



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

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This article 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 type 1 diabetes (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 (T1DGC). The risk of progression to T1D was not different among those with or without a family history of T1D ($P = 0.39$) or HLA-DR-DQ genotypes ($P = 0.74$). Age at developing multiple autoantibodies (hazard ratio = 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 single nucleotide polymorphisms were associated with increased diabetes risk (rs10517086_A [$P = 0.03$], rs1534422_G [$P = 0.006$], and rs2327832_G [$P = 0.03$] in *TNFAIP3*) 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.

Type 1 diabetes (T1D) is an autoimmune disease preceded by the onset of one of more islet autoantibodies (IA). 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 (FDRs) of an individual with T1D as compared with the general population (GP). In addition, it is fairly well established that the incidence of autoimmunity and T1D in individuals with certain HLA loci varies considerably with a gradient that spans the range of highly susceptible to protective loci (5,6). This article examines T1D risk among those individuals who already have developed two or more IA in The Environmental Determinants of Diabetes in the Young (TEDDY) study, a large cohort of genetically

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*A complete list of the TEDDY Study Group can be found in the Supplementary Data online.

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Table 1—Characteristics of children who progressed from multiple autoantibodies to T1D and those who did not

	Did not progress to T1D	Progressed to T1D
Total, n (%)	222 (54)	190 (46)
Country of residence, n (%)		
U.S.	82 (59)	57 (41)
Finland	53 (48)	57 (52)
Germany	16 (44)	20 (56)
Sweden	71 (56)	56 (44)
Family history of T1D, n (%)		
GP	171 (55)	140 (45)
FDR: mother	12 (50)	12 (50)
FDR: father	27 (50)	27 (50)
FDR: sibling	12 (52)	11 (48)
Sex, 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)
Age at multiple persistent confirmed IA (months), median (IQR)	48 (31–74)	21 (15–31)
Type of first autoantibody, n (%)		
GADA only	85 (66)	43 (34)
IAA only	84 (53)	76 (47)
Two or more autoantibodies	49 (42)	68 (58)
IA-2A only	4 (57)	3 (43)
FDR-specific HLA-DR-DQ genotypes are DR4/4b, DR4/1, DR4/13, DR4/9, and DR3/9.		

at-risk individuals followed from birth with uniform sampling from 3 months of age onward (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 U.S. (Colorado, Georgia/Florida, and 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 GP 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 FDRs of a subject with T1D: DRB1*04-DQA1*03-DQB1*03:02/DRB1*04-DQA1*03-DQB1*02:02 (DR4/4b), DRB1*04-DQA1*03-DQB1*03:02/DRB1*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 article. 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) single nucleotide polymorphism (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 (10). 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 (11). These SNPs were reexamined in relation to the risk of T1D from the time of development of multiple IA.

IA

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, Aurora, CO; in Europe, all sera were assayed at the University of Bristol, Bristol, U.K. Both laboratories demonstrated high sensitivity and specificity as well as concordance (12). All positive IA and 5% of negative samples were retested 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 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% CI. Adjustments for population stratification were made by using the top two principal components from the Immunochip

