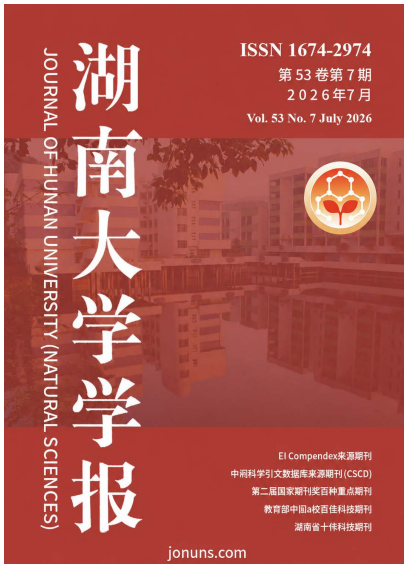

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Detection of S989P and V1016G Knockdown Resistance (kdr) Mutations in the Voltage-Gated Sodium Channel (VGSC) Gene of Aedes aegypti Populations in West Sumatra

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Abstract: *Aedes aegypti* is the principal vector of dengue and several other arboviral diseases, and its control remains heavily dependent on chemical insecticides. However, the prolonged and widespread use of insecticides has promoted the development of resistance, including knockdown resistance associated with mutations in the voltage-gated sodium channel (VGSC) gene. This study assessed insecticide susceptibility and investigated the occurrence of the S989P and V1016G *kdr mutations* in *Aedes aegypti* populations collected from dengue-endemic areas of West Sumatra, Indonesia. Mosquitoes were sampled from six districts. Larval susceptibility to temephos and adult susceptibility to malathion, permethrin, and alpha-cypermethrin were evaluated using standard World Health Organization bioassays. VGSC genotyping was performed using tetra-primer amplification-refractory mutation system polymerase chain reaction and allele-specific polymerase chain reaction. The bioassays revealed marked geographical variation in insecticide susceptibility, with widespread resistance to malathion, permethrin, and alpha-cypermethrin across the study sites. Molecular analysis detected the S989P and V1016G substitutions, corresponding to serine-to-proline and valine-to-glycine amino acid changes, respectively. These findings demonstrate reduced susceptibility to multiple insecticides and provide region-specific molecular evidence of *kdr*-associated mutations in

Aedes aegypti populations from West Sumatra. Although the number of genotyped specimens was limited, the results provide important baseline information for expanded resistance surveillance and the development of evidence-based insecticide resistance management and vector-control strategies.

Keywords: *Aedes aegypti;* insecticide resistance; knockdown resistance; voltage-gated sodium channel; S989P; V1016G; West Sumatra.

西苏门答腊埃及伊蚊种群电压门控钠通道（VGSC）基因S989P和V1016G击倒抗性（kdr）突变的检测

摘要： *Aedes aegypti* 是登革热及多种其他虫媒病毒性疾病的主要传播媒介，其防控仍在很大程度上依赖化学杀虫剂。然而，杀虫剂的长期和广泛使用促进了抗药性的产生，其中包括与电压门控钠通道（VGSC）基因突变相关的击倒抗性。本研究旨在评估印度尼西亚西苏门答腊省登革热流行地区 *Aedes aegypti* 种群对杀虫剂的敏感性，并检测 S989P 和 V1016G 击倒抗性（*kdr*）突变的存在情况。研究从6个地区采集蚊虫样本，并采用世界卫生组织标准生物测定方法评估幼虫对双硫磷以及成蚊对马拉硫磷、氯菊酯和高效氯氰菊酯的敏感性。VGSC 基因分型采用四引物扩增阻滞突变系统聚合酶链式反应和等位基因特异性聚合酶链式反应进行。生物测定结果显示，不同研究地点的杀虫剂敏感性存在明显的地理差异，且多个地区的蚊虫对马拉硫磷、氯菊酯和高效氯氰菊酯表现出广泛抗性。分子分析检测到 S989P 和 V1016G 氨基酸替换，分别对应丝氨酸向脯氨酸以及缬氨酸向甘氨酸的改变。研究结果表明，西苏门答腊省 *Aedes aegypti* 种群对多种杀虫剂的敏感性降低，并为该地区存在与 *kdr* 相关的突变提供了区域性分子证据。尽管用于基因分型的样本数量有限，本研究仍为扩大抗药性监测以及制定循证的杀虫剂抗性管理和病媒控制策略提供了重要的基线资料。

关键词： *Aedes aegypti*；杀虫剂抗性；击倒抗性；电压门控钠通道；S989P；V1016G；西苏门答腊。

1. Introduction

Aedes aegypti is the principal vector of several medically important arboviruses, including dengue, chikungunya, Zika, and yellow fever. Dengue remains a major global public health problem, with more than 120 endemic countries and an estimated 50–100 million infections annually. In Indonesia, dengue cases continue to increase, and West Sumatra is one of the provinces with widespread transmission across districts and municipalities, indicating persistent endemicity [1,2].

Vector control, particularly through the use of chemical insecticides, remains the main strategy for reducing *Aedes aegypti* populations. Organophosphates and pyrethroids are widely used due to their rapid knockdown effect and relatively low toxicity to mammals [3-4]. In Indonesia, chemical insecticides, including organophosphates and pyrethroids, remain important components of dengue vector control programs and are also commonly used in household-level mosquito control. However, prolonged and intensive insecticide use may impose selection pressure on *Aedes aegypti* populations, contributing to the emergence and spread of insecticide resistance and potentially reducing the effectiveness of control programs [5-7].

The increasing incidence of dengue in West Sumatra, despite continuous insecticide application, suggests reduced vector susceptibility and highlights the need for improved resistance monitoring strategies [2,8]. Conventional susceptibility testing using bioassay methods remains the standard approach for detecting resistance, based on mortality rates following exposure to diagnostic doses of insecticides [8–10]. However, these methods are often time-consuming and may not detect resistance at an early stage.

