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Review article

Understanding the Spread of Insecticide Resistance through Population Genetic Approach: A Review

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Abstract

This review discusses the application of the population genetic approach in elucidating the deployment of insecticide resistance to mosquito vectors. Although there have been a lot of scientific work describing population genetic research and insecticide resistance, a study focusing on the spread of insecticide resistance using the population genetic approach needs to be done. Population genetics explains how a population is diverse in response to fitness and the cost of environmental factors. Thus, readers can relate this process to how insecticides spread in the population. Additionally, some fundamental mechanisms of insecticide resistance are also covered. As successive reproduction of advantageous phenotypic traits, such as resistance depends on many factors including continuous pressure, recombination rate, migration rate, genetic drift, and so on. Currently, genome-wide association studies involve chromosome-wide SNPs in which recombination hotspots occur or microsatellite flanking region of resistance gene target in which the fixation process can potentially serve as a suitable marker for elucidating the deployment. The information provided in this review to facilitate how the susceptible individual still exists despite the predominance of resistant individuals and how the resistance reverts to the vulnerable state.

Keywords

population genetic;

insecticide resistance;

mechanism;

microsatellite;

SNPs

1. Introduction

This review sheds light on how insecticides spread from a territory across a nation. It is a common practice of the current global vector control strategy (which has been applied for decades) to use synthetic or non-synthetic insecticides against mosquito vectors. A pivotal role in these strategies is played by pyrethroids, which stand as a cornerstone of contemporary insecticidal formulations [1, 2]. However, the pervasive utilization of insecticides has spurred the emergence of challenges, concomitant with an alarming upsurge in mosquito-borne diseases [3, 4]. Since the

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1950s, researchers have been trying to discover the mechanisms underlying such resistance to insecticides [5]. This resistance primarily takes root in two fundamental biological mechanisms intrinsic to mosquito populations in response to the mode of action of insecticides: an amplified detoxification metabolism rendering insects less susceptible to the effects of the insecticide and a discernible reduction in the sensitivity of the target protein, termed target site insensitivity [3, 6-8].

Interaction at a genetic regulation level between genes connected with resistance accurately depicts how a high level of resistance grows in insects. Overexpression or amplification and mutation in a gene's coding area affect a protein's structural change. This substantial alteration is often correlated with resistance in mosquito populations. Orchestrated overexpression of gene transcripts plays a pivotal role in steering the evolutionary course of resistance within such mosquito populations [9-12]. It is evident that insecticide resistance transcends the mere culmination of intricate mechanisms; rather, it burgeons from the intricate interplay of regulatory genes that directly influence mosquito resistance, particularly genes encoding proteins integral to the resistance.

Insecticide resistance is proposed to be a pre-adaptation phenomenon in which there is an ability to resist an organism against selective pressure (in this case, how mosquitos resist insecticide). Previously, some individuals must carry one or more resistant alleles (i.e., polymorphism from resistant alleles or elevated expression of resistant alleles), due to which it is easier for them to resist the pressure/exposure of the insecticide [13, 14]. The proportion of these resistant individuals possessing polymorphism or resistant alleles can increase/escalate, depending on the selective response toward the insecticide (dead or alive). The offspring from the resistant individuals will be able to increase the numbers that can resist. Finally, these resistant individuals will be a dominant group of the population.

As part of an effort to characterize the genetic background of a resistant individual possessing a role in resistant inheritance toward insecticides and to obtain a basic understanding related to the resistance development [15], resistant inheritance to permethrin was extensively discovered in a *Culex quenquefasciatus* permethrin-resistant population using a cross-breeding method [6]. The findings underscored the autosomal inheritance of phenotypic traits among permethrin-resistant *Culex quenquefasciatus* mosquitoes, with only a fraction exhibiting recessive traits. Susceptibility and resistance were determined from more than 100 individuals in an egg colony bred from a natural population. This indicated various individuals with different levels of resistance in a population [16]. This intricate diversity emerges as a key focal point of our review, prompting us to address inquiries such as: How do the diverse individuals within the mosquito population manifest distinct resistance levels amid substantial selective pressures and the dominance of resilient individuals? What sustains these adaptive individuals within the mosquito population? How can shifts in the resistant mosquito population be precisely quantified? and how does the prevailing environment shape the diversity of mosquito vectors? By adopting a population genetics approach, our review endeavors to bridge the chasm between population genetics and the intricate propagation of insecticide resistance among mosquito populations. While preceding work delved into population genetics and insecticide resistance, none probed the propagation of insecticide resistance among mosquito populations through this specific lens. Population genetics explains how a population is diverse in response to fitness and the cost of environmental factors. Thus, readers can relate this process to how insecticide resistance has spread in the population.

