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

Huiyu Tai

Laboratoire ICU

Li Xiao

Department of ID

Daming Zhou

Department of ID

Yuanyuan Mi

Department of Urology

Wei Zhang (✉ zhangweimeta@sina.com)

Department of infectious disease

Song Yang

Department of ID

Research

Keywords: Interleukin-10, human immunodeficiency virus-1, polymorphism, meta-analysis, susceptibility

Posted Date: June 19th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-36462/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

Background

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

Methods

To find out the above doubt, a comprehensive study to evaluate the association between IL-10 polymorphisms and HIV-1 has been performed. PubMed database was chosen to identify potential articles through Feb 21, 2020. The odd ratio with 95% confidence interval (OR with 95%CI) was applied to evaluate 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

As we known, the causative agent of acquired immunodeficiency syndrome (AIDS) is human immunodeficiency virus type 1 (HIV-1), which is a kind of RNA viruses ascribed to the genus lentivirus of the retrovirus family continuing to threaten global health, about 1.8 million diagnosed new cases in 2017[1, 2]. By the end of 2018, about 37.9 million individuals were infected with HIV-1. In the same period, about 62% frequency of adults and 54% frequency of children in both low and middle income countries were infected and were received life-long antiretroviral therapy (ART)[2, 3]. HIV-1 is a virus with strong genetic variation; two different genetic groups have been observed with the major (M) and outlier (O) groups. The genetic variants of HIV-1 carry out an vital role in the design and interpretation of both viral load and recognized examinations [1, 4]. Above information demonstrated genetic factors may cause HIV-1 infection.

The activation of multiple signaling pathways in HIV-1 infected patients can cause the production of cytokines, which are mediated by the interaction of various HIV-1 viral components (eg: gp120) and cellular receptors (eg: CD47, CCR5)[5, 6]. IL-10 is a highly immunosuppressive cytokine and appears to play a critical role in HIV-related immune disorders[7–9]. Previous studies have shown that: (a) Serum IL-10 expression was positively associated with increased viral load and disease progression to HIV-1 progressors[7–9]; (b) The mutation of -592 site in IL-10 promoter may result in reduced IL-10 expression, and slow the progression of the AIDS stage[10]; (c) Controllers with seropositive status, who may not progress to AIDS status, did not show an increase expression of IL-10[11]; and (d) The phenomenon about decrease in plasma IL-10 levels paralleled with decrease in viral load were identified in patients receiving effective ART [11].

The - 592 site (rs1800872) is one of common single nucleotide polymorphisms (SNPs) in IL-10 gene promoter, and the - 592A allele has been shown with lower serum IL-10 expression[12]. Two other important SNPs (1082 A/G, rs1800896 and 819 C/T, rs1800871) were related to the transcription and secretion of IL-10 gene [13, 14]. In addition, -592C > A is also in linkage disequilibrium (LD) with the - 1082 SNP ($R^2 = 3.7$, $D' = 1.0$), which was related to the life span of population from Japan, Italy [15–17], Jordan and Bulgaria [18].

Previous studies have shown correlations between IL-10 variations and HIV-1 susceptibility [19–35]. Nevertheless, non-convincing facts have been shown and it makes sense to conduct an updated analysis, including all current studies to be re-analyzed in a timely manner.

Methods

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. Followings were the inclusion criteria: (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, studies should be deleted as following issues: (a) no control group, (b) incomplete of frequency data for each genotype, (c) duplication publication, and (d) not according with Hardy-Weinberg equilibrium (HWE) standards in control group [36].

Data extraction

The essential of data are listed as follows: first author, published year, country for corresponding author, race, total samples of case/control, each genotype both in case and control group, source of control and genotype methods. Caucasian, Asian, African, and Mixed were classified by race. The source of control subgroups included population-based (PB) and hospital-based (HB) [36].

Quality score assessment (NOS)

The NOS were applied to assess the quality of each study, which includes the selection of cases, the comparability of groups and the determination of exposure. The range of score is from 0 to 9 star. Studies with scores > 7 are to be considered as high quality [37].

Statistical analysis

95%CI were applied to calculate 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 [36]. The heterogeneity assumptions between the studies were evaluated using a Q-test based on the χ^2 -square method [36]. In Q-test, P value > 0.05 shows there is a lack of heterogeneity for included studies. The Q-statistic does not inform of the extent of true heterogeneity completely, so 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 [38]. If $P \leq 0.05$ and $I^2 \geq 50\%$, a random-effects model was adopted, otherwise a fixed-effects model was used [39, 40]. 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 evaluate the powerful of stability. The HWE was evaluated by the Pearson's χ^2 test, and the $P = 0.05$ was considered as the watershed [41]. Publication bias was appraised by both Egger's and Begg's test [42]. All statistical tests were carried out by version 11.0 Stata Software (StataCorp LP, College Station, TX, USA) [36].

