



Genetic Variation Within the *HLA-DRA1* Gene Modulates Susceptibility to Type 1 Diabetes in HLA-DR3 Homozygotes

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Type 1 diabetes (T1D) involves the interaction of multiple gene variants, environmental factors, and immunoregulatory dysfunction. Major T1D genetic risk loci encode HLA-DR and -DQ. Genetic heterogeneity and linkage disequilibrium in the highly polymorphic HLA region confound attempts to identify additional T1D susceptibility loci. To minimize HLA heterogeneity, T1D patients ($N = 365$) and control subjects ($N = 668$) homozygous for the HLA-DR3 high-risk haplotype were selected from multiple large T1D studies and examined to identify new T1D susceptibility loci using molecular inversion probe sequencing technology. We report that risk for T1D in HLA-DR3 homozygotes is increased significantly by a previously unreported haplotype of three single nucleotide polymorphisms (SNPs) within the first intron of *HLA-DRA1*. The homozygous risk haplotype has an odds ratio of 4.65 relative to the protective homozygous haplotype in our sample. Individually, these SNPs reportedly function as “expression quantitative trait loci,” modulating *HLA-DR* and *-DQ* expression. From our analysis of available data, we conclude that the tri-SNP haplotype within *HLA-DRA1* may modulate class II expression, suggesting that increased T1D risk could be attributable to regulated expression of class II genes. These findings could help clarify the role of HLA in T1D susceptibility and improve diabetes risk assessment, particularly in high-risk HLA-DR3 homozygous individuals.

Type 1 diabetes (T1D) is an autoimmune disease that results from destruction of pancreatic islet β -cells by autoreactive T cells (1). These T cells form an inflammatory infiltrate (insulinitis) in the islets of affected individuals. Clinical onset is preceded by a prodrome of β -cell autoimmunity marked by the appearance of autoantibodies. It is a non-Mendelian polygenic disorder involving interaction of multiple gene variants, environmental factors, and immunoregulatory dysfunction (1). The major genetic loci for both β -cell autoimmunity and T1D susceptibility are those encoding HLA-DR and -DQ, with a less significant contribution from genes encoding HLA class I (2,3) and HLA-DP (4). Many non-MHC loci are also associated with the disease, but their individual contributions to risk are relatively small (5). Although HLA genotyping can identify most persons at risk for T1D, only 1 in 15 (~7%) of individuals with even the highest risk HLA genotype (HLA-DR3/4) become diabetic (6). Recent genetic studies have improved our ability to predict T1D in the general population (7), but additional genetic risk likely remains to be discovered (8). Understanding of the detailed genetic risk conferred by HLA-DR and -DQ remains incomplete.

Several “extended DR3” haplotypes containing *DRB1*03:01-DQA1*05:01-DQB1*02:01*, additional single nucleotide polymorphisms (SNPs), and specific HLA class I alleles are known to modify T1D risk (3,9,10). These

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*A list of investigators of the Better Diabetes Diagnosis (BDD) Study Group can be found in the APPENDIX.

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extended haplotypes, although statistically significant, have not increased the accuracy of T1D prediction enough to be clinically useful and have not provided complete understanding of the mechanism of genetic risk. Additional data are clearly needed, but genetic heterogeneity and linkage disequilibrium in the highly polymorphic HLA region make identification of other T1D susceptibility loci difficult. Here, we report novel genetic risk elements in a cohort of individuals drawn from large genetic studies; all of whom carried the high-risk homozygous HLA-DR3 genotype to reduce HLA heterogeneity.

RESEARCH DESIGN AND METHODS

Study Samples

Case and control samples of DNA from individuals previously genotyped as homozygous for HLA-DR3 (*DRB1*03:01-DQA1*05:01-DQB1*02:01*) were selected from collections of three very large published studies. These included both T1D case subjects and control subjects without diabetes from the Type 1 Diabetes Genetics Consortium (T1DGC) (3,11), newly diagnosed T1D patients in the Swedish Better Diabetes Diagnosis (BDD) study (12), newborn children in Sweden screened in the Diabetes Prediction in Skåne (DiPiS) study (13), and children screened but not enrolled in The Environmental Determinants of Diabetes in the Young (TEDDY) study (14). No TEDDY data are included in this report. Numbers obtained from each study are shown in Table 1. Diabetes status was determined at the time of sample acquisition.

