ESM Table 1: TEDDY HLA Eligibility Criteria for a First-degree Relative (FDR) and the General population (GP)

Code	Haplotype genotypes	Abbreviation	FDR	GP	N (%)
A	*DRB1*04-DQA1*03-DQB1*03:02 / DRB1*03-DQA1*05:01-DQB1*02:01*	HLA-DR3/4	Yes	Yes	2889 (39.5%)
B	*DRB1*04-DQA1*03-DQB1*03:02 / DRB1*04-DQA1*03-DQB1*03:02*	HLA-DR4/4	Yes	Yes	1435 (19.6%)
C	*DRB1*04-DQA1*03-DQB1*03:02 / DRB1*08-DQA1*04:01-DQB1*04:02*	HLA-DR4/8	Yes	Yes	1284 (17.5%)
D	*DRB1*03-DQA1*05:01-DQB1*02:01 / DRB1*03-DQA1*05:01-DQB1*02:01*	HLA-DR3/3	Yes	Yes	1553 (21.2%)
E	*DRB1*04-DQA1*03-DQB1*03:02 / DRB1*04-DQA1*03-DQB1*02:02*	HLA-DR4/4b	Yes	No	3 (0.04%)
F	*DRB1*04-DQA1*03-DQB1*03:02 / DRB1*01-DQA1*01:01-DQB1*05:01*	HLA-DR4/1	Yes	No	98 (1.3%)
G	*DRB1*04-DQA1*03-DQB1*03:02 / DRB1*13-DQA1*01:02-DQB1*06:04*	HLA-DR4/13	Yes	No	28 (0.4%)
H	*DRB1*04-DQA1*03-DQB1*03:02 / DRB1*04-DQA1*03-DQB1*03:04*	HLA-DR4/4c	Yes	No	3 (0.04%)
I	*DRB1*04-DQA1*03-DQB1*03:02 / DRB1*09-DQA1*03-DQB1*03:03*	HLA-DR4/9	Yes	No	12 (0.2%)
J	*DRB1*03-DQA1*05:01-DQB1*02:01 / DRB1*09-DQA1*03-DQB1*03:03*	HLA-DR3/9	Yes	No	12 (0.2%)

Genotypes A, B, C, D confer general population eligibility but exclude *DRB1*04:03*. Genotypes A through J confer eligible to a first degree relative with type 1 diabetes.

ESM Table 2. Experiences of the Parent/Primary Caretaker

	Life Experience	Life Event Category
1.	You became seriously ill or injured	Disease/injury
2.	A family member became seriously ill or injured	Disease/injury
3.	You were hospitalized	Disease/injury
4.	A family member was hospitalized	Disease/injury
5.	A family member died	Significant loss
6.	A close friend died	Significant loss
7.	You separated from your spouse of significant other	Serious interpersonal
8.	You got a divorce	Serious interpersonal
9.	You got married	Serious interpersonal
10.	You experienced violence	Other*
11.	A family member experienced violence	Other*
12.	You quit or lost your job	Job-related
13.	Your spouse/significant other quite or lost his/her job	Job-related
14.	You returned to work, started a new job or started school	Job-related
15.	Your spouse/significant other returned to work, started a new job or started school	Job-related
16.	You moved	Serious interpersonal
17.	You had serious arguments/conflict with your spouse/significant other	Serious interpersonal
18.	You had serious arguments/conflict with other relatives/friends	Serious interpersonal
19.	You had financial difficulties or money problems	Financial difficulties
20.	Your spouse/significant other had financial difficulties or money problems	Financial difficulties
21.	Other life event reported by the parent/primary caretaker	Placed into one of the categories listed above or Other

* = Placed into “Other” category due to very infrequent reports.

ESM Table 3. Study Sample Characteristics: Sex, Country, Family History of Type 1 Diabetes, Type 1 Diabetes Related HLA and SNPs and Association with Risk of First-appearing Islet Autoantibodies until 6 years of age

Total = (N)	**IA Negative**	**First Appearing Islet Autoantibody (IA) until 6 years of age**					
Age of seroconversion = Median (IQR)	**(N = 6785*)**	**Any IA⁺ (N=532*) Age = 27 (15 – 48) months**		**IAA as first appearing (N = 222*) Age = 21 (12 – 36) months**		**GADA as first appearing (N = 209*) Age = 38 (21 – 58) months**	
Characteristic	**N (%)**	**N (%)**	**Multivariate HR* (95%CI)**	**N (%)**	**Multivariate HR* (95%CI)**	**N (%)**	**Multivariate HR* (95%CI)**
Child sex							
Female	3355 (50%)	241 (45%)	1.00 (reference)	98 (44%)	1.00 (reference)	98 (47%)	1.00 (reference)
Male	3430 (51%)	291 (55%)	**1.22 (1.02 – 1.45)‡**	124 (56%)	1.27 (0.98 – 1.66)	111 (53%)	1.10 (0.84 – 1.45)
Country							
U.S.	2923 (43%)	180 (34%)	1.00 (reference)	64 (29%)	1.00 (reference)	84 (40%)	1.00 (reference)
Finland	1361 (20%)	122 (23%)	1.10 (0.87 – 1.41)	64 (29%)	**1.47 (1.02 – 2.14) §**	37 (18%)	**0.86 (0.57 – 1.28) §**
Germany	392 (6%)	38 (7%)	1.13 (0.76 – 1.64)	16 (7%)	1.35 (0.76 – 2.38)	8 (4%)	0.46 (0.20 – 1.06)
Sweden	2109 (31%)	192 (36%)	1.20 (0.98 – 1.48)	78 (35%)	1.38 (0.99 – 1.93)	80 (38%)	1.10 (0.80 – 1.50)
Family history of T1D							
None	6354 (94%)	449 (84%)	1.00 (reference)	183 (82%)	1.00 (reference)	181 (87%)	1.00 (reference)
First degree relative							
Father	340 (5%)	58 (11%)	**2.39 (1.75 – 3.26)‡**	25 (11%)	**2.51 (1.56 – 4.06)**	23 (11%)	**3.09 (1.95 – 4.90)**
Sibling	91 (1%)	25 (5%)	**3.48 (2.29 – 5.29)‡**	14 (6%)	**4.97 (2.80 – 8.82)**	5 (2%)	1.98 (0.81 – 4.86)
HLA high risk							
DR-4/4	1346 (20%)	89 (17%)	1.00 (reference)	37 (17%)	1.00 (reference)	30 (14%)	1.00 (reference)
DR-4/8	1200 (18%)	84 (16%)	1.05 (0.77 – 1.42)	51 (23%)	1.47 (0.96 – 2.27)	23 (11%)	0.91 (0.52 – 1.58)
DR-4/9,X‖	126 (2%)	18 (3%)	0.70 (0.40 – 1.25)	9 (4%)	0.81 (0.36 – 1.82) §	2 (1.0%)	**0.13 (0.02 – 0.96) §**
DR-3/4	2620 (39%)	269 (51%)	1.43 (1.12 – 1.82) ‡	108 (49%)	1.35 (0.92 – 1.97)	104 (50%)	1.72 (1.14 – 2.60)
DR-3/9‖	12 (0.2%)	0 (0%)	-	0 (0%)	-	0 (0%)	-
DR-3/3	1481 (22%)	72 (13%)	**0.63 (0.46 – 0.87)c**	17 (8%)	**0.36 (0.20 – 0.65) §**	50 (24%)	1.36 (0.84 – 2.20) §
Single Nucleotide Polymorphisms (SNPs)-Minor Allele							
***PTPN22*-A allele**							
No	4957 (81%)	367 (70%)	1.00 (reference)	155 (70%)	1.00 (reference)	148 (71%)	1.00 (reference)
Yes	1195 (19%)	161 (30%)	**1.74 (1.44 – 2.10) ‡**	66 (30%)	**1.64 (1.23 – 2.20)**	60 (29%)	**1.66 (1.23 – 2.25)**
***INS*-T allele**							
No	3165 (53%)	344 (66%)	1.00 (reference)	162 (74%)	1.00 (reference)	108 (52%)	1.00 (reference)

