Association between polymorphisms (rs1800896, rs1800872, rs1800871) in IL-10 gene with human immunodeficiency virus 1-infected patients’ susceptibility

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Research

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Abstract

Background

Interleukin-10 (IL-10) is considered to play a role in the human immunodeficiency virus-1 (HIV-1) infections, and 3 common single nucleotide polymorphisms (SNPs), perhaps have an association with HIV-1 risk.

Methods

To find out the above doubt, we performed a comprehensive analysis to assess the relationship between IL-10 polymorphisms and HIV-1. The PubMed database were chosen to identify potential articles through Feb 21, 2020. The odds ratio with 95% confidence interval (OR with 95%CI) was calculated to evaluate the strength of the relationships.

Results

There have 15 different articles including 24 case-control studies including those on three different SNPs in IL-10 for HIV-1 were found. Positive increased or damaged associations were detected for rs1800872C/A with HIV-1 risk in total (such as: OR with 95%CI = 1.22 with 1.02–1.41 for A-allele vs. C-allele model), and Asians (such as: OR with 95%CI = 1.51 with 1.07–1.88 for AA vs. CC model), population-based, PCR-RFLP, sequence subgroups. Moreover, increased associations were also detected between rs1800871C/T SNP (OR with 95%CI = 1.47 with 1.08-2.00 for CC vs. CT + TT model). No association was found for rs1800896.

Conclusion

Our current study indicated that two SNPs (rs1800872C/A and rs1800871C/T) in IL-10 perhaps be potentially associated with the susceptibility for developing HIV-1 infection.

Background

Human immunodeficiency virus type 1 (HIV-1), the causative agents of the acquired immunodeficiency syndrome (AIDS), are RNA viruses belonging to the genus Lentivirus of the family Retrovirus and continues to threaten global health, with 1.8 million new infections diagnosed in 2017[1, 2]. There were approximately 37.9 million people living with HIV-1 at the end of 2018. In 2018, 62% of adults and 54% of children living with HIV-1 in low- and middle-income countries were receiving lifelong antiretroviral therapy (ART)[2, 3]. HIV-1 is a very genetically diverse virus; two distinct genetic groups have been identified, the major (M) and outlier (O) groups. The genetic diversity of HIV-1 plays an important role in the design and interpretation of viral load and resistance tests[1, 4]. Hence, genetic factors may contribute to the infection for HIV-1.

Cytokines production in HIV-1 infected patients is the result of activation of several signaling pathways mediated by the interaction of various HIV-1 viral components, including gp120, with various cellular receptors, including CD47 and CCR5[5, 6]. The IL-10, a highly immune-suppressive cytokine, also seems to play a key role in HIV associated immune dysregulation[7–9]. Previous studies have demonstrated that: (a) an increased level of IL-10 is positively correlated with increased viral load and progression to the symptomatic stage of the disease in HIV-1 progressors[7–9]; (b) patients producing less IL-10, due to the mutation IL-10-5'-592A on the IL-10 promoter, evolve less rapidly to the AIDS stage[10]; (c) elite controllers, who do not develop AIDS diseases despite their seropositive status, do not show an increase in IL-10[11]; and (d) in patients receiving effective anti-retroviral therapy, plasmatic IL-10 level decreases in parallel with the decrease in viral load[11].

The −592 C > A SNP (rs1800872) is one of common IL-10 promoter SNPs, and the −592A allele is associated with lower IL-10 levels[12]. Another two important polymorphisms in the IL-10 promoter region (1082 A/G-rs1800896 and 819 C/T-rs1800871) were associated with IL-10 gene transcription and its secretion[13, 14]. Additional, IL-10-592C > A is also in linkage disequilibrium (LD) with the IL-10 -1082 SNP (R² = 3.7, D’ = 1.0), which has been associated with longevity in samples of men from Japan, Italy[15–17], and Jordan and in a sample of both men and women from Bulgaria[18].

Many published studies have suggested relationships between IL-10 gene variations and HIV-1 risk[19–33], including previous two meta-analysis[34, 35]. However, ambiguous conclusions have been reported, it is necessary to do an undated meta-analysis including all the currently studies to reanalyze in time.