Each study cohort included approximately equal numbers of samples from males and females. HLA genotyping of the T1DGC samples was performed by one of the authors (J.A.N.) (15). HLA typing of the BDD and TEDDY samples was performed as previously described (12,14,16). All samples were originally acquired after human subject review. Reanalysis of samples in this report did not require additional approval, as they were completely de-identified.

DNA Preparation

T1DGC samples were supplied as DNA from immortalized B cells as previously described (15). Swedish samples were supplied as DNA extracted from dried blood spots using QIAamp 96 DNA Blood Kits (Qiagen, Venlo, the Netherlands).

Molecular Inversion Probe Design and Procedures

Molecular inversion probe (MIP) capture was used to sequence regions of interest in all samples (17,18). The technique permits identification and quantification of SNPs in all genes and loci targeted for analysis (19). Variant frequency was enhanced by incorporation of unique molecular identifiers within each molecule captured by an MIP (20). MIP procedures were performed as previously described (17). Probes are single-stranded oligonucleotides ~100 nucleotides in length; all have a shared backbone and also have sequences complementary to the target region. They were designed using algorithms

Table 1—Sample sources and numbers

| Source | No. of MIPs sequenced | Tri-SNP called | Case subjects | Control subjects |
|-----------------|-----------------------|----------------|---------------|------------------|
| T1DGC | 424 | 417 | 222 | 195 |
| BDD screening | 145 | 143 | 143 | 0 |
| TEDDY screening | 497 | 470 | 0 | 470 |
| DiPiS | 4 | 3 | 0 | 3 |
| Total | 1,070 | 1,033 | 365 | 668 |

Number of samples from each source that were analyzed (column 2) and that were found to generate high-quality data after quality control (column 3). Case subjects are persons with diabetes; control subjects are persons without diabetes. Tri-SNP: the haplotype of rs3135394, rs9268645, and rs3129877 in intron 1 of *HLA-DRA1* as described in RESULTS. The T1DGC samples represent the DR3/3 homozygotes of European ancestry available from the total of >16,000 samples (3,11). All BDD, DiPiS, and TEDDY samples were obtained in Sweden. The BDD and DiPiS DR3/3 cohorts represent 5% of 4,000 Swedish children diagnosed with T1D. Of 46,000 newborns screened in Sweden for the TEDDY study, 2,525 had a high-risk HLA genotype and agreed to participate. Our study includes those participants who were DR3/3 homozygous. None of the children screened for the TEDDY study who provided DNA for this study were subsequently enrolled in TEDDY. No TEDDY data are part of this report.

developed by us (17) and synthesized commercially (Integrated DNA Technologies, Coralville, IA). We report here results obtained from two probes designed to target rs9268645, a known genome-wide association study T1D susceptibility locus in intron 1 of *HLA-DRA* (21). The probe sequences are as follows: 5'-AAGGCAGGGGAATGGCTATCACTGNNNNAGATCGGAAGAGCACACGTGACTCGCCAAGCTGAAGNNNNNNNNNNAATTGCCACTATGGGTATGGGA-3' for MIP-1 and 5'-GTGCTGTTGTAAAGATGTACTGTAGAAAAGNNNNAGATCGGAAGAGCACACGTGACTCGCCAAGCTGAAGNNNNNNNNNNAAGCAACAATTTACCCAGG-3' for MIP-2. Samples were sequenced using an Illumina NextSeq 500 (www.illumina.com). We called alleles only on those samples that had a total sequence read depth of ≥ 10 per locus (17).

Genotyping

Sequence data were processed as previously described (17). One of the two MIP probes (MIP-1) used for genotyping the *HLA-DRA* intron covered the three SNPs reported here, whereas the second probe (MIP-2) covered only two of the three SNPs. Samples were excluded from analysis if the MIP-2 data were discordant with the MIP-1 data.

