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Hypothesis

Volume 8(9)

Identification and classification of detoxification enzymes from *Culex quinquefasciatus* (Diptera: Culicidae)

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Received April 12, 2012; Accepted April 28, 2012; Published May 15, 2012

Abstract:

Molecular characterization of the insecticide resistance has become a hot research topic ever since the first disease transmitting arthropod (Anopheles gambiae) genome sequence has unveiled in 2002. A recent publication of the Culex quinquefasciatus genome sequence has opened up new opportunities for molecular and comparative genomic analysis of multiple mosquito genomes to characterize the insecticide resistance. Here, we utilized a whole genome sequence of Cx. quinquefasciatus to identify putatively active members of the detoxification supergene families, namely cytochrome P450s (P450s), glutathione-S-transferases (GSTs), and choline/carboxylesterases (CCEs). The Culex genome analysis revealed 166 P450s, 40 GSTs, and 62 CCEs. Further, the comparative genomic analysis shows that these numbers are considerably higher than the other dipteran mosquitoes. These observed speciesspecific expansions of the detoxification super gene family members endorse the popular understanding of the involvement of these gene families in protecting the organism against multitudinous classes of toxic substances during its complex (aquatic and terrestrial) life cycle. Thus, the generated data set may provide an initial point to start with to characterize the insecticide resistance at a molecular level which could then lead the development of an easy to use molecular marker to monitor the incipient insecticide resistance in field environs.

Keywords: Culex quinquefasciatus, detoxification enzymes, cytochrome P450 (P450), glutathione-S-transferase (GST), choline/carboxylesterase (CCE)

Background:

The present day sustainable vector control activities are primarily dependent on use of chemical insecticides. Because of this reason, almost all of the mosquito-vectors around the globe have successfully learned to defend themselves from the existing insecticides that are being recommended by WHO. A decade ago, due to lack of genome sequence information from the disease transmitting mosquito species, it was challenging to understand the molecular aspects behind the evolution of insecticide resistance. The genome sequence of Anopheles gambiae (African malaria mosquito) was first published in 2002 [1], followed by Aedes aegypti in 2007 [2] and very recently Culex quinquefasciatus [3] genome in 2010, has opened-up new ISSN 0973-2063 (online) 0973-8894 (print)

possibilities to look into the insecticide resistance at a molecular level. Many conclusive reports on the candidate genes behind the molecular mechanisms of insecticide resistance from African malaria vector, An. gambiae have been published [4-6]; however, translating these studies for practical application is still a due. The present Cx. quinquefasciatus genome sequence further enhanced the capability to understand the molecular science of insecticide resistance through the comparative genomic studies. Culex species have acted as a model organism to study the population genetics and evolution of the insecticide resistance both in field and laboratory conditions [6-8]. Many of the long-term studies on monitoring the role of different processes that are important for insecticide resistance have been

conducted on Culex species [8]. Some of important aspects of Culex species research are; origin of new adaptive mutations against the insecticide used in the vector control program, and their interaction with the existing insecticide resistance mutations, interaction with the environment, cost of a mutation in the presence and absence of an insecticide, establishment and migration of the mutations to a wide geographical areas, pleiotropic effect of a gene mutation on the fitness characteristics of the mosquito, etc [7]. The Culex species being as an urban vector, many of its control efforts are focused on the usage of organophosphorous group based larvicides. Because of this the *Culex* species has been extensively investigated for the mechanisms behind the OP resistance. The established insecticide resistance mechanisms for OP compounds includes both target site mutations in acetylcholinesterase (ace) gene and over production of the detoxification enzymes, majorly esterases through gene amplification. The resistance mechanisms against insecticides in Culex species are similar to that of other disease causing mosquito-vectors (An. gambiae and Ae. Aegypti) and are grouped into two major groups; target site insensitivity and up-regulation of the detoxification enzymes. The detoxification enzymes consists of hundreds of genes from three supergene families, namely cytochrome P450s (P450s) or monoxygenases, glutathione-S-transferases (GSTs), and carboxyl/cholinesterases (CCEs). A plethora of information is available on the insecticide resistance in public domains that confirms the important role of detoxification enzymes (P450, GST, and CCE) in the evolution of insecticide resistance. These enzymatic groups possess a capability to virtually detoxify myriad classes of xenobiotics that are found in nature. In contrary, the target site mutations contribute resistance against a particular selected insecticide. Due to continuous vector control efforts using various strategies by placing the chemical insecticides at a center stage has created multiple insecticide selection pressure on the mosquito vectors. This particular situation has resulted in the appearance of mosquito isolates that are resistant to more than one insecticide. One such mosquito species with multiple insecticide resistance mechanisms is Culex. Nonetheless, this species has shown multiple resistances to all of the four major classes of insecticides, namely organochlorines, organophosphates, carbamates, and pyrethroids, especially in field situations [9]. These aspects coupled with the availability of a past history of chemical control activities and multiple-insecticide resistance information makes this species special to investigate the molecular insecticide resistance aspects in-depth. Giving a due importance to dissect the molecular basis of insecticide resistance through analysis of the detoxification supergene families, here, we utilized *Cx. quinquefasciatus* genome sequence to in silico fish-out the detoxification enzymes that belong to three major groups; P450s, GSTs, and CCEs. The aim of the present study was to investigate the detoxification enzymes from the Culex whole genome sequence and to classify them into respective gene families such that the information could be easily retrieved for further studies on delineation of the insecticide resistance processes. In addition, the comparative genomic analysis of Culex detoxification genes with Drosophila, Aedes and Anopheles was performed. Apart from common disease vectors (Aedes and Anopheles-model organisms for hostparasite interaction), the Drosophila was selected for comparative genomics due to its importance as a model organism.

