Investigation of susceptibility genes for chickenpox disease across multiple continents

by Lalu Muhammad Irham

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Lalu Muhammad Irham [a,*], Wirawan Adikusuma [b], Lolita Lolita [a], Anisa Nova Puspitaningrum [a], Arief Rahman Afief [a], Made Ary Sarasmita [c], Haafizah Dania [a], Sabiah Khairi [d], Gina Noor Djalilah [e], Barkah Djaka Purwanto [f,g], Rocky Cheung [h]

[a] Faculty of Pharmacy, Universitas Ahmad Dahlan, Yogyakarta, Indonesia
[b] Department of Pharmacy, University of Muhammadiyah Mataram, Mataram, Indonesia
[c] Pharmacy Study Program, Faculty of Science and Mathematics, Udayana University, Bali, Indonesia
[d] School of Nursing, College of Nursing, Taipei Medical University, Taipei, 11031, Taiwan
[e] Medical Faculty Muhammadiyah Surabaya, Surabaya, 60115, Indonesia
[f] Faculty of Medicine, University of Ahmad Dahlan, Yogyakarta, 55191, Indonesia
[g] PKU Muhammadiyah Bantul Hospital, Bantul, Yogyakarta, 55711, Indonesia
[h] Department of Chemistry and Biochemistry, University of California, Los Angeles, USA

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ABSTRACT

Chickenpox (varicella) is caused by infection with the varicella-zoster virus (VZV), a neurotropic alpha herpes virus with a double-stranded DNA genome. Chickenpox can cause life-threatening complications, including subsequent bacterial infections, central nervous system symptoms, and even death without any risk factors. Few studies have been reported to investigate genetic susceptibility implicated in chickenpox. Herein, our study identified global genetic variants that potentially contributed to chickenpox susceptibility by utilizing the established bioinformatic-based approach. We integrated several databases, such as genome-wide association studies (GWAS) catalog, GTEx portal, HaploReg version 4.1, and Ensembl databases analyses to investigate susceptibility genes associated with chickenpox. Notably, increased expression of *HLA-S*, *HCG4P5*, and *ABHD16A* genes underlie enhanced chickenpox susceptibility in the European, American, and African populations. As compared to the Asian population, Europeans, Americans, and Africans have higher allele frequencies of the extant variants rs9266089, rs10947050, and rs79501286 from the susceptibility genes. Our study suggested that these susceptibility genes and associated genetic variants might play a critical role in chickenpox progression based on host genetics with clinical implications.

1. Introduction

Chickenpox, also known as varicella, is an infectious disease caused by the varicella-zoster virus (VZV) [1]. The VZV, also known as herpesvirus 3, is a type of alpha herpesvirus which has double-stranded Deoxyribonucleic Acid (DNA). The primary targets of VZV infection are T lymphocytes, ganglia, and epithelial cells [2]. The most common symptoms of chickenpox in children are fever, headache, backache, chills, nausea, and vomiting [3]. These symptoms are often accompanied by the appearance of a rash that spreads across the entire body's surface skin [4].

VZV infections occur globally, but the epidemiology of these infections varies by region depending on the geographical location. This infection typically occurs in tropical and subtropical regions. In temperate zones, the incidence of chickenpox infection is quite high during the winter and early summer [5]. The majority of individuals living in the United States and Great Britain have had chickenpox by age 15 [6]. In other temperate regions, such as Slovenia, three-to four--year-old children account for 75% of chickenpox infections [7]. In tropical and subtropical climates, adults are more frequently infected with varicella than children [8].

VZV DNA detection in blood and saliva are helpful for the diagnosis and prognosis of varicella/chickenpox infections. VZV DNA can be found in T cells after 10 days of rash and remains there a week after [9].

* Corresponding author.
E-mail address: lalu.irham@pharm.uad.ac.id (L.M. Irham).

