Associations of polymorphisms in \textit{CTLA-4} and \textit{IL-18} with liver diseases: evidence from a meta-analysis

Running title: Polymorphisms in \textit{CTLA-4/IL-18} and liver diseases

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Abstract

**Background:** Associations between polymorphisms in *cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4)* / *interleukin-18 (IL-18)* and susceptibility to liver diseases were already reported by many publications. The aim of this meta-analysis was to clarify associations between polymorphisms in *CTLA-4/IL-18* and liver diseases by combing the results of all relevant publications.

**Methods:** Eligible publications were searched from Pubmed, Embase, WOS and CNKI. The latest literature searching update was performed on 2nd October, 2019. We used Review Manager to combine the results of individual studies.

**Results:** Sixty-seven studies were included in this study. Combined results revealed that *CTLA-4* rs231775 (dominant comparison: OR 0.83, 95 % CI 0.79-0.88; recessive comparison: OR 1.33, 95 % CI 1.23-1.43; allele comparison: OR 0.84, 95 % CI 0.78-0.90), *IL-18* rs1946518 (dominant comparison: OR 0.85, 95 % CI 0.78-0.92; recessive comparison: OR 1.29, 95 % CI 1.13-1.48; allele comparison: OR 0.79, 95 % CI 0.71-0.88) and *IL-18* rs187238 (dominant comparison: OR 1.28, 95 % CI 1.07-1.53; over-dominant comparison: OR 0.81, 95 % CI 0.68-0.97; allele comparison: OR 1.22, 95 % CI 1.07-1.39) polymorphisms were all significantly associated with liver diseases in the general population. We also obtained similar significant associations for *CTLA-4* rs231775, *CTLA-4* rs5742909, *CTLA-4* rs3087243, *IL-18* rs1946518 and *IL-18* rs187238 polymorphisms in subgroup analyses.

**Conclusions:** Collectively, this meta-analysis proved that *CTLA-4* rs231775, *CTLA-4*
rs5742909, CTLA-4 rs3087243, IL-18 rs1946518 and IL-18 rs187238 polymorphisms may confer susceptibility to various types of liver diseases.

**Keywords:** Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4); Interleukin-18 (IL-18); Liver diseases; Meta-analysis

**Introduction**

Liver disease is one of the leading causes of death all over the world [1-2]. Although we still did not figure out the exact mechanism of its pathogenesis, it was believed that genetic components were essential in the development of various types of liver diseases. Firstly, the incidences of liver diseases in different populations were quite different [3-4], and different genetic background was probably one of reasons behind differences in disease prevalence across different populations. Secondly, numerous susceptible genetic loci of different types of liver diseases were identified and validated by existing genetic association studies [5-6]. Nevertheless, the etiologies of liver diseases are highly complex and the genetic determinants underlying liver disease are not fully elucidated. Since genetic makeup could substantially influence and contribute to the development of liver diseases, it is believed that identifying potential genetic biomarkers is of critical importance for further improving early diagnosis of liver diseases.

Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) belongs to the
immunoglobulin super-family. It is a negative regulator of T cells and plays vital roles in inducing immune tolerance [7]. Interleukin-18 (IL-18) is a cytokine that resembles IL-1 structurally and IL-12 functionally. It enhances the activity of NK cells and cytotoxic T cells [8]. Although their functions are somehow different, CTLA-4 and IL-18 are both crucial modulators of T cell activation and proliferation. So if a genetic polymorphism could alter the transcription activity of CTLA-4/IL-18 or the protein structure of CTLA-4/IL-18, there is possibility that this polymorphism may impact function of T cells, give rise to immune dysfunction and inflammatory cellular injuries, and ultimately lead to the development of many types of diseases (including but not limited to infectious, auto-immune, inflammatory and malignant diseases).

In the past twenty years, many publications reported findings about associations between polymorphisms in CTLA-4/IL-18 and liver diseases, yet the conclusions of these publications were somehow inconsistent. To better clarify associations between polymorphisms in CTLA-4/IL-18 and liver diseases, we designed this study to get a more credible conclusion by combing the results of all relevant publications.

**Materials and methods**

We wrote this meta-analysis as requested by PRISMA guideline [9].

**Literature search and inclusion criteria**

To retrieve eligible articles, we searched Pubmed, WOS and Embase with key words
listed below: (interleukin-18 or IL-18 or interleukin 18 or IL 18 or cytotoxic T lymphocyte antigen-4 or CTLA-4) and (polymorphism or variant or variation or mutation or SNP or genome-wide association study or genetic association study or genotype or allele) and (liver disease or viral hepatitis or hepatitis or HAV or HBV or HCV or HDV or HEV or non-alcoholic fatty liver disease or non-alcoholic fatty liver or non-alcoholic steatohepatitis or alcoholic liver disease or autoimmune hepatitis or liver failure or liver cirrhosis or hepatocellular carcinoma). The latest literature searching update was performed on 2nd October, 2019. The references of retrieved articles were also screened by us in case some related publications may be missing.

To be included in this meta-analysis, some criteria must be met: I. About associations between polymorphisms in CTLA-4/IL-18 and liver diseases in humans; II. Offer genotypic or allelic distribution of CTLA-4/IL-18 polymorphisms in patients with liver diseases and controls; III. Full manuscript in English is retrievable. Publications were deemed to be ineligible if: I. Not about polymorphisms in CTLA-4/IL-18 and liver diseases; II. Narrative reviews, systematic reviews or comments; III. Studies only involved liver diseases patients. We only included the most up to date study if duplicate publications were found during literature search.

Data extraction and quality assessment

Two authors extracted following essential information from eligible publications: I. Name of the leading author; II. Published year; III. Country of the leading author; IV. Ethnicity of involved participants; V. Number of patients with liver diseases and
controls in each study; VI. Genotype distributions of polymorphisms in \textit{CTLA-4/IL-18} among patients with liver diseases and controls. \(P\) values of Hardy-Weinberg equilibrium (HWE) were also calculated.

