

Supplementary Table S2. Overall Characteristics of Autoantibody-positive Relatives

Characteristics	N=1,061
Age (Years)	16.3±13.0
Age <18 years old: N (%)	768 (72.4%)
Male: N (%)	504 (47.7%)
Non-Hispanic: N (%)	932 (91.1%)
BMI Z-score	0.6 ±1.1
Abnormal OGTT (%)	318 (30.0%)
<i>TCF7L2</i> SNP: T2D-associated alleles: N (%)	
0 alleles	510 (48.1%)
1 allele	466 (43.9%)
2 alleles	85 (8.0%)

Values are mean ±SD except if otherwise noted. Missing values: BMI Z-score: N=68, ethnicity: N=38, sex: N=4

Supplementary Table S3. Interaction between BMI and *TCF7L2* SNP in Autoantibody-positive Relatives

Age group (Separate models)	Interaction term	Dependent outcomes		
	BMI* <i>TCF7L2</i> 0 alleles v	1/I _F	30-min C-Peptide Index	oDlc
All ages	1 or 2 alleles	0.5822	0.6845	0.7276
Adults	1 or 2 alleles	0.9704	0.7924	0.9056
Children	1 or 2 alleles	0.6765	0.8248	0.5832

P-values for interaction terms. All models include BMI Z-score and *TCF7L2*. P-values under the Bonferroni-corrected level of significance of p-values <0.0086 are bolded.

Supplementary Table S4: Analysis with unrelated participants only (n=1,022), after exclusion of n=39 individuals from 35 multi-member families. For families with more than one relative, only one relative, selected at random, has been included.

Table S4-A. Univariable Analysis (N=1,022)

Predictor	1/I _F	30-min C-peptide index	Disposition index (original)	Disposition index (corrected)
Age	<0.0001 <i>r</i> =-0.3208	<0.0001 <i>r</i> =0.3747	0.0591 <i>r</i> =0.0724	<0.0001 <i>r</i> =-0.1974
BMI Z-score	<0.0001 <i>r</i> =-0.4416	<0.0001 <i>r</i> =0.2737	0.0003 <i>r</i> =-0.1433	<0.0001 <i>r</i> =-0.3655
Ethnicity (Non-Hispanic v Hispanic)	0.0010 NH > H	0.0109 NH > H	0.6086	0.0139 NH > H
Sex (Male v Female)	0.0652	0.0184	0.9917	0.1675
<i>TCF7L2</i> (1 or 2 v 0 alleles)	0.2043	0.8073	0.7516	0.2549

Numbers represent p-values except where noted. For statistically significant correlations, Spearman correlation coefficients (*r*) are shown for continuous variables and direction of difference for categorical variables. P-values under the Bonferroni-corrected level of significance of p-values <0.0086 are bolded.

Table S4-B. Multivariable Analysis for Each Dependent Outcome (All Ages, N=1,022)

Predictor	Dependent outcome			
	1/I _F	30-min C-Peptide index	Disposition index, original	Disposition index, corrected
Age	0.0237 Est=-0.0042	<0.0001 Est=0.0143	<0.0001 Est=0.0099	0.7755
BMI Z-score	<0.0001 Est=-0.2257	<0.0001 Est=0.1234	<0.0001 Est=-0.1087	<0.0001 Est=-0.5451
Ethnicity (Non-Hispanic v Hispanic)	0.0264	0.1582	0.7350	0.0906
Sex (Male v Female)	0.0229	0.5363	0.5697	0.0581
<i>TCF7L2</i> (1 or 2 v 0 alleles)	0.2507	0.8675	0.7224	0.5040

All models have been adjusted for age, BMI- Z-score, ethnicity and sex. Numbers represent p-values except where noted. Regression model parameter estimates (Est) are given for statistically significant relationships. P-values under the Bonferroni-corrected level of significance of p-values <0.0086 are bolded.

Table S4-C. Multivariable Analysis for Each Dependent Outcome (Adults, Ages 18 Years Old or Older, N=283)

Predictor	Dependent outcome			
	1/I _F	30-min C-peptide index	Disposition index, original	Disposition index, corrected
Age	0.0474	0.4237	0.4163	0.1017
BMI Z-score	<0.0001 Est=-0.3429	0.0720	0.0056 Est=-0.2230	<0.0001 Est=-0.9159
Ethnicity (Non-Hispanic v Hispanic)	0.0482	0.4328	0.1546	0.0470
Sex (Male v Female)	0.6748	0.4708	0.0295	0.3886
<i>TCF7L2</i> (1 or 2 v 0 alleles)	0.1627	0.5197	0.2960	0.1508

All models have been adjusted for age, BMI- z-score, ethnicity and sex. Numbers represent p-values except where noted. Regression model parameter estimates (Est) are given for statistically significant relationships. P-values under the Bonferroni-corrected level of significance of p-values <0.0086 are bolded

