Role of Type 1 Diabetes–Associated SNPs on Autoantibody Positivity in the Type 1 Diabetes Genetics Consortium: Overview

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OBJECTIVE

Type 1 diabetes (T1D) arises from the autoimmune destruction of the β-cells of the pancreas, resulting in dependence on exogenously administered insulin for survival. Key biomarkers of the autoimmune process in T1D are the occurrence of autoantibodies directed against β-cells and other antigens. The Type 1 Diabetes Genetics Consortium (T1DGC) assembled collections to *1*) discover genes that modify the risk of T1D, *2*) conduct phenotyping related to risk, and *3*) make available biologic and genetic resources for research. The goal of the T1DGC Autoantibody Workshop was to use T1DGC phenotypic, genotypic, and autoantibody data on affected sibling pair (ASP) families to discover genes accounting for variation in presence of autoantibodies.

RESEARCH DESIGN AND METHODS

The T1DGC provided the working groups with autoantibody and genetic data on 9,976 subjects from 2,321 ASP families. Data were distributed to numerous working groups for analyses of specific autoantibody subsets and targets.

RESULTS

Seven groups analyzed the joint autoantibody and genetic data within the ASP families. Six reports are provided in this collection, ranging from candidate gene analyses of selected autoantibodies to evaluation of regions of genetic variants associated with autoimmunity on the collection of autoantibodies.

CONCLUSIONS

Although selected variants in the available genes remain important genetic predictors for prevalence of T1D, other genes and nongenetic factors are expected to contribute to the initiation of islet autoimmunity, the first step in the pathogenesis of T1D.

Type 1 diabetes (T1D) arises from the autoimmune destruction of the insulin-producing β-cells of the pancreas, resulting in dependence on exogenously administered insulin to maintain glucose homeostasis. T1D is the third most common autoimmune disease of childhood, affecting 0.2–0.4% of the general population of Northern European ancestry by age 20 years and a lifetime risk of nearly 1%. T1D is a complex human disease and its etiology is attributed to the interaction of different environmental and genetic factors. Twin and family studies suggest that there is a major role of genetic/familial factors in risk, with monozygotic twin concordance of ∼40%, dizygotic twin concordance of ∼8%, and the sibling risk ratio (λ_S) of 15 (1,2).

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T1D is distinctive among autoimmune disorders in that genes in the MHC region on chromosome 6p21 contribute a substantial portion (~50%) of the total genetic risk for disease (3–6), with only ankylosing spondylitis having a greater contribution, primarily due to HLA-B27. The primary risk genes in the human MHC include the HLA class II (HLA-DR, HLA-DQ, HLA-DP) and class I (HLA-A, HLA-B, HLA-C) genes, but many other candidates reside in this region (7,8). Many autoimmune diseases have strong associations with HLA alleles, including classic determinants that affect risk (9). Further, many non-MHC susceptibility loci for T1D are also implicated in contributing to susceptibility to other autoimmune diseases, suggesting that there are likely to be common pathways by which autoimmunity arises (10).

The Type 1 Diabetes Genetics Consortium (T1DGC) was established to ascertain and assemble large collections of affected sibling pair (ASP) families as well as case subjects with T1D and control subjects to conduct genetic studies for the discovery of genes and variants that modify risk (11). Early efforts to localize and identify genes that contribute to the occurrence of T1D or components of its initiation/progression (e.g., development of autoantibodies, age at onset of T1D, sex and ethnic differences in occurrence and severity) often interrogated variants in candidate genes, either in case-control association analyses or family-based linkage studies. Candidate genes were often selected based on a perceived biological mechanism, with variants within each candidate selected on the basis of putative functional effects. However, at the time that most of these candidate gene studies were performed, there was limited available information on the numbers of variants in different genes and even less information on the functional implications of known variants. As a result, many of these candidate gene studies had low statistical power and, often, limited examples of replication.

As genotyping strategies and technologies evolved, there was a shift from candidate gene studies to genome-wide linkage scans in families, yet the need for large collections of families limited the number of well-powered studies. The collection of thousands of ASP families required a major effort in ascertainment, recruitment, and evaluation, although still at a cost much less than that of genotyping. The primary focus of genome-wide linkage scans was families with multiple affected individuals, with the primary contributor to genetic susceptibility residing in the human MHC (HLA region). The primary association between T1D and the MHC appears to occur with the class II loci, although there has been evidence for effects of class I (HLA-A and HLA-B) (8). Additional candidate genes for T1D have been identified or confirmed from earlier candidate gene studies using linkage. As the samples typically were small, each locus had relatively large effect sizes estimated, including insulin (*INS*) (rs698 perfectly tagging the VNTR) (12), *CTLA4* (13), *PTPN22* (14), and *IL2RA* (15). Subsequent linkage analyses by the T1DGC in ~2,500 multiplex families (16) have confirmed some loci, if not the specific single nucleotide polymorphism (SNP) or size of effect, in contribution to risk.

