Review Article

The Association between rs2292239 Polymorphism in ERBB3 Gene and Type 1 Diabetes: A Meta-Analysis

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Objectives. The purpose of this study was to explore the association between rs2292239 polymorphism in ERBB3 gene and type 1 diabetes (T1D).

Methods. A systematic search of studies on the association of rs2292239 polymorphism in ERBB3 gene with T1D susceptibility was conducted in PubMed, Web of science, Elsevier Science Direct, and Cochrane Library. Eventually, 9 published studies were included. The strength of association between rs2292239 polymorphism and T1D susceptibility was assessed by odds ratios (ORs) with its 95% confidence intervals (CIs).

Results. A total of 9 case-control studies, consisting of 5369 T1D patients and 6920 controls, were included in the meta-analysis. This meta-analysis showed significant association between ERBB3 rs2292239 polymorphism and T1D susceptibility in overall population (A vs. C, OR: 1.292, 95% CI= 1.224-1.364, \( P_{H} = 0.450 \), \( P_{H} \) is P value for the heterogeneity test). Similar results were found in subgroup analysis by ethnicity.

Conclusions. ERBB3 rs2292239 polymorphism is associated with T1D susceptibility and rs2292239-A allele is a risk factor for T1D. However, more large-scale studies are warranted to replicate our findings.

1. Introduction

Type 1 diabetes (T1D), a kind of autoimmune disease, is characterized by the progressive loss of insulin-secreting pancreatic beta cells [1–3]. The etiology of T1D is very complex, which is affected by both genetic and environmental factors. Although it may occur at any age, compared with other age groups, the incidence of T1D in children is higher. The incidence of T1D is also significantly different due to region and ethnicity [4, 5]. The destruction of pancreatic beta-cells and the lack of insulin lead to hyperglycemia. T1D patients require exogenous insulin to survival. Therefore, those affected patients are insulin-dependent for life [6, 7]. The complications with T1D are serious.

ERBB3 gene encodes erb-b2 receptor tyrosine kinase 3 (ErbB3), which is a member of the epidermal growth factor receptor (EGFR) family [8, 9]. ErbB3 interacts more specifically with PIK3 regulatory subunits, which transduce signals downstream to mTOR signaling pathway and in turn regulate insulin production in beta-cells and subsequent glucose metabolism [10]. ERBB3 gene is located on chromosome 12q13; rs2292239 SNP is located in intron 7 of ERBB3 gene [11, 12]. ERBB3 gene can also be expressed in pancreatic beta cells. ERBB3 gene is widely known for its role in cancer, but some studies have shown that the ERBB3 rs2292239 polymorphism might also play an important role in the pathogenesis of T1D due to immune regulation and apoptosis of beta-cells [13, 14].

Considering the results of ERBB3 gene polymorphism with T1D susceptibility are inconsistent [15], this discrepancy might be due to studies with small sample size, inadequate statistical power, ethnic differences, and publication bias. Therefore, it is necessary to conduct meta-analysis to explore this association.

2. Methods

2.1. Search Strategy. A systematic search of studies on the association of rs2292239 polymorphism in ERBB3 gene with T1D susceptibility was conducted in PubMed, Web of science,
Elsevier Science Direct, and Cochrane Library. Keywords for the search were as follows: (“ERBB3” or “rs2292239”) and (“Diabetes” or “T1D”) and (“polymorphism” or “variant” or “SNP” or “genotype” or “mutations”). The last search was updated on 15 January, 2019. All relevant studies were retrieved carefully.

2.2. Eligibility Criteria. The inclusion criteria were as follows: (I) studies evaluating the association between rs2292239 polymorphism in ERBB3 gene and T1D; (II) case-control studies; (III) studies based on humans; (IV) studies providing the detailed relevant genotype data of both case group and control group. Studies were excluded if (I) the study was a review, editorial, abstract, case report, or unpublished article; (II) there were nonhuman studies or animal experiments or cell experiments; (III) studies had no controls or no detailed relevant genotype data.

2.3. Data Extraction. The data of the eligible studies were extracted by one investigator (Mr. Wang). The following information was collected: name of first author, year of publication, country, ethnicity, genotyping methods, number of cases and controls in each study, genotype frequency in cases and controls, the value of $P$ in Hardy–Weinberg equilibrium (HWE), and other additional information. Different ethnicity descendants were classified as Caucasian and Asian.

2.4. Quality Assessment. The qualities of the included studies in this meta-analysis were assessed by another investigator (Dr. Pan). The quality assessment was based on the modified Newcastle-Ottawa Quality Assessment Scale (NOS). The scale consists of eight multiple-choice questions that involve subjects selection, comparability in cases and controls, and assessment of exposure. High-quality response earns a point, totaling up to nine points (the comparability question earns up to two points) [16]. The higher score indicates better quality.

