A Type 1 Diabetes Genetic Risk Score Can Aid Discrimination Between Type 1 and Type 2 Diabetes in Young Adults

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OBJECTIVE

With rising obesity, it is becoming increasingly difficult to distinguish between type 1 diabetes (T1D) and type 2 diabetes (T2D) in young adults. There has been substantial recent progress in identifying the contribution of common genetic variants to T1D and T2D. We aimed to determine whether a score generated from common genetic variants could be used to discriminate between T1D and T2D and also to predict severe insulin deficiency in young adults with diabetes.

RESEARCH DESIGN AND METHODS

We developed genetic risk scores (GRSs) from published T1D- and T2D-associated variants. We first tested whether the scores could distinguish clinically defined T1D and T2D from the Wellcome Trust Case Control Consortium (WTCCC) (n = 3,887). We then assessed whether the T1D GRS correctly classified young adults (diagnosed at 20–40 years of age, the age-group with the most diagnostic difficulty in clinical practice; n = 223) who progressed to severe insulin deficiency <3 years from diagnosis.

RESULTS

In the WTCCC, the T1D GRS, based on 30 T1D-associated risk variants, was highly discriminative of T1D and T2D (area under the curve [AUC] 0.88 [95% CI 0.87–0.89]; $P < 0.0001$), and the T2D GRS added little discrimination (AUC 0.89). A T1D GRS >0.280 (>50th centile in those with T1D) is indicative of T1D (50% sensitivity, 95% specificity). A low T1D GRS (<0.234, <5th centile T1D) is indicative of T2D (53% sensitivity, 95% specificity). Most discriminative ability was obtained from just nine single nucleotide polymorphisms (AUC 0.87). In young adults with diabetes, T1D GRS alone predicted progression to insulin deficiency (AUC 0.87 [95% CI 0.82–0.92]; $P < 0.0001$). T1D GRS, autoantibody status, and clinical features were independent and additive predictors of severe insulin deficiency (combined AUC 0.96 [95% CI 0.94–0.99]; $P < 0.0001$).

CONCLUSIONS

A T1D GRS can accurately identify young adults with diabetes who will require insulin treatment. This will be an important addition to correctly classifying individuals with diabetes when clinical features and autoimmune markers are equivocal.

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Rising obesity rates are making it more difficult to distinguish between type 1 diabetes (T1D) and type 2 diabetes (T2D), particularly in young adults. It is increasingly recognized that autoimmune T1D may occur at older ages (1,2); with increasing population obesity, more young people are developing T2D, and many with T1D will be obese (3). Determining the correct diagnosis is important because the best treatment for each condition is different. People with T1D will require insulin treatment because the insulin-producing pancreatic β-cells are rapidly destroyed by an autoimmune process. Severe endogenous insulin deficiency results in high glycemic variability and a requirement for treatment with exogenous insulin, with additional measures such as carbohydrate counting and intensive insulin treatment (4). T2D is caused by a gradual decline in β-cell function in the face of insulin resistance, and initial management is most commonly accomplished with diet or therapy with oral hypoglycemic agents. Up to 15% of young adults with diabetes are wrongly classified and incorrectly treated (5). Initial clinical diagnosis is not systematic and once made is rarely changed. The misdiagnosis of T2D as T1D results in unnecessary initial insulin treatment, leading to higher drug/monitoring costs and more side effects (weight gain, hypoglycemia). Misdiagnosis of T1D as T2D results in poor glycemic control, frequent health care contact for increased treatment, inappropriate insulin regimens, and the risk of life-threatening ketoacidosis (5).

The current diagnostic tests used to diagnose diabetes subtypes have limitations. The presence of one or multiple islet autoantibodies (GAD, IA-2, IAA, and ZnT8) is a defining feature of T1D with >90% of newly diagnosed patients being positive for at least one of four autoantibodies at diagnosis (6). However, autoantibodies are not perfect discriminators because of the following: *1*) they can also present in individuals without T1D; *2*) comprehensive testing of autoantibodies is not usually performed in clinical practice; *3*) islet autoantibody positivity is lower for individuals with T1D when diagnosed in adulthood rather than childhood; and *4*) islet autoantibody positivity is also lower in individuals with T1D if they were tested after diagnosis (6–8). The measurement of endogenous insulin (using either serum or urine C-peptide) can accurately distinguish between T1D and T2D outside of the honeymoon period (9,10), but its use is more limited at diagnosis (11).