The authors used Newcastle-Ottawa scale (NOS) to assess the quality of eligible publications [10]. The score range of NOS is between zero and nine, when a publication got a score of seven or more, we considered that the methodology of this publication is good.

Two authors extracted data and assessed quality of eligible publications. The authors wrote to the leadings authors for additional information if essential information was found to be incomplete.

\textbf{Statistical analyses}

We used Review Manager to combine the results of individual studies. \(Z\) test was employed to assess associations between polymorphisms in \textit{CTLA-4/IL-18} and liver diseases in dominant, recessive, over-dominant and allele models. All investigated polymorphisms contain a major allele (M) and a minor allele (m), the dominant comparison is defined as MM versus Mm + mm, recessive comparison is defined as mm vs. MM + Mm, over-dominant comparison is defined as Mm versus MM + mm, and the allele comparison is defined as M versus m. The statistical significant threshold of \(p\) value was set at 0.05. We used \(I^2\) statistics to assess between-study heterogeneities. We used Random-effect models (DerSimonian-Laird method) to combine the results if \(I^2\) is larger than 50\%. Otherwise, fixed-effect models
(Mantel-Haenszel method) were used to combine the results. We further carried out subgroup analyses by ethnicity to get ethnic-specific results. We also carried out subgroup analyses by type of disease. We examined the stability of combined results by deleting one study each time and combining the results of the rest of studies. We used funnel plots to estimate whether our combined results may be influenced by publication biases.

**Results**

**Characteristics of included studies**

We found five hundred and seven publications during literature searching. Ninety-two publications were assessed for eligibility after excluding unrelated or duplicate publications. We further excluded seventeen reviews and five case controls, and another three publications were excluded because of missing crucial data. Totally sixty-seven publications were ultimately found to be eligible for inclusion (Fig. 1). Extracted data of eligible publications were summarized in Table 1.

**Meta-analyses results for polymorphisms in CTLA-4 and liver diseases**

CTLA-4 rs231775 (dominant comparison: OR 0.83, 95 % CI 0.79-0.88; recessive comparison: OR 1.33, 95 % CI 1.23-1.43; allele comparison: OR 0.84, 95 % CI 0.78-0.90) polymorphism was found to be significantly associated with liver diseases in overall combined analyses. Subgroup analyses showed positive findings for
CTLA-4 rs231775 polymorphism in Caucasians (dominant and over-dominant comparisons), East Asians (dominant, recessive and allele comparisons) and South Asians (recessive and allele comparisons). Moreover, we found that CTLA-4 rs5742909 polymorphism was significantly associated with liver diseases in Caucasians (allele comparison) and South Asians (dominant and allele comparisons), and we also found that CTLA-4 rs3087243 polymorphism was significantly associated with liver diseases in East Asians (recessive comparison). Significant associations with CTLA-4 rs231775 polymorphism were observed in patients with hepatitis B virus infection (HBV), autoimmune hepatitis (AIH), liver cirrhosis (LC) and hepatocellular carcinoma (HCC). Positive relationships with CTLA-4 rs5742909 polymorphism were observed in patients with hepatitis C virus infection (HCV). CTLA-4 rs3087243 polymorphism was also found to be significantly associated with susceptibility to AIH (see Table 2).

Meta-analyses results for polymorphisms in IL-18 and liver diseases

IL-18 rs1946518 (dominant comparison: OR 0.85, 95 % CI 0.78-0.92; recessive comparison: OR 1.29, 95 % CI 1.13-1.48; allele comparison: OR 0.79, 95 % CI 0.71-0.88) and IL-18 rs187238 (dominant comparison: OR 1.28, 95 % CI 1.07-1.53; over-dominant comparison: OR 0.81, 95 % CI 0.68-0.97; allele comparison: OR 1.22, 95 % CI 1.07-1.39) polymorphisms were both found to be significantly associated with liver diseases in overall combined analyses. Subgroup analyses showed positive findings for IL-18 rs1946518 polymorphism in South Asians (dominant, recessive and
allele comparisons). Moreover, we also found that *IL-18* rs187238 polymorphism was significantly associated with liver diseases in East Asians (dominant, over-dominant and allele comparisons). Significant associations with *IL-18* rs1946518 polymorphism were observed in patients with HBV and HCV, and positive relationships with *IL-18* rs187238 polymorphism were also observed in patients with HBV and LC (see Table 2).

Sensitivity analyses

We examined the stability of combined results by deleting one study each time and combining the results of the rest of studies. The trends of associations remained consistent in sensitivity analyses, which indicated that the combined results were statistically stable.

Publication biases

Funnels plots were employed to estimate whether our combined results may be influenced by publication biases. Funnel plots of every comparison were symmetrical, which indicated that the combined results were unlikely to be seriously impacted by overt publication biases (see Supplementary figure 1).

Discussion

The combined results of this meta-analysis revealed that *CTLA-4* rs231775,
rs5742909 and rs3087243 polymorphisms were significantly associated with susceptibility to various types of liver diseases. Moreover, IL-18 rs1946518 and rs187238 polymorphisms were also found to be significantly associated with susceptibility to various types of liver diseases. The trends of associations remained consistent in sensitivity analyses, which indicated that the combined results were stable. These results also suggested that the above mentioned CTLA-4/IL-18 polymorphisms may serve as potential genetic biomarkers of liver diseases.