Methodology:

Utilizing the published sequences of P450s, GSTs, and CCEs from An. gambiae and D. melanogaster, the whole genome sequence of Cx. quinquefasciatus (Cx. quinquefasciatus JHB CpipJ1.2, June 2008 data base) was scanned using the tBLASTn with default parameters (E-value-10, word size-3, similarity matrix-Blosum62, Gap penalties-opening: 11 and extension: 1) as a first step to find out the putatively active detoxification enzymes. Following which, the special characteristics of each of the enzyme group, namely cysteine heme-iron ligand signature i.e. conserved FXXGXXXCXG motif and ~ 500 amino acids (a. a.) protein length for P450s; SNAIL/TRAIL motif and ~ 200 a. a. protein length for GSTs; and catalytic triad sequence (Ser-His-Glu) and \sim 500 a. a. protein sequence length for CCEs, were applied to preliminarily confirm the status to their candidature. Following this, each of the putatively identified sequence was evaluated for having complete protein domains' structure and absence of multiple domains that are characteristics of a functional protein. Final list of detoxification enzymes were tabulated by removing the proteins with incomplete domain structure (possible pseudogene), and/or with multiple domains. For this, Conserved Domain (CD) search was performed against Conserved Domain Database using the protein sequence as a query. CD-search uses the RPS-BLAST to scan the pre-calculated PSSM. The result of CD search are graphical that identify and enlist the domain architecture present in the given protein sequence (the CD-search can be performed through NCBI and can be accessed at http://www.ncbi.nlm.nih.gov/Structure/cdd/cdd.shtml). Any partial domains in a given protein can be identified through this procedure.

Further to this, the confirmed enzymes were classified into various gene families based on their phylogenetic relationship with the classified gene family members' from An. gambiae and/or Ae. aegypti. The phylogenetic analysis of Cx. quinquefasciatus detoxification enzymes was performed by downloading the An. gambiae P450s and GSTs from VectorBase database AgamP3 build available at http://www.vectorbase.org/Anopheles_gambiae/Info/Index and the D. melanogaster esterase sequences from FB2012_02 available at http://www.flybase.org. The P450 sequences of the Culex and Anopheles; GST sequences of Culex and Anopheles; and CCE sequences of Culex and Drosophila were analyzed for drawing the evolutionary relationships among the genes. For all the phylogenetic analysis MEGA4.0 software was employed as described in Raghavendra et al. [10]. To construct phylogeny, the final protein multiple sequence alignment was used as an input with Jones-Taylor-Thornton (JTT) evolutionary model to assess the genetic distance between various taxa. Finally, the obtained phylogenies were statistically evaluated using the bootstrap test with 500 replicates.

Discussion:

The recent genomic sequences from *Anopheles* and *Aedes* species have enabled us to utilize the genomic sequence to develop and standardize the procedure to fish-out the detoxification enzymes. In the year 2010, Arensburger et al. have published the genome sequence of *Cx. quinquefasciatus* [3], and to date, to the best of our knowledge the *Culex* detoxification enzymes' related information is yet to be made available. Although the post-genomic era has brought simplifications in the way to analyze the genomic data, the manual screening and annotation

is necessary in order to obtain specific function related information from the genomes **[11]**. Ever since the first disease causing mosquito genome has completed, the two mosquito biology research areas, namely insecticide resistance and understanding of the processes or basic genomic elements that are responsible for blockage of the pathogen growth inside the mosquito have flourished in comparison to the other scientific areas. The genomic and bioinformatic analysis of *Cx. quinquefasciatus* genome revealed 166 P450s, 40 GSTs, and 62 CCEs **Table 1 (see supplementary material) & (Figure 1)**. The total numbers of each of the supergene family are significantly expanded in *Culex* genome as compared to other sequenced dipteran mosquito species **Table 2a (see supplementary material)**. The differential expansion of the detoxification enzymes in *Culex* species is due to the expansion of the insecticide resistance causing gene families **Table 2b (see supplementary material)**.



Figure 1a: The NJ based phylogenetic analysis of 166 CuP450s and 105 AgP450s; **Figure 1b**: The NJ based phylogenetic analysis of glutathione-S-transferases from *An. gambiae* (31 genes) and *Cx. quinquefasciatus* (40); **Figure 1c**: The NJ based carboxylesterase *Ae. aegypti* (49 genes) and *Cx. quinquefasciatus* (62).

Today it is known that CYP3 and CYP4 clan members from P450s, Delta-Epsilon gene family members from GSTs, and alpha-beta esterases from general esterases are primarily responsible for the insecticide resistance **[6]**. The substantial expansion of detoxification enzymes in *Culex* might have occurred due to the species breeding preference to highly polluted water. Due to this, *Culex* mosquitoes might get exposed (some chemicals might have similar chemical structures as that of the insecticides that are being used in the vector control programs) to numerous kind of chemical ISSN 0973-2063 (online) 0973-8894 (print) Bioinformation 8(9): 430-436 (2012)

molecules during the early stages of their development (aquatic phase of life cycle). David *et al.* **[12]** showed that larval breeding site has a significant influence over detoxification responses of the mosquitoes to various pesticides. According to Liska **[13]** the detoxification processes can be classified into two steps: (1) functionalization- where the foreign compound(s) get oxidized to create a reactive site (electrophilic site) by the phase I detoxification enzymes (P450s and esterases), (2) conjugation – utilizing the reactive site facilitated by the phase I system a water soluble compound will be added to the reactive site by

the GSTs. This particular action results in the biotransformation of lipophilic xenobiotic compounds into a more water soluble byproducts and thus facilitates in easy excretion [13, 14].

The phase I detoxification enzymes (P450s) are categorized into four clans, viz. CYP2, CYP3, CYP4, and mitochondrial P450s [15]. Of these, mitochondrial and CYP2 clans are important for performing the developmental regulations by facilitating in the production of juvenile hormone, while CYP3 and CYP4 clan members are important for detoxification of the xenobiotics. Furthermore, each of these four clans are divided into individual gene families based on the protein sequence identity (>55% and >40-55% protein identity is used to define a subfamily and a gene family, respectively). Of 16 P450 gene families identified in An. gambiae, the CYP4, CYP6, CYP9, and CYP325 gene families are important for insecticide resistance in insects [16-22]. Due to the involvement of CYP2 and mitochondrial P450s in developmentally important functions, these gene families are least prone to gene duplications (Table 1a); in contrary CYP3 and CYP4 clan gene families' that are implicated in metabolizing and detoxification of foreign compounds are expanded grossly in the mosquito genomes (Table 2b). Of a total 166 Culex P450s, 77 and 66 genes belong to CYP3 and CYP4 clans, respectively that accounts for 86% of total P450s Table 2b (see supplementary material) & (Figure 1a). The comparative genomic analysis of P450s from the dipteran species revealed that CYP3 and CYP4 clans are alone contribute to 64-86% of the P450s Table 2b (see supplementary material). The gene families (CYP2 and mitochondrial) that are responsible for developmental regulation are not expanded Table 2a (see supplementary material). Furthermore, they have shown 1:1 secure orthologs in dipteran species (data not shown). The comparative genomic analysis shows that Drosophila has got least numbers of CYP3 and CYP4 clan members as compared with the other disease causing dipteran species. This may be due to restricted exposure of Drosophila to pesticides. In contrast, the rest of the three disease vectors are primary targets of human interventions to control the disease/s that are basically centered in using the insecticides to kill the vectors.