Insecticide resistance in mosquitoes is mainly driven by two mechanisms: target site resistance and

metabolic resistance. Target site resistance occurs when mutations alter the binding site of the insecticide, whereas metabolic resistance involves increased activity of detoxifying enzymes such as esterases, oxidases, and glutathione-S-transferases. One of the most important forms of target-site resistance is knockdown resistance (kdr), which is associated with point mutations in the voltage-gated sodium channel (VGSC) gene, the primary target site of pyrethroids and DDT. Several non-synonymous mutations in the VGSC gene have been identified in *Aedes aegypti*, including widely reported ones such as S989P, V1016G/I, V410L, and F1534C, which have been associated with reduced susceptibility to pyrethroids [5,11]. Among these, mutations in domain II, particularly S989P and V1016G, have been strongly associated with pyrethroid resistance in mosquito populations. These mutations reduce the sensitivity of sodium channels to insecticides, thereby decreasing the knockdown effect and increasing mosquito survival. The F1534C substitution in domain III is also one of the most widely reported kdr mutations associated with pyrethroid resistance in *Aedes aegypti* [11-12].

Globally, kdr mutations have been reported in *Aedes aegypti* populations from various regions, including Mexico [13-14], Thailand and Myanmar [15], Brazil [16], India [11,17], Malaysia [18], China [12,19], and Indonesia [20], particularly in Central Java [21], Yogyakarta [22], and Bali [23]. However, molecular data on S989P and V1016G mutations in *Aedes aegypti* populations from West Sumatra remain limited, despite the high burden of dengue and extensive insecticide use in this region. Molecular detection of resistance through identification of single nucleotide polymorphisms (SNPs) in the VGSC gene provides a sensitive and specific approach to complement conventional bioassays [24–25]. Therefore, this study aimed to detect the presence of S989P and V1016G allele mutations in the kdr mutations in the VGSC gene locus of *Aedes aegypti* populations collected from West Sumatra. By positioning the findings within previous Indonesian and regional reports, this study provides region-specific baseline molecular evidence for kdr-associated mutations in West Sumatra and supports the need for local resistance surveillance to guide evidence-based vector control decisions.

2. Methods and Materials

2.1. Study Area and Mosquito Collection

Larvae and pupae of *Aedes aegypti* were collected from domestic water-holding containers during household surveys conducted between February and August 2017 in six dengue-endemic districts of West Sumatra Province, Indonesia, namely Padang, Pariaman, Bukittinggi, Solok, Batusangkar, and Dharmasraya (Figure 1). These districts were selected based on historical dengue incidence and to represent both urban and peri-urban transmission settings.

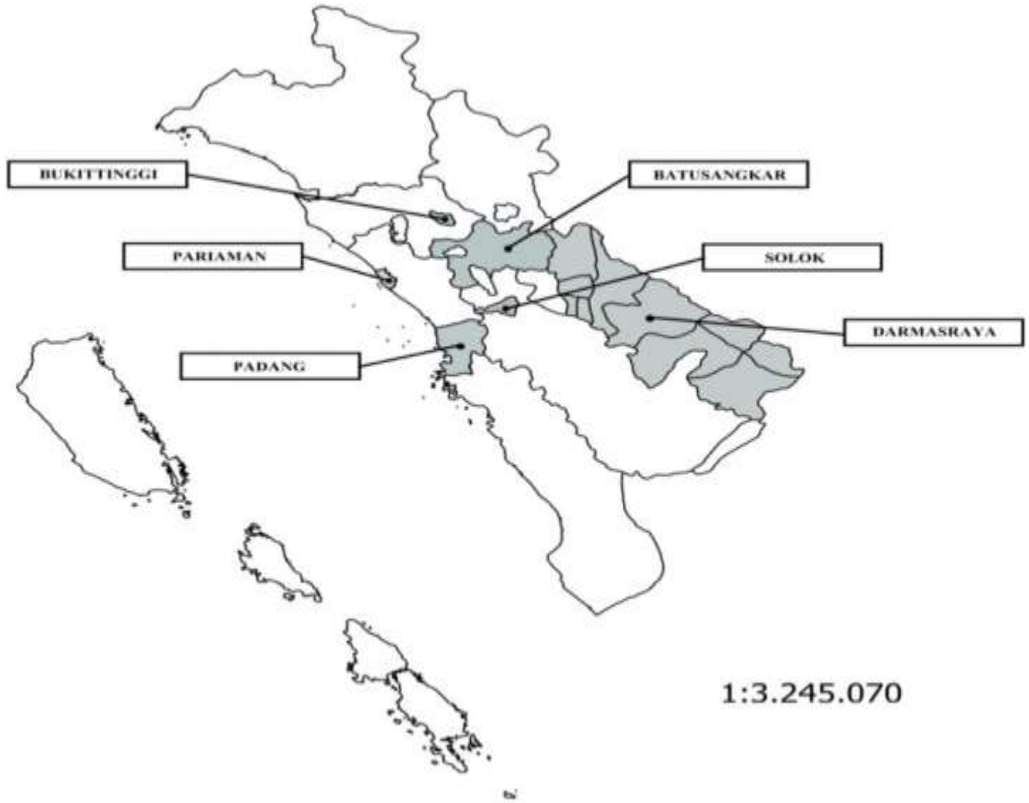

Figure 1. Location map of *Aedes aegypti* larvae collection in several regencies/cities in West Sumatra.

Collected immature stages were transported to the Parasitology Laboratory, Faculty of Medicine, Andalas University, and reared to adulthood under controlled laboratory conditions (27 ± 1 °C, relative humidity 70 ± 10%, and a 12:12 h light–dark cycle). Larvae were fed with ground fish meal, and adult mosquitoes were maintained on a 10% sucrose solution.

