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Gene Duplication in Insecticide Resistance

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1. Introduction

Gene duplication is a widely observed phenomenon in all three kingdoms of life and is considered to be a major driving force in the evolution of genomes and organisms. Gene duplication refers to any duplication event of a region of DNA that contains genes, eventually giving rise to gene families. In a classical sense, gene duplication is considered to predate functional diversification. When a duplicated copy is generated, the surplus copy is released from the selective pressure that is posed by random mutations, which allows the rapid accumulation of mutations without deleterious consequences to the organism (Zhang, 2003). The accumulated mutations can increase the fitness of the organism or create a novel function, thereby playing a major role in evolution through functional divergence (Ohno, 1970; Taylor and Raes, 2004). Paralogous gene family members that share a common ancestor gene are generated from a duplication event, which is distinguished from the orthologous genes in different genomes that share a common ancestor as a result of a speciation event (Hurles, 2004). In another theory, instead one copy retains the original function after gene duplication, both of the two copies become to undergo complementary functional diversification, allowing the evolution of an organism over generations (Force et al., 1999). Whole genome duplication events are also common particularly in plant species having polyploidy genomes. Whole genome duplication has influenced the evolutionary path in many species.

One example of extensive gene duplication is the gene amplification. Contrary to gene duplication, which is a doubling mechanism of one gene, gene amplification refers to the process by which the copy number of a particular gene is specifically increased to a greater extent compared to those of other genes, resulting in a dramatic increase in gene dosage. Gene amplification generally results from the repeated replication of a stretch of DNA in a specific region of a genome. Because gene amplification increases the copy number of a gene relatively quickly, it is commonly involved in gene expression control during the development of an organism. Increased copy numbers of a particular gene enables rapid production of a large amount of protein within a short period.

The most common mechanism of gene duplication is homologous recombination by unequal crossing-over between short repeated sequences on homologous segments of chromosomes during meiosis. The replication slippage is also responsible for the duplication of small contiguous repeats of DNA. The possibility and frequency of gene duplication depend on the degree of repetitive sequence distribution between two homologous chromosomes. Detailed information on gene duplication mechanisms can be found elsewhere in this book.

Gene duplication has been implicated as one of insecticide resistance mechanisms. Amplification of detoxification genes such as esterase in the *Culex* mosquito and green peach aphid, *Myzus persicae*, is the first example of a gene duplication (amplification) that is associated with insecticide resistance. These aspects of gene amplification were previously reviewed by Devonshire and Field (Devonshire and Field, 1991). Although the degree is not as extensive as the gene amplification, another example of detoxification gene duplication is found in organophosphate (OP)-resistant sheep blow flies, in which $\alpha E7$ gene is duplicated. In this case, the duplication of $\alpha E7$ is considered as a way to simultaneously maintain two different resistance alleles. Tandem duplication of two cytochrome P450 (Cyp450) genes was found in a pyrethroid-resistant strain of a major malaria vector mosquito species, suggesting that Cyp450 gene duplication may contribute to pyrethroid resistance by enhancing monooxygenase activity.

Insecticide target gene duplication is involved in insecticide resistance as well. Duplication of the Rdl γ -amino butyric acid (GABA) receptor subunit gene is a possible cause for the resistance to cyclodiene insecticides in *M. persicae*. Dual copies of acetylcholinesterase (AChE) play a role in resistance and adaptation in *Culex* mosquitoes. AChE duplications reduce the fitness cost associated with the mutant *ace* allele in *Culex* mosquitoes. Recently, multiple copies of AChE were confirmed to confer resistance to an OP insecticide in the two-spotted spider mite. Such extensive duplication of AChE provides adaptive advantages in fitness compensation and resistance. Unlike the duplication of detoxification genes, gene dosage control may become a more important issue in the duplication of insecticide target genes because the encoded gene products are directly involved in the transmission of nerve impulses and the maintenance of nervous system homeostasis. Therefore, adaptive compensation for target gene duplication is necessary, particularly when the extent of duplication is severe and linked to a fitness disadvantage.

In this chapter, we reviewed various reported cases of gene duplication involved in insecticide resistance, and we discussed its roles in the resistance evolution and fitness compensation.

