Identification of A New Biomarker For Herpes Zoster Infection in Rheumatoid Arthritis

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Abstract

Herpes zoster (HZ) is known as a side effect of using biologics in rheumatoid arthritis (RA). Incidence of this side effect may be different depending on genetic factors because susceptibility to HZ infection varies by race. Here, we analyzed the statistical relationships of whole genome single nucleotide polymorphisms (SNPs) with HZ infection in biologics-treated RA patients.

The subjects were 321 Japanese female patients (including 56 herpes virus infected patients) of RA using biologics. The relationships of 302,814 SNPs with HZ infection were analyzed using case-control analyses by Fisher's exact tests. We picked up SNPs ($P < 10^{-8}$) significantly associated with HZ infection. Then, herpes infection was compared among the genotypes using a multivariate logistic regression analysis adjusted for onset age of RA.

Rs10774580 located in 2'-5'-oligoadenylate synthetase like gene (*OASL*) was significantly associated with herpes virus infection. The minor allele homozygous carrier was positively associated with herpes virus infection in multivariate analysis.

We for the first time showed a significant relationship between a genetic factor and HZ infection among RA patients. Rs10774580 may be one of the biomarkers for HZ infection.

Introduction

Rheumatoid arthritis (RA) is a progressive autoimmune disease well defined by widely accepted symptoms such as chronic joint inflammation and structural damage[1]. In treatment for RA at present, using biological agents such as tumor necrosis factor (TNF), interleukin-6 (IL-6) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) blockades is extremely useful because these agents specifically inhibit immune responses and inflammation. On the other hand, because these agents are immunosuppressant, infectious diseases become a significant problem in treatment for RA.

Herpes zoster (HZ) is one of the most common viral infections in treatment for RA with immunosuppressants such as biological agents. In fact, it has been reported that RA patients have a higher risk of HZ compared with the general population[2, 3, 4]. Therefore, a number of studies analyzed relationships of the incidence of HZ with various possible risk factors. As the result, aging, high disease activity and corticosteroid, methotrexate and biological agents were reported as the risk for HZ[5]. These studies, however, have not taken genetic factors into consideration. On the other hand, several studies have identified genetic loci associated with onset of RA[6]. It has also been reported that the effectiveness of biologic agents can be predicted by combination of single nucleotide polymorphisms (SNPs)[7]. These studies used genome-wide association study (GWAS) in order to identify the genetic factors. Thus, conducting GWAS is thought to be valuable in order to identify unknown genetic factors associated with HZ in RA.

In this study, in order to identify SNPs associated with HZ infection, we analyzed the statistical relationships of whole genome SNPs with HZ infection among biological agents-treated RA patients.

Results

The basic characteristics of the patients are presented in Table 1. The total patients were 320 aged 45.5 ± 13.9 years (mean ± SD).

Only one SNP was identified that was significantly associated with HZ infection (Fig. 1). The SNP was rs10774580 in 2'-5'-oligoadenylate synthetase like gene (*OASL*).

Table 2 presents the relationships of *OASL* genotype and onset age of RA with HZ infection. The minor allele homozygous of rs10774580 and the onset age of RA (≥ 65 years) were positively associated with HZ infection. Adjusted OR for the minor allele homozygous was 15.6 (95 % CI 3.9 − 61.4). Adjusted OR for the onset age (≥ 65 years) was 2.6 (95 % CI 1.1 − 6.4).

Discussion

To our knowledge, our study is the first to analyze the relationships of whole genome SNPs with HZ infection among bDMARDS-treated RA patients and to identify a SNP as one of the biomarkers for HZ infection.

It has been reported that aging, high disease activity, corticosteroid use and the use of methotrexate are risk factors for HZ infection in RA patients[5]. In addition, it has been reported that susceptibility to HZ infection in RA varies by race[8]. In fact, Japanese and Taiwanese have a higher risk compared to Americans and Europeans[9]. In this regard, genetic background may also affect the susceptibility. However, because there are not studies that take into account genetic polymorphisms such as SNPs, it is likely that genetic polymorphisms associated with the susceptibility were overlooked. Therefore, we conducted GWAS which is powerful tool to collectively identify SNPs associated with the susceptibility.

In our study, rs10774580 located in intron region of *OASL* gene was significantly associated with HZ infection. The minor allele homozygous were positively associated with HZ infection. Human OASL has an antiviral activity against RNA viruses[10,11]. On the other hand, OASL inhibits type I interferon (IFN) induction during DNA virus infection such as herpes simplex, vaccinia and adenovirus[12]. This is because OASL binds to cylic GMP-AMP synthase (cGAS) known as DNA sensor, and inhibits cyclic GMP-AMP (cGAMP) synthesis in cGAS-STING (stimulator of interferon gene) pathway sensing the majority of DNA viruses[12]. Inhibiting IFN induction leads to enhancing DNA virus replication. Therefore, rs10774580 may affect the transcription of *OASL* because this SNP is intronic variation without amino acid substitution. As the result, the expression levels among *OASL* genotypes vary, and then differences of the susceptibility may be caused.

Interestingly, several previous studies revealed that using Janus Kinase (JAK) inhibitors increased the risk of HZ infection compared to bDMARDS[13, 14]. In this regard, it is unclear if rs10774580 is also associated with HZ infection in JAK inhibitors-treated RA patients. Thus, further analyses are needed in JAK inhibitors-treated RA patients.