2. Mechanism of Insecticide Resistance in Response to Insecticide Mode of Action in Mosquito Population

2.1. Insensitivity of target sites

The insensitivity of target sites is generated by a mutation (point mutation) or structural modification from a gene that encodes the target protein directly interacting with the insecticide [17]. Generally, the target site insensitivity mechanism is differentially caused by three types of insecticide families. First, dichlorodiphenyltrichloroethane (DDT) binds to the sodium channel, along with other compounds that target pyrethroids. The binding causes repeated termination of the nerve system of the mosquito and depolarisation of the nerve membrane, which eventually leads to death. Second, acetylcholinesterase (AChE), a key enzyme in the nervous system, breaks down acetylcholine neurotransmitters, leading to the inhibition of nerve impulses. This enzyme is the target of organophosphate and carbamate insecticides. Third, other insecticide types that can target the γ-aminobutyric acid (GABA) receptor [18-20].

2.1.1 Sodium channel

When the toxic pyrethroid and DDT enter the mosquito body, their specific mode of action is to bind to the sodium channel. This changes the gate activity of the sodium channel and maintains the gate to keep it open for a more extended time [21]. Modification of the sodium channel structure, either by point mutation or substitution of nucleotide base, is led by single nucleotide polymorphism. This modification affects insensitivity to DDT and pyrethroid in sodium channels of the nervous system, reducing or eliminating insecticide-bound affinity toward the target protein [21-24]. The phenomenon may indirectly change the natural trait of the sodium channel gate, reducing the insecticide's toxicity and eventually affecting resistance to the insecticide [23, 25]. The word knockdown resistance (kdr) is a frequently utilised term to reflect resistance to DDT and pyrethroid in insects in conjunction with alleviation of site target sensitivity of sodium channel [26-29].

Over the last decade, research data from molecular analysis, toxicology, and pharmacology have proven the critical role of point mutation in the voltage-gated sodium channels (abbreviated as VGSC) in resistance to DDT or pyrethroid. The VGSC mutation appears in some important insect species that play crucial roles in ecosystems or agriculture [22-24, 30]. This was observed by Rinkevich *et al.* [23], who provided a comprehensive review of current research on the influence of kdr mutation in insects that are resistant to a particular insecticide type. Located in domain II (IIS6), replacement of leucine with phenylalanine (Leu to Phe) which is the initial substitution found in *Musca domestica*-resistant pyrethroids and *Blatella germanica*, was also found in other insect species resistant to pyrethroids [23]. In mosquitoes, there were ten synonymous mutations detected, four of which were Leu to Trp/Ser/Phe/Cys located on codon 1014 (L1014(W/S/F/C)), IIe to Val/Met located on codon 1011 (I1011V/M), phenylalanine to cysteine (F1534C) and valine to glycine (V1016G). Moreover, the other mutations found in mosquito species were I1011V/M, S989P, V1016I/G, L1014S/F, D1763Y and F1534C, the function of which had already been discovered in the Xenopus oocyte expression system [31]. The combination of several mutations, such as $V_{1016}G$ and $S_{989}P$ in *Aedes aegypti* [32], L1014S and V1010L in *Anopheles culicifacies* [33], $N_{1575}Y$ and $L_{1014}F$ in *Anopheles gambiae* [34], and $D_{1794}Y$ and $V_{1016}G$ in *Aedes aegypti* [35], were found to be the main factors in the emergence of co-conferring phenotypes in the form of resistance to insecticide in mosquitoes. Furthermore, the combination of mutations synergically affects the sensitivity of the sodium channel to the pyrethroid [36]. Overall, this observation suggests that several interacting mutational regions may affect the response of an insect's sodium channel to insecticide. Identifying mutational regions correlating with resistance on

