SUPPLEMENTAL DATA

Working group members

ProDiGY

The following individuals constitute the ProDiGY Study Group:

M.H. Black (Janssen Pharmaceuticals), B. Burke (George Washington University), L. Chen (Massachusetts General Hospital), D. Dabelea (University of Colorado), J. Divers (New York University), K. Drews (George Washington University), J. Flannick (Boston Children's Hospital & Broad Institute), J.C. Florez (Massachusetts General Hospital & Broad Institute), M. Kelsey (University of Colorado), J. Mercader (Massachusetts General Hospital & Broad Institute), A. Manning (Massachusetts General Hospital & Broad Institute, T. Pollin (University of Maryland), N. Santoro (Yale University), R.Shah (Children's Hospital of Philadelphia), S. Srinivasan (University of San Francisco), J Todd (University of Vermont), P. Zeitler (University of Colorado).

TODAY and TODAY Genetics

The following individuals and institutions constitute the TODAY and TODAY Genetics Study Groups (* indicates principal investigator or director):

CLINICAL CENTERS Baylor College of Medicine: S. McKay*, M. Haymond*, B. Anderson, C. Bush, S. Gunn, H. Holden, G. Jeha, S.M. Jones, N. Kamith, S. McGirk, N. Miranda, A. Pihlaskari, S. Thamotharan, R. Zagado **Case Western Reserve University:** L. Cuttler (deceased)*, S. Narasimhan* E. Abrams, T. Casey, W. Dahms (deceased), C. Ievers-Landis, B. Kaminski, M. Koontz, S. MacLeish, P. McGuigan **Children's Hospital Central California:** S. Banerjee*, A. Bily, N. Delabruere, A. Evaristo **Children's Hospital Los**

Angeles: M. Geffner*, V. Barraza, N. Castaneda, N. Chang, B. Conrad, D. Dreimane, S. Estrada, L. Fisher, E. Fleury-Milfort, S. Hernandez, B. Hollen, F. Kaufman, E. Law, V. Mansilla, D. Miller, C. Muñoz, R. Ortiz, A. Ward, K. Wexler, Y.K. Xu, P. Yasuda **Children's Hospital of Philadelphia:** L. Levitt Katz*, R. Berkowitz, S. Boyd, N. Chaudhary, C. Clark, K. Gralewski, B. Johnson, P. Kanan, J. Kaplan, C. Keating, C. Lassiter, R. Liillii, T. Lipman, G. McGinley, H. McKnight, B. Schwartzman, R.Shah, R. Volpe, S. Willi **Children's Hospital of Pittsburgh:** S. Arslanian*, L. Bednarz, F. Bacha, S. Foster, B. Galvin, T. Hannon, A. Kriska, I. Libman, M. Marcus, K. Porter, D. Shearer, T. Songer, E. Venditti **Children's Mercy Hospital Kansas City:** F. Ugrasbul*, J. Bedard, J. Jacobson, T. Luetjen **Columbia University Medical Center:** R. Goland*, G. Covington, D. Gallagher, P. Kringas, N. Leibel, D. Ng, M. Ovalles, B. Park, D. Seidman **Connecticut Clinical Medical Center Children's Hospital:** E. Estrada*, H. Nielsen **Emory University:** A. Muir*, E. Ivie, P. Jenkins, K. Lindsley **Indiana University:** Z. Nabhan*, P. Didrick **Joslin Diabetes Center:** L. Laffel*, A. Benier, A. Goebel-Fabbri, M. Hall, L. Higgins, J. Keady, M. Malloy, K. Milaszewski, L. Rasbach **Massachusetts General Hospital:** D.M. Nathan*, L. Levitsky*, A. Angelescu, L. Bissett, C. Ciccarelli, L. Delahanty, V. Goldman, O. Hardy, E. Javier, M. Larkin, R. McEachern, D. Norman, D. Nwosu, S. Park-Bennett, R. Pompei, D. Richards, N. Sherry, B. Steiner **Saint Louis University:** S. Tollefsen*, S. Carnes, D. Dempsher, D. Flomo, T. Whelan, B. Wolff **State University of New York Upstate Medical University:** R. Weinstock*, R. Izquierdo, D. Bowerman, S. Bzdick, J. Bulger, P. Conboy, J. Hartsig, R. Izquierdo, J. Kearns, R. Saletsky, P. Trief **Texas Tech University:** D. Dreimane*, C. Lovett, C. Scott-Johnson **University of Arkansas:** A. Morales*, C. Moreau **University of California San Diego:** M. Gottschalk* **University of Colorado Denver:** P. Zeitler* (Steering Committee Chair), N. Abramson, A. Bradhurst, N. Celona-Jacobs, M. Downey, J. Higgins, A.