With the improved genomic coverage afforded by SNPs, coupled with continued decrease in cost of genotyping, genome-wide association scans (GWAS) with robust statistical power could be conducted, using large collections of case and control subjects. GWAS studies succeeded in identifying and replicating novel associations of common genetic variants with a variety of diseases, including T1D (17). The T1DGC GWAS meta-analysis identified 40 loci associated with T1D, with 18 of these being novel, and confirmed most of these in a large series of T1DGC ASP families (18). However, each associated SNP accounted for only a small portion of the familial clustering for T1D, and most of the more than 40 risk loci contained multiple genes (median gene count 3, range 0–28) (19).

In order to further refine the localization of risk variants and genes within T1D-associated regions, as well as test for sharing of risk loci across autoimmune diseases, the T1DGC contributed to the design of the ImmunoChip, a custom Illumina Infinium high-density genotyping array with coverage of significant GWAS regions for 12 autoimmune diseases (20). The T1DGC used the ImmunoChip to genotype all available samples, including the ASP families. Analysis of ImmunoChip data suggested that, among autoimmune disorders, T1D is genetically most similar to those disorders that include the production of autoantibodies as a phenotype, showing the most similarity to juvenile idiopathic arthritis and the greatest dissimilarity to ulcerative colitis (21).

Given the evidence of shared genetic risk loci for T1D and other autoimmune disorders in which autoantibodies are a feature, an examination of the influence of genetics on autoantibody production seems well justified. A large case series was examined for two anti-islet autoantibodies (GADA and IA-2A), antibodies against thyroid peroxidase (TPO) associated with autoimmune thyroid (Graves) disease, and antibodies against gastric parietal cells (PCA) associated with autoimmune pernicious anemia (22). Two loci passed a genome-wide significance level: 1q23/*FCRL3* with IA-2A and 9q34/*ABO* with PCA. Eleven of 52 non-MHC T1D-associated variants in GWAS-defined loci (17) showed evidence of association, although not significant, with at least one autoantibody. Given the evidence of shared genetic determinants with other autoimmune disorders in which autoantibodies are detected, the evidence from Orban et al. (23) of genetic associations with autoantibody production, and the importance of autoantibodies as an early biomarker of risk of T1D, the T1DGC initiated a detailed examination of the genetic basis of islet-specific and other organ-specific autoimmunity (T1DGC Autoantibody Workshop), taking advantage of the available SNP genotypes from its collection of ASP families.

The T1DGC had the foresight to collect sera from subjects enrolled in the study to facilitate testing for autoantibodies. Nevertheless, the T1DGC Autoantibody Workshop was years in preparation, while the T1DGC Coordinating Center oversaw the organization of the project, the selection and distribution of samples to laboratories, compilation and quality control of data sets, and the multiple laboratories conducting the analysis of samples for determination of autoantibody status. The set of autoantibodies selected for analysis were those critical to islet autoimmunity—the islet autoantigens, GAD65 (GADA) and the intracellular portion of protein tyrosine phosphatase (IA-2ic [IA-2A]), and those associated with related organ sites (TPO, TG, 21-OH, and H+/K+-ATPase).

Although a great strength of the workshop was the use of a broad panel of autoantibody measures, it should be noted that the titers of many autoantibodies decline after diagnosis. The T1DGC ASP collection has participants with varying duration of disease, so the collection of samples obtained years after diagnosis

may not be the most powerful design for detection of genetic association with autoantibody status. In addition, it should be noted that while the sample size is large, the data made available to the investigators were not genome-wide but focused on HLA genotypes (used by the majority of reports), candidate gene SNPs (used by many reports, focused often on *PTPN22* and *CTLA4*), and ImmunoChip data (used by one report, based on robustly significant associations with autoimmunity). Thus, there are limitations related to the absence of genomic coverage to detect initiation effects (either genetic or nongenetic) and the sample collection for autoantibody assessment in prevalent individuals with T1D of varying duration. Nonetheless, the insights obtained from the analyses of genetic variants with autoantibody results in T1D may provide new avenues for targeted research.

The genetic and autoantibody data were distributed to working groups for data analysis, with a presentation of the results in Bethesda, MD, on 7 June 2011. The goal of the workshop was to determine whether SNPs previously shown to be associated with T1D or other autoimmune diseases conferred an increased risk for autoantibody prevalence in the T1DGC ASP families, a process that represents an early and observable step in the progression to T1D. During the workshop, there were individual presentations related to the structure and generation of the data and the analysis of individual autoantibodies with respect to specific T1D and autoimmune gene variation. As this collection demonstrates, the data provide important insights into the role of genes in the generation of autoantibody biomarkers that are the early hallmarks of disease development. These data are available from the National Institute of Diabetes and Digestive and Kidney Diseases Central Repository for research into the etiology of T1D and its complications (https://www.niddkrepository.org/studies/t1dgc/).

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