Methods

Search strategy and criteria

The PubMed database through Feb 21, 2020 were conducted, using the keywords “Interleukin-10,” “IL-10,” “polymorphism,” and “HIV or Human immunodeficiency virus type 1 or AIDS.” A total of 60 papers were identified, 15 of which were consistent with our criteria. The inclusion criteria were as follows (a) to about relationship between HIV-1 susceptibility and IL-10 variations, (b) to be case-controlled, and (c) contain a complete number of
genotypes (MM + MW + WW) in cases and controls, respectively. Otherwise, studied should be deleted as following issues: (a) no control, (b) incomplete genotype frequency data, (c) duplication publication, and (d) not according with Hardy-Weinberg equilibrium (HWE) standards in controls.

Data extraction

The essential data of are listed as follows: first author name, publication year, original country, race, total samples of case/control, each genotype both in case/control, source of control and genotype methods. Race was classified as Caucasian, Asian, African, and Mixed. The source of control subgroups included population-base (PB) and

Quality score assessment (NOS)

The NOS were selected to assess the quality of each study and to assess the various aspects of the methodology used by the observational research, which are relevant to the quality of the study, including the selection of cases, the comparability of groups and the determination of exposure. The total score is from 0 to 9 star. Studies with scores more than 7 are to be as high quality [36].

Statistical analysis

95%CI were used to measure the correlation between SNPs in IL-10 and HIV-1 risk, depending on the genotype frequency of the case and control groups. The Z-test determines the above statistical significance. The heterogeneity assumptions between the studies were evaluated using a Q-test based on the \( \chi^2 \)-square method. In Q-test, \( P \) value more than 0.05 shows that there is a lack of heterogeneity between the studies. Because the Q-statistic does not inform of the extent of true heterogeneity for its statistical significance, the \( I^2 \) test was applied to better access the extent of heterogeneity. As a guide, \( I^2 \) values are divided into three categories (0-25%, 25-50%, 50%), corresponding to low risk, medium risk, and high risk, respectively [37]. If \( P \leq 0.05 \), or \( I^2 \geq 50\% \), a random-effects model was adopted, otherwise a fixed-effects model was used [38, 39]. We accessed the association among SNPs in MBL2 and PTB risk by testing the allelic contrast, heterozygote comparison, homozygote comparison, recessive genetic model and dominant genetic model.

Sensitivity analysis was applied to assess the stability of the results. The HWE was evaluated by the Pearson's \( \chi^2 \) test, and the \( P = 0.05 \) was considered as the watershed [40]. Publication bias was appraised by both Egger's and Begg's test [41]. All statistical tests were carried out by version 11.0 Stata Software (StataCorp LP, College Station, TX, USA).

Results

Study characteristics

A total of 60 article titles were garnered by a search using the PubMed database by using various combinations with above keywords. 31 articles were removed because of unrelated information. Next, 29 articles with full texts were evaluated, and 14 other articles were excluded because meta-analysis (3), review (5), not related to IL-10 polymorphisms (6) (Figure 1). Finally, 15 different articles about 3 SNPs in IL-10 and HIV-1 susceptibility were included (10 articles for rs1800896, 11 for rs1800872 and 3 for rs1800871 SNP) (Table 1). Overall, 24 case-control studies with 3957 cases of HIV-1 as well as 4845 controls were included[19-33]. The controls were mainly healthy individuals. The average NOS of including studies is 7.8, which means our results is credible and representational. Finally, we checked the Minor Allele Frequency (MAF) reported for the five main worldwide populations in the 1000 Genomes Browser (https://www.ncbi.nlm.nih.gov/snp): because the frequency is the same for rs1800871 and rs1800872, so we combined these two sites into a set of bar graph for presentation (Figure 2).

Quantitative synthesis

Results of the 3 SNPs in IL-10 and HIV-1 risk are presented in Table 2 and Figure 3-7. For rs1800896 polymorphism (1503 cases and 2089 controls), no association was found in the total and each subgroup, such as the allelic contrast (OR: 1.00, 95% CI: 0.84-1.18, \( P \)(heterogeneity): 0.009, \( P = 0.985 \) (Figure 3).

