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HLA Association with Type 2 Diabetes Mellitus and Hypertension among the Kami Population from Sub-Himalayan West Bengal

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ABSTRACT The Kami population is an Indo-Aryan caste group from the Gorkha community of the Sub-Himalayan region. This study aims to investigate the association of Human Leukocyte Antigen (HLA) genes with Type 2 Diabetes Mellitus (T2DM) and hypertension (HT) among the Kami population. One hundred fifty unrelated Kami individuals were recruited from the sub-Himalayan region of West Bengal, India. Twenty of them had a history of T2DM, and 15 had HT. The enrolled individuals provided blood samples, which were then utilized to perform HLA typing using PCR-SSP A, B, and DR typing kits. The findings showed that T2DM cohort had a higher frequency of HLA-B*13 and HLA-B*15 and a lower frequency of HLA-A*33. Conversely, a significantly high frequency of HLA-A*24 and HLA-B*13 was observed among the HT cohort. The study demonstrates the presence of susceptibility genetic factors at HLA loci for T2DM and HT among the Kami population.

INTRODUCTION

The incidence and burden of Type 2 Diabetes Mellitus (T2DM) and hypertension (HT) have increased considerably in the last three decades among the world population (Danaei et al. 2011). Both these diseases have multifactorial aetiology with prevalence varying widely across geographical region and ethnicity. The susceptibility of T2DM varies across various populations with studies reporting higher risk for Asian Indians, Native Americans, and Pacific Islanders (Pradeepa and Mohan 2021). It is suggested that the aetiology of type II diabetes involves interactions between multiple genes, and gene-environment interactions (Chen et al. 2012). Since interactions between genes and the environment are involved, delineating the specific genetic and environmental factors in the etiopathology of T2DM has been a daunting task (Barroso 2005). Similarly, interactions between genetic, environmental, and demographic factors are suggested aetiological factors for hypertension (Kato 2012). In addition, ethnic and genetic factors are implicated in the disparity in the rate of prevalence of hypertension among the populations (Tomson and Lip 2005). Diabetes and hypertension are common in India across all ages and all regions of the country (Geldsetzer et al. 2018). Given the genetic diversity found in people with varying ethnic backgrounds, genetic factors that contribute to the aetiology of these two diseases may play a significant role. Many researchers have attempted to correlate type II diabetes and hypertension to different genetic loci across various populations of different ethnic origins (Sladek et al. 2007; Chauhan et al. 2010; Yamamoto et al. 2006; Shimodaira et al. 2010; Kamide et al. 2011; Zhang et al. 2013; Zhang et al. 2016).

Of all the gene loci in the human genome, the human leukocyte antigen (HLA) is among the most researched and has been connected to more disorders than any other genes (Trowsdale 2011). Due to the substantial amount of polymorphism and the notable variations in HLA gene frequencies among various ethnic groups, it is imperative that the ethnic composition of the population be taken into account when performing studies related to

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HLA-associated diseases (Perez-Luque et al. 2003). Numerous investigations have tried to look at the possible relationship between HLA and T2DM in various ethnic groups. HLA-DR7 and DR11 alleles were identified as probable susceptible genes for type 2 diabetes mellitus among the population from Yunnan (Yang et al. 2007). Likewise, research has demonstrated a positive association of DRB1*040101 and DRB1*070101 and a negative association of DRB1*110101 and DRB1*160101 with T2DM among Bahrainis population (Motala et al. 2005). Furthermore, Pakistani patients with non-insulin-dependent diabetes mellitus showed a higher incidence of HLA DRB1*13 (Tipu et al. 2011). Recently, HLA B gene variant rs2308655 was suggested as a risk variant for T2DM susceptibility in the Pashtun population of Khyber Pakhtunkhwa (Jan et al. 2021). Susceptibility to HT in diverse populations has been explored considering the frequency distribution of HLA. Research has shown an association of HLA-DRB1*1501/2 and HLA-DR2 with HT among the Chinese population (Shao et al. 2004; Tao et al. 1995). Additionally, research has demonstrated the presence of HLA-DRB1*0101/2 DQB1*0501/2 DQA1*0102 may increase the risk of essential hypertension in Slovenians (Vidan-Jeras et al. 2000).

The Indian Kami population is a socio-ethnic caste group mostly distributed in the Sub-Himalayan region of Nepal, West Bengal, and other North Eastern states of India (Singh et al. 2020). Traditionally, they are metalsmiths and are known to make various metal tools used in household and agriculture. They are primarily endogamous, however polygamy in the past cannot be ruled out.

