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Indonesians Human Leukocyte Antigen (HLA) Distributions and Correlations with Global Diseases

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ABSTRACT

In Human, Major Histocompatibility Complex known as Human Leukocyte Antigen (HLA). The HLA grouped into three subclasses regions: the class I region, the class II region, and the class III region. There are thousands of polymorphic HLAs, many of them are proven to have correlations with diseases. Indonesia consists of diverse ethnicity people and populations. It carries a unique genetic diversity between one and another geographical positions. This paper aims to extract Indonesians HLA allele data, mapping the data, and correlating them with global diseases. From the study, it is found that global diseases, like Crohn's disease, rheumatoid arthritis, Graves' disease, gelatin allergy, T1D, HIV, systemic lupus erythematosus, juvenile chronic arthritis, and Mycobacterial disease (tuberculosis and leprosy) suspected associated with the Indonesian HLA profiles.

Introduction

The Human Leukocyte Antigens (HLAs) are grouped into three subclasses regions: the class I, II and III regions. The class I region, the classical group contains highly polymorphic *HLA-A*, *HLA-B*, and *HLA-C* genes, and the nonclassical exhibits limited polymorphism, i.e. *HLA-E*, *HLA-F* and *HLA-G* genes. The class II region, involved in antigen processing and presentation, consists of the *HLA-DPA1, HLA-DPB1, HLA-DQA1, HLA-DQA2, HLA-DQB1, HLA-DQB2, HLA-DRA, HLA-DRB1, HLA-DRB2, HLA-DRB3, HLA-DRB4* and *HLA-DRB5* genes. The class III region, contains genes implicated in inflammatory responses, leukocyte maturation and the complement cascade (Dendrou et al. 2018). Many cases are associated with the HLA profiles, and more cases are found since the first discovery of Hodgkin Lymphoma is related to *HLA-B* profile (Amiel 1967). As mentioned before, HLA contains regions that carrying highly polymorphic genes and those unique characteristic makes HLA precisely fit within its interaction through immunology view. Those highly polymorphic genes sequences leads to the invention of HLA profiles by several generations methods for determination the alleles in an individual person: PCR-RFLP, SSOP, immobilized probes, PCR-SSP, Sanger sequencing, and lately Next Generation Sequencing (NGS) (Carapito et al. 2016; Erlich 2012; Hosomichi et al. 2015; Kishore and Petrek 2018). From the data mining through thousands of research on HLA, now the big data are available. This large data can be translated not only for genome mapping but also can be used for connecting between allele type with diseases, allele type with genome

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defect by natural selections (Meyer et al. 2018). With the fact that specific alleles have correlations with specific diseases comes together as information for susceptibility of illness preventive medication. Indonesia is the fourth most significant populations in the world, with more than 268,361,538 people (Indonesia Population 2019; Anonim 2019). Until now, no information about HLA correlation with disease on Indonesian populations. This research aims to extract Indonesians HLA allele data, mapping the data, and correlating with global diseases so at the end of the research could be used as the basics information of Indonesians HLA alleles associated with diseases.

Indonesians HLA data

Indonesia is an ethnic, race, and cultural group diverse population. As mentioned before, with more than 268 million citizens and divided into 34 provinces in total, Indonesia becomes the place where the various gene can be found. Indonesian HLA allele frequencies were recorded, the late study in 2010 (Yuliwulandari et al. 2010b). Data from the Indonesians HLA database (AlleleFrequency.net), from 9 research data in total (Moluccan Island (Maluku), Central Java, West Java, Nusa Tenggara Island, and Indonesia Singaporean) will be extracted and clustered by the allele type (Anonim, 2019; Charron et al., 1997; Gao et al. 1992; Gao and Matheson 1996; Mack et al. 2000; Meyer et al. 2018; Nagy et al. 2007; Yuliwulandari et al. 2009, 2010a, 2010b, 2017; Zimdahl et al. 1999).

HLA associations with diseases

The HLA genes involved in antigen processing and presentation The class III region contains genes implicated in inflammatory responses, leukocyte maturation and the complement cascade (Dendrou et al. 2018). The T cells receive the peptide from HLA class I and II molecules discriminate between *self* and *non-self* (Murphy 2014). More than thousands of variations of HLA class I and II alleles have been reported in IMGT – HLA database (Robinson et al. 2016). Those variations of HLA genes give us more insight on how does the diseases correlated by the presentation of HLA molecules (peptide) to the immune cells. The polymorphism of HLA molecules drives to the variations of the peptide binding structure. For example, Trp at position 156 in *HLA-B*35:62* was shown to confer a TAP-independent (antigen presentation complex) mode of peptide loading. This could be suggestive of consulting the ability of peptide presentation via non-classical pathways and its potential role in immune response against viral infections (Manandhar et al. 2016). The specific recognition of HLA–peptide combinations is mediated by αβ T cell receptors (TCRs) on CD8$^+$ T cells, which bind class I molecules, and on CD4$^+$ T cells, which bind class II molecules. The TCR displays substantial sequence heterogeneity that arises as the different variable (V), diversity (D) and joining (J) gene segments come together through somatic, convergent recombination; additional variation is introduced by the semi-random insertion or deletion of nucleotides at segment junctions (Quigley et al. 2010). Furthermore, each TCR chain contains three highly variable complementarity determining region (CDR) loops: CDR1 and CDR2 diversity is germline-encoded, whereas the CDR3 loop is hypervariable, as it are encoded by the sequences generated by nucleotide insertion and deletion. Fine-tuning of lymphocyte activity is gained by molecules belonging to two different classes of class I specific complex histocompatibility complex (MHC) inhibitory receptors. While killer

immunoglobulin-receptors (KIR) are integral type I membrane proteins that interact with certain human leukocyte antigens (HLA) -A, HLA-B, or HLA-C alleles, receptors that killer lectin resemble cells (KLR) represent membrane proteins type II integral of type C lectin family (Eberl et al. 2005). There are kind of mechanism to know how HLA initiate disease, first, HLA–peptide–TCR binding, second, epitope variation, including molecular mimicry, post-translational epitope modification and the generation of hybrid peptides; in further and deep explanation, molecular mechanism which are involved including alternate docking, low-affinity-mediated thymic escape, T cell receptor stabilization of weak peptide–HLA complexes, altered register, 'Hotspot' molecular mimicry, post-translational modification, hybrid peptides, regulation of HLA expression, and HLA stability (Dendrou et al. 2018).