For the rs1800872 polymorphism (1883 cases and 2036 controls), individuals carrying the A-allele had an increased association with HIV-1 risk in the total sample population (the allelic contrast: OR: 1.22, 95% CI: 1.02-1.41, \( P = 0.007 \) for heterogeneity, \( P = 0.033 \), Figure 4A; AA vs. CC: OR: 1.51, 95% CI: 1.10-2.06, \( P = 0.084 \) for heterogeneity, \( P = 0.011 \); AA vs. AC+CC: OR: 1.49, 95% CI: 1.21-1.83, \( P = 0.120 \) for heterogeneity, \( P = 0.000 \)). In the stratified analysis by ethnicity subgroup, a similar significant association was detected for the Asian population (allelic contrast: OR: 1.17, 95% CI: 1.02-1.34, \( P = 0.141 \) for heterogeneity, \( P = 0.021 \), Figure 4B; AA vs. CC: OR: 1.42, 95% CI: 1.07-1.88, \( P = 0.203 \) for heterogeneity, \( P = 0.014 \); AA vs. AC+CC: OR: 1.35, 95% CI: 1.04-1.75, \( P = 0.334 \) for heterogeneity, \( P = 0.024 \)). In addition, in the subgroup analysis by source of control, a significant risk effect was observed in PB (AA vs. CC: OR: 1.69, 95% CI: 1.25-2.27, \( P = 0.191 \) for heterogeneity, \( P = 0.001 \), Figure 5; AA vs. AC+CC: OR: 1.69, 95% CI: 1.28-2.33, \( P = 0.291 \) for heterogeneity, \( P = 0.000 \)). Finally, different genotype methods were applied, so we tried to analyze the associations, increased trends were found in both PCR-RFLP (AA vs. CC: OR: 1.60, 95% CI: 1.15-2.22, \( P = 0.125 \) for heterogeneity, \( P = 0.005 \); AA vs. AC+CC: OR: 1.46, 95% CI: 1.07-1.98, \( P = 0.367 \) for heterogeneity, \( P = 0.016 \), Figure 6A) and sequence methods (AA+AC vs. CC: OR: 1.70, 95% CI: 1.08-2.68, \( P = 0.520 \) for heterogeneity, \( P = 0.022 \), Figure 6B).

For the rs1800871 polymorphism (571 cases and 720 controls), increased associations were observed in total in two models (TT vs. CC: OR: 1.46, 95% CI: 1.04-2.04, \( P = 0.337 \) for heterogeneity, \( P = 0.028 \); TT vs. TC+CC: OR: 1.47, 95% CI: 1.08-2.00, \( P = 0.720 \) for heterogeneity, \( P = 0.015 \), Figure 7).

Bias diagnosis and sensitivity analysis for rs1800896 and rs1800872
Begg’s funnel diagram and Egger’s test were used to evaluate the publication bias of the literature. The shape of the funnel diagram did not show obvious asymmetry, and the Egger’s test did not show publication bias (the allelic contrast, t = 1.5, P = 0.172 for Egger’s test; z = 1.43, P = 0.152 for Begg’s test for rs1800896, Figure 8A,B, and the allelic contrast, t = 1.43, P = 0.189 for Egger’s test; z = 1.43, P = 0.152 for Begg’s test for rs1800872, Figure 8C,D, Table 3). We use sensitivity analysis to determine whether changes in a single study will affect final outcomes. To delete studies which may influence the power and stability of whole study, we applied the sensitive analysis, finally, no sensitive case-control studies were found (rs1800896, Figure 8E; rs1800872, Figure 8F).

Gene-gene network diagram and interaction of online website

String online server indicated that IL-10 gene interacts with numerous genes. The network of gene-gene interaction has been illustrated in Figure 9.

