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HLA DQA1* and HLA-DQB1* alleles and genetic susceptibility to autoimmune thyroiditis in Down syndrome children: An Indonesian study

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Objective. The purpose of this study was to investigate the role of the HLA-DQA1 and HLA-DQB1 alleles in Indonesian children who had autoimmune thyroiditis (AITD) and Down syndrome (DS).

Methods. At Dr. Soetomo Hospital, 49 DS-AITD patients and 42 controls participated in a cross-sectional study. Alleles of HLA-DQA1*0103 and HLA-DQB1*0401 were genotyped by PCR-RFLP assays. Allelic relationships were assessed by statistical studies.

Results. In the DS-AITD group, the HLA-DQA1*0103 and HLA-DQB1*0401 alleles were more frequently found. The HLA-DQB1*0303, *0402, and *0501/0604 alleles, on the other hand, were significantly more common in the control group. While the HLA-DQB1 *0303 (odds ratio [OR]=0.169, 95% confidence interval [CI]: 0.065–0.435, p=0.000) alleles significantly reduced AITD risk, the HLA-DQA1*0103 (OR=3.9, 95% CI: 1.552–9.797, p=0.003), and HLA-DQB1*0401 (OR=4.5, 95% CI: 1.326–15.277, p=0.010) alleles considerably increased AITD risk.

Conclusion. HLA-DQA1*0103 and HLA-DQB1*0401 are risk alleles, while HLA-DQB1 *0303 are protective alleles for AITD in children with DS. Further studies are required to obtain more data on Indonesians with DS.

Keywords: HLA-DQA1, HLA-DQB1, gene polymorphism, autoimmune thyroiditis, Down syndrome, Indonesia

The most prevalent autoimmune condition affecting people is autoimmune thyroid disease (AITD) (Boguslawska et al. 2022). Hashimoto's disease (HD) and Graves' disease (GD) are its two primary clinical entities. T cell and B cell infiltration of the thyroid and the development of antibodies against thyroid antigens are its hallmark characteristics (Shin et al. 2019). The loss of immune response to autoantigens, both central and peripheral, is the main mechanism behind the development of AITD. However, the thyroidal accumulation of antigen-presenting cells that express major histocompatibility complex (MHC) class II molecules is the crucial stage in the development of AITD (Boguslawska et al. 2022). It is generally agreed that the development of AITD is influenced by both hereditary and environmental factors (Shin et al. 2019). However, compared to late-onset AITD in adults, genetic factors have a larger role in early-onset AITD in children and adolescents (Kacem et al. 2003; Cho et al. 2011).

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Immune-related genes such as human leukocyte antigen (HLA), CD40 molecule (CD40), protein tyrosine phosphatase-22 (PTPN22), and cytotoxic T lymphocyte-associated factor 4 (CTLA4) have been linked to an increased risk of AITD. Furthermore, the most notable potential genetic factor for a number of autoimmune illnesses, including AITD, is the MHC, which is highly polymorphic and contains numerous immune response genes (Shin et al. 2019).

Several HLA genes linked to the operation of the human immune system, such as HLA class I (A, B, and C), HLA class II (DP, DM, DOA, DOB, DQ, and DR), and additional HLA immune proteins, are found in the MHC. By attaching to peptide antigens and delivering them to T cell receptors, HLA-DR3 is the primary HLA causing GD in adult Caucasian research. It also plays a crucial part in the normal immune response (Davies et al. 2012). Other reported associations include HLA-DQA1, -DQB1, and -DRB1 with GD and of HLA-DRB1, -DQA1, and -DQB1 with HD (Bogner et al. 1992; Petrone et al. 2001; Tomer and Davies 2003; Zeitlin et al. 2008). It is known that the HLA genes of the Caucasian population that are linked to AITD differ from those of other racial groups. HLA-B, -DRB1, -DQB1, and -DPB1 in Japanese (Ueda et al. 2014), HLA-DRB1 in Koreans (Myoung et al. 2005; Jang et al. 2011) and HLA-A, HLA-B, -DRB1, -DQB1, and -DPB1 in Chinese (Chen et al. 2011) have all been linked to GD in non-Caucasians. HT was reportedly associated with HLA-A, and -DRB4 in Japanese (Ueda et al. 2014). Unfortunately, data on children and adolescents are rare (Giza et al. 2008).