Global diseases correlated with HLA profile

In a worldwide view, HLA molecules do not only act as graft uses nor immunology things. HLA could be used as a marker of the possibility on the appearance of any diseases. From the latest review and research article exist on the database, we collect the associations between HLA profile with diseases. Since the previous explanations about how the HLA molecules give an effect on disease through its molecular mechanism of action, now we can truly understand everything about the mechanism itself in many diseases (Table 1). There will be an explanation what type of disease, how the effect on disease, molecular mechanism, and actions among the literature that exists (Dendrou et al. 2018). While on previous explanation was talking about the arrangement, in other research found the HLA allele associated with the appearance of diseases and it potential to influence the disease borne Table 2

Global disease HLA profile as representation of indonesian HLA allele coherence

The mechanism of HLA on disease was clearly explained (Dendrou et al. 2018). Indonesia has a great problem related to HLA database due to disease research. This problem can be solved by general relating between Indonesian allele and the global disease related with HLA profile. From the previous research and the HLA data collected (Tables 1 & 2), the diseases like Crohn's disease, rheumatoid arthritis, Graves' disease, gelatin allergy, T1D, HIV, systemic lupus erythematosus, juvenile chronic arthritis, and Mycobacterial disease (tuberculosis and leprosy) suspected to be associated in the Indonesian HLA profiles. More specific, the alleles give some clue of disease deployment (Table 4). The output could be translated into variated applications, such as drugs design (including cellular and non-cellular therapy), and graft transplant susceptibility.

Indonesia HLA profile correlated with diseases

From the literatures of 1000 original research articles searched using Taylor and Francis, Google Scholar, SCOPUS, and PubMed, the 19 articles were selected, processed and extracted (Table 3). From the study, pulmonary tuberculosis, elephantiasis, spondyloarthropathy (SpA), leprosy, ankylosing spondylitis, chronic and occult hepatitis B infection, *H. pylori* infection, and Steven-Johnson syndrome/toxic epidermal necrolysis are identified as diseases that correlated with HLA. Indonesia as the one of 22 countries with high Tuberculosis (TB) prevalence,

Table 1. The map of disease caused by HLA allomorph and the mechanism of action (Dendrou et al. 2018).

HLA allomorph and associated SNPs (effect on disease)	Autoimmune disease	Molecular mechanism of action	Refs
Alternate docking **HLA-DR15** (risk) Associated SNPs: rs3135338-A, rs9271640-A, rs3957148-A, rs3135388-A, rs6457617-G, rs6457617-A	Multiple sclerosis	• Alternate docking of a TCR may allow MBP peptide-specific T cells to escape thymic selection • In the periphery, such cells may be cross-reactive with microbial peptides	(Madsen et al. 1999; Hahn et al. 2005; Jakkula et al. 2010; Goris et al. 2015)
Low-affinity-mediated thymic escape **HLA-A*02:01** (risk) Associated SNPs: rs3135002-A, rs2647044-A	T1D	• The low affinity of a TCR for preproinsulin signal peptide–HLA may allow autoreactive T cells to escape thymic selection • This mechanism may depend on the thymic expression level of the autoantigen • In the periphery, these cells may bind microbial peptides with a high affinity	(Pugliese et al. 1997; Hakonarson et al. 2007; Bulek et al. 2012; Cole et al. 2016; Roshandel et al. 2018)
TCR stabilization of weak peptide–HLA complexes **HLA-DR4** (risk) Associated SNPs: rs3135338-A, rs9271640-A, rs3957148-A, rs3135388-A, rs6457617-G, rs6457617-A	Multiple sclerosis	• Weak MBP peptide–HLA-DR4 interaction is stabilized by binding of a patient-derived TCR • Low autoantigen density in the thymus may enable the escape of autoreactive T cells from negative selection • Higher autoantigen density in the periphery could trigger an autoreactive response	(Quandt et al. 2004; Armstrong et al. 2008; Yin et al. 2011)
Altered register **HLA-DQ2** and **HLA-DQ8** (risk) Associated SNPs: rs3135002-A, rs2647044-A	T1D	• Insulin B-chain peptide binds HLA-DQ2 and HLA-DQ8 with a low-affinity peptide register • Low affinity may allow autoreactive T cells to escape thymic selection • In the periphery, autoreactive T cells may be cross-reactive with microbial peptides via molecular mimicry	(Hakonarson et al. 2007; Stadinski et al. 2010; Yang et al. 2014a; Roshandel et al. 2018)
HLA-DR15 (risk) **HLA-DR1** (dominant protection) Associated SNPs: rs1050501	Goodpasture disease	• HLA-DR15 and HLA-DR1 both bind an α3-chain of type IV collagen peptide (α3 $_{135-145}$) but with a different binding register • When HLA-DR1 is present, this promotes the generation of autoantigen-specific regulatory T cells as opposed to effectors	(Zhou et al. 2010; Ooi et al. 2017)