To better understand the combined results of this meta-analysis, some points should be considered. First, past basic researches revealed that rs231775, rs5742909 and rs3087243 polymorphisms in CTLA-4 as well as rs1946518 and rs187238 polymorphisms in IL-18 could alter transcription activity of CTLA-4/IL-18 or protein structure of CTLA-4/IL-18 [11-13]. So these variations may influence biological function of CTLA-4/IL-18, result in immune dysfunction, cause hepatocellular injury and ultimately confer susceptibility to various liver diseases. Thus, our meta-analysis may be statistically insufficient to observe the real underlying associations between polymorphisms in CTLA-4/IL-18 and liver diseases in certain subgroups. Therefore, future studies still need to confirm our findings. Second, significant heterogeneities were found to be existed among eligible publications for CTLA-4 rs5742909, CTLA-4 rs3087243 and IL-18 rs1946518 polymorphisms in some of comparisons. Nevertheless, an obvious reduction of heterogeneity was observed in further subgroup analyses by ethnicity, which indicated that ethnic background differences could explain part of heterogeneities among eligible publications. The heterogeneities
among eligible publications and opposite trends of associations observed in subgroup analyses by ethnicity also indicated that the distributions of $CTLA-4$ rs5742909, $CTLA-4$ rs3087243 and $IL-18$ rs1946518 polymorphisms vary significantly from population to population. So the genetic associations between polymorphisms in $CTLA-4/IL-18$ and liver disease may be ethnic-specific, and we should not try to generalize the combined results to a broader population. Thirdly, the etiologies of liver diseases are very complicated, so we highly recommend further genetic association studies to explore the effects of haplotypes and gene-gene interactions on disease susceptibility [14]. Fourthly, we aimed to investigate associations between all polymorphisms in $CTLA-4/IL-18$ and liver diseases in the very beginning. However, we did not find any study on other $CTLA-4/IL-18$ polymorphisms, so we only focused on five polymorphisms in this meta-analysis.

Some limitations of this meta-analysis should also be mentioned. Firstly, the results regarding associations between polymorphisms in $CTLA-4/IL-18$ and liver diseases were based on combining unadjusted findings of eligible publications due to lack of raw data [15]. Secondly, relationship between polymorphisms in $CTLA-4/IL-18$ and liver diseases may also be affected by environmental factors. Unfortunately, the majority of eligible publications only focused on associations between polymorphisms in $CTLA-4/IL-18$ and liver diseases, so we could not explore genetic-environmental interactions in this meta-analysis [16]. Thirdly, grey literatures were not searched. So although funnel plots of every comparison were symmetrical, it is still possible that the combined results may be affected by publication biases [17].
In summary, this meta-analysis proved that \textit{CTLA-4} rs231775, \textit{CTLA-4} rs5742909, \textit{CTLA-4} rs3087243, \textit{IL-18} rs1946518 and \textit{IL-18} rs187238 polymorphisms may confer susceptibility to various types of liver diseases. These results supported that the above mentioned polymorphisms may be used to identify individuals at higher risk of developing liver diseases in the general population. However, the combined results of this meta-analysis should still be verified by studies with larger sample sizes. Besides, given that the etiologies of liver diseases are extremely complex, despite our comprehensive analyses, we still strongly recommend further studies to explore potential roles of gene-gene interactions and gene-environmental interactions in the development of liver diseases.

\textbf{Authors' contributions}

Shenglong Zhang and Wentao Wang conceived and designed the study. Shenglong Zhang and Xianwei Yang conducted the literature review. Shenglong Zhang and Xianwei Yang analyzed data. Shenglong Zhang and Wentao Wang drafted the manuscript. All authors have read and approved the final manuscript.

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Conflict of interest

The authors declare that they have no conflict of interest.

Ethical statement

This article does not contain any studies with human participants or animals performed by any of the authors, thus ethical approval and informed consent are not required.

Data availability statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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Figure legends

