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Setting the stage

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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 prevalent chronic disease of childhood, affecting 0.2–0.4% of the general population by 20 years of age and a lifetime risk of nearly 1%. Approximately 1.4 million in the USA (10–20 million worldwide) have T1D. The majority of cases have increased morbidity and mortality because of its complications, and T1D has no cure. The cost to health care resulting from T1D and its complications are in the billions of dollars per year.

Type 1 diabetes is a complex disorder and arises from the interaction of different environmental and genetic risk factors. Many studies have been conducted to identify genes for T1D. To date, approximately 12 T1D risk loci have been identified and confirmed. Interestingly, some of the genes identified as playing a role in T1D have also been identified in determining susceptibility to other autoimmune diseases – confirming that there are likely to be common pathways to multiple autoimmune diseases. T1D is distinctive in that genes in the major histocompatibility complex (MHC) region on chromosome 6p21 contribute to ~50% of the total genetic risk for disease. The MHC has also been shown to contribute to the risk for other autoimmune diseases. The primary risk genes in the human MHC include the human leucocyte antigen (HLA) class I (HLA-A, HLA-B and HLA-C) and class II (HLA-DR, HLA-DQ and HLA-DP) genes, but many other candidates reside in this region.

The Type 1 Diabetes Genetics Consortium (T1DGC) is an NIDDK- and JDRF-sponsored project whose primary aims are to (i) discover genes that modify risk of T1D and (ii) expand upon existing genetic resources for T1D research. Given the importance of the human MHC in risk of T1D, the T1DGC initiated a detailed examination of the MHC, using both classical HLA genotyping and a framework map that included 66 highly polymorphic microsatellites and over 3000 single nucleotide polymorphism (SNP) markers across the 4 Mb region. The source of samples for this experiment was 9976 samples from 2321 affected sib-pair families, part of the T1DGC collection. (These samples were also used in genome-wide linkage scans and other T1DGC experiments.) In keeping with one of its primary aims, the data from the MHC experiment is available by request (see www.t1dgc.org for access to these data).

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Conflict of Interest:

The author declares that he has no conflicts of interest in publishing this article.

The MHC Fine Mapping Workshop was years in preparation and execution. As noted in the manuscript by Brown et al. (this volume), the organization of data sets, samples and selection of genotyping facilities was an enormous task. Following the receipt of genotyping data, extensive data cleaning and curation had to occur before release to analytic groups. The analytic groups themselves formed the central focus of the Workshop, and 20 participants received data, performed analyses and participated in the experiment. From the initial organizational meeting in New Orleans (13 October 2006) to the presentation of initial findings in Washington, DC (27–28 August 2007), there were continual streams of information exchanged, through the T1DGC web site (www.t1dgc.org). As this volume demonstrates, the data provides important insights into the role of genes in the MHC that modify risk of T1D. These data are available (see www.t1dgc.org) for innovative methods of gene discovery and they provide a basis for discovery for years to come.