a sodium channel gene has generally been carried out using analysis/comparison of the complementary DNA (cDNA) parts in mosquitoes. This approach, however, has raised questions concerning how mutations at the genomic level and the entire sodium channel of mosquitoes contribute to insecticide resistance, how the mutations interact, and how they collectively work to establish a resistance form to insecticides. A recent discovery by Xu *et al*. [14] and Li *et al*. [28] addressed the problems by changing the current research paradigm and globally analysing naturally occurring mutations. Synonymous and non-synonymous mutations and the combination of mutations of all parts of the sodium channel of *Culex quinquefaciatus* were analysed to interpret the evolutionary species' role in insecticide resistance. It was done by conducting a series of systematic comparisons of nucleotide polymorphism spanning through the overall cDNA of the mosquito sodium channel individually from either susceptible or resistant strains and the descents of parental field individuals that had relatively low levels and high levels of resistance (with the selection of cross-breeding that had been exposed to permethrin to some degree of generations). Non-synonymous mutations (W1573R, L982F and A109S) and synonymous mutations (P1249, G1733, G891, A1241, D1245 and L852) were recognised in the whole sodium channels of distinct field strains of *Culex* spp. (resistant and susceptible) and descendants of specifically selected strains either extremely resistant or susceptible toward permethrin insecticide. A strong association between the frequency distribution of synonymous and non-synonymous polymorphisms and the degree of resistance against permethrin between each mosquito group indicated that these two mutational forms have particularly been connected to the evolution of resistance and hereditary mutational trait in each permethrin-exposed generation.

Co-existence analysis of 9 mutational sites, either synonymous or non-synonymous, in their homozygosity from two distinct fields and descendants of permethrin-selected mosquito populations as well as in the group of mosquitoes that had a different level of resistance revealed 13 mutational combinations from these nine mutational sites [37]. The apparent shift in the combination explained that there was a progress from a specific strain possessing a susceptible homozygote allele with the heterozygote one into a polymorphic homozygote allele in the mutational site. In this regard, this shift was responsible for the increased resistance level.

Studies indicated a strong association between the cases of (a) the co-existence of sodium channel non-synonymous and synonymous mutations of resistant-mosquitoes and the synergistic mutational response, and (b) mutational hereditary traits in a descendant of field-strain mosquitoes through insecticide selection. The synonymous mutation may have been correlated with various biological factors. It may have had a notable impact on the function alteration of genes, including the expression [38], protein secondary structure formation [39] and protein-substrate interaction [40]. This raises curiosity concerning the potential of synonymous mutation contribution to resistance as it is generally believed that mutations (synonymous) do not alter the coding sequences of a protein, hence, do not influence the function of the protein [40]. Functional characterization of the synonymous mutation in sodium channel of mosquitoes will be helpful in determining the way synonymous mutations influence the sensitivity of the mosquitoe sodium channel to insecticide selection. This characterization is crucial for understanding the role of synonymous mutations in the unique function of the sodium channel. It involves the modification of the protein's secondary structure, protein fold, and gene splicing—a process in the preparation of DNA recombination.

2.1.2 Acetylcholinesterase

AchE1 and AchE2 have been extensively found in distinct species of mosquitoes. Only AchE1 is involved in resistance phenomenon toward organophosphate (OP) and carbamate insecticides [41-43]. In several species, some mutations have been reported to relate to insecticide resistance. However, in mosquito populations, only 2 mutations on the active site of AchE1 have been

correlated with insensitivity to carbamate and OP. G119S was identified in different species of mosquitoes, including *An. gambiae*, *An. albimanus*, *Cx. vishnui*, *Cx. pipiens* and *Cx. quinquefasciatus* [13, 17, 41, 44]. 3-D modelling indicated that substitution of G (guanine) for S (serine) established interference or inhibition of a synthetic reaction (steric hindrance), reducing accessibility of inhibitor or substrate [41]. Functional research of the ace-1 gene in the nerve cells of baculovirus insect verified that OP resistance in *Cx. tritaeniorhynchus* was a result of substitution of F455W in ace-1 [10]. Substitution of F455W in carbamate-resistant *Myzus persicae* [10], OP-resistant *Tetranychus urticae* spider mite [45] and OP-resistant *Bemisia tabaci* [46] were reported, indicating the important role of this mutation in insect resistant to general insecticides.

2.1.3 GABA receptor

The main neurotransmitter inhibitor in mammalia and insects is known as GABA. It functions as an agonist (a substance that has affinity for a certain receptor) of pentameric transmembrane chlorine channel [18, 19]. GABA receptors, known as the receptors for the neurotransmitter γ-aminobutyric acid, are targeted by several insecticides such as phenyl pyrazole and dieldrin. GABA receptor contains 5 subunits. Each subunit contains cys-loop extracellular domains and transmembrane domains (M1-M4). The M2 domain reresents the uppermost part of the ion channel [47]. The mutation at 296 (A to S/G) is the main associated mutation of GABA receptor for dieldrin resistance in several types of insects [26, 48, 49]. The lower resistance level to fipronil in insects including *Culex* spp.and *Anopheles* spp. has been identified [7, 50, 51]. However, there is no specific unambiguous mutation for coding the sequence of GABA receptor involved in fipronil resistance. This indicates a distinct mechanism or mutation that may contribute to varying types of insecticides with similar mode of action (for the same class of insecticide).

