ERBB3-rs2292239 as primary type 1 diabetes association locus among non-HLA genes in Chinese

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A R T I C L E  I N F O
Article history:
Received 15 March 2016
Revised 18 April 2016
Accepted 11 May 2016
Available online 12 May 2016

Keywords:
Type 1 diabetes
Genetic association
Single nucleotide polymorphism
ERBB3

A B S T R A C T
Type 1 diabetes (T1D) is an autoimmune disease that has strong contribution of genetic factors to its etiology. We aimed to assess the genetic association between non-HLA genes and T1D in a Chinese case-control cohort recruited from multiple centers consisting of 364 patients with T1D and 719 unrelated healthy children. We genotyped 55 single nucleotide polymorphisms (SNP) markers located in 16 non-HLA genes (VTNC1, PTN22, CTLA4, SUMO4, CYP27B1, IL2RB, INS, DHCR7, ERBB3, VDR, CYP27B1, CD69, CD276, PTNP2, UBASH3A, and IL2RB) using SNaPshot multiple single-base extension methods. After multivariate analysis and correction for multiple comparisons, we identified the SNP rs2292239 in ERBB3 gene were significantly associated with T1D. The frequency of the major G allele was significantly decreased in patients with T1D (68.8% in T1D vs 77.3% in controls; OR 0.65, 95% CI 0.53–0.79, P = 0.02), and the minor allele T was associated with an increased risk of T1D (OR 1.55, 95% CI 1.26–1.90, P = 0.02). Our haplotype analysis confirmed that rs2292239 was the primary T1D association locus in our current investigation. These results indicated that the ERBB3-rs2292239 was the primary T1D association locus among the investigated 55 SNPs in 16 non-HLA genes in Chinese Han population.

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1. Introduction

Type 1 diabetes (T1D) is an autoimmune disease influenced strongly by genetic factors (Atkinson et al., 2014). It was indicated that the life time concordance rate of T1D related autoimmunity in monozygotic twins can be as high as 65% (Redondo et al., 2008). The incidence of T1D varies remarkably among different ethnic/geographical populations and ranges from around 5/100,000 person-years in East Asian populations to ~40/100,000 person-years in some European populations (Patterson et al., 2009; Lu et al., 2014; Zhao et al., 2014). Although the incidence of T1D is rising worldwide, East Asian populations remained to have low incidence (Lu et al., 2014; Zhao et al., 2014). These facts suggested that the genetic heterogeneity between ethics can be one of the essential factors that form the incidence gap between populations (Ikegami et al., 2007).

Recent genome-wide association studies (GWAS) revealed many T1D association loci located in genes related to T1D autoimmunity, including PTNP22, CTLA4, IL2RA, INS, CD69, ERBB3, CYP27B1, PTNP2, UBASH3A and IL2RB (Barrett et al., 2009; Bradfield et al., 2011; Burren et al., 2011). In addition, there were other studies suggested that small ubiquitin like modifier 4 gene (SUMO4) (Guo et al., 2004); members of B7 family, B7-H1 (CD274), B7-H3 (CD276) and B7-H4 (VTNC1) (Dai et al., 2014); genes in vitamin D metabolism and signaling (DHCR7 and VDR) genes (Cooper et al., 2011) were also candidate genes involved in the pathogenesis of T1D.

Chinese Han population is among the East Asians with the lowest incidence of T1D around the world (Lu et al., 2014; Zhao et al., 2014). Similar to other East Asian populations, the Chinese Han maintains at a low level of T1D incidence despite rapid changing in environmental factors (Zha et al., 2014). In our previous study, we identified among Chinese Han that rs1217419 is the primary T1D association locus in PTNP22 and revealed the heterogeneity in PTNP22 association between Chinese Han and Caucasians (Pei et al., 2014). Nevertheless genetic studies using
candidate gene approach were likely to create spurious results even after statistical adjustment (Qu et al., 2005). Therefore in our current study aiming to minimize the insufficient protection against biased results, we used our multi-center cohort of patients with T1D in the Chinese Han population and multivariate analysis to investigate the genetic association of non-HLA genes by genotyping 55 single nucleotide polymorphisms (SNPs) in VTCN1, PTPN22, CTLA4, SUMO4, CD274, IL2RA, INS, DHCR7, ERBB3, VDR, CYP27B1, CD69, CD276, PTPN2, UBASH3A and IL2RB genes.

