

Progression from islet autoimmunity to clinical type 1 diabetes is influenced by genetic factors – results from the prospective TEDDY study

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Abstract

Background: Progression time from islet autoimmunity to clinical type 1 diabetes is highly variable and the extent that genetic factors contribute is unknown.

Methods: In 341 islet autoantibody positive children with the human leukocyte antigen (HLA) DR3/DR4-DQ8 or the HLA DR4-DQ8/DR4-DQ8 genotype from the prospective TEDDY study, we investigated whether a genetic risk score that had previously been shown to predict islet autoimmunity is also associated with disease progression.

Results: Islet autoantibody positive children with a genetic risk score in the lowest quartile had a slower progression from single to multiple autoantibodies ($p=0.018$), from single autoantibodies to diabetes ($p=0.004$), and by trend from multiple islet autoantibodies to diabetes ($p=0.06$). In a Cox proportional hazards analysis, faster progression was associated with an increased genetic risk score independently of HLA genotype (hazard ratio for progression from multiple autoantibodies to type 1 diabetes, 1.27; 95% confidence interval, 1.02-1.58 per unit increase), an earlier age of islet autoantibody development (hazard ratio, 0.68; 95% confidence interval, 0.58-0.81 per year increase in age) and female sex (hazard ratio, 1.94; 95% confidence interval, 1.28-2.93).

Conclusions: Genetic risk scores may be used to identify islet autoantibody positive children with high risk HLA genotypes who have a slow rate of progression to subsequent stages of autoimmunity and type 1 diabetes.

Introduction:

Type 1 diabetes begins with a pre-clinical phase which is defined by the presence of islet autoantibodies. This pre-clinical phase is variable in duration with onset of clinical diabetes occurring months to decades after the appearance of islet autoantibodies ¹. Features of autoimmunity that include autoantibody titer or specificity, age and sex, have been used to stratify the rate of progression to type 1 diabetes ²⁻⁵. Genes that confer susceptibility to type 1 diabetes, in particular the human leukocyte antigen (HLA) class II genes, usually exert a stronger effect on the development of autoimmunity than on disease progression ⁶ and, although there are reports of genes that influence the progression to clinical diabetes ^{5 7 8}, the extent to which genetic information may be used to stratify the rate of progression to clinical diabetes in islet autoantibody positive individuals is unknown. Here, we investigated whether a previously established genetic risk score for islet autoimmunity ⁹ is associated with progression to clinical diabetes in the longitudinal TEDDY (The Environmental Determinants of Diabetes in the Young) study.

Research Design and Methods:

TEDDY is an ongoing prospective cohort study that enrolled 8,676 children with high-risk type 1 diabetes HLA genotypes between 2004 and 2010 in six clinical research centers located in the USA, Finland, Germany, and Sweden ¹⁰⁻¹². The families of children with risk HLA genotypes were invited to participate in the follow-up study in which blood samples were obtained every 3 months for the first 4 years and biannually thereafter for the measurement of islet autoantibodies (glutamic acid decarboxylase

antibody, insulinoma antigen-2 antibody, and insulin autoantibodies) by radiobinding assays as previously described^{13 14}. Samples positive for islet autoantibodies were retested at the second reference laboratory for confirmation. The outcome of islet autoantibody positivity was defined as a positive result at both reference laboratories (confirmed) and by the presence of islet autoantibodies (GADA, IA-2A, or IAA) on two or more consecutive visits (persistent). The date of seroconversion to islet autoimmunity was defined as the date of drawing the first of two consecutive autoantibody-positive samples. The presence of persistent multiple islet autoantibodies was defined as the presence of at least two persistent and confirmed islet autoantibodies. The date of persistent multiple islet autoantibodies was defined as the date of drawing the first sample when the second persistent and confirmed islet autoantibody was detected. Children with positive islet autoantibodies that were due to maternal IgG transmission were not considered to be positive for that autoantibody unless the child had a negative sample before the first positive sample or the autoantibody persisted beyond 18 months of age¹³. Type 1 diabetes was diagnosed according to ADA criteria¹⁵, using standardized case report forms for diabetes symptoms, height and weight at diagnosis, and laboratory values such as ketones in urine and blood.