	Disease	Mechanism	References
'Hotspot' molecular mimicry HLA-DR15 (risk) Associated SNPs: rs3135338-A, rs9271640-A, rs6457617-G, rs3957148-A, rs3135388-A, rs645617-A	Multiple sclerosis	• The probability of aberrant, off-target TCR reactivity induced by pathogen-derived peptides is increased for autoreactive TCRs with a highly focused footprint that predominantly binds only a small area of peptide • Patient TCRs have been identified that cross-react with *HLA-DR15*-restricted MBP and *Escherichia coli* or EBV-derived peptides	(Wucherpfennig and Strominger 1995; Lang et al. 2002; Harkiolaki et al. 2009; Sethi et al. 2011; Cole et al. 2016; Jakkula et al. 2010; Goris et al. 2015)
Post-translational modification HLA-DQ2.5 and HLA-DQ8 (risk) Associated SNPs: rs2187668-A, rs2187668-A	Coeliac disease	• *HLA-DQ2.5* and *HLA-DQ8* present deamidated gliadins with high kinetic stability, leading to sustained antigen presentation that may promote a pathogenic T cell response	(Molberg et al. 1998; Van et al. 2007, p. 21; Hovhannisyan et al. 2008; Fallang et al. 2009; Dubois et al. 2010; Bodd et al. 201...)
HLA-DR4 (risk) Associated SNPs: rs9275428, rs9275406-T, rs3104413, rs3129769, rs6931277, rs9275334, rs9784858, rs3129890, rs3129891, rs9268557, rs6457617, rs2157337, rs3104413, rs3129769, rs6931277, rs9275495, rs9784858, rs3129890, rs3129891, rs9268557, rs2157337, rs9268839-A	Rheumatoid arthritis	• Citrullination of autoantigens (for example, vimentin) facilitates binding to *HLA-DR4* • Citrullination can also modify peptide cleavage, enabling retention of autoantigens	(Hüffmeier et al. 2010; Padyukov et al. 2011; Scally et al. 2013; Negi et al. 2013; Govind et al. 2014; Koning et al. 2015; Stuart et al. 2015; Jiang et al. 2016; Wei et al. 2017; Laufer et al. 2019)
HLA-DR4 (risk) Associated SNPs: rs3135002-A, rs2647044-A	T1D	• Vicinal disulfide bond creation in an insulin A-chain peptide presented by *HLA-DR4* is needed for recognition by a patient-derived autoreactive TCR	(Mannering et al. 2005; Hakonarson et al. 2007; Roshandel et al. 2018)
Hybrid peptides HLA-DQ8 (risk) Associated SNPs: rs3135002-A, rs2647044-A	T1D	• Hybrid proinsulin peptides present in pancreatic β-cells may drive a breakdown in immune tolerance	(Hakonarson et al. 2007; Ooi et al. 2017; Roshandel et al. 2018)
Regulation of HLA expression MHC risk variants in distal intergenic XL9 regulatory element Associated SNPs: rs2187668-A, rs2301271-T, rs2647012-A, rs3135394-G, rs2187668, rs9273076-T, rs9271100, rs9270984-T	Systemic lupus erythematosus	• Risk variants alter the binding of the IRF4 and CTCF factors that regulate the transcription of *HLADRB1*, *HLADQA1*, and *HLADQB1*, resulting in a 2.5-fold increase in the levels of the *HLA-DR*, and *HLA-DQ* proteins implicated in lupus	(Hom et al. 2008; Gateva et al. 2009; Han et al. 2009; Bentham et al. 2015; Raj et al. 2016)

Table 1. (Continued).

HLA allomorph and associated SNPs (effect on disease)	Autoimmune disease	Molecular mechanism of action	Refs
Highly expressed *HLA-C* allotypes (risk) rs140068907-C, rs9271366-C, rs114985235-C, rs9271060-G, rs9271366-A, rs184950714, rs113653754-C, rs116392568-G, rs9264942, rs9264942-C, rs9469220-A	Crohn's disease	• *HLA-C* allotypes with a high expression correlate with Crohn's disease risk • This expression is partly regulated by the microRNA miR-148a, which is itself subject to regulation by genetic variation	(PMC 2007; O'hUigin et al. 2011; Okada et al. 2011; Jostins et al. 2012; Yang et al. 2014b; Liu et al. 2015; Jung et al. 2016; Kakuta et al. 2019) [22]
HLA stability *HLA-DQ2* and *HLA-DQ8* (risk) *HLA-DQ6* (protection) Associated SNPs: rs3135002-A, rs2647044-A	T1D, coeliac disease T1D, autoimmune polyglandular syndrome, IgA deficiency	• *HLA-DQ2* and *HLA-DQ8* instability could confer risk by allowing escape of autoreactive T cells from thymic negative selection but also by the formation of weak peptide–HLA complexes in the periphery with a range of autoantigens [1] • By a converse mechanism, the stability of *HLA-DQ6* may confer protection against autoimmune disease; despite such a mechanism, *HLA-DQ6* confers risk of narcolepsy	(Mignot et al. 2001; Hakonarson et al. 2007; Weinstock et al. 2011; Ferreira et al. 2012; Zhou and Jensen 2013; Miyadera et al. 2015; Hu et al. 2015; Roshandel et al. 2018) [36]

[62]

CTCF, transcriptional regulator CTCF; EBV, Epstein–Barr virus; IgA, immunoglobulin A; IRF4, interferon regulatory factor 4; MBP, myelin basic protein; T1D, type 1 diabetes; TCR, T cell receptor.

Table 2. Global diseases associated with various HLA allele.

HLA Type	Disease	Results	Refs
B*51	Behçet's disease	• Three microsatellite alleles (MICAA6, MIB-348, C1-4-1-217) and HLA-B51 were found to be strongly associated with BD	(Yabuki et al. 1999; Mizuki et al. 2001b; Mizuki et al. 2001a; Mizuki et al. 2002a; Mizuki et al. 2002b; Itoh et al. 2006)
B*51:01		• In the genotyping of B*51 alleles, 33 out of the 36 B*51-positive patients possessed B*51:01 and the remaining 3 carried B*51:08.	
B*51:02		• B*51 antigen was significantly increased in the patient group as compared to the ethnically matched control group (76.9% in patients vs. 22.2% in controls), but no significant difference was observed in HLA-A, –DRB1, –DQB1 or –DPB1 alleles between the patients and controls, as previously observed in Japanese BD.	
B*51:08			
A*26:02			
B*39:01		• Phenotype frequency of the B*51 antigen was confirmed to be remarkably increased in the patient group as compared to the ethnically matched control group (59.4% in patients vs. 13.6% in controls; Pc50.0000000000098, R.R.59.3).	
		• In the B*51 allele genotyping, 56 out of 57 B*51-positive patients were defined as B*51:01 and the remaining one was B*51:02.	
		• The significant increase of HLA-A*26:02 and B*39:01 in the patient group without HLA-B*51 suggests that these two alleles might also have some secondary influence on the onset of BD	
DRB1*04:05	Meniere's disease	• Association of HLA-DRB1*04:05 with anti-CII positive Meniere's disease in this study suggests that it shares a specific HLA-DR sequence, QRRAA, as a genetic susceptibility factor with the anti-CII positive rheumatoid arthritis.	(Koo et al. 2003)
DQB1*04:02 lDRB1*15:02	Crohn's disease	• CD in the Japanese population, HLA-linked disease susceptibility alleles appear to be DQB1*04:02 and DRB1*15:02, a disease resistance allele. In UC, DRB1*15:02 appears to be a disease susceptibility allele.	(Yoshitake et al. 1999)

(Continued)

Table 2. (Continued).