One of every 400–1500 live newborns has Down syndrome (DS), the most prevalent chromosomal anomaly. Of them, 95% have trisomy 21 (non-disjunction) type (Kazemi et al. 2016). DS is categorized by certain researchers as an inborn error of immunity. The B cell population's proportion indicates an increase in autoreactive B cells and a decrease in shifted memory B cells (Verstegen et al. 2014). Developmental problems in thymocytes, naive T cells, and memory T cell proliferation are caused by abnormalities in thymic architecture (Marcovecchio et al. 2019). Natural killer (NK) cells increase but suppressive function decreases, and chemotactic defects in neutrophils (Ram and Chinen 2011). The IFN-stimulated gene (ISG) at trisomy 21 is overexpressed in four of the six interferon receptors (IFNRs), which consistently activates the IFN transcriptional response and causes notable increases in inflammatory cytokines linked to IFN signaling, including interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and monocyte chemotactic protein/MCP-1 (Sullivan et al. 2017). The expression of an essential actor of B cell or T cell development (the AIRE gene, for example) is likely modified by a number of epigenetic-related genes that are also encoded on chromosome 21 (Satge and Seidel 2018). Patients with DS also experience increased oxidative stress caused by overexpression of the copper-zinc superoxide dismutase (SOD1) gene encoded by chromosome 21. These characteristics put DS children at four to six times the risk of autoimmunity, particularly AITD, compared to the general population (Ferrari and Stagi 2021). Among people with DS, autoimmune hypothyroidism is the most prevalent autoimmune condition. 13% to 46% of patients have anti-thyroid antibodies. Remarkably, nearly half acquire positive thyroid antibodies prior to the age of eight (Wei et al. 2019). HT in people with DS differs from the general population in additional ways, including: (1) no sex preference; (2) a lower incidence of positive family history for thyroidopathy; (4) a higher prevalence of SH at presentation and a lower prevalence of euthyroidism; (5) progressive decline in function of the thyroid as time passed (median interval of 5.1 years); and (6) more frequent evolution to GD (Kyritsi and Kanaka-Gantenbein 2020).

Few studies have studied the relationship between genetic factors and AITD in children with DS (Faizi et al. 2023a,b). The HLA-DQA1*0301 allele was linked to an increased incidence of autoimmune hypothyroidism, according to the only study conducted on people with DS and AITD (Nicholson et al. 1994). However, studies on children without DS showed different HLA allelic associations between early-onset and late onset AITD, Therefore, the findings of risk alleles in adult may differ from those in children with DS (Shin et al. 2019). To our knowledge, no studies have determined the role of HLA allele in the risk of AITD in children with DS. The purpose of this study was to investigate how Indonesian children with DS were genetically susceptible to AITD in relation to the HLA DQA1 and HLA-DQB1 alleles.

Material and Methods

Subjects. This study included 62 Indonesian children with DS, 49 of whom had AITDs. The AITD diagnosis was based on the elevated titers of anti-thyroid peroxidase (anti-TPO; >50 IU/mL) and/or anti-thyroglobulin (anti-TG; >150 IU/ mL) autoantibodies. Clinical and demographic information was documented. Forty-two healthy Indonesians who were selected at random, had no familial history

of thyroid or other autoimmune diseases and had negative anti-thyroid antibodies made up the control group. The informed consent was offered by controls, patients and their parents. The Dr. Soetomo General Hospital's Institutional Review Board granted permission to this study (0397/KEPK/III/2022).

Biochemical analysis. Enzyme-linked immunosorbent test kits (catalog numbers CAN-FT4-4340 and CAN-TSH-4080 [DBC-Diagnostics Biochem Canada Inc], and DE7580 and DE7590 [Demeditec Diagnostics GmbH]) were used for measuring serum-free thyroid hormones, thyroid stimulating hormone (TSH), anti-TPO, and anti-TG titers. respectively. The manufacturer-specified cutoffs of >75 IU/mL (positive), 50–75 IU/mL (borderline), and <50 IU/mL (negative) for anti-TPO and >150 IU/mL (positive), 100–150 IU/mL (intermediate), and <100 IU/mL (negative) for anti-TG were used for interpreting the autoimmune thyroid markers. The range of reference values for pediatric treatment published by Sperling et al. were used to calculate thyroid function (Faizi et al. 2023a).