Yes	2759 (47%)	180 (34%)	**0.62 (0.52 – 0.75)** ‡	57 (26%)	**0.43 (0.32 – 0.58)** §	98 (48%)	1.06 (0.81 – 1.40) §
***ERBB3*-T allele**							
No	2871 (47%)	207 (39%)	1.00 (reference)	84 (38%)	1.00 (reference)	85 (41%)	1.00 (reference)
Yes	3280 (53%)	321 (61%)	**1.38 (1.16 – 1.64)** ‡	137 (62%)	**1.47 (1.12 – 1.94)**	123 (59%)	1.26 (0.96 – 1.67)
***SH2B3*-T allele**							
No	1961 (32%)	127 (24%)	1.00 (reference)	60 (27%)	1.00 (reference)	44 (21%)	1.00 (reference)
Yes	4191 (68%)	401 (76%)	**1.36 (1.11 – 1.66)** ‡	161 (3%)	1.19 (0.88 – 1.61)	164 (79%)	**1.58 (1.13 – 2.21)**
***BACH2*-T allele**							
No	2067 (34%)	167 (32%)	1.00 (reference)	85 (39%)	1.00 (reference)	50 (24%)	1.00 (reference)
Yes	4059 (66%)	360 (68%)	1.12 (0.93 – 1.34)	135 (61%)	0.87 (0.66 – 1.14) §	158 (76%)	**1.57 (1.14 – 2.16)** §
***CTLA4*-G allele**							
No	1951 (32%)	160 (30%)	1.00 (reference)	73 (33%)	1.00 (reference)	54 (26%)	1.00 (reference)
Yes	4200 (68%)	368 (70%)	1.02 (0.84 – 1.23)	148 (67%)	0.86 (0.65 – 1.15) §	154 (74%)	1.28 (0.94 – 1.76) §
***BTNL2*-A allele**							
No	4389 (71%)	406 (77%)	1.00 (reference)	172 (78%)	1.00 (reference)	157 (76%)	1.00 (reference)
Yes	1763 (29%)	122 (23%)	**0.73 (0.58 – 0.90)** ‡	49 (22%)	**0.66 (0.47 – 0.92)**	51 (25%)	0.91 (0.65 – 1.27)

* = multivariate model included gender, country, family history with T1D and HLA available on all children, and SNPs available on 5841/6785 negative and on 523/532 IA positive including 219/222 IAA-first and 206/209 GADA-first.

+ = an additional 10 children developed IA2A and 91 multiple as their first IA (GADA-IA2A n=1; GADA-IAA, n=72; IA2A-IAA, n=4; GADA-IAA-IA2A, n=14). They were censored in multivariate models at age of seroconversion (median (IQR) = 55 (38 – 67) for IA2A, 27 (15 – 42) for multiple IA)

‡ = an association exists with IA overall (p-value <0.05)

§ = the association with IAA-first and GADA-first is different (p-value<0.05)

‖ = children with a family history of T1D were included as HLA high risk if they had an additional haplotype, see ESM Table 1

ESM Table 4. Maternal Life Events Reported during Pregnancy in Relation to the Risk of Islet Autoantibodies in the Child until 6 years of age

Life Event categories mother experienced during pregnancy		Maternal LE on risk of IA		Maternal LE on risk of IAA-first		Maternal LE on risk of GADA-first	
	N (%)[$]	HR*(95%CI)	p-value	HR*(95%CI)	p-value	HR*(95%CI)	p-value
None	2667 (35.6%)	1.00 (reference)		1.00 (reference)		1.00 (reference)	
At least one	4097 (64.4%)	0.99 (0.82 – 1.18)	0.86	0.78 (0.60 – 1.03)[+]	0.08	1.18 (0.88 – 1.58)[+]	0.28
One	2086 (32.8%)	0.96 (0.78 – 1.18)		0.69 (0.50 – 0.96)		1.06 (0.75 – 1.49)	
Two	1218 (19.1%)	1.07 (0.85 – 1.37)		0.88 (0.61 – 1.27)		1.42 (0.98 – 2.06)	
Three	493 (7.7%)	0.78 (0.51 – 1.12)		0.76 (0.44 – 1.34)		1.06 (0.59 – 1.89)	
Four or more	300 (4.7%)	1.27 (0.82 – 1.95)	0.36	1.28 (0.68 – 2.42)	0.14	1.25 (0.62 – 2.53)	0.12

* = Presence and number life event categories (Disease/Injury, Significant loss, Serious Interpersonal, Job Related, Financial Difficulties or other) examined on the hazard of IA overall and first appearing IAA and GADA until 6 years of age adjusting for family history with type 1 diabetes, gender, country of residence, HLA and SNPs as shown in ESM Table 3.

[$] = full models included 6364 total children including 523 of 532 IA positives, 219 of 222 IAA-first and 206 of 209 GADA-first.

+ = life event is associated differently with hazard of IAA-first as compared to GADA-first (p-value<0.05)

ESM Table 5. Multivariate Logistic Regression Model of Prenatal Factors in Relation to Job-related or Serious Interpersonal Life Events.

