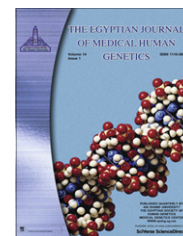




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REVIEW

Non-HLA gene polymorphisms and their implications on dengue virus infection

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Abstract Exposure to the dengue virus (DENV) evokes a variety of genetically-controlled immunological responses. Genetic variants involved in viral entry, replication and innate immunity pathways play an important role in the causal pathway of dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS). Here we have reviewed implications of some genetic polymorphisms of the pathways related to DENV infection susceptibility, protection and severity. Large case-control studies examining a variety of single-nucleotide polymorphisms (SNPs) in a variety of genes have been performed in DENV patients in some countries. SNP gene candidates that have shown associations with DENV infection are mannose-binding lectin (MBL), interleukin (IL)-4, IL-6, IL-10, interleukin-1 receptor antagonist (IL-1RA), toll-like receptor 4 (TLR4), cytotoxic T-lymphocyte antigen 4 (CTLA-4), tumor necrosis factor (TNF)- α , transforming growth factor (TGF)- β 1, Fc γ receptor II (Fc γ RII), vitamin D receptor (VDR), interferon (IFN)- γ , human platelet antigens (HPA), transporters associated with antigen processing (TAP), dendritic cell-specific ICAM3-grabbing non-integrin (DC-SIGN) and Janus kinase 1 (JAK1), although some of these genes failed to show statistical significance. Briefly, polymorphism in TNF- α , Fc γ RII, CTLA-4, TGF- β 1, HPA, DC-SIGN, TAP and JAK1 genes has been associated with DHF/DSS development. Polymorphism in MBL2 gene was shown to be associated with thrombocytopenia and increased risk of DHF development. In

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contrary, polymorphism in VDR gene shows moderate associations with resistance to the most severe form of DHF. However, neutral associations have been reported for IL-4 promoters, IL-1RA, IFN- γ , IL-6, TLR4 and IL-10 gene polymorphism. In conclusion, there are strong evidences from several epidemiological studies indicating host genetic factors as important components in DENV infection susceptibility, protection and severity.

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1. Introduction

Dengue virus (DENV) is a mosquito-borne flavivirus infection of major international public health threat. DENV cause a spectrum of disease in humans, ranging from dengue fever (DF) to a severe, life-threatening syndrome called dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS). It is estimated that 50 million dengue infections occur annually worldwide [1] and it has increased dramatically in recent years [2]. Approximately 2.5 billion people live in dengue endemic countries [1] and two fifths of the world's population are at risk from DENV [3].

Clinical outcome following secondary DENV infection appears to be related to the extent to which viral spread is limited by innate immunity, DENV-specific antibody and DENV specific T cells [4]. Perturbations in immune responses, augmented virus uptake, and delayed virus clearance may result in increased pathogenicity of dengue infections [5]. Vast majority of DENV infections result in no symptoms or a mild febrile illness, less than 2% of individuals infected with DENV develop DHF, strongly suggesting the important role of host genetic factors [5]. Halstead et al. [6] found that although multiple DENV serotypes circulate in West Africa, there have been no reports of DHF. They also found an absence of DHF/DSS in the Haitian population despite hyperendemic transmission of DENV serotypes. Furthermore, blacks were less likely

to be hospitalized during Cuban DENV epidemics [5]. Although pre-existing immunity may be a confounding factor, these reports argue strongly that genetic predisposition is an important factor as well.

Polymorphisms in cytokine regulatory gene regions have been described, some of these polymorphisms seem to correlate with its production, potentially conferring the flexibility to immune response. The presence of certain genotypes influences the course of both viral and bacterial infections [7]. Variations in immune response as a consequence of polymorphisms in regulatory regions of cytokine genes and other genes may have influence on the DENV infection susceptibility and outcome [8]. In addition, genetic variants involved in viral entry and replication may play an important role in the causal pathway of DHF [9]. Here we have reviewed the implications of some non-human leukocyte antigen (HLA) gene polymorphisms to susceptibility, protection and severity of DENV infection based on publication from some of the countries.

