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

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ABSTRACT

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 (VTCN1, PTPN22, CTLA4, SUMO4, CD274, IL2RA, INS, DHCR7, ERBB3, VDR, CYP27B1, CD69, CD276, PTPN2, 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 ethnics 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 PTPN22, CTLA4, IL2RA, INS, CD69, ERBB3, CYP27B1, PTPN2, 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 (VTCN1) (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 (Zhao et al., 2014). In our previous study, we identified among Chinese Han that rs1217419 is the primary T1D association locus in PTPN22 and revealed the heterogeneity in PTPN22 association between Chinese Han and Caucasians (Pei et al., 2014). Nevertheless genetic studies using

candidate gene approach were likely to create specious 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, Tiagen, Beijing, China). The genotyping was carried out by SNaPshot 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 χ^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 significant. 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.

Table 1
List of studied SNP markers in the candidate genes.

Chromosome	Nearest gene	Marker	MAF in CHB	MAF in CEU
1p13.1	VTCN1	rs10158166	0.20 (T)	0.12 (T)
		rs1937956	0.11 (T)	0.30 (T)
1p13.2	PTPN22	rs1217385	0.17 (C)	0.44 (A)
		rs2488457	0.33 (C)	0.22 (G)
		rs1217414	0.12 (A)	0.26 (A)
		rs1217419	0.14 (G)	0.48 (T)
		rs3765598	0.20 (T)	0.23 (T)
		rs2476601	0.02 (A)	0.12 (A)
2q33	CTLA4	rs5742909	0.11 (T)	0.08 (T)
		rs231775	0.30 (A)	0.39 (G)
		rs3087243	0.20 (G)	0.20 (G)
6q25	SUMO4	rs6570965	0.39 (C)	0.36 (A)
		rs237027	0.17 (T)	0.12 (T)
		rs763590	0.10 (T)	0.23 (T)
		rs600739	0.49 (A)	0.08 (G)
		rs237025	0.20 (G)	0.50 (G)
9p24	CD274	rs702275	0.29 (G)	0.48 (T)
		rs822338	0.45 (T)	0.23 (G)
		rs2282055	0.39 (T)	0.27 (G)
		rs6415794	0.12 (A)	0.48 (A)
		rs2297137	0.46 (A)	0.22 (A)
10p15	IL2RA	rs12251307	0.20 (T)	0.10 (T)
		rs4749955	0.34 (T)	0.44 (C)
		rs3118470	0.45 (T)	0.31 (T)
		rs706778	0.38 (C)	0.40 (T)
		rs2104286	0.11 (C)	0.25 (C)
11p15.5	INS	rs689	0.05 (T)	0.24 (T)
		rs7924316	0.46 (T)	0.41 (G)
		rs1004446	0.33 (A)	0.39 (A)
		rs3741208	0.17 (A)	0.36 (A)
11q13.4	DHCR7	rs12785878	0.47 (G)	0.27 (G)
12p13	CD69	rs3136563	0.47 (G)	NA
		rs4763879	0.48 (A)	0.38 (A)
		rs10844706	0.39 (A)	0.39 (A)
		rs917911	0.35 (T)	0.34 (G)
12q13	ERBB3	rs2292239	0.27 (T)	0.33 (T)
		rs705708	0.33 (A)	0.50 (A)
		rs2292238	0.38 (C)	0.41 (C)
12q13.11	VDR	rs2228570	0.44 (A)	0.41 (A)
		rs7975232	0.31 (A)	0.43 (C)
		rs1544410	0.04 (T)	0.44 (T)
12q14.1	CYP27B1	rs4646536	0.24 (A)	0.34 (G)
15q23	CD276	rs11574483	0.11 (A)	0.10 (A)
		rs3825859	0.11 (A)	0.07 (A)
18p11.3	PTPN2	rs478582	0.15 (C)	0.46 (C)
		rs2542157	0.26 (G)	0.43 (G)
		rs2542151	0.15 (G)	0.12 (G)
21q22.3	UBASH3A	rs2277798	0.40 (G)	0.42 (A)
		rs2277800	0.14 (T)	0.04 (T)
		rs9976767	0.28 (G)	0.40 (G)
		rs3827233	0.33 (C)	0.41 (C)
		rs2839519	0.16 (A)	0.11 (A)
22q13.1	IL2RB	rs228942	0.26 (T)	0.16 (T)
		rs228941	0.37 (G)	0.31 (G)

