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Lack of significant association between selected *STAT3* polymorphisms and rheumatoid arthritis in the Polish population

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Abstract

Objectives: Rheumatoid arthritis (RA) is the most common systemic inflammatory disease and is of unknown etiology. The altered balance between immunosuppressive and inflammatory T cell subpopulations exerts a huge impact on RA pathogenesis. The *STAT3* protein regulates genes involved in the immune responses. It regulates maturation of T and B cells. Its abnormal activity is significantly associated with autoimmune diseases and cancer development. We aimed to evaluate the contribution of three potentially functional single nucleotide polymorphisms (SNPs) within the *STAT3* gene to susceptibility and severity of RA in the Polish population.

Material and methods: A total of 595 patients with RA and 330 healthy individuals were included in the study. DNA from patients and healthy subjects was obtained from peripheral blood using standard DNA isolating methods. The *STAT3* rs1053005, rs1026916 and rs2293152 polymorphisms were genotyped using the TaqMan SNP genotyping assay. The accuracy of SNP genotyping was confirmed using direct DNA sequence analysis.

Results: The distribution of *STAT3* polymorphisms did not differ significantly between cases and controls. Our results revealed a tendency only, where rs1026916 AA genotype occurred more frequently in RA patients compared to healthy controls, in codominant ($p = 0.09$), dominant ($p = 0.06$) and recessive ($p = 0.09$) models. *STAT3* rs2293152 polymorphism was associated with higher DAS28 ($p = 0.014$ codominant model; $p = 0.003$ dominant model), increased number of swollen joints ($p = 0.02$), higher VAS ($p = 0.01$) and higher HAQ score ($p = 0.05$).

Conclusions: We did not observe a significant association between the three studied *STAT3* genetic variants and increased susceptibility to or severity of RA. Only the *STAT3* rs2293152 polymorphism was associated with parameters that indicate a more severe course of the disease. However, its distribution did not differ between RA and control groups. According to our observations these 3 studied *STAT3* SNPs may not be used as risk factors for developing RA.

Key words: signal transducer and activator of transcription 3 (*STAT3*), rheumatoid arthritis.

Introduction

Rheumatoid arthritis (RA) is an autoimmune inflammatory disease that affects up to 1.5% of the worldwide population. RA patients suffer from progressive inflammation, degeneration of joints and disability [1]. The etiology of RA is unknown. However, the combination of both the chronic inflammatory response and genetic factors has been implicated in its development. Familial studies and genome-wide association studies (GWAS) highlighted the essential role of genetic factors in RA vulnerability [2, 3].

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The heritability of RA has been estimated at about 50–60%, suggesting the remarkable influence of genetic factors on disease susceptibility. GWAS have identified over 110 susceptibility loci for RA in European and Asian populations [4]. Risk factors, identified as the biggest genetic contributors to RA sensitivity, are *HLA-DRB1* and the group of alleles referred to as the shared epitope (SE). Loci such as *PTPN22*, *PTPN2*, *STAT4*, *CD40*, *CTLA4*, *IL2*, *IL21*, *IL-6R*, *GATA3*, *CCR6*, *IL-2R*, *IL-7R*, and *CD28* were also strongly associated with the risk for RA [5, 6]. A substantial proportion of RA risk variants are related to T cell activation and signaling. The altered balance between immunosuppressive and inflammatory T cell subpopulations exerts a huge impact on RA pathogenesis [7].