Discussion

Despite the gratifying progress carried out in the HIV/AIDS diagnosis, prevention and treatment, HIV/AIDS remains the most important public health problem globally[42, 43]. HIV/AIDS is a kind of infectious diseases, whose communication must be according with three conditions: source route and susceptible population. In addition, studies on the impact of host genetics on the susceptibility to HIV infection and rate of disease progression have suggested associations with considerable number of individual genes. Other words, the susceptibility of population may attribute to the polymorphism of key genes, such as encoding proteins that control viral entry (CCR5, CCR2, RANTES, and SDF1)[44–47], immune regulation (IL-10, TNF-α, and MBL-2)[48, 49] and adaptive immune recognition by T-cells (human leukocyte antigen or HLA)[50].

Cytokines play a vital role in regulating the homeostasis of the immune system and alterations in their relative levels play critical roles in the immune response against HIV-1 infection and the progression of HIV-1 infection to clinical AIDS[51]. Many reports have documented that HIV infection is characterized by generalized immune activation with high levels of circulating cytokines, such as TNF-α, IL-6, and IL-10[26, 52, 53]. Numerous PB studies have been conducted to authenticate the hypothesis that IL-10 gene polymorphisms may boost the susceptibility to HIV-1[21, 24, 33]. Polymorphisms associated with decreased IL-10 production have been associated with increased likelihood of HIV-1 acquisition and accelerated rate of CD4 + T cell decline particularly in late stage disease[21, 28], suggesting that high IL-10 production may reduce susceptibility to HIV-1 infection and protect against disease progression[25].

Previous two meta-analysis have been reported, however, some limitations should be considered. Jiang et al.[34] first performed a meta-analysis about these three SNPs in IL-10 gene and HIV-1 risk, and found that no association was observed between rs1800896 polymorphism and HIV-1, decreased associations and increased correlations were detected for rs1800872 and rs1800871 SNPs, respectively. Due to its limitation for the samples (six articles for rs1800872, 7 for rs1800872 and 2 for 1800871), the results may not be credible. Tsaiara et al.[35] made an updated analysis including 8 papers related to rs1800896 and 9 related to rs1800872, suggested no significant association was exist both for rs1800896 (such as: AA homozygotes had marginally no-significant risk, OR: 1.39, 95%CI: 0.97–2.01) and rs1800872 (for example: AG versus AA genotype, OR: 1.05, 95%CI: 0.72–1.53). To the best knowledge, our present analysis including comprehensive information about 10 studies for rs1800896, 11 for rs1800872 and 3 for rs1800871 SNPs. The conclusion from our analysis was that both rs1800872 rs1800871 polymorphisms act as risk factors for the susceptibility of HIV infection, which was partly different to previous two meta-analysis, in other words, individuals carrying A-allele or AA genotype for rs1800872 and T-allele or TT genotype for rs1800871, may have a higher frequency to be infected of HIV-1, who should be gained with early detection, early intervention and early treatment. TNF-α and IL-6 molecular were elaborated in above paragraph.

In addition, the online analysis system-String was applied to predict potential and functional partners related to IL-10, which can help us to better understand the value for detection and concern. Finally, ten potential genes were predicted. The average score is more than 0.99, which suggests these genes may have deep interactions with IL-10. Five genes in all ten molecular are ascribed to cytokines family. Among them, the highest score of association was IL-10RA (0.998), which is the receptor of IL-10 and binds with a high affinity. In addition, IL-10RA rs2244305 polymorphism had a suggested associations with considerable number of individual genes. Other words, the susceptibility of population may attribute to the polymorphism of key genes, such as encoding proteins that control viral entry (CCR5, CCR2, RANTES, and SDF1)[44–47], immune regulation (IL-10, TNF-α, and MBL-2)[48, 49] and adaptive immune recognition by T-cells (human leukocyte antigen or HLA)[50].

Gene-gene network diagram and interaction of online website

String online server indicated that IL-10 gene interacts with numerous genes. The network of gene-gene interaction has been illustrated in Figure 9.

