The Association of CTLA-4 rs231775 and rs3087243 Polymorphisms with Latent Autoimmune Diabetes in Adults: A Meta-Analysis

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Abstract
Polymorphisms rs231775 and rs3087243 of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) gene have been associated with risk of latent autoimmune diabetes in adults (LADA). However, the results were inconsistent. The purpose of this study was to quantitatively assess the relationship between polymorphisms rs231775 and rs3087243 of CTLA-4 and LADA in a larger pooled population by performing a meta-analysis. Systematic search for eligible studies was conducted in PubMed, Web of Science, and Embase. Case–control studies containing genotype frequencies of polymorphisms rs231775 or rs3087243 were selected, and pooled odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the associations between polymorphisms of CTLA-4 and LADA in allelic, dominant and recessive genetic model. A total of eleven studies, in which five studies reported rs231775, two studies reported rs3087342, and four studies reported both rs231775 and rs3087243, were identified. Among them, one study wasn’t included in the following meta-analysis because the distribution of genotypes in the control group didn’t comply with Hardy–Weinberg equilibrium. Significant associations with susceptibility to LADA were detected for rs231775 (785 cases and 3435 controls) and for rs3087243 (820 cases and 4824 controls) in overall population. Further subgroup analyses for ethnicity (Asian, Caucasian, and African) have also indicated the positive association between rs231775 and LADA. As for rs3087243, subgroup analyses detected the association between polymorphism and LADA in Caucasian population under recessive model. Polymorphisms rs231775 and rs3087243 of CTLA-4 gene are potential risk factors for LADA and may serve as novel genetic biomarkers of LADA.

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Background

Latent autoimmune diabetes in adults (LADA), also termed as “type 1.5 diabetes mellitus”, “slowly progressive insulin-dependent diabetes mellitus”, or “latent type 1 diabetes”, is defined as an autoimmune disease (Liu et al. 2020). Patients with LADA are always initially misdiagnosed as type 2 diabetes mellitus (T2DM) because of the lack of ketoacidosis and requirement of insulin treatment but exhibit positive diabetic-associated autoantibodies and faster deterioration of beta-cell function, which are characteristics of type 1 diabetes mellitus (T1DM). Results from multiple large multicenter studies have indicated the prevalence of LADA accounts for 2–10% of all patients with diabetes (Hawa et al. 2013; Sachan et al. 2015; Zhou Z, Xiang Y, Ji L, Jia W, Ning G, Huang G, Yang L, Lin J, Liu Z, Hagopian WA, Leslie RD and Group LCS 2013). The ethnic and geographical characteristics of LADA were similar to T1DM. For example, studies have demonstrated that the positivity of diabetic-associated autoantibodies in phenotypic T2DM were higher in Caucasians than in Asians (Xiang et al. 2013). Furthermore, in the Europe, the frequency of GADA in T2DM was higher in the northern countries than in the south (Buzzetti R, Di Pietro S, Giaccheri A, Petrone A, Locatelli M, Suraci C, Capizzi M, Arpi ML, Bazzigaluppi E, Dotta F, Bosi E and Non Insulin Requiring Autoimmune Diabetes Study G 2007; Radtke et al. 2009; Tuomi et al. 1999). A similar trend was also reported in the LADA China Study (Zhou Z, Xiang Y, Ji L, Jia W, Ning G, Huang G, Yang L, Lin J, Liu Z, Hagopian WA, Leslie RD and Group LCS 2013). These findings indicate that LADA may share common pathogenic mechanisms with T1DM.

However, the exact pathogenesis of LADA was still unclear. Whether LADA is a distinct disease or just intermediate condition between T1DM and T2DM remains controversial (Leslie et al. 2006; Rolandsson and Palmer 2010). In addition, the diagnostic criteria of LADA are not categorical. Determining the phenotypic and immunogenetic features of LADA is rather challenging because LADA is a clinical and metabolic hybrid of T1DM and T2DM (Buzzetti et al. 2017; Leslie and Pozzilli 1994; Redondo et al. 2019; Tuomi et al. 2014). Therefore, efforts on revealing the underlying pathogenic mechanisms of LADA are critical for applying targeted treatment and exploring early detection.