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 T 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

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
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)		
	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	
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)		
	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	
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)		
	GG	70.5	64.3	1.33 (1.00–1.76)	0.05	
	GA	27.3	31.8	0.81 (0.60–1.07)	0.1	
	AA	2.2	3.9	0.56 (0.22–1.28)	0.2	
ERBB3-rs2292239	G	68.8	77.3	0.65 (0.53–0.79)	0.0003	0.02
	T	31.2	22.7	1.55 (1.26–1.90)		
	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	
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)		
	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	
	GG	3.9	2.5	1.58 (0.72–3.41)	0.3	
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)		
	GG	51.0	45.6	1.24 (0.95–1.61)	0.1	
	GC	42.1	44.5	0.91 (0.70–1.18)	0.5	
	CC	6.9	9.9	0.68 (0.40–1.11)	0.1	

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).

genes (INS, PTPN2, UBASH3A and ERBB3). Our results showed that the haplotypes in INS, PTPN2 and UBASH3A genes were not associated with T1D (Table 3). However the ERBB3 haplotype (rs2292239, rs705708 and 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 ERBB3 gene.

The association between 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 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 ERBB3 gene encodes erb-b2 receptor tyrosine kinase 3 (ErbB3), a member of the epidermal growth factor receptor (EGFR) family (Avraham and Yarden, 2011). Dislike other members in the EGFR family, ErbB3 interacts more specifically with PIK3 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 ERBB3-rs2292239 in T1D is still obscured since it had no apparent effects on 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 ERBB3 was located in rs2292239, recent finer mapping of association surrounding ERBB3 in European population indicated that the association of rs2292239 can be secondary to adjacent SNPs such as rs2271189 and rs11171747 (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 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 3
Haplotype frequencies of INS and ERBB3 in patients with T1D and healthy controls.

Gene	Blocks	Haplotype	Haplotype frequency		OR (95% CI)	P value	Pcorr
			T1D n = 364	Controls n = 719			
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
ERBB3	rs2292239/rs705708/rs2292238	GGA	0.417	0.502	0.71 (0.55–0.92)	0.0006	0.03
		TGA	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 *PTPN22* (Pei et al., 2014). In addition, we did not confirm other common T1D candidate genes such as *CTLA4*, *VDR* and *SUMO4*. Reasons for these discrepancies can be partly subjected to the rarity of minor alleles (such as *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 statistical adjustment, we believe that the current study is still limited in sample size to reach convincing statistical power to ascertain the association of alleles with lower frequencies. Despite the low incidence of T1D in East Asians creates a difficulty for studies to increase sample size, future investigations in these populations should recruit more subjects and involving larger scale of genetic regions in order to forge the genetic association of T1D in these populations.

In conclusion, the results of our genetic analysis in Chinese Han population showed that the *ERBB3*-rs2292239 was the primary T1D association locus among the investigated 55 SNPs in 16 non-*HLA* genes.

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Conflicts of interest

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

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References

Atkinson, M.A., Eisenbarth, G.S., Michels, A.W., 2014. Type 1 diabetes. Lancet 383, 69–82.

Avraham, R., Yarden, Y., 2011. Feedback regulation of EGFR signalling: decision making by early and delayed loops. Nat. Rev. Mol. Cell Biol. 12, 104–117.

Barrett, J.C., Clayton, D.G., Concannon, P., Akolkar, B., Cooper, J.D., Erlich, H.A., Julier, C., Morahan, G., Nerup, J., Nierras, C., Plagnol, V., Pociot, F., Schuilenburg, H., Smyth, D.J., Stevens, H., Todd, J.A., Walker, N.M., Rich, S.S., Type 1 Diabetes Genetics, C., 2009. Genome-wide association study and meta-analysis find that over 40 loci affect risk of type 1 diabetes. Nat. Genet. 41, 703–707.

Bradfield, J.P., Qu, H.Q., Wang, K., Zhang, H., Sleiman, P.M., Kim, C.E., Mentch, F.D., Qiu, H., Glessner, J.T., Thomas, K.A., Frackelton, E.C., Chiavacci, R.M., Imielinski, M., Monos, D.S., Pandey, R., Bakay, M., Grant, S.F., Polychronakos, C., Hakonarson, H., 2011. A genome-wide meta-analysis of six type 1 diabetes cohorts identifies multiple associated loci. PLoS Genet. 7, e1002293.