2. Subjects and methods

2.1. Study design and subjects

We recruited a case-control study cohort involving 364 patients with T1D and 719 unrelated healthy children. These subjects of Chinese Han origin were recruited in six medical centers across China as previously described in details (Pei et al., 2014). The study protocol was reviewed and approved by the medical ethics committee of the Children’s Hospital of Fudan University. Written informed consent was obtained from the legal guardian of every participant, or the participants themselves when legally applicable.

2.2. Single nucleotide polymorphisms and genotyping

We studied 55 SNPs that are mapped to genes previously implicated in the pathogenesis of T1D (described above in the introduction section and listed in Table 1). These SNPs were retrieved from the HapMap database (HapMap Public Release #27) with correlation coefficient $r^2 > 0.8$. We performed genotyping of those SNPs using genomic DNA extracted from 500 μl peripheral blood of the subjects (RelaXGene Blood DNA System, Tiangen, Beijing, China). The genotyping was carried out by SNPShot multiple single-base extension (SBE) reaction using purified PCR products amplified from genomic regions containing target SNPs as previously described (Pei et al., 2014). Genotype data were derived from the analysis on SBE products by an ABI PRISM 3130XL DNA sequencer (Applied Biosystems) and GeneMapper 4.0 (Applied Biosystems). The genotyping was performed at least in duplicates to avoid ambiguous genotype data.

2.3. Statistical analysis

We conducted data analysis using R (version 3.2.3, www.r-project.org). Deviation from the Hardy-Weinberg equilibrium (HWE) was first evaluated using Pearson’s $\chi^2$-test. The allelic association between each SNP and T1D were tested using logistic regression. P values <$0.05$ after Bonferroni correction were considered statistical significance. We conducted haplotype analysis using Haploview (version 4.1) with 10,000 permutations; a P-value <$0.05$ after Bonferroni correction was considered significant. Odds ratios (OR) and 95% confidence intervals (CI) of each haplotype were calculated using Fisher’s exact test by comparing the haplotype frequencies predicted by Haploview.

3. Results

3.1. Single marker association

We identified three SNPs in INS gene that had marginal association with T1D. The frequencies of rs689-T allele, rs1004446-G allele and rs3741208-G allele were higher in T1D as compared to controls (P value 0.01, 0.02 and 0.008 respectively). However these associations were no longer significant after Bonferroni correction (Table 2). In addition, we identified another two SNPs, PTPN2-rs2532151 and UBASH3A-rs3827233 had weak association with T1D. The frequencies of G allele in PTPN2-rs2542151 and G allele in UBASH3A-rs3827233 were slightly increased in patients with T1D than in controls but the significance lost after statistical correction for multiple comparisons.

| Chromosome | Nearest gene | Marker | MAF in CHB | MAF in CEU |
|------------|--------------|--------|------------|------------|
| 1p13.1 | VTCN1 | rs10158166 | 0.20 (T) | 0.12 (T) |
| 1p13.2 | PTPN22 | rs1217385 | 0.17 (C) | 0.44 (A) |
| 6q25 | SUMO4 | rs5570965 | 0.39 (C) | 0.36 (A) |
| 9p24 | CD274 | rs702275 | 0.29 (G) | 0.48 (T) |
| 10p15 | IL2RA | rs12251307 | 0.20 (T) | 0.10 (T) |
| 11p15.5 | INS | rs689 | 0.05 (T) | 0.24 (T) |
| 11q13.4 | DHCR7 | rs12785378 | 0.47 (G) | 0.27 (C) |
| 12p13 | CD69 | rs136563 | 0.47 (G) | NA |
| 12q13 | ERBB3 | rs2292239 | 0.27 (T) | 0.33 (T) |
| 13q33 | VDR | rs2282570 | 0.44 (A) | 0.41 (A) |
| 14q1.1 | CYP27B1 | rs4646536 | 0.24 (A) | 0.34 (G) |
| 15q23 | CD276 | rs11574483 | 0.11 (G) | 0.10 (A) |
| 18p11.3 | PTPN2 | rs478582 | 0.15 (C) | 0.46 (C) |
| 21q2.2 | UBASH3A | rs2277998 | 0.40 (G) | 0.42 (A) |
| 22q13.1 | IL2RB | rs228942 | 0.26 (T) | 0.16 (T) |