2.2. Metabolic detoxification mechanisms in reponse to insecticides in mosquito population

Detoxification to insecticides in the mosquito involves 3 families of the main metabolic detoxifying genes: glutathione S-transferases (GSTs), esterases and cytochrome P450s (P450s). P_{450}s has the highest number of genes in its families and has an important role in various physiological and biochemical functions. It is notable for its detoxification and/or activation of xenobiotic and endogenous components [52]. GSTs is a dimeric protein with significant solubility, playing a crucial role in the metabolism, detoxification and excretion of a various kinds of endo- and exo-genous components [53-55]. The main characteristic of GSTs and P450s in insects is their upregulation of transcription, affecting the enhancement of the level of protein production and enzyme activation. This mechanism eventually increases the detoxifying metabolism of insecticides resulting in insecticide resistance progress [56-58]. Esterase, a hetero-geneous enzyme cluster, appears in a large number of organisms. Overly secreted esterase have been discovered as periodic amplification and/or overexpressed esterase gene, which reduces the need for the production of detoxifying proteins [11, 59, 60]. Research on metabolic detoxifying enzymes has followed a trajectory similar to that of insect species research, evolving from preliminary studies to complex characterizations. The research has been conducted on a range of genes from sole genes to genome wide analysis, from a mere sole gene expression to complex interactional genes, and from traditional transcription analysis [9] to characterization of protein function [57, 61-63].

3. Population Genetic Concept: an Approach for Quantifying the Spread of Insecticide Resistance

Population genetics is principally concerned with elucidating the determinants of gene composition within a given population and delineating their functional manifestations. Given the intricate interdependence characterizing the myriad variables at play within population genetics research, a comprehensive inquiry becomes indispensable. A nuanced exploration of several cardinal evolutionary processes, each of which exerts discernible influence on population dynamics, is imperative.

Foremost among these processes is mutation, an elemental and ineluctable factor serving as the ultimate wellspring of genetic diversity. It stands as the wellspring from which all genetic variations emanate, constituting an elemental driver of evolutionary change. Subsequently, recombination emerges as a secondary conduit of genetic diversity, engendering novel allelic combinations while not precipitating the emergence of entirely new alleles. These innovative allelic configurations can engender novel phenotypic manifestations, upon which the crucible of natural selection operates with transformative consequences.

The tenets of natural selection, as conceived by Darwin, proffer a seminal theoretical framework. It posits that individuals harboring heritably advantageous variations are poised to demonstrate superior survival and procreative success, a phenomenon succinctly encapsulated by the term 'natural selection'. The offspring borne of these fortuitous individuals inherit the coveted genetic attributes, thereby accentuating the prevalence of these salutary traits across successive generations.

Integral to the construct of natural selection is the concept of fitness, a quantitative metric quantifying the reproductive output amassed over the course of an individual's lifespan. The confluence of individual fitness aggregates into a metric termed population fitness or mean fitness. Counterintuitively, the ascendancy of natural selection does not invariably entail an elevation in mean fitness.

A compendium of factors, including genetic drift, emerges as a salient evolutionary agent. This stochastic perturbation of allelic frequencies is caused by the random sampling of gametes and the chance events inherent in each generational iteration. Over extended temporal scales, genetic drift constricts the amplitude of genetic variance within a population, engendering discernible patterns of divergence amidst isolated populations.

Gene flow, as another transformative mechanism, transpires upon the migration of individuals between divergent populations. This migratory interplay culminates in the infusion of genetic substrates from one population into another, with the attendant consequence of mitigating inter-population disparities over prolonged temporal horizons.

Nonrandom mating, a phenomenon predicated on genetic relatedness or phenotypic concordance between mating pairs, emerges as an additional determinant of population genetic dynamics. This nonrandom assortment during mating affairs can furnish impetus for population divergence and, at its apotheosis, catalyze the very process of speciation.

Core tenets in the purview of population genetics find articulation in the precepts of the Hardy-Weinberg principle, which undergird the edifice of equilibrium genetic distributions. Violations of these tenets portend potential disequilibrium, engendering shifts within the genetic landscape and potential entanglement with genetic linkage phenomena.