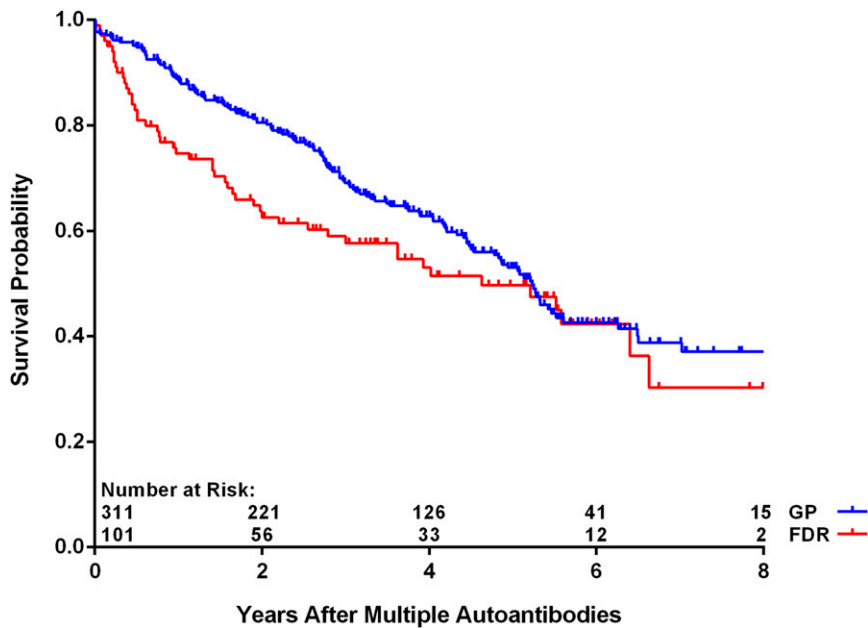


Figure 1—Progression from multiple autoantibodies to T1D by FDR status ($P = 0.39$ from Cox regression).

SNP data as covariates in the proportional hazards model (13). 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 8,676 children at birth and has followed them quarterly for the appearance of autoantibodies and

T1D. Follow-up of children with one or more IA 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 30 June 2016, 412 children (4.8%) have developed multiple persistent confirmed IA, and of these, 190 (46.1%) have progressed to T1D (Table 1). The median (IQR) duration of follow-up from the appearance of multiple

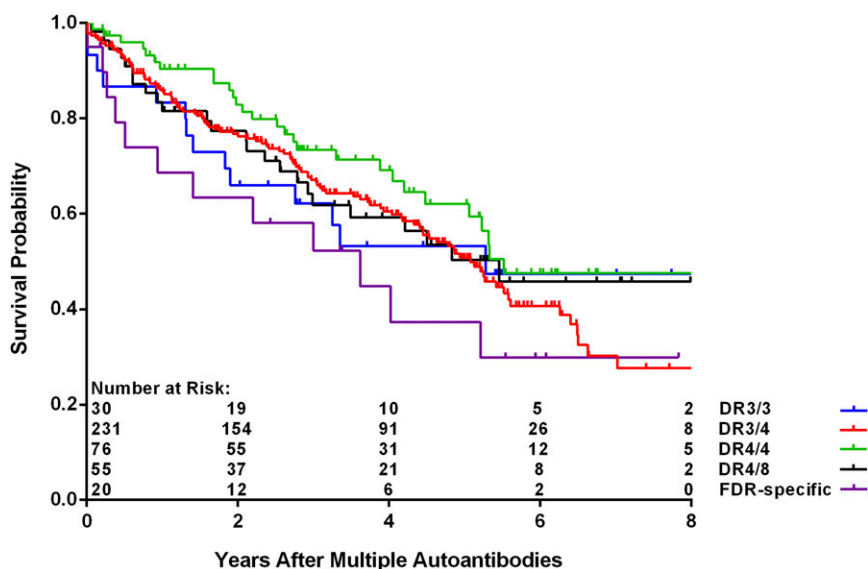


Figure 2—Progression from multiple autoantibodies to T1D by HLA-DR-DQ genotypes ($P = 0.74$ from Cox regression). FDR-specific HLA-DR-DQ genotypes are DR4/4b, DR4/1, DR4/13, DR4/9, and DR3/9.

Table 2—Cox regression analysis of risk factors for progression from multiple autoantibodies to T1D

	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]	
Two or more 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
U.S.	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 (<i>INS</i>)	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 (<i>TNFAIP3</i>)	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

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. FDR-specific HLA-DR-DQ genotypes are DR4/4b, DR4/1, DR4/13, DR4/9, and DR3/9.