Table I. Clinical characteristics of rheumatoid arthritis patients

Characteristics	RA patients	
	N	Mean ±SD
Age (years)	587	55.93 ±12.57
Disease duration (years)	470	11.17 ±8.53
Larsen	512	2.97 ±0.98
Number of swollen joints	304	4.67 ±4.96
Number of tender joints	304	8.05 ±6.2
ESR (mm/h)	509	34.62 ±24.48
CRP (mg/l)	306	22.6 ±24.69
Hemoglobin (g/dl)	306	12.51 ±1.46
VAS (mm)	299	50.8 ±23.94
DAS28-CRP	300	4.85 ±1.42
HAQ	286	1.45 ±0.74
PLT ($\times 10^3/\mu l$)	306	325.63 ±106.73
Creatinine	305	0.73 ±0.24
	N	*n* (%)
Women	595	524 (88.06)
RF presence	505	346 (68.51)
ACPA presence	309	249 (80.58)
Morning stiffness	330	256 (77.57)
Organ symptoms	512	109 (21.29)
Coronary artery disease	304	42 (13.81)
Hypertension	305	109 (35.73)
Myocarditis	302	10 (3.31)
Diabetes	304	15 (4.93)
Renal syndrome	303	2 (0.66)
Renal failure	304	13 (4.27)

N – number of patients with clinical information; n – number of patients with positive clinical manifestation; ESR – erythrocyte sedimentation ratio; CRP – C-reactive protein; VAS – Visual Analogue Scale; DAS28 – disease activity score for 28 joints; HAQ – Health Assessment Questionnaires; PLT – plates; RF – rheumatoid factor; ACPA – anti-citrullinated protein antibodies

Treg cells, involved in immune system regulation, maintain immune homeostasis and tolerance to self-antigens. In contrast, Th17 cells promote inflammatory responses in tissues. Imbalance between Treg and Th17 inflammatory activities has been implicated not only in the pathogenesis of RA but also in many other autoimmune diseases [8, 9].

Signal transducer and activator of transcription 3 (*STAT3*) is an important transcription factor that regulates genes involved in cell growth, division, differentiation, and apoptosis. Therefore, it is engaged in the function of certain body systems. For example, in the immune system, *STAT3* is involved in the regulation of inflammation. It regulates maturation of T and B cells [10]. Many studies have proved *STAT3*'s importance in development of autoimmune diseases and cancers. According to GWAS, *STAT3* SNPs are associated with Crohn's disease [11], psoriasis [12] and multiple sclerosis [13]. These reports may suggest that certain autoimmune diseases share a common mechanism arising out of *STAT3* abnormal activity and Treg/Th17 imbalance [14].

We chose three *STAT3* gene polymorphisms that were previously analyzed in other autoimmune disorders, although they have never been investigated for RA. Significant association of these *STAT3* single nucleotide polymorphisms (SNPs) was found with both clinical phenotypes of inflammatory bowel disease (IBD) [15], ankylosing spondylitis (AS) [16], obesity [17] and cancer [18]. The association of *STAT3* variants with those conditions may indicate that there is a linking mechanism of disease pathogenesis that has the same effect on Th17 cells [16]. The main goal of our study was to determine the prevalence of selected *STAT3* gene polymorphisms in patients with RA, in relation to a group of healthy volunteers in the Polish population. We also determined the correlation between prevalence of *STAT3* gene polymorphisms and the laboratory, clinical and radiological parameters.

Material and methods

Patients and study protocol

A total of 595 patients with RA, recruited from the Connective Tissue Diseases Department of the National Institute of Geriatrics, Rheumatology and Rehabilitation in Warsaw and from the Pomeranian Medical University in Szczecin, and 330 healthy individuals were included in the study. All our patients met the American College of Rheumatology Diagnostic Criteria for RA (ACR 1987). Information on the main demographic data, clinical and biochemical characteristics is presented in Table I. The control group (206 females and 124 males, age be-

Table II. SNPs information and genotyping results for rheumatoid arthritis patients and control group

SNP ID	Allele	SNP type	MAF			*p* (HWE)	
			RA	Control	1000 genome EUR or HapMap CEU	RA	Control
rs1026916	A/G	Intron	0.33	0.27	0.39	0.31	0.55
rs1053005	A/G	3'UTR	0.17	0.19	0.2	0.97	0.41
rs2293152	C/G	Intron	0.43	0.43	0.39	0.27	0.11

MAF – minor allele frequency; HWE – Hardy-Weinberg equilibrium; EUR – European; CEU – Utah Residents (CEPH) with Northern and Western Ancestry

tween 18 and 63 years) consisted of healthy volunteers who showed no clinical or laboratory signs of any autoimmune disease. Blood donors were randomly selected and matched the patients' ethnicity. All patients and healthy subjects were of Polish Caucasian descent and they all had the same socioeconomic status. All participants gave informed, written consent, and the study was approved by the relevant ethics committee.