It is imperative to disentangle the nuanced distinction between the processes of natural selection and the broader framework of evolution. While evolution is delineated as the transformative shift in phenotypic or genetic composition across successive generations, natural selection is one cardinal force underpinning this transformation. While natural selection may act as a conduit for evolutionary shifts by bestowing advantageous phenotypic attributes, it is not the

exclusive architect of evolutionary change. Genetic drift, mutation, and gene flow each substantiate their claims to effectual roles in steering evolutionary trajectories.

In the milieu of natural selection, the concept of positive selection assumes prominence, engendering perturbations in patterns of genetic variation vis-à-vis neutral model expectations. This manifestly manifests through skewed allelic frequency distributions, precipitating an attenuation of genetic diversity and concurrent amplification of linkage disequilibrium—a phenomenon well in excess of neutral anticipations [64, 65]. However, the task of ascertaining selective influences is complex, partly confounded by the influence of demographic history on the fabric of DNA sequence variation patterns [66].

4. Applying Population Genetic Approaches to Understand the Spread of Insecticide Resistance

In order to avoid the established resistant population, it is common to change the regimen of insecticide class when the resistant population has already been discovered. Usually avoiding the established resistant population is done by shifting from one class of insecticide (either synthetic or non-synthetic) to another. It is also common to use the WHO standard procedure of insecticide testing using impregnated paper, or glass chamber, or other related testing procedures. However, this can be indeed complicated since there may be different insecticide ingredients used in private or governmental sectors. Moreover, there are further difficulties on ascertaining the possibility of revertant or newly emerging resistance in a population. Therefore, it is more practical to use population genetics to map the two.

Initially, it is important to obtain systematic information about the type of insecticide used in a population and initial reports of resistance. This needed information includes the length of time over which resistance has been reported and the number of types of insecticide the population has been exposed to. As part of the related factors, the epidemiological importance of vector borne diseases as an impact of the emerging resistance problem needs to be discovered to comprehensively analyze the situation over time. Additionally, understanding the distribution of the prominent vector across the island or archipelago is crucial information for mapping the significant impact of insecticide resistance and correlating it with epidemiological patterns. Eventually, the genotypic distribution of genes needs to be examined to inform the variations that exist in the population and to be analyzed further.

As commonly discussed, insecticide resistance leads to ineffective vector control management which all this time relies on insecticide deployment as the form of LLINs or IRS. However, in some circumstance, this may not always occur. A study conducted by Kleinschmidt *et al*. [64] through multi-country observational cohorts reported that net users had relatively lower infection prevalence and disease incidence regardless of the varying resistance level. It has been previously proven that the utilization of ITNs in the area of high pyrethroid-resistance was still considerably effective in reducing transmission. Moreover, an experimental hut study by N'Guessan *et al*. [65] revealed that pyrethroid resistance undermined the effectiveness of control measures based on ITNs. In contrast, as reviewed by Rivero *et al*. [66], in some circumstances, insecticide resistance possibly lessens vector longevity, infectiousness and behavioral change which are not detrimental as commonly thought if the effect is sufficiently large. However, insecticide resistance may result in the opposite effect, increasing vectorial capacity which may lead to a dramatic increase in the transmission of the disease and even to a higher incidence or prevalence than in the absence of insecticides. Although insecticide resistance can affect vector longevity, vector competence and vector behavior, there are more variables that deserve attention. As reviewed by Alout *et al*. [67], and aside of the aforementioned variables, there are several other important factors to be considered.

There are overestimated phenotypic abilities to resist insecticides compared to natural population (possibility of flaws of WHO standard procedure for insecticide testing); the fitness cost associated with insecticide resistance (on mosquito density, biting behavior, vector competence and survival); insecticide-resistant mosquitoes are more likely to be vulnerable of mortality when infected by the parasite (interactive cost between infection and resistance); the impact of insecticides on vector-parasite interactions (i.e., increased toxicity on infectious vector, reduced parasite development, and reduced transmission). Therefore, interpreting the impact of insecticide-resistant mosquitoes is problematic. Notwithstanding, insecticide resistance can threaten public health control of the disease and thus the monitoring of insecticide resistance and its spread is undoubtedly important.

