Zinc Transporter 8 Autoantibodies (ZnT8A) and a Type 1 Diabetes Genetic Risk Score Can Exclude Individuals With Type 1 Diabetes From Inappropriate Genetic Testing for Monogenic Diabetes

Kashyap A. Patel,[1] *Michael N. Weedon,*[1] *Beverley M. Shields,*[1,2] *Ewan R. Pearson,*[3] *Andrew T. Hattersley,*[1,2] *and Timothy J. McDonald,*[1,4] *on behalf of the UNITED study team*

Diabetes Care 2019;42:e16–e17 | https://doi.org/10.2337/dc18-0373

We have recently shown that the detection of monogenic diabetes in a population can be improved by excluding individuals with type 1 diabetes (T1D) identified by having low C-peptide levels and/or the presence of GAD autoantibodies (GADA) or IA-2 autoantibodies (IA-2A) in the Using pharmacogeNetics to Improve Treatment in Early-onset Diabetes (UNITED) study (1). Since completion of the study, there are now two new tests that also robustly identify T1D: zinc transporter 8 autoantibodies (ZnT8A) (2) and the T1D genetic risk score (T1D GRS) (3,4). It is not known the extent to which the addition of these new tests will improve the diagnostics (1). Autoantibodies assessment was performed at recruitment. The median duration of diabetes at recruitment was 7.4 years (interquartile range [IQR] 2.5–17.3). GADA and IA-2A were measured as previously described (1). ZnT8A was measured by ELISA (RSR Ltd, Cardiff, U.K.) on a Dynex DS2 ELISA robot (Dynex, Preston, U.K.). The RSR ZnT8A ELISA is capable of detecting and quantifying autoantibodies specific to R325 or to W325, or to residue 325 nonspecific variants. We used >99th centile of a control population (n = 1,559, age range 1–69 years) to define the positivity of ZnT8A (≥126 units for age <30, ≥26 units for age ≥30). The T1D GRS was derived from genotyping 30 common polymorphisms as described previously. We used >50th centile of T1D GRS, derived from a large reference population of individuals with T1D from the Wellcome Trust Case Control Consortium (n = 1,963), to define those at high genetic risk of T1D (3,4). All subjects who were GADA and IA-2A negative had a next-generation targeted panel test for 35 genes causing monogenic diabetes (1). A total of 15/212 individuals with monogenic diabetes were identified. Their mutations and clinical characteristics are described in Table 1 of our previous article (1) under the following identification numbers: 175, 377, 540, 80089, 80173, 80541, 82003, 82006, 82010, 82013, 82014, 82038, 82316, 82352, and 82399.

ZnT8A were present in 39/212 (18%) individuals. This increased the number of autoantibody-positive individuals from 58 (27%, GAD and/or IA2 positive) to 75 (35%) (P = 0.008) (Fig. 1). A single autoantibody was found in 44, two autoantibodies were found in 26, and 5 had all three autoantibodies. None of the individuals who were positive for ZnT8A only had monogenic diabetes.

The T1D GRS 50th centile cutoff identified 48/212 individuals with probable T1D (those at high genetic risk of T1D). Of these, 21 were negative for all three autoantibodies (Fig. 1). None of these 21 individuals had monogenic diabetes. Thus, addition of the T1D GRS increased the number of people that can be excluded for genetic testing from 35% with all three autoantibodies to 45% (P = 0.003) (Fig. 1).

Overall, in individuals with significant endogenous insulin secretion, ZnT8A and T1D GRS excluded an additional 18% of individuals (P < 0.001) without missing any monogenic diabetes. These individuals had an age of diagnosis, BMI, and urine C-peptide creatinine ratio similar to those from the 27% identified by GADA and IA-2A alone. However, the duration of diabetes was longer in autoantibody-negative T1D individuals who were identified by T1D GRS compared with autoantibody-positive T1D (3.6 years [IQR 1.2–9.9] vs. 14 years [5.8–21.1], P = 0.002). These two additional tests reduced the number of patients with persistent insulin secretion who needed to be tested for monogenic diabetes from 73% to 55% (P < 0.001).

[1]*Institute of Biomedical and Clinical Science, University of Exeter Medical School, Exeter, U.K.*
[2]*National Institute for Health Research Exeter Clinical Research Facility, Royal Devon and Exeter NHS Foundation Trust, Exeter, U.K.*
[3]*Division of Molecular and Clinical Medicine, School of Medicine, University of Dundee, Dundee, U.K.*
[4]*Blood Sciences, Royal Devon and Exeter NHS Foundation Trust, Exeter, U.K.*

Corresponding author: Timothy J. McDonald, timothy.mcdonald@nhs.net

Received 20 February 2018 and accepted 8 September 2018

See accompanying articles, pp. 189, 192, 200, 208, and 215.