There is a strong genetic component to T1D and T2D susceptibility that can be measured by single nucleotide polymorphism (SNP) genotyping. The HLA region contains several strong risk and protective alleles for T1D. A tag SNP genotyping approach can capture much of the risk in the HLA region more simply than classic HLA typing (12,13); genotyping just two SNPs can accurately capture the high-risk DR3 (DRB1*0301-DQA1*0501-DQB1*0201) and DR4-DQ8 (DRB1*04-DQA1*0301-DQB1*0302) alleles (12). Outside the HLA region, >40 SNPs have been robustly associated with T1D (14). Combining HLA and non-HLA variants was recently shown to be significantly better than HLA alone for predicting the development of T1D and islet autoantibodies both in offspring of T1D parents (15,16) and subjects with high-risk HLA genotypes (17). More than 69 SNPs have also been associated with T2D from genome-wide association studies (GWAS) (18).

In this study, we assessed whether a genetic risk score (GRS) could provide a simple and inexpensive test for the classification of diabetes. Although the classification of T1D and T2D is etiological, an important outcome is progression to severe insulin deficiency because this determines whether treatment with insulin is required soon after diagnosis and whether noninsulin therapy is likely to be effective (19). Therefore, we also tested the ability of a GRS to predict severe insulin deficiency that requires insulin treatment within 3 years of diagnosis.

RESEARCH DESIGN AND METHODS

Subjects: Wellcome Trust Case Control Consortium

To test whether the T1D or T2D GRS can discriminate between clinically strictly defined T1D and T2D, we used the Wellcome Trust Case Control Consortium (WTCCC) study (20). The classification of diabetes was determined largely based on clinical features in this cohort. The WTCCC subjects have been described in detail previously; in brief, the WTCCC T1D patients (*n* = 1,938) all received a clinical diagnosis of T1D at <17 years of age and were treated with insulin from the time of diagnosis. The WTCCC T2D patients (*n* = 1,914) were diagnosed at >25 and <75 years of age, were GAD autoantibody negative on testing, and were either treated with diet/oral hypoglycemic agents or had an interval of at least 1 year between diagnosis and the institution of insulin therapy.

Subjects: Progression to Insulin Deficiency: South West England Cohort

We assessed a cross-sectional cohort of people in whom diabetes was diagnosed between the ages of 20 and 40 years (*n* = 223), who had had diabetes for >3 years, and who had self-reported as white European from Devon and Cornwall in South West England. Known monogenic diabetes and secondary diabetes patients were excluded. At study recruitment, BMI was recorded, and GAD and IA-2 autoantibodies were measured as previously described (21).

All participants were assessed for the presence or absence of severe insulin deficiency (requiring insulin treatment at 3 years after diagnosis). We categorized people as severely insulin deficient if they received continuous insulin treatment at <3 years from the time of diagnosis and had a low measured C-peptide level (nonfasting measured <0.6 nmol/L or equivalent fasting blood glucose level or posthome meal urine C-peptide–to–creatinine ratio [10]) (Supplementary Fig. 1).

Subjects: Type 1 Diabetes Genetics Consortium

To enable the accurate imputation of classic HLA types, we used the Type 1 Diabetes Genetics Consortium (T1DGC) Immunochip/HLA Reference Panel provided by the SNP2HLA program (described in the study by Jia et al. [22]). This panel is a European ancestry reference panel based on data collected by the T1DGC from 5,225 individuals (23) (http://www.t1dgc.org).

GRSs

We generated GRSs for T1D and T2D using robustly associated genetic variants from published studies. A GRS is the sum across SNPs of the number of risk-increasing alleles (0, 1, or 2) at that SNP multiplied by the ln(odds ratio [OR])

for each allele divided by the number of alleles. This assumes that each of the risk alleles has a log-additive effect on T1D risk. The DR3 (DRB1*0301-DQA1*0501-DQB1*0201) and DR4-DQ8 (DRB1*04-DQA1*0301-DQB1*0302) haplotypes do not fit this log-additive model, with DR3/DR4-DQ8 individuals having the highest OR; weights for DR3/DR4-DQ8 were assigned based on imputed haplotypes (see Winkler et al. [15] and Supplementary Table 1).

Selection of SNPs for Generating the T1D GRS

For the T1D GRS, we combined both SNPs in the HLA region and non-HLA loci. We then selected a set of 40 non-HLA SNPs that have been robustly associated with T1D (24). ORs for each SNP were obtained from the largest available meta-analysis study using T1Dbase (https://www.t1dbase.org/page/Welcome/display). Common T1D risk and protective HLA alleles were selected based on the study by Noble et al. (25). ORs for the DR3/DR4-DQ8 haplotype combinations were obtained from Winkler et al. (15). ORs for the remaining HLA alleles were obtained from published literature (25,26). We used two SNPs (rs2187668 and rs7454108) to capture the DR3/DR4-DQ8 haplotypes (12). These SNPs were shown by Barker et al. (12) to be 98.6% sensitive and 99.7% specific for tagging DR3/DR4-DQ8. For the remaining HLA alleles, we used the 5,224 individuals in the T1DGC panel who have been genotyped for both the classic HLA alleles and used the dense immunochip to select single tag SNPs for HLA_DRB1_15 (rs3129889, r^2 = 0.77), HLA_A_24 (rs1264813, r^2 = 0.81), and HLA_B_5701 (rs2395029, r^2 = 1.00) (22). Supplementary Table 1 provides a list of the SNPs included in the GRS and the ORs that were used as weights in this study.