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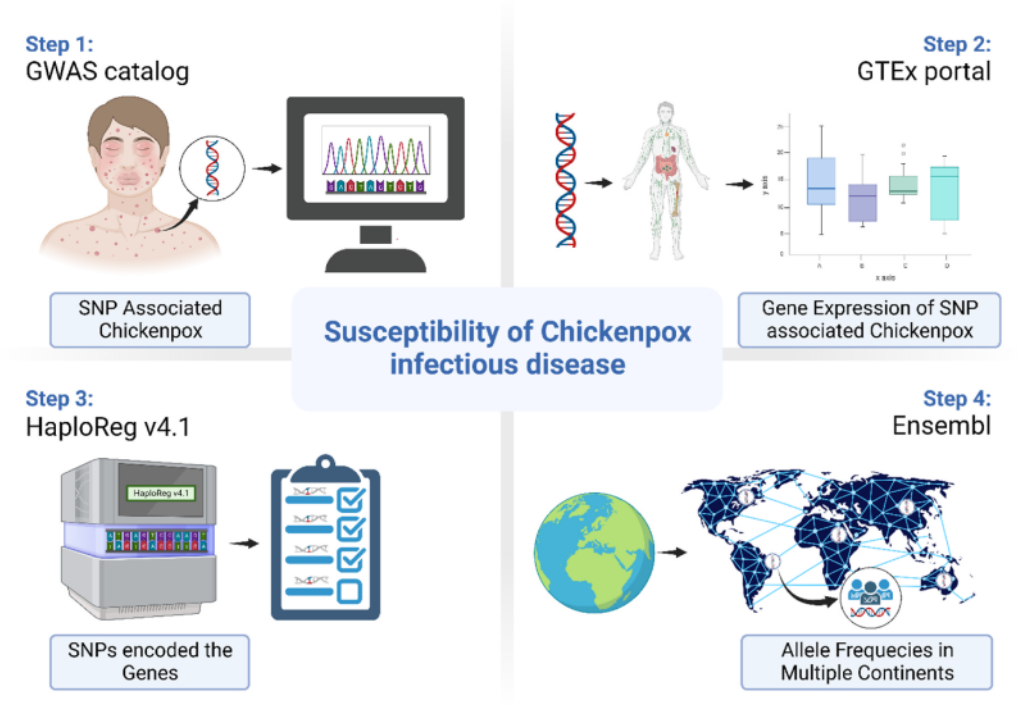

Fig. 1. Schematic of custom bioinformatics pipeline to identify chickenpox disease susceptibility genes across multiple continents. This figure was created with BioRender.com under agreement number "BH24OEAKNY ".

Variations in genes can aggravate chickenpox infection, but it is questionable whether they affect gene expression. Furthermore, a population with a high proportion of susceptibility gene carriers should be more susceptible to the disease.

To date, few studies have linked host genetic variation to chickenpox susceptibility [10]. As of this time, a previous study primarily focuses on the identification of the VZV genotype. The goal of the current study is to identify genetic variations that may contribute to Chickenpox disease transmission by utilizing bioinformatic-based approach. We integrated the genome-wide association studies (GWAS) catalog database with genomic datasets to identify gene expression associated with chickenpox. Therefore, our findings will provide the opportunity for future research to investigate whether these variants might be associated with different risks and susceptibility to chickenpox infection. Additionally, this discovery can be used to identify new candidate drugs for treating chickenpox disease.