Single nucleotide polymorphisms (SNPs) were genotyped using the Illumina ImmunoChip¹⁶. We previously used ImmunoChip data of 4,543 TEDDY participants without a family history of type 1 diabetes and with the HLA DR3/DR4-DQ8 or the HLA DR4-DQ8/DR4-DQ8 genotype to develop a genetic risk score to predict islet autoimmunity development from birth⁹. The genetic score of each individual was derived from weighted values given to the HLA DR3/DR4-DQ8 or DR4-DQ8/DR4-DQ8

genotype plus a weighted value assigned to each susceptible allele of HLA class I and non-HLA SNPs (supplementary table 1) and was applied also in this analysis. Written informed consent was obtained for all study participants from a parent or primary caretaker for genetic screening and to participate in the prospective follow-up. The study was approved by local institutional review boards and is monitored by an external advisory board established by the US National Institutes of Health.

Here, we analyzed the data of all 341 children who had developed islet autoantibodies during follow-up and for whom the genetic risk score could be determined. We calculated Kaplan-Meier curves for progression from (a) any autoantibodies to multiple autoantibodies, (b) any autoantibodies to type 1 diabetes onset, and (c) multiple autoantibodies to type 1 diabetes onset in children stratified by quartiles of the genetic risk score (lower quartile: <13.47; upper quartile: >14.88; the two middle quartiles were combined into one group, i.e. 13.47-14.88). In order to determine the potential contribution of HLA and non-HLA SNPs and explore potential confounding by other – basically unmodifiable factors, we applied Cox proportional hazards regression analysis for the three progression times with the genetic risk score as the main predictor variable, and with HLA genotype (DR3/DR4-DQ8 or DR4-DQ8/DR4-DQ8), sex, age at onset of the previous event (e.g., of any autoantibodies in the model of progression from any autoantibodies to type 1 diabetes), and country of ascertainment as confounder variables. Specifically, the HR of each outcome variable was determined as $\log(\text{HR}) = \beta_{\text{GRS}} * \text{genetic risk score} + \beta_{\text{HLA}} * \text{HLA genotype (reference: HLA DR4-DQ8/DR4-DQ8)} + \beta_{\text{SEX}} * \text{sex (reference: boys)} + \beta_{\text{AGE}} * \text{age at onset (continuous variable)} + \beta_{\text{COUNTRY}} * \text{country (reference: US)}$. In these models, we used the genetic risk score without inclusion of the

HLA class II genotypes so that the contributions of HLA class II genotype and the remainder of the genes in the risk score could be determined separately. All analyses were performed using R 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria). Significance was defined by a two-sided significance level of 0.05.

Results:

There were 341 children who developed islet autoantibodies at a median age of 2.7 (interquartile range, IQR, 1.5-5.0) years, of which 141 (41.3%) were female, and 250 had the HLA DR3/DR4-DQ8 and 91 the HLA DR4-DQ8/DR4-DQ8 genotype. The subjects were followed to a median age of 7.9 (IQR, 6.2-9.5) years. During this follow-up period, 214 children (62.8%) developed multiple autoantibodies at a median age of 2.8 (IQR, 1.8-5.1) years, and 107 (31.4 %) of the children developed clinical type 1 diabetes at a median age of 5.0 (IQR, 3.0-7.1) years, with 96 children (28.2%) developing both multiple autoantibodies and type 1 diabetes. The median genetic risk score was 14.23 (IQR, 13.47-14.88) in all children and was higher in the children who developed clinical type 1 diabetes (median, 14.36; IQR, 13.73-15.03) as compared to the children who remained single islet autoantibody positive at last visit (median, 14.0; IQR, 13.15-14.56; $p=0.007$ from Mann-Whitney U test). The children with a genetic risk score in the lowest quartile progressed more slowly from single to multiple islet autoantibodies ($p=0.018$), from single autoantibodies to diabetes ($p=0.004$), and by trend from multiple islet autoantibodies to type 1 diabetes ($p=0.06$; Figure 1) than the children with genetic risk scores in the upper three quartiles. In a Cox proportional hazards analysis, an increased genetic risk score calculated without HLA genotype and an earlier age of islet

autoantibody development were consistently associated with a faster progression to subsequent stages of autoimmunity and type 1 diabetes. Girls progressed faster from multiple autoantibodies to type 1 diabetes than boys. The HLA DR3/4-DQ8 genotype and country of ascertainment was not associated with the rate of progression at any stage after the appearance of islet autoantibodies (table 1).