The GST supergene family of insects is divided into eight (that include one unclassified GST class) classes, namely Delta, Epsilon, Theta, Sigma, Omega, Iota, Unclassified, and microsomal GSTs. Of these, Delta-and Epsilon-classes are important for the detoxification of xenobiotics [11, 23]. The GST supergene family forms the phase II detoxification system where the conjugation reactions occur to render the xenobiotics more soluble or to make them sequestered so that xenobiotics or insecticides will become inactive in the cell. In Culex 57% (23/40) of total GSTs belong to the Delta-Epsilon class Table 2b (see supplementary material) & (Figure 1b). The comparative GST supergene family analysis suggests that 55 to 66% of total GSTs belong to the Delta-Epsilon class. Delta-Epsilon classes are primarily responsible for detoxification process while the function of other GST classes is yet to be elucidated [23]. The comparative genomic analysis show that classes lota, Unclassified, and Microsomal GSTs are absent from the Drosophila, while class Zeta is absent from the Culex. The maximum number of variations in the gene copy numbers is observed in Delta- and Epsilon-classes Table 1 (see supplementary material).

Esterases are classified into two major groups based on their cellular functions; (a) metabolic enzymes (dietary detoxification, pheromone processing esterases) hormone and (b) neuro/developmental functions [24, 25]. These two groups are further classified into gene families, namely alpha, beta, acetylcholinesterases, neurotactin, neuroligin, gliotactin, glutactin, juvenile, and unknown (still to classify) gene families [24, 25]. Of which alpha esterases (phase I detoxification enzymes) are majorly involved in xenobiotic-detoxification processes. Of a total 62 CCEs identified in *Culex* genome 50% (28 genes) of which are belonging to the alpha-esterases Table 2 (see supplementary material) & (Figure 1c). The comparative analysis of dipteran CCEs revealed that 30 to 50% of total CCEs are alpha-esterases. The rest of the gene families identified in the *Culex* genome and their respective copy numbers are given in Table 1 (see supplementary material). As described in the methods section, the classification of the Culex esterases were preformed based on the phylogenetic relationship with the reference Drosophila esterases (Figure 1c). Similar to the case with P450s and GSTs, the gene families that are responsible for the detoxification of the xenobiotics are expanded in esterases, i.e., alpha esterases. The highest number of alpha esterases is reported from Culex (28 genes). The comparative genomic analysis show that except Drosophila (3 genes) rest of the dipteran mosquitoes have lost the integument esterases during the evolution. Furthermore, there is considerable expansion of the juvenile hormone gene copies observed in the mosquitoes (10-13) while only three were reported from Drosophila. Interestingly, in all the analyzed species, a single ortholog gene copy that is classified under uncharacterized esterases is reported Table 2a (see supplementary material). Finally, the Cx. quinquefasciatus detoxification enzyme's data further corroborate the popular understanding that detoxification enzymes undergo adaptive evolution to satisfy the need of an organism for its broad environmental adaptability [26]. Furthermore, it is evident from the analysis that the strong Darwinian selection will favor the organism to evolve new functions through the extensive duplication of genes. Such a mechanism is evident from the significant expansion (locally and globally in the genome) of CYP4, CYP6, CYP9, and CYP325 cytochrome P450 gene families, Delta and Epsilon GSTs, and alpha esterases Table 2b (see supplementary material) that are implicated in causing insecticide resistance in the class Insecta.

In conclusion, the present study identified 268 detoxification genes that belong to P450, GST, and CCE supergene families. This is the first report on the full information about these genes in *Cx. quinquefasciatus*. These data may act as a raw material for further studies on insecticide resistance. Molecular characterization of the detoxification enzymes involves retrieval, identification, confirmation, and transcriptional profiling of the genes. This needs an expert curated detoxification gene's data set, and the process involved herein is not straightforward [3, 24, 25, 27]. The comprehensive listing of the detoxification enzymes along with their groupings may helps in easy in silico retrieval of the enzyme related information for molecular characterization of insecticide resistance. The present information may also help in understanding evolution of the detoxification supergene families that are directly and/or indirectly responsible for insecticide resistance in insects. However, as the generated information on Culex detoxification genes is based on in silico analyses and thus further studies are needed to confirm the

exact number of active genes and their functional roles in various biological processes in *Culex* mosquitoes.

Acknowledgement:

BPNR was supported by Council of Scientific and Industrial Research (CSIR)-SRF fellowship. BPR was supported by Indian Council of Medical Research (ICMR-SRF) fellowship. We are highly grateful to the continuous support provided by the Director, National Institute of Malaria Research, New Delhi.

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Edited by P Kangueane

Citation: Reddy et al. Bioinformation 8(9): 430-436 (2012)

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Supplementary material:

Table 1: The comprehensive list of the detoxification enzymes -cytochrome P450s (P450s), glutathione-S-transferases (GSTs), and carboxylesterases (CCEs) - of *Culex quinquefasciatus*. The table also shows the total number of genes of each of the gene family that are identified in the present analysis of the *Culex* genome sequence. The P450 enzyme supergene family is divided into four clans, viz. mitochondrial, CYP2, CYP3, and CYP4. Each of the clan is further divided into gene families, namely mitochondrial gene families (CYP12 gene family, 301, 302, 314, 315), CYP2 clan (CYP15, 303, 304, 305, 306, 307), CYP3 clan (CYP6, 9, 329), and CYP4 clan (CYP4, 325 gene families). In the similar way, GST supergene family has been classified into Delta, Epsilon, Sigma, Theta, Omega, Unclassified, and microsomal GST classes. Likewise, the CCE supergene family divided into alpha, beta, Juvenile hormone processing, glutactin, gliotactins, neuroligins, and neurotactins (pl. see ref [24-25] for the basis of classification of these supergene families).