		Prenatal factors in relation to odds of mother reporting a job related life event during pregnancy [a]		Prenatal factors in relation to odds of mother reporting a serious interpersonal life event during pregnancy [a]	
Maternal prenatal factors	**N or mean (SD)**	**OR (95%CI)**	**p-value**	**OR (95%CI)**	**p-value**
Maternal age (/year)[a]					
up to 29 years of age	2591	**0.96 (0.94 – 0.98)**	0.0005	**0.89 (0.87 – 0.91)**	<0.0001
29 years of age and older	4573	**0.97 (0.05 – 0.98)**	0.0002	0.99 (0.97 – 1.01)	0.21
Residence of mother					
US	3011	1.00 (reference)		1.00 (reference)	
EU	4143	**0.82 (0.74 – 0.92)**	0.0007	**0.84 (0.76 – 0.94)**	0.002
Number of maternal illnesses reported during pregnancy					
Illness	2.3 (1.8)	**1.06 (1.03 – 1.09)**	0.0001	**1.06 (1.03 – 1.10)**	<0.0001
Mother's first child					
no	3556	1.00 (reference)		1.00 (reference)	
Yes	2913	**1.22 (1.09 – 1.38)**	0.0009	**1.46 (1.30 – 1.63)**	<0.0001
No information	695	0.99 (0.82 – 1.21)	0.95	**1.32 (1.10 – 1.58)**	0.003
Mother smoked during pregnancy					
No	6205	1.00 (reference)		1.00 (reference)	
yes	959	0.96 (0.82 – 1.13)	0.58	**1.69 (1.46 – 1.96)**	<0.0001
Mother drank alcohol during pregnancy					
No	4716	1.00 (reference)		1.00 (reference)	
Yes	2448	**1.22 (1.08 – 1.36)**	0.001	**1.24 (1.11 – 1.38)**	0.0002

a = the predicted probability from each logistic regression model was used to calculate the propensity of having a job related or serious interpersonal life event during pregnancy. Stabilized weights for Inverse Probability Treatment (exposure) Weighting (IPTW) analysis were calculated from the propensity scores to reduce selection bias (1). The calculation was as followed; when mothers had the life event the stabilized weight was the proportion of mothers with the life event (pLE) divided by the propensity score (PS); when mothers did not have the life event the stabilized weight was (1- pLE)/(1-PS). Maternal age was included in logistic model as a linear spline centered around 29 months of age and for serious interpersonal life even as the outcome, an interaction between maternal age and maternal smoking was included to ensure both variables were correctly controlled for when examining life event on risk of islet autoimmunity. An Inverse Probability of Treatment (Life event) Weighting analysis was performed by weighting children in the Proportional Hazard models by the stabilized weight created from the LE propensity score. Since the propensity score was an estimate and not a known quantity, variances were calculated

from performing analysis on 1000 bootstrap samples. Job related LE remained associated with IAA-first, HR (95%CI) = 0.59 (0.40 – 0.88), and Serious Interpersonal life event with GADA-first HR (95%CI) = 1.55 (1.13 – 2.11).

References

1. Xu S, Ross C, Raebel M, Shetterly S, Blanchette C, Smith D. Use of stabilized inverse propensity scores as weights to directly estimate relative risk and its confidence intervals. Value Health 2010;13:273-7

ESM Table 6. Respiratory Illness and Job-related Life Event During Pregnancy Examined in Univariate and Multivariate Models on Risk of IAA-first Stratified by Genetic Subgroups of Children Showing Where Respiratory Illness Has Strongest Influence on IAA-first.

Genetic subgroup of children	**Gestational Predictor (yes vs. no)**	**Univariate[+] on IAA-first**		**Multivariate[+] On IAA-first**	
		HR(95%CI)	**p-value**	**HR(95%CI)**	**p-value**
All children	Respiratory Illness	0.87 (0.66 – 1.15)	0.34	0.89 (0.67 – 1.18)	0.41
	Job related LE	0.58 (0.40 – 0.84)	0.004	0.54 (0.37 – 0.80)	0.002
CTLA-4-AA genotype	Respiratory Illness	1.51 (0.92 – 2.47)	0.10	1.52 (0.93 – 2.49)	0.10
	Job related LE	0.77 (0.41 – 1.43)	0.41	0.77 (0.41 – 1.43)	0.41
CTLA-4-(AG, GG) genotype	Respiratory Illness	0.64 (0.45 – 0.91)	0.01	0.66 (0.46 – 0.94)	0.02
	Job related LE	0.50 (0.32 – 0.80)	0.004	0.45 (0.27 – 0.74)	0.002
CTLA-4-(AG, GG) & HLA-DR4/8 genotypes	Respiratory Illness	0.28 (0.12 – 0.65)	0.003	0.27 (0.12 – 0.64)	0.003
	Job related LE	0.31 (0.11 – 0.94)	0.04	0.22 (0.06 – 0.79)	0.02

[+] = All models adjusted for factors shown in ESM table 3 including life events other than job-related. Univariate includes respiratory illness and job related LE in separate models. Multivariate includes both predictors in same model.

Note: Job related LE is associated with IAA-first in offspring of mother who have a respiratory illness (HR = 0.51, 95%CI = 0.45 – 0.90, p=0.02) and mothers who did not (HR = 0.58, 95%CI = 0.34 – 1.00, p=0.049)

References

1. Lynch KF, Hye-Seung L, Torn C, et al (2018) Gestational respiratory infections interacting with offspring HLA and *CTLA-4* modifies incident B-cell autoantibodies. J Autoimmun 86:93-103. doi: 10.1016/j.jaut.2017.09.005.

ESM Table 7. Genetic Factors and Job-related Life Event During Pregnancy on the Risk of IAA as the First-appearing Islet Autoantibody Adjusting for Country, Child Sex, Father or Sibling with T1D