Results

Study characteristics

A number of 60 articles were garnered through a searching from the PubMed database. 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) (Fig. 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 is 7.8, which stands for the credible and representational for including studies. In final, the Minor Allele Frequency reported for the five main worldwide populations in the 1000 Genomes Browser was checked: because the frequency is the same for rs1800871 and rs1800872, so we combined these two sites into a set of bar graph for presentation (Fig. 2)

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

Author	Year	Country	Ethnicity	Case	Control	SOC	Case	Control	Cases			Controls			HWE
rs1800896 -1082									GG	GA	AA	GG	GA	AA	
Sunder	2012	India	Asian	121	102	HB	121	102	2	83	36	2	43	57	0.056
Singh	2016	India	Asian	260	260	PB	260	260	21	119	120	21	125	114	0.098
Kallas	2015	Estonia	Caucasian	172	496	PB	172	496	32	78	62	104	251	141	0.692
Erikstrup	2007	Denmark	Caucasian	195	175	PB	195	175	22	73	100	17	82	76	0.448
Chatterjee	2009	India	Asian	180	305	HB	180	305	20	60	100	27	122	156	0.653
Freitas	2015	Brazil	Mixed	216	294	HB	216	294	14	79	123	24	111	159	0.459
Ramezani	2015	Iran	Asian	70	31	HB	70	31	10	32	28	3	15	13	0.655
Naicker	2009	South Africa	African	64	195	PB	64	195	5	22	37	27	80	88	0.206
Singh	2019	India	Asian	131	155	PB	131	155	5	52	74	7	59	89	0.476
Wang	2004	UK	Caucasian	94	76	PB	94	76	6	61	27	4	33	39	0.373
rs1800872 -592							Case	Control	AA	AC	CC	AA	AC	CC	
Singh	2016	India	Asian	260	260	PB	260	260	39	115	106	29	122	109	0.555
Kallas	2015	Estonia	Caucasian	172	496	PB	172	496	10	49	113	23	167	306	0.972
Erikstrup	2007	Denmark	Caucasian	194	174	PB	194	174	43	71	80	25	81	68	0.911
Chatterjee	2009	India	Asian	180	305	HB	180	305	39	74	67	43	122	140	0.054
Ramezani	2015	Iran	Asian	70	31	HB	70	31	4	35	31	4	11	16	0.357
Naicker	2009	South Africa	African	64	195	PB	64	195	17	23	24	18	80	97	0.797
Piddubna	2013	Ukraine	Caucasian	78	30	HB	78	30	8	28	42	0	5	25	0.618
Corchado	2013	Spain	Caucasian	88	51	HB	88	51	7	38	43	6	21	24	0.672
Sobti	2010	India	Asian	300	300	HB	300	300	36	137	127	34	146	120	0.295
Harishankar	2018	India	Asian	100	122	PB	100	122	22	51	27	18	54	50	0.585
Shin	2000	USA	Mixed	377	72	PB	377	72			207			50	
rs1800871 -819							Case	Control	TT	TC	CC	TT	TC	CC	
Singh	2016	India	Asian	260	260	PB	260	260	39	115	106	29	122	109	0.555
Chatterjee	2009	India	Asian	180	305	HB	180	305	39	74	67	43	122	140	0.054
Singh	2019	India	Asian	131	155	PB	131	155	21	59	51	21	84	50	0.125
HB: hospital-based; PB: population-based; SOC: source of control; PCR-RFLP: polymerase chain reaction followed by restriction fragment length polymorphis amplification refractory mutation system-PCR; HWE: Hardy–Weinberg equilibrium of control group; NOS: quality score assessment.															

Quantitative Synthesis

Results of the 3 SNPs in IL-10 and HIV-1 risk are presented in Table 2 and Fig. 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, $P_{\text{(heterogeneity)}}$: 0.009, P : 0.985 (Fig. 3).

