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Review

Host Genetics, Population Diversity, and Dengue Infection: An Unsolved Paradigm

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Abstract

This narrative review examines recent literature on human genetic variation and the clinical spectrum of dengue. A comprehensive search through different databases (PubMed, Scopus, Web of Science, SciELO, and LILACS) up to September 2026 synthesized findings from genetic association studies, HLA typing, and genome-wide studies. Large patient cohorts mostly come from Southeast Asia, while cohorts from Africa and Latin America are small ($\leq$ 150 patients). World Health Organization guidelines from 1997 and 1999 were the most frequent. Notably, specific HLA alleles—particularly HLA-A*24—along with MICB and PLCE1 gene variants show the strongest associations with severe dengue; however, these associations vary by population and viral serotype. Other immune response genes, including CD209, FCGR2A, and TNF, have also been implicated, although their effects exhibit inconsistency across several cohorts and epidemiological settings. Conversely, certain variants, such as FCγR2A R/R131, appear to be modulated by population context, infecting serotype, and infection history. A major limitation of the existing body of research is the prevalence of small sample sizes, heterogeneity in case definitions across guidelines, and insufficient adjustment for genetic diversity. To date, no genetic marker has been validated for routine global clinical use; nevertheless, large-scale genetic analyses have yielded novel insights that warrant further investigation in large, multi-ethnic studies integrating host and viral genomic data. Genetic analyses are crucial for vaccine efficacy studies and for identifying therapeutic targets to prevent dengue infection and reduce the risk of severe disease.

Keywords: dengue; severe dengue; host genetic susceptibility; immunogenetics; genetic association study; endemic regions; bioinformatic analysis

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1. Introduction

Dengue is a mosquito-borne viral infection endemic to more than 100 countries and occurring in tropical and subtropical regions across all continents [1]. The virus circulates as four serotypes (DENV-1 to DENV-4) [2] and is transmitted primarily by *Aedes aegypti*, with other Aedes species, chiefly *Aedes albopictus*, playing a secondary role [1]. About half of the world's population is at risk, and annual infections range from 100 to 400 million, with a modeled 390 million per year, of which 96 million are clinically apparent [1,3]. Asia bears the greatest burden (about 75%), followed by Latin America and Africa [4]. In 2024

alone, WHO reported more than 14.6 million cases, over 13 million from the Americas, though reported numbers underestimate the true burden [1]. In the Americas, Brazil has the best epidemiological record and, consequently, the most reported cases (>80% of the total), while other countries lack robust epidemiological reporting. As documented in September 2026 by the European Center for Disease Prevention and Control (https://www.ecdc.europa.eu/en/dengue-monthly, accessed on 30 September 2026) and the Pan American Health Organization (PAHO) (https://www.paho.org/sites/default/files/2026/09/2026-cde-dengue-sitrep-americas-epi-week-35-sep.pdf, accessed on 30 September 2026), there has been a decrease in cases in the Americas, while a marked increase has been reported in the Southeast Asia and Western Pacific Regions, and there is limited data from Africa. Climate change, shifting vector distribution, urbanization, and population movement may contribute to its spread [1].

The clinical picture varies widely. Most infections cause no symptoms or a self-limited febrile illness [1,4,5]. Some patients develop dengue with warning signs, such as abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleeding, lethargy, hepatomegaly, or a rapid fall in platelet count accompanied by a rising hematocrit [1,4,5]. A minority progress to severe dengue, defined by severe plasma leakage, severe bleeding, or severe organ involvement [1,4–6]. This three-tier scheme replaced the earlier division into dengue fever, dengue hemorrhagic fever, and dengue shock syndrome, yet many genetic studies still use the older clinical categories, complicating literature analysis [2].

The most robustly established risk factor for severe dengue is secondary infection with a heterologous serotype, which significantly increases the likelihood of severe clinical manifestations [1]. In such cases, heterotypic antibodies elicited by prior infection may enhance viral entry into Fc receptor-bearing cells, a process known as antibody-dependent enhancement [6]. Other determinants include viral serotype, viral load, and viral genotype, as well as host factors such as age and comorbidities, including diabetes mellitus and chronic kidney disease [6–9]. Investigations have also addressed the roles of blood group, ethnicity, and nutritional status in modulating disease risk [10]. However, these variables do not fully account for the divergent clinical trajectories observed among individuals with similar exposure histories. This is underscored by the fact that over 99% of secondary infections remain clinically mild [4,5]. Geographic variation is also apparent: severe manifestations are more prevalent in Southeast Asia, whereas in Latin America the clinical presentation is typically less severe and predominantly affects adults [4,5]. Intra-regional ancestry differences are also relevant, as African genetic ancestry has been associated with protection against severe dengue in Colombian populations [11].

This review examines host genetic susceptibility to dengue, focusing on progression from mild disease to warning signs and severe clinical outcomes. It analyzes current findings on HLA alleles, haplotypes, and polymorphisms in immune-related genes and compares findings across several endemic regions. It also provides a general overview of new approaches and techniques. The review also highlights methodological limitations that constrain the interpretation of existing genetic association studies. Thus, the review is narrative and not analytic.

2. Methods

This narrative review provides a methodologically informed synthesis of human genetic association studies in dengue. Although this review is not a formal systematic review or meta-analysis was performed, a close attention to study heterogeneity and limited sample sizes, which we recognized as significant analytical limitations. Studies were included based on rigorous criteria: well-defined clinical phenotypes and robust genetic methodologies. Given the marked variability in participant characteristics, genetic markers, case definitions,

and analytical methods, the principal objective was to integrate and interpret findings across assorted populations. Unpublished sources were excluded.

A formal systematic review protocol and meta-analysis were not implemented due to significant heterogeneity and the limited sample sizes of available studies, which increased the overall risk of bias. Comprehensive literature searches were performed in major international databases (PubMed, Scopus, Web of Science), Latin American databases (SciELO, LILACS), and local Venezuelan sources up to 30 September 2026. Manual searches of regional journals further supplemented these efforts. The search strategy employed terms related to dengue and host genetics. Inclusion was restricted to complete, well-documented reports published in English, Spanish, or Portuguese; for Asian studies, only those published in English were considered. Duplicate reports were excluded based on title, authorship, sample size, and analytical approach. Detailed attention was paid to the characterization of study settings, including geographic origin and population definitions, to minimize the risk of duplicate or fragmented genetic reports. The description of control groups was carefully evaluated, though in some studies it was not possible to confirm geographic comparability between cases and controls.

Included studies investigated germline variants—such as HLA alleles, candidate gene polymorphisms, and genome-wide markers—in relation to dengue susceptibility or severity in patients with laboratory-confirmed infection and a defined comparison group, following WHO clinical criteria. Exclusions comprised animal or in vitro studies, case reports, viral genetic studies without host genotyping, conference abstracts, and preprints.

Data extracted included study population, sample size, case definitions, dengue serotype, genetic variants, and effect estimates. Results were synthesized qualitatively by gene family and clinical category. No formal risk-of-bias assessment was performed due to study heterogeneity and the narrative approach.

The 2009 WHO classification system delineates dengue into three clinical categories: dengue without warning signs, dengue with warning signs, and severe dengue [5]. This system replaced the 1997 classification, which was based on dengue fever, dengue hemorrhagic fever, and dengue shock syndrome. Notably, most genetic association studies were conducted before the revised WHO guidelines and therefore used the earlier clinical categories. For example, the Venezuelan [12] and Brazilian [13] HLA cohort studies adopted the 1997 framework. To maintain methodological consistency with primary sources, a major review of the field retained the 1997 categories in its analysis [2]. Similarly, a recent meta-analysis examining HLA-A*24 and HLA-B*44 associations restricted its inclusion criteria to studies using the 1997 classification, thereby excluding those using the 2009 scheme [14].

Accurate definition of clinical phenotypes is essential in dengue genetic association studies. Studies vary in their comparators, contrasting healthy controls, asymptomatic, mild, or severe cases, and increasingly distinguishing dengue shock syndrome per the 2009 WHO guidelines [1]. Because genetic associations depend on context, this review specifies the reference group for each cited study.

3. Host Genetic Factors

Host genetic factors affect dengue risk, but most associations remain unconfirmed [1,4,5,15–17]. The geographic distribution of this research is uneven. A 2025 meta-analysis of HLA studies included 19 case–control studies worldwide and identified several key associations in Southeast Asian populations [17]. Although the Americas accounted for most of the world's cases in 2024 [1,18,19], few complete reports were available [18,19]. The genetic data from African populations are scarce [17]. A recent meta-analysis found no HLA case–control study from tropical Africa [17]. This information gap matters because Latin American populations carry a mixture of Amerindian, European,

and African ancestry, so their HLA and immune gene diversity may differ from Asian cohorts. For example, in Venezuela's central urban population, ancestry has been estimated at roughly 60% European, 24% Amerindian, and 16% African [20]. This heterogeneity included differences across Africa, where populations were introduced (e.g., Western or Eastern Africa), with distinct Amerindian and Caucasian populations resulting in admixed populations that were difficult to define precisely.

3.1. HLA Alleles

As described in Table 1, HLA molecules present viral peptides to T cells, influencing dengue susceptibility. HLA-A*24 is the most frequent allele in Asian populations. Meta-analyses show that individuals with the HLA-A*24 allele have higher odds of developing DHF [14] and symptomatic dengue infections in Asian and Caribbean populations [15]. A*33 appears protective in Southeast Asia. Most associations are region-specific and often do not replicate across populations [17,21–25]. Evidence for A*24 in non-Asian groups is limited.

Other HLA class I associations exhibit considerable heterogeneity, with allele–disease relationships varying across viral subtypes and serotypes. In a Thai study, no HLA-A or -B association was seen in primary infection [25]. For secondary infections, A*0203 was more common in dengue fever than in controls and less common in hemorrhagic fever, both findings holding after correction [25]. A*0207 was associated with hemorrhagic fever for certain serotypes but was not significant after correction [25]. A meta-analysis found A*02 was associated with dengue fever mainly in Southeast Asia, with high heterogeneity [16]. The Thai study reported A*03 as a risk allele for hemorrhagic fever [25], while a Filipino study reported the opposite [21]. In Venezuela [12], A*03 was absent in patients with hemorrhagic fever, but this did not hold after strict statistical correction [11]. A Malaysian study found A*03 to be less frequent in hemorrhagic fever than in controls, but the difference was not significant after correction [22]. Overall, A*03's effect varies across populations, even within Southeast Asia.

In other assessments, A*33 appeared protective in some analyses, though results varied, with one Caribbean study showing the opposite [16].

In a Thai study by Zivna et al. [23], T cell responses to an HLA-B*07-restricted NS3 epitope correlated with increased disease severity. T cell responses have been analyzed in the context of memory responses [24], dengue vaccine responses [26], and their limitations [27].