2. Methods

A summary of the methodology of screening variants-associated with chickenpox disease is illustrated across the various steps in the bioinformatics pipeline (Fig. 1). We leveraged several bioinformatic-based approaches to integrate the variants of chickenpox disease, including GWAS catalog, GTEx portal, HaploReg version 4.1, and Ensembl databases. In the present study, the initial screening of Single Nucleotide Polymorphism (SNP) associated with chickenpox was obtained from the GWAS catalog database [https://www.ebi.ac.uk/gwas/] (accessed on August 19, 2022). We used the keyword "*chickenpox and susceptibility of chickenpox* "to obtain the GWAS-associated chickenpox. To determine the SNP associated with chickenpox, we strictly selected p-value $< 10^{-8}$ as inclusion criteria. In our analysis, we removed all duplicate variants from the dataset in order to guarantee these variants are unique SNPs. Subsequently, a bioinformatic-based approach was employed to interrogate the expression of these variants. Next, we validated the SNPs that had been rigorously filtered using the GTEx portal database [http://www.gtexportal.org/home/] (accessed on August 29, 2022). The purpose of this step is to evaluate these genetic variants with gene expression profiles in numerous body tissues. Following a search through the GTEx portal database, we further retrieved the SNPs encoded genes to identify the gene expression profiles. Herein, we leveraged the expression quantitative trait loci (eQTL) are regions harboring nucleotides correlated with alterations in gene expression. Therefore, the variants may cause changes in gene expression in the direction of the tissues involved (i.e., our analyses focused on the skin). Chickenpox is a highly contagious viral infection that causes a blistering, itchy rash on the skin accompanied by fever, viremia, and vesicular lesions that spread over the skin and are frequently reported in children [9]. We used Haploreg version 4.1 and Ensembl genomic databases to map the epidemiological distribution of the genetic basis of allele frequency in different populations. The allele frequencies associated with chickenpox were retrieved from a genetic database such as Haploreg version 4.1 [https://pubs.broadinstitute.org/mammals/haploreg/haploreg.php] (accessed on August 29, 2022) and Ensembl Genome Browser [http://www.ensembl.org/index.html] (accessed on August 30, 2022). Detection of the allele frequencies of each variant is intended to confirm the allele frequencies in populations from multiple continents (Africa, America, Asia, and Europe).

3. Results

Chickenpox-related SNPs were extracted from the GWAS catalog database. We identified 33 SNPs related to chickenpox that passed the inclusion criteria (Supplementary Table 1). Then, SNP data was filtered based on p-value $<10^{-8}$ and three SNPs were obtained related to

Table 1
Chickenpox associated Variant with criterion p-value $<10^{-8}$.

SNP	p-value	chr_pos
rs9266089	$1{,}00 \times 10^{-10}$	31352732
rs10947050	$1{,}00 \times 10^{-10}$	30072514
rs79501286	$2{,}00 \times 10^{-09}$	31475135

chickenpox (Table 1). Using the GTEx portal database, we later evaluated the tissue expression of three SNPs associated with chickenpox. This procedure is intended to verify that the three SNPs are closely associated with gene expression in skin tissues. Our study proposed that the SNPs, including rs9266089, rs10947050, and rs79501286 could affect the tissue expression of chickenpox.

4. Chickenpox gene expression in various tissues

We utilized the GTEx portal database in order to evaluate the expression of related genes in human tissues. This database focuses on the expression of eQTL in various human tissues, especially for the skin. The eQTL analysis could display gene expression data and describes the differences in gene expression caused by the tissue's natural genetic variations [10]. Intriguingly, the GTEx portal database identified three symbol genes associated with chickenpox, namely *HLA-S, HCG4P5*, *ABHD16A* (Table 2), which exhibit gene expression in the skin. It is important to note that patients with chickenpox typically present with a rash and fever [9]. Therefore, our study focused on gene and variant expression in skin tissues.

5. *Cis*-eQTL of *HLA-S, HCG4P5,* and *ABHD16A genes* in skin tissue

In the present study, we utilized the GTEx portal database with the knowledge that the functional roles of these variants affect protein expression. The eQTL associated with chickenpox expression in skin tissue were identified using the GTEx portal database. Forty different gene variants demonstrated the expression in skin tissues. However, only three genes respectively demonstrated a dominant effect on the expression of *HLA-S* (Fig. 2A), *HCG4P5* (Fig. 2B), and *ABHD16A* (Fig. 2C) in the skin. Furthermore, an additional search using PubMed database text mining was conducted to investigate the three associated eQTL in the skin tissues to determine whether the genetic variants might have clinical significance.