Objective

To date, studies are lacking in understanding the role of HLA genes in the susceptibility to T2DM and HT among the Kami population. Therefore, the objective of the present study is to investigate the association of HLA genes (if any) with T2DM and HT among the Kami population. The investigation might help to better understand the genetic underpinnings of T2DM and HT among the Kami population.

METHODOLOGY

One hundred and fifty individuals belonging to the Kami ethnic group were chosen at random from the Kalimpong, Darjeeling, and Dooars regions of sub-Himalayan West Bengal. Among the selected individuals, 15 individuals were identified as having T2DM, and 20 had HT. Following a careful examination of their medical histories, the patients were included in the study. Individuals with any secondary cause for hypertension were excluded. A total of 80 normotensive and 60 healthy individuals belonging to the Kami population were considered as controls for comparison with HT and T2DM, respectively. The GPower programme was used to determine the statistical power. The goodness of fit method was used and the test was set with the following input parameters of effect size = medium, α err prob =0.05, df =1. The power of 0.88 with a total sample size of 88 was observed. The patient control ratio of 1:4 was maintained to improve the statistical power of the study (Coggon et al. 2009). Each participant gave their written, informed consent, and the study was carried out in compliance with the Declaration of Helsinki. The Institutional Ethical Committee of Sikkim University approved the study.

From all the recruited individuals 5 ml blood samples were collected by venipuncture method. Isolation of DNA from the blood samples was performed by DNA isolation kit (Qiagen). Low-intermediate resolution HLA-A, B and DRB1 genotyping of patients and controls was performed using a PCR SSP ABDR typing kit (Inno-Train Diagnostik GmbH, Germany). There were 22 HLA-A, 35 HLA-B, and 13 HLA DRB1 genes that the kit may potentially identify. The programme 'Ready Gene V.1.0.0.0' was utilized to assign HLA genotypes.

Statistical Analysis

The statistical analysis was conducted using SPSS software, version 22. The goodness of fit $\chi 2$ test was conducted to ascertain the Hardy-Weinberg equilibrium (HWE) for all the three HLA loci. The gene frequencies at HLA-A, -B and -DRB1 loci were calculated by direct counting method using the formula: AF= n/2N, where n = total number of a particular gene, and N = total number of individuals. Odds ratio (OR) at 95 percent confidence interval (CI) was calculated for the comparison of gene frequency between the patients and controls. Additionally, a Chi-square test was run to compare the allele frequencies between the patients and the controls. The *P* value of ≤ 0.05 was considered to be statistically significant.

RESULTS

Table 1 provides a summary of the HLA gene frequency distribution for T2DM patients and controls. HWE test showed that gene frequency among the patient and controls were in equilibrium (P>0.05). The result shows a significantly high frequency of HLA-B*13 (χ^2=3.66, p= 0.05) and HLA-B*15 (χ^2=4.41, p=0.03) among the T2DM patients than the controls. Conversely, a low frequency of HLA-A*33 (χ2=5.07, p=0.02) was observed. Even though the frequency distribution of some of the genes at HLA-DRB1 loci were found to vary among the T2DM patients and controls, it was not significant.

The frequency distribution of HLA genes among the HT patients and controls are summarised in Table 2. The examined loci for HWE showed no deviations for HT patients and controls (P>0.05). Results showed that HT patients had significantly increased frequencies of HLA-A*24 (χ2=8.69, P=0.03) and HLA-B*13 (χ2=4.89, P=0.02) than controls. Comparable with the T2DM cohort, no significant variation in the distribution of DRB1 genes was observed among the HT patients and controls.

DISCUSSION

It is well established that genetic, ethnic and environmental components are instrumental in the aetiology of T2DM and HT. Owing to the intricate multifactorial aetiology of both HT and T2DM, identifying the genetic factors linked to the aetiology of each disease may be helpful in managing the conditions appropriately and comprehending their pathophysiology. This study is the first of its kind to look into the potential association between HLA-A, B and DRB1 gene with T2DM and HT in Kami population.