Morphological identification of *Aedes aegypti* was performed using standard taxonomic keys to confirm species identity [26]. Only non-blood-fed female mosquitoes aged 2–3 days were used for adult susceptibility testing. A laboratory-maintained colony obtained from the Parasitology Laboratory, Faculty of Medicine, Gadjah Mada University, Yogyakarta, was used as a comparative control population.

2.2. Insecticide Susceptibility Bioassays

Insecticide susceptibility testing was conducted in accordance with World Health Organization (WHO) standard procedures. For larval bioassays, third-instar larvae were exposed to temephos (Temephos Pestanal®, Sigma-Aldrich) at the WHO diagnostic concentration of 0.012 mg/L. Each assay consisted of four replicates of 20 larvae per treatment group, with corresponding untreated controls maintained under identical environmental conditions. Larval mortality was recorded after 24 hours of exposure.

Adult susceptibility testing was performed using WHO insecticide-impregnated papers containing malathion 5%, permethrin 0.75%, and alpha-cypermethrin 0.15%. Batches of 20 female mosquitoes were exposed for 1 hour in WHO exposure tubes. After exposure, mosquitoes were transferred to holding tubes, provided with a 10% sucrose solution, and maintained under standard laboratory conditions. Mortality was assessed 24 hours post-exposure. Susceptibility status was classified according to WHO criteria, with mortality rates of 98–100% considered susceptible, 90–97% indicating possible resistance requiring confirmation, and less than 90% classified as resistant. Following scoring, both dead and surviving mosquitoes were individually preserved in 70% ethanol and stored at −20 °C until DNA extraction.

2.3. DNA Extraction

Genomic DNA was extracted individually from resistant (alive) and susceptible (dead) mosquitoes after WHO bioassay exposure. For molecular analysis, five resistant and five susceptible mosquitoes were selected from each insecticide exposure group and collection site when sufficient specimens were available. Mosquitoes were selected from individually preserved samples to represent phenotypically resistant and susceptible groups based on their survival status 24 h after insecticide exposure. Genomic DNA was extracted using the DNAzol® extraction kit (Invitrogen, USA) following the manufacturer's protocol. DNA concentration and purity were determined using a NanoDrop 2000 spectrophotometer (Thermo Scientific, USA), and DNA samples were stored at −20 °C until further analysis.

2.4. Detection of kdr Mutations

Two knockdown resistance (kdr) mutations in the voltage-gated sodium channel (VGSC) gene, S989P and V1016G, were investigated. Genotyping of the S989P mutation was performed using tetra-primer amplification refractory mutation system PCR (ARMS-PCR) following established protocols [27,28]. PCR reactions were prepared using PCR master mix, template DNA, mutation-specific primers, and nuclease-free water according to the manufacturer's instructions and previously published protocols. PCR amplification included an initial denaturation at 95 °C for 3 minutes, followed by 35 cycles of denaturation at 95 °C for 30 seconds, annealing at 61.4 °C for 30 seconds, and extension at 72 °C for 30 seconds, with a final extension at 72 °C for 5 minutes.

Detection of the V1016G mutation was conducted using allele-specific PCR (AS-PCR), as previously described [29,30]. PCR reactions were prepared using PCR master mix, template DNA, allele-specific primers, and nuclease-free water according to the manufacturer's instructions. The PCR program consisted of an initial denaturation at 94 °C for 3 minutes, followed by 35 cycles of denaturation at 94 °C for 30 seconds, annealing at 60 °C for 30 seconds, and extension at 72 °C for 30 seconds, with a final extension at 72 °C for 5 minutes. PCR products were separated on 1.5% agarose gels at 100 V for approximately 45 minutes and visualized under ultraviolet illumination. Genotypes were assigned based on the expected allele-specific PCR product sizes shown in Table 1. Primer sequences used in this study are presented in Table 1 [29-30].

Table 1. Specific primers used for amplification of the VGSC gene to detect S989P and V1016G mutations in *Aedes aegypti* populations in West Sumatra.

Mutation	Forward Primer	Reverse Primer	Allele Type	PCR Product Size (bp)	Primer Sequence (5′–3′)
S989P	VGSC	S989	T	108	GGACAAAGACCTGCCACG
	S989P	VGSC	C	405	AGCATACAATCCCACATGGA CGGCGAGTGGATCGAAC

V1016G	VGSC	V1016	G	445	CGACAGCGAGGATGAACC GGACAAAGACCTGCCACG
	V1016G Rev	V1016 -For	T	74	GCAAGGCTAAGAAAAGGTTAACTC CGAAGGCTAAGAAAAGGTTAAGTC TTTCCCACCCGCACAGGT

2.5. Sequencing Confirmation

Representative PCR products from different genotype patterns were purified and subjected to DNA sequencing to confirm nucleotide substitutions at codons 989 and 1016 of the VGSC gene. Sequencing results were compared with the expected wild-type and mutant nucleotide sequences to verify the presence of S989P and V1016G substitutions.

2.6. Data Analysis

Mortality rates were calculated as percentages for each insecticide and collection site. Genotype and allele frequencies were determined separately for resistant (alive) and susceptible (dead) mosquitoes. Because the genotyping analysis was performed on a limited number of mosquitoes (n = 5 per group), all genotype and allele frequency data were treated as descriptive findings. No formal genotype–phenotype association testing was performed because the small cell counts could produce statistically unstable estimates and reduce the reliability of inferential analysis. Therefore, the estimated allele frequencies should be interpreted as preliminary indicators rather than definitive population-level estimates or statistically confirmed evidence of association between kdr mutations and phenotypic resistance.