It has been clearly indicated that genetic factors contribute to development of diabetes and genome-wide association studies (GWAS) have identified a great many of risk loci to T1DM and T2DM. The known susceptible loci even can explain 80–85% of the heritability of T1DM (Pang et al. 2021). By contrast, the genetic association study is relatively lacking with regard to LADA. However, some recent available studies indicate a genetic overlap between LADA and T1DM (such as HLA-DRB1-DQB1, PTPN22, CTLA-4, and SH2B3) as well as T2DM (such as TCF7L2, FTO, and KCNQ1) (Andersen and Hansen 2019; Grant et al. 2010). Cytotoxic T-lymphocyte antigen-4 (CTLA-4) is an important candidate gene of T1DM and has been confirmed by several studies (Nistico et al. 1996; Ueda et al. 2003).
CTLA-4 protein, as a co-stimulatory molecule, can inhibit T cell activation, and therefore repress autoimmune response (Xie et al. 2014). Previous studies have indicated that the single nucleotide polymorphisms (SNPs) rs231775 and rs3087243 of CTLA-4 were potential risk factors for T1DM (Korolija et al. 2009; Sharma and BRA et al., 2021). These two polymorphisms may cause enhanced T-cell activation and resultant autoimmune responses due to decreased function of CTLA-4 (Ueda et al. 2003; Xie et al. 2014). In addition, many studies have evaluated the association between polymorphisms (rs231775 and rs3087243) and LADA in multiple populations (Alshareef et al. 2019; Caputo et al. 2005; Cosentino et al. 2002; Delitala et al. 2015; Douroudis et al. 2009; Haller et al. 2007; Jin et al. 2011, 2015; Kisand and Uibo 2012; Pettersen et al. 2010; Qi et al. 2014). However, the results are inconclusive. Therefore, we performed this meta-analysis to further assess their associations based on existing relevant studies and aimed to improve the acknowledgement of pathogenesis of LADA.

Methods

Publication Search

This meta-analysis was complied with the PRISMA guideline (Moher D, Liberati A, Tetzlaff J, Altman DG and Group P 2009). Systematic literature searches (up to May 2021) were performed by using PubMed, Web of Science, and Embase. The searching strategy was as follows: (“LADA” OR “latent autoimmune diabetes in adults”) and (“CTLA-4” OR “cytotoxic T-lymphocyte antigen-4”) and (“polymorphism” OR “SNP” OR “allele” OR “variant” OR “genotype”). In addition, the reference list of original studies was manually screened to identify potentially relevant articles.

Inclusion and Exclusion Criteria

The included studies must meet the following criteria: (1) case–control study written in English; (2) report the associations between polymorphisms (rs231775 or rs3087243) of CTLA-4 and LADA; (3) provide odds ratios (ORs) and 95% confidence intervals (CIs) or detailed data to calculate ORs and 95% CIs. Family-based association studies, letters, conference abstracts, case reports, reviews, and commentary were excluded.

Data Extraction and Quality Assessment

The following data were collected from the included articles: (1) name of the first author; (2) publication year; (3) region and ethnicity of participants; (4) the genotyping methods (5) the number of cases and controls; (6) genotype frequencies of investigated polymorphisms of cases and controls; (7) OR value and 95% CI. The Hardy–Weinberg equilibrium (HWE) of control group was tested by online software (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl). The Newcastle–Ottawa Scale (NOS) was...
applied to assess the quality of included studies from three aspects: the selection of case and control (0–4 points), comparability (0–2 points), and exposure assessment (0–3 points). Studies with at least 6 points were assumed to be of high quality.

**Statistical Analysis**

All statistical analyses were performed by the software STATA version 12.0 (STATA, College Station, TX). Higgins I-squared statistic and Cochran’s Q test were used to evaluate the heterogeneity of included studies. If $P_{\text{heterogeneity}} > 0.1$ and $I^2 < 50\%$, the fixed-effects model was used to calculate the pooled ORs and 95\% CIs, otherwise the random-effects model was applied. The subgroup analysis, sensitivity analysis, and meta-regression were used to seek the source of heterogeneity. Begg’s test and Egger’s test were used to assess the publication bias. $P$ value less than 0.05 was considered as statistically significant.

**Results**

**Study Characteristics**

Totally, eleven studies in which five studies reported rs231775, two studies reported rs3087342, and four studies reported both rs231775 and rs3087243, were identified (Fig. 1) (Alshareef et al. 2019; Caputo et al. 2005; Cosentino et al. 2002; Delitala

![Flowchart of study selection](image-url)

**Fig. 1** Flowchart of study selection
et al. 2015; Douroudis et al. 2009; Haller et al. 2007; Jin et al. 2011, 2015; Kisand and Uibo 2012; Pettersen et al. 2010; Qi et al. 2014). Characteristics of identified articles were shown in Table 1. Among them, one study wasn’t included in the following meta-analysis because the distribution of genotypes in the control group wasn’t in accordance with HWE.

