The Influence of Type 1 Diabetes Genetic Susceptibility Regions, Age, Sex, and Family History to the Progression from Multiple Autoantibodies to Type 1 Diabetes: A TEDDY Study Report

Running Title: Progressing from Multiple Autoantibodies to T1D

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Abstract

This paper seeks to determine whether factors related to autoimmunity risk remain significant after the initiation of two or more diabetes-related autoantibodies and continue to contribute to T1D risk among autoantibody positive children in The Environmental Determinants of Diabetes in the Young (TEDDY) study. Characteristics included are age at multiple autoantibody positivity, sex, selected high-risk HLA-DR-DQ genotypes, relationship to a family member with T1D, autoantibody at seroconversion, INS gene (rs1004446_A), and non-HLA gene polymorphisms identified by the Type 1 Diabetes Genetics Consortium. The risk of progression to T1D was not different among those with or without a family history of T1D (p=0.39) nor HLA-DR-DQ genotypes (p=0.74). Age at developing multiple autoantibodies (HR=0.96 per 1 month increase in age, 95% CI=0.95, 0.97, p<0.001) and the type of first autoantibody (when more than a single autoantibody was the first appearing indication of seroconversion [p=0.006]) were statistically significant. Female sex was also a significant risk factor (p=0.03). Three SNPs were associated with increased diabetes risk (rs10517086_A, [p=0.03], rs1534422_G, [p=0.006], and rs2327832_G in TNFAIP3 [p=0.03]), and one with decreased risk (rs1004446_A in INS, [p=0.006]). The TEDDY data suggest that non-HLA gene polymorphisms may play a different role in the initiation of autoimmunity than they do in progression to T1D once autoimmunity has appeared. The strength of these associations may be related to the age of the population and the high-risk HLA-DR-DQ subtypes studied.
Keywords:
Autoimmunity
Type 1 diabetes

Abbreviations
CI confidence intervals
DNA deoxyribonucleic acid
FDR first degree relative
GADA glutamic acid decarboxylase autoantibodies
GP general population
HLA human leukocyte antigen
HR hazard ratio
IA islet autoimmunity
IAA islet autoantibodies to insulin
IA-2A insulinoma antigen-2
IQR interquartile range
PCR polymerase chain reaction
PH proportional hazard
SNP single nucleotide polymorphism
T1D type 1 diabetes
T1DGC Type 1 Diabetes Genetics Consortium
Introduction

Type 1 diabetes (T1D) is an autoimmune disease preceded by the onset of one or more islet cell autoantibodies. The presence of two or more autoantibodies is generally felt to increase that risk significantly, especially among young children (1,2). Previous studies have shown that the incidence of T1D is increased in individuals with another family member known to have the disease (3,4). The risk of T1D is on the order of 10-fold higher in first degree relatives (FDR) of an individual with T1D as compared to the general population (GP). In addition, it is fairly well established that the incidence of autoimmunity and T1D in individuals with certain human leukocyte antigen (HLA) loci varies considerably with a gradient that spans the range of highly susceptible to protective loci (5,6). This paper examines T1D risk among those individuals who already have developed two or more islet cell autoantibodies (IA) in The Environmental Determinants of Diabetes in the Young (TEDDY) study, a large cohort of genetically at risk individuals followed from birth with uniform sampling from three months of age onwards (7,8). It seeks to determine whether factors significant for autoimmunity risk remain significant after the initiation of autoimmunity and continue to contribute to our understanding of the highly variable rate of progression to T1D among autoantibody positive children.

