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ORIGINAL RESEARCH

HLA-DQA1 and HLA-DQB1 Gene Polymorphism in Indonesian Children with Type 1 Diabetes Mellitus

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Background: More than 40 genes influence the progression of type 1 diabetes mellitus (T1DM), including human leukocyte antigen (HLA) alleles. Different HLA genotype patterns result in diverse rates of T1DM development. HLA class II DR, DQ, and DP vary among different populations and ethnicities. Data on HLA polymorphism in T1DM in Indonesia are lacking. Therefore, this study was designed to evaluate the gene polymorphism of HLA-DQA1 and HLA-DQB1 in Indonesian children with T1DM.

Patients and Methods: In this study, 31 patients with T1DM and 31 controls were enrolled from April 2020 to April 2021. This study was conducted at Dr. Soetomo Hospital, Indonesia. We evaluated the gene polymorphism of HLA-DQA1 and HLA-DQB1 using polymerase chain reaction–restriction fragment length polymorphism. The primers used were as follows: for HLA-DQA1, DQAS34: 5′-GGTGTAAACTTGTACCAG-3′ (forward) and DQAA261: 5′-ATTGGTAGCAGCGGTAGA-3′ (reverse); for HLA-DQB1, DQBS43: 5′-TGCTACT-TCACCAA(C/T)GGG-3′ (forward) and DQBA249: 5′-GTAGTTGTGTCTGCA (C/T)AC-3′ (reverse).

Results: The most common HLA-DQA1 subtype in the T1DM group was 0101/0102 accounting for 67.6%, and 01/03 and 02/03 were found in the T1DM group only. Meanwhile, the most common HLA-DQB1 subtype in the T1DM group was 0301, accounting for 54.8%. Most subjects in this study were Javanese.

Conclusion: HLA-DQA1 0101/0102 and HLA-DQB1 0301 were commonly found in Indonesian children with T1DM.

Keywords: T1DM, HLA-DQA1, HLA-DQB1, gene polymorphism

Introduction

Type 1 diabetes mellitus (T1DM) is one of the most frequent chronic illnesses among children. The prevalence of T1DM is 5%–10% of all diabetes mellitus cases. Approximately 30 million people live with T1DM worldwide, with an estimated three-fold increase in prevalence by 2040.[1] The prevalence of T1DM in Asia is surprisingly low, with 0.4–1.1 cases per 100,000 individuals per year.[2] Studies have shown that T1DM has genetic susceptibility associated with gene polymorphisms or mutations. More than 40 genes influence the progression of T1DM, including human leukocyte antigen (HLA). Different HLA genotype patterns result in diverse rates of T1DM development. HLA class II DR, DQ, and DP vary among different populations and ethnicities.[3] Associations between HLA genes and T1DM were first reported among Caucasians with class I molecules B8 or B15 1. For example,

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the high-risk HLA haplotypes in Caucasian populations, DRB1*03:01-DQB1*02:01 and DRB*04:01-DQB1*03:02, were found to be low in incidence in Japan and Southeast Asia.[4] A study conducted in Southeast Asia has proven this finding, where the most prevalent HLA types were DQA1*0501 (50.7% vs 20.4%; RR = 3.97; Pc < 0.01), DQB1*0201 (48% vs 19.1%; RR = 3.86; Pc < 0.05), and DRB1*0301 (38.7 vs 6.8%; RR = 8.36; 95% Pc < 0.05).[5]

The pathophysiology of T1DM revolves around B cell destruction. It is thought to be related to autoreactive CD4+ helper and CD8+ cytotoxic T cells in response to at least four major antigens (ie, insulin derivatives, glutamic acid decarboxylase-65 [GAD-65], tyrosine phosphatase, and zinc transporter-8 [ZnT8]) present in pancreatic B cells. Antibodies found against these elements are good markers for T1DM.[6–8] In India, a study on the prevalence of GAD antibody (GADA), ZnT8, and HLA and their diagnostic values in T1DM has found a low sensitivity of GADA and ZnT8. They concluded that for diagnosing T1DM, GADA is the most superior autoantibody. Its sensitivity is low; hence, it should be combined with HLA.[9] This finding is similar to those found in Asian literature and contradicts those found in some Western studies.[10–12]

Studies on this particular area in Asia remain limited.[9] Therefore, this study was designed to evaluate gene polymorphisms of HLA-DQA1 and HLA-DQB1 in Indonesian children with T1DM.