2. Amplification and duplication of detoxification genes

2.1 Esterase gene in *Culex* mosquitoes

The overexpression of two types of esterases, coded at two loci, Est-3 (A esterase) and Est-2 (B esterase), increases esterase activity to confer resistance to OP insecticides in *Culex* mosquito species (Mouches et al., 1986; Mouches et al., 1990; Guillemaud et al., 1997). Multiple overexpressed allozymes have been described as follows: six at the B esterase locus (B1, B2, B4, B5, B6 and B7) and four (A1, A2, A4 and A5) at the A esterase locus (Raymond et al., 1998). In *Culex pipiens quinquefasciatus*, an 800-fold OP resistance is caused by ca. 250-fold amplification of the B1 esterase (*Est-2* locus) (Mouches et al., 1986). Sequence analysis and the characterization of the amplified gene structure has revealed that the amplicon covers at least 30 kb and contains a highly conserved 25-kb "core" carrying a single copy of the esterase gene (2.8 kb) (Mouches et al., 1990). The core is enclosed by two repetitive DNA sequences in other parts of the genome, but not in proximity to the B1 esterase gene, suggesting that the repetitive sequences have a role in the amplification process (Mouches et al., 1990). Analysis of the genomic structure of the Est genes in different OP-resistant strains revealed that two types of genetic alteration mechanisms (transcriptional regulation and gene amplification) are involved in the development of resistance. Overexpression of one A1

esterase reported in the southern French mosquito strain was due to a transcriptional regulatory mechanism, whereas in other cases, the coamplification of the A and B esterase loci or an amplification of the B esterase locus alone resulted in overproduction of esterase (Guillemaud et al., 1997; Raymond et al., 1998). The level of gene amplification varies depending on different esterase alleles. For example, the copy number of B1 esterase reached 250 copies (Mouches et al., 1986), whereas that of B4 esterase did not exceed a few copies (Guillemaud et al., 1997). The level of gene amplification is also different within and between populations as in the case of the coamplified A2-B2 esterases (Callaghan et al., 1998). The number of independent amplification events at the loci of A and B esterases cannot be precisely estimated. Considering the protein quantification profiles and the molecular data published to date, however, the number of independent amplification events may range from five to ten events as a minimum figure (Raymond et al., 1998). This relatively low frequency of independent amplification events on a global scale suggests that the fitness advantage of esterase gene amplification may be restrictive (Raymond et al., 1998).

2.2 Esterase gene in the green peach aphid, *Muzus persicae*, and other aphids

Overexpression of the esterase (E4) responsible for broad insecticide resistance in the green peach aphid, *M. persicae* Sulz, was also associated with amplification of the structural E4 gene or its closely related variant (FE4). The extent of amplification was well correlated with the activity of the esterase and the level of resistance (Field et al., 1988). Molecular studies revealed that the presence of the amplified E4 gene is correlated with an autosomal 1,3 translocation, whereas amplified FE4 genes are found in insecticide-resistant aphids with normal untranslocated chromosomes (Field et al., 1988). Subsequent *in situ* hybridization assays revealed that a single amplified site is located on autosome 3 near the breakpoint of the autosomal 1,3 translocation in all of the E4-producing aphid clones except one having two other E4 loci. In the most resistant aphid clone producing FE4, however, the amplification sites were widely distributed around the genome (from three to eight sites) (Blackman et al., 1995; Blackman et al., 1999). The relative esterase gene copy numbers in aphid clones with different levels of insecticide resistance (R1, R2 and R3) were determined to increase ca. 4-fold between susceptible, R1, R2 and R3 aphids, reaching a maximum increase of approximately 80-fold amplification in R3 aphids. This proportionate correlation between amplification and resistance further suggested that transcriptional upregulation of amplified genes may not be involved in resistance (Field et al., 1999). The amplified esterase genes are arranged as tandem repeats at a single locus in some aphid clones, whereas amplicons are dispersed throughout the genome in other clones. The amplified *E4* and *FE4* genes are methylated at the CpG repeats within the gene (Hick et al., 1996). However, the methylation is absent from upstream regions, including the 5' CpG-rich region around the regulatory region, and from 3' flanking DNA. Contrary to the common belief that methylation suppresses gene expression, methylated E4 genes are expressed and loss of the 5-methylcytosine is correlated with transcription suppression, suggesting that the methylation of *E4* has a positive role in expression (Field, 2000).

2.3 Esterase gene in the sheep blow fly, *Lucilia cuprina*

Resistance to diazinon and malathion is primarily due to two point mutations (Gly137Asp and Trp251Leu) in a carboxylesterase gene (*LcaE7*), encoding both OP hydrolase and malathion carboxylesterase (MCE) activities (Campbell et al., 1997; Campbell et al., 1998).