Research Design and Methods

Participants. TEDDY is a prospective cohort study funded by the National Institutes of Health with the primary goal to identify environmental causes of T1D. It includes six clinical research centers - three in the US: Colorado, Georgia/Florida, Washington and...
three in Europe: Finland, Germany, and Sweden. Detailed study design and methods have been previously published (7-9). Written informed consents were obtained for all study participants from a parent or primary caretaker, separately, for genetic screening and participation in the prospective follow-up. The high-risk genotypes for participants screened from the general population were as follows: DRB1*04-DQA1*03-DQB1*03:02/DRB1*03-DQA1*05-DQB1*02:01 (DR3/4), DRB1*04-DQA1*03-DQB1*03:02/DRB1*04-DQA1*03-DQB1*03:02 (DR4/4), DRB1*04-DQA1*03-DQB1*03:02/DRB1*08-DQA1*04-DQB1*04:02 (DR4/8) and DRB1*03-DQA1*05-DQB1*02:01/DRB1*03-DQA1*05-DQB1*02:01 (DR3/3). Additional genotypes were included for first degree relatives (FDRs) of a subject with T1D: DRB1*04-DQA1*03-DQB1*03:02/DRB1*04-DQA1*03-DQB1*03:02 (DR4/4b), DRB1*04-DQA1*03-DQB1*01- DQA1*01-DQB1*05:01 (DR4/1), DRB1*04-DQA1*03-DQB1*03:02/DRB1*13-DQA1*01-DQB1*06:04 (DR4/13), DRB1*04-DQA1*03-DQB1*03:02/DRB1*09- DQA1*03-DQB1*03:03 (DR4/9), and DRB1*03-DQA1*05-DQB1*02:01/DRB1*09- DQA1*03-DQB1*03:03 (DR3/9). The HLA-DR-DQ genotype abbreviations shown in parentheses will be used throughout this paper. Genotyping was confirmed by reverse blot hybridization at the central HLA Reference Laboratory at Roche Molecular Systems, Oakland, CA [9], along with the INS-23Hph1 (rs689), CTLA4 T17A (rs231775) and PTPN22 R620W (rs2476601) SNP primer pairs. The study was approved by local Institutional Review or Ethics Boards and is monitored by an External Evaluation Committee formed by the National Institutes of Health.
SNP analysis was performed by the Center for Public Health Genomics at University of Virginia, using the Illumina Immunochip which is a custom array for genotyping of SNPs selected from regions of the human genome firmly associated with autoimmune diseases (11). The final selection of SNPs containing ~ 186 000 SNPs in 186 regions, for 12 autoimmune diseases was decided by the Immunochip Consortium. TEDDY previously examined whether any of 41 non-HLA SNPs previously shown to be associated with T1D conferred risk for IA (12). These SNPs were re-examined in relation to the risk of T1D from the time of development of multiple islet autoantibodies.

*Islet Autoantibodies.* Islet autoantibodies to insulin (IAA), glutamic acid decarboxylase (GADA) or insulinoma antigen-2 (IA-2A) were measured in two laboratories by radiobinding assays (7,8). In the U.S., all sera were assayed at the Barbara Davis Center for Childhood Diabetes at the University of Colorado Denver; in Europe, all sera were assayed at the University of Bristol, U.K. Both laboratories demonstrated high sensitivity and specificity as well as concordance (10). All positive islet autoantibodies and 5% of negative samples were re-tested in the other reference laboratory and deemed confirmed if concordant. Persistent islet autoimmunity was defined as confirmed positive autoantibodies to insulin, GAD65, or IA-2A in at least two consecutive samples.

*Statistical Methods.* Characteristics of those who progressed to T1D and those who did not are presented for descriptive purposes. Cox proportional hazards (PH) models were applied to examine factors related to the risk of progression from the detection of multiple autoantibodies to T1D. The magnitudes of the associations were described by
hazard ratios (HR) with 95% confidence intervals (CI). Adjustments for population stratification were made by using the top two principal components from the Immunochip SNP data as covariates in the proportional hazards model (15). Data were analyzed using the Statistical Analysis System software (version 9.4; SAS Institute, Cary, NC). Two-tailed p-values less than 0.05 were considered to be statistically significant. No adjustment in type 1 error was made for multiple comparisons except in the context of the multiple Cox regression model.

Results

TEDDY enrolled 8676 children at birth and has followed them quarterly for the appearance of autoantibodies and T1D. Follow up of children with one or more islet autoantibody continued on this schedule, whereas children who were autoantibody negative were followed semiannually after 4 years of age. Excluded from this analysis are 172 children who were either ineligible or whose autoantibody status was indeterminate. The median (interquartile range, IQR) age at last follow up was 8.0 (6.7-9.3) years.

