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Research Article

Strong Association Of The Rs4986790 Single Nucleotide Polymorphism (Snp) Of The Toll-Like Receptor 4 (Tlr4) Gene With Human Immunodeficiency Virus (Hiv) Infection:a Meta-Analysis.

Yong-Chan Kim and Byung-Hoon Jeong.

Department of Stomatology, Beijing Luhe Hospital, Capital Medical University, Beijing, China.

Abstract

The human immunodeficiency virus (HIV) penetrates the host cell through CD4 and either CXC-chemokine receptor 4 (CXCR4) or CC-chemokine receptor 5 (CCR), which results in acquired immune deficiency syndrome (AIDS). Toll-like receptor 4 (TLR4) directly detects HIV and has downstream effects.signaling pathways linked to the immune system. Furthermore, the TLR4 gene's rs4986790 single nucleotide polymorphism (SNP) (D299G) raises the likelihood of HIV-1 infection in the Indian population, and stimulated TLR4 prevents HIV-1 invasion. We gathered genetic data from HIV-1 patients in earlier research and conducted an association analysis with a matched control group sourced from the 1000 Genomes Project in order to assess whether the rs4986790 SNP of the TLR4 gene is linked to susceptibility to HIV-1 infection.We also conducted a meta-analysis to support the findings of association analysis. In earlier research, we found a substantial correlation between the rs4986791 SNP with HIV infection susceptibility in patients with HIV and a matched control.

The derived from the 1000 Genomes Project population. Furthermore, in a metaanalysis, we discovered that the G allele of the rs4986791 SNP in the TLR4 gene is highly associated with HIV infection susceptibility in all four populations (odd ratio = 2.22, 95% CI: 1.74–2.84, $p = 2 \times 10^{-10}$) and three Caucasian populations (odd ratio = 2.29, 95% CI: 1.72–3.07, $p = 1.438 \times 10^{-7}$). To the best of our knowledge, this was the first meta-analysis to examine the relationship between HIV infection susceptibility and the TLR4 gene's rs4986791 SNP.

Keywords: *HIV; susceptibility; TLR4; rs4986790; SNP; D299G; meta-analysis.*

INTRODUCTION

The retrovirus known as the human immunodeficiency virus (HIV) has a positive sense single strand RNA genome. Essential regulatory elements (Tat and Rev), auxiliary proteins (Gag, Env, and Pol), and viral structural proteins are all translated from the viral genome.Nef, Vpr, Vif, and Vpu are regulatory proteins [1,2]. During the 1900s, there were theories that HIV originated in nonhuman primates and spread to humans by bodily fluids such blood, semen, vaginal or rectal fluids, and breast milk. Using host receptor proteins, such as CD4 and either CC-chemokine receptor 5 (CCR) or CXC-chemokine receptor 4 (CXCR4), HIV is internalized by host cells. Therefore, HIV primarily targets CD4+ T cells and, by disarming the host immune system, can cause acquired immune deficiency syndrome (AIDS) [3,4].Toll-like receptors (TLRs), RIG-I-like receptors (RLRs), and NOD-like receptors (NLRs) are examples of pattern recognition receptors (PRRs) that identify a pathogen-related pattern of external invaders and trigger the host immune system through downstream regulators, such as nuclear factor kappa-light-chain-enhancer, in order to prevent external infection.of interferon type I, mitogen-activated protein kinase (MAPK), and activated B cells (NF-κB) [5–9]. TLR4 on the cell surface was found to be increased in monocyte-derived macrophages (MDM) in response to HIV-1 infection, according to a prior study. and mononuclear cells of the peripheral blood (PBMC) [10]. Furthermore, HIV-1's Tat protein binds directly to TLR4 and triggers the activation

***Corresponding Author:** Byung-Hoon Jeong, Department of Stomatology, Beijing Luhe Hospital, Capital Medical University, Beijing, China.
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of interleukin-10 (IL-10) and tumor necrosis factor-α (TNF-α) [11]. According to these findings, TLR4 and HIV infection are related. In vitro, TLR4 activation remarkably prevents HIV infection from CD4+ T cells [12]. Furthermore, the rs4986790 single nucleotide polymorphism (SNP) (D299G), a functional variant of TLR4, raises the incidence of HIV-1 infection in the Indian population [13].We gathered three studies that include genetic data on ethnic origins and allele frequencies of the TLR4 gene's rs4986790 SNP from HIV-infected individuals in order to confirm whether the SNP is linked to vulnerability to HIV-1 infection [14–16].