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

Variables	N	Case/	M-allele vs. W-allele	MW vs. WW	MM + MW vs. WW	MM vs. WW	MM vs. MW + WW
		Control	OR(95%CI) P_h P	OR(95%CI) P_h P	OR(95%CI) P_h P	OR(95%CI) P_h P	OR(95%CI) P_h P
rs1800896 -1082							
Total	10	1503/2089	1.00(0.84–1.18)0.009 0.985	1.02(0.76–1.37)0.000 0.880	1.02(0.77–1.35)0.000 0.869	0.88(0.69–1.12)0.717 0.302	0.96(0.76–1.21)0.916 0.701
Ethnicity							
Asian	5	762/853	1.11(0.87–1.41)0.074 0.407	1.16(0.73–1.83)0.002 0.535	1.18(0.77–1.80)0.003 0.448	1.08(0.72–1.60)0.950 0.715	1.12(0.76–1.64)0.930 0.571
Caucasian	3	461/747	1.02(0.70–1.49)0.018 0.921	1.04(0.50–2.15)0.001 0.920	1.05(0.53–2.09)0.001 0.885	0.85(0.58–1.25)0.275 0.415	0.97(0.68–1.37)0.691 0.844
SOC							
HB	4	587/737	1.13(0.81–1.57)0.026 0.470	1.20(0.65–2.19)0.001 0.558	1.22(0.70–2.14)0.001 0.482	1.02(0.66–1.57)0.113 0.929	1.06(0.70–1.61)0.678 0.784
PB	6	916/1357	0.93(0.76–1.14)0.055 0.488	0.93(0.66–1.30)0.009 0.658	0.92(0.66–1.27)0.007 0.613	0.82(0.60–1.10)0.517 0.187	0.91(0.69–1.21)0.835 0.519
Genotyping							
PCR-RFLP	4	648/856	1.09(0.81–1.47)0.027 0.557	1.20(0.70–2.03)0.001 0.508	1.19(0.73–1.95)0.001 0.483	0.96(0.63–1.47)0.786 0.852	0.99(0.66–1.50)0.733 0.966
ARMS PCR	2	324/455	0.85(0.68–1.07)0.135 0.170	0.83(0.61–1.31)0.368 0.239	0.81(0.61–1.09)0.220 0.170	0.74(0.43–1.27)0.216 0.277	0.82(0.48–1.38)0.287 0.446
rs1800872 -592							
Total	11	1883/2036	1.22(1.02–1.41)0.007 0.033	1.02(0.88–1.91)0.115 0.775	1.23(0.99–1.53)0.018 0.059	1.51(1.10–2.06)0.084 0.011	1.49(1.21–1.83)0.120 0.000
Ethnicity							
Asian	5	910/1081	1.17(1.02–1.34)0.141 0.021	1.09(0.90–1.33)0.245 0.372	1.16(0.97–1.14)0.162 0.109	1.42(1.07–1.88)0.203 0.014	1.35(1.04–1.75)0.334 0.024
Caucasian	4	532/751	1.16(0.78–1.71)0.024 0.460	0.98(0.63–1.53)0.076 0.931	1.09(0.69–1.74)0.041 0.705	1.36(0.89–2.08)0.320 0.150	1.48(0.99–2.21)0.312 0.055
SOC							
HB	5	716/717	1.21(0.86–1.71)0.041 0.067	1.13(0.90–1.42)0.142 0.303	1.28(0.86–1.91)0.045 0.218	1.32(0.94–1.84)0.107 0.112	1.26(0.92–1.73)0.144 0.153
PB	6	1167/1319	1.24(0.99–1.55)0.013 0.269	0.95(0.77–1.16)0.183 0.599	1.22(0.92–1.62)0.039 0.167	1.69(1.25–2.27)0.191 0.001	1.69(1.28–2.23)0.291 0.000
Genotyping							
ARMS PCR	2	324/455	1.42(0.84–2.38)0.031 0.187	1.01(0.74–1.40)0.632 0.934	1.19(0.88–1.60)0.189 0.262	2.20(0.82–5.94)0.040 0.119	2.15(0.87–5.33)0.043 0.098
TaqMan	2	260/547	0.91(0.70–1.18)0.883 0.470	0.84(0.60–1.17)0.569 0.302	0.86(0.62–1.18)0.800 0.355	0.99(0.51–1.91)0.416 0.972	1.03(0.54–1.96)0.340 0.928
PCR-RFLP	4	658/757	1.44(0.99–2.10)0.005 0.057	1.36(0.88–2.09)0.045 0.166	1.53(0.94–2.49)0.010 0.084	1.60(1.15–2.22)0.125 0.005	1.46(1.07–1.98)0.367 0.016
sequence	2	447/103			1.70(1.08–2.68)0.520 0.022		

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

Variables	N	Case/	M-allele vs. W-allele	MW vs. WW	MM + MW vs. WW	MM vs. WW	MM vs. MW + WW
rs1800871 -819							
Total	3	571/720	1.16(0.99–1.36)0.131 0.071	0.99(0.77–1.26)0.189 0.910	1.09(0.87–1.37)0.113 0.449	1.46(1.04–2.04)0.337 0.028	1.47(1.08–2.00)0.720 0.015
P_h : value of Q -test for heterogeneity test; P : Z -test for the statistical significance of the OR							