As of June 30, 2016, 412 children (4.8%) have developed multiple persistent confirmed islet autoantibodies and, of these, 190 (46.1%) have progressed to T1D (Table 1). The median (IQR) duration of follow up from the appearance of multiple autoantibodies was 3.0 (1.4-5.1) years. The age at which multiple autoantibodies first appeared was associated with increased risk of progression to T1D (p<0.001), as was the appearance of multiple autoantibodies at first appearance (p=0.006). The risk to progress to T1D was not significantly different when the data were analyzed by country of residence, family
history, sex, and HLA-DR-DQ genotype (p not significant). A multiple Cox regression analysis of these same characteristics confirmed the lack of statistical significance associated with family history (FDR vs. GP) (Figure 1) (p=0.39) or HLA-DR-DQ genotype (p=0.74) (Figure 2). Relationship of the TEDDY child to the family member with T1D among the FDRs compared to GP was also not significantly different (offspring of father with T1D (p=0.29), mother (p=0.42) or sibling (p=0.96)) (Table 2). Age at multiple autoantibodies (HR=0.96 per 1 month increase in age, 95% CI 0.95, 0.97, p<0.001) and when more than a single autoantibody was first appearing indication of seroconversion (HR=1.66 compared to IAA only, p=0.006) were statistically significant (Figure 3). In the multiple Cox regression female (as compared to male) sex became a significant risk factor (HR=1.43, 95% CI 1.04, 1.96, p=0.03) (Figure 4).

Among those with multiple autoantibodies, SNPs rs10517086_A (p=0.03), rs1534422_G (p=0.006) and rs2327832_G in TNFAIP3 (p=0.03) were significantly associated with increased risk of progression to T1D and SNP rs1004446_A in INS (p=0.03) was associated with decreased risk (Table 2 and Figure 5). There was a significant interaction between the SNP rs2327832_G in TNFAIP3 and the type of first autoantibody (p=0.003), indicating much higher risk of T1D with rs2327832_G polymorphism in the subjects who had the appearance of multiple autoantibodies as the first indication of seroconversion (HR=2.37 95% CI 1.52 3.70, p<0.001) (Figure 6). No interaction was found between the other SNPs and first appearing autoantibody. A table of all SNPs included in this analysis appears in the Online Supplemental appendix.
Discussion

While HLA-DR-DQ haplotypes have been shown to be associated with the incidence of autoimmunity, our data does not show that it continues to be related to progression to T1D in the HLA-selected high-risk TEDDY cohort among those who have multiple diabetes related autoantibodies. As well, the risk of progression to T1D was not different among those with or without a family history of T1D, for the high-risk genotypes followed in TEDDY. TEDDY has previously shown (16) that, among those who initially seroconvert to 2 autoantibodies, family history of T1D is a significant risk factor for progression to T1D by 5 years of age, but not among those who initially seroconvert to 3 autoantibodies. The results reported herein, now with additional follow-up to a median of 8 years of age, indicate that family history is no longer significant among those with 2 or more antibodies from the time of becoming multiple autoantibody positive.

Despite the lack of association with HLA-DR-DQ, we did find three SNPs that were associated with increased diabetes risk and one associated with decreased risk. Only SNP rs1004446_A in INS was reported to be significantly protective SNP of T1D from birth in TEDDY overall and in this multiple autoantibody positive subset. The other SNPs tested were not significantly related to T1D in the multiple autoantibody positive population, despite their association with autoimmunity in TEDDY and diabetes in the Type 1 Diabetes Genetics Consortium (T1DGC) (13) suggesting a genetic contribution to progression to diabetes after the appearance of autoantibodies that might be different than in the initiation of autoimmunity.
Of note, the three SNPs associated with an increased diabetes risk in this population of children with multiple diabetes related autoantibodies were not associated with T1D in TEDDY overall despite their significant association reported by others (14). This might be due to the fact that the TEDDY study is limited to certain at risk HLA subgroups or that they play a role in progression of autoimmunity toward T1D, but not in initiation of autoimmunity. SNP rs1534422_G in *TNFAIP3* has also been recently shown to be associated with multiple sclerosis (MS) risk (17) which is also an auto-inflammatory disease with genomic-environmental risk factors involving the HLA locus. SNP rs2327832_G has been reported to be in with a risk factor for rheumatoid arthritis (18) and celiac disease (19,20), whereas SNP rs10517086_A has been shown to have an age-related association with IA with increased risk in children under age 2 (21).