Patients and Methods

Study Design

This was a case–control study comparing HLA-DQA1 and HLA-DQB1 gene polymorphisms between children with T1DM and those without T1DM (control).

Subjects

In this study, 31 children with T1DM who were present for follow-up at the pediatric endocrine clinic at Dr. Soetomo General Hospital Surabaya were enrolled. For comparison, we included 31 healthy children without a history of T1DM who also attended the pediatric clinic at Dr. Soetomo General Hospital Surabaya as controls. The inclusion criteria for the subjects were as follows:

1. The T1DM group included children diagnosed with T1DM according to the diagnostic criteria from American Diabetes Association (ADA) 2012, as follows: (1) glucosuria symptoms, ketonuria, and random plasma glucose of more than 200 mg/dL or (2) fasting blood glucose of more than 126 mg/dL with a plasma glucose level of more than 200 mg/dL 2 hours after oral glucose tolerance test (OGTT) or (3) a plasma glucose level of more than 200 mg/dL 2 hours after OGTT or (4) Glycated hemoglobin (HbA1c) of ≥6.5%. Meanwhile, the control group consisted of healthy children without a history of T1DM.
2. Children aged 4–18 years.
3. Children with low C-peptide or at least 1 antibody marker detected.
4. Children whose parents consented to participate in the study.

Patients with T1DM who were admitted to the pediatric intensive care unit with severe disease were excluded. The exclusion criteria for the control group were as follows: (1) ongoing infection, (2) history of other autoimmune diseases, (3) history of allergy, and (4) history of malignancy. Sampling for both the T1DM and control groups was performed using a consecutive sampling method. Ethical approval was obtained by the Ethical Board Committee of Dr. Soetomo Hospital, Indonesia (approval no. 1889/KEPK/III/2020). All participants and their parents provided informed consent, and this study was conducted in accordance with the Declaration of Helsinki.

DNA Extraction and Genotyping

DNA was obtained from peripheral blood mononuclear cells with a standard method using the QIAmp DNA Mini Kit (Qiagen©). HLA-DQA1genotyping was performed using polymerase chain reaction (PCR) with forward primer DQAS34: 5′-GGTGTAAACTTGTACCAG-3′ and reverse primer DQAA261: 5′-ATTGGTAG CAGCGGTAGA-3′, resulting in a 228bp DQA1 segment. Meanwhile, for HLA-DQB1, we used forward primer DQBS43: 5′-TGCTACT- TCACCAA(C/T)GGG-3′ and reverse primer DQBA249: 5′-GTAGTTGTGTCTGCA (C/T)AC-3′, resulting in a 207bp DQB1 segment.[13] For amplification, 35 cycles were performed using the following steps: denaturation at 94°C for 1 min, annealing at 60°C for 2 min, and extension using Taq DNA polymerase at 72°C for 3 min, with the final step after 35 cycles at 72°C for 3–10 min. Amplificated DNA was precipitated with ethanol and underwent acrylamide gel 3%.

Polymorphisms were evaluated using PCR–restriction fragment length polymorphism. To evaluate polymorphisms of HLA-DQA1, DdeI and RsaI restriction enzymes were used. Four alleles of DQA1 could be observed after restriction with DdeI: (1) DQA1*01 (113bp, 74bp, and 41bp fragments); (2) DQA1*02 (127bp and 98bp fragments); (3) DQA1*03 (228bp fragment); and (4) DQA1*04 (154bp and 74bp fragments). The RsaI enzyme was used to further differentiate DQA1*01 and DQA1*04 to DQA1*0101 (188bp), DQA1*0102 (40bp), DQA1*0103 (228bp), DQA1*0401 (185bp), DQA1*0501 (40bp), and DQA1*0601 (225bp).[13] The visualization result of PCR-RFLP is shown in Figure 1.

