Computers in Biology and Medicine 64 (2015) 268–275

Contents lists available at ScienceDirect

Computers in Biology and Medicine

journal homepage: www.elsevier.com/locate/cbm

Contribution of *CD24* polymorphisms to autoimmune disease: A meta-analysis

Jihae Baek, Soowon Kang, Hyeyoung Byeon, Kwang Woo Hwang, Hyeyoung Min *

College of Pharmacy, Chung-Ang University, Seoul 156-756, Korea

ARTICLE INFO

Article history:
Received in revised form
14 July 2015
Accepted 15 July 2015

Keywords:
CD24
Polymorphism
Genetic variants
Autoimmune disease
Meta-analysis

ABSTRACT

Purpose: To determine the relationship between two *CD24* polymorphisms, rs8734/rs52812045 and rs3838646, and autoimmune disease.
Design: Meta-analysis.
Methods: The Medline, EMBASE, Web of Science, and Cochrane Library databases were searched for studies reporting the association between *CD24* polymorphisms and autoimmune disease. Two of the authors selected eligible studies and extracted and analyzed the data independently.
Results: Compared with carriers of the C allele (CC, CT, CT+CC), individuals homozygous for the T allele (TT) and heterozygous (CT+TT) at rs8734/rs52812045 have a higher incidence of autoimmune disease, whereas rs3838646 is not associated with autoimmune disease. Subgroup analysis found an increased risk of multiple sclerosis with the TT vs. CC, TT vs. CT, and TT vs. CC+CT alleles.
Conclusion: The *CD24* polymorphism rs8734/rs52812045 contributes to the development of autoimmune disease.

1. Introduction

Autoimmune disease occurs when the immune system produces antibodies against the body's own tissues [1,2]. Although many archetypes exist, autoimmune disease is classified into two major categories: tissue-specific and non-tissue-specific. Multiple sclerosis (MS), autoimmune thyroid diseases such as Grave's disease and Hashimoto's thyroiditis, and inflammatory bowel diseases including Crohn's disease (CD) and ulcerative colitis (UC) are tissue specific, whereas systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), sarcoidosis, systemic sclerosis, and giant cell arteritis are non-tissue-specific autoimmune diseases [1].

The pathogenesis and factors affecting the severity of autoimmune disease are elusive, but numerous reports have suggested their association with genetic and environmental factors [3–7]. Because the occurrence of MS, SLE, UC, and RA is linked with familial clustering and the frequency of monozygotic twins, the presence of genetic factors has drawn attention, and many studies have reported associations between autoimmune disease and genetic polymorphisms [6,8,9]. For example, relationships between the following autoimmune diseases and specific genes have been examined: autoimmune thyroid disease and interleukin-5 (*IL-5*), *IL-6*, and *IL-13*; CD and the IL-23 receptor gene, *NOD2*, and *PTPN2*; UC and *NOD2*, human leukocyte antigen-DR (*HLA-DR*), and *PTPN2*; MS and *HLA-DRB1*, *HLA-DR2*, the *IL-2* receptor gene, and *IL-1*; and RA and *IL-18*, *IRF5*, and *PTPN22* [10–19].

CD24, or heat-stable antigen, is a small, highly glycosylated glycophosphatidylinositol-anchored cell surface protein [20]. CD24 is expressed in most hematopoietic cells, including activated T cells, B cells, dendritic cells, macrophages, and mature granulocytes, as well as non-hematopoietic cells such as astrocytes [21–26]. CD24 was first identified as a lymphoid differentiation marker, but its diverse functions are only now being revealed. For example, it promotes the differentiation and activation of B cells and the activation and clonal expansion of T cells [23,26,27]. It also functions as a checkpoint for T-cell homeostasis by protecting autoreactive T cells from clonal deletion and by maintaining T cells during their migration to the central nervous system [25,26]. When overexpressed in solid tumors, CD24 acts as an adhesion molecule in endothelial cells; promotes the proliferation, metastasis, and dissemination of tumor cells; and affects survival rates in cancer patients [20,21,28]. Furthermore, many *in vivo* studies have reported the association of CD24 with autoimmune disease. CD24 is required for the induction of experimental autoimmune encephalomyelitis (EAE) in an animal model of MS, and thus, EAE induced by myelin-based, protein-pulsed dendritic cells is inhibited when CD24 is down-regulated [25,29,30]. In addition, CD24 is upregulated in CD, which increases the colony-forming capability and motility of cells, whereas the initial phase of experimental autoimmune thyroiditis is more severe in CD24-deficient mice [31,32].

* Corresponding author. Tel.: +82 2 820 5618; fax: +82 2 816 7338.

http://dx.doi.org/10.1016/j.compbiomed.2015.07.012
0010-4825/

The human *CD24* gene is located in the chromosome 6q21 region and comprises a 0.24-kb open reading frame and a 1.8-kb 3′ untranslated region [33,34]. This chromosome is associated with susceptibility to RA, MS, and SLE [3,6,8]. Single-nucleotide polymorphisms (SNPs) in *CD24* influence the occurrence and seriousness of autoimmune diseases, and all of the SNPs are in linkage disequilibrium [6,8,35,36]. The currently known SNPs in the *CD24* gene are rs1058818, rs1058881, rs1136210, rs1136221, rs3840378, rs3810761, rs3838646, rs3950479, rs4030413, rs4030414, rs4030415, rs6530597, rs6530598, rs6530599, rs6530602, rs6530600, rs6530603, rs7892940, rs10465459, rs10482600, rs10482601, rs11545327, rs11545328, rs11545329, rs1136498, rs7892847, rs35795274, rs7892996, rs7893001, rs7893092, rs34905207, rs6530596, rs8734/rs52812045, rs58481495, rs7892847, rs7892864, rs1059138, and rs1136498 (all of which are found in the National Institutes of Health/National Center for Biotechnology Information SNP database: http://www.ncbi.nlm.nih.gov/projects/SNP/).