Conclusions:

This study suggests that an islet autoimmunity genetic risk score is predictive of the rate of progression to clinical onset of type 1 diabetes in islet autoantibody positive children with the HLA DR3/DR4-DQ8 or the HLA DR4-DQ8/DR4-DQ8 genotype. Importantly, this risk score was predictive also when weighting for the HLA class II genes was not included, suggesting the impact of genetic variants on progress is independent of either HLA DR3/4-DQ8 or DR4-DQ8/DR4-DQ8 genotypes in these TEDDY participants. Previous studies have indicated that protective HLA genotypes are associated with a slower progression to clinical diabetes in islet autoantibody positive individuals¹⁷, but there are little or no differences in the progression rate between the high risk HLA class II genotypes⁷. Our findings are consistent with previous reports of associations between the rate of progression from pre-clinical to clinical type 1 diabetes and individual type 1 diabetes susceptibility genes^{5 7 8}. Of practical relevance, a low genetic risk score may be used to identify a subset of islet autoantibody positive children with slower progression to clinical type 1 diabetes, and, therefore, be an exclusion criterion for some immunotherapy prevention trials. In conclusion, our data indicate the age of islet autoantibody

development and a type 1 diabetes genetic risk score may be used to stratify the rate of progression to diabetes in prevention trials.

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Disclosure: A patent has been applied for (LU100334) with the title "Method the risk to develop type 1 diabetes" by Helmholtz Zentrum München Deutsches Forschungszentrum für Gesundheit und Umwelt (GmbH). EB, AGZ and CW are one of the inventors. The patent includes the genetic score that is examined in the manuscript. The other authors declared no conflict of interest.

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Figure 1. Cumulative risks of A) development of multiple islet autoantibodies after first appearance of any autoantibodies, B) development of type 1 diabetes after first appearance of any autoantibodies, and C) development of type 1 diabetes after first appearance of multiple autoantibodies, in children with the HLA DR3/DR4-DQ8 or the HLA DR4-DQ8/DR4-DQ8 genotype. P-values were calculated using log-rank tests. The groups were defined by quartiles of the genetic risk score (green: lower quartile, blue: two medium quartiles, orange: upper quartile).

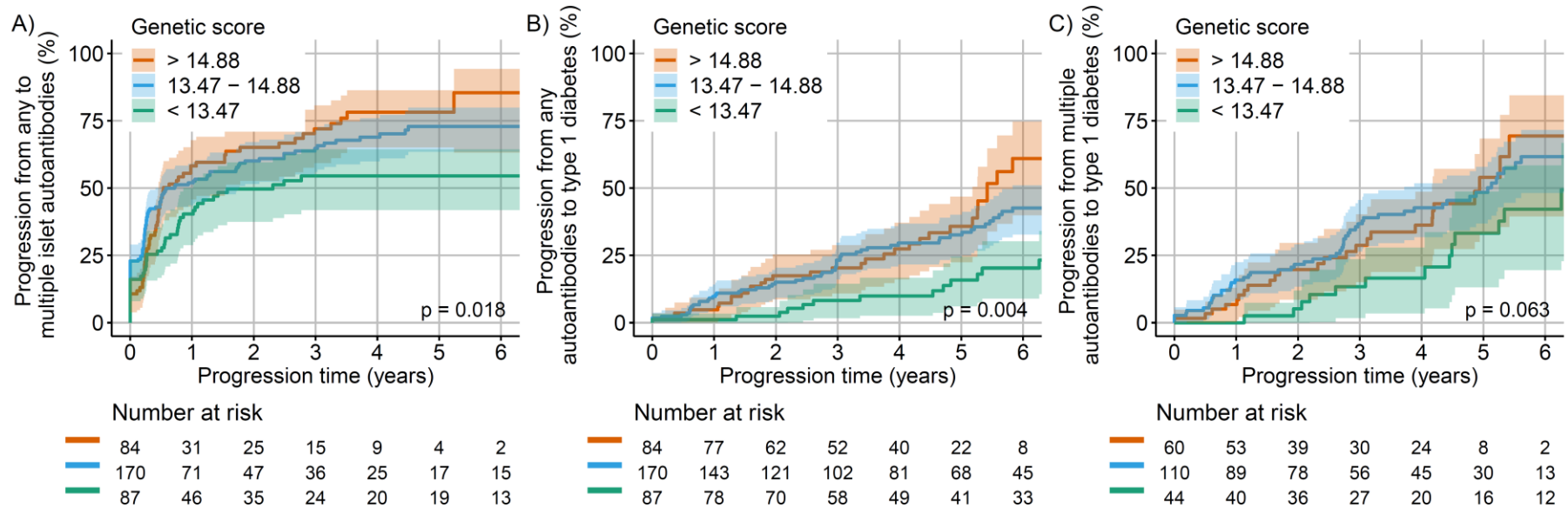


Table 1. Hazard ratios (HRs) and 95% confidence intervals (CIs) of development of multiple islet autoantibodies after first appearance of any autoantibodies, development of type 1 diabetes after first appearance of any autoantibodies, and development of type 1 diabetes after first appearance of multiple autoantibodies in children with the HLA DR3/DR4-DQ8 or the HLA DR4-DQ8/DR4-DQ8 genotype as calculated from Cox proportional hazard models.