Table S4-D. Multivariable Analysis for Each Dependent Outcome (Children, Ages <18 Years Old, N=739)

Predictor	Dependent outcome			
	1/I _F	30-min C-peptide Index	Disposition index, original	Disposition index, corrected
Age	<0.0001 Est=-0.0713	<0.0001 Est=0.0656	0.5021	<0.0001 Est=-0.1467
BMI Z-score	<0.0001 Est=-0.2073	<0.0001 Est=0.1434	0.0008 Est=-0.0905	<0.0001 Est=-0.4957
Ethnicity (Non-Hispanic v Hispanic)	0.5862	0.9657	0.4756	0.9959
Sex (Male v Female)	<0.0001 Est=0.1693	0.4261	0.0081 Est=0.1601	<0.0001 Est=0.5034
<i>TCF7L2</i> (1 or 2 v 0 alleles)	0.2735	0.4993	0.8338	0.3892

All models have been adjusted for age, BMI- z-score, ethnicity and sex. Numbers represent p-values except where noted. Regression model parameter estimates (Est) are given for statistically significant relationships. P-values under the Bonferroni-corrected level of significance of p-values <0.0086 are bolded.

Supplementary Table S5: Comparison of 2 versus 0 alleles in unrelated participants only (n=1,022). For families with more than one relative, only one relative, selected at random, has been included.

Table S5-A. Univariable Analysis (N=575)

Predictor	1/I _F	30-min C-peptide index	Disposition index (original)	Disposition index (corrected)
Age	<0.0001 <i>r</i> =-0.3328	<0.0001 <i>r</i> =0.4032	0.1746 <i>r</i> =0.0684	<0.0001 <i>r</i> =-0.2076
BMI Z-score	<0.0001 <i>r</i> =-0.3940	<0.0001 <i>r</i> =0.2686	0.0707 <i>r</i> =-0.0948	<0.0001 <i>r</i> =-0.3035
Ethnicity (Non-Hispanic v Hispanic)	0.0212 NH > H	0.0559 NH > H	0.8654	0.1612
Sex (Male v Female)	0.0371	0.0081	0.9136	0.1040
<i>TCF7L2</i> (2 v 0 alleles)	0.1277	0.3695	0.2009	0.1577

Numbers represent p-values except where noted. For statistically significant correlations, Spearman correlation coefficients (*r*) are shown for continuous variables and direction of difference for categorical variables. P-values under the Bonferroni-corrected level of significance of p-values <0.0086 are bolded.

Table S5-B. Multivariable Analysis for Each Dependent Outcome (All Ages, N=575)

Predictor	Dependent outcome			
	1/I _F	30-min C-Peptide index	Disposition index, original	Disposition index, corrected
Age	0.2560	<0.0001 Est=0.0170	0.0001 Est=0.0134	0.3951
BMI Z-score	<0.0001 Est=-0.2088	0.0002 Est=0.1134	0.0076 Est=-0.1057	<0.0001 Est=-0.5059
Ethnicity (Non-Hispanic v Hispanic)	0.1766	0.1659	0.8484	0.3322
Sex (Male v Female)	0.0434	0.6915	0.3876	0.0825
<i>TCF7L2</i> (2 v 0 alleles)	0.1655	0.4839	0.4275	0.1805

All models have been adjusted for age, BMI- Z-score, ethnicity and sex. Numbers represent p-values except where noted. Regression model parameter estimates (Est) are given for statistically significant relationships. P-values under the Bonferroni-corrected level of significance of p-values <0.0086 are bolded.

Table S5-C. Multivariable Analysis for Each Dependent Outcome (Adults, Ages 18 Years Old or Older, N=154)

Predictor	Dependent outcome			
	1/I _F	30-min C-peptide index	Disposition index, original	Disposition index, corrected
Age	0.3103	0.8711	0.3934	0.3314
BMI Z-score	<0.0001 Est=-0.3947	0.0341 Est=0.1635	0.1134	0.0006 Est=-1.0180
Ethnicity (Non-Hispanic v Hispanic)	0.0228 Est=-0.5415	0.2552	0.1644	0.0389 Est=-1.8497
Sex (Male v Female)	0.8636	0.5403	0.1589	0.4807
<i>TCF7L2</i> (2 v 0 alleles)	0.3729	0.3596	0.9897	0.5462

All models have been adjusted for age, BMI- z-score, ethnicity and sex. Numbers represent p-values except where noted. Regression model parameter estimates (Est) are given for statistically significant relationships. P-values under the Bonferroni-corrected level of significance of p-values <0.0086 are bolded.