Genetic and environmental component			Total	IAA- first	Genetic (G) and Job related life event (Job-LE) on risk of IAA as first appearing Islet autoantibody			
HLA-DR-DQ or SNP (G)		Job related life event (Job-LE)	N	n (%)	(G) and (Job-LE) combination on IAA-first	Job-LE on IAA-first within strata of genetic factor	Additive interaction	Multiplicative interaction
					HR (95%CI)	HR (95%CI)	RERI (95%CI) p-value	HR (95%CI) p-value
HLA–DR3/3	No	No	4315	172 (4.0%)	1.00 (Reference)	0.61 (0.42 – 0.89)	0.20 (-0.16 – 0.56) p-value = 0.27	0.73 (0.16 – 3.32) p-value = 0.67
Genotype	No	Yes	1449	33 (2.3%)	0.61 (0.41 – 0.89)			
	Yes	No	1174	15 (1.3%)	0.33 (0.20 – 0.57)	0.44 (0.10 – 1.94)		
	Yes	Yes	379	2 (0.5%)	0.15 (0.04 – 0.60)			
HLA–DR4/4	No	No	4380	152 (3.5%)	1.00 (Reference)	0.68 (0.47 – 0.99)	-0.44 (-0.97 – 0.09) p-value = 0.05	0.30 (0.07 – 1.30) p-value = 0.11
Genotype	No	Yes	1502	33 (2.2%)	0.69 (0.47 – 1.00)			
	Yes	No	1109	35 (3.2%)	0.95 (0.66 – 1.37)	0.22 (0.05 – 0.90)		
	Yes	Yes	326	2 (0.6%)	0.19 (0.05 – 0.78)			
HLA–DR3/4	No	No	3370	102 (3.0%)	1.00 (Reference)	0.40 (0.22 – 0.74)	0.33 (-0.30 – 0.96) p-value = 0.30	2.03 (0.96 – 4.32) p-value = 0.07
Genotype	No	Yes	1058	12 (1.1%)	0.40 (0.22 – 0.73)			
	Yes	No	2119	85 (4.0%)	1.44 (1.08 – 1.92)	0.80 (0.50 – 1.27)		
	Yes	Yes	770	23 (3.0%)	1.17 (0.74 – 1.84)			
HLA–DR4/8	No	No	4532	143 (3.2%)	1.00 (Reference)	0.65 (0.43 – 0.97)	-0.49 (-1.26 – 0.28) p-value = 0.21	0.70 (0.28 – 1.70) p-value = 0.43
Genotype	No	Yes	1501	28 (1.9%)	0.65 (0.43 – 0.98)			
	Yes	No	957	44 (4.6%)	1.53 (1.08 – 2.17)	0.56 (0.21 – 1.02)		
	Yes	Yes	327	7 (2.1%)	0.69 (0.32 – 1.49)			
Single Nucleotide Polymorphisms (SNPs) associated with IAA* - Minor Allele								
***PTPN22*-A allele**	No	No	3989	128 (3.2%)	1.00 (Reference)	0.67 (0.44 – 1.01)	-0.59 (-1.37 – 0.20) p-value = 0.14	0.68 (0.29 – 1.58) p-value = 0.37
	No	Yes	1335	27 (2.0%)	0.68 (0.45 – 1.02)			
	Yes	No	1027	58 (5.7%)	1.68 (1.23 – 2.29)	0.47 (0.22 – 0.99)		
	Yes	Yes	329	8 (2.4%)	0.76 (0.37 – 1.56)			
***INS*-T allele**	No	No	2629	134 (5.1%)	1.00 (Reference)	0.67 (0.45 – 1.01)	0.10 (-0.26 – 0.45) p-value = 0.59	0.70 (0.29 – 1.71) p-value = 0.43
	No	Yes	880	28 (3.2%)	0.66 (0.44 – 0.99)			
	Yes	No	2210	50 (2.3%)	0.45 (0.33 – 0.63)	0.45 (0.20 – 0.99)		

	Yes	Yes	729	7 (1.0%)	0.21 (0.10 – 0.45)			
***ERBB3*-T allele**	No	No	2292	70 (3.1%)	1.00 (Reference)	0.62 (0.35 – 1.10)	-0.19 (-0.81 – 0.43) p-value = 0.54	0.95 (0.46 – 2.00) p-value = 0.90
	No	Yes	786	14 (1.8%)	0.63 (0.35 – 1.12)			
	Yes	No	2723	116 (4.3%)	1.41 (1.05 – 1.90	0.60 (0.38 – 0.96)		
	Yes	Yes	878	21 (2.4%)	0.85 (0.52 – 1.39)			
***SH2B3*-T allele**	No	No	1519	50 (3.3%)	1.00 (Reference)	0.58 (0.29 – 1.15)	-0.01 (-0.58 – 0.56) p-value = 0.97	1.08 (0.48 – 2.40) p-value = 0.86
	No	Yes	569	10 (1.8%)	0.58 (0.29 – 1.14)			
	Yes	No	3497	136 (3.9%)	1.15 (0.83 – 1.59)	0.62 (0.41 – 0.95)		
	Yes	Yes	1095	25 (2.3%)	0.72 (0.44 – 1.16)			
***BACH2*-T allele**	No	No	1656	70 (4.2%)	1.00 (Reference)	0.69 (0.40 – 1.22)	-0.01 (-0.50 – 0.48) p-value = 0.97	0.88 (0.42 – 1.83) p-value = 0.73
	No	Yes	578	15 (2.6%)	0.66 (0.38 – 1.15)			
	Yes	No	3340	115 (3.4%)	0.83 (0.62 – 1.12)	0.56 (0.35 – 0.91)		
	Yes	Yes	1079	20 (1.9%)	0.48 (0.29 – 0.80)			
***CTLA4*-G allele**	No	No	1607	60 (3.7%)	1.00 (Reference)	0.76 (0.41 – 1.38)	-0.17 (-0.75 – 0.40) p-value = 0.55	0.72 (0.34 – 1.53) p-value = 0.39
	No	Yes	504	13 (2.6%)	0.76 (0.42 – 1.38)			
	Yes	No	3408	126 (3.7%)	0.91 (0.67 – 1.25)	0.55 (0.35 – 0.86)		
	Yes	Yes	1160	22 (1.9%)	0.50 (0.31 – 0.81)			
***BTNL2*-A allele**	No	No	3624	150 (4.1%)	1.00 (Reference)	0.48 (0.31 – 0.76)	**0.56 (0.05 – 1.08) p-value = 0.03 false discovery rate = 0.37**	**2.19 (1.01 – 4.77) p-value = 0.048 false discovery rate = 0.37**
	No	Yes	1171	22 (1.9%)	0.49 (0.31 – 0.76)			
	Yes	No	1392	36 (2.6%)	0.70 (0.49 – 1.01)	1.03 (0.54 – 1.95)		
	Yes	Yes	493	13 (2.6%)	0.75 (0.42 – 1.32)			

RERI = relative excess risk due to interaction (p-value tested against zero for statistically significant additive interaction) RERI >0 = statistical additive interaction

ESM Table 8. Genetic Factors and Serious Interpersonal Life Events on the Risk of GADA as the First-appearing Islet Autoantibody Adjusting for Country, Child Sex, Father or Sibling with T1D