Hull, M.M. Kelsey, G. Klingensmith, R. Morehead, K. Nadeau, H. Tyrrell, T. Witten **University of Florida:** J. Silverstein*, E. Dougherty, T. Lyles **University of Oklahoma Health Sciences Center:** K. Copeland* (Steering Committee Vice-Chair), E. Boss, R. Brown, J. Chadwick, L. Chalmers, S. Chernausek, A. Hebensperger, C. Macha, R. Newgent, A. Nordyke, D. Olson, T. Poulsen, L. Pratt, J. Preske, J. Schanuel, S. Sternlof, M. Zarate **University of Texas Health Science Center at San Antonio:** J. Lynch*, D. Hale*, N. Amodei, R. Barajas, C. Cody, J. Hernandez, C. Ibarra, E. Morales, S. Rivera, G. Rupert, A. Wauters **Vanderbilt University:** A. Potter*, M. Black, F. Brendle, A. Shannon **Washington University in St Louis:** N. White*, A. Arbeláez, D. Flomo, J. Jones, T. Jones, M. Sadler, A. Starnes, M. Tanner, A. Timpson, R. Welch **Yale University:** S. Caprio*, E. Duran, M. Grey, C. Guandalini, S. Lavietes, P. Rose, A. Syme, W. Tamborlane

COORDINATING CENTER George Washington University Biostatistics Center: K. Hirst*, B. Burke, S. Edelstein, P. Feit, N. Grover, C. Long, L. Pyle

PROJECT OFFICE National Institute of Diabetes and Digestive and Kidney Diseases: B. Linder*

CENTRAL UNITS Central Blood Laboratory (Northwest Lipid Research Laboratories, University of Washington): S.M. Marcovina*, J. Harting, M. Ramirez, G. Strylewicz

University of Maryland School of Medicine: T. Pollin*, A Shuldiner*

Definition of 99% credible sets of GWAS significant loci

We defined the 99% credible, which represent all the variants that have, in aggregate, 99% probability of containing the causal variant driving the association with T2D. By using our meta-analysis results, we constructed the 99% credible of variants considering 1 Mb downstream and upstream from the resulting top SNP. We computed the R^2 values from all the variants within 1 Mb region using the European data from 1000G with respect to the top SNP and we selected variants showing an $R^2 > 0.1$ with the leading SNP in each region with LDLink (https://ldlink.nci.nih.gov/?tab=home). Credible sets of variants are analogous to confidence intervals as we assume that the credible set for each associated region contains, with 99% probability, the true causal SNP if this has been genotyped or imputed[1, 2] (**Wakefield J: A Bayesian measure of the probability of false discovery in genetic epidemiology 705 studies. Am J Hum Genet 2007;81:208-227**). The credible set construction allows to provide for each variant placed within a certain associated *locus* a posterior probability of being the causal one[2]. We estimated the approximate Bayes' factor (ABF) for each variant as:

$$ABF = \frac{\sqrt{1-r}}{e^{(-r\cdot\frac{z^2}{2})}}$$

where:

$$r = \frac{0.04}{(SE^2 + 0.04)}$$

$$z = \frac{\beta}{SE}$$

The β and the SE are the estimated effect size and the corresponding standard error resulting from testing for association under a logistic regression model. The posterior probability for each variant was obtained as:

$$Posterior\ Probability_i = \frac{ABF_i}{T}$$

where ABF_i corresponds to the approximate Bayes' factor for the marker *i*, and *T* represents the sum of all the *ABF* values from the candidate variants enclosed in the interval being evaluated. This calculation assumes that the prior of the β corresponds to a Gaussian with mean 0 and variance 0.04.