The direction of the HLA-B*44 association changes with context. In a cohort from Recife, Brazil, infected with DENV-3, hemorrhagic fever was more frequent than dengue fever (15.8% versus 8.5%; OR 2.03, 95% CI 0.97 to 4.24; $p = 0.047$), without correction for multiple testing [14]. In the same Thai cohort, B*44 was less frequent in secondary hemorrhagic fever than in controls, along with B*62, B*76, and B*77; none of these were adjusted for multiple comparisons [14,25]. The 2025 meta-analysis found B*44 to be protective against hemorrhagic fever (OR 0.60; 95% CI 0.44 to 0.82) but not against dengue fever or symptomatic dengue overall [15]. Two Thai studies showed protection (OR 0.65; 95% CI 0.49 to 0.87) [25,28], whereas Latin American studies showed increased risk (OR 1.37; 95% CI 1.02 to 1.85), driven mainly by the southern Brazilian study [13,16]. A dedicated meta-analysis of A*24 and B*44 concluded that the two alleles have opposing effects on hemorrhagic fever [14].

In the Venezuelan case–control study, B*57 was more frequent in patients with dengue fever than in controls (7.0% versus 1.6%; OR 4.68), and B*40 was more frequent in patients with hemorrhagic manifestations than in controls (17.9% versus 8.7%; OR 2.29). B*15 and B*49 were less frequent in patients overall [12]. The study included 77 patients and 127 controls, and after statistical correction, none of the class I differences remained signifi-

cant [12]. The B*15 result is consistent with the Cuban data, in which B*15 and A*31 were associated with symptomatic dengue in patients with DENV-2 [2,29]. B*13 was linked to resistance in Thai patients with shock [2]. In a Malaysian series, it went the other way: it was more frequent in Malay patients with hemorrhagic fever (16% versus 3%; $p = 0.049$, not significant after correction) and absent in Chinese patients with the same diagnosis [30].

Class II alleles generally showed protective effects, but findings varied by population. DRB1*0901 conferred protection against shock in Vietnamese patients, particularly with DENV-2 [31]. DRB1*04 was protective in Mexican and Cuban patients [12,29,32] but not in a Brazilian cohort. DRB1*15 was the only association in the Venezuelan series to remain significant after correction, and it was also more frequent in Brazilian patients, though not after correction. DQ1 was linked to dengue fever in southern Brazil [33,34]. Some studies associated DRB1*11 with severe dengue, but results were inconsistent and often became non-significant after adjustment. However, since this serotype has been associated with serotype 3, it cannot be discarded as a genetic marker [29].

Other alleles, such as DRB1*03 and DRB1*09, have occasionally been associated with a reduced risk of disease; however, these associations demonstrate considerable regional variability and frequently do not achieve statistical significance [33,34]. For instance, in Burkina Faso, DRB1*11 and DRB1*03 alleles were less prevalent among patients, but these differences did not persist after correction for multiple comparisons [34,35]. Overall, evidence for a protective role of class II alleles remains inconclusive, mainly because of small sample sizes and inconsistent findings across regions. Nonetheless, these reports cannot be dismissed without larger, more robust studies.

Two alleles in the Brazilian cohort were associated with cross-serotype immunity rather than protection against severity [35,36]. B*07 (MHC class I allele) and DRB1*13 were less frequent in secondary than in primary DENV-3 infections (ORs of about 0.50 for each, one-sided tests without correction for multiple testing), which the authors interpreted as evidence of cross-protective T cell responses [13,35,36]. The interpretation is not straightforward. In 10 HLA-B*07-positive Thai children, T cells specific for a conserved NS3 epitope were detectable in nine, at a median frequency of about 1 in 15,000 circulating cells, and this frequency was higher in children with hemorrhagic fever than in those with dengue fever ($p = 0.03$), a difference that held after excluding the one child with primary infection ($p = 0.046$) [34].

Table 1 summarizes the genetic associations identified in the reviewed studies, along with the specific populations in which these associations were observed.

Table 1. Selected HLA associations with dengue outcomes across populations.

Gene	Population	Observation	Citeria	Ref
A*24 (codon 70 histidine)	Vietnam, two sites	Risk of DHF and DSS	WHO 1986 WHO 1997	[37] [31]
A*24	Southeast Asia (meta-analysis); Caribbean, one small study	Risk of DHF and symptomatic dengue; no association with DF	Mixed	[16]
A*02:03, A*02:07	Thailand, secondary infection	A*0203 with DF; A*0207 with DHF or DSS	WHO 1997	[25]
A*03	Southeast Asia (meta-analysis); Malaysia; Venezuela	Risk of DHF (meta-analysis, driven by one Thai study); less frequent in DHF, not significant after correction (Malaysia, Venezuela)	WHO 1997 WHO 2009	[12], [16], [22]
A*33	Southeast Asia (meta-analyses)	Protection against DHF and symptomatic dengue	Mixed	[16,30]

Table 1. *Cont.*

Gene	Population	Observation	Citeria	Ref
B*07	Thai data on T cell responses to NS3	Correlation with disease severity	WHO 1997	[23]
B*44	Brazil, DENV-3	Risk of DHF (nominal, no correction)	PAHO 1995	[13]
B*44, B*62, B*15 (B*76, B*77)	Thailand, secondary infection	Lower frequency in DHF than in controls (uncorrected)	PAHO 1995 WHO 1997	[13], [25,28]
B*51, B*52	Thailand, secondary infection	B*51 with DHF; B*52 with DF in DEN-1/DEN-2 (uncorrected)	WHO 1997	[28]
B*15	DENV-2; Mexico, Venezuela	Risk of symptomatic dengue (Mexico); lower frequency in patients (Venezuela, nominal)	WHO 1997	[12,32]
B*40, B*57	Venezuela, Thais	B*40 with hemorrhagic manifestations; B*57 with DF (nominal). Associated with THF-208, promotor B*48, and DPB1*0501 in Thais	WHO 1997	[12,28,33]
B*44	Thais	May protect against secondary infection	WHO 1997	[34]
DQ*1	Brazil	Susceptibility to dengue infection	WHO 1997	[35]
DRB1*09:01	Vietnam	Protection against DSS	WHO 1997	[31]
DRB1*04	Mexico, Cuba, Brazil	Protection in Mexico and Cuba; no effect in Brazil	WHO 1997	[13,29,32]
DRB1*15	Venezuela; southern Brazil (DENV-3)	Susceptibility to dengue (significant after correction in Venezuela; nominal in Brazil)	WHO 1997	[12,36]
DRB1*03	Venezuela; meta-analysis; Burkina Faso	Lower frequency in patients (Venezuela, nominal); lower risk of severe dengue (meta-analysis); lower odds of dengue (Burkina Faso)	WHO 1997, Mixed, Serology	[12], [30], [38]
DRB*1:07, DRB1:15, TNF rs1799964	India	Only combination significant: 114 patients, 110 controls	WHO 1999	[39]
DRB1*11	Meta-analysis; southern Brazil (DENV-3); Burkina Faso	Risk of severe dengue versus DF (meta-analysis of two studies); resistance to dengue (Brazil, not significant after correction); no association (Burkina Faso)	Mixed Serology	[30,36], [40]
B*07, DRB1*13	Brazil, DENV-3	Lower frequency in secondary infection	PAHO 1995	[13]
TNF-308 (rs1800629)	Venezuela; Cuba; Southeast Asia	Not significant after correction in Venezuela; pooled meta-analyses null	WHO 1997 Mixed	[2,41] [42]
TNF-308 (rs1800629) with IL10-1082 AA (rs1800896)	Venezuela	High TNF and low IL-10 profile is more frequent in DHF than in controls (OR 19.5) or DF (OR 17.4).	WHO 1997 Mixed	[41] [42]
TNF rs1799964	Colombia, children	C-allele carriers less frequent among patients (aOR 0.51). FDR 0.0017	WHO 2009 WHO 1997	[43] [44]

Table legend: DF, dengue fever; DHF, dengue hemorrhagic fever; DSS, dengue shock syndrome; DENV, dengue virus. Mixed refers to mixed criteria. Serology: only serological tests were described.

3.2. Haplotypes

Haplotype-level data are scarcer than allele-level data. Among 435 ethnic Thais, a TNF haplotype marked by the -238A substitution was more frequent in secondary hemorrhagic fever (15.2%) than in secondary dengue fever (4.1%; OR 4.13; 95% CI 1.59 to 11.17), a

difference that remained significant after multiple-testing correction [28]. In most carriers, the same variant was linked to a specific LTA haplotype that correlated with detectable LTA and TNF production during the acute phase [28]. In contrast, LTA variants alone were not associated with any patient group. Two extended haplotypes combining these TNF and LTA variants were found only in secondary hemorrhagic fever (7.8%) and in controls (2.1%), never in secondary dengue fever, and in the hemorrhagic fever group they co-occurred with HLA-B*48, a serotype otherwise rare in Southeast Asia, as well as with B*57 and DPB1*0501. Stratifying by infecting serotype revealed no further association [2,28]. In the Venezuelan series, the authors observed that DRB1*03 was not enriched among carriers of the TNF-308 A allele and attributed this to the population's genetic heterogeneity [12].

3.3. Cytokine Genes

Although TNF has been widely studied, most research—including meta-analyses—found no consistent association between TNF variants and severe dengue overall [41–45]. The A allele of the TNF-308 promoter showed possible links with severe disease in Venezuela and Cuba, but not in Southeast Asia, and these results often lost significance after correction [41–44]. Other TNF and IL-10 gene combinations also showed inconsistent results or wide confidence intervals. A large meta-analysis and a Brazilian study both found no significant associations [45]. In Colombia, a different TNF variant (rs1799964) was less common in patients than in controls [43,46], whereas the opposite was reported in India [39]. Overall, TNF's role in dengue severity remains unclear and likely varies by population.

A systematic review of Latin American case–control studies included 26 articles: 12 from Brazil, seven from Mexico, five from Cuba, and two from Venezuela [9]. The abstract reports 16 articles linking polymorphisms to higher risk of severe dengue and 16 linking them to protection, so some articles reported both. TNF was the most studied gene, with eight studies, and the findings were inconsistent; the authors attributed this to differences in populations, sample sizes, and genotyping methods [9]. In a Colombian sample of 226 patients, the GGT and GAC combinations of rs1800750 (TNFA), rs2069843 (IL6) and rs2069705 (IFNG) were associated with hemorrhagic fever, with and without adjustment for ancestral genetic component [44]. The A allele of rs2069843 alone was associated with hemorrhagic fever in Afro-Colombians and, after adjustment for ancestry, in the full sample. Carriers of the AGC combination had IL-6 levels 58.03 pg/mL higher than GGC carriers, independent of European, Amerindian, and African ancestry proportions [44]; rs1800750 is a different TNFA position from the -308 variant (rs1800629).

Two regulatory cytokine genes have also been studied. In Taiwanese patients, TGFB1-509 CC was about twice as frequent in hemorrhagic fever as in dengue fever, and combining it with CTLA4 +49 G further increased risk [47]. It was associated with a higher DENV-2 viral load. In Cuba, the G allele at TGFB1 codon 25 was protective [2].

3.4. Other Genes Involved in Immune Response

The FCGR2A R/R131 genotype was one of the first non-HLA genetic associations identified in dengue [48–52]. In Vietnamese children, the R/R genotype was less common among severe cases, suggesting a protective effect, though the association was borderline statistically significant [50]. In Cuban adults, R/R was also protective against hemorrhagic fever, while the H/H genotype was associated with both dengue fever and hemorrhagic fever [50,51]. However, in a Mexican cohort, the histidine (H) allele was protective, showing the opposite direction [9]. These conflicting results may reflect differences in population genetics, serotype, infection history, or case definitions. The role of FCGR2A in antibody-

dependent enhancement is plausible but not definitively proven, and its effects may differ from those observed in other viral infections, such as SARS-CoV-2.