For the rs1800872 polymorphism (1883 cases and 2036 controls), individuals carrying the A-allele existed an increased relation with HIV-1 risk in the total sample population (the allelic contrast: OR: 1.22, 95% CI: 1.02–1.41, $P_{(\text{heterogeneity})}$ = 0.007, P : 0.033, Fig. 4A; AA verse 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 < 0.01). In the stratified analysis by race subgroup, a similar significant difference was observed for the Asians (allelic contrast: OR: 1.17, 95% CI: 1.02–1.34, $P_{(\text{heterogeneity})}$: 0.141, P : 0.021, Fig. 4B; AA vs. CC: OR: 1.42, 95% CI: 1.07–1.88, $P_{(\text{heterogeneity})}$ = 0.203, P : 0.014; AA vs. AC + CC: OR: 1.35, 95% CI: 1.04–1.75, $P_{(\text{heterogeneity})}$ = 0.334, P : 0.024). In addition, in source of control group, a significant risk effect was observed in PB (AA vs. CC: OR: 1.69, 95% CI: 1.25–2.27, $P_{(\text{heterogeneity})}$ = 0.191, P < 0.01, Fig. 5; AA vs. AC + CC: OR: 1.69, 95% CI: 1.28–2.23, $P_{(\text{heterogeneity})}$ = 0.291, P < 0.01). Finally, in group for genotype method, increased trends were found in both PCR-RFLP (AA vs. CC: OR: 1.60, 95% CI: 1.15–2.22, $P_{(\text{heterogeneity})}$ = 0.125, P : 0.005; OR: 1.46, 95% CI: 1.07–1.98, $P_{(\text{heterogeneity})}$ = 0.367, P : 0.016, Fig. 6A for AA vs. AC + CC) and sequence methods (OR: 1.70, 95% CI: 1.08–2.68, $P_{(\text{heterogeneity})}$ = 0.520, P : 0.022, Fig. 6B for AA + AC vs. CC).

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, $P_{(\text{heterogeneity})}$ = 0.337, P : 0.028; TT vs. TC + CC: OR: 1.47, 95% CI: 1.08–2.00, $P_{(\text{heterogeneity})}$ = 0.720, P : 0.015, Fig. 7).

Bias Diagnosis And Sensitivity Analysis For Rs1800896 And Rs1800872

We used the Begg's funnel diagram and Egger's test to evaluate the publication bias (such as 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, Fig. 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, Fig. 8C,D, Table 3). We use sensitivity analysis to determine whether changes in a single study will affect final outcomes., We applied the sensitive analysis to delete the power and stability of each study and whole study, no significant influence was found (rs1800896, Fig. 8E; rs1800872, Fig. 8F).

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

Egger's test					Begg's test		
Genetic type	Coefficient	Standard error	t	P value	95%CI of intercept	z	P value
rs1800896 -1082							
G-allele vs. A-allele	2.683	1.787	1.5	0.172	(-1.439- 6.805)	1.43	0.152
GA vs. AA	1.846	1.412	1.31	0.227	(-1.411- 5.105)	1.07	0.283
GG + GA vs. AA	2.019	1.384	1.46	0.183	(-1.173- 5.213)	1.07	0.283
GG vs. AA	0.792	0.348	2.27	0.053	(-0.011-1.597)	1.79	0.074
GG vs. GA + AA	0.79	0.343	2.3	0.05	(-0.001-1.581)	1.79	0.074
rs1800872 -592							
A-allele vs. C-allele	1.991	1.387	1.43	0.189	(-1.208- 5.19)	1.43	0.152
AC vs. CC	1.976	1.011	1.95	0.087	(-0.356- 4.309)	1.43	0.152
AA + AC vs. CC	2.906	1.093	2.66	0.026	(-0.432- 5.379)	1.71	0.087
AA vs. CC	0.201	1.175	0.17	0.868	(-2.509-2.913)	0.36	0.721
AA vs. AC + CC	0.084	1.225	0.07	0.947	(-2.741-2.909)	0.18	0.858

Gene-gene Network Diagram And Interaction Of Online Website

IL-10 gene may interact with several genes from String online server. The network of gene-gene interaction has been shown in Fig. 9.