Genetic and environmental component			**Total**	**GADA- first**	**Genetic (G) and serious interpersonal life event (SI-LE) on risk of GADA as first appearing Islet autoantibody**			
***HLA-DR* or SNP (G)**		**Serious interpersonal life event (SI-LE)**	**N**	**n (%)**	**(G) and (SI-LE) combination on GADA-first**	**SI-LE on GADA-first within strata of genetic factor**	**Additive interaction**	**Multiplicative interaction**
					HR (95%CI)	**HR (95%CI)**	**RERI (95%CI) p-value**	**HR (95%CI) p-value**
HLA–DR3/3	No	No	4068	102 (2.5%)	1.00 (Reference)	1.53 (1.11 – 2.12)	-0.13 (-1.09 – 0.84) p-value = 0.79	0.88 (0.45 – 1.72) p-value = 0.70
Genotype	No	Yes	1696	57 (3.4%)	1.53 (1.10 – 2.11)			
	Yes	No	1078	33 (3.1%)	1.17 (0.79 – 1.74)	1.33 (0.74 – 2.40)		
	Yes	Yes	475	17 (3.6%)	1.57 (0.94 – 2.64)			
HLA–DR4/4	No	No	4145	111 (1.5%)	1.00 (Reference)	1.67 (1.24 – 2.26)	**-0.99 (-1.79 – -0.20) p-value = 0.02 false discovery rate = 0.11**	0.38 (0.15 – 0.98) p-value = 0.05
Genotype	No	Yes	1737	68 (3.9%)	1.68 (1.24 – 2.27)			
	Yes	No	1001	24 (2.4%)	0.89 (0.57 – 1.38)	0.65 (0.26 – 1.58)		
	Yes	Yes	434	6 (1.4%)	0.57 (0.25 – 1.30)			
HLA–DR3/4	No	No	3082	73 (2.4%)	1.00 (Reference)	1.13 (0.75 – 1.72)	**1.13 (0.18 – 2.08) p-value = 0.02 false discovery rate = 0.11**	1.71 (0.96 – 3.02) p-value = 0.07
Genotype	No	Yes	1346	32 (2.4%)	1.14 (0.75 – 1.73)			
	Yes	No	2064	62 (3.0%)	1.34 (0.96 – 1.89)	1.95 (1.32 – 2.90)		
	Yes	Yes	825	42 (5.1%)	2.62 (1.79 – 3.84)			
HLA–DR4/8	No	No	4260	121 (2.8%)	1.00 (Reference)	1.47 (1.09 – 1.99)	-0.10 (-0.93 – 0.72) p-value = 0.80	1.09 (0.45 – 2.65) p-value = 0.85
Genotype	No	Yes	1773	65 (3.7%)	1.47 (1.09 – 1.99)			
	Yes	No	886	14 (1.6%)	0.61 (0.35 – 1.07)	1.71 (0.73 – 4.02)		
	Yes	Yes	398	9 (2.3%)	0.98 (0.50 – 1.94)			
Single Nucleotide Polymorphisms (SNPs) associated with GADA-Minor Allele								
***PTPN22*-A allele**	No	No	3784	94 (2.5%)	1.00 (Reference)	1.55 (1.11 – 2.17)	0.08 (-1.17 – 1.33) p-value = 0.90	0.88 (0.47 – 1.66) p-value = 0.69
	No	Yes	1540	54 (3.5%)	1.55 (1.11 – 2.16)			
	Yes	No	968	40 (4.1%)	1.73 (1.20 – 2.51)	1.32 (0.77 – 2.27)		
	Yes	Yes	388	20 (5.2%)	2.36 (1.45 – 3.82)			
***INS*-T allele**	No	No	2529	69 (2.7%)	1.00 (Reference)	1.55 (1.05 – 2.30)	-0.58 (-0.87 – 0.75) p-value = 0.16	0.93 (0.53 – 1.66) p-value =0.82
	No	Yes	980	39 (4.0%)	1.54 (1.04 – 2.28)			
	Yes	No	2074	64 (3.1%)	1.10 (0.78 – 1.54)	1.45 (0.96 – 2.20)		

	Yes	Yes	865	34 (3.9%)	1.58 (1.05 – 2.38)			
***ERBB3*-T allele**	No	No	2184	52 (2.4%)	1.00 (Reference)	1.76 (1.14 – 2.73)	-0.27 (-1.21 – 0.67) p-value = 0.57	0.77 (0.43 – 1.37) p-value = 0.38
	No	Yes	894	33 (3.7%)	1.73 (1.12 – 2.68)			
	Yes	No	2568	82 (3.2%)	1.38 (0.97 – 1.95)	1.33 (0.91 – 1.94)		
	Yes	Yes	1033	41 (4.0%)	1.84 (1.22 – 2.77)			
***SH2B3*-T allele**	No	No	1427	25 (1.8%)	Reference)	1.88 (1.03 – 3.42)	0.01 (-1.19 – 1.21) p-value = 0.86	0.80 (0.40 – 1.57) p-value = 0.51
	No	Yes	661	19 (2.9%)	1.81 (1.00 – 3.29)			
	Yes	No	3325	109 (3.3%)	1.86 (1.21 – 2.89)	1.43 (1.03 – 1.98)		
	Yes	Yes	1267	55 (4.3%)	2.68 (1.67 – 4.31)			
***BACH2*-T allele**	No	No	1547	38 (2.5%)	1.00 (Reference)	0.77 (0.40 – 1.47)	**1.25 (0.50 – 2.00) p-value = 0.001 false discovery rate = 0.02**	**2.40 (1.16 – 4.94) p-value = 0.02 false discovery rate = 0.11**
	No	Yes	687	12 (1.8%)	0.77 (0.40 – 1.47)			
	Yes	No	3188	96 (3.0%)	1.21 (0.83 – 1.77)	1.85 (1.35 – 2.55)		
	Yes	Yes	1231	62 (5.0%)	2.22 (1.48 – 3.33)			
***CTLA-4*-G allele**	No	No	1528	34 (2.2%)	1.00 (Reference)	1.72 (0.99 – 2.99)	-0.15 (-1.19 – 0.88) p-value = 0.77	0.82 (0.43 – 1.56) p-value = 0.54
	No	Yes	583	20 (3.4%)	1.72 (0.99 – 2.99)			
	Yes	No	3223	100 (3.1%)	1.40 (0.95 – 2.07)	1.39 (1.00 – 1.94)		
	Yes	Yes	1245	54 (4.0%)	1.97 (1.28 – 3.03)			
***BTNL2*-A allele**	No	No	3455	100 (2.9%)	1.00 (Reference)	1.61 (1.16 – 2.23)	-0.41 (-1.20 – 0.38) p-value = 0.31	0.76 (0.39 – 1.47) p-value = 0.41
	No	Yes	1340	57 (4.3%)	1.60 (1.16 – 2.22)			
	Yes	No	1297	34 (2.6%)	0.92 (0.62 – 1.36)	1.22 (0.68 – 2.18)		
	Yes	Yes	588	17 (2.9%)	1.12 (0.67 – 1.87)			