The CD209 (DC-SIGN) promoter variant -336 G has been widely investigated for its association with dengue severity. In a study of 606 dengue patients and 696 controls from three Thai hospitals, the G allele was infrequent among individuals with dengue fever but notably more common in those with hemorrhagic fever and in controls [51]. The odds ratio (OR) for hemorrhagic fever versus dengue fever was 5.84 (95% CI: 2.77–12.31), and the OR for protection against dengue fever compared with controls was 4.90; both comparisons were highly statistically significant ($p < 10^{-6}$) across all cohorts [51]. Notably, the G allele frequency did not differ significantly from controls in hemorrhagic fever cases. In Brazilian populations, findings have been inconsistent: one study reported no association [2], while another identified a positive association [52], likely reflecting underlying population admixture. In Taiwan, the G allele was associated with hemorrhagic fever [53], whereas in a Mexican cohort, it was associated with symptomatic infection (OR 2.3; 95% CI: 0.91–6.1) [54]. Additional studies from Western India [55], a cohort of 918 Thai children [51], and Burkina Faso [56] found no significant associations. A meta-analysis of nine studies demonstrated that G allele carriers had an elevated risk of severe dengue in Asians (dominant model, OR 1.86; 95% CI: 1.01–3.45) but a reduced risk in South-Central Americans (GG vs. GA/AA, OR 0.27; 95% CI: 0.10–0.70); however, pooled estimates were not robust [57]. In Brazilian children with shock, the GG genotype appeared protective (OR 0.12; 95% CI: 0.01–0.9), although this observation was based on a single GG carrier among 85 cases and 28 among 322 controls [57]. The same study's pooled analysis indicated that the G allele was associated with severe dengue in Asians (allelic OR 2.77; 95% CI: 1.65–4.67) and with a protective effect in Brazilians (OR 0.66; $p = 0.013$) [5]. Reduced promoter activity has been suggested as a potential mechanistic explanation and requires confirmation [2,53]. Antigen processing at the platelet surface is also critical in dengue. In South Indian patients, TAP1 333 Ile/Val was associated with hemorrhagic fever, and HPA-1 1a/1b heterozygosity with shock rather than hemorrhagic fever without shock (OR 4.75). The authors linked both findings to viral peptide selection and to a cross-reactive immune response against a platelet antigen [2,52].

Mannose-binding lectin (MBL2), part of the complement lectin pathway, has also been examined in relation to platelet count. In 110 Brazilian patients infected with DENV-3, MBL2 genotype frequencies did not differ from those of healthy controls, so the gene was not associated with dengue infection [58,59]. However, among patients, the AA genotype, which produces normal amounts of the protein, was more common among those who developed thrombocytopenia than among those who did not, after adjusting for age (OR 2.32; 90% CI 1.13 to 4.79; $p = 0.056$) [60]. This is the opposite of what a simple deficiency model would predict, since low-producer genotypes are usually associated with worse outcomes in other infections [58,59]. A similar finding was reported in a study of a Vietnamese population [61]. A meta-analysis comparing host responses to dengue and West Nile infection found significant associations with several genes, including MLB2 [61].

The C-type lectin CLEC5A offers a functional link back to the cytokine signals discussed above. In the same Brazilian study, the rs1285933 TT genotype was more frequent in children with shock than in matched controls (OR 2.25; 95% CI 1.07 to 4.87) [62]. Carriers of the T allele had higher TNF levels on days 5 to 7 of illness in a functional sample of 38 patients. The association was borderline with IgG-positive controls only (OR 2.03; $p = 0.12$), and the authors consider it preliminary and requiring replication [62].

In a Vietnamese cohort study, the genotype frequencies at the vitamin D receptor (VDR) locus 352 showed no statistically significant difference between 327 cases and 247 controls [48]. However, a trend analysis of allele frequencies across two shock severity

grades indicated that the T allele was less prevalent in individuals with the more severe grade ($p = 0.033$), which the authors interpreted as suggestive of a potential protective effect [48]. The same study also assessed additional genes, including mannose-binding lectin, IL-4, and IL-1RA, but found no associations [48]. The association observed for VDR has not been replicated in the sources reviewed herein.

Table 2 provides a summary of the non-HLA genetic associations discussed in this and subsequent sections, alongside their statistical significance.

The roles of KIR are still difficult to interpret due to de limitations of studies [63–65]. Other studies involving other genes need confirmation, except for the strong association with MICB [15,43,61,66,67]. GWAS has identified a strong correlation, which upcoming studies should validate.

Table 2 summarizes the genes involved in the process and lists suitable candidates. Some genes were validated in a specific population, while others were suggested by genetic analysis, such as OAS1 (2′-5′-oligoadenylate synthetase 1), OAS3 (2′-5′-oligoadenylate synthetase 3), and SNP rs2285933, which belong to the IFN signallome but have not been directly validated in individuals with disease [68,69]. In essence, the decreased or absent IFN type I and III responses are crucial for the lack of protection against infection, severity, and chronicity in most viral diseases [70].

Table 2. Other gene associations with dengue outcomes across populations.

Gene	Population	Observations	Criteria	Ref
TNFA rs1800750, IL6 rs2069843, IFNγ rs2069705	Colombia	GGT and GAC combinations with DHF; A allele of rs2069843 with DHF after ancestry adjustment.	WHO 1997	[43,44]
TNFA rs1800629	Brazil. Meta-analysis	Allele G susceptibility, A protection; 384 patients vs. 995 controls.	Mixed	[45]
TNFA rs1800629 TGF β rs1800471 IL-10 (-1082/-819/-592)	Cuba	TNFA and TGFβ SNP associated with protection. IL-10 polymorphism with secondary infection,	WHO 1997	[46]
TGFβ1 rs1800469; TGFβ1 rs1800471	Taiwan; Cuba	-509 CC about twice as frequent in DHF as in DF, risk increased with CTLA4 +49 G; codon 25 G protective in Cuba. Uncorrected; not replicated.	Mixed	[2]
TGFβ rs1800469 CTLA rs231775	Taiwan	Combination associated with DHF and virus load.	WHO 2004	[47]
FCGR2A rs1801274	Vietnam; Cuba; Mexico	Protective against shock (Vietnam) and against DHF (Cuba); histidine allele protective against symptomatic infection in Mexico, the opposite direction.	Mixed WHO 1997	[2,48], [49,50]
CD209 (DC-SIGN) rs4804803	Thailand; Taiwan; Mexico; Brazil; India; Burkina Faso	G allele protective against DF in three Thai cohorts; risk of DHF in Taiwan; GG protective in Brazilian shock cases; no association in India, Burkina Faso, or a second Thai cohort. Replicated within Thailand; direction reverses between Asia and South-Central America.	Mixed WHO 1997 Mixed BHM 2012 WHO 2004 WHO 1999 Serology Mixed	[2], [51], [52], [53] [54] [55] [56] [57]
TAP1 rs1057141; HPA-1 1a/1b	South India	TAP1 with DHF; HPA-1 heterozygosity with shock (OR 4.75). Single cohort; not replicated.	Mixed WHO 1997	[2], [71]

Table 2. *Cont.*

Gene	Population	Observations	Criteria	Ref
MBL2 AA	Brazil, DENV-3 Vietnam Burkina Faso Meta-analysis	No association with infection in Brazil. Association in Vietnam. AA more frequent among patients with thrombocytopenia. $p = 0.056$; opposite of a deficiency model. Associated with disease with MICB, PLCE1, and IFN γ.	WHO 1999 WHO 2009 WHO 1997 Serology Mixed	[58] [59] [72] [60] [61]
CLEC5A rs1285933 TT	Brazil, children with shock	More frequent in shock than in matched controls (OR 2.25); T allele with higher TNF levels. Borderline with IgG-positive controls; authors call it preliminary.	WHO 2009	[62]
VDR rs731236	Vietnam	No difference in genotype frequencies; trend toward lower t allele with greater severity. Trend test $p = 0.033$; not replicated.	Mixed	[2,48]
KIR2DL2, KIR2DL5A, KIR2DL5B; KIR3DL3, KIR2DS5	Burkina Faso, pilot study	Three inhibitory receptor genes more frequent in patients (OR 7.32 to 15.0); KIR3DL3 and KIR2DS5 less frequent. Small sample (50 patients); DHF not recorded.	Serology	[63]
KIR2DS5, KIR2DL5, KIR AA genotype	Southern Brazil	KIR2DS5 and KIR2DL5 more frequent in patients; AA genotype protective (OR 0.46); opposite direction to Burkina Faso for two genes. Single cohort; conflicting results.	Serology	[64]
KIR3DL1, KIR3DS1/3DS1	Western India	KIR3DL1 more frequent in DF than controls (OR 4.1); KIR3DS1/3DS1 less frequent. Neither survived correction; no DHF discrimination.	WHO 1999	[65]
Toll receptor 3, 7, 8,	India, Mexico, Colombia, and Indonesia meta-analysis	TLR3 rs3775291 and rs3775290, TLR4 rs4986790 and rs4986791, and TLR7 rs179008 and rs3853839 correlate with dengue severity.	Mixed	[66]
Complement receptor type 1	Vietnam	CR1 minor allele rs6691117G associated with infection and severity. ELISA values reveal an association of complement receptor 2 with platelet number.	WHO 2009	[67]
MICB rs3132468	Vietnam (GWAS and follow-up); Cuba; Colombia; meta-analysis	Risk of shock (per-allele OR 1.34) and of dengue without shock (OR 1.15); GG genotype with symptomatic dengue in Colombia (aOR 3.01). Genome-wide significant and replicated; causal gene within MHC not defined.	WHO 2009 WHO 1997 Mixed WHO 2009 WHO 1999 WHO 1997	[15], [43], [61], [73] [74] [75]
PLCE1 rs3765524, rs3740360, rs2274223	Vietnam (GWAS and follow-up); Colombia; meta-analyses	Protective against shock (rs3765524 OR 0.80); CT genotype with symptomatic dengue in Colombia (aOR 1.78), direction consistent. Genome-wide significant and replicated; functional validation pending.	WHO 2009 WHO 1997 Mixed WHO 2009 WHO 1999	[15], [43,61], [73,75]
JAK1 rs11208534, rs2780831, rs310196	Brazil (pathway study); Colombia	Eleven of 58 nominal markers in JAK1, clustered toward the 5′ end, with DHF; rs11208534 with severity, Brazil. Nominal $p < 0.05$, no genome-wide threshold; department-specific in Colombia.	Mixed WHO 1997 WHO 1999	[2], [76], [43]

Table 2. *Cont.*

Gene	Population	Observations	Criteria	Ref
BAK1 rs5745568	Thailand, 918 children	Recessive association with DHF (adjusted OR 1.29), independent of CD209. Single cohort; causal variant possibly in linkage disequilibrium.	WHO 1997	[68]
NOD1, RIPK2, IKBKE	Colombia	NOD1 and RIPK2 variants with risk; IKBKE haplotypes with resistance; IKBKE rs1059704 reverses direction between departments. FDR-corrected; several signals present in one department only.	WHO 1997	[43]
OSBPL10, RXRA	Cuba, admixture mapping	Lower African ancestry in DHF; both genes converge on the LXR/RXR pathway; OSBPL10 knockdown reduced DENV-2 replication. Pattern held in Havana but not in Guantánamo; functional support in vitro.	Mixed WHO 1997	[16,77,78]
OAS1, OAS3 rs2285933	Meta-analysis weighted by worldwide allele frequency	OAS3 rs2285933-G protective against shock (OR 0.55). Not examined in any primary study reviewed here.	WHO 1997 Serology	[77,78]
Thrombopoietin receptor	Bangladesh	Genetic polymorphism of thrombopoietin receptor and GATA1. Response to eltrombopag (treatment for thrombocytopenia).	WHO 2011	[79]

Table legend: DF, dengue fever; DHF, dengue hemorrhagic fever; DENV, dengue virus; GWA, genome-wide association analysis; Mixed refers to mixed criteria. Serology: only serological tests were described. BHM stands for Brazilian Ministry of Health guidelines.