**Associations Between Polymorphisms of CTLA-4 and LADA**

The results of meta-analysis were shown in Table 2. Significant associations with susceptibility to LADA were detected in the meta-analysis for rs231775 polymorphism (Allelic model: OR 1.53, 95% CI 1.22–1.92, \( P_H = 0.002 \); Dominant model: OR 2.16, 95% CI 1.43–3.28, \( P_H = 0.003 \); Recessive model: OR 1.49, 95% CI 1.13–1.97, \( P_H = 0.073 \)) (Fig. 2). Under allelic and recessive model, the polymorphism rs3087243 was associated with LADA susceptibility (Allelic model: OR 1.26, 95% CI 1.03–1.55, \( P_H = 0.022 \); Recessive model: OR 1.41, 95% CI 1.07–1.86, \( P_H = 0.021 \)) (Fig. 3). Further subgroup analysis indicated that polymorphism rs231775 was associated with LADA susceptibility in Asians (Allelic model, Dominant model, and Recessive model), Caucasians (Allelic model, and Dominant model), and Africans (Allelic model, Dominant model, and Recessive model). As for polymorphism rs3087243, subgroup analysis revealed an association between rs3087243 and LADA in Caucasians (Recessive model) but not in Asians.

To explore the potential source of heterogeneity among included studies, we performed sensitivity analysis to evaluate the influence of each study. No changes of results were detected for both rs231775 (Fig. 4) and rs3087243 (Fig. 5) of CTLA-4 in allelic, dominant, and recessive models. Meta-regression analysis was also applied to try to find the source of heterogeneity. However, the ethnicity (rs231775: Allelic model, \( P = 0.218 \); Dominant model, \( P = 0.096 \); Recessive model, \( P = 0.757 \); rs3087243: Allelic model, \( P = 0.546 \); Dominant model, \( P = 0.545 \); Recessive model, \( P = 0.358 \)) and publication year (before and after year 2010) (rs231775: Allelic model, \( P = 0.399 \); Dominant model, \( P = 0.188 \); Recessive model, \( P = 0.569 \)) were not the source of heterogeneity. The statistical method or other unknown factors may contribute to the heterogeneity. The random-effects model was appropriate under this condition to obtain the pooled OR value.

**Publication Bias**

Begg’s test and Egger’s test were used to assess the publication bias. As shown in Table 3, Begg’s and Egger’s test showed statistically significant (\( P < 0.05 \)) under dominant model for both rs231775 and rs3087243. Therefore, we performed a trim and fill method to estimate the number of missing studies and recalculate the pooled OR value after combining the missing hypothetical studies (rs231775: OR 1.797, 95% CI 1.188–2.719, random-effect model; rs3087243: OR 1.000, 95% CI 0.806–1.242, fixed-effect model). The funnel plots after addition of two missing hypothetical studies for rs231775 and three missing hypothetical studies for rs3087243 were basically symmetrical, respectively (Fig. 6).
| Author/Year | SNP | alleles | Region | Ethnicity | Genotyping method | Case | Control | OR  | 95% CI | No. of Cases/Controls | HWE | NOS score |
|------------|-----|---------|--------|-----------|------------------|------|---------|-----|--------|----------------------|-----|-----------|
| Cosentino (2002) | rs231775 | G/A | Italy | Caucasian | PCR | 21 | 55 | 4 | 40 | 40 | 5 | 1.559 | 0.986–2.463 | 80/85 | Yes | 7 |
| Caputo (2005) | rs231775 | G/A | Argentina | Caucasian | PCR | 22 | 35 | 6 | 71 | 76 | 21 | 1.099 | 0.719–1.681 | 63/168 | Yes | 6 |
| Haller (2007) | rs231775 | G/A | Estonia | Caucasian | PCR–RFLP | 8 | 33 | 20 | 77 | 135 | 40 | 2.003 | 1.339–2.996 | 61/252 | Yes | 6 |
| Douroudis (2009) | rs3087243 | G/A | Estonia | Caucasian | PCR | 3 | 22 | 36 | 29 | 119 | 82 | 2.100 | 1.323–3.332 | 61/230 | Yes | 7 |
| Pettersen (2010) | rs231775 | G/A | Norway | Caucasian | Taqman | 24 | 52 | 48 | 263 | 715 | 499 | 1.072 | 0.823–1.396 | 126/1503 | Yes | 8 |
| Jin (2011) | rs231775 | G/A | China | Asian | PCR–RFLP | 11 | 73 | 51 | 70 | 239 | 167 | 1.218 | 0.920–1.615 | 135/476 | Yes | 7 |
| Kisan (2012) | rs3087243 | G/A | Estonia | Caucasian | PCR–RFLP/Taqman | 9 | 35 | 21 | 68 | 124 | 37 | 1.908 | 1.284–2.834 | 65/229 | Yes | 6 |
| Qi (2014) | rs3087243 | G/A | China | Asian | PCR–RFLP | 5 | 29 | 14 | 124 | 52 | 16 | 5.22 | 3.250–8.383 | 48/192 | No | 8 |
| Delitala (2015) | rs3087243 | G/A | Italy | Caucasian | Taqman | 60 | 90 | 52 | 563 | 966 | 375 | 1.126 | 0.917–1.383 | 202/1904 | Yes | 6 |
| Jin (2015) | rs231775 | G/A | China | Asian | PCR–RFLP | 15 | 114 | 102 | 72 | 241 | 169 | 1.468 | 1.161–1.858 | 231/482 | Yes | 7 |
| Alshareef (2019) | rs231775 | G/A | Eastern Sudan | African | PCR–RFLP | 5 | 16 | 3 | 162 | 70 | 8 | 3.877 | 2.098–7.162 | 24/240 | Yes | 8 |
Discussion