RERI = relative excess risk due to interaction (p-value tested against zero for statistically significant additive interaction) RERI >0 = statistical additive interaction

ESM Table 9. *Cis*-expression Quantitative Trait Loci (*cis*-eQTL) Associations of the rs3763305 in *BTNL2* with Different Proximate Genes in the Various Human Immune Cells

Human immune cells	Proximate genes	p-value	Reference
CD4+ memory regulatory T cells (Tregs)	*HLA-DQA2*	1.2×10^{-5}	Schmiedel BJ. *et al*. (1)
CD4+ memory follicular helper T cells (TFH)	*HLA-DQA2*	2.4×10^{-5}	Schmiedel BJ. *et al*. (1)
CD8+ T cells	*HLA-DQA2*	4.6×10^{-5}	Schmiedel BJ. *et al*. (1)
B-cells	*HLA-DQA2*	6.2×10^{-6}	Schmiedel BJ. *et al*. (1)
Monocytes	*HLA-DQA2*	8.1×10^{-6}	Schmiedel BJ. *et al*. (1)
Monocytes	*HLA-DOB*	6.6×10^{-7}	Fairfax BP. *et al*. (2)
Monocytes	*TAP2*	4.3×10^{-4}	Fairfax BP. *et al*. (2)
Monocytes non-classical	*HLA-DQA2*	4.5×10^{-5}	Schmiedel BJ. *et al*. (1)

ImmuneRegulation (https://immuneregulation.mssm.edu/) was used to identified *cis*-eQTL (3)

References

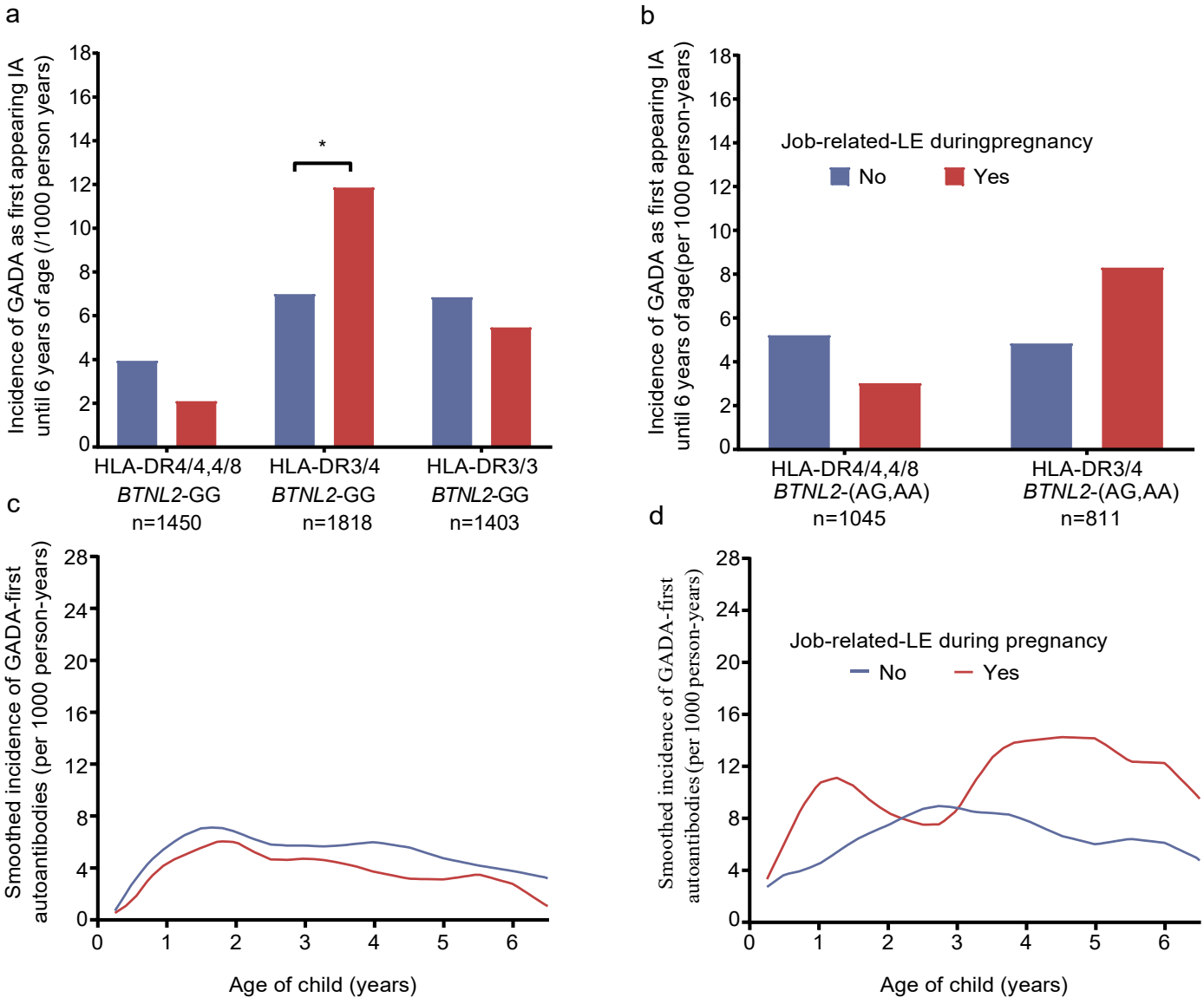
1. Schmiedel BJ, Singh D, Madrigal A et al. Impact of genetic polymorphisms on human immune cell gene expression. Cell 2018;175:1701-1715 e1716
2. Fairfax BP, Makino S, Radhakrishnan J et al. Genetics of gene expression in primary immune cells identifies cell type-specific master regulators and roles of HLA alleles. Nat Genet 2012;44:502-510
3. Kalayci S, Selvan ME, Ramos I et al. Immune Regulation: a web-based tool for identifying human immune regulatory elements. Nucleic Acids Res. 2019;47:W142-W150

ESM Table 10. Post Hoc Exploratory Analysis of Any IA by Specific Life Event Category and HLA-DR Status