In Silico HLA Class II Gene Expression Studies

Expression of HLA class II genes in defined tissues and cell types was extracted from published databases. Effects of each high-risk SNP allele on gene expression were identified using the database at <https://www.gtexportal.org/>. We also interrogated the 1000 Genomes Project (22) database for individuals expressing the three-SNP risk haplotype that we discovered (see below) using four populations

(CEU, FIN, GBR, and TSI) that reflect the ancestral origins of our T1D cohort (https://hgdownload.cse.ucsc.edu/gbdb/hg19/1000Genomes/phase3/ALL.chr6.phase3_shapeit2_mvncall_integrated_v5a.20130502.genotypes.vcf.gz). Finally, we collected class II gene expression data from experiments using Epstein-Barr virus (EBV)-transformed lymphocytes available for 483 of the individuals in the 1000 Genomes Project (<https://www.ebi.ac.uk/arrayexpress/files/E-GEUV-1/GD660.GeneQuantRPKM.txt.gz>). Class II gene expression was then stratified according to three-SNP haplotypes of interest.

Statistics

Odds ratios (ORs) were calculated using the statistical R package “epitools” (<https://cran.r-project.org/web/packages/epitools/epitools.pdf>). Two-sided *P* values were calculated using Fisher exact test in epitools to analyze 2×2 tables. The χ^2 statistic was used to analyze higher-order tables with Bonferroni adjustment for multiple comparisons. For evaluating published class II RNA expression data from EBV-transformed lymphoblasts, RPKM (reads per kilobase of transcript per million mapped reads) values were stratified by haplotype and tested for significance by two-way ANOVA (GraphPad Prism), corrected for multiple comparisons by the Holm-Šidák method, with $\alpha = 0.05$.

RESULTS

Discovery of T1D Susceptibility Haplotype in Intron 1 of HLA-DRA

We discovered a previously unreported haplotype of three SNPs, rs3135394, rs9268645, and rs3129877, located in intron-1 of the *HLA-DRA1* gene (Supplementary Fig. 1). This “tri-SNP” haplotype was identified because the MIPs designed to interrogate rs9268645 revealed the presence of the other SNPs. As shown in Table 2, this tri-SNP haplotype is strongly associated with T1D risk in DR3/3 homozygous individuals. The reference and risk alleles for each SNP are shown in Table 3. We designate the higher-T1D-risk T1D risk haplotype as “010” to designate reference (0), alternate (1), and reference (0) alleles, respectively. Table 2 shows the ORs and *P* values for the homozygous HLA-DR3 sample in the current study (for people with 010/010 [*N* = 115], 101/010 [*N* = 245], or 101/101 [*N* = 650] haplotypes) relative to the lower-risk

101/101 haplotype. The 010 haplotype is strongly associated with T1D in both the T1DGC and Swedish DR3/3 cohorts; the overall OR for the combined data set was 4.65, $P = 1.69 \times 10^{-13}$, well below the genome-wide significance threshold of 5×10^{-8} .

In our combined DR3/3 cohort, only 46 of 2,066 (2.2%) chromosomes had haplotypes other than 010 or 101. The frequencies of these SNPs and haplotypes in our HLA-selected T1D samples are quite different from those in the general population, including the CEU, FIN, TSI, and GBR cohorts documented in the 1000 Genomes Project and the cohort in the Swedish population reported in the SweGen Project (23). In those cohorts, non-101 genotypes predominate (Table 4). In contrast, in the targeted cohort of HLA-DR3/3 homozygotes, 91% (Swedish) and 81% (T1DGC) of samples had either the 101/010 or 101/101 genotype (Table 4).

Because the Swedish case and control subjects are largely derived from different studies, we tested for possible geographic stratification but found no significant difference in tri-SNP haplotype as a function of geography (Supplementary Table 1). In addition, risk association remained highly significant ($P = 1.17 \times 10^{-9}$) when data were reanalyzed restricting the Swedish cases to the Skåne region, from which all the control samples were obtained.