DNA extraction and genotyping. QI Amp DNA Mini Kit (Qiagen) was used to extract DNA from peripheral blood mononuclear cells. HLA-DQA1 (forward primer DQAS34: 5'-GGTGTAAACTTG-TACCAG-3'; reverse primer DQAA261: 5'-ATTGG-TAGCAGCGGTAGA-3') and HLA-DQB1 (forward primer DQBS43: 5'-TGCTACTTCACCAA[C/T] GGG-3'; reverse primer DQBA249: 5'-GTAGT-TGTGTCTGCA[C/T]AC-3') were genotyped by polymerase chain reactions (PCRs) (Ikegami et al. 1992).

We genotyped HLA-DQA1 and -DQB1 polymorphisms using PCR-restriction fragment length polymorphism (RFLP) tests. Following restriction with the DdeI enzyme, the following four DQA1 alleles were identified: (1) DQA1*01 (113, 74, and 41 bp fragments); (2) DQA1*02 (127 and 98 bp fragments); (3) DQA1*03 (228 bp fragment); and (4) DQA1*04 (154 and 74 bp fragments). DQA1*01 and DQA1*04 were further differentiated into DQA1*0101 (188 bp), DQA1*0102 (40 bp), DQA1*0103 (228 bp), DQA1*0401 (185 bp), DQA1*0501 (40 bp), and DQA1*0601 (225 bp; 21) using the RsaI restriction enzyme.

Using the restriction enzymes Acyl, Hhal, Sau961, and MspI, we evaluated HLA-DQB1 polymorphisms. Three different alleles were found using the Mspl restriction enzyme: (1) DQB1*0301 (fragments of 99, 72, and 36 bp); (2) DQB1*0303 (171 and 36 bp); and (3) DQB1*0601 (fragment of 207 bp). Further differentiation of DQB1*0401 and DQB1*0402 into DQB1*0401 (133, 72, and 2 bp) and DQB1*0402 (133, 46, 26, and 2 bp) was accomplished using the Hhal restriction enzyme. The Acyl restriction enzyme identified the alleles DQB1*0501 (133, 46, 26, and 2 bp) and DQB1*0502 (77, 56, 48, and 26 bp). The Sau961 restriction enzyme identified the alleles DQB1*0503 (167, 39, and l bp) and DQB1*0401/*0402 (151, 39, and 17 bp). The Hhal restriction enzyme identified the alleles DQB1*0602/*0603 (104, 46, 29, 26, and 2 bp), DQB1*0604 (133, 46, 26, and 2 bp), and DQB1*0302 (108 and 26 bp; 22) (Soetjipto et al. 2022). Figure 1 shows the visual PCR-RFLP results.

Statistical analysis. Statistical Package for Social Sciences (version 20.0) was used for all statistical

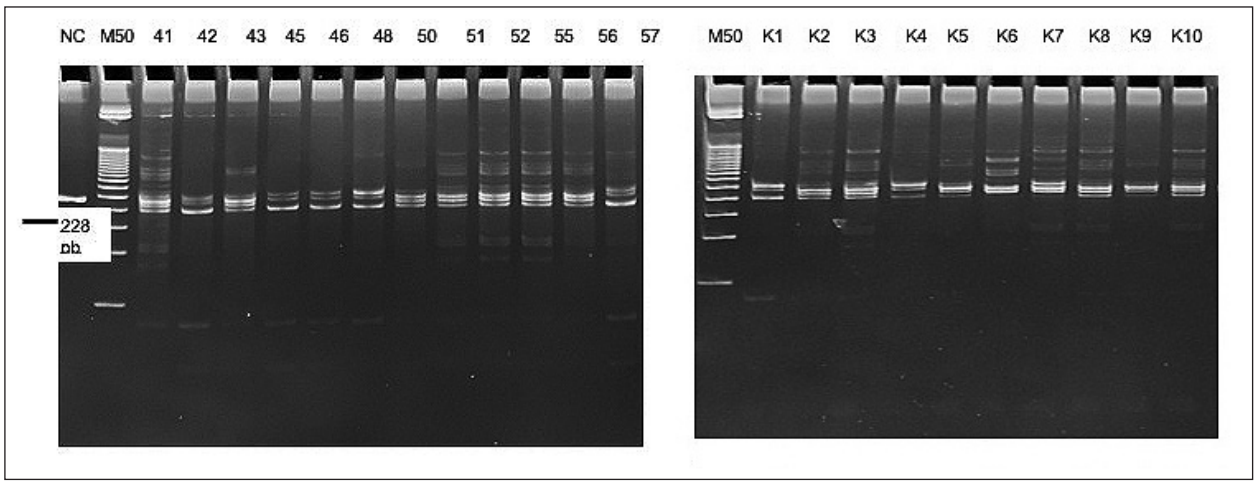

Figure 1. PCR-RFLP results for HLA-DQA1 with the Rsa1 restriction enzyme in participants with Down syndrome and autoimmune thyroiditis (DS-AITD) (**A**) and controls (**B**).