The OP hydrolase activity, which is responsible for the resistance to diazinon and the majority of other OPs, is conferred by Gly137Asp. In contrast, high MCE activity, which is associated with resistance that is limited to a type of OPs with carboxyl ester bonds such as malathion, is conferred by Trp251Leu mutation. Flies showing double resistance to both malathion and diazinon were also found though they are not common. Since the allele containing double mutations of Gly137Asp and Trp251Leu cannot confer resistance to both malathion and diazinon (Heidari et al., 2004), it was proposed that a duplication of the region containing the *LcaE7* gene generated two loci, each carrying different mutation (Newcomb et al., 2005). As in the case of *LcaE7*, when two (or multiple) mutations cannot exit together in a single locus, duplication may be the most useful option to acquire the benefits of both resistance mutations. In this scenario, the *LcaE7* duplication events most likely postdate the origin of the two resistance alleles, representing a case of gene that share preceding gene duplications (Newcomb et al., 2005). The relatively low frequencies of cases indicating double resistance suggests restrictions on the rate of recombination or fitness costs associated with the duplications.

2.4 Cyp450 gene in *M. persicae*

Cyp450-mediated detoxification acts as a primary mechanism in neonicotinoid resistance in *M. persicae* (Puinean et al., 2010). Microarray analysis of all known detoxification genes in *M. persicae* revealed constitutive over-expression (22-fold) of a single Cyp450 gene (*Cyp6CY3*). The overexpression of Cyp450 is due, at least in part, to an approximately 9-fold gene amplification, as quantitative PCR of genomic DNA showed that the diploid genome of a susceptible aphid clone carries two copies of the *Cyp6CY3*, whereas the neonicotinoid-resistant clone has 18 copies (Puinean et al., 2010). Transcriptional upregulation based on mutations in *cis*-acting and/or *trans*-acting regulatory loci has been reported to be mainly responsible for the overexpression of Cyp450 genes in insecticide-resistant insects (Li et al., 2007). Therefore, this may be the first case of Cyp450 amplification that is associated with insecticide resistance in an agriculturally important insect pest but the *Cyp6CY3* amplification mechanism remains to be elucidated.

3. Duplication of insecticide-target site genes

3.1 Duplication of γ -aminobutyric acid (GABA) receptor

A point mutation (Ala302Ser or Ala302Gly) in the 'Resistance to dieldrin' (*Rdl*) gene encoding a GABA receptor subunit is known to confer resistance to cyclodiene insecticides in *Drosophila* and other insects (ffrench-Constant et al., 1993; ffrench-Constant et al., 2000). Because *Rdl* is a single copy gene in most insects, individuals can carry only two different alleles. In contrast, *M. persicae* is reported to have up to four different *Rdl*-like alleles (Anthony et al., 1998). Along with the wild-type allele (encoding Ala302 or allele A), three other alleles encoding Gly302 (allele G), Ser302 (encoded from 'TCG' codon; allele S) and Ser302 (encoded from 'AGT' codon; allele S') were found in *M. persicae* (Anthony et al., 1998). Three of these alleles (A, G and S) were common in individual aphids or aphid clones. The presence of two independent *Rdl* loci in *M. persicae* has been confirmed by Southern analysis in conjunction with sequencing downstream of the exon containing the mutation. Sequence comparison between two loci has suggested that the loci may have been generated through a recent gene duplication event. Interestingly, only one locus carrying the opposite

alleles of the alanine vs. glycine was responsible for resistance, whereas the other locus carrying the two serine-containing alleles (S or S') was not associated with resistance (Anthony et al., 1998). Taken together, it appears that, after gene duplication, one locus (S/S') of *Rdl* likely had been fixed in aphids regardless of their resistance status, whereas the other (A/G) locus had been specialized as a mechanism for GABA receptor insensitivity to dieldrin. This is a typical example of the duplication of a gene encoding an insecticide target site followed by the functional diversification with respect to insecticide resistance.