Single nucleotide selection

STAT3 single nucleotide polymorphisms were acquired from 1000 Genomes Browser Phase 3 and on the basis of available, scientific databases. We selected three polymorphisms (minor allele frequency ≥ 0.05) – rs1026916 A/G intron variant, rs1053005 A/G 3'UTR variant and rs2293152 C/G intron variant – to study their association with RA severity and susceptibility. All selected SNPs were previously described as potential risk factors for different autoimmune diseases [15, 16]. Information about selected SNPs is summarized in Table II.

Methods

DNA from patients and healthy subjects was obtained from peripheral blood using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany) or standard DNA isolating methods.

The *STAT3* rs1053005, rs1026916 and rs2293152 polymorphisms were genotyped using the TaqMan SNP genotyping assay in a Rotor Gene 6000 RT rotary analyzer (Corbett), according to the conditions recommended by the manufacturer (Applied Biosystems, Foster City, CA). To confirm the accuracy of SNP genotyping by TaqMan assays, direct DNA sequence analysis was used to genotype all three SNPs in 27 randomly selected samples. The results from the TaqMan assays completely matched the sequencing data.

Statistical analysis

The results were presented as median and interquartile range (IQR) for non-normally distributed continuous variables or mean with one standard deviation for normally distributed continuous variables. We used the Shapiro-Wilk test as a test of normality for continuous data. Categorical variables were presented as percentages.

Differences in genotype and allele distribution between the examined groups (OR, 95% confidence intervals, *p*-value) were evaluated using logistic regression. The analysis considered the effects of possible confounders such as age and gender. The analysis was performed under 4 genetic models (dominant, codominant, overdominant and recessive). The associations between tested SNPs and disease activity parameters were analyzed using the Kruskal-Wallis test, Mann-Whitney test or analysis of variance for continuous variables and the χ^2 or Fisher's exact test for categorical variables. Statistical significance was set at $p < 0.05$. In multiple testing we used Bonferroni correction to adjust the significance of the *p*-value.

Testing polymorphisms for deviation from Hardy-Weinberg equilibrium (HWE) was performed using an online calculator (Michael H. Court [2005–2008]).

Statistical analysis was performed using the data analysis software system SAS Enterprise Guide (SAS Institute Inc., Cary, NC, USA. 2013, version 6.1 M1) and STATISTICA (StatSoft. Inc. [2011], version 10).

Results

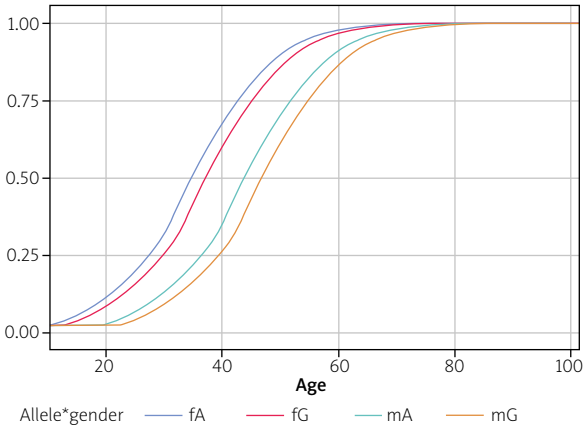
The association analysis between *STAT3* SNPs and risk of rheumatoid arthritis development

We applied four genetic models (codominant, dominant, overdominant and recessive) to assess the association between *STAT3* SNPs and RA risk. The *STAT3* polymorphism genotype distributions, in both RA patients and the control group, were in HWE. We did not observe any significant differences in distribution of the tested *STAT3* polymorphisms (rs1026916, rs1053005 and rs2293152) between cases and controls, under each genetic model (data not shown). Although there were no significant differences in distribution of SNPs, we observed a small tendency where rs1026916 AA genotype occurred more frequently in RA patients compared