The association of HLA-B*15 observed with the T2DM patients in the present study follows the previously reported studies in diabetic patients from the Papuan coast of Papua New Guinea (Bhatia et al. 1984) and North Indians (Omar et al. 1985). A significant association of HLA-B*15 with T2DM in the present study and the patients of North Indian origin (Omar et al.1985) suggests HLA-B*15 may have a strong link for T2DM in Indo-Aryan groups. In contrast to the present findings, even though frequency of HLA B*13 was observed to be higher in the Papuan patients, it was not signif-

Table 1: Frequencies for HLA-A, -B, -DR alleles in Type 2 Diabetes Mellitus and control subjects among the Kami population

HLA	*Type 2 diabetes mellitus patients (N=15) Gene frequency*	*Controls (N=60) Gene frequency*	*Odds ratio*	*95% CI*	*Chi- square*	*p-value*
A*01	0.03	0.03	3.50	0.07-0.25	2.52	0.11
A*02	0.14	0.16	1.07	0.32-3.59	0.09	0.77
A*11	0.36	0.30	1.63	0.39-5.36	0.66	0.41
A*24	0.30	0.19	2.28	0.82-7.20	2.05	0.15
A*33	0.06	0.23	0.18*	0.03-0.90	5.07	0.02*
B*13	0.10	0.05	4.75	0.85-26.45	3.66	0.05*
B*15	0.32	0.20	3.45*	1.04-11.41	4.41	0.03*
B*18	0.13	0.05	3.27	0.78-13.56	2.88	0.08
B*27	0.03	0.01	2.07	0.17-24.49	0.34	0.55
B*35	0.03	0.16	0.16	0.020-1.36	3.45	0.06
B*40	0.10	0.20	0.40	0.12-1.57	1.78	0.18
B*44	0.06	0.04	1.38	0.25-7.66	0.14	0.70
B*51	0.10	0.10	0.61	0.17-3.10	0.35	0.55
B*57	0.03	0.02	0.19	0.18-19.72	0.06	0.79
DRB1*04	0.03	0.04	2.11	0.35-12.43	0.04	1.00
DRB1*07	0.10	0.13	0.90	0.22-3.68	0.02	0.88
DRB1*12	0.10	0.06	1.62	0.37-7.05	0.42	0.51
DRB1*13	0.03	0.01	4.21	0.24-71.58	1.15	0.28
DRB1*14	0.13	0.15	0.62	0.17-2.21	0.53	0.46
DRB1*15	0.50	0.34	2.66	0.67-10.45	2.08	0.14

*=Significant

Table 2: Frequency of HLA-A, -B, -DR alleles in hypertensive and normotensive control subjects belonging to the Kami population

HLA	*Hypertensive patients (N=20) Gene frequency*	*Controls (N=80) Gene frequency*	*Odds ratio*	*95% CI*	*Chi- square*	*p-value*
A*01	0.02	0.31	0.00	0.00	0.276	0.63
A*11	0.22	0.32	0.70	0.26-1.88	0.49	0.48
B*13	0.05	0.04	4.75*	1.07-21.01	4.89	0.02*
B*15	0.22	0.20	0.90	0.32-2.49	0.04	0.83
B*18	0.10	0.04	3.08	0.77-12.2	2.77	0.09
A*24	0.37	0.18	4.60 *	1.58-13.25	8.69	0.03*
B*27	0.05	0.02	4.52	0.84-24.4	3.59	0.06
A*29	0.02	0.01	4.10	0.24-69.5	1.14	0.28
A*33	0.10	0.23	0.34	0.26-1.1	3.43	0.06
B*35	0.12	0.15	0.62	0.18-2.05	0.62	0.43
B*40	0.10	0.20	0.94	0.33-2.64	0.01	0.91
B*44	0.05	0.08	1.10	0.27-4.41	0.02	0.88
B*51	0.02	0.09	0.29	0.84-2.44	1.41	0.23
B*57	0.02	0.00	1.05	0.11-9.96	0.60	0.60
DRB1*07	0.07	0.12	0.70	0.18-2.7	0.26	0.61
DRB1*04	0.01	0.02	2.11	0.35-12.43	0.70	0.40
DRB1*10	0.02	0.04	2.17	0.49-9.58	1.09	0.37
DRB1*12	0.07	0.06	1.00	0.00	0.31	0.69
DRB1*13	0.02	0.02	1.35	0.13-13.72	0.06	0.79
DRB1*14	0.10	0.20	0.62	0.20-1.88	0.72	0.39
DRB1*15	0.45	0.35	2.33	0.77-7.04	2.34	0.12