Fig. 1. Flowchart of study selection for the present study.
| First author, year  | Country | Ethnicity | Type of disease | Sample size | Genotype distribution | P-value for HWE | NOS score |
|------------------|---------|-----------|-----------------|-------------|-----------------------|----------------|-----------|
|                  |         |           |                 |             | Cases: Controls       |                |           |
| **CTLA-4 rs231775** |         |           |                 |             |                       |                |           |
| Agarwal 2000     | UK      | Caucasian | AIH             | 155/102     | 50/84/21: 51/38/13    | 0.173          | 8         |
| Agarwal 2000     | UK      | Caucasian | LC              | 200/200     | 57/106/37: 99/80/21   | 0.424          | 8         |
| Aiba 2011        | Japan   | East Asian| LC              | 450/371     | 191/204/55: 181/124/66| <0.001         | 7         |
| Bittencourt 2003 | Brazil  | Mixed     | AIH             | 106/67      | 42/49/15: 29/30/8     | 0.955          | 8         |
| Bittencourt 2003 | Brazil  | Mixed     | LC              | 50/67       | 23/23/4: 29/30/8      | 0.955          | 8         |
| Chaouali 2017    | Tunisia | South Asian| AIH             | 50/100      | 12/24/14: 34/57/9     | 0.031          | 7         |
| Chen 2014        | China   | East Asian| HBV             | 465/204     | 198/214/53: 82/102/20 | 0.146          | 8         |
| Chen 2014        | China   | East Asian| LC              | 209/204     | 66/97/46: 82/102/20   | 0.146          | 8         |
| Chen 2014        | China   | East Asian| HCV             | 234/204     | 92/100/42: 82/102/20  | 0.146          | 8         |
| Danilovic 2012   | Brazil  | Mixed     | HCV             | 112/183     | 59/34/19: 81/67/35   | 0.003          | 7         |
| Donaldson 2007   | UK      | Caucasian | LC              | 316/390     | 115/159/42: 160/177/53| 0.716          | 8         |
| Duan 2011        | China   | East Asian| HBV             | 172/145     | 50/89/33: 61/68/16   | 0.648          | 7         |
| Enciso-Vargas 2018 | México | Mixed    | HCV             | 205/215     | 67/104/34: 93/89/33  | 0.134          | 7         |
| Fan 2004         | China   | East Asian| AIH             | 62/160      | 6/34/22: 23/93/44    | 0.021          | 7         |
| Fan 2004         | China   | East Asian| LC              | 77/160      | 6/34/37: 23/93/44    | 0.021          | 7         |
| Gu 2010          | China   | East Asian| HBV             | 570/407     | 244/251/75: 183/179/45| 0.902          | 8         |
| Gu 2010          | China   | East Asian| HCC             | 367/407     | 150/166/51: 183/179/45| 0.902          | 8         |
| Hu 2010          | China   | East Asian| HCC             | 853/854     | 367/380/106: 399/376/79| 0.476          | 7         |
| Jiang 2007       | China   | East Asian| HBV             | 24/143      | 5/15/4: 70/61/12     | 0.800          | 7         |
| Joshi 2010       | Japan   | East Asian| LC              | 308/268     | 123/143/42: 91/131/46| 0.922          | 7         |
| Juran 2010       | USA     | Mixed     | LC              | 351/205     | 131/161/59: 79/99/27 | 0.644          | 7         |
| Juran 2010 | Canada | Mixed | LC | 351/279 | 122/170/59 | 111/130/38 | 0.995 | 7 |
|---|---|---|---|---|---|---|---|---|
| Kann 2006 | Japan | East Asian | LC | 45/73 | 5/20/20 | 14/33/26 | 0.545 | 8 |
| Khorshied 2014 | Egypt | South Asian | HCV | 52/460 | 28/40/5 | 203/204/53 | 0.872 | 7 |
| Ksiaa 2015 | Tunisia | South Asian | HCV | 500/358 | 225/198/77 | 176/142/40 | 0.168 | 7 |
| Li 2013 | China | East Asian | LC | 312/375 | 20/140/152 | 40/214/112 | <0.001 | 8 |
| Liu 2015 | China | East Asian | HCC | 80/78 | 29/36/15 | 38/33/7 | 0.966 | 8 |
| Mantaka 2012 | Greece | Caucasian | LC | 100/158 | 47/50/3 | 77/72/9 | 0.136 | 7 |
| Mohammad 2006 | Iran | South Asian | HBV | 51/150 | 9/16/26 | 41/52/57 | <0.001 | 8 |
| Ng 2013 | New Zealand | Caucasian | AIH | 77/455 | 33/32/12 | 168/212/75 | 0.557 | 8 |
| Poupon 2008 | France | Caucasian | LC | 258/286 | 95/123/40 | 145/177/24 | 0.953 | 7 |
| Roy 2012 | India | South Asian | ALD | 180/107 | 68/90/22 | 42/56/9 | 0.105 | 7 |
| Schott 2007 | Germany | Caucasian | AIH | 127/202 | 41/64/22 | 78/87/37 | 0.149 | 7 |
| Schott 2007 | Germany | Caucasian | LC | 180/202 | 58/90/32 | 78/87/37 | 0.149 | 7 |
| Sepahi 2017 | Iran | South Asian | HCV | 65/65 | NA | NA | NA | 7 |
| Thio 2004 | USA | Mixed | HBV | 378/676 | NA | NA | NA | 7 |
| Umemura 2008 | Japan | East Asian | AIH | 76/100 | 11/36/29 | 22/47/31 | 0.601 | 8 |
| van Gerven 2013 | The Netherlands | Caucasian | AIH | 667/498 | 240/324/103 | 188/233/77 | 0.732 | 7 |
| Walker 2009 | Canada | Mixed | LC | 481/1245 | 162/223/96 | 493/577/178 | 0.661 | 7 |
| Xiao 2015 | China | East Asian | HCV | 816/375 | 358/375/83 | 176/168/31 | 0.300 | 8 |
| Yang 2019 | China | East Asian | HCC | 575/920 | 290/221/64 | 444/389/87 | 0.893 | 7 |
| Zhang 2012 | China | East Asian | HBV | 172/145 | 50/89/33 | 61/68/16 | 0.648 | 8 |

**CTLA-4 rs5742909**

| Chaouali 2017 | Tunisia | South Asian | AIH | 50/100 | 47/3/0 | 91/9/0 | 0.637 | 7 |
| Chen 2014 | China | East Asian | HBV | 464/200 | 342/112/10 | 160/38/2 | 0.877 | 8 |
| Chen 2014 | China | East Asian | LC | 202/200 | 136/58/8 | 160/38/2 | 0.877 | 8 |
| Chen 2014 | China | East Asian | HCC | 224/200 | 176/48/0 | 160/38/2 | 0.877 | 8 |
| Study               | Country       | Ethnicity   | Disease  | HLA-A1/RA1/RA2 | HLA-A2/RA1/RA2 | HLA-A2/RA2/RA3 | Migration | Frequency | Ref. |
|---------------------|---------------|-------------|----------|----------------|----------------|----------------|-----------|-----------|------|
| Danilovic 2012      | Brazil        | Mixed       | HCV      | 112/183        | 92/19/1        | 152/31/0       | 0.211     | 7         |      |
| Donaldson 2007      | UK            | Caucasian   | LC       | 246/289        | 215/31/0       | 252/36/1       | 0.811     | 8         |      |
| Duan 2011           | China         | East Asian  | HBV      | 172/145        | 141/28/3       | 105/39/1       | 0.194     | 7         |      |
| Enciso-Vargas 2018  | Mexico        | Mixed       | HCV      | 205/215        | 183/22/0       | 193/21/1       | 0.604     | 7         |      |
| Fan 2004            | China         | East Asian  | AIH      | 62/160         | 54/8/0         | 122/30/8       | 0.003     | 7         |      |
| Fan 2004            | China         | East Asian  | LC       | 77/160         | 63/12/2        | 122/30/8       | 0.003     | 7         |      |
| Joshi 2010          | Japan         | East Asian  | LC       | 308/268        | NA             | NA             | NA        | 7         |      |
| Juran 2010          | USA           | Mixed       | LC       | 351/279        | NA             | NA             | NA        | 7         |      |
| Khorshied 2014      | Egypt         | South Asian | HCV      | 54/503         | 33/13/8        | 403/67/29      | <0.001    | 7         |      |
| Li 2013             | China         | East Asian  | LC       | 312/375        | 246/49/17      | 288/68/19      | <0.001    | 8         |      |
| Mohammad 2006       | Iran          | South Asian | HBV      | 51/150         | 41/10/0        | 134/16/0       | 0.492     | 8         |      |
| Poupon 2008         | France        | Caucasian   | LC       | 258/286        | NA             | NA             | NA        | 7         |      |
| Schott 2007         | Germany       | Caucasian   | HBV      | 323/202        | 276/42/5       | 150/47/5       | 0.570     | 7         |      |
| Schott 2007         | Germany       | Caucasian   | LC       | 72/202         | 66/6/3         | 150/47/5       | 0.570     | 7         |      |
| Sepahi 2017         | Iran          | South Asian | HCV      | 65/65          | 55/10/0        | 55/9/1         | 0.392     | 7         |      |
| Thio 2004           | USA           | Mixed       | HBV      | 378/676        | NA             | NA             | NA        | 7         |      |
| Umemura 2008        | Japan         | East Asian  | AIH      | 76/100         | 61/14/1        | 80/20/0        | 0.267     | 8         |      |
| Walker 2009         | Canada        | Mixed       | LC       | 481/1248       | 377/99/5       | 1055/183/10    | 0.509     | 7         |      |
| Xiao 2015           | China         | East Asian  | HCV      | 816/375        | 523/269/24     | 266/99/10      | 0.829     | 8         |      |
| Zhang 2012          | China         | East Asian  | HBV      | 172/145        | 141/28/3       | 105/39/1       | 0.194     | 8         |      |