3. Results

3.1. Insecticide Resistance Status

A total of 5,200 *Aedes aegypti* individuals were evaluated for susceptibility to four commonly used insecticides, namely temephos (0.012 mg/L), malathion (5%), permethrin (0.75%), and alpha-cypermethrin (0.15%) (Table 2). Overall, resistance was widespread across all study sites, particularly for adulticides. High-level resistance to malathion was observed in most locations, with mortality rates ranging from 0% to 33%. Similarly, resistance to permethrin and alpha-cypermethrin was detected in the majority of populations, with mortality rates as low as 5%, indicating substantial loss of susceptibility. Only limited tolerance to these pyrethroids was observed in Dharmasraya and Solok. In contrast, susceptibility to temephos remained relatively higher, with some populations (e.g., Batusangkar and Solok) showing full susceptibility (100% mortality), although reduced susceptibility was evident in other locations such as Bukittinggi (5%). Overall mortality rates ranged from 0% to 100% across insecticides and study sites, indicating heterogeneous but predominantly resistant populations. Notably, reduced susceptibility was also detected in the control group, suggesting that the laboratory-maintained colony may not represent a fully susceptible reference population. Possible explanations include historical insecticide exposure before colonization, colony origin, founder effects, or genetic drift during laboratory maintenance.

Table 2. Mortality of *Aedes aegypti* populations across six districts in West Sumatra after 24 h exposure to WHO diagnostic concentrations of temephos, malathion, permethrin, and alpha-cypermethrin.

Location	24 h mortality (%)			
	Temephos 0.012 mg/L	Alpha-cypermethrin 0.15 %	Permethrin 0.75 %	Malathion 5 %
Dharmasraya	73	10	97.5	33
Batusangkar	100	100	10	0
Solok	100	90	68.33	0
Pariaman	75	100	20	15
Padang	86.7	22.5	5	0
Bukittinggi	5	5	0	0
Control	100	5	20	0

Note: Susceptible (98–100%), possible resistance (90–97%), resistant (<90%) according to WHO criteria.

3.2. Detection of kdr S989P Mutation

Genotyping of the S989P mutation in the VGSC gene detected mutant alleles in mosquito samples from all study sites examined. However, because only five mosquitoes per group were genotyped, the reported genotype and allele frequencies should be interpreted descriptively and not as precise estimates of population-level allele frequencies (Table 3 and Figure 2). Both heterozygous (TC) and homozygous mutant (CC) genotypes were detected in mosquitoes exposed to all insecticides. The frequency of homozygous mutant (CC) genotypes in resistant (alive) mosquitoes ranged from 0% to 80%, while in susceptible (dead) mosquitoes it ranged from 0% to 100%. Heterozygous genotypes (TC) were also highly prevalent, with frequencies ranging from 20% to 80% in resistant populations.

The highest heterozygous frequency (80%) was observed in Padang across multiple insecticide treatments, while a complete heterozygous pattern (100%) was detected in Solok under temephos exposure. Mutant genotypes were also detected in the laboratory-maintained control population. Because only a limited number of mosquitoes were genotyped, this finding should be interpreted cautiously and does not provide sufficient evidence for allele fixation or persistence in the wider population. Overall, the detection of both heterozygous and homozygous mutant genotypes in the examined samples indicates the presence of S989P-associated kdr alleles in West Sumatra. Nevertheless, the small genotyping sample size limits the strength of inference regarding the true distribution and frequency of this mutation in the wider *Aedes aegypti* population. Sequencing analysis confirmed a point mutation at codon 989, resulting in an amino acid substitution from serine to proline (TCC → CCC).

Table 3. Distribution of S989P (VGSC) genotypes and allele frequencies in resistant (alive) and susceptible (dead) *Aedes aegypti* populations following WHO-standard insecticide bioassays in West Sumatra.

Insecticides	Collection Site	N = 5 (per group)	Genotype Frequencies (%)			Allele Frequencies (%)	
			Wild-type (TT)	Heterozygote mutant (CT)	Homozygote mutant (CC)	C	T
Permethrin	Dharmasraya	Resistant	0	60	40	70	30
		Susceptible	0	60	40	70	30
	Pariaman	Resistant	0	60	40	70	30
		Susceptible	0	40	60	80	20
	Padang	Resistant	20	80	0	40	60
		Susceptible	0	60	40	70	30
	Solok	Resistant	0	60	40	70	30
		Susceptible	20	40	40	60	40
	Bukittinggi	Resistant	0	60	40	70	30
		Susceptible	0	80	20	60	40
	Batusangkar	Resistant	0	60	40	70	30
		Susceptible	20	60	20	50	50
	Control	Resistant	60	40	0	20	80
		Susceptible	80	20	0	10	90
Malathion	Dharmasraya	Resistant	0	20	80	90	10
		Susceptible	20	20	60	70	30
	Pariaman	Resistant	60	20	20	30	70
		Susceptible	0	60	40	70	30
	Padang	Resistant	80	20	0	10	90
		Susceptible	60	20	20	30	70
	Solok	Resistant	60	40	0	20	80
		Susceptible	20	40	40	60	40
	Bukittinggi	Resistant	0	60	40	70	30
		Susceptible	0	0	100	100	0
	Batusangkar	Resistant	40	20	40	50	50
		Susceptible	20	40	40	60	40
	Control	Resistant	0	20	80	90	10
		Susceptible	0	0	100	100	0
	Dharmasraya	Resistant	0	60	40	70	30
		Susceptible	20	60	20	50	50
	Pariaman	Resistant	40	60	0	30	70