The 010 haplotype appears to confer significant T1D risk compared with the 101 haplotype. OR for the 010/010 genotype is 7.09, relative to the 101/101 genotype, whereas the heterozygous genotype is intermediate (OR 3.42 relative to 101/101). The 101-containing haplotypes (especially 101/101) are significantly protective for T1D compared with the 010 haplotypes. These results effectively stratify the high-risk DR3/3 individuals into two groups: those who carry the 010 haplotype and those who do not (Table 2).

In Silico Analysis Suggests That the Susceptibility tri-SNP Could Act as an Expression Quantitative Trait Loci

The expression quantitative trait loci (eQTL) database at <https://www.gtexportal.org/home/> groups gene expression in numerous tissues and cell types by the allele at any given SNP. Using this eQTL database, we found that RNA expression changes have been associated with the risk alleles of each of our three SNPs and that they statistically significantly affect expression of HLA genes such as *DQB1* (data not shown).

Table 2—Association of T1D with tri-SNP haplotype

| Haplotype | OR | 95% lower CI | 95% upper CI | <i>P</i> value |
|-----------|------|--------------|--------------|------------------------|
| 101/101 | 1.00 | NA | NA | NA |
| 101/010 | 2.51 | 1.85 | 3.42 | 4.65×10^{-09} |
| 010/010 | 4.65 | 3.08 | 7.09 | 1.69×10^{-13} |

ORs for the association of HLA-DRA tri-SNP genotypes with T1D, with 101/101 used as the reference. “0” designates the reference allele and “1” the alternative allele for each of the three SNPs. The reference and risk alleles for each SNP are shown in Table 2. *P* values were calculated by Fisher exact test.

Table 3—HLA-DRA tri-SNP alleles

| SNP | Reference allele (0) | Alternate allele (1) | Risk allele |
|-----------|----------------------|----------------------|-------------|
| rs3135394 | A | G | A (0) |
| rs9268645 | C | G | G (1) |
| rs3129877 | G | A | G (0) |

Alleles of the three HLA-DRA SNPs for T1D. In vector notation, the risk haplotype is “010.”

Table 4—Tri-SNP haplotype prevalence

| Population | Population description | 010/010 | 101/010 | 101/101 | Other/other (e.g., 000) | 010/other | 101/other |
|------------|--|---------|---------|---------|-------------------------|-----------|-----------|
| CEU | Utah residents with Northern and Western European ancestry | 0.11 | 0.09 | 0.00 | 0.26 | 0.39 | 0.09 |
| FIN | Finnish in Finland | 0.12 | 0.00 | 0.00 | 0.44 | 0.32 | 0.11 |
| GBR | British in England and Scotland | 0.13 | 0.07 | 0.02 | 0.28 | 0.39 | 0.11 |
| TSI | Toscani in Italy | 0.15 | 0.05 | 0.00 | 0.17 | 0.56 | 0.08 |
| SWEDEN | Swedish population | 0.04 | 0.01 | 0.00 | 0.61 | 0.30 | 0.04 |
| SWE | Swedish DR3/DR3 homozygotes | 0.08 | 0.15 | 0.76 | 0.00 | 0.00 | 0.01 |
| T1DGC | T1DGC DR3/DR3 homozygotes | 0.16 | 0.37 | 0.44 | 0.00 | 0.00 | 0.03 |

Relative proportions of haplotypes of the tri-SNP in a variety of populations, using the vector nomenclature explained in the legends of Tables 2 and 3. Data are taken from the 1000 Genomes Project (CEU, FIN, GBR, and TSI) (22), the SweGen project (SWEDEN) (23), and our cohort (SWE and T1DGC). The 101 haplotype is much more common in our samples, which were selected to be homozygous for HLA-DR3, than in the general population cohorts. This may represent the presence of a protective element (101) in the genomes of people at high risk for T1D. Haplotype frequencies for SweGen are calculated based on individual SNP frequencies assuming independence between the SNPs, since haplotype data were not available. SNP frequencies in SweGen are 0.1105, 0.3325, and 0.339, respectively.