Abbreviations: SNP: single nucleotide polymorphism; T1D: type 1 diabetes; MAF: minor allele frequency; MAF data were derived from Hapmap database (HapMap Public Release #27) and dbSNP build 146; CHB: Han Chinese in Beijing, China; CEU: Utah Residents with Northern and Western European Ancestry.

Our results showed that the SNP rs2292239 in ERBB3 gene were strongly associated with T1D. The G allele in rs2292239 conferred protection against T1D (Table 2). The frequency of the major G allele was significantly decreased in patients with T1D (68.8% in T1D vs 77.3% in controls, OR 0.65, 95% CI 0.53–0.79, Pcorr = 0.02), and the minor allele was associated with an increased risk of T1D (OR 1.55, 95% CI 1.26–1.90, Pcorr = 0.02).

3.2. Haplotype association

To investigate whether there was combinational effect of SNPs that further affected the association between gene and T1D, we conducted haplotype analysis using genotyping data of the above identified four
genes (\textit{INS}, \textit{PTPN2}, \textit{UBASH3A} and \textit{ERBB3}). Our results showed that the haplotypes in \textit{INS}, \textit{PTPN2} and \textit{UBASH3A} genes were not associated with T1D (Table 3). However the \textit{ERBB3} haplotype (\textit{rs2292239}, \textit{rs705708} and \textit{rs2292238}) were significantly associated with T1D. After Bonferroni correction, the G-G-A haplotype were significantly less frequent in patients with T1D than in controls (OR = 0.71; Pcorr = 0.03) and the T-G-A haplotype was positively associated with T1D (OR = 1.53; Pcorr = 0.03).

### 4. Discussion

In this study, we jointly analyzed the association between type 1 diabetes (T1D) and 55 SNPs in 16 non-HLA candidate genes. Our results showed that in the Chinese Han population, after using a relative large sized sample and multivariate analysis, the genetic association between non-HLA genes and T1D was located primarily in the \textit{ERBB3} gene.

The association between \textit{ERBB3}-rs2292239 and T1D has been identified in large scaled studies in many populations, including Caucasians (allelic OR 1.3) (Barrett et al., 2009; Bradfield et al., 2011; Burren et al., 2011), Japanese (allelic OR 1.5) (Yamashita et al., 2011) and Pakistani (Kiani et al., 2015). Similar to studies in Asian populations, we confirmed that rs2292239 in \textit{ERBB3} was one of the loci with the most significant T1D association among non-HLA genes (Yamashita et al., 2011; Kiani et al., 2015). The \textit{ERBB3} gene encodes erb-b2 receptor tyrosine kinase 3 (Erbb3), a member of the epidermal growth factor receptor (EGFR) family (Avraham and Yarden, 2011). Unlike other members in the EGFR family, Erbb3 interacts more specifically with PK3 regulatory subunits (Jones et al., 2006), which transduce signals downstream to mTOR signaling pathway and in turn regulate insulin production in β-cells and subsequent glucose metabolism (Senniappan et al., 2014). However, the pathogenic role of the intronic \textit{ERBB3}-rs2292239 in T1D is still obscured since it had no apparent effects on \textit{ERBB3} expression in previous systematic genotype-expression studies (Westra et al., 2013; Consortium, 2015). Although our haplotype analysis revealed that the primary T1D association among the three investigated SNPs in \textit{ERBB3} was located in rs2292239, recent finer mapping of association surrounding \textit{ERBB3} in European population indicated that the association of rs2292239 can be secondary to adjacent SNPs such as rs2271189 and rs1117147 (Keene et al., 2012). Whether these findings apply to East Asian population is still awaiting confirmation from future studies with higher genetic coverage over the \textit{ERBB3} region.