Here we show evidence of increased risk for T1D in multiple autoantibody positive children. These findings are similar to those reported by Lempainen et al (22) in the Finnish Diabetes Prediction and Prevention (DIPP) study which also showed a lack of associated with FDR status or HLA and progression to diabetes, but a positive association with female sex in children positive for two islet autoantibodies. A difference in findings between the two studies is that the DIPP study reports a significant association of the *PTPN22* gene polymorphism with progression from multiple autoantibodies to T1D, whereas the TEDDY study does not. In contrast, the TEDDY study does find an association with the *INS* gene, but the DIPP does not. Similar to TEDDY, the *INS* gene, but not *PTPN22*, was among 5 genes that, together, stratified progression to disease in the German BABYDIAB and BABYDIET studies (23). The reported differences could be
related to the populations, since the Finnish population has a higher prevalence of the
*PTPN22* gene polymorphism than elsewhere. DIPP, DAISY and the German
BABYDIAB and BABYDIET studies (2,24) report similar findings with regard to
appearance of multiple autoantibodies at a young age and the excess risk associated with
female sex. Others have speculated a link between the observed protective effect of the
*INS* gene and immune tolerance through higher levels of expression in the thymus as a
plausible mechanism (25).

The TEDDY data suggest that non-HLA gene polymorphisms may play a different role
in the initiation of autoimmunity than they do in progression to T1D once autoimmunity
has appeared. The strength of these associations and even their direction (increased vs.
decreased risk) may vary by population and the nature of the other characteristics
included in multivariate models. While these results extend earlier TEDDY findings by
providing additional years of follow-up, it may be that the relationships described are all
age related. Cases of T1D diagnosed among older children may share the same
mechanisms and strengthen these findings or may be the result of other immunological
insults involving other exposures and gene-environmental interactions. Having already
published an age effect on the initiation of autoimmunity and differences in the pattern of
the types of autoantibodies that arise first (26), it is not inconceivable that there is also an
age related association of exposures and both HLA and non-HLA genes. Caution should
be exercised in generalizing the results presented here beyond the age range in which
they have been discovered and the selected HLA subgroups that constitute the TEDDY
population. As well, caution should be exercised in interpreting statistically significant
findings due to the number of comparisons that have been made. Adjusting the
significance level for multiple comparisons when conducting epidemiological research,
especially in the context of a multivariate analysis has both supporters (27) and detractors
(28,29). No matter what side of the argument the reader falls on, the associations reported
herein should be viewed in the larger context of the results of other studies and other
populations to be properly interpreted.

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study, proposed the analysis, interpreted the findings, and wrote the manuscript. X.L.
performed the analysis and contributed to the manuscript. Å.L., W.H., M.R., J-X.S., J.T.,
A.Z., and B.A. designed the study and reviewed/edited manuscript. J.K. and X.L. are the
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**Electronic supplementary material:** A complete list of the members of the TEDDY Study Group can be found in the online version of this article.
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| Characteristic                | Did not progress to T1D (%) | Progressed to T1D (%) |
|------------------------------|-----------------------------|-----------------------|
| Total n                      | 222 (54)                    | 190 (46)              |
| Country of residence n (%)   |                             |                       |
| US                           | 82 (59)                     | 57 (41)               |
| Finland                      | 53 (48)                     | 57 (52)               |
| Germany                      | 16 (44)                     | 20 (56)               |
| Sweden                       | 71 (56)                     | 56 (44)               |
| Family History of T1D n (%)  |                             |                       |
| General Population           | 171 (55)                    | 140 (45)              |
| FDR: Mother                  | 12 (50)                     | 12 (50)               |
| FDR: Father                  | 27 (50)                     | 27 (50)               |
| FDR: Sibling                 | 12 (52)                     | 11 (48)               |
| Gender n (%)                 |                             |                       |
| Female                       | 88 (49)                     | 92 (51)               |
| Male | 134 (58) | 98 (42) |
|------|----------|---------|
| HLA-DR-DQ genotypes n (%) | | |
| DR3/4 | 121 (52) | 110 (48) |
| DR4/4 | 46 (61) | 30 (39) |
| DR4/8 | 31 (56) | 24 (44) |
| DR3/3 | 16 (53) | 14 (47) |
| FDR Specific | 8 (40) | 12 (60) |
| Median (IQR) Age at multiple persistent confirmed IA (months) | 48 (31 -74) | 21 (15 -31) |
| Type of first autoantibody n (%) | | |
| GADA only | 85 (66) | 43 (34) |
| IAA only | 84 (53) | 76 (47) |
| 2+ autoantibodies | 49 (42) | 68 (58) |
| IA2A only | 4 (57) | 3 (43) |
Table 2