2. Discussion

2.1. Mannose-binding lectin (MBL)

A majority of studies examining complement-DENV interactions have focused on the role of complement in the context of DHF/DSS pathogenesis [10]. In a prospective study, nonstruc-

tural protein 1 (NS1) of DENV could activate complement [11]. Moreover, levels of NS1 and several complement proteins were correlated with dengue severity [11]. MBL, a member of the collectin family, mediates carbohydrate dependent activation of the classical complement pathway and play an important role in pattern recognition and innate immune defense [12,13]. MBL deficiency has been associated with increased susceptibility to many infectious diseases, including viral infections [14]. In a prospective study, the levels of the MBL protein were found to be higher in DHF patients than in DF individuals [15]. However a recent study by Avirutnan et al. [16] examined the role of the complement system in protection against DENV infection, and the results provide support for an important role of the complement system in controlling DENV infection and potentially influencing the severity of dengue disease in humans. Avirutnan et al. [16] also demonstrated that the MBL pathway was critical for neutralization of both insect and mammalian cell-derived DENV serotype 2 (DENV2). Shrestha et al. [10] study found a positive correlation between MBL concentration in human serum and the level of DENV2 neutralizing activity, indicated a depressed level of MBL protein or its activity as it is an independent risk factor for DENV infection's morbidity and mortality.

Several mutations in the MBL gene have been associated with a marked reduction in serum MBL levels and MBL-mediated complement activation [17]. A study that performed in Vietnam by Loke et al. [12] found that there were no significant differences in MBL genotypes or allele frequencies between DHF patients and controls. This study showed that individuals with low serum MBL concentrations due to a variant MBL allele do not impact the risk of DHF/DSS.

Mutation in the promoter region of MBL2 resulting in low serum levels of MBL has been reported [18]. According to a study in Brazil, a combination of SNP markers associated with the low producer phenotype of MBL (low levels of MBL), significantly associates with DF but not DHF and it protects against the development of thrombocytopenia associated with severe dengue phenotype [19]. However, high MBL levels appear to be correlated with severe disease [15]. Experiments by Avirutnan et al. [16] with sera obtained from individuals with different levels of MBL2 due to known polymorphisms in the MBL2 gene corroborated the positive correlation between human MBL2 levels and neutralization of DENV2. This result linked together to subsequent findings related to humans with particular polymorphisms in the MBL2 gene suggested that the MBL pathway contributes to protection against DENV infection in humans [10].

2.2. Toll-like receptor 4 (TLR4)

TLR4 is a key receptor for the lipopolysaccharide (LPS) components of Gram-negative bacteria and for structures of mycobacteria, fungi, and malarial parasites [20]. Two common non-synonymous polymorphisms in the human TLR4 gene (referred to as Asp299Gly and Thr399Ile based on the amino acid permutations they encode) potentially impact function of the receptor [21] and expression of these mutants *in vitro* shows reduced activation in response to LPS [22]. Some studies concerning TLR4 polymorphisms and their association with many infectious diseases, including sepsis, Gram-negative infections, tuberculosis, malaria and respiratory syncytial virus have been reported [23]. Recently, Lavoie et al. [24] found that TLR4

polymorphisms influence bronchopulmonary dysplasia severity in some populations of high-risk preterm infants.

In Central Java, Indonesia, Djamiatun et al. [25] investigated the influence of TLR4 polymorphisms Asp299Gly and Thr399Ile for susceptibility and severity of DENV infection. They investigated 201 Javanese children with DHF and 179 healthy controls. The TLR4 299/399 genotype was found in five patients and four controls. Prevalence of this genotype did not differ significantly between controls and DHF patients or between patients with different severities of DHF. Djamiatun group also found that vascular leakage in patients with different TLR4 genotypes did not differ. Thus, the 299/399 TLR4 haplotype has only a minor influence on the susceptibility and severity of complicated DENV infection.

2.3. Fcγ receptor II (FcγRII)

FcγRII is a widely distributed receptor for all subclasses of IgG and it is able to mediate antibody dependent enhancement (ADE) *in vitro* by binding to virus-IgG complexes [26]. Charconsirisuthigul et al. [27] demonstrated that DENV infection of human acute monocytic leukemia 1 (THP-1) cells via FcR suppressed the transcription and production of IL-12, IFN-γ, TNF-α, and nitric oxide but enhanced the expression of anti-inflammatory cytokines IL-6 and IL-10. This indicates that FcR receptor is important in DENV infection pathogenesis by mediating ADE [13]. A polymorphism at 131 position of the FcγRIIA gene, an arginine to histidine substitution, changes the IgG binding affinity of the receptor, with reduced opsonization of IgG2 antibodies causally associated with the arginine variant [28]. There is evidence that homozygotes for the arginine variant are more susceptible than homozygotes for the histidine variant to infections with encapsulated bacteria [29]. Loke et al. [12] performed a study in Vietnam to investigate that homozygosity for the arginine variant might be associated with a reduced risk of DHF caused by ADE. They found that neither genotype nor allele frequencies for the FcγRII polymorphism were significantly different between DHF patients and controls. However, homozygote for arginine variant showed moderate associations with resistance to the most severe form of DHF.