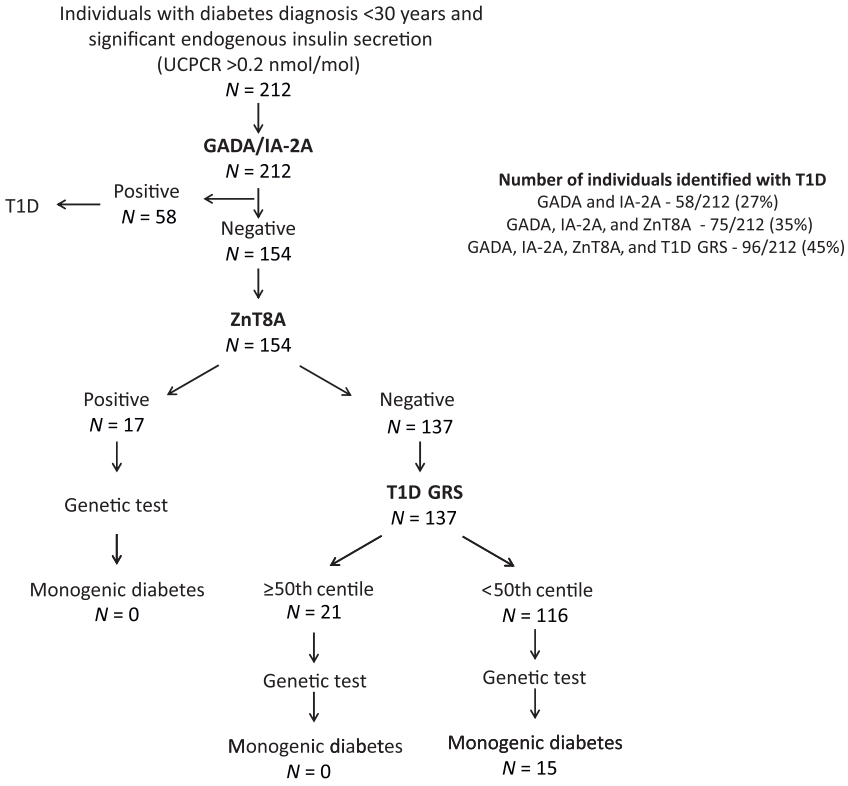

Figure 1—Benefit of ZnT8A and T1D GRS, in addition to GADA/IA-2A, for excluding individuals with T1D who have significant endogenous secretion from genetic testing for monogenic diabetes. UCPCR, urine C-peptide creatinine ratio.

The main drawback of these new tests, like those for GADA and IA-2A, is that they do not discriminate between type 2 diabetes and monogenic diabetes.

In conclusion, two new tests, ZnT8A and the T1D GRS, helped identify an additional 18% of probable T1D in individuals with significant endogenous insulin secretion, excluding the need for monogenic testing. The additional testing is likely to be cost effective, as the tests cost ~$15 each, which is ~1/100th of the cost of a full genetic test.

Funding. This study was supported by the Department of Health and Health Innovation Challenge Award (HICF-1009-041 and WT-091985). K.A.P. has a postdoctoral fellowship funded by the Wellcome Trust (110082/Z/15/Z). A.T.H. is a Wellcome Trust Senior Investigator (WT098395/Z/12/Z) and is also supported by a National Institute for Health Research (NIHR) Senior Investigator award. M.N.W. is supported by the Wellcome Trust Institutional Strategic Support Fund (WT097835MF) and the Medical Research Council (MR/M005070/1). B.M.S. and A.T.H. are core members of the NIHR Exeter Clinical Research Facility. T.J.M. is supported by an NIHR HEE Senior Clinical lectureship.

The views expressed are those of the authors and not necessarily those of the Wellcome Trust, the National Health Service, the NIHR, or the Department of Health.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. K.A.P. and T.J.M. designed the study. K.A.P., M.N.W., and B.M.S. researched data and performed statistical analyses. K.A.P. and T.J.M. wrote the first draft of the manuscript, which was modified by all authors. All authors contributed to the discussion and reviewed or edited the manuscript. T.J.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Shields BM, Shepherd M, Hudson M, et al.; UNITED study team. Population-based assessment of a biomarker-based screening pathway to aid diagnosis of monogenic diabetes in young-onset patients. Diabetes Care 2017;40:1017–1025

2. Vermeulen I, Weets I, Asanghanwa M, et al.; Belgian Diabetes Registry. Contribution of antibodies against IA-2β and zinc transporter 8 to classification of diabetes diagnosed under 40 years of age. Diabetes Care 2011;34:1760–1765

3. Patel KA, Oram RA, Flanagan SE, et al. Type 1 diabetes genetic risk score: a novel tool to discriminate monogenic and type 1 diabetes. Diabetes 2016;65:2094–2099

4. Oram RA, Patel K, Hill A, et al. A type 1 diabetes genetic risk score can aid discrimination between type 1 and type 2 diabetes in young adults. Diabetes Care 2016;39:337–344