2.5. Statistical Analysis. This meta-analysis was conducted following the guidelines from PRISMA and MOOSE statement [17, 18]. Hardy–Weinberg equilibrium (HWE) was evaluated for each study by Chi-square test in control groups. And $P > 0.05$ was considered as genetic balance in the study population. All statistical analysis was performed by Stata 12.0 software (Stata Corporation, College Station, TX, USA). OR and 95% CI were used to evaluate the strength of association between ERBB3 rs2292239 polymorphism and T1D susceptibility. The $\chi^2$ test-based Q statistic was generally used to assess the heterogeneity. Heterogeneity was recognized as statistically significant when $P_{H} < 0.05$. According to the value of $P_{H}$, we chose fixed-effects model or random-effects model. All subgroups were analyzed. Sensitivity analysis was used to evaluate the influence of individual study on the overall OR. Publication bias was assessed by Funnel's plot, Begg's test, and Egger's test. An asymmetric plot and the $P$ value of Egger's test or Begg's test less than 0.05 were considered as significant publication bias.

3. Results

3.1. Literature Search. A total of 82 studies were retrieved from PubMed, Web of science, Elsevier Science Direct, and Cochrane Library. Finally, 9 eligible studies were included in this meta-analysis. A flowchart of the included and excluded studies was shown in Figure 1.

3.2. Characteristics of the Included Studies. Table 1 showed the main features of those included studies. Those studies were published from 2009 to 2016. Nine studies involving 5369 T1D patients and 6920 controls were included in this meta-analysis. All included studies met the Hardy–Weinberg equilibrium.

3.3. Meta-Analysis of Association between rs2292239 Polymorphism and T1D Susceptibility. Meta-analysis indicated significant association between ERBB3 rs2292239 polymorphism and T1D susceptibility in the overall population (A vs. C, OR: 1.292, 95% CI= 1.224-1.364, $P_{H}=0.450$; AA vs. AC+CC, OR: 1.426, 95% CI=1.275-1.594, $P_{H}=0.636$; AA+AC vs. CC, OR: 1.374, 95% CI=1.277-1.479, $P_{H}=0.732$). Then, subgroup analysis was conducted according to ethnicity. In Caucasians, the significant association was identified in all genetic models (A vs. C, OR: 1.262, 95% CI=1.190-1.339, $P_{H}=0.762$; AA vs. AC+CC, OR: 1.395, 95% CI=1.239-1.570, $P_{H}=0.805$; AA+AC vs CC, OR: 1.332, 95% CI=1.228-1.446, $P_{H}=0.894$). In Asians, the significant association was also identified in all genetic models (A vs. C, OR: 1.455, 95% CI=1.273-1.663, $P_{H}=0.388$; AA vs. AC+CC, OR: 1.701, 95% CI=1.214-2.384, $P_{H}=0.183$; AA+AC vs. CC, OR: 1.560, 95% CI=1.322-1.841, $P_{H}=0.680$). The forest plots for rs2292239 with T1D were shown in Figure 2. The results of subgroup analysis were shown in Table 2.

3.4. Heterogeneity and Publication Bias. There was no significant heterogeneity across these studies ($P_{H} > 0.05$); therefore the fixed-effect models were performed. Publication bias was assessed by Begg’s funnel plot, Begg’s test, and Egger’s test. The Begg’s funnel plot showed that the shape of the funnel plot seemed symmetrical (Figure 3(a)). And there was no significant evidence of publication bias found in this meta-analysis (Table 3). The plot of sensitivity analysis was shown in Figure 3(b).

4. Discussion

The ERBB3 gene might play a key role in immune regulation and cytokine-induced pancreatic beta-cell apoptosis, which related to T1D pathogenesis [19–21]. The association between ERBB3 rs2292239 and T1D susceptibility has been identified in genome-wide association studies, such as TEDDY study [22–24]. However, only few studies evaluated ERBB3 gene polymorphism and T1D susceptibility in different ethnicities. Therefore, we conducted this meta-analysis. In this meta-analysis, 9 eligible case-control studies including 5369 T1D patients and 6920 controls were analyzed. The present study showed significant association between ERBB3 rs2292239 and T1D susceptibility.
### Table 1: The main features of included studies.

| Polymorphism | Author    | Year | Country | Ethnicity | Case               | Control          | Genotyping methods | No. of Cases/Controls | P for HWE | NOS score |
|--------------|-----------|------|---------|-----------|--------------------|------------------|--------------------|----------------------|-----------|-----------|
| rs2292239    | Nikitin AG| 2010 | Russia  | Caucasian | 19 (10.73)         | 85 (48.02)       | PCR-RFLP          | 177/205              | 0.165     | 5         |
|              | Reddy MV  | 2011 | USA     | Caucasian | 207 (14.44)       | 676 (47.14)      | TaqMan            | 1434/1864            | 0.993     | 7         |
|              | Kiani AK  | 2015 | Pakistan| Caucasian | 8 (8.79)          | 37 (40.66)       | TaqMan            | 91/100               | 0.855     | 7         |
|              | Awata T   | 2009 | Japan   | Asian     | 46 (6.26)         | 299 (40.68)      | TaqMan            | 735/621              | 0.591     | 6         |
|              | Sun C     | 2016 | China   | Asian     | 38 (10.44)        | 152 (41.76)      | TaqMan            | 364/719              | 0.992     | 5         |
|              | Wang H    | 2010 | USA     | Caucasian | 207 (14.44)       | 676 (47.14)      | TaqMan            | 1434/1865            | 0.991     | 6         |
|              | Maziarz M | 2015 | Sweden  | Caucasian | 44 (15.77)        | 134 (48.03)      | TaqMan            | 279/190              | 0.981     | 6         |
|              | Lemos NE  | 2017 | Brazil  | Caucasian | 78 (18.53)        | 178 (42.28)      | TaqMan            | 421/510              | 0.052     | 7         |
|              | Espino Paisan L | 2011 | Spain   | Caucasian | 82 (18.89)        | 225 (51.84)      | TaqMan            | 434/846              | 0.780     | 6         |