HLA Type	Disease	Results	Refs
!DRBI*04:05 DRBI*10:01 DRB1*14:02 [8] DRB1*09:01 DRB1*10 DQB1*03:02 DRB1*04 [60] DQB1*03:01 DR*4	Rheumatoid arthritis	• RA patients had higher frequencies of DRB1*04:05 (40 vs 125%; corrected probability value (PC)<0.02, relative risk (RR) = 4,7, 95% confidence limit (CL) 2.1–10.6), DRBI*10:01 (14.3 vs 1.3%; PC = 0.06, RR = 13.2,95% CL 1.6–105.7), DQB1*04:01 (38.6 vs 125%; P = .006, RR = 4.4,95% CL 1.9–10.0) and DQBI*05:01 (20vs 5% PC = 0.048, RR = 4.8, 95% CL 1.5–15.2). • The most notable observation is the high prevalence of the DRwI4 allele DRB 1*14:02, found in 91% of cases, but also present in 80% of controls (OR = 2,4, p = .20). This allele was present in 16 of 17 cases (94%) and 31 of 34 (91%) controls. DRB1*09:01 was also increased in RA cases (19%) compared with controls (8%) (OR = 2.6, p = .18). • A number of HLA class II disease associations appear to be unique to southern African populations. DRB1*10 and DQB1*03:02 with rheumatoid arthritis susceptibility in the South African (SA) Indian and SA Coloreds, respectively [12] [12] • The increase in DRB1*04 corresponds to a serologically defined increase in DR4, which was previously found in a small group of Zimbabwean RA patients and we now show that this increase was caused by the DRB1 * 04:05 subtype associated with DQB1*03:02. • HLA-DR4 is significantly associated with rheumatoid arthritis in whites (P less than 0.0001), blacks (P less than 0.001) and patients of mixed ancestry (P less than 10–6) [53]	(Martell et al. 1989; Nelson et al. 1992; Cutbush et al. 1993; Chan et al. 1994; Lombard et al. 2006) [28]
A*9 B*27:05	Ankylosingspondylitis	• We found that HLA-B*27:05 conferred a relative risk of 126 for AS in this group. HLA-A*9 (A*24:02) allele was significantly increased in AS patients compared with healthy controls and B*27–positive control group (P corr 0.0001) and also increased in patients affected with peripheral arthritis [14]	(de Juan et al. 1999) [14]
!DRB1*16:02 [4] DQA1*01:02 !DQB1*05:02	Graves' disease	• The DRB1*16:02-DQA1*01:02-DQB1*05:02 haplotype was significantly increased in GD patients (P = .0209, OR = 2.55), DRB1*07-DQA1*02:01-DQB1*02:01 haplotype (P = .039, OR = 0.32) and HLA-DRB1*12-DQA1*06:01-DQB1*03:01 haplotype (P = .0025, OR = 0.28) were significantly decreased in GD patients. Interestingly, a protective DRB1*07 allele in Thai population lacks an arginine at position 74 similar to DRB1*03:11 (a protective allele in Caucasians) [7] [7] [7]	(Wongsurawat et al. 2006) [43]
!DPB1*04:02 [4] !DQB1*03:03	Gelatin Allergy	• DQB1*03:03 and DPB1*0402 were positively associated with the IgE response for gelatin, while DRB1*15 was negatively associated with it	(Sakaguchi et al. 2002)

Allele(s)	Disease	Description	References
A*2	Cardiovascular disease	• HLA-A*2 alleles give 4.94 times the rate of death from CVD (95% C.I. 1.91–12.77). When controlled for potential confounding variables, cholesterol, average blood pressure, smoking, body mass index, rheumatoid factor titter, and nephropathy, the mortality ratio (MRR) was 5.42 (95% C. 1.98–14.82) There was no relationship between mortality that was statistically significant with HLA-A or other HLA-B alleles, or for causes of death not related to cardiovascular disease.	(Williams et al. 1996)
A*1, DQw2	Idiopathic Peyronie's disease	• A1 (p, <0.05) and DQw2 (p, < 0.01) remained significant [59]	(Rompel et al. 1991)
!DRB1*14:01:01	Insulin-dependent diabetes mellitus (T1D)	• Some of HLA class II disease associations appear to be unique to southern African populations. These include DRB1*14:01:01 association with insulin-dependent diabetes mellitus susceptibility in the Xhosa [39][12]	(Lombard et al. 2006)
DRB1*03, DQB1*02, DR2, !DQB1*06:03, !DQB1*02:01, !DRB1*03:01, DQB1*02:01, DRB1*15:03, DQB1*06:02	HIV	• Seronegative partners with either DRB1*03:01, DQB1*02:01 or DRB1*15:03-DQB1*06:02 demonstrated accelerated seroconversion [58] [31] • HLA-DR2 has been shown to be related to p24 antigen levels in HIV-1 positive subjects, and because p24 detection before the disease becomes symptomatic correlate strongly with rapid disease progression, then DR2 antigen could be associated with disease progression	(Achord et al. 1996; Al Jabri 2002; Lombard et al. 2006; Goulder and Walker 2012)
DR2, DRB1*07, DQB1*06:02, !DQA1*01:02, !DQA1*05:01, !DQB1*04:02, DRB1*15	Systemic lupus erythematosus	• HLA-DR2 was significantly associated with Caucasian SLE (R2 = 0.63, p less than 0.0012). Multivariate analysis demonstrated that the HLA-DR2 antigen and C4A null allele contributed independently to the risk of SLE (relative risk 3.0 and 3.2, respectively); when HLA-DR2 and the homozygous C4A null phenotype were present together, the relative risk of SLE was 24.9. [67][28] [52] • HLA-DQA1*01:02 and DQA1*05:01 were significantly increased in SLE patients. Allele distribution comparison showed in the SLE group a significant increase in HLA-DQA1*01:02, DQB1*04:02, and DRB1*15. SLE patients showed haplotype DQB1*06:02-DQA1-*01:02-DRB1*15 increased. As expected, patients with SLE have a reduced haplotype genetic diversity. [15][15]	(Howard et al. 1986; Klemp et al. 1988; Rudwaleit et al. 1995; Ayed et al. 2004; Cortes et al. 2004)
!DRB1*04:01, !DRB1*07:01	Juvenile chronic arthritis	• The DRB1*15:01 effect was shown to reduce risk across the whole cohort, whereas DRB1*04:01 and DRB1*07:01 were protective for selected subtypes, [29]	(Hollenbach et al. 2010)

(Continued)

Table 2. (Continued).