3.2 Duplication of acetylcholinesterase (AChE) gene in *Culex* mosquitoes

In *C. pipiens* mosquitoes, the *ace1* locus encodes acetylcholinesterase 1 (AChE1), which is the target of OP and carbamate insecticides. Most OP-resistant populations showed insensitive AChE1, whereas, in two Caribbean populations, individual mosquito displayed a mixture of sensitive and insensitive AChE1. The parsimonious explanation for these phenomenon is the existence of two *ace1* loci encoding both resistant and susceptible AChE1 (phenotype RS), which were most likely generated by gene duplication (Bourguet et al., 1996). The OP-resistant allele, *ace1R*, has been determined to be due to a single amino acid substitution, Gly119Ser (Weill et al., 2003; Weill et al., 2004), which causes not only reduced sensitivity to OP insecticide but also high fitness cost by modifying the catalytic properties of AChE1 (Weill et al., 2003). Later on, a similar duplication event was suggested for *C. pipiens* populations from Southern France, where an excess of the [RS] phenotype was observed in natural populations (Lenormand et al., 1998). The duplication event in Southern France was dated back to 1993, 15 years after *ace1R* was first detected in the area, and then has gradually replaced the *ace1R* allele in treated areas (Lenormand et al., 1998).

Advantages and costs of *ace1* duplications in relation to OP resistance have previously been described from the perspective of gene dosage (Labbé et al., 2007). Gene dosage is very important to maintain essential cellular processes, and increase in gene dosage by duplication likely disturb this balance (Kondrashov et al., 2002; Papp et al., 2003; Veitia, 2005). Duplication of *ace1* produces higher levels of AChE1, resulting in hyperactivity. In the resistant form of AChE1 (AChE1R), however, the catalytic activity is less than 60% of the susceptible form of AChE1 (AChE1S) (Bourguet et al., 1996; Bourguet et al., 1997). Therefore, *ace1* duplication may restore its normal gene dosage, otherwise phenotypically reduced by the resistance mutation (Labbé et al., 2007). A duplication of two *ace1R* copies may partly restore normal AChE1 activity to a level that is comparable to that of a single copy of *ace1S*, serving as a transitional step to *ace1D* haplotypes (having both *ace1S* and *ace1R*). AChE1 activity in *ace1D* homozygotes is similar to or greater than those in susceptible *ace1S* homozygotes (Bourguet et al., 1996). The slightly higher AChE1 activity generated by *ace1D* may result in another type of fitness cost by rapidly degrading the neurotransmitter acetylcholine. In summary, *ace1* duplication generating both resistant and susceptible copies may be selected as a compensatory mechanism for the fitness cost by the homozygous *ace1R* allele (Labbé et al., 2007). The generation of persistent heterozygosis, in which the susceptible *ace1* allele is always expressed, likely reduces the fitness cost associated with the resistant allele. The duplication event was proposed to occur relatively more frequently than generally conceived and very recently (i.e., within less than past 40 years), demonstrating that the gene duplication associated with insecticide resistance is a typical example of rapidly developing evolutionary events (Labbé et al., 2007).

3.3 Extensive duplication of AChE gene in the two-spotted spider mite (TSSM)

Three point mutations (Gly228Ser, Ala391Thr and Phe439W) have been identified using extensive sequence comparisons of the AChE gene from the TSSM (*Tuace*) between OP-resistant and susceptible strains. In addition, their functional roles have been assessed by analyzing the correlation between mutation frequencies and actual resistance levels of several field populations (Kwon et al., 2010b). The frequencies of the Gly228Ser and Phe439Trp mutations in resistant strains never reached 100% even after extensive selection with monocrotophos (Kwon et al., 2010b). To determine whether the lack of saturation for these mutation frequencies is due to the heterozygosity of the *Tuace* allele in individual mites, the frequencies of the three mutations in an individual diploid virgin female and her parthenogenetic haploid male progenies were determined using quantitative sequencing (Kwon et al., 2010a). The actual frequencies of the G228S, A391T and F439W mutations in a female mite and its haploid male progenies have been estimated as approximately 50%, 100% and 75%, respectively. These findings clearly suggested the presence of multiple copies of *Tuace*. Determination of *Tuace* copy number in three mite strains (highly resistant AD, moderately resistant PyriF and susceptible UD strains) using quantitative PCR has revealed that resistant strains have relatively more *Tuace* copies than the susceptible strain and that the levels of transcript were directly proportional to copy numbers (Kwon et al., 2010a). AChEs from the AD and PyriF strains have shown reduced catalytic efficiencies based on lower k_{cat} values, suggesting that the resistant form of AChE is likely accompanied by fitness cost. Relative copy numbers of *Tuace* in field populations of TSSM ranged from 2.4 to 6.1 and are highly correlated with the respective resistance level, suggesting that *Tuace* duplication itself contributes to resistance (Kwon et al., 2010a).