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 ($P = \text{NS}$). A multiple Cox regression analysis of these same characteristics confirmed the lack of statistical significance associated with family history (FDR vs. GP) (Fig. 1) ($P = 0.39$) or HLA-DR-DQ genotype ($P = 0.74$) (Fig. 2). Relationship of the TEDDY child to the family member with T1D among the FDRs compared with 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 with IAA only [$P = 0.006$]) were statistically significant (Fig. 3). In the multiple Cox regression, female (as compared with male) sex became a significant risk factor (HR = 1.43; 95% CI 1.04, 1.96; $P = 0.03$) (Fig. 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* ($P = 0.006$) was associated with decreased risk (Table 2 and Fig. 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; $P < 0.001$) (Fig. 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 Supplementary Data.

DISCUSSION

Although HLA-DR-DQ haplotypes have been shown to be associated with the incidence of autoimmunity, our data do 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 (14) that family history of T1D is a significant risk factor for progression to T1D by 5 years of age among those who initially seroconvert to two autoantibodies, but not among those who initially seroconvert to three 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 two 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 a 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) (15), 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 (16). This might be due to the fact that the TEDDY study is limited to certain at-risk HLA subgroups

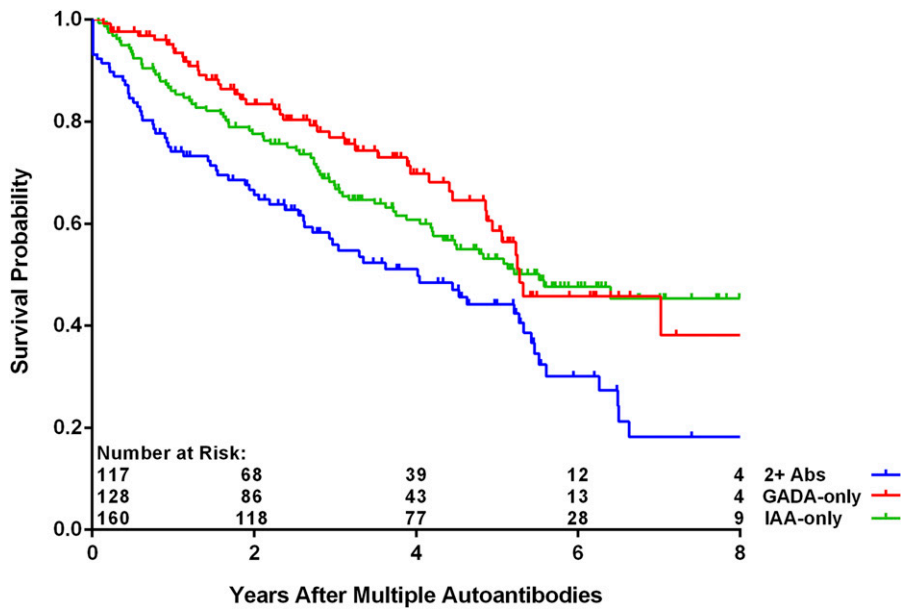


Figure 3—Progression from multiple autoantibodies to T1D by type of first autoantibody (Ab) ($P = 0.02$ from Cox regression).

or that the SNPs 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 risk (17), which is also an autoinflammatory disease with gene–environment risk factors involving the HLA locus. SNP rs2327832_G has been reported to be 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 the age of 2 years (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 that also showed a lack of association 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 the 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