MATERIALS AND METHODS

Literature Search

The corresponding white control groups, which included northern and western Europeans from Utah, Tuscans from Italy, and Iberian people from Spain, were utilized for an association study after being acquired from the 1000 Genomes Project [17]. Next, we gathered information from relevant papers and conducted a meta-analysis to assess the relationship between HIV-1 infection susceptibility and the TLR4 gene's rs4986790 SNP.A PubMed literature search was done to find papers that reported the TLR4 gene's rs4986790 SNP. The following keywords were used in the search: "Polymorphism" or "susceptibility" in conjunction with "TLR4", "SNP," and "HIV" (the last search The update was completed on July 18, 2020. Following the initial screening of abstracts and titles, reports that were deemed irrelevant were eliminated. Studies that meet the following inclusion requirements are eligible: (1) looking into the relationship between rs4986790 and HIV-1; (2) a case-control or cohort research; (3) genetic data on rs4986790 of patients infected with HIV-1, (4) in full text; and (5) published in English. The following were the criteria for exclusion: (1) animal research; (2) reviews or case reports; and (3) lacking adequate genetic information.

Association Analysis

A PubMed literature search was done to find papers that reported the TLR4 gene's rs4986790 SNP. The following keywords were used in the search: "Polymorphism" or "susceptibility" in conjunction with "TLR4", "SNP," and "HIV" the last search.

The update was completed on July 18, 2020. Following the initial screening of abstracts and titles, reports that were deemed irrelevant were eliminated. Studies that meet the following inclusion requirements are eligible: (1) looking into the relationship between rs4986790 and HIV-1; (2) a case-control or cohort research; (3) genetic data on rs4986790 of patients infected with HIV-1, (4) in full text; and (5) published in English. The following were the criteria for exclusion: (1) animal research; (2) reviews or case reports; and (3) lacking adequate genetic information.Crude additive odd ratios and 95% CIs were computed for each research to assess susceptibility to HIV infection. An additive genetic model (A allele vs. G allele) was used to compute the pooled odd ratios. The p-value and I2 were used to determine heterogeneity. worth. The pooled odd ratios were computed using a fixed effect model. Egger's weighted regression and Begg's funnel plot were used to analyze publication bias. Every statistical analysis was carried out using the R program's meta package.3.1. In three Caucasian populations, there is a strong correlation between susceptibility to HIV infection and the TLR4 gene's rs4986790 SNP (D299G).

Meta-Analysis

We used the search phrases "TLR4," "SNP," and "HIV" to go through 20 research publications. paired with "susceptibility" or "polymorphism" (the most recent search update was carried out PubMed, July 18, 2020. Four pertinent studies in all were taken from the databases using our inclusion and exclusion criteria after duplicate articles were eliminated. To determine whether the rs4986790 SNP (D299G) and susceptibility are related We conducted an association analysis between HIV patients and matched Caucasian control populations, including Iberian populations in Spain, Tuscans from Italy, and northern and western Europeans from Utah, derived from the 1000 Genomes Project, in order to determine the ethnic background and allele frequencies of the rs4986790 SNP of the TLR4 gene, which were documented in earlier studies [14–16]. Notably, in every analyzed group, allele frequencies of the TLR4 gene's rs4986790 SNP showed a substantial correlation ($p < 0.05$) with HIV infection susceptibility.Four studies in all that documented a link between the rs4986790 SNP and HIV infection susceptibility were found in the literature and incorporated into our metaanalysis (Figure 1). The meta-analysis comprised 1209 controls and 1028 HIV-positive patients in totale.Comprehensive details on the studies that qualify are provided in last page.TLR4 detects bacterial lipopolysaccharide (LPS) and is found on the cell surface. Thus, prior research has demonstrated a correlation between TLR4 and phenotypes associated with bacteria, such as cirrhosis, ascites, scrub typhus, Crohn's disease, and tuberculosis [18,19].In this regard, the TLR4 gene's rs4986790 SNP (D299G) has also been studied to describe how the risk allele of the rs4986790 SNP explains the variation in disease-related characteristics.Furthermore, variations in the TLR4-MD2-LPS complex's local crystal structure were observed between TLR4 carrying the G299 allele and the wild type allele [20,21]. These results suggest that the rs4986790 SNP of the TLR4 gene is connected to the antibacterial properties of TLR4 because genetic changes result in functional alteration [22–24].