HWE: Hardy–Weinberg equilibrium; PCR-RFLP: polymerase chain-reaction fragment length polymorphism; NOS: Newcastle–Ottawa Quality Assessment Scale.
polymorphism and T1D susceptibility under all genetic models. Similar results were found in subgroup analysis by ethnicity.

The ERBB3 gene is located on chromosome 12q13; some studies have shown that the protective genotypes for T1D are associated with higher ERBB3 mRNA level in peripheral blood mononuclear cells (PBMCs). ErbB3 protein can be expressed on the surface of CD11c+ cells (dendritic cells and monocytes) in peripheral blood after stimulation. Subjects with protective genotypes have significantly higher percentages of ERBB3+ monocytes and dendritic cells, and the percentages of ERBB3+ cells are positively correlated with the ability of antigen presenting cells (APCs) to stimulate T cell proliferation [13]. Furthermore, as a member of the epidermal growth factor receptor (EGFR) family, ErbB3 is critical to the activation of the ERBB3-P13K-Akt cascade induced by EGFR/ERBB3 heterodimers. Deficiency or inhibition of the P13K pathway can lead to reduced numbers of regulatory T cells and autoimmunity [9, 10, 13]. It suggests that the ERBB3 gene might play an important role in potential T1D pathogenesis.

The rs2292239 SNP is located in intron 7 of ERBB3 gene and this SNP has significant functional effects. Some studies have shown that rs2292239 associates with residual beta-cell function and metabolic, ERBB3 dysfunction could decrease basal and cytokine-induced apoptosis. The rs2292239-A allele might change ERBB3 expression in immune cells and pancreatic beta-cells, influencing APC function, immunity, and beta-cells apoptosis [9]. Moreover, rs2292239 has been associated with the production of TID specific autoantibody [23]. Therefore, rs2292239 might be involved in TID pathogenesis and confer disease susceptibility.

Of course, there were some limitations in this meta-analysis. First, the number of included studies was not sufficient, which could not conduct comprehensive analysis. Second, our data of meta-analysis was from retrospective

**Table 2**: The results of meta-analysis.

| Polymorphism | Allelic model | Dominant model | Recessive model |
|--------------|---------------|----------------|-----------------|
| rs2292239    | A versus C    | AA versus AC+CC | AA+AC versus CC |
|              | OR (95% CI)   | OR (95% CI)    | OR (95% CI)    |
| overall      | 1.292(1.224-1.364) | 1.426(1.275-1.594) | 1.374(1.277-1.479) |
| P_H          | 0.450         | 0.636          | 0.732           |
| Ethnicity    |               |                |                 |
| Caucasian    | 1.262(1.190-1.339) | 1.395(1.239-1.570) | 1.332(1.228-1.446) |
|              | 0.762         | 0.805          | 0.894           |
| Asian        | 1.455(1.273-1.663) | 1.701(1.214-2.384) | 1.560(1.322-1.841) |
|              | 0.388         | 0.183          | 0.680           |

P_H: the value of P in the heterogeneity test.
Overall (I−squared = 0.0%, p = 0.636)
Subtotal (I−squared = 0.0%, p = 0.805)

Asian
Nikitin AG (2010)
Kiani AK (2015)
Awata T (2009)

Overall (I−squared = 43.5%, p = 0.183)
Subtotal (I−squared = 0.0%, p = 0.894)

Nikitin AG (2010)
Caucasian
Reddy MV (2011)
Wang H (2010)
Maziarz M (2015)

In conclusion, the present study indicates that ERBB3 rs2292239 polymorphism is associated with T1D susceptibility. However, it is still necessary to conduct more large-scale studies to further explore the pathogenetic mechanisms of ERBB3 in T1D.

Table 3: The results of publication bias.

| Polymorphism | Test of publication bias | Begg's test | Egger's test |
|--------------|--------------------------|-------------|--------------|
|              | Z            | P          | Z            | P          |
| Allelic model| -0.10        | 1.000      | -0.12        | 0.909      |
| Dominant model| 0.10        | 0.917      | 0.31         | 0.769      |
| Recessive model| 1.15        | 0.251      | -0.40        | 0.698      |

Conflicts of Interest
All members declare they have no conflicts of interest.

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Figure 3: Results of Beggs’s funnel plot and sensitivity analysis. (a) Beggs’s funnel plot of rs2292239-A with T1D. (b) The sensitivity analysis results of rs2292239-A with T1D.

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