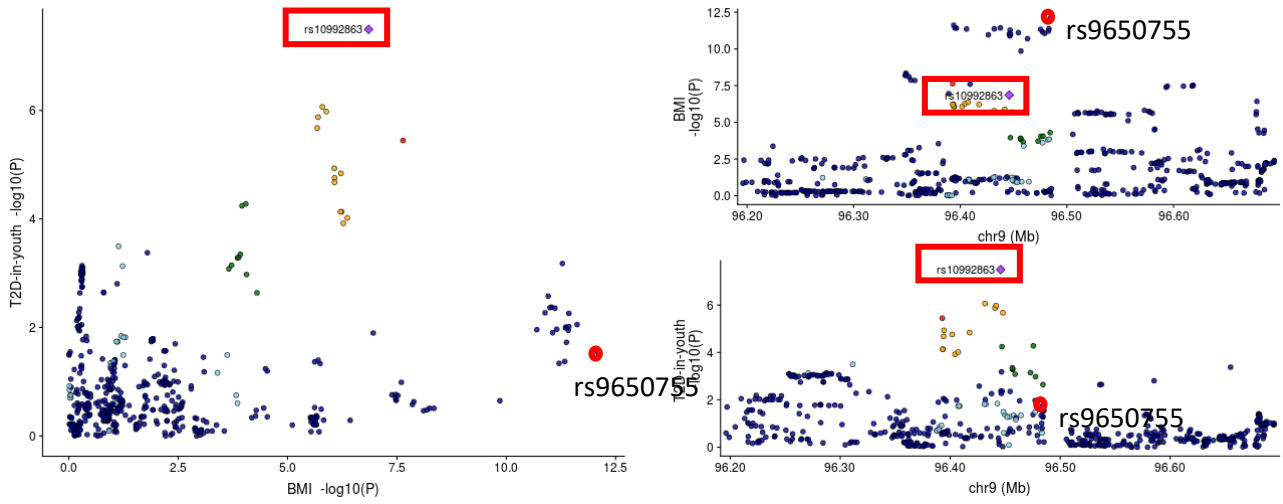
Finally, we ranked variants according to the *ABF* (in decreasing order) and from this ordered list, we calculated the cumulative posterior probability. We included variants in the 99% credible set of each region until that SNP that pushed the cumulative posterior probability of association over 0.99. The 99% credible set of variants for this region is summarized in Supplementary Table 2.

References

1. Morris AP. Fine mapping of type 2 diabetes susceptibility loci. Curr Diab Rep. 2014;14(11):549. Epub 2014/09/23. doi: 10.1007/s11892-014-0549-2. PubMed PMID: 25239271; PMCID: PMC4169615.

2. Wellcome Trust Case Control C, Maller JB, McVean G, Byrnes J, Vukcevic D, Palin K, Su Z, Howson JM, Auton A, Myers S, Morris A, Pirinen M, Brown MA, Burton PR, Caulfield MJ, Compston A, Farrall M, Hall AS, Hattersley AT, Hill AV, Mathew CG, Pembrey M, Satsangi J, Stratton MR, Worthington J, Craddock N, Hurles M, Ouwehand W, Parkes M, Rahman N, Duncanson A, Todd JA, Kwiatkowski DP, Samani NJ, Gough SC, McCarthy MI, Deloukas P, Donnelly P. Bayesian refinement of association signals for 14 loci in 3 common diseases. Nat Genet. 2012;44(12):1294-301. Epub 2012/10/30. doi: 10.1038/ng.2435. PubMed PMID: 23104008; PMCID: PMC3791416.

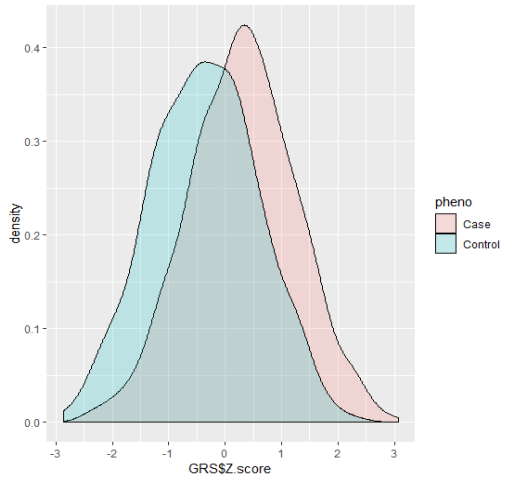
SUPPLEMENTAL FIGURE 1: Co-localization analyses for lead type 2 diabetes SNP rs10992863 with lead BMP SNP rs 9650755 at the same locus