Cox regression analysis of risk factors for progression from multiple autoantibodies to type 1 diabetes. The top two principal components (PC1 and PC2) from the principal components analysis on Immunochip data were included as covariates to correct for population stratification.

| Factor                                  | HR (95% CI)         | p     |
|-----------------------------------------|---------------------|-------|
| Age at multiple autoantibodies onset (months) | 0.96 (0.95, 0.97)  | <0.001|
| HLA-DR-DQ genotype                      | 0.74                |       |
| DR3/4                                   | 1.24 (0.79, 1.93)  | 0.35  |
| DR4/4                                   | 1 [Reference]       |       |
| DR4/8                                   | 1.22 (0.68, 2.18)  | 0.50  |
| DR3/3                                   | 1.44 (0.70, 2.96)  | 0.32  |
| FDR specific                            | 1.58 (0.73, 3.41)  | 0.25  |
| Family history of T1D                   | 0.69                |       |
| FDR: Mother                             | 1.34 (0.66, 2.75)  | 0.42  |
| FDR: Father                             | 1.30 (0.80, 2.09)  | 0.29  |
| FDR: Sibling                            | 0.98 (0.48, 2.01)  | 0.96  |
| GP                                      | 1 [Reference]       |       |
| Type of first autoantibody              | 0.02                |       |
| GADA only                               | 1.16 (0.76, 1.78)  | 0.49  |
| IAA only                                | 1 [Reference]       |       |
| Variable                        | Odds Ratio (95% CI) | P-value |
|--------------------------------|---------------------|---------|
| 2+ autoantibodies              | 1.66 (1.15, 2.39)   | 0.006   |
| Sex                            |                     |         |
| Female                         | 1.43 (1.04, 1.96)   | 0.03    |
| Male                           | 1 [Reference]       |         |
| Country of residence           |                     | 0.84    |
| US                             | 1 [Reference]       |         |
| Finland                        | 1.05 (0.53, 2.10)   | 0.89    |
| Germany                        | 1.13 (0.59, 2.14)   | 0.71    |
| Sweden                         | 0.88 (0.58, 1.34)   | 0.55    |
| SNP rs1004446_A (INS)          | 0.71 (0.55, 0.91)   | 0.006   |
| SNP rs10517086_A               | 1.31 (1.03, 1.67)   | 0.03    |
| SNP rs1534422_G                | 1.39 (1.10, 1.76)   | 0.006   |
| SNP rs2327832_G (TNFAIP3)      | 1.34 (1.03, 1.74)   | 0.03    |
| PC1                            | 1.11 (0.91, 1.35)   | 0.32    |
| PC2                            | 0.96 (0.72, 1.28)   | 0.78    |
Figure legends:

Figure 1. Progression from multiple autoantibodies to type 1 diabetes by FDR status (p=0.39 from Cox regression).

Figure 2. Progression from multiple autoantibodies to type 1 diabetes by HLA-DR-DQ genotypes (p=0.74 from Cox regression). FDR-specific are DR4/4b, DR4/1, DR4/13, DR4/9, and DR3/9.