4. Population Genetics and Statistical Inconsistencies

Tables 1 and 2 summarize key findings from studies conducted in diverse populations, with the most comprehensive data available from Asian cohorts. This emphasis on Asian populations is a limitation, given the relatively few studies from African and Latin American groups.

Research on host genetic factors and dengue in Africa is scarce and inconclusive. No studies have established links between viral genotype or serotype and disease severity [70,80]. Limited pilot studies suggest possible roles for KIR genes, but findings are inconsistent and based on small samples [63–65]. Only DRB1*03 has shown potential protection among HLA class II alleles in Burkina Faso, with no significant associations found for DC-SIGN or other HLA variants [38,81]. Overall, evidence from African populations remains limited and inconsistent [82,83].

Genetic association studies in Latin America mainly come from Venezuela, Brazil, Mexico, Cuba, and Colombia, and focus on admixed populations [9]. A systematic review identified Brazil and Mexico as the most frequently studied countries [9]. Only the DRB1*15 allele has shown a consistent association with dengue across the region, replicated in both Venezuelan and southern Brazilian cohorts [11,26]. Most other genetic associations, such as TNF -308A, DRB1*04, and FCGR2A, vary between countries and lack consistent replication [11,14,29,32,39,41,42,54,62,84].

Several hypotheses on the importance of ABO blood groups and dengue complications have been studied [85,86]. However, more studies are required to confirm the link.

These inconsistencies may reflect variations in methodological guidelines and factors such as circulating dengue serotype, infection status (primary versus secondary), co-

infections, patient nutritional status, and genetic background (e.g., admixed, Amerindian, or Caucasian populations). Validating genetic analyses from Latin American and African reports is challenging because of incomplete data and, in some cases, inadequately characterized control groups that may not represent the same geographic populations as the cases. Nevertheless, the available genetic data remain valuable and point to the need for rigorously designed studies in well-defined populations with diverse genetic backgrounds.

No genome-wide association study has been carried out in an admixed Latin American population. The two loci with genome-wide support, MICB and PLCE1, are from Vietnam and were tested in a candidate-gene manner, not genome-wide, in a Colombian study that examined them [15,43]. Given the ancestral diversity within Latin American populations, this gap may matter as much as the one already noted for Africa [17].

Genetic data from country-specific clusters, such as Brazil, Colombia, India, and Burkina Faso, offer limited insight into local population diversity. Broader international participation is essential to achieve a comprehensive understanding. Notably, HLA data collected for transplant programs may serve as a foundational resource in countries where large-scale sequencing initiatives are economically unfeasible. Future research needs to use mathematical modeling to elucidate relationships between dengue serotype protein characteristics and potential binding sites in HLA, TCR αβ, γδ, and TLR molecules. Ultimately, identifying genetic markers must move beyond descriptive studies toward mechanistic investigations to further understand immune response to the virus, pathogenic factors, and post-dengue syndrome [87].

5. Genes and Cell Targets That Require Further Exploration

In recent years, gene-level analyses and GWAS have shown only partial insight into susceptibility and protection, and that cellular-level data are needed to understand dengue viral infection and its severity. Latif and coworkers [88] used in silico approaches to identify several key transcription factors involved in infection, viral replication, and chronicity that are new to the analysis. They identified the roles of the transcription factors FOXC1, GATA2, RELA, TP53, and PPARG [88]. Moreover, PTEN and BIRC5 could inhibit the host's IFN responses, consequently facilitating viral infection [88]. This study suggests further analysis of the genetics of IFN type I and III signaling pathways in dengue infection.

Josyula et al. [89] analyzed gene signatures in dengue infection and identified seven hub genes, PIK3R1, GATA3, ZFPM, SKAP1 (involved in hemostasis, platelet activation, aggregation, and production), TP63, ZBTB20, and ZEB2 (associated with abnormal hard palate morphology), for dengue diagnosis. Although these genes do not directly relate to Latif's targets, dengue infection involves a more complex array of genes and proteins than previously thought, and this complexity could be critical in post-dengue syndrome.

Datta and Gosh [90] applied an interesting rationale. They analyzed different dengue types and genetics in the Indian population. Ten hubs were defined in each condition: DF, DHF, and DSS. It became clear that the hubs represented most of the intermediates involved in IFN signaling [90]. Two of the most critical genes in dengue infection are IFIT1, an innate immune sensor and antiviral effector that restricts viral infection by identifying foreign viral RNA and blocking its translation, and interferon-stimulated gene 15 (ISG15), a ubiquitin-like modifier protein induced by type I interferons that acts both as an intracellular protein tag (ISGylation) and an extracellular cytokine to fight infections and regulate immune responses [90]. For DHF, other genes have been related: (1) FXR2, FMR1 Autosomal Homolog 2, a protein-coding gene belonging to the fragile X-related family; (2) the E3 ubiquitin-protein ligaseZNF598; (3) SMG1, a protein-coding gene that encodes an atypical serine/threonine protein kinase belonging to the phosphatidylinositol 3-kinase-related kinase family SMG1; (4) Pumilio RNA-Binding Family Member 2 (PUM2); it encodes a

sequence-specific RNA-binding protein that acts as a post-transcriptional regulator of genes; (5) Replication initiator 1 (REPIN1), which enables RNA-binding activity as a replication factor; (6) parafibromin (CDC73), which regulates gene transcription, RNA processing, and histone modifications; (7) CDK19 is a serine-threonine kinase that regulates RNA polymerase II; (8) CACTIN is a nuclear scaffold protein involved in pre-mRNA splicing; PAGR1; and (9) RPS6KB2 is a ribosomal protein S6 kinase beta-2, a serine/threonine kinase that controls protein synthesis and cell proliferation. DSS: (1) Phosphatidylinositol 3-Kinase Catalytic Subunit Type 3, PIK3C3, is a class III lipid kinase; (2) alpha subunit of hypoxia-inducible factor 1, HIF1A, a master transcription factor that coordinates how cells adapt to low oxygen levels; (3) SBF1 regulates membrane dynamics and endosomal trafficking; (4) FZR1 is a crucial substrate-specific activator and adapter for the anaphase-promoting complex/cyclosome (APC/C) E3 ubiquitin ligase complex; (5) ROCK1 is a Rho-associated protein kinase 1, a crucial serine/threonine protein kinase activated by the small GTPase RHOA; (6) DICER1 is an enzyme that builds microRNAs; (7) dynamin-related protein 1, DNM1L, controls how cells divide and controls mitochondrial energy production; (8) STK11 is a serine/threonine protein kinase that acts as a major tumor suppressor by regulating cell metabolism, polarity, and growth; (9) ABL1 is a non-receptor tyrosine kinase protein; and (10) BRD1 is a human protein-coding gene that acts as an epigenetic regulator and a core component of histone acetyltransferase (HAT) complexes. Although researchers have analyzed several genes in viral infections [91], some candidates identified by Datta and Ghosh [90] have not been linked to viral infection or the innate immune response. Subsequent research should validate these targets.

Khare et al. [92] published a preliminary study analyzing T cell receptor αβ and γδ genetics in 112 dengue patients. Although this report draws no major conclusions, future studies should explore this further, as the role of innate lymphoid cell populations in dengue infection remains poorly understood [6]. As recently reviewed, several controversies regarding severe dengue infection warrant further analysis [93].

These new approaches and models require clinical validation and underscore the need for new, well-defined human population studies involving genetics and pharmacogenetics. Research on immune responses, including antigen presentation, humoral immunity, innate immunity, and adaptive immunity, is urgently needed.

6. Discussion

Genetic associations remain inconsistent across both mechanistic pathways and populations, as shown in Tables 1 and 2. Figure 1 summarizes the overall information.

Only three findings are supported by more than one independent study: HLA-A*24 in Vietnamese cohorts; FCGR2A R/R131 in Vietnamese and Cuban patients (with conflicting evidence from Mexico); and MICB and PLCE1, detected in Vietnam and observed again in Colombian children. These findings are largely limited to Southeast Asia, Cuba, and Colombia. Numerous genetic associations show substantial heterogeneity and often vary across cohorts and populations. For example, HLA-B*44 is associated with increased risk in Brazilian DENV-3 cases but is less common among Thai patients with secondary hemorrhagic fever. HLA-B*35 is significantly less frequent among Mexican dengue patients than controls, and this association persists after correction. HLA-B*15 is linked to symptomatic dengue in Cuba but is less frequent in Venezuela. DRB1*04 confers protection in Mexican and Cuban cohorts but has no detectable effect in the Brazilian cohort. DQB1*0302 and DQB1*0202 frequencies also vary by clinical manifestation, yet their associations do not withstand multiple-testing correction. The TNF -308A allele appears to confer risk in South America but not in Southeast Asia, with meta-analyses showing no overall effect. Similarly, the DC-SIGN -336G allele is a risk factor in Asian populations and appears protective in

South-Central Americans, yet some large Thai cohorts report no association. The FCGR2A R/R131 genotype is protective in Vietnam and Cuba but associated with risk in Mexico. DRB1*11 is inconsistently associated with disease severity across studies and regions, while DRB1*03 appears protective in some populations but not in others. Although several loci (including MICB, TNF, CD209, FCGR2A, TPSAB1, CLEC5A, IL10, and PLCE1) have been proposed as markers for dengue infection and severity, evidence supporting their roles varies by ancestry, geography, and study design across populations.