Acyl, Hhal, Sau961, and MspI restriction enzymes were used to evaluate the polymorphism of HLA-DQB1. The Acyl enzyme produced DQB1*0501 (133bp, 46bp, 26bp, and 2bp) and 0502 (77bp, 56 bp, 48bp, and 26bp). The Sau961 enzyme produced 0503 allele (167bp, 39bp, and lbp) and 0401 or 0402 (151 bp, 39bp, and 17 bp). The Hhal enzyme produced 0602 or 0603 (104bp, 46bp, 29bp, 26bp, and 2bp), 0604 (133bp, 46bp, 26bp, and 2bp), and 0302 (108bp and 26bp). The Mspl restriction enzyme produced the following alleles: (1) DQB1*0301 (99bp, 72bp, and 36bp fragments); (2) DQB1*0303 (171bp and 36bp fragments); and (3) DQB1*0601 (207bp fragment). The Hhal enzyme was used to further differentiate DQB1*0401 and DQB1*0402 to DQB1*0401 (133bp, 72 bp, and 2bp) and DQB1*0402 (133 bp, 46bp, 26bp, and 2bp), respectively.[13]

Outcomes

The primary outcome of this study was the subtypes of HLA polymorphism in children with T1DM in Indonesia.

Statistical Analysis

All statistical analyses were performed using Statistical Package for Social Sciences, version 20.0. Descriptive analysis was conducted to explain the distribution of the subjects' characteristics and HLA polymorphisms. Values are described using mean ± standard deviation, and nominal variables are described using numbers (percentages).

Results

Clinical Characteristics

The T1DM group consisted of 31 subjects (including 19 girls and 12 boys) with a mean age of 15 ± 3.88 years and body mass index (BMI) of 19.37 ± 4.46 kg/m^2. The mean age at the onset of T1DM was 8 ± 3.72 years, and the mean T1DM duration was 7 ± 4.19 years. The baseline characteristics are presented in Table 1.

Allele Frequencies of HLA-DQA1 in the T1DM and Control Groups

In this study, HLA-DQA1 polymorphism was evaluated using two restriction enzymes: DdeI and RsaI. DdeI produced *01, *02, *03, and *04 subtypes and their combinations. The most common subtype found in the control group was 0601, whereas the most common subtype in the T1DM group was 0101/0102. However, polymorphism between 01/03 and 02/03 was found only in the T1DM group. A complete list of HLA-DQA1 subtypes in the T1DM and control groups is presented in Table 2.

Allele Frequencies of HLA-DQB1 in the T1DM and Control Groups

HLA-DQB1 polymorphism was evaluated using the Acyl, Hhal, Sau961, and MspI restriction enzymes. The most

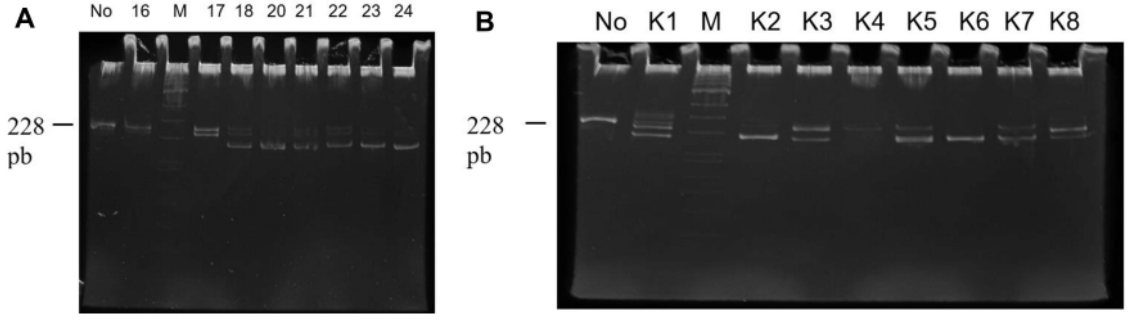

Figure 1 (**A**) Electrophoresis result from PCR-RFLP of HLA-DQA1 with Rsa I restriction enzyme in T1DM groups. (**B**) Electrophoresis result from PCR-RFLP of HLA-DQA1 with Rsa I restriction enzyme in control groups.

