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Article

Class I MHC Polymorphisms Associated with Type 2 Diabetes in Mexican Population

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Abstract: Type 2 diabetes (T2D) has been linked to the expression of Human Leukocyte Antigens, principally to the major Histocompatibility Complex (MHC) Class II and only scarce reports to MHC class I (MHCC-I) in specific populations. The objective of the present work was to explore the presence of polymorphisms in the MHC-I related to T2D in Mexican population using the GWAS SIGMA database. There were made two study groups from the database. Group with T2D with 3,848 individuals and without clinical or hereditary history of T2D with 4,366 individuals. The searching criteria considered $p < 0.005$ and odds ratios (OR) > 1.0. Ten novel statistically significant nucleotide variants were identified: four polymorphisms associated with HLA-A (A*03:01:01:01), and six with HLA-C (C*01:02:01:01). These alleles have a high prevalence in Latin American populations and could potentially be associated with autoimmunity mechanisms related with the development of T2D complications.

Keywords: HLA ; MHC class I; polymorphism; variant; type 2 diabetes; mexican

1. Introduction

Diabetes is a chronic illness, identified by high concentrations of glucose as results from defects on metabolism of glucose through the insulin disfunction by resistance, secretion o both. Individuals with Diabetes without glycemic control have high risk to develop severe damage in organs like heart, kidney, eyes among others [1].

Specifically Type 2 Diabetes (T2D) is defined as polygenic disease. Diverse studies have found that epigenetic and environmental factors could affect key genomic regions

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on the β-cell function. [2,3]. In contrast, Type 1 Diabetes (T1D) is considered an autoimmune disease with pancreatic β-cell loss and insulin deficiency [4].
Long term researches in subjects with T2D have indicated that speed of dysfunction or lose of pancreatic β-cell influences the progress of disease as well as treatment and needs of insulin[5,6]. ADOPT study showed that the main classes of antidiabetics used in monotherapy resulted in a progressive glycemic increase over time, which may reflect a reduction in insulin secretion [7]. This evidence suggests a progressive disease not related with peripheral glucose resistance and probably associated with auto immunological damage. It has T1D and T2D share some pathophysiological mechanisms, however, the elements involved in this association have not been defined [8,9].

The Major Histocompatibility Complex (MHC), initially defined in humans as the Human Leukocyte Antigen (HLA), is located on chromosome 6p21.3 [10]. The MHC is made of glycoprotein molecules bound to the cell membrane, which act inducing specific immune response presenting the antigen to the T lymphocytes [11].

Most of the experts agree that HLA is the principal region of risk to developing T1D, and less important to T2D. However recent experimental research has shown evidence about the effects of hyperglycemia on metabolic stress with biochemical consequences on the non-enzymatic reaction of oxidative in key components of MHC. These alterations are related to change on epitope-specific endosomal processing efficiency, MHC class II (MHC-II) peptide binding and editing activity [12]. Therefore, the glycation reactions could be related to alternated MHC antigen presentation increasing de risk of complications in T2D.

Although the relation of T2D with some MHC-II variants has been more frequently expressed [13–15], the association with polymorphic regions in loci A, B and C related to MHC class I (MHC-I) is less mentioned [16]. The genome-wide association studies have linked MHC loci with T2D [17], killer-cell immunoglobulin-like receptor, and MHC-I interactions that modify the NK cell cytotoxic activity and NK cell cytokine production profile. These relations could be implicated in the develop of an inmune-mediated T2D [18].

The main genetic determinants of T1D are the regions of the MHC, followed by insulin gene (INS) and the protein tyrosine phosphatase non-receptor type 22 gene (PTPN22) in chromosome 6 and 11 [19–21]. Some authors have mentioned the association between T2D and histocompatibility antigens and most of the HLA haplotypes have been associated with a high risk to develop both, insulin and non-insulin dependent diabetes [22–24] and most of the reports associated with MHC-II [13–15,25–31].