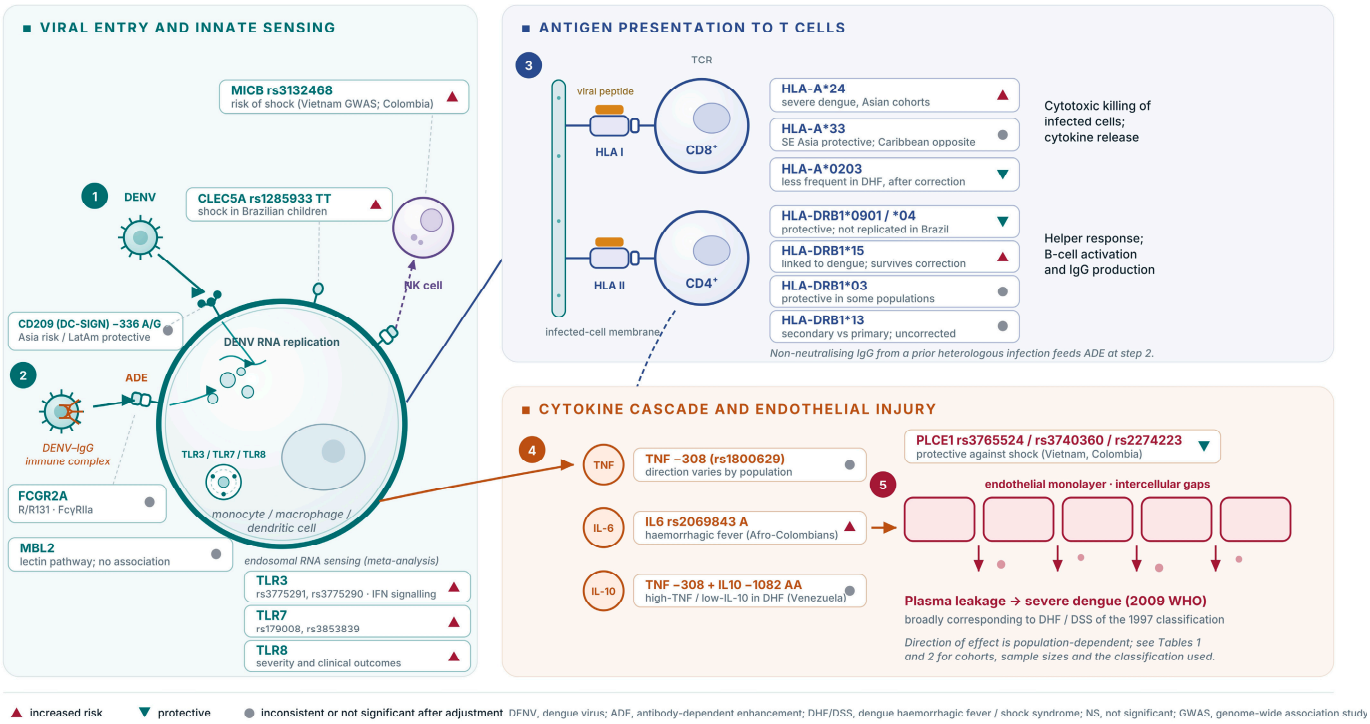

Figure 1. Host genetic variants mapped onto the cellular events of dengue virus infection. (1) DENV attachment and entry into mononuclear phagocytes through DC-SIGN, encoded by CD209. (2) In secondary heterologous infection, non-neutralizing IgG forms immune complexes that enter through FcγRIIa, encoded by FCGR2A, producing antibody-dependent enhancement (ADE). Endosomal sensing of viral RNA by TLR3, TLR7, and TLR8 is shown within the infected cell; TLR3 is central to type I and III interferon signaling, and variants in these receptors correlated with dengue severity in a meta-analysis of Indian, Mexican, Colombian, and Indonesian cohorts. Innate sensing also involves CLEC5A and MBL2 through the lectin complement pathway, and MICB on the infected cell, which engages natural killer cells. (3) Viral peptides are presented on HLA class I and class II molecules to CD8+ and CD4+ T cells. Among class II alleles, DRB1*03 was protective in some populations but not in others, and one-sided tests without multiple-testing correction reported a lower frequency of DRB1*13 in secondary than in primary infection, which was interpreted as cross-serotype immunity rather than protection against severity. (4) The resulting cytokine cascade, involving TNF, IL-6 and IL-10, acts on (5) the endothelial monolayer, where intercellular gaps lead to plasma leakage. Gene symbols are placed beside the step at which each product acts. Markers indicate the direction of effect reported in the studies reviewed: triangle up, increased risk; triangle down, protective; circle, inconsistent between populations or not significant after adjustment for multiple comparisons. Several loci, notably CD209 -336 and FCGR2A R/R131, show opposite directions of effect in Asian and Latin American cohorts. Tables 1 and 2 provide sample sizes, cohorts, and the WHO classification used in each study. Abbreviations: ADE, antibody-dependent enhancement; DENV, dengue virus; DHF, dengue hemorrhagic fever; DSS, dengue shock syndrome; GWAS, genome-wide association study; IFN, interferon; NS, not significant.

These inconsistencies have given rise to four principal hypotheses about population-specific effects, serotype and infection history, and the nature of the immune response, each of which warrants further empirical investigation.

1. Methodological heterogeneity and bias. The manuscripts analyzed differ in study design, selection criteria, WHO guidelines (1997, 1999, 2004, 2011), serology assessment, and molecular biology. It is difficult to conceive that these heterogeneous criteria are consistent. A significant number of studies analyzed a small cohort of patients < 100 samples (25); others do not have controls or have not defined which controls were used (6); and others have stratified patient samples into several subcategories and may have incurred type 2 statistical errors (5). The cited meta-analysis studies overlook some of the previous heterogeneity and calculated risk factors despite these limitations. In some cases, the results seem consistent with the gene-candidate hypothesis [61]. However, their results must be validated in studies with methodological homogeneity.

Methodological homogeneity denotes the systematic application of uniform research methodologies, study designs, data collection procedures, and statistical analyses across multiple studies, a single comprehensive research initiative, or within a specific scientific domain. This consistency is fundamental to improving the reliability and comparability of multicenter studies and meta-analyses. As demonstrated in the present review, methodological homogeneity is urgently needed in genetic research, particularly in the context of dengue infection. Furthermore, such homogeneity is essential for validating genome-wide studies in diverse populations, thereby facilitating the definition or corroboration of previously obtained data.

The second is dengue serotype and infection history. HLA molecules present different peptides, and some epitopes are more conserved across serotypes than others [94,95] and are critical in mapping the immune response. Most dengue associations appeared only in secondary infections and varied by infecting serotype, suggesting that a single analysis may overstate the conclusions.

The third is population structure. Susceptibility and infection severity vary between populations. Several studies have highlighted the risk of conducting meta-analyses with heterogeneous reports [14,16,30,42,45,57,61,75]; these studies draw few conclusions. It is unclear whether, in the Latin American admixed population, Caucasian genes are associated with susceptibility and African genes with resistance, given that gene segregation across countries varies with the origin of the Caucasian and African populations. In consequence, it is risky to conclude that African ancestry is protective.

The fourth is the role of type I and type III IFNs and the immune cell response in viral infection. The data analysis discussed in point 8 of this manuscript is critical for properly defining the genes and proteins involved in dengue infection and severity. Many unresolved issues remain.

Upcoming research should adopt the latest World Health Organization classification and systematically document serotype and primary versus secondary infection status to ensure phenotype comparability across cohorts, as well as the clinical characteristics [2,37]. Functional validation of associations, alongside adequately powered genome-wide analyses, are needed in diverse, well-defined populations. If these associations prove robust, they may inform preventive and immunotherapeutic strategies, including vaccine design, and help identify individuals at heightened risk for disease progression [2]. Comparative analyses with SARS-CoV-2, which shares key immunopathogenic mechanisms, may further elucidate host genetic determinants relevant to both infections [6]. Ongoing dengue vaccine trials offer valuable opportunities for genetic analyses to evaluate immune response efficacy and disease severity. Additionally, a comprehensive assessment of viral coinfections is essential,

especially in regions with substantial prior exposure to other flaviviruses, as these factors may influence clinical outcomes.

7. Methodological Limitations

This review has its own limits. In a narrative review, study selection reflects the search strategy and the authors' judgment and provides no formal risk-of-bias score or pooled estimate. We acknowledge that we did not consult the Virtual Health Library of the Brazilian Ministry of Health. Most included work consists of modest candidate-gene analyses, and small samples tend to overestimate effects.

Clinical definitions vary because of different clinical guidelines: WHO 1997, 1999, 2004, and 2009. The Pan American Health Organization (PAHO) follows similar guidelines but also includes additional criteria for DHF (2011, 2026). Some countries have their own guidelines for severe dengue, for example, Brazil's Ministry of Health and India's Ministry of Health and Family Welfare.

The available data analysis in the literature only partially covered populations across different countries and, as described in this report, results within a country may be heterogeneous depending on the collection site. Some studies focus on susceptibility to infection, while others focus on secondary infection and severity. Few studies examine individuals who experience only mild symptoms despite multiple infections.

8. Conclusions

Host genetic variation considerably impacts the clinical course of dengue infection; however, the supporting evidence remains heterogeneous across studies and populations. The alleles HLA-A*24 and HLA-A*0203, as well as the MICB and PLCE1 loci, represent the most robust genetic associations to date, predominantly in Southeast Asian populations. Notably, DRB1*15 is the only allele to show a statistically significant association after multiple-testing correction in more than one Latin American cohort. The FCGR2A R/R131 polymorphism has been found to confer protection in some populations yet exhibits the opposite effect in Mexican cohorts. These findings highlight the importance of population-specific, serotype-aware analyses, as genetic associations vary by population, serotype, and infection history. Studies involving Latin American and African cohorts are limited by small sample sizes, limiting the generalizability of their findings. Novel approaches provide a stronger rationale for analyzing host and population genetics in dengue infection. To analyze risk stratification in vaccine development and therapeutic targets, larger, multi-ethnic studies with harmonized case definitions and appropriate adjustment for genetic ancestry are required.