Selection of SNPs for Generating the T2D GRS

To generate a T2D GRS, we selected a set of 69 SNPs that have been robustly associated with T2D (27). We obtained OR estimates for these SNPs from the most recent version of the DIAGRAM consortium GWAS meta-analysis ([27]; http://diagram-consortium.org/index.html), which consists of 12,171 T2D patients and 56,862 control subjects.

Generating GRSs in the WTCCC Cohort

The WTCCC genotyping and quality control of the T1D and T2D samples has been described in detail previously (20). All individuals were genotyped using the Affymetrix 500K SNP Chip. To obtain genotypes for the SNPs selected for inclusion in the T1D and T2D GRSs, we imputed genotypes from the 1,000 genomes and T1DGC reference panels using minimac (28) and SNP2HLA (22), and only included SNPs with an imputation quality R^2 or INFO >0.8. We simulated *INS* (rs689), under Hardy-Weinberg equilibrium, with an allele frequency of 58% and an OR of 1.75, because it was not imputable from the Affymetrix 500K SNP Chip.

Genotyping and Quality Control of the T1D Risk SNPs in the Insulin Deficiency Cohort

We genotyped 31 T1D SNPs (SNP assays for all SNPs could not be designed or were not imputable in the WTCCC) using the KASP genotyping assay by LGC Genomics (Hoddesdon, UK). We excluded SNPs with a genotype success rate of <98% and a Hardy-Weinberg equilibrium of $P < 0.001$. This left 30 SNPs (no SNPs with an OR >1.3 were excluded) and 223 samples for analysis. We excluded four samples in which genotyping results were missing for any of the alleles that had the greatest influence on the GRS (DR3/DR4-DQ8 or HLA_DRB1_15) or more than two other SNPs.

Statistical Methods

We tested the ability of the two GRSs to discriminate between T1D and T2D, and between insulin-deficient individuals and non–insulin-deficient individuals by using the area under the curve (AUC) of the receiver operator characteristic (ROC) statistic. For assessing the discriminative ability of predictors (T1D GRS, T1D autoantibodies, BMI at recruitment, and age at diagnosis) in combination, logistic regression was used, and ROC analysis was performed on the log ORs obtained for each individual from the regression equation. We generated GRS centiles of T1D risk based on the distribution of T1D GRSs in individuals with T1D and T2D from the WTCCC. Positive predictive values (PPVs) and negative predictive values (NPVs) were calculated based on the proportion of people with severe insulin deficiency in our study (20.6%, which is similar to the proportion of incident T1D in the Scottish Diabetes Survey 2013 in this age-group [21.4%], http://www.diabetesinscotland.org.uk/). All analyses were performed using Stata 13 (StataCorp LP, College Station, TX).

RESULTS

A T1D GRS Is Highly Discriminative of Clinically Defined T1D and T2D

Initial testing of the scores was performed in the WTCCC cohort (20), which used strict clinical criteria to define T1D and T2D. The T1D GRS was highly discriminatory, with an AUC of 0.88 (95% CI 0.87–0.89) (Fig. 1). The mean (SD) T1D GRS was 0.279 (0.026) in T1D patients vs. 0.229 (0.034) in T2D patients ($P <$ 0.0001). The T2D GRS was much less discriminatory (AUC 0.64 [95% CI 0.63–0.66]) and only added a small amount of discriminatory power to the T1D GRS (combined GRS AUC 0.89 [95% CI 0.88–0.90]) (Fig. 1). We therefore focused subsequent analyses on the T1D GRS.

Defining Clinically Useful Cut Points for the T1D GRS

The T1D GRS is a quantitative trait, but we explored cutoffs to help the clinical classification of individuals with diabetes as T1D or T2D. Supplementary Table 2 provides a set of examples of T1D GRS cutoffs, sensitivities, and specificities. Scores with 95% specificity for T1D or T2D were identified as being useful for future classification. A GRS of >0.280 (50th centile of T1D GRS in the WTCCC T1D cohort) is indicative of T1D, with 95% specificity and 50% sensitivity. A GRS <0.234 (5th centile of T1D GRS in the WTCCC T1D cohort) is indicative of T2D, with 95% specificity and 53% sensitivity. Other more specific cut points can be used to more reliably rule out T1D or T2D at the expense of the test being useful in a smaller number of people.