HLA Type	Disease	Results	Refs
DQB1*05:03 DRB1*08:03:02 DQB1*06:01 DRB1*13:02	Mycobacterial disease (tuberculosis and leprosy)	• HLA-DQB1*05:03 allele is significantly associated with susceptibility to TB in Cambodian patients and is the first identified gene associated with development of clinical TB • The frequency of HLA–DQB1*06:01, strongly associated with DRB1*08:03:2 in Koreans, was also significantly higher in MDR–TB patients (35.8%: primary 37.5%, acquired 33.3%) than in normal controls (15.5%) (OR 3.05 [95% CI 1.54–6.01], p 0.0009, corrected p 0.01). HLA–DRB1*08:03:02–DQB1*06:01 haplotype is strongly associated with genetic susceptibility to MDR–TB and disease progression in Korean • The DRB1*13:02 phenotype was significantly associated with TB occurring at the allele frequency which was much higher in cases than controls and was found in the haplotype with DQB1*06:02/3. The DQB1*03:01–03:04 phenotype was significantly associated with TB and was found in haplotypes with DRB1*11:01–11:21, indicating a significant association (LD) disequilibrium in both cases and controls.	(Goldfeld 1998; Park et al. 2002; Lombard et al. 2006)
DR*3 DQw2 DPBI	Addison's disease	• Addison's disease is associated with HLA-DR3, DQw2 and DPBI in a series of 33 consecutive Caucasian patients. There were negative associations with DR6, DR7/9, DQw7 and DPB2.1, although only that with DQw7 survived correction	(Weetman et al. 1991)

*: Suspected allele compare to Indonesian HLA database

reported there are 1.017.378 active patient (Collins et al. 2017). Those number of TB patients contrast with the research of HLA correlation with TB in Indonesia. In 2017, a total 12.677 patient recorded for having elephantiasis and the highest number is for Papua Island (Harpini 2018). High prevalence of those diseases and lack of information makes researcher and academician turn in concern of this subject. As early detection, HLA could be used as important molecular marker and statistically associated for any diseases such as diabetes, hepatitis B virus infection, breast cancer, Behçet's, tuberculosis, spondyloarthropathy, leprosy, ankylosing spondylitis, *H. pylori* infection, and Steven-Johnson syndrome (Chen et al. 2017; Ding et al. 2010; Elfishawi et al. 2019; Gönen et al. 2017; Hajjej et al. 2019; Kankonkar and Shankarkumar 2008; Khor et al. 2017; Krause-Kyora et al. 2018; Matei et al. 2018; Ouni et al. 2019; Smith 2013)

Indonesia HLA profile

Indonesia HLA profile is similar to people in South East Asia because they have high frequency variation in *HLA-B*15:02* and *HLA-DRB1*12:02* especially for Javanese, Mollucan, and Nusa Tenggara people (Sanchez-Mazas et al. 2005; Yuliwulandari et al. 2010a). Unfortunately, not all Indonesian people is typed on HLA variably. Almost West Javanese have been typed (Yuliwulandari et al. 2009, 2017, 2010a, 2010b). Only few populations that have been done outside West Javanese which are Yogyakarta, Molluca, and Nusa Tenggara people (Gao et al. 1992; Sanchez-Mazas et al. 2005). In other hand, from single nucleotide polimorphism (SNP) genome wide association study (GWAS), Indonesia carry an unique genetic diversity between one and another geographical position (Hudjashov et al. 2017).

The closest ethnicity with Indonesian ethnics is Malaysian and other South East Asian countries (Figure 1). It happens because there were two different era groups which were 40,000 BP and 6000–5000 BP migrated to Indonesian region (Yuliwulandari et al. 2010a). The first group migrated from Indian subcontinent through Indo-Malaysian archipelago. At that time, Indonesia was divided into 3 islands which were Greater Sunda Land, Wallacea, and Sahul Island. Later, the second group which was Austronesian moved into Java and forced the first group to move away to Oceania although there was

Figure 1. An illustrated geographical migrations map of South East Asia and Indonesian populations.

Table 3. HLA correlated diseases within Indonesian populations.

HLA Type	Disease Related HLA	Geographical Position	Number of Sample	Typing Method	Year of Discovery	Reference
DR2 and DQwl	Sputum smear-positive pulmonary tuberculosis	Surabaya, East Java	165	Epitope-specific antibody	1989	(Bothamley et al. 1989)
HLA-B*27 and HLA-DQ5	Elephantiasis	Rengat, Sumatera	161	Epitope-specific antibody	1995	(Yazdanbakhsh et al. 1995)
HLA-B*27	Spondyloarthropathy (SpA)	Java	60	PCR-SSO	1997	(Nasution et al. 1997)
HLA-DR and HLA-DQ	Elephantiasis	Mangkutane, South Sulawesi	117	PCR-SSO	1997	(Yazdanbakhsh et al. 1997)
HLA-DRB1 HLA-DRB1*02 HLA-DRB1*12	Leprosy	Yogyakarta, Central Java	129	PCR-SSO	1997	(Soebono et al. 1997)
HLA-B*27	Ankylosing Spondylitis (AS) or related spondyloarthropathies	Jakarta	351	Epitope-specific antibody	1999	(Mardjuadi 1999)
HLA-B*27:04	Spondyloarthropathy (SpA)	Jakarta	2 families	PCR-SSOP	1999	(Mardjuadi 1999)
HLA-A, -B, and -DRB1 HLA-B*18:02 ($p = .014$) HLA-B*40:01 ($p = .015$) HLA-DRB1*11:01 ($p = .008$) HLA-A and -DRB1 ($p = .034$)	Pulmonary tuberculosis (PTB)	West Java	257	PCR-SSO	2010	(Yuliwulandari et al. 2010b)
HLA-DR and HLA-DP	Chronic hepatitis B infection	Batam, North Sumatera	3614	WGG	2011	(Png et al. 2011)
HLA-DQA1 and DQB1	*Helicobacter pylori* Infection	Mataram, Lombok Island	294	PCR-RFLP	2012	(Zhao et al. 2012)
HLA-B*15:02 and HLA-DPA1 and DPB1	Stevens–Johnson syndrome/toxic epidermal necrolysis	Jakarta	29	PCR-SSP	2015	(Yano 2015)
	Hepatitis B virus (HBV) infection	Yogyakarta, Central Java	686	PCR-SSP	2016	(Wasityastuti et al. 2016)
HLA-DRB1*12	Typhoid fever	Semarang, Central Java	63	PCR-SSOP	2017	(Dharmana et al. 2002)