Figure 3. Progression from multiple autoantibodies to type 1 diabetes by type of first autoantibody (p=0.02 from Cox regression).

Figure 4. Progression from multiple autoantibodies to type 1 diabetes by sex (p=0.03 from Cox regression).

Figure 5. Progression from Multiple Autoantibodies by number of minor alleles of single nucleotide polymorphism within panels (a) rs10517086_A (p=0.03 from Cox regression), (b) rs1004446_A (p=0.006 from Cox regression), (c) rs1534422_G (p=0.006 from Cox regression), and (d) rs2327832_G (p=0.03 from Cox regression).

Figure 6. Progression from multiple autoantibodies to type 1 diabetes by number of minor alleles of SNP rs2327832_G in the subset of more than one autoantibody as first appearing autoantibody (p<0.001 from Cox regression).
Progression from multiple autoantibodies to type 1 diabetes by FDR status ($p=0.39$ from Cox regression).

167x120mm (300 x 300 DPI)
Progression from multiple autoantibodies to type 1 diabetes by HLA-DR-DQ genotypes (p=0.74 from Cox regression). FDR-specific are DR4/4b, DR4/1, DR4/13, DR4/9, and DR3/9.
Progression from multiple autoantibodies to type 1 diabetes by type of first autoantibody (p=0.02 from Cox regression).

178x120mm (300 x 300 DPI)
Progression from multiple autoantibodies to type 1 diabetes by sex (p=0.03 from Cox regression).

173x120mm (300 x 300 DPI)
Progression from Multiple Autoantibodies by number of minor alleles of single nucleotide polymorphism within panels (a) rs10517086_A (p=0.03 from Cox regression), (b) rs1004446_A (p=0.006 from Cox regression), (c) rs1534422_G (p=0.006 from Cox regression), and (d) rs2327832_G (p=0.03 from Cox regression).

260x195mm (300 x 300 DPI)
Progression from multiple autoantibodies to type 1 diabetes by number of minor alleles of SNP rs2327832_G in the subset of more than one autoantibody as first appearing autoantibody (p<0.001 from Cox regression).

169x120mm (300 x 300 DPI)
**Supplemental Table.** Cox regression analysis of the 41 type 1 diabetes risk loci on the risk of progression from multiple autoantibodies to type 1 diabetes. Cox model for each SNP was adjusted for age at multiple autoantibodies onset, HLA-DR-DQ genotype, sex, family history of T1D, type of first autoantibody and the top two principal components from the principal components analysis on TEDDY Immunochip data. The minor allele frequency (MAF) for the respective SNP was calculated from the study population.