Table S5-D. Multivariable Analysis for Each Dependent Outcome (Children, Ages <18 Years Old, N=421)

Predictor	Dependent outcome			
	1/I _F	30-min C-peptide Index	Disposition index, original	Disposition index, corrected
Age	<0.0001 Est=-0.0700	<0.0001 Est=0.0666	0.6958	<0.0001 Est=-0.1465
BMI Z-score	<0.0001 Est=-0.1967	0.0002 Est=0.1192	0.0111 Est=-0.0959	<0.0001 Est=-0.4818
Ethnicity (Non-Hispanic v Hispanic)	0.7701	0.6597	0.3726	0.4451
Sex (Male v Female)	0.0003 Est=0.2056	0.4365	0.0177 Est=0.1918	0.0003 Est=0.5895
TCF7L2 (2 v 0 alleles)	0.0430	0.7669	0.3544	0.0515

All models have been adjusted for age, BMI- z-score, ethnicity and sex. Numbers represent p-values except where noted. Regression model parameter estimates (Est) are given for statistically significant relationships. P-values under the Bonferroni-corrected level of significance of p-values <0.0086 are bolded.

Supplementary Table S6: Analysis with non-Hispanic White, unrelated participants only (n=839). For families with more than one relative, only one relative, selected at random, has been included.

Table S6-A. Univariable Analysis (N=839)

Predictor	1/I _F	30-min C-peptide index	Disposition index (original)	Disposition index (corrected)
Age	<0.0001 <i>r</i> =-0.3333	<0.0001 <i>r</i> =0.3716	0.0957 <i>r</i> =0.0702	<0.0001 <i>r</i> =-0.2045
BMI Z-score	<0.0001 <i>r</i> =-0.4435	<0.0001 <i>r</i> =0.2618	0.0003 <i>r</i> =-0.1560	<0.0001 <i>r</i> =-0.3740
Sex (Male v Female)	0.5063	0.0952	0.6853	0.7189
TCF7L2 (1 or 2 v 0 alleles)	0.0926	0.6879	0.5786	0.0976

Numbers represent p-values except where noted. For statistically significant correlations, Spearman correlation coefficients (*r*) are shown for continuous variables and direction of difference for categorical variables. P-values under the Bonferroni-corrected level of significance of p-values <0.0086 are bolded.

Table S6-B. Multivariable Analysis for Each Dependent Outcome (All Ages, N=839)

Predictor	Dependent outcome			
	1/I _F	30-min C-Peptide index	Disposition index, original	Disposition index, corrected
Age	0.0761	<0.0001 Est=0.0143	<0.0001 Est=0.0109	0.4853
BMI Z-score	<0.0001 Est=-0.2262	<0.0001 Est=0.1258	0.0003 Est=-0.1079	<0.0001 Est=-0.5427
Sex (Male v Female)	0.1360	0.9501	0.7349	0.2162
TCF7L2 (1 or 2 v 0 alleles)	0.0630	0.5706	0.6092	0.2653

All models have been adjusted for age, BMI- Z-score, ethnicity and sex. Numbers represent p-values except where noted. Regression model parameter estimates (Est) are given for statistically significant relationships. P-values under the Bonferroni-corrected level of significance of p-values <0.0086 are bolded.

Table S6-C. Multivariable Analysis for Each Dependent Outcome (Adults, Ages 18 Years Old or Older, N=234)

Predictor	Dependent outcome			
	1/I _F	30-min C-peptide index	Disposition index, original	Disposition index, corrected
Age	0.0169	0.3864	0.2449	0.0360
BMI Z-score	<0.0001 Est=-0.3655	0.1247	0.0014 Est=-0.2831	<0.0001 Est=-1.0206
Sex (Male v Female)	0.8699	0.8042	0.0258	0.1995
TCF7L2 (1 or 2 v 0 alleles)	0.1221	0.7606	0.2158	0.1058

All models have been adjusted for age, BMI- z-score, ethnicity and sex. Numbers represent p-values except where noted. Regression model parameter estimates (Est) are given for statistically significant relationships. P-values under the Bonferroni-corrected level of significance of p-values <0.0086 are bolded.

Table S6-D. Multivariable Analysis for Each Dependent Outcome (Children, Ages <18 Years Old, N=605)

Predictor	Dependent outcome			
	1/I _F	30-min C-peptide Index	Disposition index, original	Disposition index, corrected

Age	<0.0001 Est=-0.0698	<0.0001 Est=0.0616	0.5187	<0.0001 Est=-0.1434
BMI Z-score	<0.0001 Est=-0.2034	<0.0001 Est=0.1443	0.0088 Est=-0.0771	<0.0001 Est=-0.4701
Sex (Male v Female)	<0.0001 Est=0.1546	0.6242	0.0153 Est=0.1585	0.0006 Est=0.4650
<i>TCF7L2</i> (1 or 2 v 0 alleles)	0.0397 Est=0.0967	0.9382	0.9149	0.1337

All models have been adjusted for age, BMI- z-score, ethnicity and sex. Numbers represent p-values except where noted. Regression model parameter estimates (Est) are given for statistically significant relationships. P-values under the Bonferroni-corrected level of significance of p-values <0.0086 are bolded.