HLA Type	Disease Related HLA	Geographical Position	Number of Sample	Typing Method	Year of Discovery	Reference
HLA-DP	Occult hepatitis B infection (OBI)	Yogyakarta, Central Java	456	PCR-SSOP	2017	(Mardian et al. 2017)
HLA-DQB*03:02 and HLA-DQA*01:02	Drug-induced liver injury (DILI)	Yogyakarta, Central Java and Lampung, South Sumatera	207	PCR-SSP	2018	(Perwitasari et al. 2018)
HLA-B*15:02 and HLA-B*15:21	Stevens–Johnson syndrome/toxic epidermal necrolysis	Jakarta	265	PCR-SSOP	2017	(Yuliwulandari et al. 2017)
HLA-E*01:01 and HLA-E*01:03	HCV/TTV and TTV co-infection	Surakarta, Central Java	320	PCR-SSP	2016	(Prasetyo et al. 2016)
HLA-C	Multidrug-Resistant Tuberculosis	Yogyakarta, Central Java	236	PCR-SSP	2016	(Hani 2015)
HLA-DR	Plasmodium infection/malaria	Timika, Papua	330	Flow-cytometri	2015	(Kho et al. 2015)

a possbility that the first group might blend together with the second group. The second group later predominates West Indonesia region and later become Javanese. This is the reason why Indonesia genetic is similar to Malaysia since Malaysia is also considered as Austronesian based on Sanchez-Mazas research (Sanchez-Mazas et al. 2005). This theory is also proved by occurrence of *HLA-A*3401* that a sign for the first group existence in Indonesia (Yuliwulandari et al. 2010a).

Although Indonesia has similarity with South East Asian countries, but Indonesia still has unique HLA characteristics. Yogyakarta people tend to have high frequency at *DQA1*06:01, DQB1*03:01, DRB1*12:02* (Gao et al. 1992) and Western Javanese people have *HLA-A*2407* (Yuliwulandari et al. 2010b). Those HLA regions are not familiar in other countries which are needed to be confirmed using different Indonesian ethnicity.

Indonesia HLA profile correlation with global disease

Based on Table 4, Indonesia HLA profile has high variation at *DQA1*06:01, DQB1*03:01, DRB1*12:02, HLA-A*24:07, HLA-B*15:02, HLA-B*75, HLA-B*18:02*. Those alleles are significant in researches statistical model (Yuliwulandari et al. 2009, 2017, 2010a, 2010b). Further research is important to explore those alleles because those alleles have roles in diseases, except *DQA1*06:01* (Table 4). Other alleles in Table 4 still have not been known whether it will affect Indonesian health condition or not but, in another countries, based on Global-Allele frequency.net, some of alleles affect human health condition.

For example, *HLA-A*02:01:01:01, HLA-A*02:03:01, HLA-A*02:06:01, HLA-A*02:11* in Table 4 show variation in Javanese but nobody have done research regarding those alleles correlation with many diseases as Rasmussen encephalitis (RE), carbamazepine-induced hypersensitivity reactions and also for vaccine development amongst Indonesian (Dandekar et al. 2016; Maira et al. 2014; Song et al. 2013; Zhang et al. 2018). Therefore, further research is needed to be done because it has potential might affect Indonesian. Another case is *DQA1*06:01*. This allele is related with rheumatoid arthritis (Table 4). However, nobody has done the research for Indonesian because that allele is found for anthropology purpose at that time (Gao et al. 1992). Otherwise, The most unique Indonesian HLA, *HLA-A*24:07* (Yuliwulandari et al. 2010a), is related to Diabetes type 1 (Ghodke et al. 2005) but there is no research about Indonesia Diabetes type 1 patient and that allele relationship.

Current research that has been done is *HLA-B*15:02* and *HLA-B*75*. It shows that those alleles are connected to Steven Johnson Syndrome. The research suggests *HLA-B*75* is needed to be further explored because it affects the disease more than *HLA-B*15:02*. Other research that has been done is the correlation between HLA and tuberculosis disease (Yuliwulandari et al. 2010a). The result shows the most affective HLA alleles that affect tuberculosis disease are *HLA-B*18:02* and *HLA-DRB1*12:02*. It has potential to protect the patient against tuberculosis disease. Nonetheless, the research needs to be done in more samples. As a conclusion, from the Table 3, other than Sputum smear-positive pulmonary tuberculosis, Elephantiasis, Pulmonary tuberculosis (PTB), Ankylosing Spondylitis (AS) or related spondyloarthropathies, chronic hepatitis B infection, *Helicobacter pylori* infection, Stevens–Johnson syndrome/toxic epidermal necrolysis, hepatitis B virus (HBV) infection, drug-induced liver injury (DILI), HCV/TTV and TTV co-infection, multidrug-resistant tuberculosis, and *Plasmodium* infection/malaria research, nobody has done the HLA-

Table 4. Indonesian allele population associated with global disease and Indonesia disease prevalence.