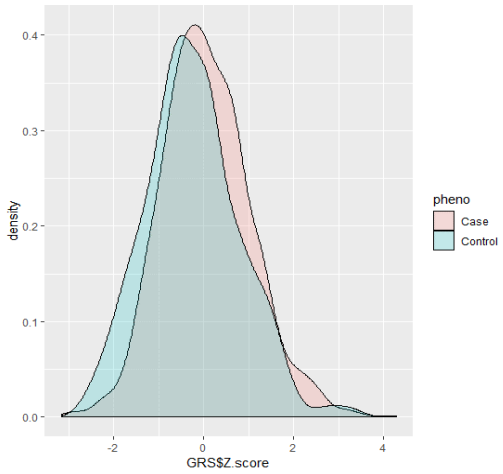
Supplementary Figure 2: Polygenic risk score analysis

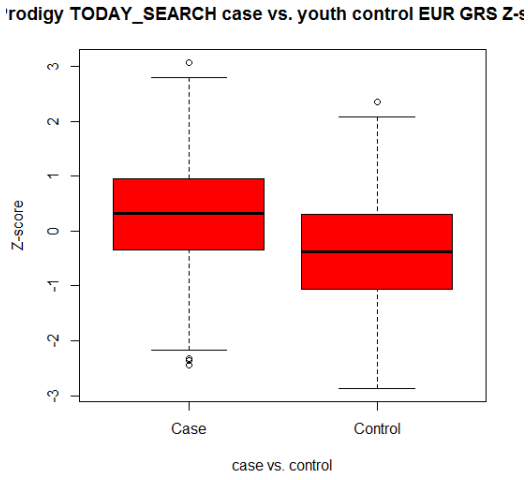
The frequency distribution and box plots for analyses of GRS in ProDIGY youth cases vs adult controls is shown. EUR- Europeans, AFR- African Americans, AMR- Hispanic Americans

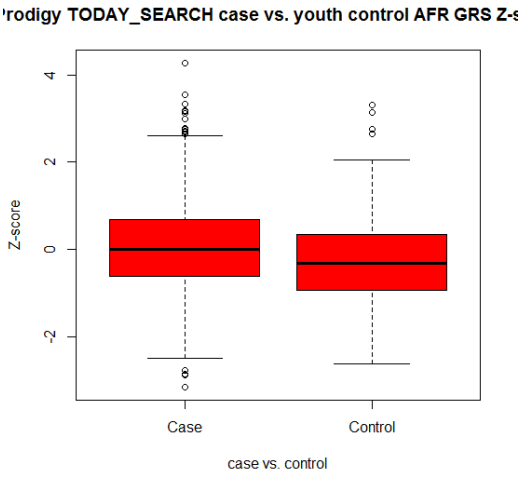
EUR



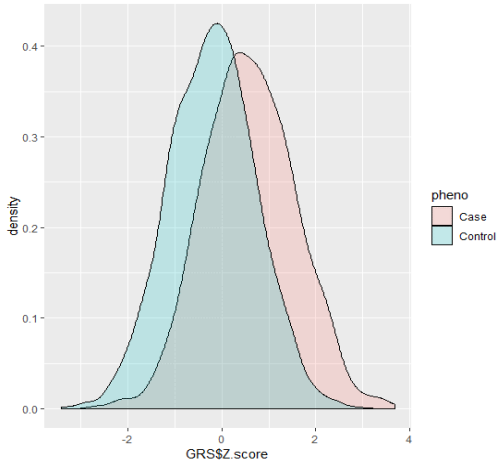
AFR

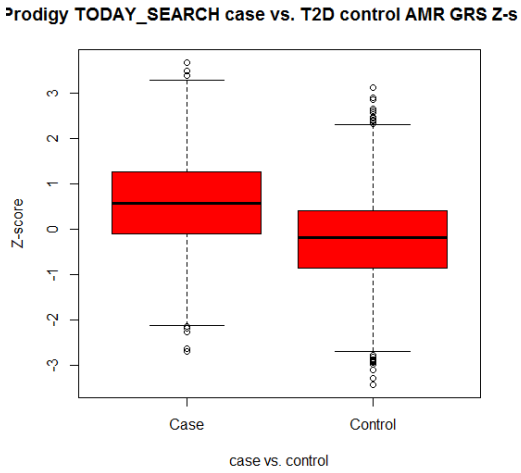






AMR


density
0.0
0.1
0.2
0.3
0.4
-2
0
2
4
GRS$Z.score
pheno
Case
Control


Prodigy TODAY_SEARCH case vs. T2D control AMR GRS Z-s
Z-score
-3
-2
-1
0
1
2
3
Case
Control
case vs. control