2.4. Vitamin D receptor (VDR)

VDR mediates the immunoregulatory effects of 1,25-dihydroxyvitamin D3 (1,25D3), which activates monocytes, stimulating cellular immune responses and suppressing immunoglobulin production and lymphocyte proliferation [30]. The tt genotype of a SNP at position 352 of the VDR gene has been associated with tuberculoid leprosy, enhanced clearance of hepatitis B virus (HBV) infection and resistance to pulmonary tuberculosis [17]. Recent studies suggested a protection association between this SNP with infectious diseases including tuberculosis [31], *Leishmania major* [32], Human Immunodeficiency Virus (HIV) [33] and *Staphylococcus aureus* infection [34]. These associations led to the suggestion that the tt genotype may be associated with a relatively stronger TH1-type cellular immune response than the TT genotype; interestingly, 1,25D3 has been found to alter IL-12 expression and dendritic cell (DC) maturation [35].

Study by Loke et al. [12] in Vietnam found that genotype frequencies for VDR polymorphism did not differ between

DHF cases and controls, but allele frequency analysis showed that there was an association between VDR polymorphism and DHF disease severity. This result suggests that the t allele may be protective against severe DHF. Expression of VDR may affect the susceptibility to DHF since it activates B and T lymphocytes and affects monocytes, the main sites of DENV infection [17]. However, further work will be required both to confirm this association and to explore possible mechanisms.

2.5. Cytotoxic T-lymphocyte antigen 4 (CTLA-4)

The pathogenesis of DHF has been considered to be massive immune activation of T cells. Abnormal expression of the immune regulatory molecules, CTLA-4 and TGF- β 1, leads to disturbances of regulatory T cell immune response [36]. The CTLA-4 together with cluster differentiation (CD)-28, a co-stimulatory molecule, plays a significant role in the T-cell mediated immune response, which is initiated when the antigen-specific T-cell surface receptor encounters an antigen presented by the antigen presenting cell (APC) complexes with major histocompatibility complex (MHC) class II molecule [37].

The CTLA-4 gene located on chromosome 2q33 includes a SNP in exon 1, where there is an adenine (A) for guanine (G) substitution at position 49 resulting in a threonine for alanine substitution in the expressed protein [38]. It has been reported that the CTLA-4 +49 A allele yields a variant that interacts more with B7.1 (CD28 ligand) and endows Tregs (regulatory T cell) with greater suppressive activity [37,39]. Similarly, T cells from patients with this allele displayed a diminished proliferative response which was more susceptible to intervention by CTLA-4 blockade [40].

Polymorphism of CTLA-4 gene has been associated with an increased risk of autoimmune and infectious diseases [41]. This gene polymorphism has been associated with parasitic infections [41], Human Papilloma Virus (HPV) infection [42], invasive bacterial infections [43], autoimmune hepatitis and primary biliary cirrhosis [44], and clearance of HBV [45]. Recently, Duan et al. [46] confirmed that CTLA-4 +49 A/G polymorphism confer susceptibility to chronic HBV infection in Chinese Han patients. A study in Taiwan by Chen et al. [36] found that the presence of the CTLA-4 +49 G allele and TGF- β 1 -509 CC genotype increased the susceptibility to risk of DHF and significantly higher virus load.

2.6. Dendritic cell-specific ICAM3-grabbing non-integrin (DC-SIGN)

Dendritic cells (DCs) are major *in vivo* targets of DENV, DC interact with glycan moieties on the DENV E protein and mediate the entry of all four serotypes, and thus it can confer DENV susceptibility to normally nonpermissive cells [47]. DC-SIGN, a C-type lectin, is expressed on subsets of DCs [48] and is encoded by CD209 gene located on chromosome 19p13.3 [49]. DC-SIGN plays an important role in the early interaction of a pathogen with a DC and has a key role in DC-T cell interaction, DC migration, and pathogen uptake [50]. DC-SIGN is known to be the major DENV receptor on human DCs and induces endocytosis of several pathogens, including DENV [50,51].

Numerous SNPs in DC-SIGN gene have been reported, one of these SNPs represents a guanine (G) to adenine (A) transition at position -336 within the DC-SIGN promoter

(DC-SIGN -336 A/G) [50]. This variant affects DC-SIGN promoter activity with multiple transcription factor binding sites for transcription factors [52]. This variant has been associated with an increased risk for parenteral acquisition of HIV infection [53], increased susceptibility for tuberculosis [48], human T-cell lymphotropic virus type 1 [54] and Kawasaki disease [55].