	Progression from any to multiple autoantibodies		Progression from any autoantibodies to type 1 diabetes		Progression from multiple autoantibodies to type 1 diabetes	
	<i>HR (95% CI)</i>	<i>p-value</i>	<i>HR (95% CI)</i>	<i>p-value</i>	<i>HR (95% CI)</i>	<i>p-value</i>
Genetic risk score (per unit increase) *	1.22 (1.07, 1.40)	0.003	1.48 (1.21, 1.80)	0.0001	1.27 (1.02, 1.58)	0.03
HLA DR3/DR4-DQ8**	1.11 (0.81, 1.51)	0.52	1.49 (0.94, 2.37)	0.09	1.33 (0.82, 2.18)	0.25
Female child	1.01 (0.77, 1.34)	0.92	1.35 (0.91, 1.98)	0.13	1.94 (1.28, 2.93)	0.002
Age at onset of previous event (per year) ***	0.89 (0.83, 0.95)	0.0003	0.70 (0.60, 0.82)	<0.0001	0.68 (0.58, 0.81)	<0.0001
Finland****	0.83 (0.59, 1.18)	0.31	1.10 (0.67, 1.81)	0.70	0.95 (0.56, 1.63)	0.86
Germany	0.67 (0.31, 1.46)	0.32	0.40 (0.10, 1.67)	0.21	0.39 (0.09, 1.66)	0.20
Sweden	0.81 (0.58, 1.12)	0.19	0.98 (0.61, 1.57)	0.92	0.99 (0.60, 1.62)	0.96

* Genetic risk score is calculated without inclusion of HLA class II genotype; ** Reference is HLA DR4-DQ8/DR4-DQ8; *** Age at onset of the previous event (i.e. of any islet autoantibodies in models 1 and 2, and of multiple islet autoantibodies in model 3); the HRs

for age are reported as per one year increase for the sake of interpretability; however, exact age (i.e. not rounded) was used in the regression models. **** Country is coded as dummy variable with US as reference.

Supplementary Table 1. Weights for single nucleotide polymorphisms used to calculate the genetic risk score.

SNP	Gene, Allele, Genotype	Risk Score Weight
HLA class II		
rs17426593	HLA DR4-DQ8/ DR4-DQ8	3.15
rs2187668	HLA DR3/ DR4-DQ8	3.98
rs7454108		
Other SNPs		
rs1264813	HLA A 24	0.43
rs2395029	HLA B 5701	0.92
rs2476601	PTPN22	0.76
rs2816316	RGS1	0.16
rs3024505	IL10	0.22
rs1990760	IFIH1	0.16
rs3087243	CTLA4	0.16
rs10517086	C4orf52	0.19
rs2069763	IL2	0.11
rs6897932	IL7RA	0.19
rs3757247	BACH2	0.19
rs9388489	C6orf173	0.14
rs6920220	TNFAIP3	0.15
rs1738074	TAGAP	0.05

rs7804356	SCAP2	0.15
rs4948088	COBL	0.17
rs7020673	GLIS3	0.23
rs12722495	IL2RA	0.47
rs947474	PRKCQ	0.15
rs10509540	RNLS/C10orf59	0.25
rs1004446	INS	0.65
rs4763879	CD69	0.06
rs2292239	ERBB3	0.36
rs3184504	SH2B3	0.24
rs1465788	ZFP36L1	0.13
rs17574546	RASGRP1	0.13
rs3825932	CTSH	0.15
rs12708716	CLEC16A	0.15
rs4788084	IL27	0.20
rs7202877	CTRB2	0.19
rs2290400	ORMDL3	0.25
rs7221109	CCR7	0.15
rs45450798	PTPN2	0.09
rs763361	CD226	0.12
rs425105	PRKD2	0.21
rs2281808	SIRPG	0.07
rs3788013	UBASH3a	0.16

rs5753037	RPS3AP51	0.15
rs229541	IL2B	0.18
rs5979785	TLR8	0.09
rs2664170	GAB3	0.14

SNP, single nucleotide polymorphism; HLA, human leukocyte antigen