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Results of the MHC Fine Mapping Workshop

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Introduction

Type 1 diabetes (T1D) is strongly clustered in families, with an overall sibling risk ratio (λ_S) of approximately 15. One region (comprised of multiple loci) that contributes greatly to the familial clustering of T1D is the Major Histocompatibility Complex (MHC) on chromosome 6p21. The locus-specific sibling risk ratio (λ_S) of the MHC region is approximately 3, thereby contributing as much as 40% to the observed familial clustering. Genetic, functional, structural and model studies all suggest that the human leucocyte antigen (HLA) class II genes (*HLA-DRB1* and *HLA-DQB1*) are the major determinants of T1D risk in the MHC region. Despite the recognized effect of HLA class II genes on risk, it is not clear what contributions other genes in this region may make.

The Type 1 Diabetes Genetics Consortium (T1DGC) launched an initiative to more comprehensively examine the genetic basis of T1D in the extended MHC region encompassing 4 Mb (between 29 and 34 Mb). Characterization of genes in this region used classical HLA genotyping and a framework map of 66 microsatellite markers and over 3000 single nucleotide polymorphisms (SNPs) in 2321 affected sib-pair families. The reports in this Supplement, sponsored by the T1DGC, reflect multiple analytic approaches applied to a common set of

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data. Analyses of individual SNPs as well as haplotypes in the region have been performed and have incorporated the effect of the classical HLA class II gene contributions.

Summary of the Exploration of the Data

The T1DGC recognized that the richness of the MHC Fine Mapping data could be explored in many ways. T1DGC organized an MHC Working Group to perform analyses of the data set, and invited participation from investigators with a diversity of analytic approaches, background in T1D and experience in the MHC.

The charge given to the investigators of the MHC Fine Mapping Workshop was to better define the region(s) of the MHC that would likely contain T1D susceptibility genes and, hence, would merit further genetic and analytic examination. The investigators were encouraged to use the genetic data to its fullest extent, including information from SNPs, microsatellite markers and classical HLA genotyping, and to include all data from all participants in primary analyses, regardless of contributing T1DGC recruitment network. At the same time, secondary data analyses using network membership or other data (age at onset, antibody status, etc.) would be permissible. Even with the different approaches to the data, a few common themes emerged, summarized below.

Multiple approaches incorporated the effects of HLA class II genes. Single SNP analyses identified a number of associations, including SNPs in the vicinity of the HLA-G and HLA-A gene (including HLA-A*24), HLA-B (in particular alleles B*18 and 39), C6orf10, HLA-DPB1 (in particular alleles DPB1*0301 and 0402) and downstream of the *COL11A2* and *RING1* genes, HLA-DRA, *BAT4-LY6G5B-BAT5*, *NOTCH4*, and *MSH5* genes. Two central issues emerged from these analyses. The first is that there are multilocus effects because of the classical *HLA* genes, and taking these effects into account is a major analytic challenge. A second issue is the recognition that the MHC contains extensive linkage disequilibrium (LD). Depending upon the alleles of the HLA genes, the LD could span the entire region, and there could be haplotype-specific (or *cis*-) effects.

There are multiple analytic approaches available to model, rather than conventional subgroup analyses, the data to account for the effects of individual HLA genes on T1D risk. One promising method involves use of stepwise conditional logistic regression with recursive partitioning. These analyses identified significant contributions to risk of T1D by HLA-B and HLA-A independent of the large effects of HLA-DRB1 and HLA-DQB1. Even in the presence of these independent effects, the method identified SNP rs439121 and HLA-DPB1 as markers of T1D susceptibility loci while not finding significant associations at previously supported HLA-C, HLA-DQA1, *UBD/MAS1L* or *ITPR3* gene regions. Haplotype effects, especially in the presence of extensive LD (the origin of which is not fully understood), remain to be resolved.

Other (non-heritable?) effects were also examined in these data. There was evidence supporting an MHC effect by year of onset, as well as MHC seasonality effects. At the same time, there was little support for maternal–offspring HLA compatibility, parent-of-origin and non-inherited maternal effects at the eight classical HLA loci. Thus, while it is clear that non-genetic factors contribute to T1D risk, these data have a limited ability to identify those factors.

Future Directions

This Workshop has provided important insights and directions for future research into the genetic basis of T1D. The primary findings of the Workshop relate to the smaller but multiple, statistically significant and biologically meaningful contribution to T1D risk of MHC genes beyond that attributed to the classical HLA class II loci. These novel genes require fine

mapping, resequencing and future functional characterization. Another area of interest is in modelling the combined effects of multiple variants within the region on risk (through haplotype or combinatorial analyses).

Genes in the MHC do not act alone in defining T1D risk. While the MHC contributes substantially to the genetic risk, there are many non-MHC T1D susceptibility genes contributing independently, and perhaps interacting with MHC region genes. Thus, identification of potential interaction partners of the MHC would be of interest. One method used in this Workshop combined SNP data with protein–protein interaction networks to identify modules ‘enriched’ for proteins encoded from the MHC region. Other approaches of network modelling are continually being developed and could be applied to these data and those emerging from genome-wide linkage and genome-wide association scans. Indeed, as these data are derived from the T1DGC collection that also has plasma and serum samples, more detailed phenotyping is possible, to correlate with the genetic data.

It should also be recognized that these T1DGC MHC Fine Mapping Workshop data represent the largest collection of families with T1D affected sib-pairs genotyped at this level of detail. The joint contribution of families, classical HLA genotyping, microsatellite markers and SNPs make these data unique. The data set is available (through the T1DCG at www.t1dgc.org) to all researchers for further examination. While it is clear that both genetic and environmental factors contribute to T1D risk, the genes of the MHC – the most significant for T1D – will need to be included to complete our understanding of the disease and the means to predict, prevent and develop effective therapies. Moreover, the complexity of the genetic basis of the disease indicate that even larger sample sets may be required for the complete resolution of these gene effects on risk of T1D.