6. Relationship between gene variation and gene expression in skin tissue

Using the publicly available GTEx portal database, we identified minor alleles of *HLA-S* rs9266089, *HCG4P5* rs10947050, and *ABHD16A* rs79501286 respectively associated with chickenpox. As shown in Table 2 and Fig. 3, the *HLA-S* rs9266089 AA genotype was associated with increased expression in skin tissue compared to the GA and GG genotypes. The *HCG4P5* rs10947050 TT genotype had a greater expression in the skin than the CT and CC genotypes. Meanwhile, the *ABHD16A* rs79501286 AA genotype had a higher expression in the skin than the GA and GG genotypes.

7. Allele frequencies of selected variants in different populations

The genetic basis of allele frequency of three genes *HLA-S, HCG4P5,* and *ABHD16A* expression and function in different populations is still largely unknown. Therefore, we determined allele frequencies from human populations across multiple continents after identifying chickenpox expression variations. Table 3 shows allele frequencies in African, American, Asian, and European populations. The above allele frequencies were obtained from the Haploreg version 4.1 database, available at https://pubs.broadinstitute.org/mammals/haploreg/haploreg.php (accessed on August 29, 2022). There was a variation in the allele frequencies across the population for each of the SNPs shown in Fig. 4, which were obtained from the Ensembl Genome Browser database http://www.ensembl.org/Homo_sapiens/Variation (accessed on August 30, 2022). Table 3 and Fig. 4 reveal the global allele frequencies for each SNP. The frequency of the A allele at rs9266089, which was associated with the highest expression of *HLA-S* in chickenpox, was significantly lower in Asian populations (2%) than in American (11%), African (10%), or European (15%) populations. T allele frequency showed a higher expression in *HCG4P5* rs10947050, whereas it showed much a lower expression in African (13%) populations compared to Asians (28%), Americans (23%), and Europeans (31%). The A allele of rs79501286 in *ABHD16A* was much less common in Africa (1%), Asia (1%), and America (4%), than in Europe (10%). The allele frequencies of *HLA-S* variant rs9266089, *HCG4P5* variant rs10947050, and *ABHD16A* variant rs79501286 indicated that Asian populations might express these genomic variants less than European and American populations. Our current finding suggested that these susceptibility genes and associated genetic variants might play a critical role in chickenpox progression based on host genetics with clinical implications.

8. Discussion

Chickenpox is a virus-indused disease that infects humans and is transmissible via airborne or direct contact [11]. In this study, we examined the influence of *HLA-S*, *HCG4P5*, and *ABHD16A* on the tissue expression of chickenpox. Chickenpox symptoms include fever, headache, backache, chills, nausea, and vomiting [3] and accompanied by a rash on the entire body's skin surface [4]. The gene responsible for chickenpox, *HLA-S*, has been reported as a potential factor in herpes zoster disease [12], whose primary cause is VZV [13]. It is important to note that *HLA* belongs to the human leukocyte antigen (HLA) family, which produces a protein that plays a critical role in the immune system. *HLA-S* is part of a family of genes called *HLA* complex. The previous study reported that the *HLA* complexes assist the immune system in distinguishing between proteins made by the body and those made by foreign invaders such as viruses and bacteria [14]. It is known that the previous study reported the variants of *HLA-A*33* and *HLA-B*44* were at a strongly higher risk of developing Postherpetic neuralgia (PHN) in patients suffering from VZV infectious disease [13]. Other findings supported the study by revealing that the *HLA-A*02* in patients with atherosclerosis is associated with VZV seropositivity [15].

According to HaploReg version 4.1 bioinformatic database revealed that [https://pubs.broadinstitute.org/mammals/haploreg/haploreg.php], these three variants (rs9266089, rs10947050, and rs79501286) were involved in the changing chromatin status of primary T cells from

Table 2
Variants associated with chickenpox were expressed in the skin tissue.