A T1D GRS Is Highly Discriminative of Individuals Who Will Progress to Insulin Deficiency

We next assessed the diagnostic accuracy of the T1D GRS in identifying severe insulin deficiency in 223 individuals with diabetes who had received a diagnosis between 20 and 40 years of age, the age-group with the most difficulties in diagnosis in current clinical practice. Characteristics

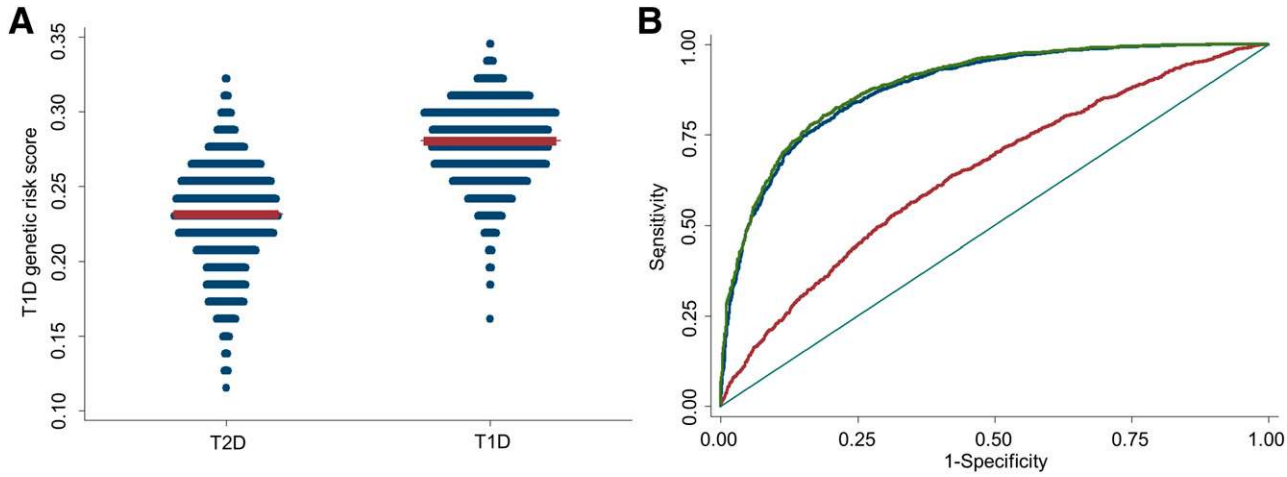

Figure 1—The ability of a T1D risk score to discriminate between clinically defined T1D and T2D diabetes in the WTCCC study. *A*: A dot plot of T1D GRSs by T1D and T2D status. The width of the blue bars indicates frequency, and the red line is the median. *B*: ROC curve of the T1D, T2D, and combined GRSs for discriminating between T1D and T2D. The red line represents the T2D GRS, the blue line represents the T1D GRS, and the green line represents the T1D plus T2D GRS. The respective ROC AUCs are as follows: 0.64, 0.88, and 0.89.

of the South West England cohort are shown in Table 1; 21% of these individuals (46 of 223 individuals) were severely insulin deficient (Supplementary Fig. 1 and Table 1). The T1D GRS was highly discriminatory in this cohort (AUC 0.87 [95% CI 0.82–0.92]) (Figs. 2 and 3). T1D GRS cutoff scores, defined in the WTCCC study above, were similarly sensitive and specific for severe insulin deficiency (Supplementary Table 2). A T1D GRS >0.280 (50th centile of T1D GRS in WTCCC T1D cohort) had 92% specificity and 54% sensitivity for severe insulin deficiency, with a PPV of 63% and an NPV of 88%. A T1D GRS <0.234 (5th centile of T1D GRS in the WTCCC T1D cohort) had 96% specificity and 56% sensitivity for the absence of severe insulin deficiency with a PPV of 98% and an NPV of 37% (Supplementary Table 2). Supplementary Table 2 provides a set of examples of T1D GRS cutoffs, sensitivities, and specificities and the NPV and PPV for the South West England cohort.