Alpha-cypermethrin	Padang	Susceptible	0	60	40	70	30
		Resistant	20	80	0	40	60
	Solok	Susceptible	60	40	0	20	80
		Resistant	20	80	0	40	60
	Bukittinggi	Susceptible	20	60	20	50	50
		Resistant	0	20	80	90	10
	Batusangkar	Susceptible	20	60	20	50	50
		Resistant	0	80	20	60	40
	Control	Susceptible	0	60	40	70	30
		Resistant	80	20	0	10	90
		Susceptible	60	40	0	20	80
Temephos	Dharmasraya	Resistant	20	40	40	60	40
		Susceptible	20	60	20	50	50
	Pariaman	Resistant	40	60	0	30	70
		Susceptible	60	40	0	20	80
	Padang	Resistant	0	80	20	60	40
		Susceptible	40	60	0	30	70
	Solok	Resistant	60	40	0	20	80
		Susceptible	0	100	0	50	50
	Bukittinggi	Resistant	0	60	40	70	30
		Susceptible	0	40	60	80	20
	Batusangkar	Resistant	20	80	0	40	60
		Susceptible	20	60	20	50	50
	Control	Resistant	60	40	0	20	80
		Susceptible	80	20	0	10	90

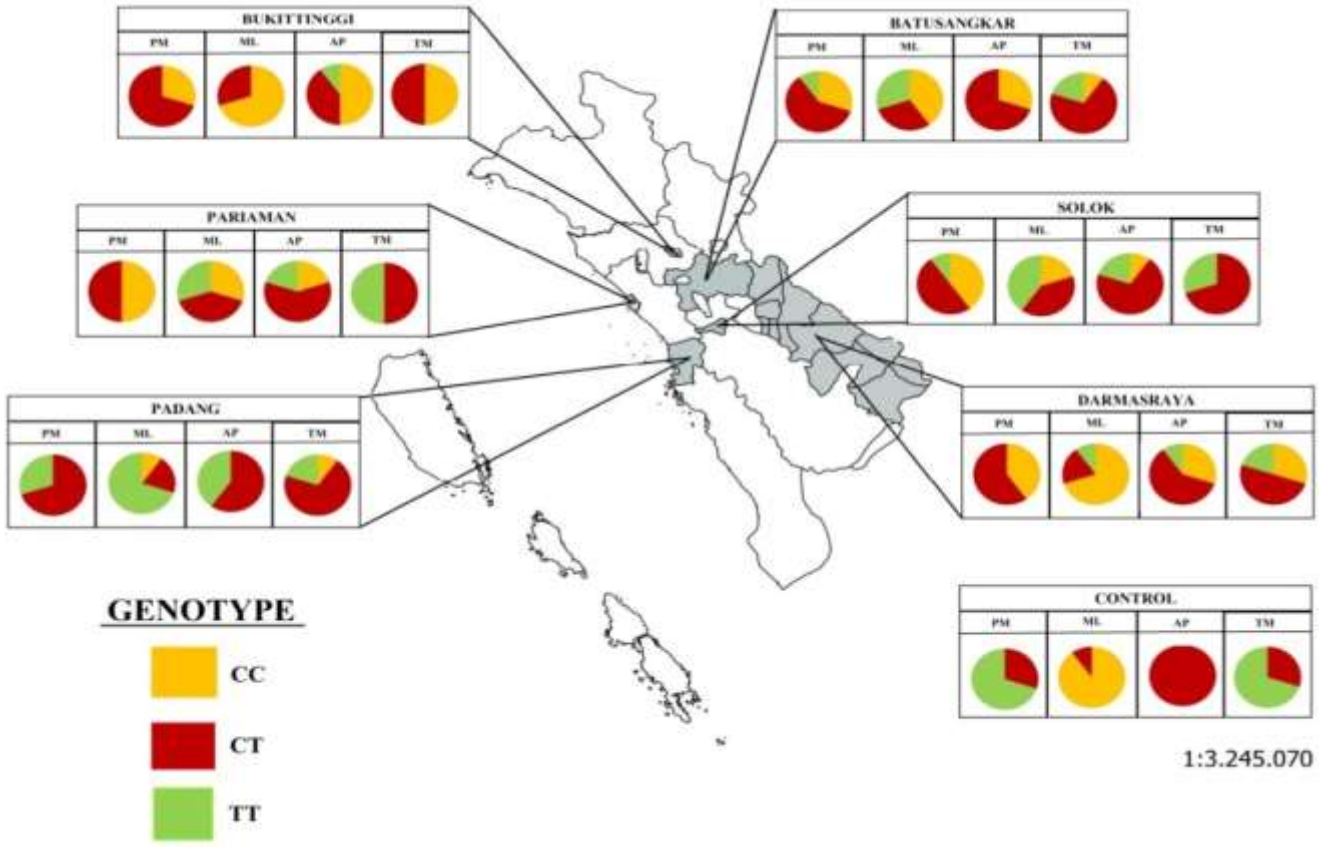

Figure 2. Spatial distribution of S989P (VGSC) genotype frequencies (TT, CT, CC) in *Aedes aegypti* populations across six districts in West Sumatra under different insecticide exposures (PM: permethrin; ML: malathion; AP: alpha-cypermethrin; TM: temephos).

3.3. Detection of kdr V1016G Mutation

Genotyping of the V1016G mutation in the VGSC gene detected mutant alleles in the examined mosquito samples from all study sites. Because the molecular analysis was based on a small number of genotyped individuals per group, the observed frequencies should be considered descriptive and preliminary (Table 4 and Figure 3). Both heterozygous (TG) and homozygous mutant (GG) genotypes were detected in mosquitoes exposed to all insecticides. In the examined samples, the homozygous mutant genotype (GG) was observed in several populations and reached 100% in some genotype groups, including malathion-resistant mosquitoes in Dharmasraya and permethrin-resistant mosquitoes in Bukittinggi. The frequency of GG genotypes ranged from 0% to 100% across study sites and insecticide treatments. Heterozygous genotypes (TG) were also highly prevalent, with frequencies ranging from 0% to 100%, and in several locations (Pariaman, Solok, Bukittinggi, and Batusangkar), heterozygosity reached 100% in both resistant and susceptible populations exposed to malathion. Mutant V1016G genotypes were also detected in the laboratory-maintained control population. This observation should be interpreted cautiously because the molecular analysis was based on a limited number of genotyped mosquitoes. Overall, the detection of V1016G in both resistant and susceptible mosquitoes suggests that this kdr allele is present among the sampled *Aedes aegypti* populations. However, the limited number of genotyped mosquitoes precludes firm conclusions regarding selection intensity, fixation, or the true population-level prevalence of this allele.