**CTLA-4 rs3087243**

| Study               | Country       | Ethnicity   | Disease  | HLA-A1/RA1/RA2 | HLA-A2/RA1/RA2 | HLA-A2/RA2/RA3 | Migration | Frequency | Ref. |
|---------------------|---------------|-------------|----------|----------------|----------------|----------------|-----------|-----------|------|
| Aiba 2011           | Japan         | East Asian  | LC       | 450/371        | NA             | NA             | NA        | 7         |      |
| Chaouali 2017       | Tunisia       | South Asian | AIH      | 50/100         | 4/29/17        | 22/50/28       | 0.971     | 7         |      |
| Chen 2014           | China         | East Asian  | HBV      | 467/203        | 301/148/18     | 116/79/8       | 0.223     | 8         |      |
| Chen 2014           | China         | East Asian  | LC       | 211/203        | 121/72/18      | 116/79/8       | 0.223     | 8         |      |
| Chen 2014           | China         | East Asian  | HCC      | 231/203        | 134/81/16      | 116/79/8       | 0.233     | 8         |      |
| Study          | Country          | Ethnicity      | Disease | IL-18 SNP | MAF (log10) | Age (median) | Sex | IL-18 rs1946518 |
|---------------|------------------|----------------|---------|-----------|-------------|--------------|-----|-----------------|
| **Danilovic 2012** | Brazil           | Mixed          | HCV     | 112/183   | 38/53/21    | 62/95/26     |     | 0.279           |
| **Donaldson 2007** | UK               | Caucasian      | LC      | 195/276   | 32/104/59   | 57/137/82    |     | 0.987           |
| **Joshita 2010**   | Japan            | East Asian     | LC      | 308/268   | NA          | NA           |     | NA              |
| **Juran 2010**     | USA              | Mixed          | LC      | 351/205   | 117/168/66  | 70/94/41     |     | 0.005           |
| **Ksiaa 2015**     | Tunisia          | South Asian    | HCV     | 500/358   | 194/217/89  | 124/158/76   |     | 0.056           |
| **Li 2013**        | China            | East Asian     | LC      | 312/375   | 159/112/41  | 170/152/53   |     | 0.048           |
| **Mantaka 2012**   | Greece           | Caucasian      | LC      | 100/158   | 32/43/25    | 37/84/37     |     | 0.426           |
| **Oertelt 2005**   | USA              | Mixed          | LC      | 154/166   | 27/87/40    | 45/72/49     |     | 0.089           |
| **Thio 2004**      | USA              | Mixed          | HBV     | 378/676   | NA          | NA           |     | NA              |
| **Umemura 2008**   | Japan            | East Asian     | AIH     | 76/100    | 3/35/38     | 12/47/41     |     | 0.792           |
| **Walker 2009**    | Canada           | Mixed          | LC      | 481/1248  | 198/205/78  | 362/613/273  |     | 0.656           |
| **Xiao 2015**      | China            | East Asian     | HCV     | 816/375   | 555/231/30  | 266/99/10    |     | 0.829           |
| **Yang 2019**      | China            | East Asian     | HCC     | 575/921   | 325/221/29  | 609/282/30   |     | 0.703           |

