondylitis [23, 24]. NKG2D variants have also been linked to rheumatoid arthritis susceptibility and severity [18]. Given the complex gene sequences and protein expression profiles of MICA/NKG2D, studies of the pathogenesis of immune-mediated SpA are essential. To address this issue, we genotyped MICA129 and MICA A5.1 polymorphisms, and two NKG2D SNPs (rs1049174 for NKC3 and rs2255336 for NKC4) in patients with SpA and in healthy controls.

Our study population of mainly Caucasian patients was similar to the literature data with regard to age at diagnosis, sex ratio, the frequency of AS vs. PsA and the percentage of patients bearing HLA-B*27 alleles [2, 3]. We had a small number of patients meeting the mNY criteria because the majority of our patient did not have the result of SI X-ray in their data (the result was not available at the time of collecting data and/or the used of MRI is more common than the SI X-ray to diagnose a SpA). However, all patients met ASAS criteria.

We found that MICA 129 Val/Val constituted a genetic association with SpA (i.e., both AS and PsA). In the study of Zhou et al. [23] of 1070 American patients with AS (all of whom met the New York modified criteria), the same result was found both before and after adjustment for HLA-B*27 status. We found that MICA-129 Val/Val protected against PsA. We also found that this polymorphism constituted a genetic association with X-ray-confirmed sacroiliitis. In view of the link between MICA129 Val/Val and low affinity for its receptor, one pathophysiological hypothesis holds that patients with SpA and MICA129 Val/Val polymorphism have lower levels of inflammation near their sacroiliac joint and thus suffer less damage from sacroiliitis.

In the study of Zhou et al. [23], heterozygous and homozygous MICA A5.1 mutations protected against AS in 1070 American patients (OR = 0.35 (0.29–0.42)) and 473 Chinese patients (0.51 (0.39–0.67) [23]. Our present results also showed that heterozygous and homozygous MICA A5.1 mutations were linked to PsA.

To the best of our knowledge, the association between NKC3 polymorphisms and SpA has not previously been studied. Here, we found that the presence of a G mutation in NKC3 was a risk factor for SpA both before and after adjustment for HLA-B*27 status. NKC3 G/G status could be used to refine the diagnosis of SpA, particularly when a patient is negative for HLA-B*27 status. Given the association between NKC3 G/G and high levels of cytotoxicity [12], it would be interesting to understand the relationship between this polymorphism and severe, aggressive forms of the disease.

It is well established that the MICA gene confers susceptibility to SpA [23]; indeed, MICA*007:01 is a significant risk allele for SpA in Caucasian and Han Chinese populations, and MICA*019 is a major risk allele in Chinese patients. Moreover, the MICA129 met/met genotype was linked to juvenile SpA (independently of HLA-B*27 status) in Algerian patients [24], rheumatic disease-associated IBD in Spanish patients [25] and systemic lupus erythematosus in Japanese patients [19]. NKG2D gene variants have also been linked to rheumatoid arthritis susceptibility and severity [18]. Indeed, the frequencies of the NKG2D9 A allele and the NKG2D10 T allele were significantly higher in patients with deformities, whereas the frequencies of the NKG2D9 G allele and the NKG2D10 A allele were higher in patients without deformities. The mechanism by which MICA/NKG2D polymorphisms protect against inflammatory rheumatic diseases has not been fully elucidated. However, Nielsen et al. [26] showed that fibroblast-like synoviocytes from patients with rheumatoid arthritis (RA-
FLS) express many ligands of activating and inhibitory NK cell receptors. Blockade of the interaction between CD94/NGA (an inhibitory receptor) and its ligand HLA-E expressed on RA-FLSs enhanced degranulation of the Nishi human NK cell line [26]. Moreover, blockade of NKG2D in a murine model of collagen-induced arthritis was associated with significant joint protection, relative to control animals [27]. Patients with psoriatic arthritis have elevated expression levels of interleukin-15 and MIC in their affected synovial tissues, and this inflammatory environment enabled NK cell activation and tissue destruction through NKG2D [28].