We performed a meta-analysis to determine the effects of polymorphisms rs231775 and rs3087243 of CTLA-4 on the LADA. In this meta-analysis, ten eligible studies including 785 cases and 3435 controls for rs231775 and 820 cases and 4828 controls for rs3087243 were analyzed. The present study revealed a significant association between polymorphism rs231775 and LADA under allelic, dominant, and recessive models. Similar positive associations were obtained in the following subgroup analysis by ethnicity except under recessive model in Caucasians. As for polymorphism rs3087243, significant association with LADA was identified in overall populations under allelic and recessive models. Subgroup analysis reported an association between rs3087243 and LADA in Caucasians under recessive model. Asian-derived populations indicated an unrelated result. Different genetic background and limited study may partially explain the difference.

The CTLA-4 gene is located on human chromosome 2q33.2. Its encoding product expressed on the cell surface of T lymphocytes and served as a negative regulator of T-cell activation (Ounissi-Benkalha and Polychronakos 2008). Therefore, dysfunction of CTLA-4 can increase self-reactivity of T lymphocyte and may

| Table 2 The results of meta-analysis |
|-------------------------------------|
| SNP | Allelic model G/A | Dominant model GG + GA/AA | Recessive model GG/GA + AA |
| OR (95%CI) | I² | PH | OR (95%CI) | I² | PH | OR (95%CI) | I² | PH |
|-------|------------|-------|------------|------|-----|------------|------|-----|
| rs231775 | | | | | | | | |
| Overall | 1.53(1.22–1.92) | 68.70% | 0.002 | 2.16(1.43–3.28) | 68% | 0.003 | 1.49(1.13–1.97) | 46% | 0.073 |
| Ethnicity | | | | | | | | |
| Asian | 1.36(1.14–1.63) | 0 | 0.318 | 2.26(1.46–3.50) | 0 | 0.560 | 1.32(1.02–1.70) | 4% | 0.307 |
| Caucasian | 1.45(1.10–1.92) | 62.80% | 0.030 | 1.78(1.09–2.90) | 65.80% | 0.020 | 1.53(0.96–2.44) | 56.10% | 0.059 |
| African | 3.88(2.10–7.16) | NA | NA | 7.89(2.84–21.92) | NA | NA | 4.14(1.02–16.8) | NA | NA |
| rs3087243 | | | | | | | | |
| Overall | 1.26(1.03–1.55) | 62.10% | 0.022 | 1.11(0.88–1.40)* | 0.40% | 0.413 | 1.41(1.07–1.86) | 62.50% | 0.021 |
| Ethnicity | | | | | | | | |
| Asian | 1.15(0.94–1.41) | 0 | 0.531 | 1.37(0.73–2.56) | 0 | 0.931 | 1.16(0.91–1.49) | 0 | 0.473 |
| Caucasian | 1.37(0.99–1.91) | 76.20% | 0.006 | 1.07(0.83–1.38) | 33.60% | 0.211 | 1.63(1.06–2.50) | 71.70% | 0.014 |