This study has several limitations. First, rs10774580 was identified by the result of GWAS among Japanese RA patients. It is well known that allele frequencies of most SNPs vary in different ethnic groups. The allele frequency of rs10774580 we identified also varied compared with the allele frequency of other ethnic groups reported in the HapMap database (https://www.ncbi.nlm.nih.gov/snp). Therefore, rs10774580 may not be applicable to non-Japanese RA patients as the biomarker. A second limitation is that this study didn't take into consideration the incidence of HZ in each patient. It is well known that some RA patients repeatedly develop HZ. Therefore, in order to identify the other biomarkers, further studies taking in the incidence of HZ into consideration are desired.

Patients And Methods

Patients. We recruited 321 Japanese female patients of RA receiving treatment with biological disease-modifying antirheumatic drugs (bDMARDs). They included 56 HZ infected patients. Written informed consent to participate in this study was obtained from each patient. This study was approved by the ethical committee for analytical research on the human genome of the Matsubara Mayflower Hospital. All methods were performed in accordance with relevant guidelines and regulations.

Genome-wide SNP genotyping. The patients' whole blood samples were used for DNA extraction at Mitsubishi BCL Inc. Genome wide SNP genotyping were performed at deCode genetics Inc. (Reykjavic, Iceland) using Illumina HumanHap300K chip technology (Illumina Corp., San Diego, CA, USA). After genotyping, 302,814 of 317,503 SNPs excluded SNPs with call rates < 90 % and minor allele frequency < 1 % were used in the case-control analysis described below.

Statistical analysis. We used case-control analysis to analyze the relationship of 302,814 SNPs with onset of HZ by Fisher's exact tests using SVS 8.1.1 (Golden Helix Inc.). After case-control analyses, we picked up SNPs significantly associated with HZ infection. Univariate and multivariate logistic regression analyses were used to examine the effects of the SNP and onset age of RA on the risk for HZ infection. The logistic regression analyses were carried out using EZR[15] (Saitama Medical Center, Jichi Medical University, Saitama, Japan). EZR is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria, version 2.13.0). *P* values < 10^{-8} were considered significant in case-control analysis. *P* values < 0.05 were also considered significant in the logistic regression analyses.

Conclusion

This is the first report of a significant association between a genetic factor and HZ infection among bDMARDS-treated RA patients. As the result of GWAS, we showed that rs10774580 in *OASL* gene was

significantly associated with HZ infection. Therefore, this SNP may be one of the biomarkers for predicting HZ infection among RA patients before using biologics.

Declarations

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Author contributions

M.H., K.Fun., K.T., Y.T., T.Mae., K.Fuk., S.H., R.K. and T.Mat. participated in the study design. K.Fun. contributed to data collection. M.H. carried out the statistical analyses. M.H. and T.Mat contributed to drafting of the manuscript. M.H. and T.Mat. were responsible for the analysis and interpretation of data.

Competing Interests

The authors declare that they have no competing interests.

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Tables

Table 1. Characteristics of patients.

variables	
Number of patients (%)	321
Non herpes zoster	265 (82.6)
Herpes zoster	56 (17.4)
Onset age (years)	45.5 ± 13.9
≥ 65 years	26 (8.1)
< 65 years	257 (80.1)
unknown	38 (11.8)
OASL genotype (%)	
major allele homozygous	186 (58.0)
heterozygous	122 (38.0)
minor allele homozygous	13 (4.0)
Values are mean ± SD, number of the patients	

Table 2. Relationships between the *OASL* genotypes and onset age with HZ infection.

Variables (high-risk group)	Univariate		Multivariate[a]	
	OR	95 % CI	OR	95 % CI
OASL genotype (minor allele homozygous)	19.0	5.0–71.6	15.6	3.9–61.4
Onset age (≥ 65 years)	2.1	0.8–5.3	2.6	1.1–6.4
Abbreviation: OR, odds ratio. [a]Adjusted for all variables				

Figures

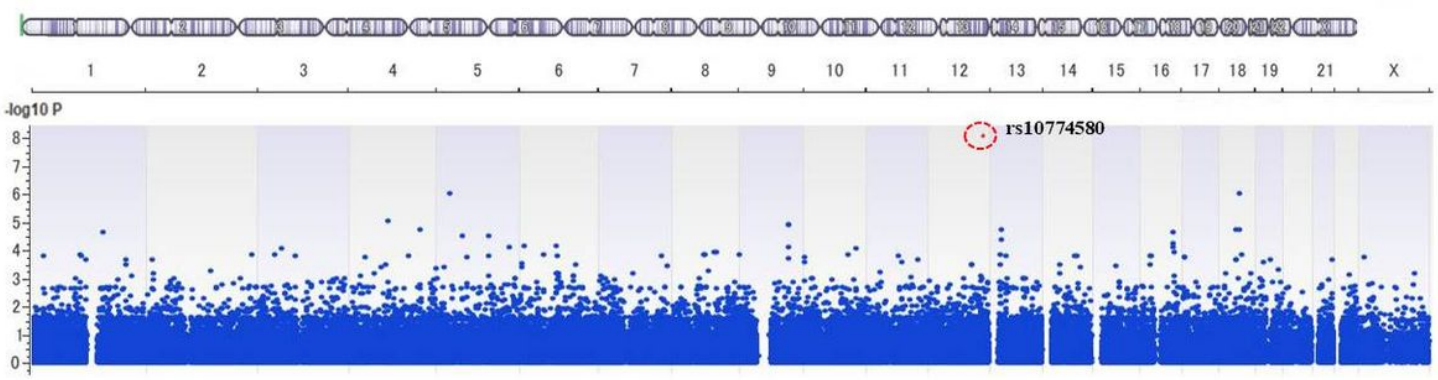

Figure 1

Manhattan plot showing Fisher's exact tests' results.