Table 1
Clinical characteristics of the DS and control groups

Characteristics	DS group (n=49)	Control group (n=42)
Sex (n, %)		
Male	34 (63.0 %)	20 (37.0 %)
Female	15 (40.5%)	22 (59.5%)
Ethnicity (n, %)		
Japanese	38 (47.5%)	42 (52.5%)
Maduranesse	5 (100%)	0
Bugis	1 (100%)	0
Minang	1 (100%)	0
Chinese	3 (100%)	0
Batak tribes	1 (100%)	0
Age (median [min–max], months)	17 (1–190)	60 (24–96)
BMI (mean±SD)	–1.54±1.99	0.01±1.41
Thyroid antibodies (mean±SD, IU/mL)		
Anti-TPO	601.28±254.49	–
Anti-TG	2040.56±2311.28	0.128±0.081
Thyroid function (n, %)		
Euthyroidsm	21 (33.3%)	42 (66.7%)
Hypothyroidism	16 (100%)	0
Hyperthyroidism	12 (100%)	0

Abbreviations: Anti-TG – anti-thyroglobulin; Anti-TPO – anti-thyroid peroxidase; BMI – body mass index; DS – Down syndrome.

analyses. To clarify the distribution of the subjects' traits and HLA polymorphisms, an analysis of descriptive statistics was carried out. The mean ± standard deviation (SD) is used to express values, and percentages are used to indicate nominal variables. Fisher's exact and Chi-Square tests were performed to compare the frequency of HLA-DQB1 alleles in children with DS-AITD with controls. Using two-by-two contingency tables, odds ratios (ORs) were computed, and Cornfield's approximation was used to get 95% confidence intervals (CIs). One-way analyses of variance (ANOVA) was used to compare the data throughout several groups. The p values were adjusted for the total amount of alleles that were examined (Pc). It was considered statistically significant when the p value was less than 0.05.

Results

Forty-nine children with DS and AITD were compared with 42 healthy children as a control group. Table 1 shows a list of their biochemical measures and clinical features.

The patients in the DS-AITD group were primarily male and female, and most had the euthyroid thyroid function with positive thyroid antibody markers. They had a younger median age than the control group.

Tables 2 and 3 show the distributions of the HLA-DQA1 and HLA-DQB1 alleles in participants and controls, respectively. The HLA-DQA1*0103 allele was significantly more frequent in the DS-AITD group (39/49 [63.9%]) than in the control group (21/42 [36.1%]; p=0.003). AITD and the HLA-DQA1*0103 allele had a significant association (OR=3.9, 95% CI: 1.552–9.797), p=0.003). The HLA-DQB1*0401 allele was significantly more frequent in the DS-AITD group (45/49 [91.8%]) than in the control group (30/42 [71.4%]; p=0.011). On the other hand, the DS-AITD group had 9/49 [18.4%], p<0.05, whereas the control group had 24/42 [57.1%] HLA-DQB1 *0303 alleles. An increased risk for AITD was significantly associated with the HLA-DQB1*0401 allele (OR=4.5, 95% CI: 1.326–15.277, p=0.010). Conversely, the HLA-DQB1 *0303 alleles were substantially linked to a reduced risk of AITD (p<0.05) (OR=0.169, 95% CI: 0.065–0.435). The control group had a significantly higher frequency of the HLA-DQB1*0402 alleles (41/42 [97.6%]) than the DS-AITD group (41/49 [83.7%]; p=0.013). In the same way, the control group (42/42 [100%]) had significantly more DQB1*0501/0604 alleles than the DS-AITD group (42/49 [85.7%]; p=0.014).