Based on this evidence, there are several loci not yet classified in or near the HLA complex, which can modulate the risk and evolution of T2D and some complications. Other important evidence is the effects of treatments like metformin in T2D improve glycemic levels, delay the onset of chronic complications, and other significant clinical findings through immunomodulation related to the antigen-presenting function of antigen-presenting cells (APCs). Metformin may affect in many ways the activity of presentation of antigens decreasing the expression of both MHC-I and MHC-II-restricted and also may suppress the expression of both MHC molecules and co-stimulatory factors such as CD54, CD80 and CD86 in Dendritic Cels (DCs). However, did not affect the activity of phagocytic activity by exogenous antigens [32].

The Slim Initiative in Genomic Medicine for the Americas (SIGMA) project (https://www.broadinstitute.org/sigma;https://www.broadinstitute.org/diabetes/sigma-t2) set out to systematically identify the genetic risk factors that contribute to this disparity, and translate those findings into improved methods of diabetes treatment and prevention. In the first phase of the project, SIGMA scientists sequenced and characterized more than 10,000 tissue samples from Mexican and Mexican Americans. This unprecedented analysis led to the discovery of the first identified common genetic variant shown to predispose Latin American populations to the disease. This finding provides unique biological insight into T2D and may present opportunities for therapeutic research

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and development. Going forward, SIGMA is focused on completing the genetic analysis of T2D in Mexico, and translating this knowledge into more effective new approaches to prevention and treatment.

To date, there is no published study using the Genome Wide Association Studies (GWAS) SIGMA database that explains the relationship between MHC class I and T2D. The aim of the present work was to explore the presence of polymorphisms in the MHC-I related to T2D in Mexican population using the GWAS SIGMA database.

2. Materials and Methods

2.1. Exploration of SIGMA Database

The GWAS SIGMA T2D database available at http://www.type2diabetesgenetics.org/ was used to explore the frequency of polymorphisms in Mexican population using the tool variant finder in analysis modules, specifying multiple search criteria to find genetic variants meeting those criteria. The pipeline criteria were T2D in phenotype or trait; as a dataset, we use the GWAS SIGMA database with $p < 0.005$ and $OR > 1$ in HLA-A, HLA-B and HLA-C loci related to MHC-I. The polymorphisms found were pointed using the LocusZoom interactive visualization to explore associations of other variants in the HLA region. Linkage disequilibrium (r2) values are based on the 1000G ALL reference panel (including every sample available in the 1000 Genomes project) (http://www.internationalgenome.org/home) and are supplied by the Michigan Imputation Server (https://imputationserver.sph.umich.edu/).

2.2. Analysis and documentation of found variants

The results were tabulated and documented the coordinates of the position in chromosome 6 in GRCh37/hg19 to explore the sequences in UCSC Genome Browser, NCBI dbSNP database number ID, the change in the polymorphisms as reference/effect allele, the minimum and maximum effect allele average frequency in general population using the available information published in GnomAD (https://gnomad.broadinstitute.org/), ExAC (http://type2diabetesgenetics-old.org/variantSearch/variantSearchWF) which had permission for limited access to the Variant Search database, 1000G (http://www.internationalgenome.org/), ALSPAC (http://www.bristol.ac.uk/alspac/), TWINSUK (http://twinsuk.ac.uk/) and GO-ESP (https://evs.gs.washington.edu/EVS/); the effect allelic frequency and the effect genotype frequency in heterozygous and homozygous estimated to Mexican population database using using 1000G available in Ensemble (http://grch37.ensembl.org/index.html); the protein change and the consequence clinical significance using phenotype, diseases or trait related in ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) and OMIM databases (https://www.omim.org/); and finally, the P-value and odds ratio estimated.