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References

1. World Health Organization. *Dengue*; World Health Organization: Geneva, Switzerland, 2025. Available online: https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue (accessed on 20 September 2026).
2. Lan, N.T.P.; Hirayama, K. Host genetic susceptibility to severe dengue infection. *Trop. Med. Health* **2011**, *39*, S73–S81. [CrossRef] [PubMed]
3. Bhatt, S.; Gething, P.W.; Brady, O.J.; Messina, J.P.; Farlow, A.W.; Moyes, C.L.; Drake, J.M.; Brownstein, J.S.; Hoen, A.G.; Sankoh, O.; et al. The global distribution and burden of dengue. *Nature* **2013**, *496*, 504–507. [CrossRef] [PubMed]
4. Clinical Features of Dengue. 2026. Available online: https://www.cdc.gov/dengue/hcp/clinical-signs/index.html (accessed on 28 September 2026).
5. World Health Organization. *Dengue: Guidelines for Diagnosis, Treatment, Prevention and Control, New Edition*; Report No.: WHO/HTM/NTD/DEN/2009.1; World Health Organization: Geneva, Switzerland, 2009.
6. García, A.H.; De Sanctis, J.B. Exploring the contrasts and similarities of dengue and SARS-CoV-2 infections during the COVID-19 era. *Int. J. Mol. Sci.* **2024**, *25*, 11624. [CrossRef] [PubMed]
7. Vaughn, D.W.; Green, S.; Kalayanarooj, S.; Innis, B.L.; Nimmannitya, S.; Suntayakorn, S.; Endy, T.P.; Raengsakulrach, B.; Rothman, A.L.; Ennis, F.A.; et al. Dengue viremia titer, antibody response pattern, and virus serotype correlate with disease severity. *J. Infect. Dis.* **2000**, *181*, 2–9. [CrossRef] [PubMed]
8. Rico-Hesse, R.; Harrison, L.M.; Salas, R.A.; Tovar, D.; Nisalak, A.; Ramos, C.; Boshell, J.; de Mesa, M.T.; Nogueira, R.M.; da Rosa, A.T. Origins of dengue type 2 viruses associated with increased pathogenicity in the Americas. *Virology* **1997**, *230*, 244–251. [CrossRef] [PubMed]
9. Salazar Flórez, J.E.; Segura Cardona, A.M.; Restrepo Jaramillo, B.N.; Arboleda Naranjo, M.; Giraldo Cardona, L.S.; Echeverri Rendón, A.P. Immune system gene polymorphisms associated with severe dengue in Latin America: A systematic review. *Rev. Inst. Med. Trop. Sao Paulo* **2023**, *65*, e58. [CrossRef] [PubMed]
10. Mehak, M.A.; Khan, M.; Razu, M.H. Host factors and genetic polymorphisms influencing dengue infection. *Virus Res.* **2025**, *360*, 199623. [CrossRef] [PubMed]
11. Chacón-Duque, J.C.; Adhikari, K.; Avendaño, E.; Campo, O.; Ramirez, R.; Rojas, W.; Ruiz-Linares, A.; Restrepo, B.N.; Bedoya, G. African genetic ancestry is associated with a protective effect on Dengue severity in Colombian populations. *Infect. Genet. Evol.* **2014**, *27*, 89–95. [CrossRef] [PubMed]
12. Fernández-Mestre, M.; Navarrete, C.V.; Brown, J.; Brown, C.; Correa, E.; Layrisse, Z. HLA alleles and dengue virus infection in Venezuelan patients: A preliminary study. *Inmunología* **2009**, *28*, 96–100. [CrossRef]
13. de Alencar, L.X.E.; Braga-Neto, U.M.; do Nascimento, E.J.M.; Cordeiro, M.T.; Silva, A.M.; de Brito, C.A.A.; da Silva Mda, P.; Gil, L.H.; Montenegro, S.M.; Marques, E.T., Jr. HLA-B*44 is associated with dengue severity caused by DENV-3 in a Brazilian population. *J. Trop. Med.* **2013**, *2013*, 648475. [CrossRef] [PubMed]
14. Cook, A.C.; Thibaut, D.; Pettersen, T. Major histocompatibility complex class I and dengue hemorrhagic fever: A meta-analysis of human leukocyte antigens A*24 and B*44. *Cureus* **2022**, *14*, e31485. [CrossRef] [PubMed]
15. Khor, C.C.; Chau, T.N.B.; Pang, J.; Davila, S.; Long, H.T.; Ong, R.T.H.; Dunstan, S.J.; Wills, B.; Farrar, J.; Van Tram, T.; et al. Genome-wide association study identifies susceptibility loci for dengue shock syndrome at MICB and PLCE1. *Nat. Genet.* **2011**, *43*, 1139–1141. [CrossRef] [PubMed]
16. Ghosh, A.G.; Kim, H.L.; Khor, S.S. HLA alleles and dengue susceptibility across populations in the era of climate change: A comprehensive review. *Front. Immunol.* **2025**, *16*, 1473475. [CrossRef] [PubMed]
17. Asaga, P.M.; Kadukkatti, V.; Airiohuodion, P.; Danaan, D.A.; Ibeh, D.C.; Kroeger, A. Viral and host determinants of arboviral disease severity in African populations: A systematic review with meta-analysis. *PLoS Negl. Trop. Dis.* **2026**, *20*, e0014663. [CrossRef] [PubMed]
18. Haider, N.; Hasan, M.N.; Onyango, J.; Billah, M.; Khan, S.; Papakonstantinou, D.; Paudyal, P.; Asaduzzaman, M. Global dengue epidemic worsens with record 14 million cases and 9000 deaths reported in 2024. *Int. J. Infect. Dis.* **2025**, *158*, 107940. [CrossRef] [PubMed]
19. Epidemiological Update Dengue in the Americas Region—18 February 2026. Available online: https://www.paho.org/en/documents/epidemiological-update-dengue-americas-region-18-february-2026 (accessed on 20 September 2026).

20. Del Pilar Fortes, M.; Gill, G.; Paredes, M.E.; Gamez, L.E.; Palacios, M.; Blanca, I.; Tassinari, P. Allele and haplotype frequencies at human leukocyte antigen class I and II genes in Venezuela's population. *Ann. Biol. Clin.* **2012**, *70*, 175–181. [CrossRef] [PubMed]
21. Mercado, E.S.; Espino, F.E.; Perez, M.L.; Bilar, J.M.; Bajaro, J.D.; Huy, N.T.; Baello, B.Q.; Kikuchi, M.; Hirayama, K. HLA-A*33:01 as a protective allele for severe dengue in a population of Filipino children. *PLoS ONE* **2015**, *10*, e0115619. [CrossRef] [PubMed]
22. Appanna, R.; Ponnampalavanar, S.; Lum Chai See, L.; Sekaran, S.D. Susceptible and protective HLA class 1 alleles against dengue fever and dengue hemorrhagic fever patients in a Malaysian population. *PLoS ONE* **2010**, *5*, e13029. Erratum in *PLoS ONE* **2011**, *6*. https://doi.org/10.1371/annotation/972cc8f0-5c9e-4d74-b98b-217a2f80a4bd. [CrossRef] [PubMed] [PubMed Central]
23. Zivna, I.; Green, S.; Vaughn, D.W.; Kalayanarooj, S.; Stephens, H.A.F.; Chandanayingyong, D.; Nisalak, A.; Ennis, F.A.; Rothman, A.L. T cell responses to an HLA-B*07-restricted epitope on the dengue NS3 protein correlate with disease severity. *J. Immunol.* **2002**, *168*, 5959–5965. [CrossRef] [PubMed]
24. Tian, Y.; Grifoni, A.; Sette, A.; Weiskopf, D. Human T Cell Response to Dengue Virus Infection. *Front. Immunol.* **2019**, *10*, 2125. [CrossRef] [PubMed]
25. Stephens, H.A.F.; Klaythong, R.; Sirikong, M.; Vaughn, D.W.; Green, S.; Kalayanarooj, S.; Endy, T.P.; Libraty, D.H.; Nisalak, A.; Innis, B.L.; et al. HLA-A and -B allele associations with secondary dengue virus infections correlate with disease severity and the infecting viral serotype in ethnic Thais. *Tissue Antigens* **2002**, *60*, 309–318. [CrossRef] [PubMed]
26. Wullimann, D.; Ljunggren, H.G. Human T Cell Responses to Flavivirus Vaccines. *Eur. J. Immunol.* **2025**, *55*, e70027. [CrossRef] [PubMed]
27. Ma, M.; Ye, P.; Pan, J.; Zhang, Y.; Yan, W.; Xu, B.; Ding, J.; Jiang, L. Research progress of dengue virus T cell epitope mediated cellular immunity in avoiding ADE. *Front. Immunol.* **2026**, *17*, 1785887. [CrossRef] [PubMed]
28. Vejbaesya, S.; Luangtrakool, P.; Luangtrakool, K.; Kalayanarooj, S.; Vaughn, D.W.; Endy, T.P.; Mammen, M.P.; Green, S.; Libraty, D.H.; Ennis, F.A.; et al. TNF and LTA gene, allele, and extended HLA haplotype associations with severe dengue virus infection in ethnic Thais. *J. Infect. Dis.* **2009**, *199*, 1442–1448. [CrossRef] [PubMed]
29. Sierra, B.; Alegre, R.; Pérez, A.B.; García, G.; Sturn-Ramírez, K.; Obasanjo, O.; Aguirre, E.; Alvarez, M.; Rodriguez-Roche, R.; Valdés, L.; et al. HLA-A, -B, -C, and -DRB1 allele frequencies in Cuban individuals with antecedents of dengue 2 disease: Advantages of the Cuban population for HLA studies of dengue virus infection. *Hum. Immunol.* **2007**, *68*, 531–540. [CrossRef] [PubMed]
30. Chen, Y.; Liao, Y.; Yuan, K.; Wu, A.; Liu, L. HLA-A, -B, -DRB1 alleles as genetic predictive factors for dengue disease: A systematic review and meta-analysis. *Viral Immunol.* **2019**, *32*, 121–130. [CrossRef] [PubMed]
31. Lan, N.T.P.; Kikuchi, M.; Huong, V.T.Q.; Ha, D.Q.; Thuy, T.T.; Tham, V.D.; Tuan, H.M.; Van Tuong, V.; Nga, C.T.P.; Van Dat, T.; et al. Protective and enhancing HLA alleles, HLA-DRB1*0901 and HLA-A*24, for severe forms of dengue virus infection, dengue hemorrhagic fever and dengue shock syndrome. *PLoS Negl. Trop. Dis.* **2008**, *2*, e304. [CrossRef] [PubMed]
32. LaFleur, C.; Granados, J.; Vargas-Alarcón, G.; Ruiz-Morales, J.; Villarreal-Garza, C.; Higuera, L.; Hernández-Pacheco, G.; Cutiño-Moguel, T.; Rangel, H.; Figueroa, R.; et al. HLA-DR antigen frequencies in Mexican patients with dengue virus infection: HLA-DR4 as a possible genetic resistance factor for dengue hemorrhagic fever. *Hum. Immunol.* **2002**, *63*, 1039–1044. [CrossRef] [PubMed]
33. Townsley, E.; Woda, M.; Thomas, S.J.; Kalayanarooj, S.; Gibbons, R.V.; Nisalak, A.; Srikiatkhachorn, A.; Green, S.; Stephens, H.A.; Rothman, A.L.; et al. Distinct activation phenotype of a highly conserved novel HLA-B57-restricted epitope during dengue virus infection. *Immunology* **2014**, *141*, 27–38. [CrossRef] [PubMed]
34. Vejbaesya, S.; Thongpradit, R.; Kalayanarooj, S.; Luangtrakool, K.; Luangtrakool, P.; Gibbons, R.V.; Srinak, D.; Ngammthaworn, S.; Apisawes, K.; Yoon, I.K.; et al. HLA Class I Supertype Associations With Clinical Outcome of Secondary Dengue Virus Infections in Ethnic Thais. *J. Infect. Dis.* **2015**, *212*, 939–947. [CrossRef] [PubMed]
35. Polizel, J.R.; Bueno, D.; Visentainer, J.E.L.; Sell, A.M.; Borelli, S.D.; Tsuneto, L.T.; Dalalio, M.M.; Coimbra, M.T.; Moliterno, R.A. Association of human leukocyte antigen DQ1 and dengue fever in a white Southern Brazilian population. *Mem. Inst. Oswaldo Cruz.* **2004**, *99*, 559–562. [CrossRef] [PubMed]
36. Cardozo, D.M.; Moliterno, R.A.; Sell, A.M.; Guelsin, G.A.S.; Beltrame, L.M.; Clementino, S.L.; Reis, P.G.; Alves, H.V.; Mazini, P.S.; Visentainer, J.E. Evidence of HLA-DQB1 contribution to susceptibility of dengue serotype 3 in dengue patients in Southern Brazil. *J. Trop. Med.* **2014**, *2014*, 968262. [CrossRef] [PubMed]
37. Loke, H.; Bethell, D.B.; Phuong, C.X.T.; Dung, M.; Schneider, J.; White, N.J.; Day, N.P.; Farrar, J.; Hill, A.V. Strong HLA class I-restricted T cell responses in dengue hemorrhagic fever: A double-edged sword? *J. Infect. Dis.* **2001**, *184*, 1369–1373. [CrossRef] [PubMed]
38. Sorgho, P.A.; Kafando, A.O.; Ouedraogo, R.A.; Kabre, K.M.; Nacoulma, S.F.; Adico, M.D.W.; Ouedraogo, T.C.; Yelemkoure, E.T.; Sombie, H.K.; Kiendrebeogo, T.I.; et al. HLA-DRB1*03 and HLA-DRB1*04 alleles in patients infected with dengue virus in Burkina Faso. *Infect. Genet. Evol.* **2026**, *143*, 105983. [CrossRef] [PubMed]
39. Alagarasu, K.; Mulay, A.P.; Singh, R.; Gavade, V.B.; Shah, P.S.; Cecilia, D. Association of HLA-DRB1 and TNF genotypes with dengue hemorrhagic fever. *Hum. Immunol.* **2013**, *74*, 610–617. [CrossRef] [PubMed]

