Type 1 Diabetes: Prediction and progression

K M Gillespie, A E Long, I Wilson Karolinska University Hospital Huddinge, Sweden
University of Cambridge, UK

Abstract

Multiple islet autoimmunity increases risk of diabetes but not all individuals positive for two or more islet autoantibodies progress to disease within a decade. The SNAIL study seeks to harmonize data from longitudinal studies to identify the characteristics of slow progression to type-1 diabetes. Samples from 125 individuals with multiple islet autoantibodies (IAA, GADA, IA-2A and ZnT8A) for more than 10 years without progression were available from four studies (Bart-Oxford (BOX), UK; BABYDIAB, Germany; DAISY and Pittsburgh Diabetes, USA). Individuals enrolled in BOX provided Rapid Progressorâ • (diagnosed) 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 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 The ability to identify individuals at high risk for type 1 diabetes using genetic and/or autoantibody markers 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: Clinical trials to evaluate potential preventative interventions are more efficient if the recruited subjects are at high T1D risk, and 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 , 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.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 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 . 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.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). Type 1 Diabetes (T1D) is one of the most common chronic autoimmune diseases in children. The disease is characterized by the destruction of beta cells, leading to hyperglycemia, and to a lifelong insulin-dependent state. Although several studies in the last decades have added relevant insights, the complex pathogenesis of the disease is not yet completely understood. Recent studies have been focused on several factors, including family history and genetic predisposition (HLA and non-HLA genes) as well as environmental and metabolic biomarkers, with the aim of predicting the development and progression of T1D. Once a child becomes symptomatic, beta cell mass has already reached a critical threshold (usually a residual of 20–30% of normal amounts), thus representing only the very late phase of the disease. In particular, this final stage follows two preceding asymptomatic stages, which have been precisely identified. In view of the long natural history and complex pathogenesis of the disease, many strategies may be proposed for primary, secondary, and tertiary

prevention. Strategies of primary prevention aim to prevent the onset of autoimmunity against beta cells in asymptomatic individuals at high risk for T1D. In addition, the availability of novel humoral and metabolic biomarkers that are able to characterize subjects at high risk of progression, have stimulated several studies on secondary and tertiary prevention, aimed to preserve residual beta cell destruction and/or to prolong the remission phase after the onset of T1D. This review focuses on the major current knowledge on prediction and prevention of T1D in children

Biography:

K M Gillespie is a Molecular Biologist with a long term interest in the genetic mechanisms underlying autoimmunity. She has joined the Diabetes and Metabolism Unit in 1998 as a Non-Clinical Lecturer having worked previously as a Post-doctoral Researcher at the Academic Renal Unit in Bristol and at the Department of Medicine, University of Cambridge. Her current research projects include further analysis of the novel observation that maternal cells have the capacity to differentiate into functional pancreatic beta cells, studies into the role of NK cells in autoimmune diabetes and the immunogenetic characterization of Diabetes in Down's syndrome. She has research interests in autoimmunity, genetic mechanisms, maternal cells, functional pancreatic beta cells, NK cells, autoimmune diabetes and diabetes.

Email: K.M.Gillespie@bristol.ac.uk