4.1. Genome wide association study and positive selection

The common disease – common variant (CDCV) hypothesis suggests that common or complex diseases have an inherited component that is caused by alleles at moderate frequency (minor allele frequency > 0.05). Mendelian disease observation, was especially the main source of this hypothesis, which indicated that there was a strong association between genetic markers and phenotype status. Genome wide association studies (GWAS) are the main methodologies used for CDCV. The two main types of GWAS are dictated by phenotype; discrete (case-control) and quantitative. A case control design consists of two types of samples, which are affected samples (cases) and unaffected sample cohort (controls). A quantitative trait design consists of a random collection of samples for which a continuous trait is tested (e.g., blood pressure or drug response). Ideally, for both designs, an homogenous population is needed. However, this is rarely the case. Generally, samples are derived from multiple sites which consist of various populations, creating population structure in these cohorts because allele frequency varies between populations. However, false positive associations can arise due to population structure, which involves variance in allele frequencies both within and between populations. Established particular research designs were proposed to address the issue of population structure. These designs involved incorporation of cases and controls based on ethnicity or sampling site to standardize population representation. This methodology can eventually alleviate the effects of false positive associations since standardizing population representation also standardizes allele frequency variance between cohorts. Alternatively, measuring population structure by principle component analysis [68], or structure software [69] can be cofactors in association tests. Microarray technologies like Affimetrix's SNP-chip and Illumina's Bead-chip have been used to extract the genotype data for cohorts in GWAS. Case control commonly uses the X2 and the Armitage-Cohran trend test [70] as well as logistic regression. For quantitative trait, linear regression, correlation tests and likelihood tests are also used. Both logistic and linear regression-based measurement can also include covariates, such as gender, population structure and environment. Variants whose SNPs have P value meeting a cutoff (e.g. P value>0.05) after various correction testing (e.g. Bonferroni) or a False Discovery Rate (FDR) [71] cutoff (e.g. 0.01) can become candidate variants. Taken together, the effect of the allele on the phenotype can be summarized in one of three ways: an odds ratio (OR), an effect size or relative risk (RR).

Conducting a genome-wide association study in mosquito populations is rare, primarily because well-established markers have already been identified. However, since the implementation of insecticides that was deployed decades ago with frequently shifted, the probability of cross-resistance between or within class of insecticides has become more likely to occur. GWAS offers a firm foundation to confirm the established variants of insecticide resistance genes following WHO standard protocol testing with regards to varying insecticide families in the population. Therefore, it is possible to have a closer look at the associated genomic regions with either conducting microsatellite flanking region (for selective sweep, population structuring and diversity) or chromosome-wide SNPs (for detecting recombination hotspot) as explained below.

As the current situation is evolving, it is essential to analyze genomic regions potentially affected by positive selection linked to insecticide resistance. Positive selection is a crucial factor in the evolutionary process and plays a significant role in detection. The signatures of positive selection narrow down regions of the specific genome that are, or have been, functionally important. Positive selection interferes with the patterns of genetic variation relative to expectation of standard neutral model. This is described by skewed allele frequency distribution induced positive selection (i.e. an excess of low and/or high frequency derived alleles), which reduces the levels of genetic variation and increases the levels of linkage disequilibrum (LD) relative to neutral expectations [72, 73]. For example, a study showed the Tajima's D distribution versus neuclotide diversity for 259 genes suggested two important points. First, there was an extremely variably distributed Tajima's D in both the population samples. Second, there was a considerable difference in the distribution of Tajima's D average number between populations. A plausible explanation of these differences was the potential contribution effect of distinct demographic history, selective history or a combination of both [74]. From these data, there were clear unusual patterns of variation of the genes compared to other loci, but the question was were they the specific targets of selection or simply the extreme cases of a neutral process? The enthusiasm for genome-wide analysis of genetic variation is predicted on the basis of variation caused by demographic interference (e.g. genetic drift) which can be appropriately accounted for the genes robust signatures of natural selection revealed. In the context of insecticide resistance, these problematic issues can be the same challenging issues since mosquitoes commonly have diversity or structuring of the population due to frequent migration. This discrepancy should be taken into account and carefully analyzed as aforementioned examples with or without other statistical analysis apart from Tajima's D such as Fu and Li's D and F, Fay and Wu's H, Long range haplotype, LD decay, and so on.

4.2. Microsatellite flanking region for detecting selective sweep

Microsatellites (1 to 10 nucleotides) are subcategories of tandem repeats (STRs) that are spread all over the entire genome which make up genomic repetitive regions [75]. They are evolutionarily relevant because of their instability, which can be up to 10 orders of magnitude greater than that of point mutations. They are commonly and frequently used for population genetics analysis (population structuring and diversity). However, the currently available notion of microsatellites that flank a specified genomic region related to a specific phenotype is as important in elucidating evolutionary process from the majority of population genetics variables.