After recent large genetic association studies conducted in Caucasian populations, nearly 60 T1D risk loci have been identified (Barrett et al., 2009; Bradfield et al., 2011; Burren et al., 2011). While these outstanding studies greatly unveiled the underlying mechanism of T1D pathogenesis, replication of their findings in East Asian populations sometimes leads to

### Table 2

Allele and genotype frequencies of SNPs with significant association in patients with T1D and healthy controls.

| SNP         | Allele/Genotype | T1D (%) n = 364 | Controls (%) n = 719 | OR (95%CI) | P value | Pcorr |
|-------------|-----------------|-----------------|----------------------|------------|---------|-------|
| \textit{INS}-rs689 | T               | 98.5            | 95.2                 | 3.16 (1.65–6.68) | 0.01     | NS    |
|             | A               | 1.5             | 4.8                  | 0.32 (0.15–0.61) | 0.07     |       |
|             | TT              | 97.2            | 90.5                 | 3.61 (1.82–7.97) | 0.002    |       |
|             | TA              | 2.5             | 9.5                  | 0.25 (0.11–0.51) | 0.0007   |       |
|             | AA              | 0.3             | 0.0                  | NA         | NA      |       |
| \textit{INS}-rs1004446 | G               | 75.8            | 71.3                 | 1.26 (1.02–1.56) | 0.02     | NS    |
|             | A               | 24.2            | 28.7                 | 0.79 (0.64–0.98) | 0.11     |       |
|             | GG              | 59.9            | 50.5                 | 1.47 (1.13–1.92) | 0.003    |       |
|             | GA              | 31.7            | 41.5                 | 0.65 (0.49–0.86) | 0.002    |       |
|             | AA              | 8.4             | 8.0                  | 1.06 (0.64–1.71) | 0.8      |       |
| \textit{INS}-rs3741208 | G               | 84.1            | 80.2                 | 1.31 (1.03–1.68) | 0.008    | NS    |
|             | A               | 15.9            | 19.8                 | 0.76 (0.60–0.98) | 0.003    | 0.02  |
| \textit{PTPN2}-rs2542151 | G               | 68.8            | 77.3                 | 0.65 (0.53–0.79) | 0.0003   |       |
|             | T               | 31.2            | 22.7                 | 1.55 (1.26–1.90) | 0.002    |       |
| \textit{INS}-rs689 | GG              | 47.9            | 59.8                 | 0.62 (0.48–0.81) | 0.0002   |       |
|             | GT              | 41.7            | 35.0                 | 1.33 (1.01–1.74) | 0.04     |       |
|             | TT              | 10.4            | 5.2                  | 2.12 (1.28–3.51) | 0.002    |       |
| \textit{PTPN2}-rs2542151 | T               | 78.5            | 83.5                 | 0.72 (0.57–0.91) | 0.006    | NS    |
|             | G               | 21.5            | 16.5                 | 1.39 (1.10–1.75) | 0.005    |       |
|             | TT              | 61.0            | 69.6                 | 0.68 (0.52–0.90) | 0.005    |       |
|             | GT              | 35.1            | 27.9                 | 1.40 (1.06–1.85) | 0.01     |       |
| \textit{UBASH3A}-rs3827233 | G               | 72.0            | 67.9                 | 1.22 (1.00–1.49) | 0.02     | NS    |
|             | C               | 28.0            | 32.1                 | 0.82 (0.67–1.00) | 0.3      |       |
|             | GC              | 51.0            | 45.6                 | 1.24 (0.95–1.61) | 0.1      |       |
|             | CC              | 42.1            | 44.5                 | 0.91 (0.70–1.18) | 0.5      |       |

Only significant results are shown. Abbreviations: SNP: single nucleotide polymorphism; T1D: type 1 diabetes; OR: odds ratio; 95% CI: 95% confidence interval; Pcorr: P value after Bonferroni correction (n = 55).