The present study was performed in a large, representative cohort of patients with SpA with the use of asymptomatic control patient. It constituted a multidisciplinary collaboration between geneticists and rheumatologists. In view of the retrospective, single-center design, our study had some limitations. Furthermore, the PsA subgroup was relatively small (n = 46), even though the proportion of patients with PsA was much the same as in other cohorts [3].

Studies of the association between MICA/NKG2D polymorphisms and inflammatory diseases have generated conflicting results. Our present results show that MICA A5.1, MICA129 val/val and NKC3 C/C polymorphisms (related to low levels of cytotoxic activity in NK cells) protected against SpA. In contrast, MICA129 met, NKC3 G/G and G/C polymorphisms (related to elevated levels of cytotoxic activity and an inflammatory environment) were risk factors for SpA. Further research must focus on the involvement of MICA/NKG2D signaling in rheumatic disease.

Methods

Study participants

We performed a retrospective, single-center study of Caucasian patients with SpA being treated in the Rheumatology Department at Amiens University Hospital (Amiens, France). The procedures were approved by the Nord Ouest II ethics committee, Amiens, France. In accordance with French legislation and the Declaration of Helsinki, all participants gave their prior, written, informed consent to genetic testing. Spondyloarthritis had been diagnosed by an experienced rheumatologist in all cases.

A total of 214 patients with SpA were screened between August 2014 and May 2015. We excluded 52 patients who were lost to follow-up or had not provided written, informed consent. Hence, 162 patients were included in the study. Demographic, clinical, laboratory, radiological and HLA-B*27 genotyping (performed by PCR-SSP: Single Specific Primer-Polymerase Chain Reaction, Bionobis, Paris, France) data were extracted from the patients’ medical records. All the radiological data had been analyzed by the same specialist radiologist at the time of diagnosis. Sacroiliac joint damages were diagnosed on an X-ray, CT scan or MRI of the sacroiliac joint [29, 30]. Erosions were diagnosed on hands and foot X-rays. Retrospectively, patients were classified with mNY and ASAS criteria [29, 30].

Controls

One hundred and twenty healthy control Caucasian participants were selected from adult hematopoietic stem cell donor registries. In line with the World Marrow Donor Association’s guidelines, none had a history of autoimmune disease, neoplastic disease or thromboembolic events.

NKG2D and MICA polymorphisms

NKG2D genotyping was performed as described previously [31], using a TaqMan® allelic discrimination method on a 9700-HT real-time polymerase chain reaction (PCR) system (Applied Biosystems, Foster City, CA, USA). An allele-specific fluorogenic oligonucleotide (Applied Biosystems) was used to discriminate between genotypes for each studied pair of alleles. The following two SNPs were probed: (i) rs1049174, featuring a G-C substitution that distinguishes between the high-activity-related HNK1 NKG2D haplotype (G) and the low-activity-related LNK1 (C) haplotype (NKC3); and (ii) rs2255336, featuring a C-T substitution that distinguishes between the HNK2 (T) and LNK2 (C) haplotypes (NKC4). All participants underwent sequence-based typing for MICA. PCR primers were designed to amplify MICA exons 3 and 5, as described previously [31]. Sequencing was performed on an automatic 24-capillary ABI Prism system (Applied Biosystems), and the electropherogram was interpreted using SeqPilot® software (JSI Medical Systems GmbH, Ettenheim, Germany).

Statistical analysis

Data were quoted as the mean and range (for continuous variables) or the number and percentage (for categorical variables). Univariate logistic regression was used to compare the frequency of polymorphism in patients vs. controls. The odds ratio was adjusted (ORadj) for HLA-B*27 status by including this variable in the logistic regression. Each genotype was compared with the others as the reference. Variables with a p value < 0.1 in a univariate analysis were included in a multivariate model, where the threshold for statistical significance was set to p < 0.05. Associations
between clinical and radiological features and polymorphisms were also probed. All analyses were performed with R software (version 3.1).

Funding This work was funded by Amiens University Hospital as part of the French government’s hospital-based clinical research program.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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