The effect of DC-SIGN -336 A/G was assessed in a Thai study conducted by Sakuntabhai et al. [52]. The G allele (GG or GA) was found to be infrequent in individuals with DF compared with controls and no protective effect was seen in DHF. However, the G allele was strongly associated with risk of DHF. Recently, a strong association between GG/AG genotypes of DC-SIGN and risk of DHF was found when compared with DF, other non-dengue febrile illnesses (OFI) and controls [50]. The AA genotype was associated with protection against DENV infection compared with OFI and controls. Moreover, Wang et al. [50] also generated monocyte derived dendritic cells (MDDCs) from individuals with AA or AG genotype of DC-SIGN to study the viral replication and immune responses for functional validation. They found that MDDCs from individuals with AG genotype with a higher cell surface DC-SIGN expression had a significantly higher TNF- α , IL-12p40, and interferon-inducible protein-10 (IP-10) production than those with AA genotype in response to DENV infection. However, the viral replication in MDDCs with AG genotype was significantly lower than those with AA genotype. This study confirmed that DC-SIGN -336 A/G contributes to susceptibility to DENV infection and complication of DHF and this SNP with AG genotype affects the cell surface DC-SIGN expression related to immune augmentation and less viral replication.

2.7. Transporters associated with antigen processing (TAP)

TAP, a member of the ATP binding cassette (ABC) transporter family, plays a crucial role in the processing and presentation of the MHC class I restricted antigens [56]. MHC class I molecules present intracellular peptides to cytotoxic T cells [57]. The antigen peptides are generated in the cytosol and TAP translocates antigenic peptides from cytoplasm into the endoplasmic reticulum (ER) for binding the MHC class I molecules for presentation to CD8⁺ cytotoxic T cells [57,58]. The translocation of cytosolic peptides into ER lumen is a crucial step in the presentation of intracellular antigen to T cells by MHC class I molecules [57].

TAP consists of two homologous subunits, TAP1 and TAP2 [57]. The genes for TAP are located within the MHC class II region of chromosome 6 [58]. The polymorphisms located at these gene coding regions affect the specificity of peptide presentation and transport process which furthermore alter the immune response regulation [58,59]. Several polymorphisms that have been reported in TAP gene, several dimorphic sites are TAP1³³³ (A → G, Ile → Val), TAP1⁶³⁷ (A → G, Asp → Gly), TAP2³⁷⁹ (G → A, Val → Ile), TAP2⁵⁶⁵ (G → A, Ala → Thr) and TAP2⁶⁶⁵ (A → G, Thr → Ala) [60]. Polymorphisms in TAP gene have been associated with systemic lupus erythematosus [61], rheumatoid arthritis [62], allergic rhinitis [60], hypersensitivity pneumonitis [63] and TB [58].

The first study on TAP gene polymorphism and DENV infection was conducted by Soundravally & Hoti [64] in India. They found that the frequencies of Val at TAP1³³³ were in-

creased significantly among DHF in comparison to controls. The frequency of genotype TAP1³³³ Ile/Val was significantly higher in DHF compared with control or DF patients. This research confirmed that heterozygous pattern at the TAP1³³³ locus genotypes confers susceptibility to DHF. The risk of DHF was increased 2.58 times with the TAP1³³³ Ile/Val genotype. In the other publication in 2008, Soundravally & Hoti found that homozygous patterns for Ile at TAP1³³³, Asp at TAP1⁶³⁷ and Val at TAP2³⁷⁹ were found to be a protective factor against DHF and DSS development among the primary-infected individuals, respectively [65]. From this study, it is possible to state that homozygous patterns at TAP1^{333,637} and TAP2³⁷⁹ probably lead to selection of immunodominant epitopes that bring protective immunity against primary DHF.

2.8. Janus kinase 1 (*JAK1*)

JAK/signal transducers and activators of transcription (JAK/STAT) cascade is essential for cytokines, growth factors, G-proteins and hormones and the STA of JAK/STAT pathway controls the signal transduction between cell surface receptors and the nucleus [66,67]. JAK1 is essential for signaling for certain type I and type II cytokines [68]. It interacts with the common gamma chain (γ) of type I cytokine receptors, to elicit signals from IL-2, IL-4 and gp130 receptor family [68]. JAK1 is also important for transducing a signal by type I (IFN- α/β) and type II (IFN- γ) interferons, and members of the IL-10 family via type II cytokine receptors [68].