SNP Id	Genecode Id ENSG00000	Gene Symbol	*p*-value	NES	Tissue	Expression
rs9266089	225851.1	*HLA-S*	4.8×10^{-14}	00.54	Skin - Sun Exposed (Lower leg)	AA > GA > GG
rs10947050	227766.1	*HCG4P5*	2.2×10^{-11}	00.36	Skin - Sun Exposed (Lower leg)	TT > CT > CC
rs79501286	204427.11	*ABHD16A*	0.00031	00.18	Skin - Sun Exposed (Lower leg)	AA > GA > GG

The source of expression data was obtained from the GTEx portal database https://www.gtexportal.org/home/

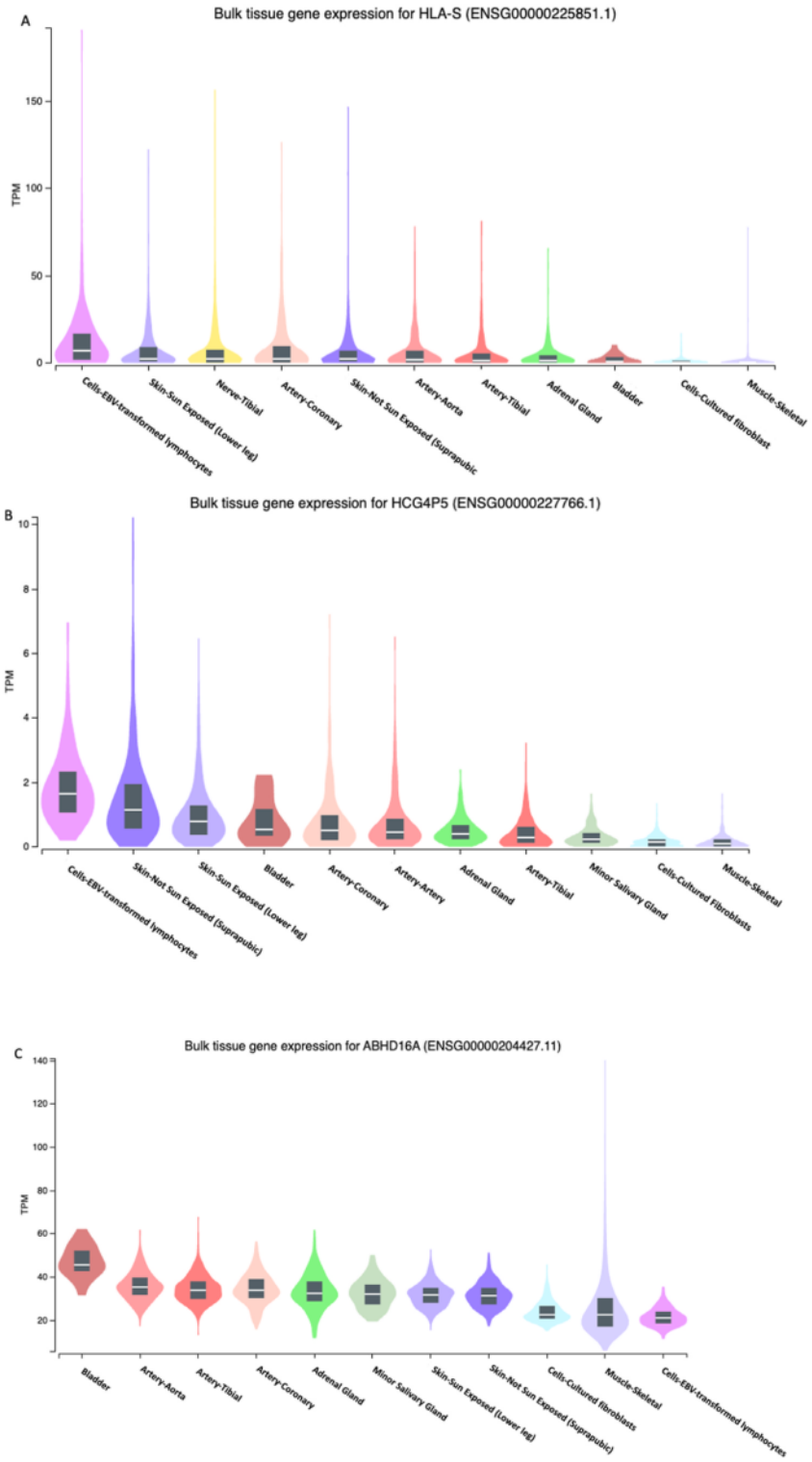

Fig. 2. Expression of chickenpox susceptibility genes across various human tissues: (**A**) *HLA-S*; (**B**) *HCG4P5*, and (**C**) *ABHD16A*.

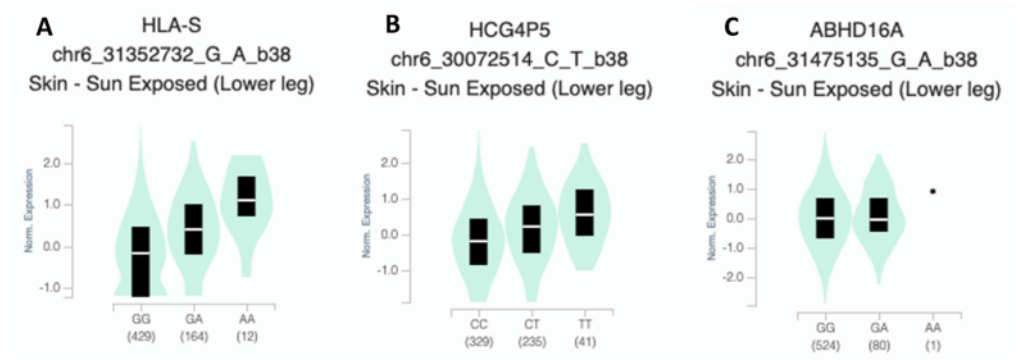

Fig. 3. SNP expression for each genotype across chickenpox disease susceptibility alleles. (**A**) rs9266089 (for *HLA-S* gene); (**B**) rs10947050 (for *HCG4P5* gene); (**C**) rs79501286 (for *ABHD16A* gene).

Table 3
Allele frequencies for each variant associated with chickenpox.

SNP	Position	Gene	Allele		Allele Frequencies			
			Ref	Eff*	AFR	AMR	ASN	EUR
rs9266089	Chr 6 : 31352732	*HLA-S*	G	A	0.10	0.11	0.02	0.15
rs10947050	Chr 6 : 30072514	*HCG4P5*	C	T	0.13	0.23	0.28	0.31
rs79501286	Chr 6 : 31475135	*ABHD16A*	G	A	0.01	0.04	0.01	0.10

AFR, Africa; AMR, America; ASN, Asian; EUR, Europe; Ref, Reference; Eff, Effect allele; AFR, AMR, ASN, EUR, extracted from Haploreg version 4.1 (https://pubs.broadinstitute.org/mammals/haploreg/haploreg.php). *Effect alleles were defined as alleles associated with higher expression of *HLA-S*, *HCG4P5* and *ABHD16A*.