Discussion

According to our study, the DS-AITD group had considerably higher frequencies of the HLA-DQA1*0103 and HLA-DQB1*0401 alleles, whereas the control group had significantly higher frequencies of the HLA-DQB1*0303, HLA-DQB1*0402, and HLA-DQB10501/0604 alleles. No similar studies in children have been published, making it difficult to compare our results with other studies. Our results differ from the study exploring the role of HLA in adults with DS and autoimmune hypothyroidism, which has found the HLA-DQA*0301 allele to be significantly more common in the AITD group and a risk allele for autoimmune hypothyroidism in adults with DS (Nicholson et al. 1994). Different HLA allelic associations have been reported between AITD in adults and early-onset AITD in children. According to a study conducted on 106 Japanese GD patients between the

Table 2
Comparison of HLA-DQA1 allele frequencies in the DS-AITD and control groups

HLA-DQA1 allele	Patients (n, %)	Controls (n, %)	P	OR (95% CI)	P_c
*0101/*0102	27 (49.2%)	28 (50.9%)	0.261[C]	0.614 (0.261–1.441)	0.266
*0103	39 (65.0%)	21 (67.7%)	0.003[*,C]	3.900 (1.552–9.797)	0.003[†]
*0201	15 (71.4%)	6 (28.6%)	0.065[C]	2.647 (0.920–7.613)	0.067
*0301	34 (55.7%)	27 (44.3%)	0.606[C]	1.259 (0.524–3.024)	0.610
*0401/*0501	21 (45.7%)	25 (54.3%)	0.113[C]	0.510 (0.221–1.177)	0.115
*0601	44 (53.0%)	39 (47.0%)	0.607[C]	0.677 (0.152–3.018)	0.612

Abbreviations: AITD – autoimmune thyroiditis; C – Chi-square test; DS – Down syndrome; Pc – corrected P-value from a one-way ANOVA test. *Significant at P <0.05; †significant at Pc <0.05.

Table 3
Comparison of HLA-DQB1 allele frequencies in the DS-AITD and control groups

HLA-DQB1 allele	Patients (n, %)	Control (n, %)	P	OR (95% CI)	P_c
*0303	9 (27.3%)	24 (72.7%)	0.000[*,C]	0.169 (0.065–0.435)	0.000[†]
*0401	45 (60.0%)	30 (40.0%)	0.011[*,C]	4.500 (1.326–15.277)	0.010[†]
*0402	41 (49.4%)	41 (50.0%)	0.006[*,F]	–	0.006
*0501/*0604	42 (50.0%)	42 (50.0%)	0.014[*,F]	–	0.010
*0502	7 (70.0%)	3 (30.0%)	0.331[C]	2.167 (0.523–8.973)	0.283
*0503	48 (53.3%)	42(46.7%)	1.000[*,F]	–	0.357
*0601	49 (53.8%)	42 (46.2%)	–	–	–

Abbreviations: AITD – autoimmune thyroiditis; C – Chi-square test; DS – Down syndrome; F – Fisher's exact test; Pc – corrected p value from a one-way ANOVA test. †,*Significant at P or Pc <0.05.

ages of 14 and 59, the HLA-DPB1*0501 allele was absent in the adult GD group and was strongly linked to early-onset GD (Onuma et al. 1994).

According to our study, children with DS, who had HLA-DQA1*0103 and HLA-DQB1*0401, had high risk alleles for AITD, whereas children with DS who had HLA-DQB1*0303, had significant protective alleles. Only few studies have investigated the significance of HLA in early-onset AITD in children. A study conducted in Greece has reported that the HLA-DQB1*05 allele was markedly more prevalent among 17 Caucasian children with HT aged over 10 years (Giza et al. 2008). A study in Hong Kong was done on 67 children with GD reported DQB1*0303 as a risk allele (OR=4.2) and HLA-DQB1*0201 as a protective allele (OR=0.20; 8). A further study conducted in Italy has revealed that the HLA-A1, HLA-B8, and HLA-DRB1*0301 alleles were markedly more prevalent among 90 Caucasian children diagnosed with AITD (Larizza et al. 2006). A study conducted in Korea has identified HLA-A*02, HLA-B*46, HLA-Cw*01, and HLA-DRB1*08 as risk alleles for AITD in 73 affected children, with relative risks of 1.561, 5.455, 2.208, and 2.019, respectively. A subsequent study in Korea involving 116 children with AITD has revealed that GD was associated with the HLA-B*46:01, HLA-C*01:02, HLA-DPB1*02:02, and HLA-DPB1*05:01 alleles (relative risks of 3.96, 2.51, 3.99, and 4.60, respectively), whereas HT was linked to the HLA-A*02:07 and HLA-DPB1*02:02 alleles (relative risks of 4.68 and 6.57, respectively).