The JAK family consists of four members, JAK1, JAK2, JAK3 and TYK2 [67]. JAK-1 gene, which is located on chromosome 1p31.1, has a highly polymorphic flanking region [67]. JAK family gene polymorphism is associated with erythrocytosis [69], leukemias [69,70], polycythemia vera [71], Crohn's disease [66], gigantism [69] and cardiovascular diseases [72]. A recent study found JAK-1 polymorphisms are associated with higher susceptibility to asthma [67].

Silva et al. [73] genotyped about 593 SNPs in 56 genes across the type 1 interferon (IFN) response pathway as well as other important candidate genes. By single locus analysis comparing DHF with DF, 11 of the 51 markers with $p < 0.05$ were in the JAK1 gene. This association remained significant after controlling for ancestry and income. An association between DHF and JAK1 polymorphisms is in agreement with expression profiles showing generalized decreased type 1 IFN-stimulated gene expression in these patients. These arguments support with animal studies. Mouse studies have shown that some components of the type 1 IFN response pathway can control the response to all flaviviruses [74]. In addition, flaviviruses have developed specific strategies to neutralize signaling downstream of the receptor to circumvent this response [75]. Supportive evidence is also provided by a global analysis of expression profiles in individuals with DSS compared with DF, which indicated that multiple IFN- α -regulated genes were under-expressed [76]. This study provides evidence that polymorphisms in the JAK1 gene, including this one, may provide differential susceptibility to DENV infection.

2.9. Interleukin-4 (*IL-4*)

Several studies have shown that concentrations of multiple cytokines, soluble receptors and other mediators are significantly increased during severe dengue infections [77]. DSS is

associated with marked changes in vascular permeability potentially due to inflammatory mediators and complement activation [13]. DENV-infected DC induces the interacting T cells to proliferate and produce some of cytokines such as IL-4 [78]. The key cytokines that have been associated with DHF include the shift from Th1-type response in DF to the Th2- type cytokine response in DHF, with increased levels of IL-10 and IL-4 [79]. IL-4 is primarily produced by Th2 subset of CD4⁺ T cells [12]. It regulates B cell growth and IgG class switching, as well as suppresses Th1-type responses [12].

An SNP identified within the IL-4 promoter has been reportedly associated with increased levels of gene transcription [80]. Interestingly Loke et al. [12] found no differences between cases and controls for the IL-4 promoter polymorphism, neither at the genotypic level nor at the allelic level. However, higher plasma levels of IL-4 have been found in patients with severe DENV infections [13].

2.10. Interleukin-1 receptor antagonist (*IL-1RA*)

The IL-1 family consists of IL-1 alpha (IL-1 α), IL-1 beta (IL-1 β), and IL-1ra [81]. IL-1 α and IL-1 β that bind to IL-1 receptor (IL-1R) and initiate an inflammation cascade to induce vascular dilation and fever [82]. IL-1ra is involved in the regulation of IL-1-mediated inflammatory responses by competitive binding to IL-1R [17]. The polymorphic region within intron 2 of the IL-1RN* gene that contains variable numbers of tandem repeats (VNTR) of 86 bp, five alleles of the IL-1RN* have been reported (*1-*5), corresponding to 2, 3, 4, 5 and 6 copies of the 86-bp sequence respectively [7]. A two-repeat allele (IL-1RA2) of an 86-base pair VNTR in the IL-1RA gene is associated with increased serum levels of IL-1ra [7]. Thus, persons homozygous for allele 2 of the IL-1RA gene (IL1RN*2) have a more prolonged and more severe proinflammatory immune response than persons with other IL-1RA genotypes [82]. Some studies have shown that there are negative associations between IL1RN*2 homozygosity and vaginal colonization with mycoplasmas, infection with human cytomegalovirus and Epstein-Barr virus, and HIV proliferation [82]. Recently, Hsu et al. [81] found that IL-1RA polymorphism was associated with the risk of multidrug-resistant *Acinetobacter baumannii*-related pneumonia. However, based on a study in Dong Nai pediatric Centre Vietnam found no difference neither in genotype nor in allele frequencies of the IL-1RA repeat polymorphisms between DHF cases and controls [12].