$ \begin{array}{c c} CYF & CYP4 & CYP32 & CYP 301 & Delta GSTs & Mitochondrial & secreted & Juvenile \\ CPJ00298 & CPI[00346 & CPI[00297] & CPI[01724] & AB43867 & CPI[000047 & CPI[00207] \\ CPI[00225 & CPI[00347 & CPI[017290 & CPI[01724] & AB43867 & CPI[000047 & CPI[00207] \\ CPI[00225 & CPI[00347 & CPI[017290 & CPI[01724] & AB43867 & CPI[000048 & CPI[013027] \\ CPI[00225 & CPI[00347 & CPI[01729 & CPI[01724] & CPI[02263 & CPI[00544 & CPI[013029 & CPI[013029 & CPI[0037] & CPI[0037] & CPI[00370 & CPI[00380 & CPI[00389 & CPI[00380 & C$	P450s				GSTs	COEs	
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$\begin{array}{c} \mbox{CP1} 003356 & \mbox{CP1} 00397 & \mbox{CP1} 00398 & \mbox{CP1} 002678 & \mbox{CP1} 0000049 & \mbox{CP1} 001375 & \mbox{CP1} 000376 & \mbox{CP1} 000378 & \mbox{CP1} 001386 & $	CPIJ002538	CPIJ009476	CPIJ017199	5	CPIJ002675	CPIJ005694	CPIJ013028
$\begin{array}{c} CP1[003375 \\ CP1[003377 \\ CP1[01356 \\ CP1[003377 \\ CP1[015861 \\ CP1[003378 \\ CP1[005376 \\ CP1[005389 \\ CP1[005389 \\ CP1[005389 \\ CP1[005718 \\ CP1[00577 \\ CP1[00577 \\ CP1[00577 \\ CP1[00577 \\ CP1[00528 \\ CP1[005899 \\ CP1[00577 \\ CP1[00577 \\ CP1[00528 \\ CP1[005899 \\ CP1[00577 \\ CP1[00577 \\ CP1[00528 \\ CP1[00578 \\ CP1[00577 \\ CP1[00576 \\ CP1[00528 \\ CP1[00578 \\ CP1[00578 \\ CP1[00578 \\ CP1[00577 \\ CP1[00577 \\ CP1[01528 \\ CP1[00578 \\ CP1[00599 \\ CP1[00539 \\ CP1[00539 \\ CP1[00530 \\ CP1[00540 \\ CP1$	CPIJ003361	CPIJ009477	CP1J015958	CYP 307	CPIJ002674	CP1J000051	CPIJ013029
$\begin{array}{c} \mbox{CPI}(0) (37) & \mbox{CPI}(0) (38) & \m$	CPIJ003375	CPIJ020229	CPIJ010810	CPIJ000989	CPIJ002678	CPIJ000049	CPIJ013175
$\begin{array}{c} CP[00337 \\ CP[00339 \\ CP[00389 \\ CP[00389 \\ CP[001386 \\ CP[001396 \\ CP[001421 \\ CP[001421 \\ CP[001421 \\ CP[001422 \\ CP[001423 \\ CP[001423 \\ CP[00142 \\ CP[001442 \\ CP[001442 \\ CP[001442 \\ CP[001442 \\ CP[001442 \\ CP[001442 \\ C$	CPIJ003376	CPIJ009478	CPIJ015961	1	CPIJ002679	CPIJ016025	CPIJ014154
$\begin{array}{c} CP [003398 \\ CP [004376 \\ CP [001377 \\ CP [001277 \\ CP [001277 \\ CP [001276 \\ CP [001281 \\ CP [002583 \\ CP [001283 \\ CP [001284 \\ CP [001284 \\ CP [001286 \\ CP [001280 \\ CP [001282 \\ CP [001280 \\ CP [001281 \\ CP [001282 \\ CP [001281 \\ CP [001282 \\ CP [001281 \\ CP [001282 \\ CP [001282 \\ CP [001282 \\ CP [001281 \\ CP [001282 \\$	CPIJ003377	CPIJ015681	CPIJ015960	CYP 301	CPIJ002660	CPIJ016026	CPIJ020045
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$\begin{array}{c} CPIJ005900 & CPIJ007825 & CPIJ01229 & CPIJ002800 & CPIJ007826 & CPIJ007826 \\ CPIJ005953 & CPIJ008937 & CPIJ01230 & CPIJ00230 & CPIJ002676 & CPIJ016336 & 1 \\ \hline \\ CPIJ005953 & CPIJ008937 & CPIJ014220 & CPIJ010231 & 14 & CPIJ007824 & neuroligin \\ CPIJ005955 & CPIJ01754 & CPIJ014221 & 5 & Epsilon & CPIJ007827 & CPIJ007493 \\ CPIJ005955 & CPIJ01755 & CPIJ01247 & CPIJ0108628 & CPIJ01839 & CPIJ007495 \\ CPIJ005955 & CPIJ001755 & CPIJ01247 & CPIJ010826 & CPIJ018628 & CPIJ01833 & CPIJ01755 \\ CPIJ005957 & CPIJ000293 & CPIJ010534 & 1 & CPIJ018630 & CPIJ018233 & neurolatin \\ CPIJ005959 & CPIJ010494 & CPIJ010537 & CPIJ01880 & CPIJ018631 & CPIJ018233 & CPIJ008533 \\ CPIJ005959 & CPIJ010494 & CPIJ010537 & CPIJ01880 & CPIJ018625 & CPIJ018231 & 1 \\ CPIJ009085 & CPIJ010540 & CPY 315 & CPIJ018625 & CPIJ018231 & 1 \\ CPIJ009085 & CPIJ010540 & CPY 315 & CPIJ018625 & CPIJ018624 & 26 \\ CPIJ011297 & CPIJ010534 & CPIJ010544 & 9 & CPIJ018624 & 26 \\ CPIJ015223 & CPIJ010544 & CPIJ010544 & 9 & CPIJ018624 & 1 & Glutactin \\ CPIJ015223 & CPIJ01884 & CPIJ010545 & 1 & CPIJ018626 & Microsomal alpha & 1 \\ CPIJ015223 & CPIJ01884 & CPIJ010545 & CPIJ018626 & Microsomal alpha & 1 \\ CPIJ015428 & CPIJ01884 & CPIJ010543 & Omega & CPIJ02786 & CPIJ004852 & CPIJ010864 & 1 & Glutactin \\ CPIJ016847 & 32 & CPIJ010546 & 1 & Glutactin & CPIJ002786 & CPIJ016661 & CPIJ002785 & CPIJ016661 & CPIJ002785 & CPIJ016661 & CPIJ00675 & CPIJ016661 & CPIJ002785 & CPIJ016851 & CPIJ00532 & 1 & CPIJ006436 & CPIJ016661 & CPIJ004636 & CPIJ016661 & CPIJ014051 & Beta & pheromone & CPIJ016853 & CPIJ00685 & CPIJ010655 & CPIJ014051 & Beta & pheromone & CPIJ016683 & CPIJ000655 & CPIJ014051 & Beta & pheromone & CPIJ014651 & CPIJ016683 & CPIJ00799 & 2 & unclassified & CPIJ016685 & CPIJ00799 & CPIJ014051 & CPIJ016685 & CPIJ010685 & CPIJ010776 & CPIJ014051 & CPIJ014651 & CPIJ014655 & CPIJ00799 & CPIJ01494 & CPIJ014654 & CPIJ014685 & CPIJ00799 & CPIJ01494 & CPIJ014654 & CPIJ014685 & CPIJ017763 & C$	CPIJ005899	CPIJ001758	СҮР9	CPIJ010228	CPIJ002681	CPIJ007825	Uncharacterized
$\begin{array}{c} CPIJ005952 \\ CPIJ005953 \\ CPIJ005953 \\ CPIJ005954 \\ CPIJ005954 \\ CPIJ005954 \\ CPIJ005955 \\ CPIJ00754 \\ CPIJ012421 \\ S \\ CPIJ005955 \\ CPIJ001755 \\ CPIJ014218 \\ CPIJ01555 \\ CPIJ011247 \\ CPIJ01555 \\ CPIJ011247 \\ CPIJ01555 \\ CPIJ000293 \\ CPIJ010542 \\ I \\ CPIJ01555 \\ CPIJ000293 \\ CPIJ010542 \\ I \\ CPIJ01555 \\ CPIJ000294 \\ CPIJ010595 \\ CPIJ010540 \\ CPIJ010530 \\ CPIJ018631 \\ CPIJ018632 \\ CPIJ018632 \\ CPIJ018632 \\ CPIJ018231 \\ I \\ CPIJ018632 \\ CPIJ018625 \\ CPIJ018624 \\ 26 \\ CPIJ018231 \\ I \\ CPIJ018626 \\ PIJ01129 \\ CPIJ018854 \\ CPIJ010544 \\ CPIJ018626 \\ I \\ CPIJ018626 \\ CPIJ018626 \\ CPIJ010544 \\ 9 \\ CPIJ013917 \\ CPIJ01542 \\ CPIJ018854 \\ CPIJ010544 \\ CPIJ001543 \\ CPIJ018626 \\ CPIJ018626 \\ CPIJ01291 \\ CPIJ01542 \\ CPIJ018854 \\ CPIJ010544 \\ PIJ010544 \\ PIJ010545 \\ CPIJ010545 \\ CPIJ010545 \\ CPIJ010546 \\ I \\ CPIJ002786 \\ CPIJ010278 \\ CPIJ002786 \\ CPIJ002785 \\ CPIJ01885 \\ CPIJ001686 \\ CPIJ010545 \\ CPIJ000382 \\ I \\ CPIJ016850 \\ CPIJ01183 \\ CPIJ00278 \\ CPIJ016851 \\ CPIJ001685 \\ CPIJ001865 \\ CPIJ01183 \\ CPIJ00278 \\ CPIJ014051 \\ PIJ01685 \\ CPIJ001865 \\ CPIJ001865 \\ CPIJ000382 \\ I \\ CPIJ014051 \\ PIJ014051 \\ PIJ01405 \\ CPIJ004635 \\ CPIJ004635 \\ CPIJ004635 \\ CPIJ004635 \\ CPIJ004635 \\ CPIJ0004635 \\ CPIJ0004635 \\ CPIJ0004635 \\ CPIJ004635 \\$	CPIJ005900	CPIJ001757	CPIJ019765	CPIJ010229	CPIJ002680	CPIJ007826	CPIJ007638
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CPIJ009085 CPIJ011810 CPIJ010540 CYP 315 CPIJ018625 CPIJ013679 gliotactin CPIJ010858 CPIJ018943 CPIJ010541 CPIJ018624 26 CPIJ000482 CPIJ01129 CPIJ017351 CPIJ010536 1 CPIJ018624 26 CPIJ00482 CPIJ015223 CPIJ018854 CPIJ010544 9 CPIJ013917 CPIJ013918 CPIJ016356 CPIJ010543 Omega CPIJ013918 CPIJ013918 CPIJ016846 CPIJ010545 CPIJ0100031 2 CPIJ016847 32 CPIJ010546 1 Glutactin CPIJ016847 32 CPIJ010547 CPIJ006160 CPIJ002786 CPIJ016847 CPIJ011837 CPIJ003082 1 CPIJ002785 CPIJ016851 CPIJ011337 CPIJ003082 1 CPIJ004636 CPIJ016851 CPIJ01138 CPIJ000655 CPIJ014053 5 CPIJ016852 CPIJ011838 CPIJ000655 CPIJ014051 Beta & pheromone CPIJ016853 CPIJ005684 1 CPIJ014054 CPIJ01169 CPIJ016855 CPIJ0007085 CPIJ0	CPIJ008566	CPIJ016284	CPIJ010538	1	CPIJ018632	CPIJ018231	1
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	CPIJ009085	CPIJ001810	CPIJ010540	CYP 315	CPIJ018625	CPIJ013679	gliotactin
CPIJ011129 CPIJ017351 CPIJ010536 1 CPIJ018626 Microsomal alpha 1 CPIJ015223 CPIJ018854 CPIJ010544 9 CPIJ013917 CPIJ015428 CPIJ018844 CPIJ010543 Omega CPIJ013918 CPIJ016356 CPIJ010545 CPIJ000031 2 CPIJ016846 CPIJ00155 Sigma CPIJ002786 CPIJ016847 32 CPIJ010547 CPIJ006160 CPIJ002785 CPIJ016848 CYP325 CPIJ0105332 1 CPIJ002785 CPIJ016849 CPIJ011837 CPIJ003082 Theta CPIJ004636 CPIJ016850 CPIJ011838 CPIJ003082 Theta CPIJ004636 CPIJ016851 CPIJ011841 CYP329 CPIJ014052 CPIJ004637 CPIJ016852 CPIJ005683 CPIJ000655 CPIJ014051 Beta & pheromone CPIJ016855 CPIJ005684 1 CPIJ010572 CPIJ001522 CPIJ016857 CPIJ007086 CPIJ001038 CPIJ0102766 CPIJ001763 CPIJ016857 CPIJ007086 CPIJ001038 CPIJ0107763 CPIJ0116681 CPIJ	CPIJ010858	CPIJ018943	CPIJ010541	CPIJ011843	CPIJ018624	26	CPIJ000482