*Significant

icant (Bhatia et al.1984). Conversely, a significantly higher frequency of HLA-A*33 was observed in controls than the patients in this study, which suggests a protective role of HLA-A*33 for T2DM among the Kami population. It could be proposed that HLA-A*33 may augment self-tolerance reducing the phenomenon of autoimmunity involved in T2DM (Williams et al. 2011). Contrary to the findings, HLA-A*33 association was observed with T2DM among South Indian patients (Chinniah et al. 2016). These discrepancies in the findings may be because T2DM is a multifactorial disorder and factors such as serum uric acid, sleep amount and quantity, smoking, dyslipidemia, hypertension, ethnicity, and obesity may play an essential part in the aetiology of T2DM (Ismail et al. 2021). In the present study even though a high frequency of HLA DRB1*15 was observed among the patients, it was not found to vary significantly from the controls. The results align with the research that was conducted on South Indian patients (Chinniah et al. 2016). However, the frequency of HLA-DRB*15 was found to be low in the findings made by Chinniah et al. (2016). In contrast to the current findings the studies have reported the association of HLA-DRB1*040101 and HLA-DRB1*070101 with T2DM in patients from Bahrain (Motala et al. 2005). In concordance with the findings by Motala et al. (2005), HLA-DRB1*070101 was also found to have an association with T2DM in patients from Lebanon (Almawi et al. 2006). The discrepancy between the results of this study with the finding among Bahrain and Lebanon patients might be linked to the ethnic differences between the studied populations. A recent genome-wide association study (GWAS) conducted among the Pashtun community of Khyber Pakhtunkhwa, Pakistan, showed a positive association of T2DM with single nucleotide polymorphisms (SNPs) rs2308655 in the HLA-B gene (Jan et al. 2021). The heterogeneous spectrum of HLA genetic markers implicated in T2DM study across diverse racial and ethnic cohorts implies that variations within the HLA genes may have a substantial influence on the disease susceptibility within specific populations.

HLA association with HT has been documented in several populations (Vidan-Jeras et al. 2000; Shao et al. 2004). The results of this study suggest

that HLA-A*24 may be linked to hypertension in the Kami population. The outcome is consistent with the finding among Greek populations (Diamantopoulos et al. 2000). Furthermore, the current study found an association between HT and HLA-B*13 in the Kami population. The findings are in concordance with earlier studies among the Russian and Caucasian HT patients (Shkhvatsabaia et al. 1988; Gladman et al. 2005). The presence of HLA-A*24 and HLA-B*13 as potential risk factors to HT is a major finding of the current study. It has been noted in the previous studies among Chinese individuals with essential hypertension, the HLA-DRB1*04 gene increases the risk for Angiotensin-1 receptor (AT1-AA) autoantibodies (Zhu et al. 2011). Similarly, certain HLA-DRB*1 bearing haplotype, HLA-DRB1*0406-DQB1*0302 has been linked with Idiopathic Pulmonary Arterial Hypertension (IPAH) in Korean patients and HLA-DRB1*0101/2 DQB1*0501/2 DQA1*0102 has been reported to heighten the risk of Essential Hypertension in Slovenians (Vidan-Jeras et al. 2000). Nevertheless, no association between the HLA*DRB1 gene and hypertension was observed in the current investigation. It can be attributed to factors including relatively modest sample size, methodological variations, and the complex interplay of genetic and environmental factors influencing the observed relationships.

The present investigation is subject to certain limitations that warrant consideration. Primarily, the study was constrained by a relatively modest sample size. Secondly, HLA polymorphism was studied only at the first field level. Thirdly, the clinical parameters were not studied and correlated with HLA. Notwithstanding these limitations, the current investigation provides preliminary substantiation of the association between HLA genes and HT and T2DM.

CONCLUSION

According to results from the current exploratory study, HLA genes are linked to both HT and T2DM in the Kami population. The results of the study should be regarded as preliminary since they do not correspond with the patients' clinical features. In light of the small sample size of the current study, the finding should be interpreted with caution. Although the precise process by which HLA and T2DM and HT are associated is yet unknown, the current study suggests that the susceptibility of the Kami population to T2DM and HT may be associated with specific HLA-related genetic pathways.

RECOMMENDATIONS

The results of the current study demonstrate an association of HLA with T2DM and HT among the Kami population. Further studies in larger samples and high-resolution HLA typing along with the consideration of demographic and clinical parameters of the patients are warranted to throw more light on the association of HLA with T2DM and HT among the Kami population.

AUTHORS CONTRIBUTION

Bisu Singh prepared the study design, received the funding, and edited the final draft of the paper. Dependra Chamlagai collected the blood samples and performed the laboratory experiment and statistical analysis. Jiwan Gurung contributed to blood sample collection, laboratory experiments, and statistical analysis.

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