Western blot analysis using AChE-specific antibodies has been conducted to determine whether *Tuace* duplication results in TuAChE overproduction. The protein quantities of TuAChE in seven field-collected mite populations precisely correlated with the copy numbers (Lee and Kwon, unpublished data). To investigate the effects of each mutation on AChE insensitivity and possible fitness costs, eight variants of TuAChE were expressed *in vitro* using the baculovirus expression system. Kinetic analysis revealed that the Ala391Thr mutation did not alter the kinetic properties of AChE, whereas the Gly228Ser and Phe439Trp mutations significantly increased the insensitivity to monocrotophos. Moreover, when the Gly228Ser and Phe439Trp mutations were co-expressed, insensitivity increased over 1000-fold. These results show that both mutations confer resistance in a synergistic manner. However, the presence of the mutations considerably reduced the catalytic efficiency of AChE, suggesting an apparent fitness cost in monocrotophos-resistant mites. Reconstitution of the multiple copies of AChE with different compositions of the mutations revealed that the catalytic efficiencies of the six-copy and two-copy AChEs (resembling the AD and PyriF strains of mite, respectively) were lower but comparable to that of wildtype AChE. These finding clearly suggest that multiple rounds of *Tuace* duplication is needed to compensate the reduced catalytic activity of AChE caused by mutations. Whether mutation or gene duplication occurs first is unknown. However, the introduction of a single mutation (Gly228Ser or Phe439Trp) or a double mutation in a single copy of *Tuace* is unlikely because the fitness cost is severe based on the dramatic reductions in the catalytic efficiency. Therefore, at least a single event of *Tuace* duplication predates the introduction of mutations. A single Gly228Ser mutation likely occurs first in one of the duplicates as seen in the PyriF strain, in which the Gly228Ser mutation has been identified in one of the *Tuace* duplicates. Under continuous selection pressure by OPs, further duplication of mutations might have

been required to compensate for the further reduction of catalytic efficiency that is attributed to an additional Phe439Trp mutation. In summary, monocrotophos resistance in TSSM may have evolved through a combination of phased gene duplication and mutation accumulation.

4. Conclusions

Duplications (or amplifications) of resistance-related genes are frequent mechanisms in insecticide resistance. Extensive forms of gene duplication (i.e., amplification) are commonly found in metabolic genes that are involved in insecticide detoxification, including esterase and Cyp450. In these cases, even with dramatically increased gene dosage, the apparent fitness cost is not severe. In other words, low fitness costs that are associated with high dosages of metabolic genes allow the amplification of genes. Gene duplication events have been found in insecticide target genes, including *ace* and *Rdl*, which play crucial functions in nerve impulse transmission. Unlike the amplification of metabolic genes, the level of duplication of these genes is precisely regulated due to the necessity to maintain the normal gene dosage. Mutations conferring target site insensitivity are always accompanied with duplication events. Because mutations in the insecticide target sites frequently alter catalytic or functional properties of target proteins, which usually increase fitness costs, duplication may act as a compensatory mechanism to restore the normal activity of the target protein, which is otherwise detrimental to maintaining the nervous system homeostasis. Conversely, if the increase of the target protein dose due to an incidental gene duplication event has different fitness consequences, the introduction and selection of any target site mutations conferring insecticide resistance is facilitated following duplication because the mutations that are associated with resistance usually reduce the normal function of target proteins. Taken together, it is difficult to determine whether duplication or mutation occurs first. However, these evolutionary events to acquire insecticide resistance may interact each other to balance the level of resistance and accompanied fitness costs. Genetic introgression between different populations plays a crucial role in spreading and formulating the degree of gene duplication and mutation. In *Anopheles gambiae*, for example, the genetic traits of the *ace1R* mutation and the *ace1* duplication are shared between populations through introgression (Djogbénou et al., 2008).

5. References

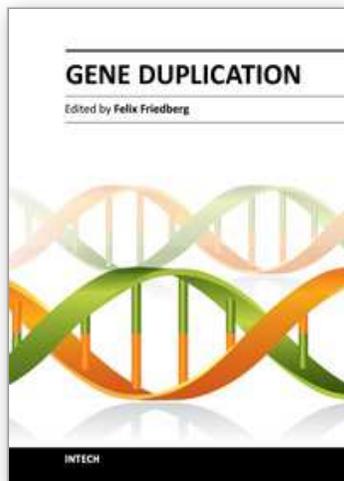
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