### Table 3

Haplotype frequencies of \textit{INS} and \textit{ERBB3} in patients with T1D and healthy controls.

| Gene       | Blocks | Haplotype | Haplotype frequency | OR (95% CI) | P value | Pcorr |
|------------|--------|-----------|---------------------|------------|---------|-------|
| \textit{INS} | rs689/rs7924316/rs1004446/rs3741208 | ATAG | 0.014 | 0.042 | 0.32 (0.10–0.84) | 0.005 | NS    |
|            |        | TTGG      | 0.558               | 0.486      | 1.34 (1.03–1.73) | 0.01 | NS    |
| \textit{ERBB3} | rs2292239/rs705708/rs2292238 | GCA | 0.417 | 0.502 | 0.71 (0.53–0.92) | 0.0006 | 0.03 |
|            |        | TCA       | 0.227               | 0.161      | 1.53 (1.10–2.13) | 0.0006 | 0.03 |

Only significant results are shown. Abbreviations: T1D: type 1 diabetes; OR: odds ratio; 95% CI: 95% confidence interval; Pcorr: P value after Bonferroni correction (n = 55).
inconsistent results (Yamashita et al., 2011; Tang et al., 2012; Kiani et al., 2015). In addition, the majority of these susceptible genes have association odds ratios below 1.75 in most case-control studies (Pociot et al., 2010). The genetic effect of each gene alone might be too trivial to ascertain by individual studies. Indeed, while compare to studies scaled similar to ours in the East Asian populations, we were only able to replicate the T1D association in ERBB3-rs2292239 however not in INS or IL2A (Yamashita et al., 2011). Meanwhile, using the current data with expanded genetic coverage, our results revoked the previously reported T1D association in HLA-INS/rs689) in the East Asian populations therefore studies results are more likely to be influenced by statistical stringency and other variations across study protocols. Furthermore, the weak association between non-HLA susceptible genes made the inter-ethnic association easily influenced by variations of allele distributions across populations (Thomson et al., 2007).

To the best of our knowledge, we have performed the largest genetic association study in Chinese patients with T1D. Although we endeavored to increased protection against biased results, after applying centralizing cohort recourses, multivariate statistical method and a strict adjustment, we believe that the current study is still limited to increased protection against biased results, after applying centralizing cohort recourses, multivariate statistical method and a strict adjustment, we believe that the current study is still limited to increased protection against biased results, after applying centralizing cohort recourses, multivariate statistical method and a strict adjustment, we believe that the current study is still limited. In addition, the majority of these susceptible genes have association odds ratios below 1.75 in most case-control studies (Pociot et al., 2010). The genetic effect of each gene alone might be too trivial to ascertain by individual studies. Indeed, while compare to studies scaled similar to ours in the East Asian populations, we were only able to replicate the T1D association in ERBB3-rs2292239 however not in INS or IL2A (Yamashita et al., 2011). Meanwhile, using the current data with expanded genetic coverage, our results revoked the previously reported T1D association in HLA-INS/rs689) in the East Asian populations therefore studies results are more likely to be influenced by statistical stringency and other variations across study protocols. Furthermore, the weak association between non-HLA susceptible genes made the inter-ethnic association easily influenced by variations of allele distributions across populations (Thomson et al., 2007).

Funding

This study received financial support from the Science and Technology Commission of Shanghai Municipality (STCSM 12410709700), National Chinese Twelfth Five Year Key Science and Technology Plan (2012BAIO9080) and National Natural Science Foundation of China (NSFC-81500959).

Conflicts of interest

The authors declare that there is no conflict of interest related to this article.

Acknowledgements

We are grateful to all the patients with type 1 diabetes, the healthy individuals and their families who participated in our study. CS thanks support from EFSID in the form of EFSID/DS/Lilly fellowship and support from Chinese Scholarship Council (2009610015).

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