2.11. Interleukin 6 (*IL-6*)

IL-6, a pleiotropic cytokine, is a major mediator of fever and acute-phase reactions and is produced during innate and adaptive immune response by T and B lymphocytes, macrophages, monocytes, fibroblasts and activated endothelium cell (EC), besides some tumoral cells [13,83]. A study confirmed that IL-6 mediates derangement of coagulation and fibrinolysis [84]. Briefly, IL-6 is likely to be associated with dengue diseases by taking several roles: (a) IL-6 together with other proinflammatory cytokines potentiates the coagulation cascade; (b) IL-6 downregulates the production of TNF- α and TNF receptors; (c) IL-6, together with IL-1, is a potent fever inducer [13].

High concentrations of IL-6 have been implicated in capillary leakage and development of hypovolemic shock in patients with anaphylaxis and meningococcal sepsis [85]. In an

animal model study IL-6 levels have been shown to be high in sera of DENV infected mice [86]. In human, higher levels of IL-6 are measured in the plasma in patients with severe DENV infections [87,88].

A biallelic polymorphism within the human IL-6 gene promoter region (−174 G/C) has been shown to affect IL-6 transcription *in vitro* and IL-6 plasma levels [7]. SNP IL-6 −174G > C has been related to various infectious diseases [89]. Moreira et al. [90] found that patients who expressed IL-6 −174 GG (high production of IL-6) promote protection against DF clinical symptoms development. This association is based on two biological activities of IL-6. First, IL-6 has an action in viral eradication by stimulating a TH1 immune response, and second IL-6 promotes the decrease of consequential symptoms to infection, since it inhibits the acute phase of the inflammatory response through induction of pro-inflammatory cytokine antagonists as IL-1ra and soluble TNF receptor (sTNFR) p55 [90].

A research in Brazil conducted by Moreira et al. [90] found that there was a negative association between IL-6 −174 GC genotype and DF. However, a significant statistical difference with cytokine production phenotypes or alleles was not observed. Moreira et al. [90] argued that the SNP IL-6 −174 G > C is part of a haplotype of SNPs, genetically and functionally linked, including the positions −634 G > C, −597 G > A, −572 G > C and −373AnTn. Thus, a specific polymorphism of this haplotype may exert influence on IL-6 transcription, but each SNP would not act independently from others.

2.12. Interleukin-10

IL-10 is a major anti-inflammatory cytokine that has been associated with several diseases being considered an important immunoregulatory mediator produced by monocytes, DCs, and T and B lymphocytes [91]. IL-10 has been involved in the thrombocytopenia and hemorrhagic manifestations observed during DENV infection [92]. In addition, plasma levels of IL-10 correlated with platelet decay in DENV-infected patients [93] and may modulate the activation of coagulation [13]. Moreover, IL-10 downregulates the inflammatory response and creates a proviral survival milieu. Then it inhibits the expression of tissue factor (TF) and furthermore inhibits fibrinolysis [13]. Also IL-10 levels have been found to be high in the sera of DENV infected mice [84] and in patients with severe DENV infections [94].

IL-10 gene SNPs (−1082 A/G, −819 C/T and −592 A/C) in a group of individuals with the antecedent of DHF during a secondary infection were studied in Cuba [95]. However, there were no statistically significant differences in the frequencies of IL-10 allele and genotypes between DHF and control groups. However, the haplotype (IL-10 −1082/−819/−592) ACC/ATA carriage was more frequent in DHF than in controls (OR = 2.54, 95% CI = 1.12 – 5.73, $p = 0.02$). Perez et al. [95] also found that individuals with the TNF- α or IFN- γ high genetic variants and IL-10 or TGF- β 1 low genetic variants were more frequently distributed in DHF group compared with the controls. In addition, associations between the TGF- β 1 low producer genotypes (codon 25 CC and CG) and IL-10 low producer haplotype (ACC/ATA) with DHF were found. In the same study, the association between the TNF- α high/IL-10 low genotype and DHF was also reported.

This study suggests that IL-10 low producer haplotype was associated with DHF.

2.13. Tumor necrosis factor-alpha (TNF- α)

TNF- α , an important proinflammatory cytokine, plays a role in the regulation of cell differentiation, proliferation and death, as well as in inflammation, innate and adaptive immune responses, and also implicated in a wide variety of human diseases [96]. Several SNPs found in the regulatory region influence transcription of TNF- α gene and circulating level of TNF- α [7] and thus increases the susceptibility to human diseases including viral diseases [96]. Dewi et al. [97] performed experiments showing that TNF- α is capable of increasing endothelium cell (EC) permeability *in vitro*, which suggests its possible role in pathogenesis of DHF. In a mouse model of DENV-induced hemorrhage, high levels of TNF- α in some tissues correlated with EC apoptosis and hemorrhage [98]. TNF- α level has been shown to be high in sera of DENV infected mice [86].