In the previous study, we have collected all the eligible studies, however, the sample size of these studies is not yet large enough, especially in certain ethnic groups. Therefore, not only is the likelihood of I/II type errors increasing, but there is insufficient statistical capacity to assess the correlation between the three SNPs and HIV-1 risk. Second, the expression of IL-10 in the serum is lacking in our study, which is necessary because it is convenient to detect and more to understand the mechanism of SNPs in IL-10 gene. Third, some items such as age, sex, smoking, familial history, disease stage, specific environmental factors and lifestyles should be included. Fourth, the included cases do exist very heterogeneous population, which is depend on the original articles. Finally, all included studies are about epidemiological survey, plausible biological hypothesis and some mechanism study must not appear. We just try to know whether there has a relationship among this gene variant and HIV-1 susceptibility. Further studies should focus on above questions and try to solve.

Conclusion

To sum up, our present study indicated that the rs1800872 and rs1800871 polymorphisms in IL-10 gene may be related with HIV-1 risk based on 24 case-control studies with 3957 cases and 4845 controls. Larger sample sizes and considering additional gene-environment interactions should be added in the further studies.
Abbreviations

HIV-1, Human immunodeficiency virus type 1; AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy; LD, linkage disequilibrium; HWE, Hardy-Weinberg equilibrium; OR, odds ratio; 95%CI, 95% confidence interval; NOS, Quality score assessment; PB, population-base; HB, hospital-based.

Declarations

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Not applicable.

Author Contribution

HT and LX designed and conceived this study. DZ contributed to literature searching. YM were involved in data extraction. WZ analyzed the data. SY wrote the manuscript. WZ revised the paper. All authors have approved the final edition of the manuscript.

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Availability of data and materials

All the data generated in the present research is contained in this manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 Characteristics of included studies in IL-10 polymorphisms and HIV risk.

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| Author       | Year | Country | Ethnicity | Case | Control | SOC | Case | Control | Cases | Control | Genotype | NOS |
|--------------|------|---------|-----------|------|---------|-----|------|---------|-------|---------|----------|-----|
| Singh        | 2012 | India   | Asian     | 121  | 102     | HB  | 121  | 102     | 2     | 83      | 36       |     |
|             | 2016 | India   | Asian     | 260  | 260     | PB  | 260  | 260     | 21    | 119     | 120      |     |
| Kallas       | 2015 | Estonia | Caucasian | 172  | 496     | PB  | 172  | 496     | 32    | 78      | 62       |     |
| Erikstru...  | 2007 | Denmark | Caucasian | 195  | 175     | PB  | 195  | 175     | 22    | 73      | 100      |     |
| Chatter...   | 2009 | India   | Asian     | 180  | 305     | HB  | 180  | 305     | 20    | 60      | 100      |     |
| Freitas      | 2015 | Brazil  | Mixed     | 216  | 284     | HB  | 216  | 284     | 14    | 79      | 123      |     |
| Rameza...    | 2015 | Iran    | Asian     | 70   | 31      | HB  | 70   | 31      | 10    | 32      | 28       |     |
| Naicker      | 2009 | South Africa | African | 64   | 195     | PB  | 64   | 195     | 5     | 22      | 37       |     |
| Singh        | 2019 | India   | Asian     | 131  | 155     | PB  | 131  | 155     | 5     | 52      | 74       |     |
| Wang         | 2004 | UK      | Caucasian | 94   | 76      | PB  | 94   | 76      | 6     | 61      | 27       |     |
|             |      |         |           |      |         |     |      |         |       |         |          |     |
| Singh        | 2016 | India   | Asian     | 260  | 260     | PB  | 260  | 260     | 39    | 115     | 106      |     |
| Kallas       | 2015 | Estonia | Caucasian | 172  | 496     | PB  | 172  | 496     | 10    | 49      | 113      |     |
| Erikstru...  | 2007 | Denmark | Caucasian | 194  | 174     | PB  | 194  | 174     | 43    | 71      | 80       |     |
| Chatter...   | 2009 | India   | Asian     | 180  | 305     | HB  | 180  | 305     | 39    | 74      | 67       |     |
| Rameza...    | 2015 | Iran    | Asian     | 70   | 31      | HB  | 70   | 31      | 4     | 35      | 31       |     |
| Naicker      | 2009 | South Africa | African | 64   | 195     | PB  | 64   | 195     | 17    | 23      | 24       |     |
| Piddab...    | 2013 | Ukraine | Caucasian | 78   | 30      | HB  | 78   | 30      | 8     | 28      | 42       |     |
| Corcha...    | 2013 | Spain   | Caucasian | 88   | 51      | HB  | 88   | 51      | 7     | 38      | 43       |     |
| Sobti        | 2010 | India   | Asian     | 300  | 300     | HB  | 300  | 300     | 36    | 137     | 127      |     |
| Harish...    | 2018 | India   | Asian     | 100  | 122     | PB  | 100  | 122     | 22    | 51      | 27       |     |
| Shin         | 2000 | USA     | Mixed     | 377  | 72      | PB  | 377  | 72      | 207   | 50      |          |     |