CPIJ015223 CPIJ018854 CPIJ010544 9 CPIJ013917 CPIJ015428 CPIJ018944 CPIJ010543 Omega CPIJ013918 CPIJ016356 CPIJ018668 CPIJ010545 CPIJ00031 2 CPIJ016846 CPIJ009415 CPIJ010546 1 Glutactin CPIJ016847 32 CPIJ010547 CPIJ006160 CPIJ002786 CPIJ016848 CYB225 CPIJ010547 CPIJ006160 CPIJ002787 CPIJ016849 CPIJ011837 CPIJ000332 1 CPIJ002785 CPIJ016850 CPIJ011837 CPIJ000382 Theta CPIJ004636 CPIJ016851 CPIJ01841 CYP329 CPIJ014052 CPIJ014637 CPIJ016852 CPIJ005683 CPIJ000655 CPIJ014051 Beta & pheromone CPIJ016853 CPIJ005684 1 CPIJ014054 CPIJ011169 CPIJ016855 CPIJ007086 CPIJ001038 CPIJ0122 CPIJ01169 CPIJ016857 CPIJ007086 CPIJ010038 CPIJ0102053 CPIJ017763 CPIJ017642 CPIJ007089 2 unclassified CPIJ016683 CPIJ016683	CPIJ011129	CPIJ017351	CPIJ010536	1	CPIJ018626	Microsomal alpha	1
CPIJ015428 CPIJ018944 CPIJ010543 Omega CPIJ013918 CPIJ016356 CPIJ018668 CPIJ010545 CPIJ000031 2 CPIJ016846 CPIJ009415 CPIJ010546 1 Glutactin CPIJ016847 32 CPIJ010547 CPIJ002786 CPIJ016848 CYP325 CPIJ010547 CPIJ002785 CPIJ016849 CPIJ011837 CPIJ000332 1 CPIJ016850 CPIJ011838 CPIJ000382 Theta CPIJ016851 CPIJ011636 21 CPIJ014052 CPIJ004636 CPIJ016851 CPIJ0015683 CPIJ000655 CPIJ014053 5 CPIJ016852 CPIJ0005683 CPIJ014051 Beta & pheromone CPIJ016854 CPIJ0005685 CYP 306 CPIJ0114054 CPIJ011169 CPIJ016855 CPIJ007086 CPIJ001038 CPIJ0122 CPIJ01763 CPIJ016857 CPIJ007086 CPIJ001038 CPIJ0122 CPIJ016851 CPIJ017014 CPIJ007089 2 unclassified CPIJ016863 CPIJ017609 CPIJ007090 CYP 305 CPIJ016212 CPIJ016685 CPIJ	CPIJ015223	CPIJ018854	CPIJ010544		9	CPIJ013917	
CPIJ016356 CPIJ018668 CPIJ010545 CPIJ000031 2 CPIJ016846 CPIJ009415 CPIJ010546 1 Glutactin CPIJ016847 32 CPIJ01075 Sigma CPIJ002786 CPIJ016848 CYP325 CPIJ010547 CPIJ002785 CPIJ002787 CPIJ016849 CPIJ011837 CPIJ005332 1 CPIJ002785 CPIJ016850 CPIJ011838 CPIJ003082 Theta CPIJ004636 CPIJ016851 CPIJ011636 21 CPIJ014052 CPIJ004636 CPIJ016851 CPIJ011636 21 CPIJ014053 5 CPIJ016852 CPIJ011841 CYP329 CPIJ014051 Beta & pheromone CPIJ016853 CPIJ005683 CPIJ000655 CPIJ014054 CPIJ011169 CPIJ016855 CPIJ000568 CYP 306 CPIJ012053 CPIJ017763 CPIJ016857 CPIJ007086 CPIJ001038 CPIJ0122 CPIJ016681 CPIJ017642 CPIJ007089 2 unclassified CPIJ016683 CPIJ01769 CPIJ007091 CPIJ014940 CPIJ016212 CPIJ016685 CPIJ01769	CPIJ015428	CPIJ018944	CPIJ010543		Omega	CPIJ013918	
CPIJ016846 CPIJ009415 CPIJ010546 1 Glutactin CPIJ016847 32 CPIJ01075 Sigma CPIJ002786 CPIJ016848 CYP325 CPIJ010547 CPIJ002786 CPIJ002787 CPIJ016849 CPIJ011837 CPIJ005332 1 CPIJ002785 CPIJ016850 CPIJ011837 CPIJ003082 Theta CPIJ004636 CPIJ016851 CPIJ011838 CPIJ003082 Theta CPIJ004636 CPIJ016851 CPIJ011838 CPIJ004053 5 CPIJ016853 CPIJ005683 CPIJ016852 CPIJ005683 CPIJ000655 CPIJ014051 Beta & pheromone CPIJ016854 CPIJ005684 1 CPIJ014054 CPIJ011169 CPIJ016855 CPIJ0005684 1 CPIJ014054 CPIJ0105122 CPIJ016855 CPIJ007086 CPIJ001038 CPIJ0120053 CPIJ017763 CPIJ016857 CPIJ007085 CPIJ001038 CPIJ016851 CPIJ016853 CPIJ007089 CPIJ016853 CPIJ017642 CPIJ007090 CYP 305 CPIJ0090434 <td>CPIJ016356</td> <td>CPIJ018668</td> <td>CPIJ010545</td> <td></td> <td>CPIJ000031</td> <td>2</td> <td></td>	CPIJ016356	CPIJ018668	CPIJ010545		CPIJ000031	2	