Discussion

Despite the gratifying progress carried out in the HIV/AIDS from diagnosis, prevention to treatment, HIV/AIDS remains the vital public health problem in global[43, 44]. 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 effect of host genes on susceptibility to HIV infection and the rate of disease progression have shown that host genes

are associated with a significant number of individual genes. Other words, the susceptibility of population may attribute to the polymorphism of key genes, such as proteins related to control viral entry (CCR5, CCR2, RANTES, and SDF1) [45–48], immune regulation (IL-10, TNF- α , and MBL-2) [49, 50] and adaptive immune recognition by T-cells (human leukocyte antigen or HLA) [51].

Cytokines play significant roles in the immune response against HIV-1 infection and the interval between HIV-1 infection and clinical AIDS[52]. Several previous researches have demonstrated that HIV infection was characterized by extensive immune activation and high levels of circulating cytokines (TNF- α , IL-6, and IL-10) [26, 53, 54]. Many PB studies have been conducted to confirm the hypothesis that IL-10 gene polymorphisms may increase sensitivity to HIV-1 [21, 24, 33]. Reduced IL-10 production by related polymorphisms were associated with increased likelihood about the infection and prevention of HIV-1, and accelerated rate of decline in CD4 + T cell, especially in advanced disease [21, 28]. This indicated that high IL-10 production may decrease the HIV-1 susceptibility or 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. Tsiara et al.[35] made an updated analysis including 8 papers related to rs1800896 and 9 related to rs1800872, suggested no significant association was existed 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, potential and functional partners related to IL-10 are predicted by using the on-line analysis system, which helps us to better understand the detection value and concerns of IL-10. Eventually, 10 related 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 significant association for HIV-1 susceptibility[55]. IL1B rs1143642 may play a risk factor, but rs1143623 acts as a protecting item for HIV-1 susceptibility[56]. TNF- α and IL-6 have been covered in the previous content, which prompted their relationship with HIV-1 infection.

Some limitations in our study should be explained. At the beginning, 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 heterogonous 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

Acknowledgements

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.

Funding

This work was supported by the Taizhou science and technology support plan (social development) project number: TS202014, project name: discussion on clinical emergency treatment plan of COVID-19 or similar epidemic.

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.

Author details

¹Department of Intensive Care Unit, Taizhou People's Hospital, Taizhou 225300, China. ²Department of Infectious Disease, Taizhou People's Hospital, Taizhou 225300, China. ³Department of Urology, Affiliated Hospital of Jiangnan University, Wuxi 214000, China. ⁴Department of Oncology, Taizhou People's Hospital, Taizhou 225300, China.

References

1. Caliendo AM: **Human Immunodeficiency Virus Type 1. *Molecular Pathology in Clinical Practice* Springer, New York, NY 2007:399–410.**
2. Organization WH. **HIV/AIDS [Internet]. Available from:** <https://www.who.int/en/news-room/fact-sheets/detail/hiv-aids> 2019 [cited 2019 Nov 15].
3. Riddler SA, Aga E, Bosch RJ, Bastow B, Bedison M, Vagratian D, Vaida F, Eron JJ, Gandhi RT, Mellors JW. Continued Slow Decay of the Residual Plasma Viremia Level in HIV-1-Infected Adults Receiving Long-term Antiretroviral Therapy. *The Journal of infectious diseases*. 2016;213(4):556–60.
4. Luban J. The hidden cost of genetic resistance to HIV-1. *Nature medicine*. 2019;25(6):878–9.
5. Gorry PR, Ahmad F, Mohl J, Alkhatib G. Low levels of HIV-1 envelope-mediated fusion are associated with long-term survival of an infected CCR5-/- patient. *AIDS*. 2018;32(16):2269–78.
6. Herbein G, Khan KA. Is HIV infection a TNF receptor signalling-driven disease? *Trends Immunol*. 2008;29(2):61–7.
7. Clerici M, Shearer GM. A TH1→TH2 switch is a critical step in the etiology of HIV infection. *Immunology today*. 1993;14(3):107–11.
8. Orsilles MA, Pieri E, Cooke P, Caula C: **IL-2 and IL-10 serum levels in HIV-1-infected patients with or without active antiretroviral therapy. *APMIS: acta pathologica, microbiologica, et immunologica Scandinavica* 2006, 114(1):55–60.**
9. Stylianou E, Aukrust P, Kvale D, Muller F, Froland SS. IL-10 in HIV infection: increasing serum IL-10 levels with disease progression—down-regulatory effect of potent anti-retroviral therapy. *Clin Exp Immunol*. 1999;116(1):115–20.
10. Mahajan SD, Agosto-Mojica A, Aalinkel R, Reynolds JL, Nair BB, Sykes DE, Martinez J, Adams J, Singh N, Bernstein Z, et al. Role of chemokine and cytokine polymorphisms in the progression of HIV-1 disease. *Biochem Biophys Res Commun*. 2010;396(2):348–52.
11. Brockman MA, Kwon DS, Tighe DP, Pavlik DF, Rosato PC, Sela J, Porichis F, Le Gall S, Waring MT, Moss K, et al. IL-10 is up-regulated in multiple cell types during viremic HIV infection and reversibly inhibits virus-specific T cells. *Blood*. 2009;114(2):346–56.
12. Turner DM, Williams DM, Sankaran D, Lazarus M, Sinnott PJ, Hutchinson IV. An investigation of polymorphism in the interleukin-10 gene promoter. *European journal of immunogenetics: official journal of the British Society for Histocompatibility Immunogenetics*. 1997;24(1):1–8.
13. Eskdale J, Gallagher G, Verweij CL, Keijsers V, Westendorp RG, Huizinga TW. Interleukin 10 secretion in relation to human IL-10 locus haplotypes. *Proc Natl Acad Sci USA*. 1998;95(16):9465–70.
14. Kilpinen S, Huhtala H, Hurme M. The combination of the interleukin-1alpha (IL-1alpha-889) genotype and the interleukin-10 (IL-10 ATA) haplotype is associated with increased interleukin-10 (IL-10) plasma levels in healthy individuals. *Eur Cytokine Netw*. 2002;13(1):66–71.
15. Khabour OF, Barnawi JM. Association of longevity with IL-10 -1082 G/A and TNF-alpha-308 G/A polymorphisms. *Int J Immunogenet*. 2010;37(4):293–8.