2.3. IPD-IMGT/HLA analysis

The polymorphisms found with statistical significance and odds ratio (OR) greater than 1.0 were identified and used to explore association with specific HLA allele in the Immuno Polymorphism (IPD-IMGT/HLA) database, using the polymorphism search tool available at https://www.ebi.ac.uk/ipd/imgt/hla/polymorph.html

The HLA sequences matches were corroborated by manual analysis with the next strategy: we obtained the Nucleotide Sequence Data and Genomic Sequence Data for HLA Allele Report from IPD-IMGT/HLA database available in https://www.ebi.ac.uk/ipd/imgt/hla/allele.html and alleles frequencies was evaluate in Allele Frequencies Worldwide Populations (AFWP) database (http://www.allelefrequencies.net).

2.4. Comparison with GEO dataset

Search matches obtained in GWAS SIGMA T2D database with type I HLA genetic expression were explored using the Human skeletal muscle - T2D and family history positive individuals - Mexican American dataset in Gene Expression Omnibus (GEO) Datasets with accession number GSE21340 [33]. In the same way HLA-A and HLA-C loci

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expression were explored and data mining to gene expression analysis was carried out with Orange (https://orange.biolab.si/) using the T2D pancreatic β-cells dataset in GEO with accession number GDS3782 (Data not shown) [34].

The groups were classified in three for analysis: a population of Mexican origin with diabetes (Group 1) and their respective controls with positive and negative family history (Groups 2 and 3, respectively). Mann-Whitney U test was performed to compare the levels of expression in muscle tissue of the genes identified in HLA-A and HLA-C .

3. Results

3.1. HLA variants found

From the specified search strategy, 27 variants were found in HLA-A locus (Supplementary Materials Table S1), 9 variants in HLA-B locus (Supplementary Materials Table S2) and 6 variants in HLA-C locus (Supplementary Materials Table S3) related to T2D in Mexican population with $p < 0.005$.

In the HLA-A locus, only the intronic variants rs72498368 (OR: 1.33), rs199474578 (OR: 1.27), rs707910 (OR: 1.24), and rs2571420 (OR: 1.21) obtained an OR greater than 1.0, and all were associated with A*03:01:01:01 allele; meanwhile in HLA-C locus, all intronic variants found, rs17408553, rs2308557, rs1131115, rs2001181, rs1065711, and rs7383157, obtained an OR more than 1.0, and all are associated with HLA-C antigen, Cw-1 alpha chain precursor (C*01:02:01:01 allele).

The variants found in HLA-B loci related to T2D in the Mexican population are statistically not important, therefore it was decided to focus on HLA-A and HLA-C variants.

*3.2. HLA-A*03:01:01:01 allele*

The variants found in HLA-A*03:01:01:01 in T2D in Mexican population presented in Supplementary Materials Table S1, presented specific codon changes which are different from those reported in the allele database as shown in Supplementary Materials Table S4, S6. In codons 202 and 68 of the hypervariable peptide-binding region were identified a difference between the information reported in GWAS SIGMA and the IPD-IMGT/HLA database. For the patient with the dbSNP ID rs199474578 there was no change in the threonine, the expected amino acid according to the reading frame, when it is supposed to change to an arginine. In the other two cases with OR > 1.0, we found an upstream gene and intron variants without a change in the gene sequence lecture frame that was reported.

*3.3. HLA-C*01:02:01:01 allele*

From allele C*01:02:01:01, all 6 variants found change the protein sequence and are localized in only three loci in the alpha chain of HLA-C: rs1065711 and rs2308557 in the locus 101 change serine (S) by asparagine (N) in the protein residue; rs17408553 and rs2001181 in the locus 104 change asparagine (N) by Lysine (K); and rs1131115 and rs7383157 in the locus 123 change serine (S) by tyrosine (Y) in the protein residue (Supplementary Materials Table S5, S6). In all codons, we found a different result between the ones reported in the allele database and the ones reported in the Mexican population with T2D in GWAS SIGMA. These polymorphisms, as far as we know, are not previously reported in biomedical literature related to T2D.