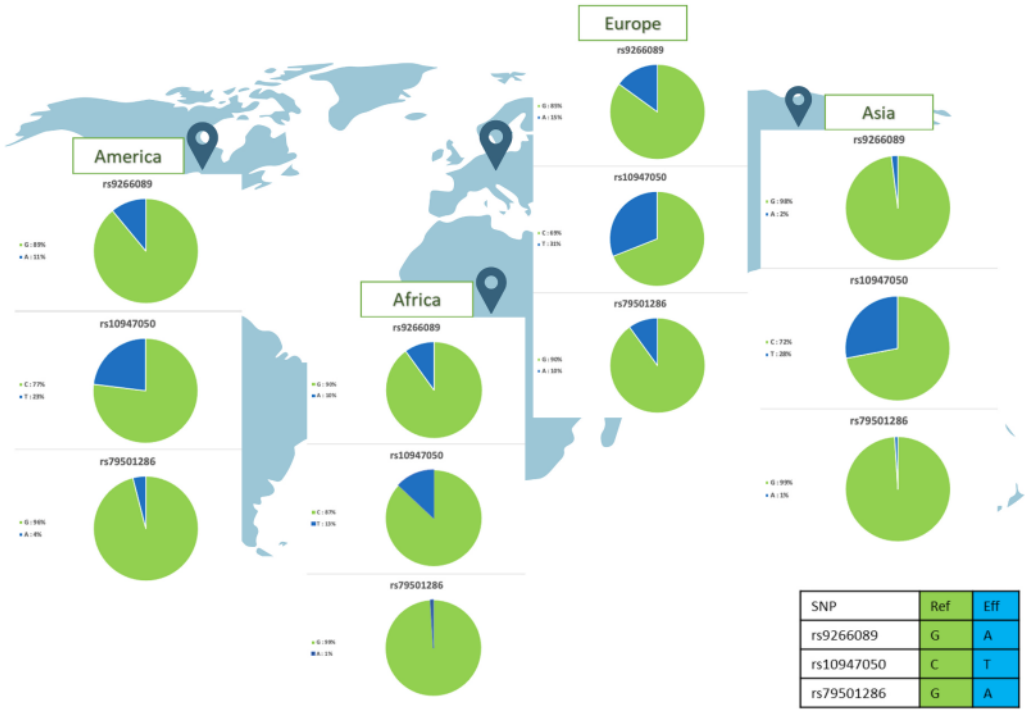

Fig. 4. Distribution of allele frequencies of the three variants (rs9266089, rs10947050, rs79501286) affecting *HLA-S*, *HCG4P5*, and *ABHD16A* among different populations across continents. This figure was created with BioRender.com under agreement number "CX24TS7TWB ".

peripheral blood, which plays a central role in the "primary immune response" of cell-mediated immunity. Furthermore, *ABHD16A* is a protein with a hydrolase/don[illegible] that has been linked to familial metabolic [illegible]rders [16]. We noted the important roles played by the *ABHD16A*, human *ABHD16A* is also known as human leukocyte antigen B (*HLA-B*). Anoth[illegible] observation of interest for gene *ABHD16A* supported that the gene could play an important role and function in immune regulation processes [17]. Moreover, *ABHD16A* is associated with immunoregulation [18], kawasaki disease, and coronary artery aneurysms [19]. Another gene, such as *HCG4P5* is also known as *HLA* complex group 4 pseudogene 5 [ENSG000002[illegible]66] *HLA* class I and functions for interferon signaling [20,21]. It is well known that Interferon plays a critical role in the human immune response [2]. Human genomic expression levels and patterns in different tissues might be critical for evaluating the susceptibility, symptoms, and outcome of disease, including for chickenpox infectious disease. We sincerely expect the results could be of immense essential in understanding the genetic basis of chickenpox infectious disease. Therefore, we strongly recommend that future research investigate these variants' functions, interactions, and mechanisms in the human body.

Multiple clinical characteristics and susceptibility loci were associated with VZV infection. *HLA* is located on chromosome 6 and is associated with VZV-caused herpes zoster [10]. *ABHD16A* is a member of the alpha-beta hydrolase domain-containing (*ABHD*) family of serine hydrolase metabolism, also referred to as leukocyte antigen-B- (*HLA-B*)-associated transcript 5 (*HLA-B*-associated transcript 5, *BAT5*), which is associated with familial hereditary metabolic disease [16]. We examined chickenpox-associated genetic variants using publicly accessible databases, such as the GWAS catalog [22], Haploreg version 4.1 [23], GTEx portal [24], and Ensembl [25]. Multiple studies have utilized these integration techniques to identify the *TMPRSS2* gene [26], the *ACE2* gene for COVID-19 [26], and a variant for Sjogren syndrome [27]. *HLA-S*, *HCG4P5*, and *ABHD16A* influence the occurrence of chickenpox, which causes fever, headache, backache, chills, nausea, vomiting, and a rash throughout the skin [3,4]. Currently, it is interesting to evaluate and use the variants for a variety of purposes. The variants are not only can guide the susceptibility of the diseases but also can be utilized to drive drug discovery [28–31].