In circumstances where selection is acting on highly polygenic quantitative traits, this process has been previously associated with the rapid adaptation of an organism, for instance, in animal breeding trials. Such traits are highly responsive to altered selective pressures through minor adjustments within the population frequencies with many previous events of polymorphisms [76]. The expected outcome of adaptation is the presence of soft signatures in population genomic data under the so-called infinitesimal model [77]. As seen in the example mentioned earlier, the fact that it is unlinked from neighboring genetic variations serves as a clear signal that the underlying polymorphisms may have persisted in the population for an extended period. Yet, recent studies suggest that only a few alleles, which were rare or absent in the population previously, have become the causal agents of rapid adaptation. There are several important examples concerned with the evolution of resistant insects to insecticides [78]. Therefore, the so-called 'selective sweep' has emerged to describe such an adaptation in a population genetics perspective [72, 79]. Contrary to the infinitesimal model, selective sweep describes the scarce adaptive alleles beforehand under linkage disequilibrium (LD) with bordering genetic variation, which eventually increase in frequency due to positive selection.

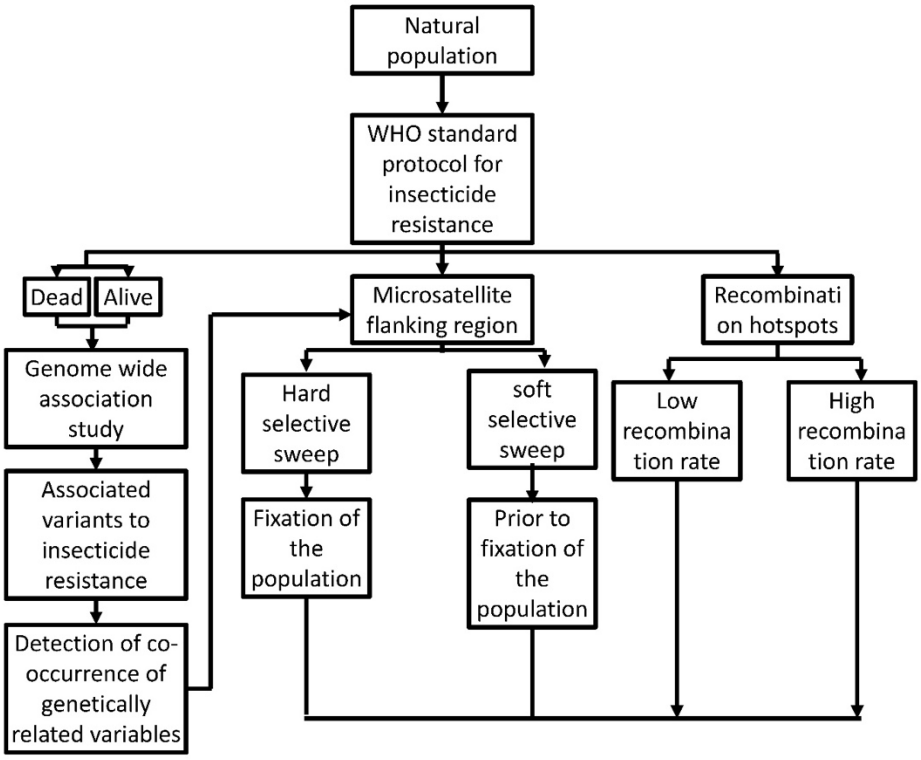

Figure 1. A graphic representation of the schematic comprehensive strategy for detecting the spread of insecticide resistance in a population. WHO-standard insecticide resistance testing must be conducted to elucidate the magnitude of the resistance and the phenotypic characteristics. A case-control study followed by genome wide association study is considerably carried out to map the genetic background associated with resistance and possibility of co-occurrence of other related genes as well as the chromosomal/genetic location under positive selection. Afterwards, as discussed above, microsatellite flanking region of the gene of interest is implemented to detect the selective sweep in the population (hard/soft selective sweep) due to the notable effect of selective sweep for evolutionary process of insecticide resistance and eventually its spread. Finally, as recombination can break down linkage or create new variants in a population, it is used to measure the recombination rate and hotspots to predict the dynamics of resistance in a population.

There are two types of selective sweeps. The first denoted as 'hard selective sweep' is described as a sole adaptive allele which sweeps all over the population, and the second is 'soft selective sweep' where numerous adaptive alleles residing in a locus sweep throughout the population simultaneously [80]. The genealogy of adaptive alleles at the selected spot determines the type of selective sweep in a given population sample. In a hard sweep, the lineages carrying the adaptive allele in the sample coalesce after the initiation of positive selection, while the advantageous allele is still present. Contrarily, a soft sweep is where the adaptive allele coalesces before the commencement of positive selection.