T1D GRS Is Independent of and an Additive to Known Discriminators for Identifying People With Diabetes in Whom Severe Insulin Deficiency Will Quickly Develop

The following standard biomarkers and clinical features were also predictors of severe insulin deficiency in this South West England cohort: islet autoantibody status (AUC 0.78 [95% CI 0.68–0.89]), BMI (AUC 0.87 [95% CI 0.81–0.92]), and age at diagnosis (AUC 0.85 [95% CI 0.79–0.92]). In combination, these predictors had an AUC of 0.94 (95% CI 0.89–0.98). In multiple logistic regression, the T1D GRS was an independent and additive predictor of severe insulin deficiency (P = 0.002) and improved the discriminatory power of the test (AUC 0.96 [95% CI 0.94–0.99]). We also tested the improvement in discrimination by T1D GRS in addition to clinical features and autoantibodies using net reclassification improvement and integrated discrimination improvement (29). The continuous net reclassification improvement showed that the T1D GRS significantly improved classification, with 68% (95% CI 25–111; P = 0.002) of individuals showing improved probability over a model based on the combination of islet autoantibodies, age,

Table 1—Clinical characteristics of local cohort diagnosed between 20 and 40 years of age

	Severely insulin deficient (N = 46)	Not severely insulin deficient (N = 177)	P for difference
Males (%)	59	43	0.23
Clinical diagnosis of T1D/T2D	42/4	9/164	<0.0001
Age at study (years)	53.9 (12.1)	48.3 (9.7)	0.001
Age at diagnosis (years)	26.0 (5.2)	33.4 (4.2)	<0.0001
Duration of diabetes (years)	27.9 (12.5)	14.9 (9.1)	<0.0001
BMI	26.5 (4.3)	37.2 (9.2)	<0.0001
T1D autoantibodies (positive GAD or IA-2/total)	15/24	9/156	<0.0001
Insulin treatment at diagnosis, *n* (%)	38 (83)	8 (5)	<0.0001
Insulin treatment at recruitment, *n* (%)	46 (100)	84 (47)	<0.0001
Time to insulin (months) Median (IQR)	0 (0, 0)	96 (36, 134)	<0.0001

Data are reported as mean (SD), unless otherwise indicated. BMI and antibodies (GAD and IA-2) were measured at study recruitment.

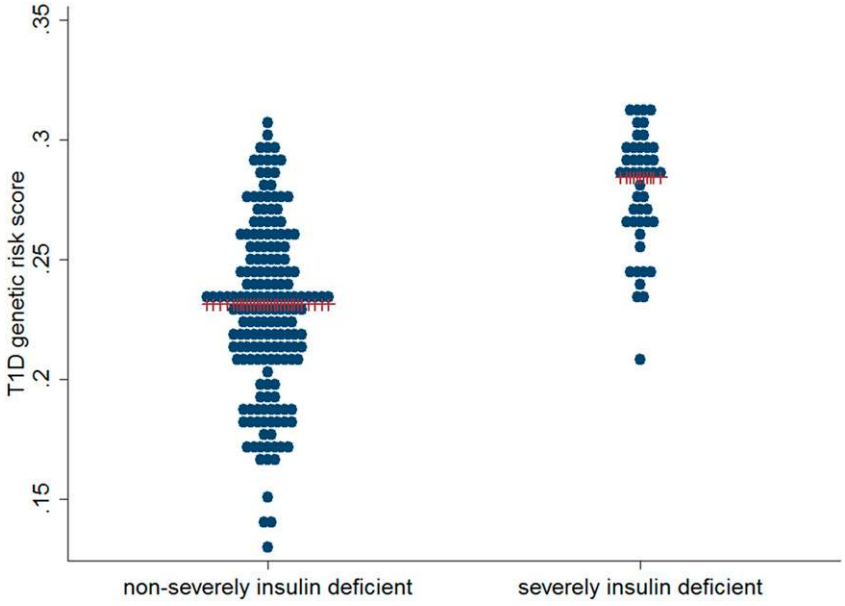

Figure 2—The ability of a T1D GRS to discriminate between severe insulin deficiency and non-insulin deficiency in young adults with diabetes. A dot plot of T1D GRS by insulin deficiency status is shown. The width of the blue bars represents frequency, and the red line represents the median.

and BMI alone. The integrated discrimination improvement statistic also showed a significant improvement in discrimination when adding the T1D GRS to a combination of these known discriminators, leading to an overall mean improvement in classification of 8.9% (95% CI 1.6–16.3; P = 0.018). The T1D GRS is therefore an independent and additive discriminator of severe insulin deficiency in young adults with diabetes.