*Present the OR value and 95% CI were obtained based on fixed-effects model, while others were obtained based on random-effects model
Fig. 2 Forest plot for rs231775 polymorphism and the risk of LADA under Allelic genetic model (a), Dominant genetic model (b), and Recessive genetic model (c)

Fig. 3 Forest plot for rs3087243 polymorphism and the risk of LADA under Allelic genetic model (a), Dominant genetic model (b), and Recessive genetic model (c)
Fig. 4 The sensitivity analysis results of rs231775 with LADA under Allelic genetic model (a), Dominant genetic model (b), and Recessive genetic model (c)

Fig. 5 The sensitivity analysis results of rs3087243 with LADA under Allelic genetic model (a), Dominant genetic model (b), and Recessive genetic model (c)
contribute to autoimmune response (Ueda et al. 2003; Atabani et al. 2005). Previous studies have also indicated associations between \( CTLA-4 \) and multiple autoimmune diseases, such as T1DM (Westra et al. 2018), systemic lupus erythematosus (Barreto et al. 2004), and rheumatoid arthritis (Lee et al. 2003). The rs231775 polymorphism located in exon 1 of \( CTLA-4 \) and led to substitution of alanine with threonine. The mutant protein caused the reduction of \( CTLAT-4 \) cell surface expression (Xie et al. 2014). Polymorphism rs3087243 located in downstream of the poly (A) termination site and might play an important role in the mRNA stability of soluble \( CTLAT-4 \) (sCTLA-4). Previous study has indicated that individuals with potential risk genotype G/G exhibited lower production of sCTLA-4 than those with A/A genotype (Ueda et al. 2003). Therefore, these two polymorphisms may lead to increased T-cell activation and higher probability of autoimmunity because of decreased function of \( CTLAT-4 \). Latent autoimmune diabetes in adults, as an autoimmune disease, has also been associated with the polymorphisms of \( CTLAT-4 \). However, the results are inconclusive. Our meta-analysis revealed significant associations between two investigated polymorphisms and susceptibility to LADA. This finding may contribute to early diagnosis and better prognosis of

| SNP       | Begg’s test | Egger’s test |
|-----------|-------------|--------------|
|           | \( Z \)     | \( P \)       | \( t \)     | \( P \)   |
| rs231775  |             |              |             |           |
| Allelic model | 1.36     | 0.174       | 2.08       | 0.082     |
| Dominant model | 2.10     | 0.035       | 5.11       | 0.002     |
| Recessive model | 0.12     | 0.902       | 0.58       | 0.582     |
| rs3087243 |             |              |             |           |
| Allelic model | 1.13     | 0.26        | 2.48       | 0.068     |
| Dominant model | 2.25     | 0.024       | 4.09       | 0.015     |
| Recessive model | 0.75     | 0.452       | 1.93       | 0.126     |

**Fig. 6** Filled funnel plot for rs231775 under dominant genetic model (a) and for rs3087243 under dominant genetic model (b)
LADA patients, and identification of the underlying pathogenic mechanisms of LADA.

There were some limitations in this meta-analysis. First, heterogeneity was detected for polymorphisms rs231775 and rs3087243 in the overall population analyses for LADA, thus the random-effects model was used. In subsequent sub-group analysis, reduced tendency of heterogeneity was observed in Asians, which indicated the ethnicity might partially explain the heterogeneity. However, other unidentified factors may still contribute to the heterogeneity of included studies. Second, the number of relevant studies was relatively limited, especially in Asians and Africans, therefore, more replication studies are warranted. Third, our results were drawn based on unadjusted data and failed to adjust baseline parameters of participants. Although the methodology quality of included studies was good, the confounding factors may influence the authenticity of our results. Finally, publication bias was detected in this meta-analysis. Although we performed trim and fill method to evaluate the potential missing studies, the results may still be influenced to some extent. Taken together, the present results should be interpreted with caution.

Conclusion

In conclusion, our results indicated the polymorphisms rs231775 and rs3087243 may serve as genetic biomarkers of LADA. Further studies, especially in Asians and Africans are needed to confirm these findings.

Author’s Contributions ZX and ZZ participated in research design. HP, SL, GH, and XL selected the articles. HP performed the data analysis. The manuscript was drafted by HP and critically reviewer and discussed with other co-authors. All the authors read and approved the final manuscript.

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Data Availability All data generated or analyzed during this study are included in this published article.

Code Availability Not applicable.

Declarations

Conflict of interest The authors declare that they have no competing interest.

Ethical Approval Not applicable.

Informed Consent Not applicable.

Consent for Publication Not applicable.
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