Prediction of Type 1 Diabetes

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Type 1 diabetes (T1D) is a chronic autoimmune disorder in which the destruction of the insulin-producing cells and resulting clinical symptoms are preceded by the appearance of a number of islet-cell specific autoantibodies. Linkage (1) and association analyses have demonstrated that type 1 diabetes has a very strong genetic component, with specific alleles and haplotypes at the HLA class II genes, as well as *HLA-A* and *-B* alleles, conferring either susceptibility to or protection from T1D (2–6). The ability to identify individuals at high risk for type 1 diabetes using genetic and/or autoantibody markers (7–10) has been a long-standing goal of the diabetes research and clinical community and a critical element in T1D prevention strategies. The role of prediction in prevention is twofold: *1*) Clinical trials to evaluate potential preventative interventions are more efficient if the recruited subjects are at high T1D risk, and *2*) interventions are likely to be more effective if administered early in disease progression or during the prediabetic phase, a stage identified by autoantibody markers in individuals who carry genetic risk alleles.

Although a large number of genetic variants associated with T1D have been identified by genome-wide association study analyses (11), the major genetic determinants remain specific alleles at the HLA class II and, to a lesser extent, class I loci. Because specific combinations of alleles at the HLA loci determine the genetic susceptibility, the risk for T1D is best captured by considering DR-DQ haplotypes and genotypes rather than alleles at individual loci. The highest-risk T1D genotype is the DRB1*03:01-DQA1*05:01-DQB1*02:01/DRB1*04-DQA1*03:01-DQB1*03:02 heterozygote (often expressed using the old serological designation as DR3/DR4 or DQ2/DQ8), with an odds ratio of 30 (2). The increase in risk of this heterozygote compared with the two (DR3/DR3 and DR4/DR4) homozygotes has been attributed to the two transcomplementing DQ heterodimers, including the α (DQA1*05:01) and β (DQB1*03:02) heterodimer, present only in this heterozygote (2). Prospective studies of HLA-typed general population samples and first-degree relatives (FDRs; siblings and offspring) have shown that the risk for DR3/DR4 (or DQ2/DQ8) in an FDR is greater than the risk for the same genotype in the general population (12), suggesting that additional loci either within or outside the HLA region also contribute to T1D risk. Among the FDRs, DR3/DR4 siblings have a greater risk than offspring, and DR3/DR4 siblings who share two HLA haplotypes with the proband have an extremely high risk (12). The incorporation of additional non-HLA genetic markers, such as *PTPN22* or *INS*, into the predictive algorithm can help refine risk estimates, particularly for the DR3/DR4 individuals in the general population (13).

Using the DR3/4 genotype (rather than DR3 or DR4) as a predictive marker will identify individuals at high genetic risk; however, DR3/DR4 individuals represent only around 20–40% of future T1D cases. In general, a "trade-off" exists between the proportion of future cases identified by the markers (sensitivity) and the positive predictive value for individuals achieved with a broad (genetic, immunological, metabolic) marker panel (specificity) (14,15) (Fig. 1).

Many prospective studies, as well as preventative intervention trials, have focused on FDRs and have also used specific autoantibodies, in addition to genetic markers, for prediction of progression to T1D, for entry into clinical trials, or for studies of environmental triggers (16). Of course, these biomarkers are fundamentally different in that genetic variants identify risk whereas autoantibodies against specific islet-cell antigen markers reflect active and targeted autoimmunity. Of the four commonly used autoantibody assays, antibodies against insulin and glutamic acid decarboxylase appear early during prediabetes, and antibodies to the antigens IA-2 and ZnT8 appear later; all of these antibodies can be detected well before the onset of clinical diabetes. Typically, autoimmunity in these prospective studies has been defined as a subject testing positive for one or more antibodies on at least two successive visits. Various prediction strategies have combined genetic and autoantibody markers, as well as metabolic markers, in different ways.