*3.4. HLA-C*01:02:01:01 and HLA-C*01:02:01:01 allelic frequencies*

The allele A*03:01:01:01 has been found in different ethnic groups like African American; Arab, Middle East, British/Irish; North America and North European Caucasoids; also Asiatic Oriental populations from China, this specific allele was reported 11 times and present in 10 populations as shown in Supplementary Materials Figure S1. The C*01:02:01:01 native American form Kaingang, Brazil, British/Irish Caucasoid , Asiatic India; Han and Hong Kong Chinese, Japanese, Korea Asiatics; this

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allele was not previously reported in AFWP database, but C*01:02:01 frequencies summary are described in Supplementary Materials Figure S2.

3.5. Differential HLA-A and HLA-C Expression using GEO

The levels of expression in muscle tissue of the genes identified in HLA-A and HLA-C were compared among three groups for analysis: population of Mexican origin with diabetes (Group 1) and their respective controls with positive family history and negative (Group 2 and 3, respectively) (Supplementary Materials Figure S3). The results were the following:

First, the Kolmogorov-Smirnov test was carried out, to know if the groups had a normal distribution and to confirm that the data were comparable, namely, if they were found in the same range. In this case the groups could be compared.

A comparison was made between the groups (1 vs 2, 2 vs 3 and 1 vs 3), for this the Kruskal-Wallis test was performed, in which no significant difference was found.

Then the comparison of the Mann-Whitney U test was made to corroborate, in more detail, that there were indeed no differences. Group 1 was compared against 2, and no significant difference was found, with the two-tailed comparison equal to 0.594. In the comparison of 1 vs 3, there was no significant difference, 0.391. Group 2 was analyzed against 3, and there was no difference. 0.165. In summary, no significant differences were found between the different groups analyzed, using the Mann-Whitney U test.

4. Discussion

The continuos high glucose levels in T2D individuals increase the expression of many pancreatic β-cell antigens and consequently the pancreatic β-cells are susceptible to autoantibodies like anti-GAD, T2S and CD8(+) T-cells may act cytotoxic upon binding to MHC-I molecules on the surface of pancreatic β-cells [35].

Only few articles had previously described the potential association between HLA-I and T2D, most of them in specific ethnic groups, like Pima indians, Finnish or Papua New Guinea population, New Zealand Maori and afro American population. The results of this and other studies shows that HLA-A alleles are most frequently related. In the Pima indians study were most common found HLA-A2 (A*02:01:01:01) and HLA-A24 (A*24:02:01:01), with frequencies of around 49% that match with the results found on Finnish population [23].

More over recent studies have demonstrated that an increase of MHC-I gene expression in target tissues may be related to the in the physiopathology of T2D. As well hyperglycemia in T2D may increase MHC-I levels in target tissues and contribute to chronic autoimmune complications in advanced disease and show specific organ and tissue damage [36] but apparently without functional defects in immune cells, at least in circulating monocytes, DCs, NK cells and T lymphocytes [37]. Also is known that CD8(+) and CD4(+) T-cell reactivity to islet-specific antigens in diabetic patients are more prevalent in T1D subjects than in healthy donors, and CD4(+) T-cell autoreactivity seems to be present in both types of diabetes, while autoreactive CD8(+) T-cells are specific to T1D [38].

Some clinical aspects, such as the early age of initiation of the disease and the rate of pancreatic β-cells destruction in large evolution T2D could be related to MHC-I [9,39,40]. Previous evidence shows a strong relationship with the HLA-B40 groups of antigens (relative risk 5.1 chi 2 = 16.8, $p < 0.001$), and this was mainly attributable to HLA-B48 and HLA-B60 in some specific populations with a high prevalence of T2D [41].

On the other hand, latent autoimmune diabetes in adults (LADA) defined as adult-onset auto-immune diabetes without not insulin therapy at least six months after diagnosis. In contrast to the young-onset autoimmune diabetes. LADA share metabolic disturbances highly variable with both T2D and T1D in pancreatic β-cell destruction, levels of insulin resistance, heterogeneous titer pattern of islet autoantibody. These data

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suggest different pathophysiological course that could partially explaining the heterogeneous phenotypes between LADA than T2D [42–44].