Briefly, TNF- α is associated with development of DHF/DSS by many pathways: (a) TNF- α is a potent activator of EC and enhances capillary permeability; (b) TNF- α upregulates expression of TF on monocytes and EC; (c) TNF- α downregulates expression of thrombomodulin on EC; (d) TNF- α has a direct effect on production of IL-6, thus an indirect effect on coagulation and fibrinolysis; (e) mediates activation-induced death of T cells, and it has therefore been implicated in peripheral T-cell deletion [13]. In addition, TNF- α induces EC production of reactive nitrogen and oxygen species and induces apoptotic cell death, thus TNF- α has been involved in the pathogenesis of hemorrhage [99].

In a clinical study, a positive correlation between soluble TNF- α concentrations and thrombocytopenia was found [100]. Another study found that plasma levels of TNF- α is significantly higher in DHF than in DF [101]. Previously Loke et al. [12] found no association between TNF- α −238 G/A and −308 G/A polymorphisms in Vietnamese DHF patients when compared with control subjects from the same population. On the contrary, in a Venezuelan study Fernandez-Mestre et al. [102] confirmed that the TNF- α −308 variant allele was present in 30% of participants with DHF versus 5% in those with DF (OR = 7.58, 95% CI = 1.23–79.2, $P = 0.02$). Fernandez-Mestre et al. [102] reported a high association of TNF- α −308A allele in DF patients with hemorrhagic manifestations, suggesting it as a possible risk factor for bleedings among DF patients. In a study conducted in Thailand, the TNF- α −238 A polymorphism combined with lymphotoxin-alpha (LTA)-3 haplotype were correlated significantly with DHF compared with DF [103]. More recently, a study by Perez et al. [95] in Cuba confirmed that the allele distribution of TNF- α promoter polymorphism revealed the association of allele A (high production of TNF- α) to DHF significantly. A higher frequency of carriers of genotype −308 GG (low production of TNF- α) was observed in controls, whereas the DHF group showed a major distribution of AA and AG genotypes (high production of TNF- α). However, the association between genotype AA and DHF was not significant. An association of AG genotype to DHF and GG genotype to controls was observed.

2.14. Transforming growth factor-beta 1 (TGF- β 1)

The pathogenesis of DHF has been considered to be massive immune activation of T cells. Abnormal expression of the immune regulatory molecule such as TGF- β 1 leads to disturbances of regulatory T cell immune response [36]. There are some pathways in which TGF- β 1 is associated with development of DHF/DSS. TGF- β 1 may act as a proinflammatory or anti-inflammatory cytokine, depending on its concentration. Early in DENV infection, low levels of TGF- β 1 may trigger the secretion of IL-1 and TNF- α . However, later in infection, TGF- β 1 inhibits the Th1 response and enhances production of Th2 cytokines such as IL-10 [13]. TGF- β 1 increases expression of TF on EC and upregulates expression and release of plasminogen activator inhibitor 1 (PAI-1) [13]. In several studies, higher plasma levels of TGF- β 1 have been found in patients with severe DENV infections, in particular in patients with DSS [104,105].

A study during an outbreak of DEN2 in Taiwan, investigated the contribution of CTLA-4 and TGF- β 1 in DHF by analyzing them for association with virus load in blood and polymorphisms of CTLA-4 +49 A/G and TGF- β 1 -509 C/T [36]. This study found that the frequency of the TGF- β 1 -509 CC genotype in patients with DHF was significantly higher compared to DF. Moreover, the presence of the CTLA-4 +49 G allele and TGF- β 1 -509 CC genotype increased the susceptibility to risk of DHF and higher virus load significantly. A study by Perez et al. [95] in Cuba was conducted to confirm the association of TGF- β 1 polymorphism (-10 T/C and -25 G/C) to DENV infection. They found no significant neither allele nor genotypes differences in codon 10 in between DHF and control groups. However, a significant difference was found for codon 25 polymorphism being G allele and GG genotype predominant in controls. Perez et al. [95] also found an association between the TGF- β 1 low producer genotypes (-25 CC and CG) and IL-10 low producer haplotype (ACC/ATA) with DHF. This result links a high production of TGF- β 1 with protection or a mild clinical outcome of dengue infection.

2.15. Interferon-gamma (IFN- γ)

IFN- γ , produced by CD3 T and natural killer (NK) cells, characterizes the Th1 pattern and has a wide range of effects, monocyte/macrophage activation being the most important [106]. IFN- γ released from T lymphocytes is activated during DENV infections [17]. T cells interact with DENV-infected cells and produce IFN- γ [107]. IFN- γ with other cytokines which activate macrophages or nearby vascular endothelium, promote leukocyte and plasma extravasations [88,101]. IFN- γ was found to be significantly higher in DHF and DSS patients than in DF patients [88,100,101]. A higher level of IFN- γ has been also associated with dengue severity [93].