Performance of T1D GRS Where Clinical Diagnosis and Autoantibody Results Are Conflicting

To assess the potential value of this additional test, we assessed how the T1D GRS performed when clinical characteristics and autoantibodies suggested contradictory classifications. We examined 22 patients with either *1*) clinical criteria suggesting T1D (BMI $\leq$30 kg/m^2 and diagnosis at $\leq$30 years of age) who were antibody negative (n = 7) or *2*) clinical criteria suggesting T2D (BMI $>$30 kg/m^2 or diagnosis at $>$30 years of age) who were antibody positive (n = 15). In these discordant patients, a T1D GRS $>$50th T1D centile correctly predicted insulin deficiency in seven of nine patients and a T1D GRS $<$5th T1D centile correctly predicted preserved insulin secretion in three of three patients. In the remaining 10 patients with an intermediate T1D GRS, 5 had preserved insulin and 5 were insulin deficient.

A Subset of Nine T1D Risk SNPs Provides Excellent Discrimination Between T1D and T2D

The efficiency of the T1D GRS (and also the cost) depends on the number of SNPs genotyped, so we compared AUC results in the WTCCC study for the discriminatory

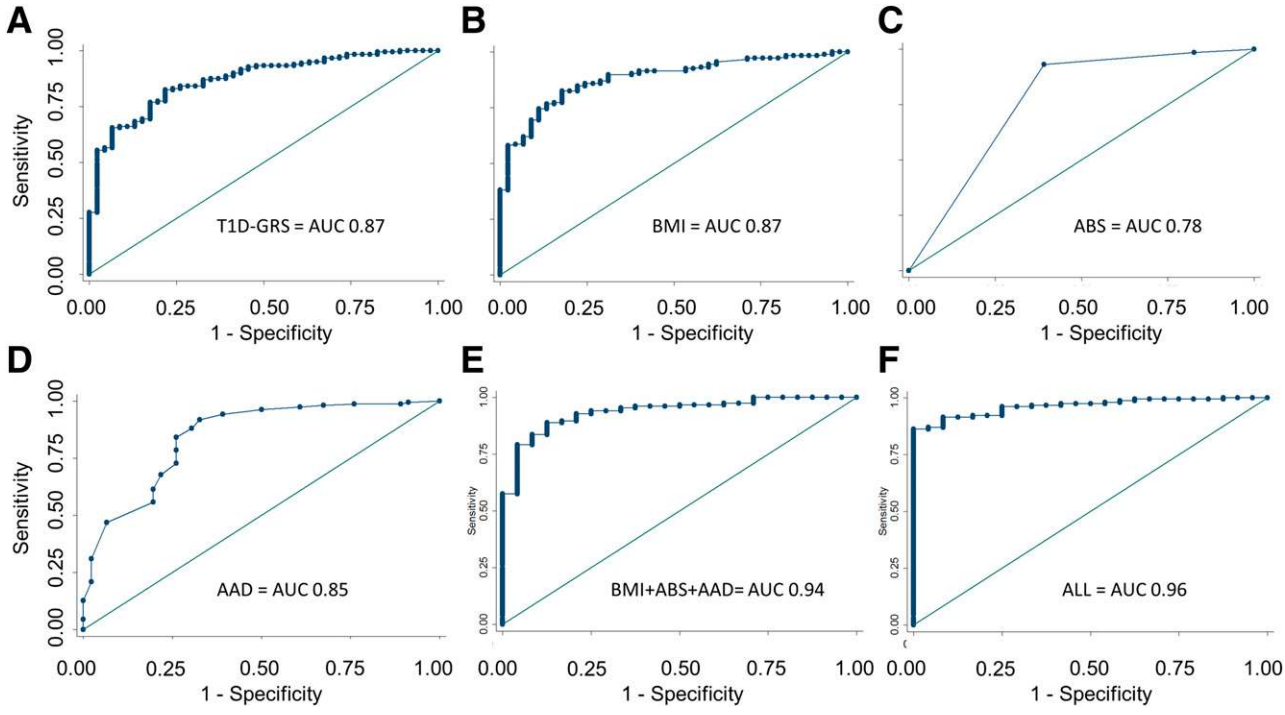

Figure 3—A series of ROC analyses demonstrating that the T1D GRS is an additive and independent predictor of insulin deficiency in young adults with diabetes when compared with known biomarker and clinical discriminators. AAD, age at diagnosis; ABS, autoantibody status for GAD and IA-2; ALL, T1D GRS, BMI, age at diagnosis, and autoantibodies as predictors. The combination of T1D GRS, autoantibodies, BMI, and age at diagnosis provides a highly discriminative test.

power as each SNP, ordered by published OR (see Supplementary Table 1), was added into the model (Fig. 4). There was no significant increase in the AUC as the number of SNPs went from 9 to 10 (P = 0.47). The AUC was 0.873 for 9 SNPs, 0.873 for 10 SNPs, and 0.880 for all 30 SNPs.