RESULTS

Fascinatingly, HIV-1 influences TLR4 expression and subsequent immunological responses, such as the NF-κB pathway, and the TLR4/MD2 complex directly interacts with the HIV-1 Tat protein [25, 26]. Furthermore, in an Indian community, the rs4986790 SNP is linked to the probability of HIV-1 infection [13]. Given that TLR4 is involved in both HIV-1 infection and antibacterial activity, the rs4986790 SNP, which is linked to structural and functional changes in TLR4, has been linked to an increased risk of HIV infection as well as bacterial-related phenotypes, such as tuberculosis. These findings suggest a potential link between HIV infection susceptibility and the TLR4 gene's rs4986790 SNP. Therefore, we conducted an association study on HIV-positive Caucasian patients from earlier research.

DISCUSSION

The prior Caucasian research lacked genetic data on control groups, which is problematic when taking into account the ethnic origin of Caucasian HIV-positive individuals. As a result, we chose and matched control groups from the 1000 Genomes Project, such as Iberian populations from Spain, Tuscans from Italy, and northern and western Europeans from Utah. Surprisingly, in every studied group, we found a substantial correlation between the rs4986790 SNP and HIV infection susceptibility . However, additional confirmation using different control Caucasian populations is urgently desired, as these results were heavily reliant on the frequency of the 1000 Genome Project control Caucasian group. Additionally, a direct sequencing case-control study.

CONCLUSIONS

from patients with HIV-1 in East Asians, North and South Americans, and Caucasians has not yet been carried out. Therefore, more research is required to validate a link between the rs4986790 SNP and HIV-1 infection susceptibility. The number of alleles is indicated by the number in each column of "Allele frequencies." "Total, n" denotes the total number of individuals. Results that are statistically significant ($p < 0.05$) are indicated by bolded text. Iberian populations from Spain (IBS), Tuscans from Italy (TSI), and northern and western Europeans from Utah (CEU) make up the control population derived from the 1000 Genome Project. We conducted a meta-analysis to support the findings. Notably, we found that all four populations and Caucasians had strong relationships. While publication bias was Heterogeneity and publishing biases were mitigated by leaving out one study, which was discovered in the Caucasian population (Caucasian-Spain-2010). Future research utilizing a greater number of and diverse ethnic groups, such as Africans and East Asians, is highly desired, as association studies on the TLR4 gene in HIV-infected patients are uncommon. Furthermore, further research should confirm the relationship of the rs4986791 SNP in HIV-infected patients, as another SNP, specifically the rs4986791 SNP (T399I) of the TLR4 gene, is similarly linked to bacterial infection. In summary, we found a significant correlation between the rs4986791 SNP and HIV infection susceptibility between a matched control population derived from the 1000 Genomes Project and HIV-infected individuals in prior research. Additionally, we discovered that Strong risk factors for HIV infection in Caucasians and all four populations included in this meta-analysis are the G allele of the rs4986791 SNP of the TLR4 gene.

To the best of our knowledge, this was the first meta-analysis to evaluate the relationship between HIV infection susceptibility and the TLR4 gene's rs4986791 SNP.

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