16. Lio D, Scola L, Crivello A, Colonna-Romano G, Candore G, Bonafe M, Cavallone L, Franceschi C, Caruso C. Gender-specific association between – 1082 IL-10 promoter polymorphism and longevity. *Genes Immun.* 2002;3(1):30–3.
17. Okayama N, Hamanaka Y, Suehiro Y, Hasui Y, Nakamura J, Hinoda Y. **Association of interleukin-10 promoter single nucleotide polymorphisms – 819 T/C and – 592 A/C with aging.** *The journals of gerontology Series A, Biological sciences and medical sciences* 2005, 60(12):1525–1529.
18. Naumova E, Mihaylova A, Ivanova M, Michailova S, Penkova K, Baltadjieva D. Immunological markers contributing to successful aging in Bulgarians. *Experimental gerontology.* 2004;39(4):637–44.
19. Chatterjee A, Rathore A, Sivarama P, Yamamoto N, Dhole TN. Genetic association of IL-10 gene promoter polymorphism and HIV-1 infection in North Indians. *J Clin Immunol.* 2009;29(1):71–7.
20. Corchado S, Marquez M, Montes de Oca M, Romero-Cores P, Fernandez-Gutierrez C, Giron-Gonzalez JA. Influence of Genetic Polymorphisms of Tumor Necrosis Factor Alpha and Interleukin 10 Genes on the Risk of Liver Cirrhosis in HIV-HCV Coinfected Patients. *PloS one.* 2013;8(6):e66619.
21. Erikstrup C, Kallestrup P, Zinyama-Gutsire RB, Gomo E, Butterworth AE, Pedersen BK, Ostrowski SR, Gerstoft J, Ullum H: **Reduced mortality and CD4 cell loss among carriers of the interleukin-10 -1082G allele in a Zimbabwean cohort of HIV-1-infected adults.** *AIDS (London, England)* 2007, 21(17):2283–2291.
22. Freitas FB, Lima SS, Feitosa RN, Azevedo VN, Ishak Mde O, Ishak R, Vallinoto AC. Polymorphisms in the IFNgamma, IL-10, and TGFbeta genes may be associated with HIV-1 infection. *Disease markers.* 2015;2015:248571.
23. Harishankar M, Ravikrishnan H, Ravishankar A, Hanna LE, Swaminathan S, Selvaraj P, Bethunaickan R. IL-10 Promoter – 592 Polymorphism may Influence Susceptibility to HIV Infection in South Indian Population. *Current HIV research.* 2018;16(1):58–63.
24. Kallas E, Huik K, Pauskar M, Jogeda EL, Karki T, Des Jarlais D, Uuskula A, Avi R, Lutsar I. Influence of interleukin 10 polymorphisms – 592 and – 1082 to the HIV, HBV and HCV serostatus among intravenous drug users. *Infection genetics evolution: journal of molecular epidemiology evolutionary genetics in infectious diseases.* 2015;30:175–80.
25. Naicker DD, Werner L, Kormuth E, Passmore JA, Mlisana K, Karim SA, Ndung'u T. Interleukin-10 promoter polymorphisms influence HIV-1 susceptibility and primary HIV-1 pathogenesis. *The Journal of infectious diseases.* 2009;200(3):448–52.
26. Piddubna A. **IL-4, IL-10 and TNF-alpha Promotor Gene Polymorphism in North-Eastern Ukrainian HIV-1 Infected Individuals.** *AIDS Research and Human Retrovired* 2013<https://www.researchgate.net/publication/257874258>.
27. Ramezani A, Kalantar E, Aghakhani A, Banifazl M, Foroughi M, Hosseini S, Eslamifar A, Esmaeilzadeh A, Mohraz M. Lack of Association between Interleukin-10 Gene Promoter Polymorphisms with HIV Susceptibility and Progression to AIDS. *Iranian journal of pathology.* 2015;10(2):141–8.