Table 4. Distribution of V1016G (VGSC) genotypes and allele frequencies in resistant (alive) and susceptible (dead) *Aedes aegypti* populations following WHO-standard insecticide bioassays in West Sumatra.

Insecticides	Collection Site	N = 5 (per group)	Genotype Frequencies (%)			Allele Frequencies (%)	
			Wild-type TT	Heterozygote Mutant GT	Homozygote Mutant GG	T	G
Permethrin	Dharmasraya	Resistant	0	100	0	50	50
		Susceptible	0	100	0	50	50
	Pariaman	Resistant	0	100	0	50	50
		Susceptible	0	100	0	50	50
	Padang	Resistant	0	60	40	30	70
		Susceptible	0	100	0	50	50
	Solok	Resistant	0	100	0	50	50
		Susceptible	0	100	0	50	50
	Bukittinggi	Resistant	0	0	100	0	100
		Susceptible	0	100	0	50	50
	Batusangkar	Resistant	0	100	0	50	50
		Susceptible	0	80	20	40	60
	Control	Resistant	0	20	80	10	90
		Susceptible	0	100	0	50	50
Malathion	Dharmasraya	Resistant	0	0	100	0	100
		Susceptible	0	40	60	20	80
	Pariaman	Resistant	0	100	0	50	50
		Susceptible	0	100	0	50	50
	Padang	Resistant	0	80	20	40	60
		Susceptible	0	20	80	10	90
	Solok	Resistant	0	100	0	50	50
		Susceptible	0	100	0	50	50
	Bukittinggi	Resistant	0	100	0	50	50
		Susceptible	0	100	0	50	50
	Batusangkar	Resistant	0	100	0	50	50
		Susceptible	0	100	0	50	50
	Control	Resistant	0	100	0	50	50
		Susceptible	0	100	0	50	50
Alpha-cypermethrin	Dharmasraya	Resistant	0	20	80	10	90
		Susceptible	0	60	40	30	70
	Pariaman	Resistant	0	40	60	20	80
		Susceptible	0	0	100	0	100

	Padang	Resistant	0	20	80	10	90
		Susceptible	0	40	60	20	80
	Solok	Resistant	0	40	60	20	80
		Susceptible	0	100	0	50	50
	Bukittinggi	Resistant	0	80	20	40	60
		Susceptible	0	80	20	40	60
	Batusangkar	Resistant	0	80	20	40	60
		Susceptible	0	60	40	30	70
	Control	Resistant	20	80	0	60	40
		Susceptible	0	60	40	30	70
Temephos	Dharmasraya	Resistant	0	20	80	10	90
		Susceptible	0	40	60	20	80
	Pariaman	Resistant	0	80	20	40	60
		Susceptible	0	80	20	40	60
	Padang	Resistant	0	40	60	20	80
		Susceptible	0	40	60	20	80
	Solok	Resistant	0	20	80	10	90
		Susceptible	0	20	80	10	90
	Bukittinggi	Resistant	0	10	90	5	95
		Susceptible	0	20	80	10	90
	Batusangkar	Resistant	0	10	90	5	95
		Susceptible	0	0	100	0	100
	Control	Resistant	0	0	100	0	100
		Susceptible	0	0	100	0	100