Table III. Distribution of genotypes and allele frequencies of STAT3 SNP rs1026916 among Polish patients with rheumatoid arthritis and healthy subjects

Rs1026916 G/A		RA, *n* (%)	Controls, *n* (%)**	OR (95% CI)	*p*-value
	Genotype				
Codominant	GG	249 (44.54)	159 (51.96)	–	–
	GA	256 (45.8)	126 (41.18)	1.4(0.88–2.22)	0.74
	AA	54 (9.66)	21 (6.86)	2.34 (1.02–5.38)	0.09
Dominant	GG	249 (44.54)	159 (51.96)	–	–
	GA + AA	310 (55.46)	147 (48.04)	1.52 (0.98–2.36)	0.06
Recessive	GG + GA	505 (90.34)	285 (93.14)	–	–
	AA	54 (9.66)	21 (6.86)	1.99 (0.89–4.46)	0.09
Overdominant	GG + AA	303 (54.2)	180 (58.82)	–	–
	GA	256 (45.8)	126 (41.18)	1.23 (0.79–1.92)	0.35
	Alleles				
	G	754 (67)	444 (73)	–	–
	A	364 (33)	168 (27)	**1.45 (1.03–2.03)**	**0.03**

OR – odds ratio; CI – confidence interval;
p-value obtained from linear regression, adjusted for gender and age; p-value ≤ 0.05 was considered significant; p-values in bold are significant



fA – female with rs1026916 A; fG – female with rs1026916 G allele;
mA – male with rs1026916 A allele; mG – male with rs1026916 GG allele

Fig. 1. Plot illustrating the probability of rheumatoid arthritis development depending on age, gender and *STAT3* rs1026916 allele.

to healthy controls in codominant (p = 0.09), dominant p = 0.06) and recessive (p = 0.09) models (Table III). However, *STAT3* rs1026916 A allele frequency differed significantly between RA patients and controls (p = 0.03; power analysis = 83%) (Table III). Figure 1 shows that rs1026916 A allele carriers, regardless of age and gender, were associated with RA development compared to the others.

STAT3 rs2293152 polymorphisms with respect to clinical parameters of patients with rheumatoid arthritis

We analyzed the association between genetic polymorphisms in the *STAT3* gene and clinical course of the disease in RA patients (disease activity parameters).

The analysis showed that only *STAT3* rs2293152 polymorphism is associated with parameters that indicate a more severe course of the disease (Table IV). We demonstrated that presence of rs2293152CC genotype is characteristic for RA patients with higher DAS28 (disease activity score for 28 joints) (p = 0.014 codominant model; p = 0.003 dominant model; power analysis = 90.2%) (Fig. 2). Moreover, rs2293152CC genotype carriers had an increased number of swollen joints (p = 0.02), felt stronger pain assessed by the Visual Analogue Scale (VAS) (p = 0.01) and also obtained a higher score in the Health Assessment Questionnaire (HAQ) (p = 0.05) (Table IV).

Discussion

Rheumatic diseases offer distinct challenges to researchers due to heterogeneity in disease phenotypes. RA is a disease with multiple genetic and environmental determinants. Although we observe growing knowledge about RA pathogenesis, unraveling its genetics still requires the greatest challenge. Gathering more information about the genetic background of RA as well as other

Table IV. Disease activity parameters in relations to STAT3 rs2293152 polymorphism