In the case women with T2D with medical history of Gestational Diabetes Mellitus (GDM) have found higher frequency developed T2D had a significantly higher frequency MHC-I locus, specifically HLA-B41 and HLA-Bf-S in MHC-I locus and HLA-DR2 in MHC-II locus, and a lower frequency of HLA-DR1 and HLA-DR6 phenotypes in MHC-II locus than control subjects.

In the cases of GDM treated with insulin, have found a significantly higher frequency of HLA-A33 in MHC-I locus and HLA-DR2, HLA-DR9, and HLA-Bf-S phenotypes in MHC-II locus than control subjects. Especially HLA-B41 and HLA-DR2 have found that can be independent predictors of the use of insulin during GDM and T2D, even after controlling for age and body mass index [45].

The seminal studies related T2D with the increase in the frequency of the MHC-I Cw4 allele with the age of onset, the body mass index, and positive family history [16,46]. Also, T2D patients with HLA-B8 and B8/B15 have shown significantly lower C-peptide concentrations ($p < 0.05$) than patients without these HLA antigens polymorphisms. However, subsequent studies using serology have not found an association between T2D and MHC-I (HLA B or C) [47].

Furthermore, it is important to consider the possibility that genetic predisposition in immediate family members with risk of TD1 given by the HLA complex could influence the long term pancreatic β-cell malfunction in patients with T2D [48] which, in turn, could strengthen the idea of the genetic relationship between T1D and T2D and its partly gene regulation in the HLA region [14].

In other study made on south Indians the HLA-A alleles were also found, but this time not just on a positive significant way, it was found that allele A*68 (A*68:01:01:01), A*03 (A*03:01:01:01) and A*11 (A*11:01:01:01) showed a significant negative association which may indicate a protective function [31]. In concordance to the previously, on a Mexican American study some HLA-A and B alleles were associated to T2D on a protective way, among these ones we find the allele HLA-A2 (A*02:01:01:01), A25 (A*25:01:01:01) and A3 (A*03:01:01:01) along some B alleles like HLA-B35 [49].

The association of both alleles was described previously in three populations, one in South Africa Indian and two in continental India. These variants on the results may indicate that it is a combination of multiple alleles the ones that determines the presence of T2D, and that the finding of some alleles they not necessarily determine a risk to develop diabetes, they also might determine the absence or the penetrance of the disease, making this one to be less serious. This can be supported by some studies like the Tuomilehto-Wolf et al. in 1993 [23], where their results show this kind of pattern and where their conclusion was similar.

5. Conclusions

The changes found in the amino acid residues pertaining to α-1 and α-2 domains, responsible for antigen recognition, could influence the generation of an immune response against potential antigens not yet defined related to the damage and deterioration of long-term target organs associated with chronic complications observed in T2D.

Ten novel statistically significant nucleotide variants were identified: four polymorphisms associated with HLA-A (A*03:01:01:01), and six with HLA-C (C*01:02:01:01). These alleles have a high prevalence in Latin American populations and could potentially be associated with autoimmunity mechanisms that participate in the development of T2D complications. This relationship could explain some phenomena related to the age of initial presentation of the symptoms, its progression and the severity of the damage in target organs.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org. Table S1: Variants found in HLA-A loci related to T2D in Mexican population with statistical significance $p < 0.005$., Table S2: Variants found in HLA-B loci related to T2D in Mexican population with statistical significance $p < 0.005$., Table S3: title Variants found in HLA-C loci related to T2D in Mexican population with statistical significance $p < 0.005$. Table S4: HLA-A*03:01:01:01 protein sequence variants found in Mexican population with T2D. Table S5: HLA-C*01:02:01:01 protein sequence variants found in Mexican population with T2D, Table S6: Polymorphisms found in HLA-A*03:01:01:01 and HLA-C*01:02:01:01 alleles., Figure S1: HLA-A*03:01:01:01 allele frequency in worldwide populations., Figure S2: title HLA-C*01:02:01:01 frequency in worldwide populations., Figure S3: HLA.A and HLA-C differential expression values from muscle tissue, Figure S4: Fisher's exact test of the expression values.

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