Among these SNPs, rs8734/rs52812045 and rs3838646 in particular been studied for their association with the onset of autoimmune disease, but studies of polymorphisms in other regions are limited [31,35–38]. The change in an amino acid from alanine to valine in rs8734/rs52812045, which is a glycophosphatidylinositol-anchor cleavage site (ω-1 position) in *CD24* exon 2, upregulates CD24 expression and increases the probability of autoimmune disease [36]. Dinucleotide deletion of TG at rs3838646 in the human *CD24* 3′ untranslated region destabilizes the messenger RNA and decreases CD24 expression, which reduces the risk of autoimmune disease [35]. However, the association of these polymorphisms with autoimmune predisposition is still under debate. Not all case-controlled studies have led to the same conclusions, and the lack of statistical power in most reports has precluded the generation of reliable results. Therefore, we conducted a meta-analysis to obtain comprehensive results.

2. Materials and methods

2.1. Identification and collection of eligible studies

We searched for relevant studies in the Medline (U.S. National Library of Medicine, National Institutes of Health), Web of Science, EMBASE, and Cochrane Library databases using the following words: (“polymorphism” or “genetic polymorphism” or “polymorphism, genetic” or “single nucleotide polymorphism” or “SNP” or “mutation” or “variant”) and (“CD24 antigen” or “CD24” or “antigen, CD24” or “Ly52” or “heat stable antigen” or “ ba-1”). All studies published before November 15, 2014, were available, and there were no language restrictions. All studies reporting associations between *CD24* polymorphisms and autoimmune disease risk were retrieved with the exception of several regional reports. In addition, the references cited in retrieved studies were scanned to avoid missing eligible studies.

Studies included in the meta-analysis satisfied the following criteria: (1) the association between *CD24* genetic polymorphisms and autoimmune disease was assessed, (2) the odds ratio (OR) with 95% confidence interval (CI) values or adequate data to infer these associations was presented, (3) genotyping and statistical methods were clearly described, and (4) the *P* values for Hardy–Weinberg equilibrium in the control group were shown or could be calculated. Studies were excluded if they were (1) non-case-control studies, (2) based on partial data, (3) duplicates of previous reports, (4) unassociated with autoimmune disease, or (5) meta-analyses, letters, or reviews. The database search and study selection were performed by two of the authors (J.B. and H.B.) independently.

2.2. Data extraction

The following data were extracted from each study: first author's name, publication year, country, subject ethnicity, disease studied, genotyping method, source of the controls, frequency of genotypes, sample size, and *P* value of Hardy–Weinberg equilibrium and minor allele frequency in the controls.

2.3. Statistical analyses

All statistical tests were performed with Review Manager (version 5.2; The Cochrane Collaboration, Oxford, UK) and Comprehensive Meta-Analysis (Biostat, Englewood, USA) software. ORs with 95% CI were used to assess the strength of the association between the *CD24* rs8734/rs52812045 and rs3838646 polymorphisms and autoimmune disease. Fixed- and random-effects models were used to calculate a pooled OR, and the statistical significance ($P < 0.05$) of pooled ORs was determined with the *Z*-test. Heterogeneity among studies was evaluated with Higgins' I^2 statistic and the chi-squared-based *Q*-test. A *P* value of < 0.10 for the *Q*-test indicated significant heterogeneity, and in this case, the random-effects model was used to calculate pooled ORs; otherwise, the fixed-effects model was used. Publication bias was assessed with either a funnel plot for visual inspection of asymmetry or Egger's linear regression test. Sensitivity analysis was performed by extracting a single study each time to check the stability of the result.

The genetic models evaluated for pooled ORs of rs8734/rs52812045 were CT vs. CC, TT vs. CC, TT vs. TC, CT+TT vs. CC, TT vs. CC+CT, and T vs. C. The genetic models for rs3838646 were TGDel vs. TGTG, DelDel vs. TGTG, DelDel vs. TGDel, TGDel+DelDel vs. TGTG, DelDel vs. TGTG+TGDel, and Del vs. TG.

3. Results

3.1. Study selection and description

A total of 861 studies reporting *CD24* polymorphisms were initially retrieved (Fig. 1). After the evaluation of titles and keywords, 795 articles were excluded, and 42 were further excluded via abstract review. The remaining 24 articles were then reviewed more thoroughly based on the inclusion and exclusion criteria, and 14 and 6 articles were finally chosen for the meta-analysis of the *CD24* rs8734/rs52812045 and rs3838646 polymorphisms, respectively. All of the data required for analysis were available in the original publications. The autoimmune diseases studied included CD, UC, MS, GD, HD, SLE, and others. All of the DNA samples were extracted from blood, and several genotyping methods were used, including polymerase chain reaction (PCR)-restriction fragment length polymorphism and competitive allele-specific PCR. Table 1 summarizes the characteristics of each report used in the meta-analysis.

3.2. Meta-analysis results

In total, 5906 and 3321 autoimmune disease cases and 6323 and 4167 controls from 14 and 8 case control studies were retrieved for the analysis of *CD24* polymorphisms rs8734/rs52812045 and rs3838646, respectively. Evidence of an association between the *CD24* rs8734/rs52812045 polymorphism and overall risk of autoimmune disease was observed for every model in the study except CT vs. CC. This result indicated a strong association between the rs8734/rs52812045 polymorphism and autoimmune disease (Table 2 and Figs. 2–4). However, none of the models tested showed a significant association between the rs3838646 polymorphism and autoimmune disease (Table 3). In the subgroup analysis, an increased risk of MS was observed for TT