40. Traoré, L.; Kouta, O.F.; Tapsoba, A.S.A.; Ouattara, A.K.; Kanfon, R.; Yougbaré, M.R.; Tassembedo, F.; Savadogo, M.; Sanon, N.; Bello, S.O.T.; et al. Involvement of HLA-DRB1*11 and HLA-DRB1*12 alleles in the occurrence of dengue fever in Burkina Faso. *J. Exp. Mol. Biol.* **2025**, *26*, 1–12. [CrossRef]
41. Fernández-Mestre, M.T.; Gendzekhadze, K.; Rivas-Vetencourt, P.; Layrisse, Z. TNF-alpha-308A allele, a possible severity risk factor of hemorrhagic manifestation in dengue fever patients. *Tissue Antigens* **2004**, *64*, 469–472. [CrossRef] [PubMed]
42. Naing, C.; Htet, N.H.; Siew Tung, W.; Basavaraj, A.K.; Mak, J.W. Association of tumor necrosis factor-α (TNF-α) gene polymorphisms (-308 G. *PLoS ONE* **2018**, *13*, e0205413. [CrossRef] [PubMed]
43. Useche, Y.M.; Ribeiro-Alves, M.; Restrepo, B.N.; Salgado, D.M.; Narváez, C.F.; Campo, O.; Avendaño, E.; Martínez, C.; Chacón-Duque, J.C.; Bedoya, G. Single-nucleotide polymorphisms in NOD1, RIPK2, MICB, PLCE1, TNF, and IKBKE genes associated with symptomatic dengue in children from Colombia. *Viral Immunol.* **2018**, *31*, 613–623. [CrossRef] [PubMed]
44. Avendaño-Tamayo, E.; Campo, O.; Chacón-Duque, J.C.; Ramírez, R.; Rojas, W.; Agudelo-Flórez, P.; Bedoya, G.; Restrepo, B.N. Variantes en los genes TNFA, IL6 e IFNG asociadas con la gravedad del dengue en una muestra de población colombiana. *Biomédica* **2017**, *37*, 485–497. [CrossRef]
45. Santos, A.C.; de Moura, E.L.; Ferreira, J.M.; Santos, B.R.; Alves, V.M.; de Farias, K.F.; de Souza Figueiredo, E.V. Meta-Analysis of the Relationship between TNF-α (-308G/A) and IL-10 (-819C/T) Gene Polymorphisms and Susceptibility to Dengue. *Immunol. Investig.* **2017**, *46*, 201–220. [CrossRef] [PubMed]
46. Pérez, A.B.; Sierra, B.; García, G.; Aguirre, E.; Babel, N.; Alvarez, M.; Sánchez, L.; Valdés, L.; Volk, H.D.; Guzmán, M.G. Tumor necrosis factor-alpha, transforming growth factor-β1, and interleukin-10 gene polymorphisms: Implication in protection or susceptibility to dengue hemorrhagic fever. *Hum. Immunol.* **2010**, *71*, 1135–1140. [CrossRef] [PubMed]
47. Chen, R.F.; Wang, L.; Cheng, J.T.; Chuang, H.; Chang, J.C.; Liu, J.W.; Lin, I.C.; Yang, K.D. Combination of CTLA-4 and TGFβ1 gene polymorphisms associated with dengue hemorrhagic fever and virus load in a dengue-2 outbreak. *Clin. Immunol.* **2009**, *131*, 404–409. [CrossRef] [PubMed]
48. Loke, H.; Bethell, D.; Phuong, C.X.T.; Day, N.; White, N.; Farrar, J.; Hill, A. Susceptibility to dengue hemorrhagic fever in Vietnam: Evidence of an association with variation in the vitamin D receptor and Fc gamma receptor IIa genes. *Am. J. Trop. Med. Hyg.* **2002**, *67*, 102–106. [CrossRef] [PubMed]
49. García, G.; Sierra, B.; Pérez, A.B.; Aguirre, E.; Rosado, I.; González, N.; Izquierdo, A.; Pupo, M.; Danay Díaz, D.R.; Sánchez, L.; et al. Asymptomatic dengue infection in a Cuban population confirms the protective role of the RR variant of the FcγRIIa polymorphism. *Am. J. Trop. Med. Hyg.* **2010**, *82*, 1153–1156. [CrossRef] [PubMed]
50. García, G.; González, D.; Sánchez, L.; Pérez, A.B.; Sierra, B.; Guzmán, M.G. Polimorfismo del receptor FcγRIIa y su posible relación con las manifestaciones clínicas del dengue. *Enferm. Infecc. Microbiol. Clin.* **2012**, *30*, 621–623. [CrossRef] [PubMed]
51. Sakuntabhai, A.; Turbpaiboon, C.; Casadémont, I.; Chuansumrit, A.; Lowhnoo, T.; Kajaste-Rudnitski, A.; Kalayanarooj, S.M.; Tangnararatchakit, K.; Tangthawornchaikul, N.; Vasanawathana, S.; et al. A variant in the CD209 promoter is associated with severity of dengue disease. *Nat. Genet.* **2005**, *37*, 507–513. [CrossRef] [PubMed]
52. Oliveira, L.F.; Lima, C.P.; Azevedo Rdo, S.; Mendonça, D.S.; Rodrigues, S.G.; Carvalho, V.L.; Pinto, E.V.; Maia, A.L.; Maia, M.H.; Vasconcelos, J.M.; et al. Polymorphism of DC-SIGN (CD209) promoter in association with clinical symptoms of dengue fever. *Viral Immunol.* **2014**, *27*, 245–249. [CrossRef] [PubMed]
53. Wang, L.; Chen, R.F.; Liu, J.W.; Lee, I.K.; Lee, C.P.; Kuo, H.C.; Huang, S.K.; Yang, K.D. DC-SIGN (CD209) promoter -336 A/G polymorphism is associated with dengue hemorrhagic fever and correlated to DC-SIGN expression and immune augmentation. *PLoS Negl. Trop. Dis.* **2011**, *5*, e934. [CrossRef] [PubMed]
54. Noecker, C.A.; Amaya-Larios, I.Y.; Galeana-Hernández, M.; Ramos-Castaneda, J.; Martínez-Vega, R.A. Contrasting associations of polymorphisms in FcγRIIa and DC-SIGN with the clinical presentation of dengue infection in a Mexican population. *Acta Trop.* **2014**, *138*, 15–22. [CrossRef] [PubMed]
55. Alagarasu, K.; Damle, I.M.; Bachal, R.V.; Mulay, A.P.; Shah, P.S.; Dayaraj, C. Association of promoter region polymorphisms of CD209 gene with clinical outcomes of dengue virus infection in Western India. *Infect. Genet. Evol.* **2013**, *17*, 239–242. [CrossRef] [PubMed]
56. Yougbare, F.; Tapsoba, A.S.A.; Sorgho, P.A.; Bayala, B.; Traore, L.; Bado, P.; Baze, N.V.E.J.T.; Zoure, A.A.; Traore, E.M.A.; Moudukede, T.; et al. DC-SIGN (CD209) promoter -336 A/G polymorphism is not associated with dengue fever at Burkina Faso, West Africa. *J. Biosci. Med.* **2023**, *11*, 175–183.
57. Ren, J.; Wang, Z.; Chen, E. Different associations between DC-SIGN promoter -336G/A (rs4804803) polymorphism with severe dengue in Asians and South-Central Americans: A meta-analysis. *Int. J. Environ. Res. Public Health* **2019**, *16*, 1475. [CrossRef] [PubMed]
58. Ornelas, A.M.M.; Xavier-de-Carvalho, C.; Alvarado-Arnez, L.E.; Ribeiro-Alves, M.; Rossi, Á.D.; Tanuri, A.; de Aguiar, R.S.; Moraes, M.O.; Cardoso, C.C. Association between MBL2 haplotypes and dengue severity in children from Rio de Janeiro, Brazil. *Mem. Inst. Oswaldo Cruz.* **2019**, *114*, e190004. [CrossRef] [PubMed]