CPIJ016847 32 CPIJ010175 Sigma CPIJ002786 CPIJ016848 CYP325 CPIJ010547 CPIJ006160 CPIJ002787 CPIJ016849 CPIJ011837 CPIJ005332 1 CPIJ002785 CPIJ016850 CPIJ011838 CPIJ003082 Theta CPIJ004636 CPIJ016851 CPIJ011636 21 CPIJ014052 CPIJ004637 CPIJ016851 CPIJ011841 CYP329 CPIJ014053 5 CPIJ016852 CPIJ005683 CPIJ000655 CPIJ014051 Beta & pheromone CPIJ016854 CPIJ005684 1 CPIJ014054 CPIJ011169 CPIJ016855 CPIJ0005685 CYP 306 CPIJ019572 CPIJ0105122 CPIJ016856 CPIJ007086 CPIJ001038 CPIJ01763 CPIJ01763 CPIJ016857 CPIJ007085 CPIJ001038 CPIJ016851 CPIJ016681 CPIJ017642 CPIJ007090 CYP 305 CPIJ016212 CPIJ016885 CPIJ017609 CPIJ007091 CPIJ014040 CPIJ014694 CPIJ016685 CPIJ017609	CPIJ016846	CPIJ009415	CPIJ010546		1	Glutactin	
CPIJ016848 CYP325 CPIJ010547 CPIJ006160 CPIJ002787 CPIJ016849 CPIJ011837 CPIJ005332 1 CPIJ002785 CPIJ016850 CPIJ011838 CPIJ003082 Theta CPIJ004636 CPIJ016851 CPIJ011636 21 CPIJ014052 CPIJ004637 CPIJ016852 CPIJ011841 CYP329 CPIJ014053 5 CPIJ016853 CPIJ005683 CPIJ000655 CPIJ014051 Beta & pheromone CPIJ016854 CPIJ005684 1 CPIJ014054 CPIJ011169 CPIJ016855 CPIJ005685 CYP 306 CPIJ019572 CPIJ005122 CPIJ016856 CPIJ007086 CPIJ001038 CPIJ020053 CPIJ01763 CPIJ016857 CPIJ007085 CPIJ001039 6 CPIJ016681 CPIJ017014 CPIJ007089 2 unclassified CPIJ014658 CPIJ017609 CPIJ007090 CYP 305 CPIJ009434 CPIJ014686 CPIJ017609 CPIJ007091 CPIJ014940 CPIJ016212 CPIJ016685 CPIJ01769	CPIJ016847	32	CPIJ010175		Sigma	CPIJ002786	
CPIJ016849 CPIJ011837 CPIJ005332 1 CPIJ002785 CPIJ016850 CPIJ011838 CPIJ003082 Theta CPIJ004636 CPIJ016851 CPIJ011636 21 CPIJ014052 CPIJ004637 CPIJ016852 CPIJ011841 CYB29 CPIJ014053 5 CPIJ016853 CPIJ005683 CPIJ000655 CPIJ014051 Beta & pheromone CPIJ016854 CPIJ005684 1 CPIJ014054 CPIJ011169 CPIJ016855 CPIJ005685 CYP 306 CPIJ019572 CPIJ005122 CPIJ016856 CPIJ007086 CPIJ001038 CPIJ020053 CPIJ01763 CPIJ016857 CPIJ007085 CPIJ001039 6 CPIJ016681 CPIJ017014 CPIJ007089 2 unclassified CPIJ016683 CPIJ017609 CPIJ007090 CYP 305 CPIJ009434 CPIJ014686 CPIJ017609 CPIJ007091 CPIJ014940 CPIJ016212 CPIJ016685 CPIJ01769 CPIJ007093 CPIJ0140102 CPIJ014694 CPIJ016685 CPIJ018494	CPIJ016848	CYP325	CPIJ010547		CPIJ006160	CPIJ002787	
CPIJ016850 CPIJ011838 CPIJ003082 Theta CPIJ004636 CPIJ016851 CPIJ011636 21 CPIJ014052 CPIJ004637 CPIJ016852 CPIJ011841 CYB29 CPIJ014053 5 CPIJ016853 CPIJ005683 CPIJ000655 CPIJ014051 Beta & pheromone CPIJ016854 CPIJ005684 1 CPIJ014054 CPIJ011169 CPIJ016855 CPIJ005685 CYP 306 CPIJ019572 CPIJ005122 CPIJ016856 CPIJ007086 CPIJ001038 CPIJ020053 CPIJ01763 CPIJ016857 CPIJ007085 CPIJ001039 6 CPIJ016681 CPIJ017014 CPIJ007089 2 unclassified CPIJ016683 CPIJ017609 CPIJ007090 CYP 305 CPIJ009434 CPIJ019485 CPIJ017609 CPIJ007091 CPIJ014940 CPIJ016212 CPIJ016686 CPIJ018494 CPIJ007093 CPIJ014012 CPIJ016685 CPIJ016685	CPIJ016849	CPIJ011837	CPIJ005332		1	CPIJ002785	
CPIJ016851 CPIJ011636 21 CPIJ014052 CPIJ004637 CPIJ016852 CPIJ011841 CYP329 CPIJ014053 5 CPIJ016853 CPIJ005683 CPIJ000655 CPIJ014051 Beta & pheromone CPIJ016854 CPIJ005684 1 CPIJ014054 CPIJ011169 CPIJ016855 CPIJ005685 CYP 306 CPIJ019572 CPIJ005122 CPIJ016856 CPIJ007086 CPIJ001038 CPIJ020053 CPIJ01763 CPIJ016857 CPIJ007085 CPIJ001039 6 CPIJ016681 CPIJ017014 CPIJ007089 2 unclassified CPIJ016683 CPIJ01760 CPIJ007090 CYP 305 CPIJ009434 CPIJ0146866 CPIJ017609 CPIJ007091 CPIJ014940 CPIJ016212 CPIJ016686 CPIJ018494 CPIJ007093 CPIJ014012 CPIJ016685 CPIJ016685	CPIJ016850	CPIJ011838	CPIJ003082		Theta	CPIJ004636	
CPIJ016852 CPIJ011841 CYP329 CPIJ014053 5 CPIJ016853 CPIJ005683 CPIJ000655 CPIJ014051 Beta & pheromone CPIJ016854 CPIJ005684 1 CPIJ014054 CPIJ011169 CPIJ016855 CPIJ005685 CYP 306 CPIJ019572 CPIJ005122 CPIJ016856 CPIJ007086 CPIJ001038 CPIJ020053 CPIJ017763 CPIJ016857 CPIJ007085 CPIJ001039 6 CPIJ016681 CPIJ017014 CPIJ007089 2 unclassified CPIJ016683 CPIJ017609 CPIJ007090 CYP 305 CPIJ016212 CPIJ0146866 CPIJ017609 CPIJ007091 CPIJ014940 CPIJ016212 CPIJ016685 CPIJ018494 CPIJ007093 CPIJ0140102 CPIJ016685 CPIJ016685	CPIJ016851	CPIJ011636	21		CPIJ014052	CPIJ004637	