In our study, we highlighted that the variants of rs9266089, rs10947050, and rs79501286 may affect the expression of *HLA-S, HCG4P5,* and *ABHD16A*, respectively. Based on our study, the AA genotype of rs9266089 had a higher *HLA-S* expression in the skin tissue than the GA (intermediate) and GG (lowest) genotypes (Table 3 and Fig. 3). The A allele frequency of SNP rs9266089 was 2% in Asians compared to Europeans, Americans, and Africans (Fig. 4). At rs10947050, the TT genotype had a higher *HCG4P5* skin expression than the heterozygous CT (intermediate) and homozygous CC (lowest) among European, American, and African populations. African populations had the lowest frequency of the T allele of SNP rs10947050, at 13%, compared to European, American, and Asian populations (Fig. 4). While the AA genotype at rs79501286 in *ABHD16A* had a higher expression in the skin than the heterozygous GA genotype (middle expression) and homozygous GG genotype (lowest expression) (Table 3 and Fig. 3), which were related to chickenpox illness susceptibility. The A allele frequency of SNP rs79501286 showed the lowest yield in Asian and African populations at 1% compared to European and American populations (Fig. 4). Asian individuals had the lowest allele frequencies in the skin for the variations (rs9266089, rs10947050, and rs79501286) related to chickenpox illness compared to European, American, and African groups. Consequently, it can be suggested that European, American, and African populations may have more individuals with the trend of elevated expression of *HLA-S, HCG4P5*, and *ABHD16A* compared to Asians, which may contribute to an increase in the susceptibility to chickenpox disease.

Overall, the allele frequencies of the variants (rs9266089, rs10947050, and rs79501286) that are associated with chickenpox disease showed the lowest allele frequencies in the Asian population. Thus, it can be assumed that European, American, and African populations may have more individuals with increased expression of *HLA-S, HCG4P5*, and *ABHD16A* compared to Asians, which may contribute to an increase in susceptibility to chickenpox disease. This study identified gene variants *in silico*, which must be validated in the clinical implementation of the varicella-zoster virus. However, we believe that meta-analysis based approach is essential to sharpen our prediction as a more comprehensive range of genetic variant data associated with chickenpox becomes available. In addition, further research is needed to validate our findings using functional studies. The validation aims to ascertain whether these variants have a critical role and could harbor a clinically actionable variant for the varicella-zoster virus.

9. Conclusion

Our study emphasizes the investigation of genetic variations influencing chickenpox that revealed the highest expression of *HLA-S*, *HCG4P5*, and *ABHD16A* in the skin tissue. These genes affected the chickenpox risk in individuals and populations. We discovered that the variants rs9266089, rs10947050, and rs79501286 affected *HLA-S*, *HCG4P5*, and *ABHD16A* expression, respectively. Allele frequency is crucial when predicting chickenpox illness susceptibility on multiple continents. Future avenues of research would aim to verify the impact of these variants and their clinical actionability in the diagnosis and management of chickenpox patients.

Author contribution

L.M.Irham and W. Adikusuma conceived and designed the study. L. M.Irham and W. Adikusuma performed the computational analysis. L.M. Irham wrote the manuscript. L.M.Irham provided the funding. A R Afief., A.N Puspitaningrum., Lolita., M.A.Sarasmita and H Dani Khairi, Gina N Djalilah, B Djaka Purwanto and Rocky Cheung revised the manuscript. All authors have read and approved the manuscript and have made significant contributions to this study.

Declaration of competing interest

The authors disclose no conflict.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbrep.2022.101419.

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