Table 1 Baseline Characteristics of the Subjects in This Study

Characteristics	N = 31			
	T1DM		Control	
	N	%	N	%
Gender				
Boys	19	61.3%	16	51.6%
Girls	12	38.7%	15	48.4%
Ethnicity				
Javanese	27	87.1%	31	100%
Madurese	1	3.2%	0	0
Chinese	1	3.2%	0	0
Malay	2	6.4%	0	0
	N	**Mean ± SD**	**N**	**Mean ± SD**
Age (years)	31	15.05 ± 3.9	31	10.58 ± 2.40
Height (m)	31	1.46 ± 0.19	31	1.29 ± 0.15
Weight (kg)	31	42.62 ± 14.35	31	30.13 ± 11.87
BMI	31	19.37 ± 4.46	31	17.26 ± 3.25

Table 2 Distribution of HLA-DQA1 Polymorphisms in the T1DM and Control Groups

Polymorphism	T1DM (%)	Control (%)	p
01	5 (16.1)	1 (3.2)	0.09
03	1 (3.2)	2 (6.5)	0.50
04	2 (6.5)	12 (38.7)	0.00
0103	17 (54.8)	18 (58.1)	0.79
0601	19 (61.3)	22 (71.0)	0.42
0101/0102	21 (67.6)	15 (48.4)	0.12
0401/0501	10 (32.3)	2 (6.5)	0.01
01/03	2 (6.5)	0 (0)	0.25
01/04	0 (0)	2 (6.5)	0.25
02/03	2 (6.5)	0 (0)	0.25
03/01	1 (3.2)	2 (6.5)	0.50
03/04	7 (22.6)	4 (12.9)	0.32
01/02/03	2 (6.5)	3 (9.7)	0.50
01/03/01	0 (0)	4 (12.9)	0.06
01/03/04	9 (29.0)	1 (3.2)	0.01

common subtype found in the control group was 0502, whereas the most common subtype in the T1DM group was 0301. The subtypes 0401, 0402, 0501, 0503, 0601, and 0604 were found in both the control and T1DM groups. A complete list of HLA-DQB1 subtypes in the T1DM and control groups is shown in Table 3.

Discussion

Most patients with T1DM in this study have HLA-DQA1 0101/0102 (67.6%); however, in the control group, most patients have HLA-DQA1 0601 (71%). Moreover, 01/04 and 01/03/01 polymorphisms were found only in the control group with a ratio of 2:4, whereas 01/03 and 02/03 was found only in the T1DM group.

The most common HLA-DQB1 polymorphism in patients with T1DM in this study was 0301 (54.8%). Furthermore, HLA-DQB1 0302, 0602, and 0603 were found in more patients with T1DM. Meanwhile, HLA-DQB1 0301, 0303, 0403, and 0502 were found in more healthy controls.

Differences in the proportion of alleles and subtypes were observed among different populations. Polymorphism HLA-DR3/DR4 is rarely found in Asia compared with that in European populations. In patients with T1DM, HLA-DQA1 0301/DQB1 0302 (HLA class II) was associated with genetic susceptibility. However, HLA-DQA1*0102/DQB1*0602 was protective for T1DM, even in individuals with HLA-DQA1*0301 /DQB1*0302. Interestingly, a study by Ettinger et al has shown that HLA-DQA1*0301/DQB1*0301, HLA-DQA1*0102/DQB1*0301, and HLA-DQA1*0102 /DQB1*0604 were not associated with T1DM although