Burren, O.S., Adlem, E.C., Achuthan, P., Christensen, M., Coulson, R.M., Todd, J.A., 2011. T1DBase: update 2011, organization and presentation of large-scale data sets for type 1 diabetes research. Nucleic Acids Res. 39, D997–1001.

Consortium, G.T., 2015. Human genomics. The genotype-tissue expression (GTEx) pilot analysis: multitissue gene regulation in humans. Science 348, 648–660.

Cooper, J.D., Smyth, D.J., Walker, N.M., Stevens, H., Burren, O.S., Wallace, C., Greissl, C., Ramos-Lopez, E., Hypponen, E., Dunger, D.B., Spector, T.D., Ouwehand, W.H., Wang, T.J., Badenhoop, K., Todd, J.A., 2011. Inherited variation in vitamin D genes is associated with predisposition to autoimmune disease type 1 diabetes. Diabetes 60, 1624–1631.

Dai, S., Jia, R., Zhang, X., Fang, Q., Huang, L., 2014. The PD-1/PD-Ls pathway and autoimmune diseases. Cell. Immunol. 290, 72–79.

Guo, D., Li, M., Zhang, Y., Yang, P., Eckenrode, S., Hopkins, D., Zheng, W., Purohit, S., Podolsky, R.H., Muir, A., Wang, J., Dong, Z., Brusko, T., Atkinson, M., Pozzilli, P., Zeidler, A., Raffel, L.J., Jacob, C.O., Park, Y., Serrano-Rios, M., Larrad, M.T., Zhang, Z., Garchon, H.J., Bach, J.F., Rotter, J.I., She, J.X., Wang, C.Y., 2004. A functional variant of SUMO4, a new I kappa B alpha modifier, is associated with type 1 diabetes. Nat. Genet. 36, 837–841.

Ikegami, H., Kawabata, Y., Noso, S., Fujisawa, T., Ogihara, T., 2007. Genetics of type 1 diabetes in Asian and Caucasian populations. Diabetes Res. Clin. Pract. 77 (Suppl. 1), S116–S121.

Jones, R.B., Gordus, A., Krall, J.A., MacBeath, G., 2006. A quantitative protein interaction network for the ErbB receptors using protein microarrays. Nature 439, 168–174.

Keene, K.L., Quinlan, A.R., Hou, X., Hall, I.M., Mychaleckyj, J.C., Onengut-Gumuscu, S., Concannon, P., 2012. Evidence for two independent associations with type 1 diabetes at the 12q13 locus. Genes Immun. 13, 66–70.

Kiani, A.K., John, P., Bhatti, A., Zia, A., Shahid, G., Akhtar, P., Wang, X., Demirci, F.Y., Kamboh, M.I., 2015. Association of 32 type 1 diabetes risk loci in Pakistani patients. Diabetes Res. Clin. Pract. 108, 137–142.

Lu, C.L., Shen, H.N., Chen, H.F., Li, C.Y., 2014. Epidemiology of childhood type 1 diabetes in Taiwan, 2003 to 2008. Diabet. Med. 31, 666–673.

Patterson, C.C., Dahlquist, G.G., Gyurus, E., Green, A., Soltesz, G., 2009. Incidence trends for childhood type 1 diabetes in Europe during 1989–2003 and predicted new cases 2005-20: a multicentre prospective registration study. Lancet 373, 2027–2033.

Pei, Z., Chen, X., Sun, C., Du, H., Wei, H., Song, W., Yang, Y., Zhang, M., Lu, W., Cheng, R., Luo, F., 2014. A novel single nucleotide polymorphism in the protein tyrosine phosphatase N22 gene (PTPN22) is associated with type 1 diabetes in a Chinese population. Diabet. Med. 31, 219–226.

Pociot, F., Akolkar, B., Concannon, P., Erlich, H.A., Julier, C., Morahan, G., Nierras, C.R., Todd, J.A., Rich, S.S., Nerup, J., 2010. Genetics of type 1 diabetes: what's next? Diabetes 59, 1561–1571.

Qu, H., Bharaj, B., Liu, X.Q., Curtis, J.A., Newhook, L.A., Paterson, A.D., Hudson, T.J., Polychronakos, C., 2005. Assessing the validity of the association between the SUMO4 M55V variant and risk of type 1 diabetes. Nat. Genet. 37, 111–112 (author reply 112-3).