**IL-18 rs1946518**

| Study          | Country          | Ethnicity      | Disease | IL-18 SNP | MAF (log10) | Age (median) | Sex | IL-18 rs1946518 |
|---------------|------------------|----------------|---------|-----------|-------------|--------------|-----|-----------------|
| **Abdelrahem 2016** | Egypt            | South Asian    | HCV     | 100/100   | 21/47/32    | 42/51/7      |     | 0.104           |
| **An 2008**    | USA              | Caucasian      | HCV     | 384/212   | NA          | NA           |     | NA              |
| **An 2008**    | USA              | African        | HCV     | 364/182   | NA          | NA           |     | NA              |
| **Bakr 2018**  | Egypt            | South Asian    | HCV     | 189/90    | 30/79/80    | 24/48/18     |     | 0.498           |
| **Bakr 2018**  | Egypt            | South Asian    | HCV     | 90/90     | 13/34/43    | 24/48/18     |     | 0.498           |
| **Bao 2015**   | China            | East Asian     | HBV     | 153/165   | 37/73/43    | 41/76/48     |     | 0.322           |
| **Bao 2015**   | China            | East Asian     | HCC     | 153/165   | 37/73/43    | 41/76/48     |     | 0.322           |
| **Bouzgarrou 2008** | Tunisia          | South Asian    | HCV     | 81/82     | 24/38/19    | 21/44/17     |     | 0.493           |
| **Bouzgarrou 2011** | Tunisia          | South Asian    | LC      | 47/34     | 7/25/15     | 12/13/9      |     | 0.181           |
| **Cheong 2010** | South Korea      | East Asian     | HBV     | 696/313   | 183/321/192 | 87/148/78    |     | 0.344           |
| **Dai 2017**   | China            | East Asian     | HBV     | 250/250   | 61/134/55   | 64/124/62    |     | 0.900           |
| **Dai 2017**   | China            | East Asian     | HCC     | 247/250   | 67/118/62   | 64/124/62    |     | 0.900           |
| Study Year | Country | Region | Disease | Genotype | Age 1/2/3 | Genotype 1/2/3 | MA 1/2/3 | Freq 1/2/3 | p-value |
|------------|---------|--------|---------|-----------|-----------|---------------|----------|-----------|---------|
| Dai 2017   | China   | East Asian | LC     | 250/250   | 72/118/60 | 64/124/62     | 0.900    | 8         |
| Estfanous 2019 | Egypt | South Asian | HCV    | 201/95    | 70/92/39  | 47/37/11      | 0.378    | 8         |
| Falleti 2007 | Italy  | Caucasian  | HCV    | 46/105    | 12/22/12  | 33/42/30      | 0.041    | 8         |
| Haas 2009   | Germany | Caucasian  | HCV    | 757/791   | 276/347/134| 300/369/122   | 0.628    | 8         |
| Hirankarn 2007 | Thailand | East Asian | HBV    | 140/140   | 33/68/39  | 39/83/18      | 0.012    | 8         |
| Imran 2014  | Pakistan | South Asian | HCV    | 140/120   | 25/50/55  | 35/53/32      | 0.203    | 7         |
| Karra 2015  | India   | South Asian | HBV    | 271/280   | 70/152/49 | 102/144/34    | 0.120    | 8         |
| Kim 2009    | South Korea | East Asian | HCC    | 55/549    | 16/23/16  | 142/254/153   | 0.082    | 7         |
| Ksiaa 2011  | Tunisia  | South Asian | HCV    | 100/100   | 30/44/26  | 26/50/24      | 0.997    | 8         |
| Lau 2016    | Taiwan   | East Asian | HCC    | 342/559   | 88/167/87 | 148/276/135   | 0.777    | 8         |
| Li 2012     | China    | East Asian | HBV    | 501/301   | 121/239/141| 85/156/60     | 0.448    | 7         |
| Lu 2015     | China    | East Asian | HBV    | 129/160   | 32/58/39  | 40/73/47      | 0.278    | 8         |
| Lu 2015     | China    | East Asian | LC     | 86/160    | 22/39/25  | 40/73/47      | 0.278    | 8         |
| Mandour 2014| Egypt    | South Asian | HCV    | 123/123   | 20/63/40  | 26/58/39      | 0.608    | 8         |
| Migita 2009 | Japan    | East Asian | HBV    | 204/63    | 55/119/30 | 20/30/13      | 0.777    | 8         |
| Santos 2015 | Brazil   | Mixed     | HCV    | 304/376   | 36/156/112| 68/192/116    | 0.459    | 8         |
| Teixeira 2013| Brazil | Mixed     | HCC    | 112/202   | 56/38/18  | 105/85/12     | 0.334    | 8         |
| Wu 2011     | China    | East Asian | HBV    | 12/109    | 3/8/1     | 37/46/26      | 0.124    | 7         |
| Yue 2013    | China    | East Asian | HCV    | 552/784   | NA        | NA            | NA       | 7         |
| Zhang 2005  | China    | East Asian | HBV    | 231/300   | 53/116/62 | 74/160/66     | 0.243    | 8         |