59. Sena, M.A.; da Silva Castanha, P.M.; Giles Guimarães, A.B.; Oliveira, P.A.D.S.; da Silva, M.A.L.; Cordeiro, M.T.; Moura, P.; Braga, C.; Vasconcelos, L.R.S. Mannose-binding lectin levels and MBL2 gene polymorphisms are associated with dengue infection in Brazilian children at the early ages. *Int. J. Infect. Dis.* **2022**, *117*, 212–219. [CrossRef] [PubMed]
60. Giang, N.T.; van Tong, H.; Quyet, D.; Hoan, N.X.; Nghia, T.H.; Nam, N.M.; Hung, H.V.; Anh, D.T.; Van Mao, C.; Son, H.A.; et al. Complement protein levels and MBL2 polymorphisms are associated with dengue and disease severity. *Sci. Rep.* **2020**, *10*, 14923. [CrossRef] [PubMed]
61. Cahill, M.E.; Conley, S.; DeWan, A.T.; Montgomery, R.R. Identification of genetic variants associated with dengue or West Nile virus disease: A systematic review and meta-analysis. *BMC Infect. Dis.* **2018**, *18*, 282. [CrossRef] [PubMed]
62. Xavier-Carvalho, C.; Gibson, G.; Brasil, P.; Ferreira, R.X.; de Souza Santos, R.; Gonçalves Cruz, O.; de Oliveira, S.A.; de Sá Carvalho, M.; Pacheco, A.G.; Kubelka, C.F.; et al. Single nucleotide polymorphisms in candidate genes and dengue severity in children: A case-control, functional and meta-analysis study. *Infect. Genet. Evol.* **2013**, *20*, 197–205. [CrossRef] [PubMed]
63. Tapsoba, A.S.A.; Djigma, F.W.; Bayala, B.; Sorgho, P.A.; Traore, L.; Zohoncon, T.M.; Bello, S.O.T.; Bado, P.; Bazie, B.V.E.J.T.; Yougbare, F.; et al. KIR2DL2, KIR2DL5A and KIR2DL5B genes induce susceptibility to dengue virus infection, while KIR3DL3 and KIR2DS5 confer protection. *Mediterr. J. Hematol. Infect. Dis.* **2022**, *14*, e2022075. [CrossRef] [PubMed]
64. Beltrame, L.M.; Sell, A.M.; Moliterno, R.A.; Clementino, S.L.; Cardozo, D.M.; Dalalio, M.M.; Fonzar, U.J.; Visentainer, J.E. Influence of KIR genes and their HLA ligands in susceptibility to dengue in a population from southern Brazil. *Tissue Antigens* **2013**, *82*, 397–404. [CrossRef] [PubMed]
65. Alagarasu, K.; Bachal, R.V.; Shah, P.S.; Cecilia, D. Profile of killer cell immunoglobulin-like receptor and its human leucocyte antigen ligands in dengue-infected patients from Western India. *Int. J. Immunogenet.* **2015**, *42*, 432–438. [CrossRef] [PubMed]
66. Candrasari, D.S.; Purwosatrio, P.G.; Purnomosari, D.; Laksanawati, I.S.; Nirwati, H. Host genetic factors modulating dengue virus: A systematic review of TLR polymorphisms. *BMC Infect. Dis.* **2026**, *26*, 399. [CrossRef] [PubMed]
67. Diep, N.T.; Giang, N.T.; Diu, N.T.T.; Nam, N.M.; Khanh, L.V.; Quang, H.V.; Hang, N.T.; Mao, C.V.; Son, H.V.; Hieu, N.L.; et al. Complement receptor type 1 and 2 (CR1 and CR2) gene polymorphisms and plasma protein levels are associated with the Dengue disease severity. *Sci. Rep.* **2023**, *13*, 17377. [CrossRef] [PubMed]
68. Dang, T.N.; Naka, I.; Sa-Ngasang, A.; Anantapreecha, S.; Wichukchinda, N.; Sawanpanyalert, P.; Patarapotikul, J.; Tsuchiya, N.; Ohashi, J. Association of BAK1 single nucleotide polymorphism with a risk for dengue hemorrhagic fever. *BMC Med. Genet.* **2016**, *17*, 43. [CrossRef] [PubMed]
69. Gokul, A.; Arumugam, T.; Ramsuran, V. Genetic Ethnic Differences in Human 2′-5′-Oligoadenylate Synthetase and Disease Associations: A Systematic Review. *Genes* **2023**, *14*, 527. [CrossRef] [PubMed]
70. Mesev, E.V.; LeDesma, R.A.; Ploss, A. Decoding type I and III interferon signaling during viral infection. *Nat. Microbiol.* **2019**, *4*, 914–924. [CrossRef] [PubMed]
71. Soundravally, R.; Hoti, S.L. Immunopathogenesis of dengue hemorrhagic fever and shock syndrome: Role of TAP and HPA gene polymorphism. *Hum. Immunol.* **2007**, *68*, 973–979. [CrossRef] [PubMed]
72. Acioli-Santos, B.; Segat, L.; Dhalia, R.; Brito, C.A.A.; Braga-Neto, U.M.; Marques, E.T.A.; Crovella, S. MBL2 gene polymorphisms protect against development of thrombocytopenia associated with severe dengue phenotype. *Hum. Immunol.* **2008**, *69*, 122–128. [CrossRef] [PubMed]
73. Whitehorn, J.; Chau, T.N.B.; Nguyet, N.M.; Kien, D.T.H.; Quyen, N.T.H.; Trung, D.T.; Pang, J.; Wills, B.; Van Vinh Chau, N.; Farrar, J.; et al. Genetic variants of MICB and PLCE1 and associations with non-severe dengue. *PLoS ONE* **2013**, *8*, e59067. [CrossRef] [PubMed]
74. García, G.; del Puerto, F.; Pérez, A.B.; Sierra, B.; Aguirre, E.; Kikuchi, M.; Sánchez, L.; Hirayama, K.; Guzmán, M.G. Association of MICA and MICB alleles with symptomatic dengue infection. *Hum. Immunol.* **2011**, *72*, 904–907. [CrossRef] [PubMed]
75. Oliveira, M.; Saraiva, D.P.; Cavadas, B.; Fernandes, V.; Pedro, N.; Casademont, I.; Koeth, F.; Alshamali, F.; Harich, N.; Cherni, L.; et al. Population genetics-informed meta-analysis in seven genes associated with risk to dengue fever disease. *Infect. Genet. Evol.* **2018**, *63*, 213–223. [CrossRef] [PubMed]
76. Silva, L.K.; Blanton, R.E.; Parrado, A.R.; Melo, P.S.; Morato, V.G.; Reis, E.A.; Días, J.P.; Castro, J.M.; Vasconcelos, P.F.; Goddard, K.A.; et al. Dengue hemorrhagic fever is associated with polymorphisms in JAK1. *Eur. J. Hum. Genet.* **2010**, *18*, 1221–1227. [CrossRef] [PubMed]
77. Sierra, B.; Triska, P.; Soares, P.; Garcia, G.; Perez, A.B.; Aguirre, E.; Oliveira, M.; Cavadas, B.; Regnault, B.; Alvarez, M.; et al. OSBPL10, RXRA and lipid metabolism confer African-ancestry protection against dengue haemorrhagic fever in admixed Cubans. *PLoS Pathog.* **2017**, *13*, e1006220. [CrossRef] [PubMed]
78. Granela, H.; Perez, A.B.; Morier, L.; Alvarez, M.; Guzmán, M.G.; Sierra, B. Possible effects of ancestry-related oxysterol-binding protein-like 10 genetic polymorphisms on dengue virus replication and anti-dengue immune response. *Heliyon* **2024**, *10*, e37535. [CrossRef] [PubMed]

79. Sayem, M.; Rimon, R.A.; Alam, S.; Saba, A.A.; Sanyal, M.; Sayem, M.; Tabassum, C.T.; Amin, M.R.; Chakraborty, S.; Kabir, A.; et al. Genetic variability in thrombopoietin receptor and GATA1 influences response to eltrombopag in dengue-induced thrombocytopenia. *Sci. Rep.* **2026**, *16*, 7918. [CrossRef] [PubMed]
80. Gainor, E.M.; Harris, E.; LaBeaud, A.D. Uncovering the Burden of Dengue in Africa: Considerations on Magnitude, Misdiagnosis, and Ancestry. *Viruses* **2022**, *14*, 233. [CrossRef] [PubMed]
81. Fatimata Belem, W.; Sangare, I.; Gilbert, C.; Wenceslas Bazié, W. Dengue Fever and Its Burden in Burkina Faso: An Overview. *Rev. Med. Virol.* **2026**, *36*, e70089. [CrossRef] [PubMed] [PubMed Central]
82. Bello, M.B.; Aljedani, S.S.; Lawal, N.; Alasiri, A.; Imam, M.U. Evolutionary history and transmission dynamics of dengue virus type 2 in Africa. *Front. Microbiol.* **2026**, *17*, 1782819. [CrossRef] [PubMed]
83. Boillat-Blanco, N.; Klaassen, B.; Mbarack, Z.; Samaka, J.; Mlaganile, T.; Masimba, J.; Narvaez, L.F.; Mamin, A.; Genton, B.; Kaiser, L.; et al. Dengue fever in Dar es Salaam, Tanzania: Clinical features and outcome in populations of black and non-black racial category. *BMC Infect. Dis.* **2018**, *18*, 644. [CrossRef] [PubMed]
84. Tassembedo, F.; Tapsoba, A.S.A.; Bello, S.O.T.; Kouta, O.F.; Savadogo, M.; Ouedraogo, R.A.; Ilboudo, D.P.; Traore, L.; Yougbare, F.; Nagalo, B.M.; et al. TNF-α 308 (rs1800629) and INF-γ +874 polymorphisms in dengue progression: Genotype-specific trends amidst allelic non-association in West Africa. *Cell Mol. Biol.* **2025**, *71*, 1–8. [CrossRef] [PubMed]
85. Kalayanarooj, S.; Gibbons, R.V.; Vaughn, D.; Green, S.; Nisalak, A.; Jarman, R.G.; Mammen, M.P., Jr.; Perng, G.C. Blood group AB is associated with increased risk for severe dengue disease in secondary infections. *J. Infect. Dis.* **2007**, *195*, 1014–1017. [CrossRef] [PubMed]
86. Ravichandran, S.; Ramya, S.R.; Kanungo, R. Association of ABO blood groups with dengue fever and its complications in a tertiary care hospital. *J. Lab. Physicians* **2019**, *11*, 265–269. [CrossRef] [PubMed]
87. García, A.H.; Crespo, F.; Isea, J.; Mayora, S.; Belisario, I.; De Sanctis, J.B. Post-Dengue Syndrome: From Immunopathogenesis to Multisystemic Clinical Sequelae. *Immuno* **2026**, *6*, 63. [CrossRef]
88. Latif, M.A.; Noman, M.A.; Ahmmed, R.; Hossain, M.S.; Ahmed, M.F.; Pappu, M.A.A.; Islam, M.S.; Noor, T.; Kabir, M.H.; Mollah, M.N.H. In-silico identification of host-key-genes associated with dengue-virus-infections highlighting their pathogenetic mechanisms and therapeutic agents. *PLoS ONE* **2025**, *20*, e0333509. [CrossRef] [PubMed]
89. Josyula, J.V.N.; Jangili, S.; Yaladanda, N.; Pillai, A.K.B.; Mutheneni, S.R. Exploring potential gene signatures in dengue through machine learning and deep learning approaches. *Virus Genes* **2026**, *62*, 51–66. [CrossRef] [PubMed]
90. Datta, D.; Ghosh, S. Analyzing the Molecular Signature Genes and Pathways of Dengue Fever, Dengue Hemorrhagic Fever and Dengue Shock Syndrome Caused by Dengue Virus in India. *Mol. Biotechnol.* **2026**, *68*, 777–794. [CrossRef] [PubMed]
91. Kenney, A.D.; Dowdle, J.A.; Bozzacco, L.; McMichael, T.M.; St Gelais, C.; Panfil, A.R.; Sun, Y.; Schlesinger, L.S.; Anderson, M.Z.; Green, P.L.; et al. Human Genetic Determinants of Viral Diseases. *Annu. Rev. Genet.* **2017**, *51*, 241–263. [CrossRef] [PubMed]
92. Khare, K.; Yadav, S.; Tarai, B.; Budhiraja, S.; Pandey, R. TCR repertoire dynamics and their responses underscores dengue severity. *iScience* **2024**, *27*, 110983. [CrossRef] [PubMed]
93. Yoo, J.S.; Shporn, O.Z.; Sklan, E.H. Dysregulated immune cell responses in severe dengue pathogenesis. *Front. Immunol.* **2025**, *16*, 1600999. [CrossRef] [PubMed]
94. Nguyen, A.T.; Szeto, C.; Gras, S. The pockets guide to HLA class I molecules. *Biochem. Soc. Trans.* **2021**, *49*, 2319–2331. [CrossRef] [PubMed]
95. Magyari, B.; Fülöp, A.T.; Kókai, D.; Tóth, F.; Balogh, G.M.; Andreu-Sánchez, S.; Innocenti, G.; Weersma, R.K.; Fu, J.; Pál, C.; et al. HLA-II peptide-binding diversity shapes humoral immune responses and susceptibility to infections. *Nat. Commun.* **2026**, *17*, 9422. [CrossRef] [PubMed]

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