Perez et al. [95] conducted a study to confirm the association of SNP IFN- γ -874A/T to DHF in Cuba. They found that allele T and TT genotype (high production IFN- γ) predominated in the DHF group but without significance. Then, they assessed the combined effect of SNP IFN- γ with other cytokine genes' polymorphism. Interestingly, although high production IFN- γ -874T allele did not associate with DHF, the presence of this variant, conjointly with the high production TNF- α -308 A variant in the same individual, was significantly associated with DHF. Besides, IFN- γ -874 T allele in combination with the

low production TGF- β 1 genotype or IL-10 haplotype, also show significant association with DHF. These results suggest that the high IFN- γ production does not define *per se* the dengue illness outcome with regard to severity. This study has shown a similar result with previous study of Sierra et al. [108] in which the peripheral blood mononuclear cells (PBMC) from DEN1-immune individuals exposed to a DEN1/2 *ex vivo* challenge had shown a higher TNF- α and IFN- γ gene expression compared with DEN1 homologous stimulation.

2.16. Human platelet antigens (HPA)

HPA are specific antigens carried by platelet glycoproteins, and 22 kinds of alloantigens have been officially named including 6 known systems, HPA-1 ~ 5 and 15 [109]. Platelet-specific antigens are membrane glycoproteins, which are largely responsible for interaction between platelets and the endothelial wall components [64]. Thrombocytopenia is one of the major pathogenic outcomes in the severe form of dengue disease. Autoimmune destruction, abnormal activation and aggregation of platelets were demonstrated as some of the causes of this condition [64]. DENV-antibody complexes have been detected on platelets from patients with DHF/DSS, suggesting a role of immune-mediated destruction of platelets in thrombocytopenia.

Polymorphisms in the genes encoding these proteins could lead to single-amino-acid substitutions that define a number of allelic variants that are immunologically distinct. Previous study found that the polymorphism in HPA-1 and HPA-2 did not correlate with an increased risk of stroke [110], a recent study confirmed that HPA-1/HPA-2 haplotypes are considered to be a major risk factor for coronary artery disease in middle-aged Tunisians [111]. A study in China indicated no significant difference in HPA-1 genotype distributions between hemorrhagic fever with renal syndrome (HFRS) patients and controls, however a significant difference was found in HPA-3 genotype and allele frequencies [112]. A recent study confirmed that polymorphism in HPA-1 genotype is associated with progression of fibrosis in chronic hepatitis C [113].

A study carried out in India found that the frequencies of HPA-1b at HPA-1 were increased among DSS in comparison to controls [64]. A significantly greater proportion of DHF patients demonstrated HPA-1a/1a and HPA-2a/2b genotypes than DF patients. DSS patients were more likely to be heterozygous at HPA-1 than DHF. This study suggested that HPA-1a/1a and HPA-2a/2b genotypes confer susceptibility to DHF and the HPA-1a/1b genotype was determined to be a genetic risk factor for DSS. This study indicated that structural variants of HPA-1 and HPA-2 appear to associate with the susceptibility to DF and DHF, respectively. HPA-2 plays a role in the interaction of platelet to fibrinogen and von Willebrand factor [114]. HPA-2 is responsible for the aberrant activation of the clotting mechanism and increases vascular permeability. In addition, cross-reacting anti DEN antibodies against HPA-2a antigen might be involved in the pathogenesis of DHF [64]. Autoimmunity against these antigens, mediated by the binding of DEN antibody-virus complex to the HPA glycoproteins, might be one of the reasons for platelet destruction in DEN infection.

3. Conclusion

In summary, we have shown that there are many scientific evidences that have proven the fact indicating host genetic factors as important components in dengue disease. SNP in human genes such as MBL2, TNF- α , Fc γ receptor, CTLA-4, TGF- β 1, HPA, DC-SIGN, TAP, VDR, and JAK1 has been associated with protection, susceptibility and severity of DENV infection. However, SNP in IL-4, IL-1RA, IFN- γ , IL-6, TLR4 and IL-10 gene did not show association with DENV infection. Further analysis of the genetic basis of severe DENV disease in different populations may contribute to the development of new preventative and therapeutic interventions.

4. Disclosure statement

There is no conflict of interest in writing of this manuscript.

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