28. Shin HD, Winkler C, Stephens JC, Bream J, Young H, Goedert JJ, O'Brien TR, Vlahov D, Buchbinder S, Giorgi J, et al: **Genetic restriction of HIV-1 pathogenesis to AIDS by promoter alleles of IL10.** *Proceedings of the National Academy of Sciences of the United States of America* 2000, 97(26):14467–14472.
29. Singh H, Samani D, Nain S, Dhole TN. Interleukin-10 polymorphisms and susceptibility to ARV associated hepatotoxicity. *Microb Pathog.* 2019;133:103544.
30. Singh S, Sharma A, Arora SK. Combination of low producer AA-genotypes in IFN-gamma and IL-10 genes makes a high risk genetic variant for HIV disease progression. *Cytokine.* 2016;77:135–44.
31. Sobti RC, Berhane N, Mahedi SA, Kler R, Hosseini SA, Kuttat V, Wanchu A. Polymorphisms of IL-6 174 G/C, IL-10 -592 C/A and risk of HIV/AIDS among North Indian population. *Molecular cellular biochemistry.* 2010;337(1–2):145–52.
32. Wang C, Song W, Lobashevsky E, Wilson CM, Douglas SD, Mytilineos J, Schoenbaum EE, Tang J, Kaslow RA. Cytokine and chemokine gene polymorphisms among ethnically diverse North Americans with HIV-1 infection. *J Acquir Immune Defic Syndr.* 2004;35(5):446–54.
33. Ramaseri Sunder S, Hanumanth SR, Nagaraju RT, Venkata SK, Suryadevara NC, Pydi SS, Gaddam S, Jonnalagada S, Valluri VL. IL-10 high producing genotype predisposes HIV infected individuals to TB infection. *Hum Immunol.* 2012;73(6):605–11.
34. Jiang C, Liu S, Liu S, Li Z, Chen P, Chen L: **Association Between the Interleukin-10-1082G/A, -592C/A, -819C/T Gene Polymorphism and HIV-1 Susceptibility: A Meta-Analysis.** *AIDS research and human retroviruses* 2017, 33(1):61–67.
35. Tsiara CG, Nikolopoulos GK, Dimou NL, Pantavou KG, Bagos PG, Mensah B, Talias M, Braliou GG, Paraskeva D, Bonovas S, et al: **Interleukin gene polymorphisms and susceptibility to HIV-1 infection: a meta-analysis.** *Journal of genetics* 2018, 97(1):235–251.
36. Shao HB, Ren K, Gao SL, Zou JG, Mi YY, Zhang LF, Zuo L, Okada A, Yasui T. Human methionine synthase A2756G polymorphism increases susceptibility to prostate cancer. *Aging.* 2018;10(7):1776–88.
37. Wells G, Shea B, O'Connell D, Robertson J, Peterson J, Welch V, Losos M, Tugwell P. **The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses.** In: *Ottawa Health Research Institute.* 21 Oct, 2011.
38. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ.* 2003;327(7414):557–60.
39. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled clinical trials.* 1986;7(3):177–88.
40. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst.* 1959;22(4):719–48.
41. Napolioni V. The relevance of checking population allele frequencies and Hardy-Weinberg Equilibrium in genetic association studies: the case of SLC6A4 5-HTTLPR polymorphism in a Chinese Han Irritable Bowel Syndrome association study. *Immunology letters.* 2014;162(1 Pt A):276–8.
42. Hayashino Y, Noguchi Y, Fukui T. Systematic evaluation and comparison of statistical tests for publication bias. *Journal of epidemiology.* 2005;15(6):235–43.
43. Bandera A, De Benedetto I, Bozzi G, Gori A. Altered gut microbiome composition in HIV infection: causes, effects and potential intervention. *Curr Opin HIV AIDS.* 2018;13(1):73–80.