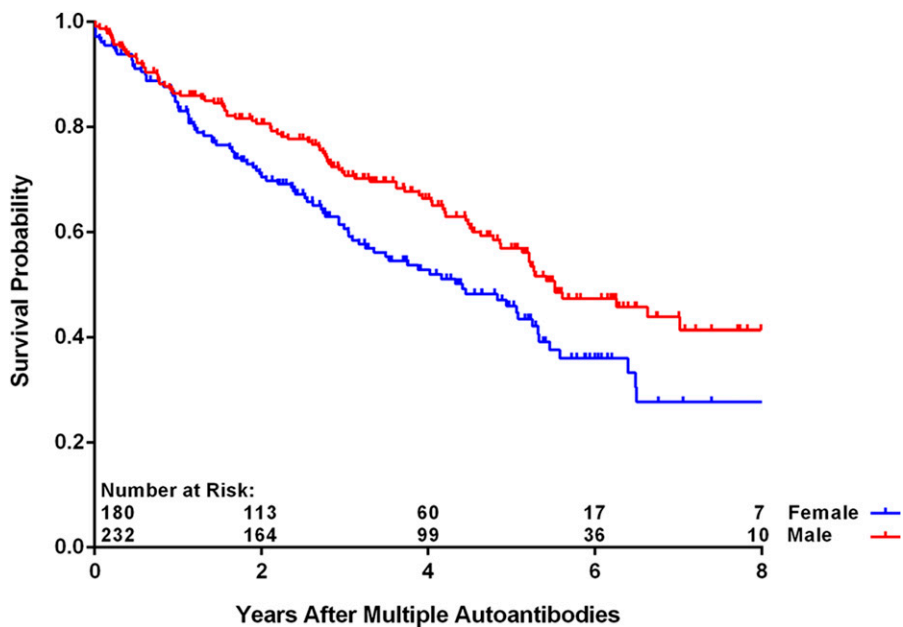


Figure 4—Progression from multiple autoantibodies to T1D by sex ($P = 0.03$ from Cox regression).