Table 2 Results of the meta-analysis on IL-10 polymorphisms and HIV risk in total and types of subgroups.

HB: hospital-based; PB: population-based; SOC: source of control; PCR-RFLP: polymerase chain reaction followed by restriction fragment length polymorphism; ARMS-PCR: amplification refractory mutation system-PCR; HWE: Hardy-Weinberg equilibrium of control group; NOS: quality score assessment.
| Variables | N  | Case/ | M-allele vs. W-allele | MM vs. WW | MM vs. WW | MM vs. WW | MM vs. WW |
|-----------|----|-------|-----------------------|-----------|-----------|-----------|-----------|
|           |    |       | Control               | OR(95%CI) | OR(95%CI) | OR(95%CI) | OR(95%CI) |
| rs1800896 | 10 | 1503/2089 | 1.00(0.84-1.18) | 0.88 | 0.869 | 1.12(0.77) | 0.302 |
|           |    |       |                      | 1.19(0.86-1.71) | 1.35 | 0.653 | 0.79 | 0.701 |
| Ethnicity |    |       | Asian                 | 1.11(0.87-1.41) | 1.17 | 0.757 | 1.16(0.72) | 0.794 |
|           |    |       | Caucasian             | 1.21(0.70-1.99) | 0.96 | 0.844 | 1.15(0.73) | 0.519 |
|           |    |       | SOA                   | 1.13(0.81-1.57) | 1.22 | 0.517 | 1.06(0.70) | 0.794 |
|           |    |       | HB                    | 0.45(0.33-0.64) | 0.19 | 0.846 | 0.01 | 0.996 |
|           |    |       | PB                    | 0.25(0.19-0.33) | 0.19 | 0.852 | 0.02 | 0.820 |
| Genotyping |    |       | ARMS PCR              | 1.22(1.02-1.41) | 0.77 | 0.003 | 0.01 | 0.995 |
|           |    |       | PCR-RFLP              | 1.39(0.93-2.00) | 0.77 | 0.488 | 0.02 | 0.846 |
|           |    |       | Caucasian             | 1.20(0.87-1.91) | 0.75 | 0.003 | 0.01 | 0.995 |
|           |    |       | SOA                   | 1.16(0.90-1.42) | 0.75 | 0.003 | 0.01 | 0.995 |
|           |    |       | HB                    | 0.43(0.35-0.53) | 0.19 | 0.852 | 0.02 | 0.820 |
|           |    |       | PB                    | 0.23(0.18-0.29) | 0.17 | 0.003 | 0.01 | 0.995 |
| Genotyping |    |       | ARMS PCR              | 1.22(1.02-1.41) | 0.77 | 0.003 | 0.01 | 0.995 |
|           |    |       | PCR-RFLP              | 1.39(0.93-2.00) | 0.77 | 0.003 | 0.01 | 0.995 |
|           |    |       | Caucasian             | 1.20(0.87-1.91) | 0.75 | 0.003 | 0.01 | 0.995 |
|           |    |       | SOA                   | 1.16(0.90-1.42) | 0.75 | 0.003 | 0.01 | 0.995 |
|           |    |       | HB                    | 0.43(0.35-0.53) | 0.19 | 0.852 | 0.02 | 0.820 |
|           |    |       | PB                    | 0.23(0.18-0.29) | 0.17 | 0.003 | 0.01 | 0.995 |
| Genotyping |    |       | ARMS PCR              | 1.22(1.02-1.41) | 0.77 | 0.003 | 0.01 | 0.995 |
|           |    |       | PCR-RFLP              | 1.39(0.93-2.00) | 0.77 | 0.003 | 0.01 | 0.995 |
|           |    |       | Caucasian             | 1.20(0.87-1.91) | 0.75 | 0.003 | 0.01 | 0.995 |
|           |    |       | SOA                   | 1.16(0.90-1.42) | 0.75 | 0.003 | 0.01 | 0.995 |
|           |    |       | HB                    | 0.43(0.35-0.53) | 0.19 | 0.852 | 0.02 | 0.820 |
|           |    |       | PB                    | 0.23(0.18-0.29) | 0.17 | 0.003 | 0.01 | 0.995 |