CONCLUSIONS

We have demonstrated that a GRS made up of common SNPs can discriminate between T1D and T2D. In young-onset adults with diabetes, the T1D GRS can help identify individuals in whom severe insulin deficiency will rapidly develop. The discriminative ability of the T1D GRS is independent of and additive to that of islet autoantibodies, BMI, and age at diagnosis. The T1D GRS is therefore a potentially important additional tool to help classify diabetes subtypes in young adults with diabetes.

There are several important attributes of the T1D GRS that will make it a useful independent addition to diagnostic testing in individuals with difficult-to-classify diabetes. First, the T1D GRS is not dependent on the time after diagnosis (an individual's genome does not change over time), whereas the discriminative ability of islet autoantibodies reduces with time after diagnosis (8), and C-peptide measurement is discriminative only 3–5 years after diagnosis due to the honeymoon period. Second, new technologies mean that SNP genotyping is relatively simple and accurate. Third, the cost of genotyping SNPs is rapidly reducing (currently <15 cents per SNP), meaning that the costs of this test are limited to the costs of blood sampling and DNA extraction. Because most of the discriminative ability can be obtained from just nine SNPs and because new genotyping technologies are being developed, it is likely that assessing an individual's T1D risk will become particularly cheap and robust.

One potential clinical use for the T1D GRS will be to help classify people with diabetes when clinical features are discordant with the results of autoantibody testing. We found that in 83% of these discordant patients (10 of 12 patients), a high T1D GRS (>50th T1D centile) or a low T1D GRS (<5th T1D centile) correctly classified whether these patients would become insulin deficient or not. The T1D GRS will not be helpful in approximately half of patients (10 of 22 patients) because values are intermediate (5th–50th T1D centile); in these patients, the diagnosis would remain indeterminate even after the T1D GRS testing.

The T1D GRS can be used in combination with other predictors, such as autoantibodies or clinical features, to estimate an individual's probability of T1D and progression to severe insulin deficiency. This is similar to our previous work (30) integrating biochemical results and clinical features to predict maturity-onset diabetes of the young (MODY). A logical aim would be to develop a simple diagnostic tool, such as the MODY calculator (30) (http://www.diabetesgenes.org/content/mody-probability-calculator), to incorporate all diagnostic information, including clinical features, biomarkers, and genetic risk, to give the most accurate diagnosis to all people with diabetes when they first present.

The prior odds of T1D when testing people who already have diabetes improve the PPVs and NPVs of the T1D GRS compared with similar scores used for