Redondo, M.J., Jeffrey, J., Fain, P.R., Eisenbarth, G.S., Orban, T., 2008. Concordance for islet autoimmunity among monozygotic twins. N. Engl. J. Med. 359, 2849–2850.

Senniappan, S., Alexandrescu, S., Tatevian, N., Shah, P., Arya, V., Flanagan, S., Ellard, S., Rampling, D., Ashworth, M., Brown, R.E., Hussain, K., 2014. Sirolimus therapy in infants with severe hyperinsulinemic hypoglycemia. N. Engl. J. Med. 370, 1131–1137.

Tang, S., Peng, W., Wang, C., Tang, H., Zhang, Q., 2012. Association of the PTPN22 gene (+ 1858C/T, − 1123G/C) polymorphisms with type 1 diabetes mellitus: a systematic review and meta-analysis. Diabetes Res. Clin. Pract. 97, 446–452.

Thomson, G., Valdes, A.M., Noble, J.A., Kockum, I., Grote, M.N., Najman, J., Erlich, H.A., Cucca, F., Pugliese, A., Steenkiste, A., Dorman, J.S., Caillat-Zucman, S., Hermann, R., Ilonen, J., Lambert, A.P., Bingley, P.J., Gillespie, K.M., Lernmark, A., Sanjeevi, C.B., Ronningen, K.S., Undlien, D.E., Thorsby, E., Petrone, A., Buzzetti, R., Koeleman, B.P., Roep, B.O., Saruhan-Direskeneli, G., Uyar, F.A., Gunoz, H., Gorodezky, C., Alaez, C., Boehm, B.O., Mlynarski, W., Ikegami, H., Berrino, M., Fasano, M.E., Dametto, E., Israel, S., Brautbar, C., Santiago-Cortes, A., Frazer de Llado, T., She, J.X., Bugawan, T.L., Rotter, J.I., Raffel, L., Zeidler, A., Leyva-Cobian, F., Hawkins, B.R., Chan, S.H., Castano, L., Pociot, F., Nerup, J., 2007. Relative predispositional effects of HLA class II DRB1-DQB1 haplotypes and genotypes on type 1 diabetes: a meta-analysis. Tissue Antigens 70, 110–127.

Westra, H.J., Peters, M.J., Esko, T., Yaghootkar, H., Schurmann, C., Kettunen, J., Christiansen, M.W., Fairfax, B.P., Schramm, K., Powell, J.E., Zhernakova, A., Zhernakova, D.V., Veldink, J.H., Van den Berg, L.H., Karjalainen, J., Withoff, S., Uitterlinden, A.G., Hofman, A., Rivadeneira, F., t Hoen, P.A., Reinmaa, E., Fischer, K., Nelis, M., Milani, L., Melzer, D., Ferrucci, L., Singleton, A.B., Hernandez, D.G., Nalls, M.A., Homuth, G., Nauck, M., Radke, D., Volker, U., Perola, M., Salomaa, V., Brody, J., Suchy-Dicey, A., Gharib, S.A., Enquobahrie, D.A., Lumley, T., Montgomery, G.W., Makino, S., Prokisch, H., Herder, C., Roden, M., Grallert, H., Meitinger, T., Strauch, K., Li, Y., Jansen, R.C., Visscher, P.M., Knight, J.C., Psaty, B.M., Ripatti, S., Teumer, A., Frayling, T.M., Metspalu, A., van Meurs, J.B., Franke, L., 2013. Systematic identification of trans eQTLs as putative drivers of known disease associations. Nat. Genet. 45, 1238–1243.

Yamashita, H., Awata, T., Kawasaki, E., Ikegami, H., Tanaka, S., Maruyama, T., Shimada, A., Nakanishi, K., Takahashi, K., Kobayashi, T., Kawabata, Y., Miyashita, Y., Kurihara, S., Morita-Ohkubo, T., Katayama, S., Japanese Study Group on Type 1 Diabetes, G., 2011. Analysis of the HLA and non-HLA susceptibility loci in Japanese type 1 diabetes. Diabetes Metab. Res. Rev. 27, 844–848.

Zhao, Z., Sun, C., Wang, C., Li, P., Wang, W., Ye, J., Gu, X., Wang, X., Shen, S., Zhi, D., Lu, Z., Ye, R., Cheng, R., Xi, L., Li, X., Zheng, Z., Zhang, M., Luo, F., 2014. Rapidly rising incidence of childhood type 1 diabetes in Chinese population: epidemiology in Shanghai during 1997–2011. Acta Diabetol.