P value of Q-test for heterogeneity test; P: Z-test for the statistical significance of OR

Table 3: Publication bias tests (Begg’s funnel plot and Egger’s test for publication bias test) for IL-10 polymorphisms.
Figures

60 records were searched in Pubmed database until 21 Feb, 2020

Improper articles were excluded after screening titles, abstracts and full texts (31)
- review (5)
- meta (3)
- Not related IL-10 gene polymorphism (6)

Finally, 15 different articles were included in our meta-analysis

- rs1800896 (-1082 A/G) (10)
- rs1800872 (-592 C/A) (11)
- rs1800871 (-819 C/T) (3)

Figure 1
A flowchart illustrating the search strategy for identifying related studies.
The MAF of minor-allele (mutant-allele) for IL-10 gene rs1800896, rs1800872, rs1800871 polymorphisms from the 1000 Genomes online database and present analysis. EAS: East Asian; EUR: European; AFR: African; AMR: American; SAS: South Asian.
Figure 3

Forest plot of HIV risk associated with IL-10 rs1800896 polymorphism (G-allele vs. A-allele) in the whole samples. Square and horizontal lines correspond to specific OR with 95% CI. The area of the squares reflects the weight (inverse proportional variance). Diamonds represent the total OR or 95% CI.
Figure 4

Forest plot of HIV risk associated with IL-10 rs1800872 combined polymorphism (allelic contrast). A: the whole samples and B: ethnicity subgroup.
Figure 5

Forest plot of HIV risk associated with IL-10 rs1800872 combined polymorphism (AA vs. CC) by source of control.
Figure 6
Forest plot of HIV risk associated with IL-10 rs1800872 combined polymorphism by genotype methods subgroup. A: AA vs. CC model, B: AA+AC vs. CC model.

Figure 7
Forest plot of HIV risk associated with IL-10 rs1800871 combined polymorphism in the total (TT vs. TC+CC).
Figure 8

Publication bias and sensitivity analysis. A: Begg's funnel plot for rs1800896 by publication bias test (allelic contrast). Each point represents a separate study for the indicated association. Log [OR], natural logarithm of OR. Horizontal line, mean effect size. B: Egger's publication bias plot for rs1800896 (allelic contrast). C: Begg's funnel plot for rs1800872 by publication bias test (allelic contrast). D: Egger's publication bias plot for rs1800872 (allelic contrast). E: Sensitivity analysis between rs1800896 and HIV risk (allelic contrast). F: Sensitivity analysis between rs1800872 and HIV risk (allelic contrast).
Figure 9

Human IL-10 interactions network with other genes obtained from String server. At least 10 genes have been indicated to correlate with IL-10 gene. IL10RA: interleukin-10 receptor subunit alpha; TNF: tumor necrosis factor; IL6: interleukin-6; CXCL8: interleukin-8; IL1B: interleukin-1 beta; STAT3: signal transducer and activator of transcription 3; CCL2: C-C motif chemokine 2; CSF2: granulocyte-macrophage colony-stimulating factor; CCL5: C-C motif chemokine 5; CD86: T-lymphocyte activation antigen CD86.