Allele	Indonesia Java	Indonesia Java Pop 2	Indonesia Java Yogyakarta Region	Indonesian Moluccans	Indonesian Nusa Tenggara Island	Indonesia Singaporean	Indonesia Sundanese and Javanese	Disease Correlated Allele (Global-Allele frequency.net)	Disease Correlated Allele (Indonesia)	Frequencies of Disease Correlated Allele (Indonesia)	Reference for Indonesia frequencies
A*01:01:01	0,028						0,025	Idiopathic Peyronie's disease		N/A	
A*02:01:01:01		0,042					0,075	Cardiovascular disease			
A*02:03:01		0,069					0,037				
A*02:06:01		0,028					0,035				
A*02:11		0,014					0				
A*03:01:01:01		0,014					0,025	N/A			
A*11:01:01		0,139					0,164				
A*11:04		0					0,003				
A*24:02:01:01		0,139					0,144				
A*24:07		0,264					0,207				
A*24:10		0,028					0,015				
A*26:01:01		0,042					0,008				
A*29:01:01:01		0,028					0,008				
A*30:01:01		0					0,012				
A*32:01		0					0,005				
A*33:03:01		0,083					0,169				
A*34:01		0,083					0,067				
A*74:01		0					0,003				
B*07:02:01		0,042					0,01				
B*07:05		0					0,022				
B*08:01:01		0					0,003				
B*13:0		0,014					0,015				
B*13:02:01		0					0,012				
B*15:01:01:01		0					0,003				
B*15:02		0,167					0,107				
B*15:10		0					0,003				
B*15:12		0,014					0,012				
B*15:13		0,125					0,11				
B*15:17:01:01		0,014					0,008				
B*15:21		0,111					0,062				
B*15:25		0					0,02				
B*15:32		0					0,01				
B*18:01:01		0,028					0,07				
B*18:02		0,014					0,017				
B*27:06		0,042					0,027				

(Continued)

Table 4. (Continued).

Allele	Indonesia Java	Indonesia Java Pop 2	Indonesia Java Yogyakarta Region	Indonesian Moluccans	Indonesian Nusa Tenggara Island	Indonesia Singaporean	Indonesia Sundanese and Javanese	Disease Correlated Allele (Global-Allele frequency.net)	Disease Correlated Allele (Indonesia)	Frequencies of Disease Correlated Allele (Indonesia)	Reference for Indonesia frequencies
B*35:01:01		0,014					0,003				
B*35:02:01		0					0,003				
B*35:05		0,056					0,09				
B*35:30		0					0,003				
B*37:01:01		0					0,003				
B*38:02:01		0,042					0,06				
B*39:15		0,014					0				
B*40:01:01		0,042					0,035				
B*40:02:01		0					0,003				
B*40:06:01:01		0,028					0,005				
B*41:01		0					0,003				
B*44:03:01		0,014					0,025				
B*44:03:02		0,042					0,07				
B*48:01		0					0,003				
B*51:01		0,028					0,032				
B*51:02:01		0,042					0,035				
B*52:01:01		0,014					0,01				
B*56:01		0					0,005	Behçet's disease			
B*56:02		0,014					0,008				
B*56:07		0					0,003	N/A			
B*57:01:01		0,028					0,01				
B*58:0		0,042					0,06				
DPB1*01:01	0,017			0,337	0,029						
DPB1*02:01	0,026			0,076	0,029						
DPB1*02-02	0,078			0	0						
DPB1*03:01	0,052			0,033	0,041						
DPB1*04:01	0,207			0,087	0,111						
DPB1*04:02	0,043			0,033	0,076			Gelatin Allergy			

Allele	Freq 1	Freq 2	Freq 3	Disease association	Disease association	Notes	Reference
DPB1*05:01	0,138	0,217	0,436	N/A			
DPB1*06:01	0,009	0	0				
DPB1*09:01	0,216	0	0,215				
DPB1*13:01	0,017	0,065	0,041				
DPB1*14:01	0,009	0,022	0				
DPB1*15:01		0	0				
DPB1*16:01	0,009	0	0				
DPB1*17:01	0,009	0	0				
DPB1*19:01		0	0				
DPB1*20:01		0	0				
DPB1*21:01		0,022	0,023				
DPB1*23:01		0	0				
DPB1*24:01		0	0				
DPB1*26:01	0,009		0				
DPB1*26:01:02		0					
DPB1*27:01	0,121	0,011					
DPB1*28:01		0,011					
DPB1*29:01		0,087					
DPB1*31:01	0,026	0					
DPB1*32:01		0					
DPB1*33:01		0					
DPB1*39:01							
DQA1*01:01			0,188				
DQA1*01:02			0,13				
DQA1*01:03			0,026	Graves' disease & Systemic lupus erythematosus	Systemic lupus erythematosus	N/A	(Kementerian Kesehatan Republik Indonesia 2017)
DQA1*02:01			0,11				
DQA1*03:01			0,046				
DQA1*04:01			0				
DQA1*05:01			0,02				
DQA1*06:01			0,481	Systemic lupus erythematosus	Systemic lupus erythematosus	N/A	(Kementerian Kesehatan Republik Indonesia 2017)
DQB1*02:01	0,029	0,076	0,091	HIV	HIV	41% HIV prevalence among people who inject drugs (PWID), 10% among direct female sex workers (FSW) and 8% among men who have sex with men (MSM)	(Rahmalia et al. 2015)

(Continued)

Table 4. (Continued).