Specific Life Events (LE)	**Reported Maternal Life Events and Risk of Islet Autoimmunity by HLA-DR Genotype of Child**					
	HLA-DR4/4, 4/8, 4/X Children, N= 2509 IA positive, n= 189		**HLA-DR3/4 Children N = 2492, IA positive, n=263**		**HLA-DR3/3, 3/X Children, N = 1363 , IA positive, n= 71**	
	HR*(95%CI)	**p-value**	**HR*(95%CI)**	**p-value**	**HR*(95%CI)**	**p-value**
Disease/Injury(self or others)	1.10 (0.79 – 1.54)	0.57	0.91 (0.68 – 1.21)	0.50	0.73 (0.42 – 1.29)	0.29
Significant loss (death of family member or friend)+	**0.45 (0.24 – 0.86)+**	**0.02**	1.04 (0.70 – 1.55)+	0.86	1.83 (0.95 – 3.53)+	0.07
Serious Interpersonal (marriage, separation, divorce, conflicts with spouse/relative/friend, move or change in family composition)	1.10 (0.79 – 1.53)	0.57	1.27 (0.96 – 1.67)	0.09	1.55 (0.94 – 2.56)	0.08
Job-related (self or spouse quit/lost job, started work/ school**)**	**0.58 (0.58 – 0.86)**	**0.01**	1.18 (0.90 – 1.56)	0.23	0.68 (0.37 – 1.25)	0.21
Financial Difficulties (self or spouse)	1.02 (0.58 – 1.80)	0.95	0.94 (0.59 – 1.50)	0.80	0.75 (0.31 – 1.83)	0.75
Other	1.13 (0.71 – 1.81)	0.60	0.67 (0.42 – 1.08)	0.10	1.41 (0.72 – 2.77)	0.32

* = Specific life event examined together in a multivariate model on the hazard of IA until 6 years of age adjusting for family history with type 1 diabetes, gender, country of residence and SNPs; full models included 6364 total children including 523 IA positives.

+ = Significant loss shows evidence of multiplicative interaction with HLA groups (p-value=0.01)



AG,AA

n

ESM Figure 1. (a) A job-related event in pregnancy was associated with GADA as the first-appearing autoantibody in HLA-DR3/4 children with the *BTNL2*-GG genotype (*p < 0.05) but not for HLA-DR4/4, 4/8 (p = 0.24)) or HLA-DR3/3 (p = 0.52)) with the *BTNL2*-GG genotype. (b)) A job-related event in pregnancy was not associated with GADA as the first-appearing autoantibody in HLA-DR4/4,4/8 children (p = 0.31) or HLA-DR3/4 children (p = 0.17) with the *BTNL2*-AG,AA genotype. (c) Age-specific incidence of GADA as the first-appearing autoantibody by job-related life eve t during pregnancy for HLA-DR4/4,4/8,3/3 children and (D) for HLA DR3/4children.

The TEDDY Study Group

Colorado Clinical Center: Marian Rewers, M.D., Ph.D., PI[1,4,5,6,9,10], Aaron Barbour, Kimberly Bautista[11], Judith Baxter[8,911], Daniel Felipe-Morales, Kimberly Driscoll, Ph.D.[8], Brigitte I. Frohnert, M.D.[2,13], Marisa Stahl, M.D.[12], Patricia Gesualdo[2,6,11,13], Michelle Hoffman[11,12,13], Rachel Karban[11], Edwin Liu, M.D.[12], Jill Norris, Ph.D.[2,3,11], Stesha Peacock, Hanan Shorrosh, Andrea Steck, M.D.[3,13], Megan Stern, Erica Villegas[2], Kathleen Waugh[6,7,11]. University of Colorado, Anschutz Medical Campus, Barbara Davis Center for Childhood Diabetes.

Finland Clinical Center: Jorma Toppari, M.D., Ph.D., PI[¥^1,4,10,13], Olli G. Simell, M.D., Ph.D., Annika Adamsson, Ph.D.[^11], Suvi Ahonen*[±§], Mari Åkerlund*[±§], Leena Hakola*, Anne Hekkala, M.D.[µ¤], Henna Holappa[µ¤], Heikki Hyöty, M.D., Ph.D.*[±6], Anni Ikonen[µ¤], Jorma Ilonen, M.D., Ph.D.[¥¶3], Sinikka Jäminki*[±], Sanna Jokipuu[^], Leena Karlsson[^], Jukka Kero M.D., Ph.D.[¥^], Miia Kähönen[µ¤11,13], Mikael Knip, M.D., Ph.D.*[±5], Minna-Liisa Koivikko[µ¤], Merja Koskinen*[±], Mirva Koreasalo*[±§2], Kalle Kurppa, M.D., Ph.D.*[±12], Jarita Kytölä*[±], Tiina Latva-aho[µ¤], Katri Lindfors, Ph.D.*[12], Maria Lönnrot, M.D., Ph.D.*[±6], Elina Mäntymäki[^], Markus Mattila*, Maija Miettinen[§2], Katja Multasuo[µ¤], Teija Mykkänen[µ¤], Tiina Niininen[±*11], Sari Niinistö[±§2], Mia Nyblom*[±], Sami Oikarinen, Ph.D.*[±], Paula Ollikainen[µ¤] , Zhian Othmani[^], Sirpa Pohjola [µ¤], Petra Rajala[^], Jenna Rautanen[±§], Anne Riikonen*[±§2], Eija Riski[^], Miia Pekkola[*±], Minna Romo[^], Satu Ruohonen[^], Satu Simell, M.D., Ph.D.[¥12], Maija Sjöberg[^], Aino Stenius[µ¤11], Päivi Tossavainen, M.D.[µ¤], Mari Vähä-Mäkilä[¥], Sini Vainionpää[^], Eeva Varjonen[^11], Riitta Veijola, M.D., Ph.D.[µ¤13], Irene Viinikangas[µ¤], Suvi M. Virtanen, M.D., Ph.D.*[±§2]. [¥]University of Turku, *Tampere University, [µ]University of Oulu, [^]Turku University Hospital, Hospital District of Southwest Finland, [±]Tampere University Hospital, [¤]Oulu University Hospital, §National Institute for Health and Welfare, Finland, [¶]University of Kuopio.

Georgia/Florida Clinical Center: Jin-Xiong She, Ph.D., PI[1,3,4,10], Desmond Schatz, M.D.*[4,5,7,8], Diane Hopkins[11], Leigh Steed[11,12,13], Jennifer Bryant[11], Katherine Silvis[2], Michael Haller, M.D.*[13], Melissa Gardiner[11], Richard McIndoe, Ph.D., Ashok Sharma, Stephen W. Anderson, M.D.[^], Laura Jacobsen, M.D.*[13], John Marks, DHSc.*[11,13], P.D. Towe*. Center for Biotechnology and Genomic Medicine, Augusta University. *University of Florida, [^]Pediatric Endocrine Associates, Atlanta.