STAT3 rs2293152	DAS 28						
	N	Mean ±SD	p^c		*N*	Mean ±SD	p^d
CC	91	5.25 ±1.34	**0.014**	GG+CG	195	4.73 ±1.42	**0.003**
CG	138	4.72 ±1.41		CC	91	5.25 ±1.34	
GG	57	4.73 ±1.46		GG	57	4.73 ±1.46	0.34
				CG+CC	229	4.93 ±1.41	
STAT3 rs2293152	Number of swollen joints						
	N	Median (IQR)	p^a		*N*	Median (IQR)	p^b
CC	94	4 (8–1)	0.03	GG+CG	196	3 (7–0)	**0.02**
CG	139	3 (6–0)		CC	94	4 (8–1)	
GG	57	3 (8–1)		GG	57	3 (8–1)	0.76
				CG+CC	233	3 (7–1)	
STAT3 rs2293152	VAS [mm]						
	N	Median (IQR)	p^a		*N*	Median (IQR)	p^b
CC	91	58 (72–43)	0.04	GG+CG	194	50 (70–30)	**0.01**
CG	137	48 (69–30)		CC	91	58 (72–43)	
GG	57	53 (75–28)		GG	57	53 (75–28)	0.75
				CG+CC	228	52 (70–32)	
STAT3 rs2293152	HAQ						
	N	Median (IQR)	p^a		*N*	Median (IQR)	p^b
CC	91	1.75 (2.13–1)	0.04	GG+CG	183	1.5 (2–0.875)	**0.05**
CG	126	1.38 (2–0.75)		CC	91	1.75 (2.125–1)	
GG	57	1.63 (2.13–1)		GG	57	1.625 (2.125–1)	0.43
				CG+CC	217	1.5 (2–0.875)	

p^a – Kruskal-Wallis test; Bonferroni corrected p-value < 0.0167 was considered significant;
p^b – Mann-Whitney U test, p-value < 0.05 was considered significant;
p^c – ANOVA test, Bonferroni corrected p-value < 0.0167 was considered significant;
p^d – t-test, p-value < 0.05 was considered significant;
p-values in bold are significant

autoimmunological disorders would be a step forward to describe a trigger of the chronic inflammatory process. We analyzed the contribution of three potentially functional single nucleotide polymorphisms within the *STAT3* gene to the susceptibility and the severity of RA in the Polish population.

STAT3 is one of the key elements of the JAK-STAT signaling pathway. It regulates the expression of genes involved in cell proliferation, differentiation, and survival. *STAT3* transmits signals for the maturation of immune system cells, especially T cells and B cells [10]. *STAT3* plays a critical role in generating Th17 cells and promotes the activation and expansion of autoimmunity reactions associated with Th17; thus it is involved in the regulation of inflammation [10]. Several mutations causing an increase or decrease in activity of *STAT3* have been identified. The *STAT3* mutations classified as

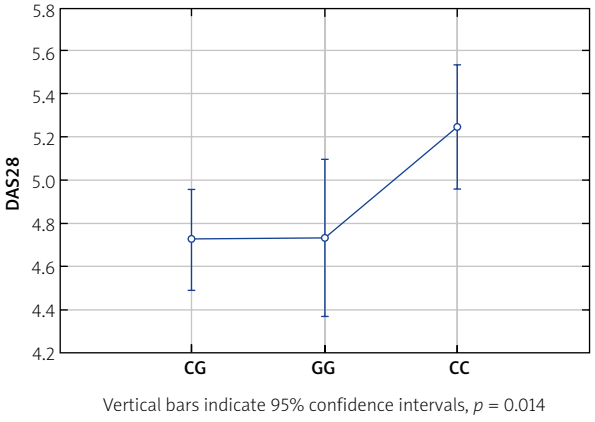


Fig. 2. Disease activity, measured by DAS28 (disease activity score for 28 joints), in relation to *STAT3* rs2293152 polymorphism.

"gain-of-function" lead to dysregulation of the immune system and autoimmune diseases like type I diabetes, autoimmune hemolytic anemia, autoimmune thrombocytopenia or autoimmune enteropathy. On the other hand, "loss-of-function" mutations in the *STAT3* gene may cause for example autosomal dominant hyper-IgE syndrome (AD-HIES) [19–21].