Allele	Indonesia Java	Indonesia Java Pop 2	Indonesia Java Yogyakarta Region	Indonesian Moluccans	Indonesian Nusa Tenggara Island	Indonesia Singaporean	Indonesia Sundanese and Javanese	Disease Correlated Allele (Global-Allele frequency.net)	Disease Correlated Allele (Indonesia)	Frequencies of Disease Correlated Allele (Indonesia)	Reference for Indonesia frequencies
*DQB1*03:01*			0,494	0,174	0,174			Rheumatoid Arthritis	HIV	41% HIV prevalence among people who inject drugs (PWID), 10% among direct female sex workers (FSW) and 8% among men who have sex with men (MSM) / N/A	(Rahmalia et al. 2015)
*DQB1*03:02*			0,013	0,011	0,023						
*DQB1*03:03*			0,052	0	0,012			Gelatin Allergy	Gelatin allergy	N/A	
*DQB1*04*										N/A	
*DQB1*04:01*			0,007	0,022	0,023						(Kementerian Kesehatan Republik Indonesia 2017)
*DQB1*04:02*			0					Systemic lupus erythematosus	Gelatin allergy & Systemic lupus erythematosus	N/A	
*DQB1*05:01*			0,169	0,098	0,221						
*DQB1*05:02*			0,085	0,413	0,25			Graves' disease	Graves' disease	N/A	(Purnamasari et al. 2013)
*DQB1*05:03*			0,007	0,044	0,058			Mycobacterial disease (tuberculosis and leprosy)	Mycobacterial disease (tuberculosis and leprosy)	360.565 cases in 2016	(World Health Organization Indonesia TB Situation Update 2017 2017)
*DQB1*06:01*			0,065	0,12	0,192						
*DQB1*06:02*			0,007	0,044	0,017			HIV & Systemic lupus erythematosus		N/A	
*DQB1*06:03*			0,007	0	0			HIV	HIV	41% HIV prevalence among people who inject drugs (PWID), 10% among direct female sex workers (FSW) and 8% among men who have sex with men (MSM) / N/A	(Rahmalia et al. 2015)
*DQB1*06:04*								N/A			
*DQB1*06:05*			0,007	0	0						
*DRB1*01:01*	0,009		0,007	0	0	0,02					
*DRB1*01:01:01*		0,014		0	0	0	0,012				
*DRB1*01:03*			0	0	0						
*DRB1*03:01*	0,017		0,017	0	0			HIV			
*DRB1*03:01:01*		0,042			0,024	0,03	0,035				
*DRB1*03:02*			0								

Allele								Disease association		Prevalence	Reference
DRB1*04:01	0		0	0	0	0	0,007	Rheumatoid Arthritis & Juvenile chronic arthritis	Rheumatoid Arthritis, T1D & Juvenile chronic arthritis	For RA: Rural Population 0.2 per 4683 and Urban Population 0.3 per 1071; for T1D: 0.6 per 176.689.336	(Darmawan et al. 1993; Kementerian Kesehatan Republik Indonesia 2014; Juvenile idiopathic arthritis – ETD UGM 2016)
DRB1*04:02	0,008					0,03	0,012	Rheumatoid Arthritis	Rheumatoid Arthritis		(Darmawan et al. 1993)
DRB1*04:03			0	0	0,018	0,03					
DRB1*04:03:01	0		0	0	0	0					
DRB1*04:04			0,007	0	0	0					
DRB1*04:05	0,026		0,007	0,025	0,018	0,03					
DRB1*04:05:01		0,014					0,017				
DRB1*04:06	0,017		0,007	0	0	0					
DRB1*04:06:01							0,005			N/A	
DRB1*04:07				0	0	0					
DRB1*04:08			0	0	0	0					
DRB1*04:10			0	0	0	0					
DRB1*04:11			0,012	0	0	0					
DRB1*07			0,11					Systemic lupus erythematosus	HIV	41% HIV prevalence among people who inject drugs (PWID), 10% among direct female sex workers (FSW) and 8% among men who have sex with men (MSM)	(Rahmalia et al. 2015)
DRB1*07:01	0,086			0,075	0	0,09	0,137	Juvenile chronic arthritis	Juvenile chronic arthritis	N/A	(Juvenile idiopathic arthritis – ETD UGM 2016)
DRB1*07:01:01		0,097						N/A	N/A	N/A	
DRB1*08:01											
DRB1*08:02			0	0	0	0,01					
DRB1*08:03	0,009		0,013	0,038	0,012	0,03		Mycobacterial disease (tuberculosis and leprosy)	Mycobacterial disease (tuberculosis and leprosy)	360.565 cases in 2016	(World Health Organization, Indonesia TB Situation Update 2017 2017)
DRB1*08:03:02		0,028					0,003	N/A		N/A	
DRB1*08:10	0							N/A			
DRB1*09:01:02	0,017	0	0,026	0	0,012	0,02	0,025	N/A	Rheumatoid Arthritis	Rural Population 0.2 per 4683 and Urban Population 0.3 per 1071	(Darmawan et al. 1993)

(Continued)

Table 4. (Continued).

Allele	Indonesia Java	Indonesia Java Pop 2	Indonesia Java Yogyakarta Region	Indonesian Moluccans	Indonesian Nusa Tenggara Island	Indonesia Singaporean	Indonesia Sundanese and Javanese	Disease Correlated Allele (Global-Allele frequency.net)	Disease Correlated Allele (Indonesia)	Frequencies of Disease Correlated Allele (Indonesia)	Reference for Indonesia frequencies
DRB1*10:01	0,017	0,042	0,026	0	0	0,03	0,01	Rheumatoid Arthritis		N/A	
DRB1*10:01:01		0,042						N/A			
DRB1*11:01	0,026		0,007	0,075	0,089	0,02	0,017				
DRB1*11:01:01			0								
DRB1*11:02			0								
DRB1*11:04			0,007	0	0,006	0,01					
DRB1*12:01			0,007	0,038	0,03	0,02					
DRB1*12:02	0,534	0,431	0,507	0,125	0,154	0,26	0,368				
DRB1*13	0,017										
DRB1*13:01			0,007	0	0,006	0,02					
DRB1*13:02		0,014	0,007	0	0	0,01	0,012	Mycobacterial disease (tuberculosis and leprosy)	Mycobacterial disease (tuberculosis and leprosy)	360.565 cases in 2016	(World Health Organization, Indonesia TB Situation Update 2017 2017)
DRB1*14:01	0		0,007	0	0,018	0,03		Insulin-dependent diabetes mellitus (T1D)			
DRB1*14:01:01		0,014					0,003	N/A		N/A	
DRB1*14:02				0	0	0					
DRB1*14:04	0,034	0,014	0	0,013	0,03	0,02	0,017				

No allele typing was performed for the populations in related research
*N/A: Not Available

disease correlation research so there is a lot questions in this topic that needs to be answered in the future.

Declaration of Interest

The authors declare that there is no conflict of interest.

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