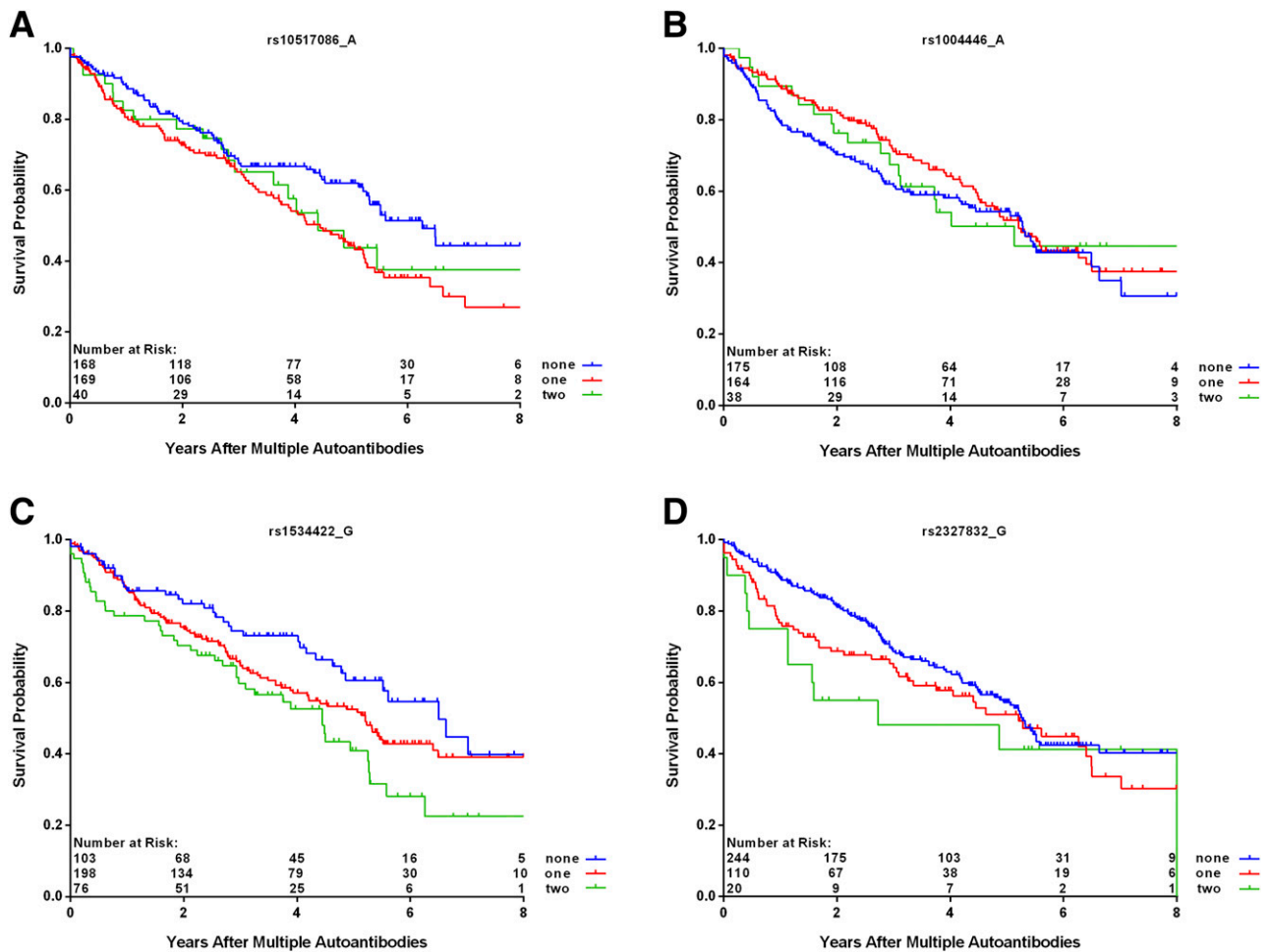


Figure 5—Progression from multiple autoantibodies by number of minor alleles of SNPs within panels rs10517086_A ($P = 0.03$ from Cox regression) (A), rs1004446_A ($P = 0.006$ from Cox regression) (B), rs1534422_G ($P = 0.006$ from Cox regression) (C), and rs2327832_G ($P = 0.03$ from Cox regression) (D).

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 five genes that, together, stratified progression to disease in the German BABYDIAB and BABYDIET studies (23). The reported differences could be related to the populations, as the Finnish population has a higher prevalence of the *PTPN22* gene polymorphism than elsewhere. DIPP, Diabetes Autoimmunity Study in the Young (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. Although 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-environment 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

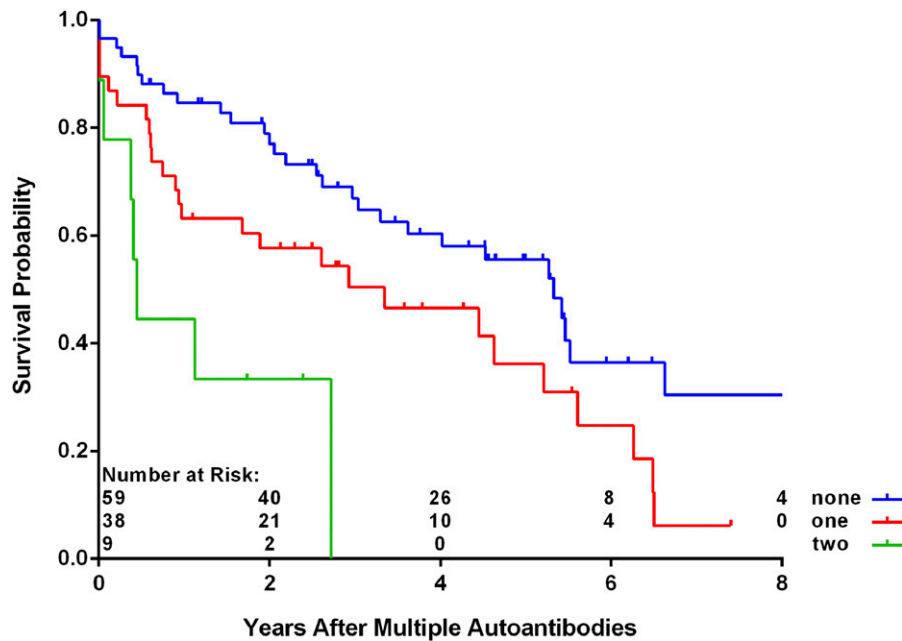


Figure 6—Progression from multiple autoantibodies to T1D by number of minor alleles of SNP rs2327832_G in the subset of more than one autoantibody as first-appearing autoantibody ($P < 0.001$ from Cox regression).

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 here should be viewed in the larger context of the results of other studies and other populations to be properly interpreted.

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