At least 20 *STAT3* gene mutations have been found to cause an autoimmune disorder. It is possible that overactivation of *STAT3* impairs proper Treg cell development and promotes Th17 cell expansion. Over the last decade, numerous studies have indicated that Treg/Th17 cell imbalance contributes to the pathogenesis of RA [22, 23]. Th17 cells are typical pro-inflammatory cells that promote inflammatory responses in tissues, while Treg cells control expansion and activation of autoreactive CD4+ T effector cells and therefore play a very important role in maintaining self-tolerance. In conclusion, predominant Th17 activity and impaired Treg cell functioning may play a pivotal role in RA pathogenesis.

Identification of disease-causing variants and assessment of their impact on the responsible genes would improve our understanding of the disease pathogenesis. Seddighzadeh et al. reported an association between the *STAT3* gene and ACPA-negative RA in a Swedish cohort [24].

The analysis of polymorphisms within the *STAT3* gene may reveal correlations with some biochemical and laboratory parameters. For our analysis we chose three *STAT3* SNPs (rs1053005 located in the 3′UTR region and rs1026916 and rs2293152 both located in an intronic region), knowing that previously a significant association of these *STAT3* SNPs was found with other Th17 cell dependent autoimmune diseases such as both clinical phenotypes of IBD [15], autoimmune thyroid diseases [25], AS [16], obesity [17] and cancers [18, 26].

Xiao et al. [25] indicate that the A allele and AA genotype of the SNP rs1053005 may decrease individual susceptibility to develop autoimmune thyroid disease (AITD). They observed that rs1053005 AA genotype was significantly less frequent in both Graves' disease (GD) and Hashimoto's thyroiditis (HT) in Chinese patients [25]. Additionally, *STAT3* rs1053005 and rs2293152 were significantly associated with AS in the Han Chinese population [16]. It was suggested that rs1053005, sited in the 3′-untranslated region (3′-UTR), may influence mRNA stability or translation efficiency of the *STAT3* gene. An allele of rs1053005 is complementary to the second nucleotide of the seed sequence of has-miR-1303. The switch from adenine to guanine may impair the perfect fit between the seed of has-miR-1303 and its target, disrupting its regulatory effect, which may lead to a higher level of expression of *STAT3* [17].

Moreover, a significantly increased frequency of the GG genotype of the *STAT3* rs2293152 was observed in patients with Behçet's disease (BD) in Han Chinese [27]. On the other hand, the C allele and its homozygous CC genotype of *STAT3* rs2293152 were more frequent in CD patients than those in control subjects in the Japanese population [28]. Rs1026916 was significantly associated with both clinical phenotypes of IBD in a Spanish cohort [15]. According to our observations none of the three selected *STAT3* SNPs were significantly associated with susceptibility to RA. We observed that *STAT3* rs1026916 only in the AA genotype revealed a slight tendency to occur more frequently in the group of RA patients, compared to the GG genotype. Although we observed significant differences in allele distribution, the tested groups were not numerous enough to confirm this with appropriate power.

In the next step of our study we performed a genotype-phenotype analysis where we investigated the correlation of selected polymorphisms with clinical parameters in RA patients. We demonstrated that rs2293152 CC genotype carriers had a significantly higher DAS28 score, an increased number of swollen joints, felt stronger pain (VAS) and obtained a higher score in the HAQ. These results may suggest that this genotype has some significance for the course of RA, but in our opinion the above results are not sufficient to make this conclusion.

It is vital to mention that our study has some limitations, which prevent us from drawing definite conclusions. First of all, the sample size may not be sufficiently large to observe an association between *STAT3* and RA susceptibility with enough strength. To confirm the possible relation between *STAT3* rs2293152 CC genotype and more severe disease outcome, further studies on a larger, replicated cohort would be needed to reach sufficient statistical power and validate the above results. However, we consider that an SNP association study should be based on a clinically well-described group, and not only on the sample size. Our strength is working on samples from a population with mono-ethnic ancestry that has been characterized in detail according to clinical phenotype and serology. The results obtained in our study suggest that none of the three tested *STAT3* SNPs has a significant impact on RA development or severity.

The authors declare no conflict of interest.

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