**IL-18 rs187238**

| Study Year | Country | Region | Disease | Genotype | Age 1/2/3 | Genotype 1/2/3 | MA 1/2/3 | Freq 1/2/3 | p-value |
|------------|---------|--------|---------|-----------|-----------|---------------|----------|-----------|---------|
| An 2008    | USA     | Caucasian | HCV    | 384/212   | NA        | NA            | NA       | NA        | 7       |
| An 2008    | USA     | African  | HCV    | 364/182   | NA        | NA            | NA       | NA        | 7       |
| Bakr 2018  | Egypt   | South Asian | HCV    | 189/90    | 99/87/3   | 30/58/2       | <0.001   | 8         |
| Bakr 2018  | Egypt   | South Asian | HCC    | 90/90     | 66/22/2   | 30/58/2       | <0.001   | 8         |
| Bao 2015   | China   | East Asian | HBV    | 153/165   | 122/28/3  | 106/54/5      | 0.548    | 8         |
| Study   | Country     | Region     | Disease | Count 1 | Count 2  | Count 3  | p-Value | Study Method |
|---------|-------------|------------|---------|---------|----------|----------|---------|--------------|
| Bao 2015 | China       | East Asian | HCC     | 153/165 | 122/28/3 | 106/54/5 | 0.548   |             |
| Bouzgarrou 2008 | Tunisia     | South Asian | HCV     | 81/82   | 38/31/12 | 35/35/12 | 0.506   |             |
| Bouzgarrou 2011 | Tunisia     | South Asian | LC      | 47/34   | 23/20/4  | 15/11/8  | 0.059   |             |
| Cheong 2010 | South Korea | East Asian | HBV     | 707/316 | 546/155/6 | 237/67/12 | 0.013   |             |
| Dai 2017 | China       | East Asian | HBV     | 250/250 | 200/48/2 | 183/65/2 | 0.142   |             |
| Dai 2017 | China       | East Asian | HCC     | 245/250 | 187/49/9 | 183/65/2 | 0.142   |             |
| Dai 2017 | China       | East Asian | LC      | 249/250 | 202/42/5 | 183/65/2 | 0.142   |             |
| Estfanous 2019 | Egypt      | South Asian | HCV     | 201/95  | 102/94/5 | 52/36/7  | 0.824   |             |
| Falleti 2007 | Italy      | Caucasian  | HCV     | 50/96   | 23/23/4  | 49/38/9  | 0.681   |             |
| Haas 2009  | Germany     | Caucasian  | HCV     | 757/791 | 386/315/56 | 439/299/53 | 0.829   |             |
| Hirankarn 2007 | Thailand  | East Asian | HBV     | 140/140 | 105/29/6 | 102/35/3 | 0.999   |             |
| Imran 2014 | Pakistan    | South Asian | HBV     | 140/120 | 57/70/13 | 43/61/16 | 0.437   |             |
| Jiang 2014 | China       | East Asian | HBV     | 276/254 | 221/51/4 | 168/80/6 | 0.324   |             |
| Karra 2015 | India       | South Asian | HBV     | 271/280 | 123/134/14 | 159/108/13 | 0.320   |             |
| Kim 2009  | South Korea | East Asian | HCC     | 56/558  | 37/17/2  | 434/122/2 | 0.031   |             |
| Ksiaa 2011 | Tunisia     | South Asian | HCV     | 100/100 | 53/33/14 | 44/44/12 | 0.845   |             |
| Lau 2016  | Taiwan      | East Asian | HCC     | 342/559 | 266/73/3 | 476/78/5 | 0.370   |             |
| Lu 2015   | China       | East Asian | HBV     | 129/160 | 100/27/2 | 103/52/5 | 0.610   |             |
| Lu 2015   | China       | East Asian | LC      | 86/160  | 69/16/1  | 103/52/5 | 0.610   |             |
| Migita 2009 | Japan      | East Asian | HBV     | 204/63  | 167/32/5 | 52/10/1 | 0.531   |             |
| Ognjanovic 2009 | USA  | Mixed      | HCC     | 117/216 | NA       | NA       | NA      |             |
| Santos 2015 | Brazil     | Mixed      | HCV     | 304/376 | 100/120/84 | 128/132/116 | <0.001 |             |
| Teixeira 2013 | Brazil     | Mixed      | HCC     | 112/202 | 57/48/7  | 100/84/18 | 0.952   |             |
| Wu 2011   | China       | East Asian | HBV     | 12/109  | 11/1/0   | 85/22/2  | 0.682   |             |
| Yue 2013  | China       | East Asian | HCV     | 552/784 | NA       | NA       | NA      |             |
| Zhang 2005 | China       | East Asian | HBV     | 231/300 | 182/45/4 | 202/90/8 | 0.588   |             |
Abbreviations: CTLA-4, Cytotoxic T-lymphocyte-associated antigen 4; IL-18, Interleukin-18; HBV, Hepatitis B virus infection; HCV, Hepatitis C virus infection; HCC, Hepatocellular carcinoma; LC, Liver cirrhosis; AIH, Autoimmune hepatitis; NAFLD, Nonalcoholic fatty liver disease; ALD, Alcoholic liver disease; HWE, Hardy-Weinberg equilibrium; NOS, Newcastle-Ottawa scale; NA, Not available.
Table 2. Meta-analysis results of this study.

| Variables     | Sample size | Dominant comparison (MM vs. Mm + mm) | Recessive comparison (mm vs. MM + Mm) | Over-dominant comparison (Mm vs. MM + Mm) | Allele comparison (M vs. m) |
|---------------|-------------|-------------------------------------|--------------------------------------|----------------------------------------|---------------------------|
|               |             | p value | OR (95%CI) | p value | OR (95%CI) | p value | OR (95%CI) | p value | OR (95%CI) |
| Overall       | 10879/12266 | <0.0001 | 0.83 (0.79-0.88) | <0.0001 | 1.33 (1.23-1.43) | 0.20 | 1.06 (0.97-1.16) | <0.0001 | 0.84 (0.78-0.90) |
| HBV           | 1832/1870   | 0.03    | 0.70 (0.51-0.96) | 0.002   | 1.46 (1.15-1.86) | 0.68 | 1.03 (0.88-1.22) | 0.0007 | 0.75 (0.63-0.88) |
| HCV           | 1750/1656   | 0.64    | 0.94 (0.73-1.21) | 0.14    | 1.19 (0.94-1.49) | 0.51 | 1.05 (0.90-1.23) | 0.07  | 0.90 (0.80-1.01) |
| AIH           | 1320/1684   | 0.02    | 0.83 (0.70-0.97) | 0.18    | 1.15 (0.94-1.41) | 0.27 | 1.09 (0.94-1.27) | 0.03  | 0.88 (0.79-0.99) |
| LC            | 3688/4486   | 0.0002  | 0.75 (0.65-0.87) | 0.02    | 1.33 (1.04-1.70) | 0.48 | 1.06 (0.90-1.24) | 0.002 | 0.81 (0.71-0.92) |
| HCC           | 2109/2463   | 0.19    | 0.92 (0.82-1.04) | 0.0004  | 1.40 (1.16-1.68) | 0.34 | 0.94 (0.84-1.06) | 0.008 | 0.89 (0.81-0.97) |
| Caucasian     | 2080/2493   | 0.005   | 0.73 (0.59-0.91) | 0.22    | 1.12 (0.94-1.33) | 0.0004 | 1.25 (1.10-1.41) | 0.06  | 0.85 (0.72-1.01) |
| East Asian    | 5867/5593   | 0.0002  | 0.86 (0.79-0.93) | <0.0001 | 1.45 (1.20-1.74) | 0.61 | 0.97 (0.86-1.09) | <0.0001 | 0.81 (0.73-0.89) |
| South Asian   | 898/1240    | 0.21    | 0.88 (0.72-1.08) | 0.002   | 1.56 (1.18-2.07) | 0.57 | 1.16 (0.70-1.91) | 0.006 | 0.81 (0.70-0.94) |