44. Cabezas MC, Fornasini M, Dardenne N, Borja T, Albert A. A cross-sectional study to assess knowledge about HIV/AIDS transmission and prevention measures in company workers in Ecuador. *BMC Public Health*. 2013;13:139.
45. Ding J, Zhao J, Zhou J, Li X, Wu Y, Ge M, Cen S: **Association of gene polymorphism of SDF1(CXCR12) with susceptibility to HIV-1 infection and AIDS disease progression: A meta-analysis.** *PloS one* 2018, **13**(2):e0191930.
46. Mutui SP, Kutima HL, Mwapagha LM, Munyao JK, Nyamache AK, Wanjiru I, Khamadi SA. RANTES Gene Polymorphisms Associated with HIV-1 Infections in Kenyan Population. *Disease markers*. 2016;2016:4703854.
47. Ngoufack MN, Nkenfou CN, Atogho Tiedeu B, Mouafo LCM, Dambaya B, Ndzi EN, Kouanfack C, Nguetack-Tsague G, Mbacham WF, Ndjolo A: **CCR2 Genetic Polymorphism And Its Potential Effect On HIV Acquisition In A Population Of Children Living In The Northern Region Of Cameroon.** *The application of clinical genetics* 2019, **12**:229–234.
48. Roop JI, Cassidy NA, Dingsen AS, Bloom JD, Overbaugh J. **Identification of HIV-1 Envelope Mutations that Enhance Entry Using Macaque CD4 and CCR5.** *Viruses* 2020, **12**(2).
49. Barros KMA, Ribeiro Paulino M, Batista M, Gueiros LAM, Souza PRE, Leao JC, de Albuquerque Tavares Carvalho A. Absence of influence of polymorphisms of the MBL2 gene in oral infections by HSV-1 in individuals with HIV. *Brazilian journal of microbiology: [publication of the Brazilian Society for Microbiology]*. 2019;50(3):663–8.
50. Pasquereau S, Kumar A, Herbein G. **Targeting TNF and TNF Receptor Pathway in HIV-1 Infection: from Immune Activation to Viral Reservoirs.** *Viruses* 2017, **9**(4).
51. Takahashi N, Matsuoka S, Thi Minh TT, Ba HP, Naruse TK, Kimura A, Shiino T, Kawana-Tachikawa A, Ishikawa K, Matano T, et al. Human leukocyte antigen-associated gag and nef polymorphisms in HIV-1 subtype A/E-infected individuals in Vietnam. *Microbes infection*. 2019;21(2):113–8.
52. Shimizu Y, Miyazaki Y, Ibuki K, Suzuki H, Kaneyasu K, Goto Y, Hayami M, Miura T, Haga T. Induction of immune response in macaque monkeys infected with simian-human immunodeficiency virus having the TNF-alpha gene at an early stage of infection. *Virology*. 2005;343(2):151–61.
53. Lopes TRR, Goncales JP, Silva Junior JVV, Lorena VMB, Toscano A, Akamatsu SM, Salles AC, Tozetto-Mendoza TR, Morais VMS, Coelho M. Association of IL-6, IL-10 and CXCL10 serum concentrations with visceral Kaposi's sarcoma in people living with HIV/AIDS. *Hum Immunol*. 2020;81(1):26–31.
54. Veloso S, Olona M, Garcia F, Domingo P, Alonso-Villaverde C, Broch M, Peraire J, Vilades C, Plana M, Pedrol E, et al. Effect of TNF-alpha genetic variants and CCR5 Delta 32 on the vulnerability to HIV-1 infection and disease progression in Caucasian Spaniards. *BMC medical genetics*. 2010;11:63.
55. Shrestha S, Wiener HW, Aissani B, Song W, Shendre A, Wilson CM, Kaslow RA, Tang J. Interleukin-10 (IL-10) pathway: genetic variants and outcomes of HIV-1 infection in African American adolescents. *PloS one*. 2010;5(10):e13384.
56. Gay CL, Zak RS, Lerdal A, Pullinger CR, Aouizerat BE, Lee KA. **Cytokine polymorphisms and plasma levels are associated with sleep onset insomnia in adults living with HIV/AIDS.** *Brain, behavior, and immunity* 2015, **47**:58–65.

Figures

Figure 1

A flowchart illustrating the search strategy for identifying related studies.

Figure 2

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). 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

IL-10 interactions network with other genes had been obtained from String server. At least 10 genes have been detected to relate to 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.