Germany Clinical Center: Anette G. Ziegler, M.D., PI[1,3,4,10], Ezio Bonifacio Ph.D.*[5], Cigdem Gezginci, Anja Heublein, Eva Hohoff[¥2], Sandra Hummel, Ph.D.[2], Annette Knopff[7], Charlotte Koch, Sibylle Koletzko, M.D.[¶12], Claudia Ramminger[11], Roswith Roth, Ph.D.[8], Jennifer Schmidt, Marlon Scholz, Joanna Stock[8,11,13], Katharina Warncke, M.D.[13], Lorena Wendel, Christiane Winkler, Ph.D.[2,11]. Forschergruppe Diabetes e.V. and Institute of Diabetes Research, Helmholtz Zentrum München, Forschergruppe Diabetes, and Klinikum rechts der Isar, Technische Universität München. *Center for Regenerative Therapies, TU Dresden, [¶]Dr. von Hauner Children's Hospital, Department of Gastroenterology, Ludwig Maximillians University Munich, [¥]University of Bonn, Department of Nutritional Epidemiology.

Sweden Clinical Center: Åke Lernmark, Ph.D., PI[1,3,4,5,6,8,9,10], Daniel Agardh, M.D., Ph.D.[6,12], Carin Andrén Aronsson, Ph.D.[2,11,12], Maria Ask, Rasmus Bennet, Corrado Cilio, Ph.D., M.D.[5,6], Susanne Dahlberg, Helene Engqvist, Emelie Ericson-Hallström, Annika Björne Fors, Lina Fransson, Thomas Gard, Monika Hansen, Hanna Jisser, Fredrik Johansen, Berglind Jonsdottir, M.D., Ph.D.[11], Helena Elding Larsson, M.D., Ph.D.[6,13], Marielle Lindström, Markus Lundgren, M.D., Ph.D.[13], Marlena Maziarz, Ph.D., Maria Månsson-Martinez, Jessica Melin[11], Zeliha Mestan, Caroline Nilsson, Karin Ottosson, Kobra Rahmati, Anita Ramelius, Falastin Salami, Anette Sjöberg, Birgitta Sjöberg, Carina Törn, Ph.D.[3], Åsa Wimar[13]. Lund University.

Washington Clinical Center: William A. Hagopian, M.D., Ph.D., PI[1,3,4,5,6,7,10,12,13], Michael Killian[6,7,11,12], Claire Cowen Crouch[11,13], Jennifer Skidmore[2], Masumeh Chavoshi, Arlene Meyer, Jocelyn Meyer, Denise Mulenga[11], Nole Powell, Jared Radtke, Matei Romancik, Shreya Roy, Davey Schmitt, Sarah Zink. Pacific Northwest Research Institute.

Pennsylvania Satellite Center: Dorothy Becker, M.D., Margaret Franciscus, MaryEllen Dalmagro-Elias Smith[2], Ashi Daftary, M.D., Mary Beth Klein, Chrystal Yates. Children's Hospital of Pittsburgh of UPMC.

Data Coordinating Center: Jeffrey P. Krischer, Ph.D.,PI[1,4,5,9,10], Sarah Austin-Gonzalez, Maryouri Avendano, Sandra Baethke, Brant Burkhardt, Ph.D.[5,6], Martha Butterworth[2], Joanna Clasen, David Cuthbertson, Christopher Eberhard, Steven Fiske[8], Jennifer Garmeson, Veena Gowda, Kathleen Heyman, Belinda Hsiao, Christina Karges, Francisco Perez Laras, Qian Li, Ph.D.[2,3], Shu Liu, Xiang Liu, Ph.D.[2,3,8,13], Kristian Lynch, Ph.D. [5,6,8], Colleen Maguire, Jamie Malloy, Cristina McCarthy[11], Hemang Parikh, Ph.D.[3], Cassandra Remedios, Chris Shaffer, Laura Smith, Ph.D.[8,11], Susan Smith[11], Noah Sulman, Ph.D., Roy Tamura, Ph.D.[1,2,11,12,13], Dena Tewey, Michael Toth, Ulla Uusitalo, Ph.D.[2], Kendra Vehik, Ph.D.[4,5,6,8,13], Ponni Vijayakandipan, Jimin Yang, Ph.D., R.D.[2]. *Past staff: Michael Abbondondolo, Lori Ballard, Rasheedah Brown, Stephen Dankyi, David Hadley, Ph.D., Hye-Seung Lee, Ph.D., Wendy McLeod, Aubrie Merrell, Steven Meulemans, Ryan Quigley.* University of South Florida.

Autoantibody Reference Laboratories: Liping Yu, M.D.[^5], Dongmei Miao, M.D.[^], Polly Bingley, M.D., FRCP*[5], Alistair Williams*, Kyla Chandler*, Ilana Kelland*, Yassin Ben Khoud*, Huma Zahid*, Matthew Randell *. [^]Barbara Davis Center for Childhood Diabetes, University of Colorado Denver, *Bristol Medical School, University of Bristol, UK.

HLA Reference Laboratory: William Hagopian[3], MD, PhD, Masumeh Chavoshi, Jared Radtke, Sarah Zink. Pacific Northwest Research Institute, Seattle WA. (Previously Henry Erlich, Ph.D.[3], Steven J. Mack, Ph.D., Anna Lisa Fear. Center for Genetics, Children's Hospital Oakland Research Institute.)

SNP Laboratory: Stephen S. Rich, Ph.D.[3], Wei-Min Chen, Ph.D.[3], Suna Onengut-Gumuscu, Ph.D.[3], Emily Farber, Rebecca Roche Pickin, Ph.D., Jonathan Davis, Jordan Davis, Dan Gallo, Jessica Bonnie, Paul Campolieto. Center for Public Health Genomics, University of Virginia.

Repository: Sandra Ke, Niveen Mulholland, Ph.D. NIDDK Biosample Repository at Fisher BioServices.

Project scientist: Beena Akolkar, Ph.D.[1,3,4,5,6,7,9,10]. National Institutes of Diabetes and Digestive and Kidney Diseases.

Other contributors: Kasia Bourcier, Ph.D.[5], National Institutes of Allergy and Infectious Diseases. Thomas Briese, Ph.D.[6], Columbia University. Suzanne Bennett Johnson, Ph.D.[8,11], Florida State University. Eric Triplett, Ph.D.[6], University of Florida.

Committees:

[1]Ancillary Studies, [2]Diet, [3]Genetics, [4]Human Subjects/Publicity/Publications, [5]Immune Markers, [6]Infectious Agents, [7]Laboratory Implementation, [8]Psychosocial, [9]Quality Assurance, [10]Steering, [11]Study Coordinators, [12]Celiac Disease, [13]Clinical Implementation.