Table 3 Distribution HLA-DQB1 Polymorphisms in the T1DM and Control Groups

Polymorphism	T1DM (%)	Control (%)	p
0201	5 (16.1)	5 (16.1)	1.00
0301	17 (54.8)	18 (58.1)	0.79
0302	15 (48.4)	3 (9.7)	0.00
0303	15 (48.4)	17 (54.8)	0.61
0401	31 (100)	31 (100)	–
0402	31 (100)	31 (100)	–
0403	0 (0)	1 (3.2)	0.50
0501	31 (100)	31 (100)	–
0502	10 (32.3)	21 (67.7)	0.01
0503	31 (100)	31 (100)	–
0601	31 (100)	31 (100)	–
0602	15 (48.4)	10 (32.3)	0.19
0603	15 (48.4)	10 (32.3)	0.19
0604	31 (100)	31 (100)	–

they have structural similarity with HLA-DQA1*0301/DQB1*0302 and HLA-DQA1*0102/DQB1*0604.[14] A more recent study by Yahaya has shown that HLA-DRB1*0302–DQA1*0301 combined with DRB1*0201-DQA1*0501 increased the risk of T1DM by 20 folds, whereas the HLA-DQ6 (HLA-DQA1*0102–DQB1*0602) haplotype conferred a protective effect.[1]

Studies have reported that the genetic susceptibility of HLA was the most frequently reported.[15–19] This genetic susceptibility varies among ethnicities.[15,18,19] Studies in Iran have reported an association between HLA, gender, specificity, and age at onset. HLA-DRB1*04:01 and DQB1*03:02 alleles and DRB1*04:01–DQB1*03:02 were the most common haplotypes found in men with T1DM. Meanwhile, DRB1*03:01, DRB1*15:01, DQB1*06:01 alleles, DQB1*03:01/05:01 genotype, DRB1*03:01–DQB1*02:01, and DRB1*15:01–DQB1*06:01 were more commonly found in female with T1DM than in males.[20]

DRB1*03:01–DQB1*02:01 and DRB*04:01–DQB1*03:02 were lower in Japan and Southeast Asia. The most common HLA polymorphisms in Japan and Korea were DRB1*04:05–DQB1*04:01 and DRB1*09:01–DQB1*03:03.[21] Meanwhile, in Arabic populations (ie, Bahrain, Lebanon, and Tunisia), the most common locus was DRB1*03:01–DQB1*02:01.[22] A study by Hanscombe has shown that the combination of DRB1*07:01 and DRB1*03:03 and DQA1*03:01–DQB1*02:01 resulted in the highest risk of T1DM in African–American populations. However, in European populations, HLA-DRB1*07:01–DQA1*02:01–DQB1*02:01 was a protective factor for T1DM.[3]

Hamzeh has reported that 80% of patients with T1DM had HLA-DR3 or HLA-DR4 polymorphisms.[23] In Japan, DR9 haplotype was the most important factor affecting the low incidence of T1DM.[24–26] The profile of HLA in Indonesia is similar to the rest of South East Asian populations. The study reported that polymorphism of HLA-B*15:02 and HLA-DRB1*12:02 was frequently found in Javanese, Mollucan, and Nusa Tenggara ethnicities. Indonesia still had different characteristics of HLA compared with other South East Asian countries. Yogyakarta people had high number of DQA1*0601, DQB1*03:01, DRB1*12:02; meanwhile, Western Javanese people had HLA-A*2407. None of those HLAs are commonly found in other countries.[27]

Most of the patients with T1DM in this study were male, accounting for 61.3% ($p = 0.45$). This result contradicted Katsarou's study that showed that T1DM is more prevalent in females than in males. Another study has reported no significant difference in T1DM prevalence between male and female patients.[28]

The mean age of onset in this study was relevant to the study reported by Katarou that the onset of T1DM increased with age and its peak onset was at the puberty period.[29] Children with T1DM also tended to be underweight at diagnosis. Underweight is a consequence of their catabolic state, resulting in weight loss before the diagnosis.[30] After receiving therapy, the weight of patients with T1DM will increase due to the anabolic effect of insulin therapy.[31]

The limitation of this study was having a small sample size of the participating patients and only conducted in one center. Conducting a multi-center study to obtain more data on Indonesian races is essential.

Conclusion

The most common HLA-DQA1 subtype in the T1DM group in this study was 0101/0102, whereas the most common HLA-DQB1 subtype is 0602. Further studies should be conducted to find new mutations.

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Disclosure

The authors report no conflicts of interest in this work.

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