The presence of adaptive mutations is the primary determinant of the production of hard or soft sweeps. The scenario of hard sweeps assumes the absence of adaptive alleles in the population

at the onset of selective stress and the prolonged delay in the occurrence of adaptive mutations. In contrast, in the case of soft sweeps, the anticipation is for a shorter time period for the occurrence of adaptive alleles compared to the duration required for the allele alteration to spread through the population [81-83]. Soft sweeps can also be derived from the independent origin of mutation in remote locations previous to one fixed alleles dispersed to the entire range due to parallel adaptation in regionally structured populations [84-87]. Therefore, in this regard, subpopulations of 'representatively localized samples' might result in hard selective sweeps, whereas subpopulations over 'globally derived samples' can generate soft sweeps.

A hard selective sweep causes a single-cluster coalescence from all lineages, leaving characteristic hallmarks in the genomic structure of a population, such as a distinctive reduction in genetic diversity close to the adaptive allele [72, 79, 88], an excessive number of descent alleles and singletons [89-92], and the existence of a sole, lengthy haplotype [93]. These hallmark indications emphasize the commonly utilized methods to identify sweeps [88, 89, 94, 95]. On the contrary, a soft sweep comprises multiple clusters of lineages, and the ubiquitous varying haplotypes can be present in the population at the adaptive locus. Accordingly, diversity is minimally reduced, and the skew in the frequency spectrum of adjacent neutral alleles is notably weaker compared to hard sweeps [83, 96-98]. Therefore, identifying soft sweeps from polymorphism statistics, such as Tajima's D [95], Fay and Wu's H [89], and the composite likelihood ration (CLR) test [99], is not stratghtforward.

In respect of resistance to insecticides, the application of microsatellites is necessary to understand the population dynamics and the ongoing evolutionary process. As previously mentioned, firstly, neutral microsatellite can be used as a tool for underlining population dynamics such as the genetic diversity across sampled population, population structuring representing migration and mating process and disequilibrium state of genomic region of interest. Secondly, the microsatellite flanking region of insecticide resistance genes is used to deeply conceive the type of sweep which occurs in the population. Since there are merely two possibilities of sweep once resistance has been established, either hard or soft sweep, tracing the spread of the insecticide resistance will be straightforward.

4.3 Recombination hotspot

Recombination by definition, is a process of one double-stranded DNA molecule combining in tandem, particularly in the meiosis process, a process in which two homological chromosomes swap a substantial portion of their genome (so-called cross-over) [100]. A particular DNA sequence/ chromosome possesses its local recombination hotspots, while crossing over may arise in a different location on the chromosome. Recombination hotspots are concentrated one/two thousand base pairs (it is difficult to measure less than such numbers) of local regions of chromosomes often flanked by cold-spot regions of lower-than-average frequency of recombination. This concentration offers a way to recognize other actions linked to recombination. Genetic recombination can create novel favorable alleles or combinations of alleles capable of scattering across the population directed by positive selection [101]. Recombination rates depend on many factors, which may elucidate distinct approximates of recombination rates acquired from two genetic crosses. Since recombination allows alleles to evolve separately, the effective rate of population recombination results are directly associated with frequencies of the out-crossing rate [102]. DNA hybridization by microarray or chromosome-wide SNPs can be employed to detect such a recombination pattern.

In the context of insecticide resistance, a recombination hotspot is crucial as it represents population signatures of evolution and contributes to the sequence patterns. The effect of a selective sweep on the population will be reduced due to strong linkage. Conversely, when recombination

rates are high enough to break the linkage, new variants may emerge in the population and are more likely to revert back to genotypic vulnerable state.

5. Conclusions

As the use of insecticide increases worldwide, the growing trend of insecticide resistance also progresses. Additionally, it is problematic to correlate the impact of insecticide resistance directly to epidemiological importance of a disease. However, there is still a view that insecticide resistance has an effect on public health control of a disease. This review is presented to give a view of how to measure insecticide resistance spread in a population using population genetics approaches. The mechanism of insecticide resistance can be divided into 2 main properties of natural adaptation, which are target site insensitivity (sodium channel, GABA, acetylcholinesterase) and metabolic detoxification. Since these mechanisms are regulated by many genes depending on the types used in the population, measuring the spread of the resistance is not straightforward. Therefore, a graphical representation of the steps is described in this review. In addition, a comprehensive step of detection should be carried out to eliminate all potential bias and other confounding factors when elucidating the spread of insecticide resistance in a population.

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