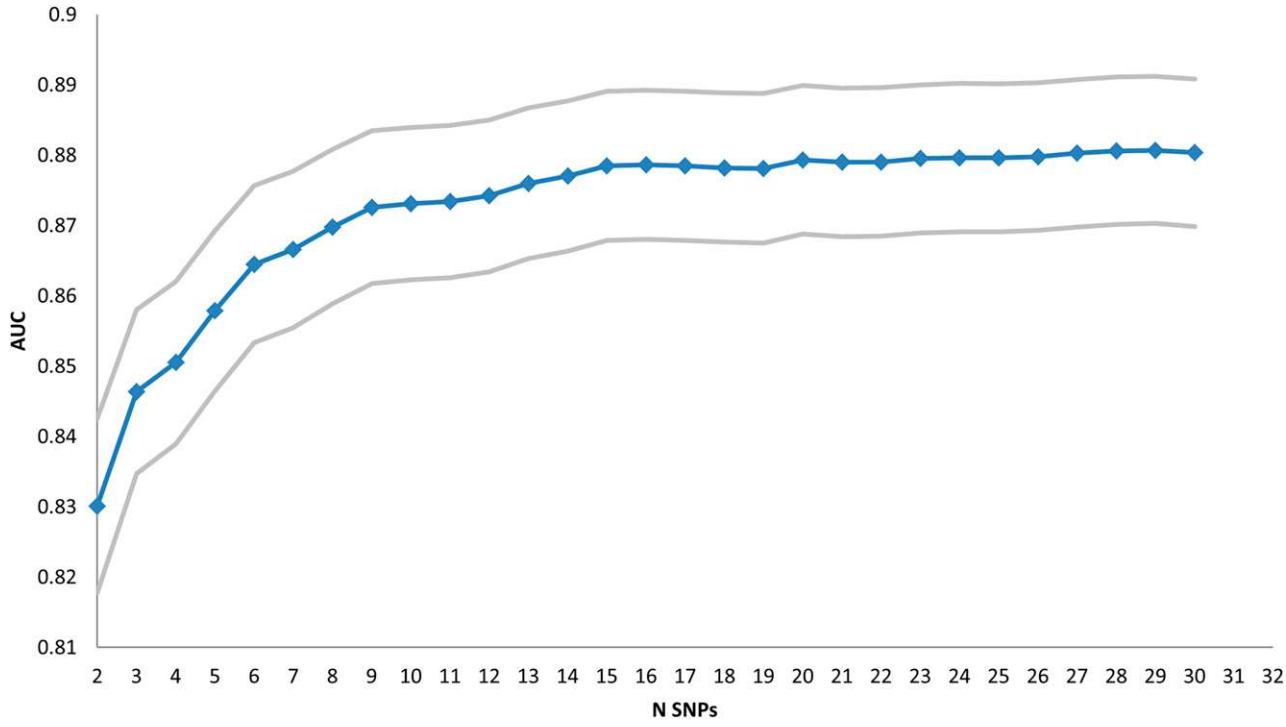

Figure 4—The incremental increase in the discriminatory power of the T1D GRS as more SNPs are added in. After ordering by published effect size, this graph shows the increasing AUC for increasing numbers of SNPs. After nine SNPs, there is no significantly increased discriminatory power to adding the next SNP. The *x*-axis starts at two SNPs that define the DR3/DR4-DQ8 high-risk haplotypes. The gray bars represent the upper and lower 95% CIs for the AUC estimate.

prediction. Winkler et al. (15) recently developed a similar T1D GRS and used it to predict T1D onset in 1,722 children selected for having a first-degree relative with T1D. They demonstrated a similar sensitivity and specificity (AUC 0.86) for the onset of T1D as we did for classifying T1D and T2D individuals. In this study, the proportion of individuals (selected as being at high risk for T1D) in whom diabetes developed was 6% and so even a high T1D genetic risk had a modest PPV (T1D developed in 19% of individuals with a T1D GRS >90th centile). This power would be limited further if a nonselected population was screened (prior probability ~0.5%). In contrast, we aimed to classify subtypes in people with known diabetes with a prior probability of having T1D of 21%. By focusing on a group of individuals in whom prior probability of a diagnosis is higher, the utility of the test becomes greater. As the ease of assessing genetic risk continues to improve, it is likely that the assessment of genetic risk at diagnosis may become a useful tool (Supplementary Table 2).

Our study has limitations. First, we tested the ability to detect insulin deficiency in a cross-sectional study where the autoantibodies and BMI were measured at study recruitment, not at diagnosis. Although the genotype will be unchanged from diagnosis, this may have reduced the discriminatory ability of autoantibodies and BMI in our sample, and we may have overestimated the independent contribution of the T1D GRS. Second, we measured only GAD and IA-2 autoantibodies, although in most clinical settings insulin and ZnT8 antibodies are not available. Third, we have not perfectly captured all T1D risk alleles. To minimize the number of SNPs genotyped, and for technical reasons of genotyping and imputing the variants, we have focused only on common and the highest-risk alleles for maximum discrimination with a minimum number of SNPs. As we show in Fig. 4, although we may have missed some low-frequency or lower-OR risk alleles in the HLA region or elsewhere in the genome, their rarity or effect size means that they would not substantially improve discriminatory ability. However, larger GWAS are finding more low-frequency and low-OR variants predisposing to T1D, and fine-mapping studies are finding causal variants at previously associated loci (e.g., Onengut-Gumuscu et al. [31]); the inclusion of these variants through future improvements in genotyping and sequencing technologies can only improve the utility of a T1D GRS. We also propose that to easily incorporate data from these constantly updated studies, reporting the T1D GRSs as centiles of a reference population of T1D and T2D patients (here the WTCCC study; Supplementary Table 2) may be a useful approach. Fourth, the T1D GRS is unlikely to discriminate T2D from other forms of non-autoimmune diabetes, and so a low T1D GRS may reflect T2D, monogenic diabetes, or secondary diabetes. Fifth, because of the nature of our local cohort and the WTCCC study, this work has focused on white British individuals. Further studies to assess the utility of the T1D GRS in other ethnic groups are needed.

Over the past 6 years, large-scale GWAS have provided an enormous advance in our understanding of the role of common genetic variation in complex human diseases such as diabetes (14,18,31–36). These GWAS have provided important new insights into the disease mechanism, but, despite dramatic reductions in the cost of genotyping, a direct impact on clinical care has lagged behind. Our use of the T1D GRS provides an example where results from GWAS can be brought into clinical practice.

In conclusion, a T1D GRS can accurately identify T1D and specifically identify which young adults with diabetes are likely to have severe insulin deficiency. This will be an important addition to correctly classifying individuals with diabetes when clinical features and autoimmune markers are equivocal.

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