The tri-SNP haplotype cannot be studied using the GTEx database because it contains data only for individual SNPs. To study the haplotypes in silico, we adapted a strategy developed previously to investigate susceptibility to multiple sclerosis (24) using both sequence and expression data available through the 1000 Genomes Project. We collected data on HLA class II gene RNA expression in EBV-transformed B lymphocytes and stratified these results by tri-SNP haplotype ($N = 93$ individuals carried at least one copy of 101 or 010). As noted above, the 101/101 haplotype is rare in the general population, and only two such individuals are included in the 1000 Genomes data set. Nonetheless, despite this limitation, we found that for people carrying the putative protective homozygous haplotype (101/101), class II gene expression in general was lower, and significantly so for *HLA-DQB1*, compared with that observed in individuals homozygous for the risk haplotype (010/010 [$N = 60$]) (Supplementary Fig. 2). In the 101/010 heterozygotes ($N = 31$), the expression of class II genes was intermediate between those values seen in either homozygote.

DISCUSSION

We report a novel approach to analyzing genetic susceptibility to T1D by minimizing HLA heterogeneity. By studying a population of case and control subjects homozygous for HLA-DR3, we were able to identify a previously unrecognized susceptibility locus within intron 1 of *HLA-DRA*. The discovery is novel and highly statistically significant. It surpasses the standard rigorous metric of genome-wide significance (5×10^{-8}) despite the relatively small sample size and the lack of polymorphism of the DR- α chain encoded by this locus. This result is consistent with discoveries reported in the multiple sclerosis literature (24), suggesting that occult, HLA-specific susceptibility loci may be important. Our data suggest a possible explanation for the fact that most persons with HLA-DR3 (>90% even for the highest-risk DR3/4 haplotype (6)) do not become diabetic. Notably, 75% of the Swedish DR3/3 samples in this study are homozygous for the relatively protective 101 haplotype.

The current study cohort is limited to people with homozygous “DR3” haplotypes. The predictive tri-SNP haplotype occurs within this cohort, but whether it exists, or is diabetes predictive for other high-risk haplotypes, such as “DR4,” is not known. *HLA-DRA1* is nearly invariant, but differences in noncoding regions of *HLA-DRA1* do occur. Planned future studies include determining whether the tri-SNP risk haplotype is present in other T1D risk haplotypes.

Studies of RNA expression by others indicate that each SNP in the tri-SNP haplotype has the characteristics of an eQTL that could influence the level of transcription of HLA and other immunologically relevant genes. Our in silico finding is preliminary, but if it can be substantiated directly by in vitro studies, it could contribute to our understanding of how the HLA-DR associations in T1D work. The data suggest that modification of class II gene expression could be a T1D risk mechanism.

In summary, we report that a three-SNP haplotype in intron 1 of *HLA-DRA1* appears to modify the risk of T1D in

individuals homozygous for the HLA-DR3 haplotype. This intronic SNP haplotype may well function as an eQTL, affecting expression of HLA class II and perhaps other genes. The data also suggest that additional genetic information relevant to susceptibility to T1D remains to be discovered.

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Author Contributions. Ö.A. oversaw all MIP sequencing and data analysis and cowrote the manuscript. J.A.N. provided the T1DGC samples, codesigned the study, and cowrote the manuscript. J.A.B. had overall responsibility for MIP sequencing and data analysis and cowrote the manuscript. Å.L. provided the Swedish samples and cowrote the manuscript. P.M. performed the MIP sequencing. A.A.S. performed the DNA extraction of the Swedish BDD samples. F.B. performed the eQTL analyses of the published 1000 Genomes data. E.P.B. oversaw all data analyses, originated and supervised the eQTL analyses, and cowrote the manuscript. J.P.M. had overall responsibility for the entire project and cowrote the manuscript. The BDD Study Group Investigators (see APPENDIX below) oversaw the collection and transmission of the BDD DNA sample set and gave permission for its use. J.P.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Appendix

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