Studies on HLA genetic associations in AITD have revealed various ethnic differences (Matzaraki et al. 2017). A strong relationship between GD and HLA-DR3 has been found in adult Caucasians (Yanagawa et al. 1994). Furthermore, investigations involving non-Caucasian populations have indicated connections between GD and HLA class II, specifically the HLA-DRB1*14:03, -DQB1*0604, and -DPB1*05:01 alleles in Japanese individuals (Onuma et al. 1994); the alleles HLA-DRB1*030101, -DRB1*080201, -DRB1*0803, -DRB1*140301, and DRB1*1602 in the Korean population (Cho et al.

2011; Shin et al. 2019); and the HLA-DRB1*15:01, -DRB1*16:02, -DQB1*05:02, and -DPB1*0501 alleles in the Chinese population (Wong et al. 1999). Fewer studies have examined HT in adult Caucasians and non-Caucasians (Tomer and Davies 2003). Unfortunately, since studies on the HLA gene in individuals with DS remain very limited, the role of ethnicity in allele differences affecting AITD development in this population is unknown.

The association between autoimmunity and HLA has generally been explained by differences in the presentation of allelic self-epitopes (Matsushita et al. 1994; Wucherpfennig et al. 1995). The MHC-self-epitope interaction exhibits a wide range of binding affinity and specificity. The capacity for antigen presentation or the stability of proteins associated with disease risk frequently lies within the peptide-binding grooves or functional pockets of HLA molecules (Miyadera et al. 2015). Amino acid polymorphisms in class I and class II HLA genes independently influence the risk of AITD (Okada et al. 2015). The structural characteristics of these pockets exhibit significant polymorphism, forming the basis for the protein's peptide-binding motif. The unique structures of HLA molecules promote various peptide binding motifs, influenced by the dimensions and configuration of their pockets, which may lead to differing interactions with specific antigenic peptides. The primary factors influencing the binding motif are pockets 1, 4, and 9 (P1, P4, and P9, respectively) (Kelly et al. 2003). A study in India done on adult patients with AITD that genotyped the HLA-DQB1* allele has reported that HT susceptibility was associated with the amino acids Glu86 and Leu87 in P1, Leu26 in P4, and His9 and Ala57 in P9. Gly86 in P1 and Asp57 in P9 were associated with susceptibility to GD. The current study demonstrated that HLA-DQB1 alleles and particular amino acids are significant factors in the susceptibility to AITD in Southern India (Ramgopal et al. 2019). Unfortunately, our study did not identify the risk and protective amino acids, which is one weakness of this study.

A variety of studies have centered on analyzing HLA in children with DS and their parents in comparison to typical families. A study conducted in 1983 indicated that parents of children with SD exhibited antigens at locus A and/or B at significantly higher levels than the control group. This finding suggested a potential association between the parental sharing of HLA-A and B antigens and the occurrence of trisomy 21 (Mottironi et al.1983). However, further research conducted in 1984 and 1988 indicated no significant difference in the HLA antigen frequencies between the parents and individuals suffering from SD when compared to controls, nor in the frequency of HLA-A, -B, or -AB homozygosity (Ayme et al. 1984) and mothers of SD did not exhibit an increased sharing of HLA antigens with their children compared to the control group (Stoll et al. 1988). In addition, to date there have been no studies linking the role of ethnic differences in the relationship between HLA genetics and AITD in this unique population. Therefore, we cannot yet know whether differences in ethnic variations in the AITD DS group will affect the results of this study.

This study's significant strength lies in its pioneering investigation into the relationship between HLA-DQA1 and HLA-DQB1 alleles and the risk of AITD in children with DS, a specific population with a younger onset and more rapid progression of thyroid dysfunction than the general population. This study exhibited several limitations. First, the cohort of participating patients was limited because of specific cases. Additionally, this study was conducted at a single center, which may limit the generalizability of its findings to the broader population of children with DS. Carrying out a multi-center study to gather additional data on Indonesian ethnic groups is crucial for assessing whether the ethnicity of patients with DS influences the differential roles of HLA alleles in AITD in an approach comparable to patients without DS.

Conflict of interest: *The authors declare no conflicts of interest.*

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