**CTL A-4 rs231775**

- Overall: 10879/12266
- HBV: 1832/1870
- HCV: 1750/1656
- AIH: 1320/1684
- LC: 3688/4486
- HCC: 2109/2463
- Caucasian: 2080/2493
- East Asian: 5867/5593
- South Asian: 898/1240

**CTL A-4 rs5742909**

- Overall: 5534/6726
- HBV: 1560/1518
- HCV: 1252/1341
- AIH: 188/360
- LC: 2052/3021
- Caucasian: 902/979
- East Asian: 2885/2328
- South Asian: 220/818

**CTL A-4 rs3087243**

- Overall: 5767/6389
- HCV: 1428/916
|                |        |          |        |        |        |        |        |        |        |        |        |
|----------------|--------|----------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
|                |        | rs187238 |        |        |        |        |        |        |        |        |        |
|                |        | OR       | CI     |        |        |        |        |        |        |        |        |
|                |        | 0.007    | 1.28   | (1.07-1.53) | 0.15 | 0.88 | (0.74-1.05) | 0.02 | 0.81 | (0.68-0.97) | 0.003 | 1.22 | (1.07-1.39) |
|                |        | 0.03     | 1.39   | (1.04-1.86) | 0.11 | 0.72 | (0.48-1.07) | 0.04 | 0.73 | (0.54-0.98) | 0.02 | 1.33 | (1.05-1.70) |
|                |        | 0.49     | 1.08   | (0.86-1.36) | 0.37 | 0.91 | (0.73-1.12) | 0.97 | 1.00 | (0.83-1.22) | 0.36 | 1.04 | (0.95-1.14) |
|                |        | 0.002    | 1.68   | (1.22-2.33) | 0.55 | 0.65 | (0.16-2.63) | 0.17 | 0.68 | (0.39-1.18) | 0.002 | 1.56 | (1.18-2.07) |
|                |        | 0.40     | 1.24   | (0.75-2.04) | 0.51 | 1.19 | (0.70-2.03) | 0.36 | 0.75 | (0.41-1.38) | 0.57 | 1.14 | (0.72-1.82) |
|                |        | 0.06     | 0.83   | (0.69-1.01) | 0.67 | 1.08 | (0.75-1.57) | 0.09 | 1.18 | (0.97-1.44) | 0.09 | 0.89 | (0.78-1.02) |
|                |        | 0.007    | 1.39   | (1.09-1.76) | 0.45 | 0.87 | (0.60-1.25) | 0.008 | 0.74 | (0.59-0.92) | 0.01 | 1.32 | (1.06-1.64) |
|                |        | 0.17     | 1.39   | (0.87-2.23) | 0.19 | 0.79 | (0.56-1.12) | 0.35 | 0.79 | (0.48-1.29) | 0.10 | 1.28 | (0.95-1.71) |

**Abbreviations:** OR, Odds ratio; CI, Confidence interval; NA, Not available; M, Major allele; m, Minor allele; HBV, Hepatitis B virus infection; HCV, Hepatitis C virus infection; LC, Liver cirrhosis; AIH, Autoimmune hepatitis; HCC, Hepatocellular carcinoma.
The values in bold represent there is statistically significant differences between cases and controls.
From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Supplementary Figure 1. Funnel plots of investigated polymorphisms

Funnel plot of CTLA-4 rs231775 polymorphism and chronic liver disease under dominant comparison

Funnel plot of CTLA-4 rs231775 polymorphism and chronic liver disease under recessive comparison
Funnel plot of CTLA-4 rs231775 polymorphism and chronic liver disease under over-dominant comparison.

Funnel plot of CTLA-4 rs231775 polymorphism and chronic liver disease under allele comparison.
Funnel plot of CTLA-4 rs5742909 polymorphism and chronic liver disease under dominant comparison

Funnel plot of CTLA-4 rs5742909 polymorphism and chronic liver disease under recessive comparison
Funnel plot of CTLA-4 rs5742909 polymorphism and chronic liver disease under over-dominant comparison

Funnel plot of CTLA-4 rs5742909 polymorphism and chronic liver disease under allele comparison
Funnel plot of CTLA-4 rs3087243 polymorphism and chronic liver disease under dominant comparison

Funnel plot of CTLA-4 rs3087243 polymorphism and chronic liver disease under recessive comparison
Funnel plot of CTLA-4 rs3087243 polymorphism and chronic liver disease under over-dominant comparison

Funnel plot of CTLA-4 rs3087243 polymorphism and chronic liver disease under allele comparison
Funnel plot of IL-18 rs1946518 polymorphism and chronic liver disease under dominant comparison

Funnel plot of IL-18 rs1946518 polymorphism and chronic liver disease under recessive comparison
Funnel plot of IL-18 rs1946518 polymorphism and chronic liver disease under over-dominant comparison

Funnel plot of IL-18 rs1946518 polymorphism and chronic liver disease under allele comparison
Funnel plot of IL-18 rs187238 polymorphism and chronic liver disease under dominant comparison

Funnel plot of IL-18 rs187238 polymorphism and chronic liver disease under recessive comparison
Funnel plot of IL-18 rs187238 polymorphism and chronic liver disease under over-dominant comparison

Funnel plot of IL-18 rs187238 polymorphism and chronic liver disease under allele comparison