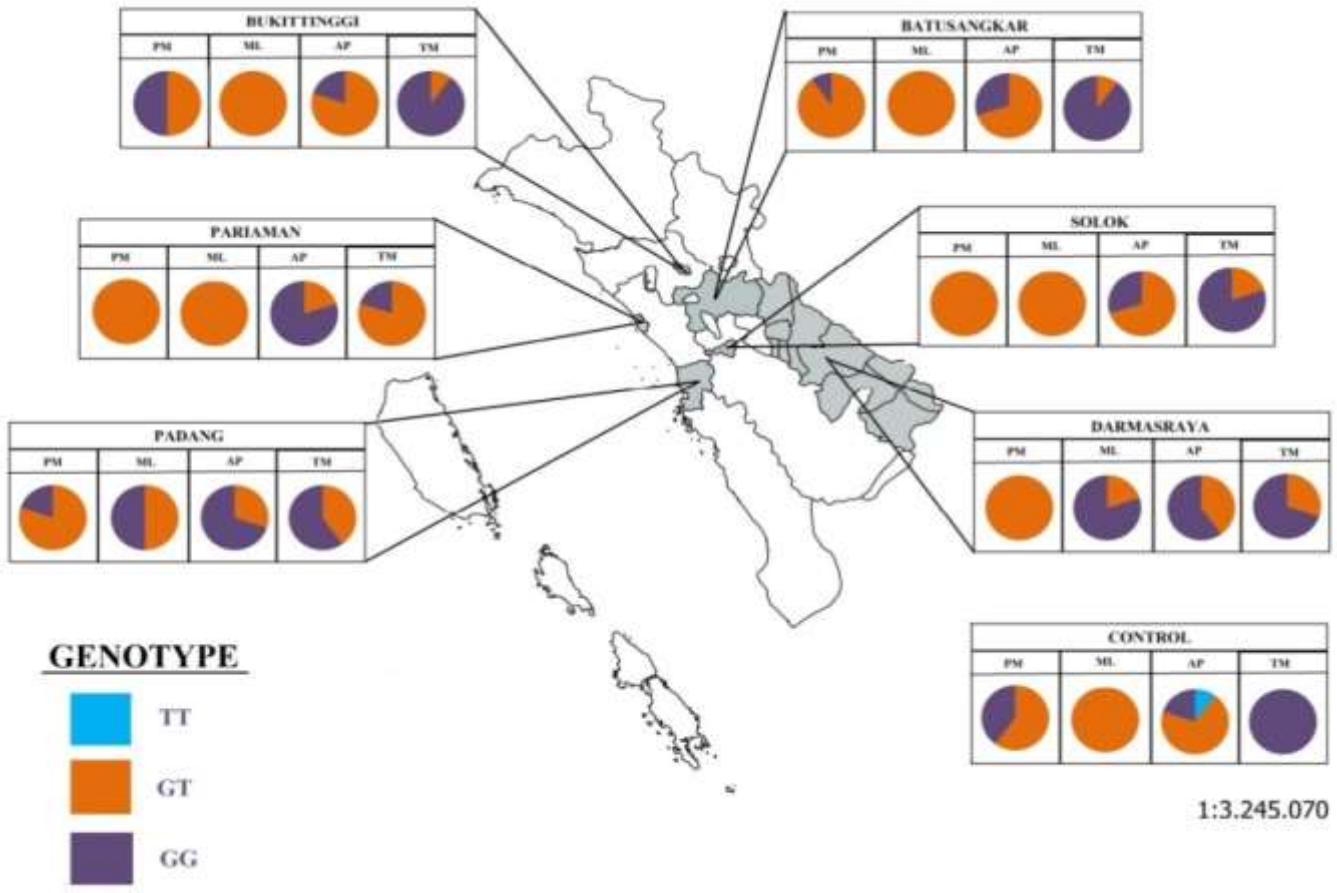

Figure 3. Distribution of V1016G (VGSC) genotype frequencies (TT, TG, GG) in *Aedes aegypti* populations across West Sumatra under different insecticide exposures (PM: permethrin; ML: malathion; AP: alpha-cypermethrin; TM: temephos).

3.4 Combined Pattern of kdr Mutations

The combined analysis of S989P and V1016G mutations showed that both mutations were detected in the examined samples from all study sites. This finding indicates the presence of multiple kdr-associated alleles in the sampled *Aedes aegypti* populations, although the limited genotyping sample size does not allow robust estimation of their population-level distribution. Both mutations were detected in resistant (alive) and susceptible (dead) mosquitoes, indicating that these alleles were not restricted to phenotypically resistant individuals in the examined samples. Within the examined samples, V1016G was more frequently observed as a homozygous mutant genotype (GG) than S989P. However, because of the limited genotyping sample size, this observation should not be interpreted as evidence of a more advanced stage of selection. In contrast, the S989P mutation was more commonly detected in heterozygous form, suggesting different genotype distribution patterns among the examined samples. The co-detection of both mutations within the sampled populations may indicate the potential involvement of multiple kdr loci in resistance phenotypes; however, this interpretation should be confirmed using larger sample sizes and additional molecular markers. Mutant alleles were also detected in the laboratory-maintained control colony. However, this observation should be interpreted cautiously because it may reflect colony history, founder effects, prior insecticide exposure, or genetic drift rather than active selection in field populations.

4. Discussion

Vector control remains the primary strategy for preventing dengue, chikungunya, and Zika transmission in the absence of widely effective antiviral therapies and long-term protective vaccines. In Indonesia, including West Sumatra, mosquito control programs rely heavily on organophosphate and pyrethroid insecticides, applied through fogging operations and household products such as vaporizers, coils, and repellents. This extensive and prolonged use of insecticides likely imposes strong selective pressure on mosquito populations, contributing to the emergence and spread of resistance.

The present study demonstrates widespread insecticide resistance in *Aedes aegypti* populations across multiple districts in West Sumatra, as evidenced by low mortality rates in WHO bioassays, particularly for pyrethroids and malathion. These findings are consistent with previous reports from limited areas in West Sumatra [31] and molecular evidence of organophosphate resistance through Ace-1 gene mutations [32]. However, this study provides more comprehensive and region-wide evidence, integrating both phenotypic resistance and molecular detection of kdr mutations, which has not been systematically reported previously in this region.

The widespread resistance observed in this study is likely associated with continuous and intensive insecticide exposure driven by repeated dengue outbreaks and routine vector control interventions. In such conditions, susceptible mosquito populations are progressively eliminated, while resistant individuals survive and reproduce, leading to a shift in population structure dominated by resistant genotypes. This process is further facilitated by the biological characteristics of *Ae. aegypti*, including egg desiccation resistance, adaptability to diverse environments, and passive dispersal through human activities, which enable rapid spread of resistance-associated alleles.

At the molecular level, resistance to pyrethroids and DDT is commonly associated with mutations in the voltage-gated sodium channel (VGSC) gene, known as knockdown resistance (kdr). These mutations alter the target site of insecticides, reducing binding affinity and decreasing susceptibility [33]. In this study, two kdr mutations, S989P and V1016G, were detected in *Aedes aegypti* populations across all study sites. Notably, these mutations were detected in resistant (alive) mosquitoes, susceptible (dead) individuals, and the laboratory-maintained control colony, indicating that resistance-associated alleles were present among the examined samples and were not exclusively detected in phenotypically resistant mosquitoes.

An important observation of this study is the detection of V1016G among the examined *Aedes aegypti* populations, with homozygous mutant genotypes (GG) observed in several populations. In contrast, the S989P mutation was more commonly detected in heterozygous form. This pattern may indicate differences in genotype distribution among the examined samples; however, the limited genotyping sample size precludes firm conclusions regarding selection stage or allele fixation. The co-detection of both mutations within the examined samples may indicate the potential involvement of multiple kdr loci in resistance phenotypes. However, confirmation requires larger sample sizes and additional molecular markers.