| Chr   | SNP      | Gene of interest | Minor allele | MAF | HR (95% CI)       | p     |
|-------|----------|------------------|--------------|-----|-------------------|-------|
| 1p13.2| rs2476601| *PTPN22*         | A            | 0.18| 1.21 (0.88, 1.65) | 0.241 |
| 1p31.3| rs2269241| *PGM1*           | C            | 0.25| 0.91 (0.70, 1.18) | 0.472 |
| 1q31.2| rs2816316| *RGS1*           | C            | 0.18| 0.88 (0.67, 1.16) | 0.371 |
| 1q32.1| rs3024505| *IL10*           | A            | 0.16| 1.06 (0.81, 1.41) | 0.661 |
| 2p25.1| rs1534422|                  | G            | 0.47| 1.39 (1.10, 1.76) | 0.005 |
| 2q24.2| rs1990760| *IFIH1*          | C            | 0.38| 1.02 (0.82, 1.28) | 0.831 |
| 2q33.2| rs3087243| *CTLA4*          | A            | 0.38| 1.16 (0.94, 1.44) | 0.171 |
| 3p21.3| rs11711054| *CCR5*         | G            | 0.31| 1.04 (0.82, 1.31) | 0.772 |
| 4p15.2| rs10517086|                | A            | 0.33| 1.31 (1.03, 1.66) | 0.026 |
| 4q27  | rs4505848| *IL2*            | G            | 0.39| 1.19 (0.95, 1.49) | 0.122 |
| 5p13.2| rs6897932| *IL7R*           | T            | 0.27| 1.15 (0.89, 1.49) | 0.284 |
| 6q22.32| rs9388489| *C6orf173*       | G            | 0.45| 0.99 (0.78, 1.25) | 0.926 |
| 6q23.3| rs2327832| *TNFAIP3*        | G            | 0.20| 1.37 (1.06, 1.78) | 0.017 |
| 6q25.3| rs1738074| *TAGAP*          | T            | 0.40| 1.12 (0.90, 1.41) | 0.305 |
| 7p12.1| rs4948088| *COBL*           | A            | 0.03| 1.11 (0.62, 1.99) | 0.718 |
| 7p15.2| rs7804356| *SKAP2*          | C            | 0.20| 1.21 (0.91, 1.62) | 0.194 |
| 9p24.2| rs7020673| *GLIS3*          | C            | 0.48| 0.95 (0.76, 1.17) | 0.613 |
| 10p15.1| rs11258747| *PRKCQ*        | T            | 0.26| 1.04 (0.82, 1.32) | 0.749 |
| 10p15.1| rs12251307| *IL2RA*        | T            | 0.11| 0.99 (0.71, 1.39) | 0.957 |
| 10q23.31| rs10509540| *RNLS*         | C            | 0.25| 1.04 (0.80, 1.34) | 0.780 |
| 11p15.5| rs1004446| *INS*            | A            | 0.32| 0.75 (0.59, 0.96) | 0.021 |
| 11p15.5| rs7111341| *INS*            | T            | 0.23| 0.88 (0.67, 1.17) | 0.376 |
| 12p13.31| rs4763879| *CD69*           | A            | 0.40| 1.04 (0.84, 1.29) | 0.716 |
| 12q13.2| rs2292239| *ERBB3*          | T            | 0.39| 1.05 (0.83, 1.33) | 0.676 |
| Chromosome | SNP | Gene(s) | Gene Type | Beta (95% CI) | P-Value |
|------------|-----|---------|-----------|--------------|---------|
| 12q24.12   | rs3184504 | SH2B3 | T | 0.52 (0.79, 1.20) | 0.790   |
| 14q24.1    | rs1465788 | ZFP36L1,C14orf181 | T | 0.29 (0.84, 1.35) | 0.627   |
| 14q33.2    | rs4900384 | C14orf64 | G | 0.31 (0.67, 1.10) | 0.219   |
| 15q25.1    | rs3825932 | CTSH | T | 0.32 (0.63, 1.04) | 0.102   |
| 16p11.2    | rs4788084 | IL27 | T | 0.44 (0.86, 1.34) | 0.538   |
| 16p13.13   | rs12708716 | CLEC16A | G | 0.29 (0.90, 1.43) | 0.287   |
| 16q23.1    | rs7202877 | CTRB2 | G | 0.12 (0.74, 1.46) | 0.832   |
| 17p13.1    | rs16956936 | 2 genes | T | 0.13 (0.72, 1.44) | 0.913   |
| 17q12      | rs2290400 | ORMEL | T | 0.48 (0.79, 1.20) | 0.771   |
| 17q21.2    | rs7221109 | CCR7 | T | 0.38 (0.85, 1.32) | 0.620   |
| 18p11.21   | rs1893217 | PTPN2 | C | 0.18 (0.82, 1.49) | 0.517   |
| 18q22.2    | rs763361 | CD226 | T | 0.49 (0.95, 1.50) | 0.135   |
| 19q13.32   | rs425105 | PRKD2 | C | 0.15 (0.67, 1.26) | 0.601   |
| 20p13      | rs2281808 | SIRPG | T | 0.31 (0.91, 1.46) | 0.232   |
| 21q22.3    | rs11203203 | UBASH3A | A | 0.38 (0.83, 1.30) | 0.732   |
| 22q12.1    | rs5753037 | HORMAD2 | T | 0.37 (0.92, 1.49) | 0.202   |
| 22q13.1    | rs229541 | C1QTNF6 | A | 0.43 (0.84, 1.31) | 0.664   |
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