In the article by Mbunwe et al. (17), the authors consider various combinations of the IA-2 and ZnT8 autoantibody markers, DR3/DR4 (written in this article as DQ2/DQ8), and HLA-A*24, a class I variant that has been associated with T1D in a variety of studies (3,6,18). Other class I alleles, notably HLA-B*39:06 (susceptible) and B*57:01 (protective) are associated with T1D, but only A*24 was used in this model. This study selected FDRs who were positive for one or more of the four autoantibodies tested; 288 of these subjects were tested for HLA-A*24 and genotyped for HLA-DQ. The HLA-A*24 typing was performed with a panel of three oligonucleotide probes that could identify but not distinguish all 255 A*24 alleles, with the exception of a few extremely rare variants. A study of T1D in Filipinos (19) showed that although some A*24 alleles, such as the common HLA*24:02, conferred increased risk, some other alleles, such as A*24:07, did not. Since virtually all A*24 alleles in Europeans are A*24:02, this limitation of the typing method should not affect the results. However, if this strategy were to be applied to other populations, a higher resolution typing system would be warranted. A significant strength of this study is that 5- and 10-year progression could be followed. The authors conclude that

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DOI: 10.2337/db12-1593

See accompanying brief report, p. 1345.

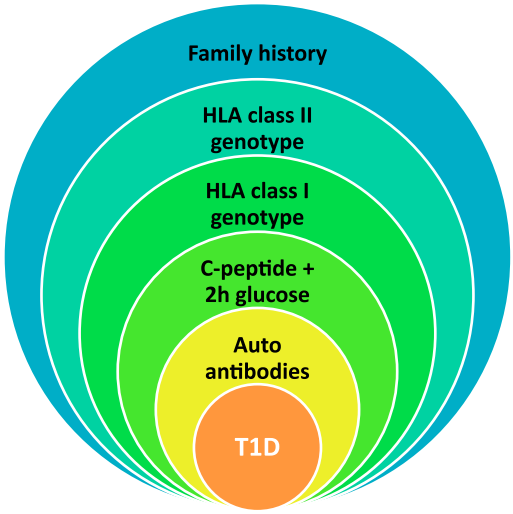

FIG. 1. Incorporating an increasing number of genetic, autoantibody, and metabolic markers in a predictive algorithm can identify a subset of the population at very high risk of T1D but at the cost of identifying only a small proportion of future T1D cases.

A*24 is an independent predictor of progression to T1D in antibody-positive FDR and that "depending on whether the screening goals intend to favor specificity or sensitivity, HLA-A*24 can help select a subgroup at extremely high risk or increase sensitivity of detecting relatives with high combined Ab- and HLA-inferred risk." Clearly, other markers could be implemented into these predictive algorithms but the trade-off between sensitivity and specificity will, as in this study, have to be weighed.

The predictive power of a given diagnostic is usually summarized by a receiver operating characteristic curve, in which subjects are ranked in descending order of their predicted risk, and the cumulative proportion of subjects who develop disease (cases) is plotted against the corresponding cumulative proportion of the population, i.e., the sensitivity (true-positive fraction) is plotted in the y-axis versus 1-specificity (the false-negative fraction) in the x-axis (20). A formal receiver operating characteristic analysis of class II and class I HLA alleles, with or without dynamic biomarkers, has yet to be performed; however, the incorporation of additional markers, such as HLA-A*24 described by Mbunwe et al., into a predictive algorithm that can increase the positive predictive value for progression to T1D, promises to facilitate the long-standing goal of T1D prevention. Therapeutic interventions are likely to be more effective when introduced during the preclinical diabetes phase, characterized by autoimmunity while residual β-cell function is present. For these preventive strategies to succeed, identification of subjects at very high risk of T1D is critical. This publication represents another step toward achieving this important goal.

ACKNOWLEDGMENTS

H.A.E. is employed by Roche Molecular Systems, Pleasanton, California. No other potential conflicts of interest relevant to this article were reported.

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