This pattern of co-occurring kdr mutations has also been reported elsewhere, including the recent detection of a novel S989P+V1016G+D1763Y haplotype in *Aedes aegypti* populations in Taiwan [34] and the simultaneous presence of F1534C, S989P, and V1016G in West African populations from Benin [35], suggesting that multi-locus kdr combinations are increasingly recognized as a feature of pyrethroid-resistant *Aedes aegypti* populations worldwide.

Similar VGSC mutations have been widely reported in *Aedes aegypti* populations in Indonesia and globally. In Central Java, multiple polymorphisms including S989P, V1016G, and F1534C have been identified [36], while studies in Yogyakarta reported additional mutations such as F1565C, V1023G, and S996P [22]. Comparable patterns have also been observed in other regions, including South China [19],

Thailand [37], Malaysia [18], and the Caribbean [38]. Additional VGSC variants, including V410L, V1016I/G, S989P, F1534C, F1534L, A1007G, and D1763Y, have been reported in different *Aedes aegypti* populations, further highlighting the global diversity of resistance-associated alleles [5,14,18,19,34,35,39-46]. Collectively, previous studies suggest convergent evolution of insecticide resistance under similar selective pressures across different geographical regions.

The detection of mutant genotypes in both field and laboratory-maintained mosquitoes indicates that these alleles were present in the examined samples. However, findings from the control colony should be interpreted cautiously because they may reflect colony origin, founder effects, genetic drift during laboratory maintenance, or previous insecticide exposure before colonization rather than current selection. Therefore, the control colony may not represent a fully susceptible wild-type genetic background for these loci. This observation highlights the importance of using well-characterized susceptible reference strains in future resistance surveillance studies.

From a population genetics perspective, the detection of both heterozygous and homozygous mutant genotypes may reflect variation in allele distribution among the examined samples. A recent study on Indian *Aedes aegypti* populations similarly reported limited recombination among haplotypes carrying V1016G, F1534C, and F1534L, suggesting that combinations of kdr alleles may be shaped by non-random population genetic processes rather than independent assortment [11]. However, because the molecular data were descriptive and based on a limited number of genotyped mosquitoes, this study cannot determine the evolutionary dynamics or rate of spread of these alleles. Larger longitudinal studies are needed to evaluate changes in genotype frequencies over time. The integration of phenotypic bioassays and molecular detection methods in this study provides useful baseline information for resistance surveillance. PCR-based approaches, including tetra-primer ARMS-PCR and AS-PCR, offer practical tools for detecting specific kdr mutations and can support larger-scale monitoring when validated by appropriate controls or representative sequencing confirmation. These findings have important implications for vector control programs in West Sumatra. The reduced susceptibility to commonly used insecticides, together with the detection of kdr mutations in the examined samples, suggests the need to review and strengthen current vector control strategies. Therefore, alternative approaches such as insecticide rotation, integrated vector management, and continuous resistance monitoring are essential to maintain the effectiveness of control interventions.

One limitation of this study is the relatively small sample size used for genotyping (n = 5 per group). This may reduce the statistical power of the molecular analysis and limit the precision of genotype and allele frequency estimates. Therefore, the observed frequencies of S989P and V1016G should be interpreted as descriptive and preliminary rather than definitive estimates of mutation prevalence in the wider *Aedes aegypti* population of West Sumatra. The limited number of genotyped mosquitoes also restricts the ability to establish robust genotype–phenotype associations between kdr mutations and resistance status. Accordingly, conclusions regarding selection pressure, allele fixation, and population-level distribution should be interpreted cautiously. The detection of resistance-associated mutations in the laboratory-maintained control colony should also be viewed with caution, as this may reflect prior insecticide exposure, colony origin, founder effects, genetic drift during laboratory maintenance, or incomplete colony history. Thus, these findings should not be interpreted as evidence of active selection or allele fixation in the control colony without additional supporting data. Future studies involving larger sample sizes, additional temporal sampling, well-characterized susceptible reference strains, and complementary resistance markers, including metabolic resistance genes, are needed to provide stronger population-level inference and clarify the operational significance of these mutations.

5. Conclusion

This study provides region-specific baseline molecular evidence for the presence of S989P and V1016G kdr mutations in examined *Aedes aegypti* populations from West Sumatra, where information on these mutations has remained limited compared with other Indonesian and regional reports. These mutations were detected in both resistant and susceptible mosquitoes, suggesting that kdr-associated alleles are present among the sampled populations. However, because genotyping was conducted on a limited number of mosquitoes per group and the molecular analysis was descriptive, the allele frequency estimates should be interpreted cautiously and should not be generalized as definitive prevalence estimates or as statistically confirmed genotype–phenotype associations. Despite this limitation, the integration of WHO bioassay results with molecular detection provides useful baseline information for insecticide resistance surveillance in West Sumatra. Larger-scale genotyping studies using well-characterized susceptible reference strains, broader temporal sampling, and additional resistance markers are required to confirm the distribution, frequency, and operational significance of these mutations. Continuous resistance monitoring, insecticide rotation, and integrated vector management remain necessary to support effective dengue vector control programs.

Declarations

Author Contributions

Conceptualization, H., and R.M.; methodology, H., R.M. and B.A.; software, B.A.; validation, R.M., H., and B.A.; formal analysis, H., and R.M.; data curation, B.A.; writing-original draft preparation, H., R.M., and B.A.; writing-review and editing, R.M., and B.A.; visualization, B.A.; supervision, H.; project administration, H.; funding acquisition, H. All authors have read and agreed to the published version of the manuscript..

Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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Conflicts of Interest

The authors declare that they have no conflicts of interest regarding the publication of this manuscript.

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