CPIJ016853 CPIJ005683 CPIJ000655 CPIJ014051 Beta & pheromone CPIJ016854 CPIJ005684 1 CPIJ014054 CPIJ011169 CPIJ016855 CPIJ005685 CYP 306 CPIJ019572 CPIJ005122 CPIJ016856 CPIJ007086 CPIJ001038 CPIJ020053 CPIJ017763 CPIJ016857 CPIJ007085 CPIJ001039 6 CPIJ016681 CPIJ017014 CPIJ007089 2 unclassified CPIJ016683 CPIJ017462 CPIJ007090 CYP 305 CPIJ009434 CPIJ019485 CPIJ017609 CPIJ007091 CPIJ014940 CPIJ016212 CPIJ016686 CPIJ018494 CPIJ007093 CPIJ014012 CPIJ016685 CPIJ016685	CPIJ016852	CPIJ011841	CYP329		CPIJ014053	5	
CPIJ016854 CPIJ005684 1 CPIJ014054 CPIJ011169 CPIJ016855 CPIJ005685 CYP 306 CPIJ019572 CPIJ005122 CPIJ016856 CPIJ007086 CPIJ001038 CPIJ020053 CPIJ017763 CPIJ016857 CPIJ007085 CPIJ001039 6 CPIJ016681 CPIJ017014 CPIJ007089 2 unclassified CPIJ016683 CPIJ017462 CPIJ007090 CYP 305 CPIJ009434 CPIJ019485 CPIJ017609 CPIJ007091 CPIJ014940 CPIJ016212 CPIJ016686 CPIJ018494 CPIJ007093 CPIJ014941 CPIJ014694 CPIJ016685 CPIJ018494 CPIJ007093 CPIJ01402 CPIJ014694 CPIJ016685	CPIJ016853	CPIJ005683	CPIJ000655		CPIJ014051	Beta & pheromone	
CPIJ016855 CYP 306 CPIJ019572 CPIJ005122 CPIJ016856 CPIJ007086 CPIJ001038 CPIJ020053 CPIJ017763 CPIJ016857 CPIJ007085 CPIJ001039 6 CPIJ016681 CPIJ017014 CPIJ007089 2 unclassified CPIJ016683 CPIJ017462 CPIJ007090 CYP 305 CPIJ009434 CPIJ019485 CPIJ017609 CPIJ007091 CPIJ014940 CPIJ016212 CPIJ016686 CPIJ018494 CPIJ007093 CPIJ014941 CPIJ016694 CPIJ016685	CPIJ016854	CPIJ005684	1		CPIJ014054	CPIJ011169	-
CPIJ016856 CPIJ007086 CPIJ001038 CPIJ020053 CPIJ017763 CPIJ016857 CPIJ007085 CPIJ001039 6 CPIJ016681 CPIJ017014 CPIJ007089 2 unclassified CPIJ016683 CPIJ017462 CPIJ007090 CYP 305 CPIJ009434 CPIJ019485 CPIJ017609 CPIJ014940 CPIJ016212 CPIJ016686 CPIJ018494 CPIJ014941 CPIJ014694 CPIJ016685 CPIJ007095 CPIJ01402 CPIJ014694 CPIJ016685	CPIJ016855	CPIJ005685	CYP 306		CPIJ019572	CPIJ005122	
CPIJ016857 CPIJ007085 CPIJ01039 6 CPIJ016681 CPIJ017014 CPIJ007089 2 unclassified CPIJ016683 CPIJ017462 CPIJ007090 CYP 305 CPIJ009434 CPIJ019485 CPIJ017609 CPIJ007091 CPIJ014940 CPIJ016212 CPIJ016686 CPIJ018494 CPIJ017093 CPIJ014941 CPIJ014694 CPIJ016685 CPIJ007097 CPIJ014012 CPIJ014694 CPIJ016685	CPIJ016856	CPIJ007086	CPIJ001038		CPIJ020053	CPIJ017763	
CPIJ017014 CPIJ007089 2 unclassified CPIJ016683 CPIJ017462 CPIJ007090 CYP 305 CPIJ009434 CPIJ019485 CPIJ017609 CPIJ007091 CPIJ014940 CPIJ016212 CPIJ016686 CPIJ018494 CPIJ007093 CPIJ014941 CPIJ014694 CPIJ016685 CPIJ017564 CPIJ014042 CPIJ014694 CPIJ016685	CPIJ016857	CPIJ007085	CPIJ001039		6	CPIJ016681	
CPIJ017462 CPIJ007090 CYP 305 CPIJ009434 CPIJ019485 CPIJ017609 CPIJ007091 CPIJ014940 CPIJ016212 CPIJ016686 CPIJ018494 CPIJ007093 CPIJ014941 CPIJ014694 CPIJ016685 CPIJ01564 CPIJ007093 CPIJ014042 CPIJ014694 CPIJ016685	CPIJ017014	CPIJ007089	2		unclassified	CPIJ016683	
CPIJ017609 CPIJ007091 CPIJ014940 CPIJ016212 CPIJ016686 CPIJ018494 CPIJ007093 CPIJ014941 CPIJ014694 CPIJ016685 CPIJ01564 CPIJ014042 CPIJ014694 CPIJ016685	CPIJ017462	CPIJ007090	CYP 305		CPIJ009434	CPIJ019485	
CPIJ018494 CPIJ007093 CPIJ014941 CPIJ014694 CPIJ016685	CPIJ017609	CPIJ007091	CPIJ014940		CPIJ016212	CPIJ016686	
CDII010E8(CDII007002 CDII014042 CDII010/022 0	CPIJ018494	CPIJ007093	CPIJ014941		CPIJ014694	CPIJ016685	
Criju19386 Criju0/092 CrijU14942 CrijU18633 8	CPIJ019586	CPIJ007092	CPIJ014942		CPIJ018633	8	
CPIJ019587 CPIJ007095 3 4 Aceltylcholines	CPIJ019587	CPIJ007095	3		4	Aceltylcholines	
CPIJ019673 CYP 15 microsomal GSTs CPIJ000662	CPIJ019673	CPIJ009570	CYP 15		microsomal GSTs	CPIJ000662	
CPIJ019700 CPIJ009569 CPIJ014944 CPIJ012756 CPIJ006034	CPIJ019700	CPIJ009569	CPIJ014944		CPIJ012756	CPIJ006034	
CPIJ019702 CPIJ010272 1 CPIJ018241 2	CPIJ019702	CPIJ010272	1		CPIJ018241	2	
CPIJ019703 CPIJ011835 CYP 303 CPIJ012754	CPIJ019703	CPIJ011835	CYP 303		CPIJ012754		
CPIJ019704 CPIJ000925 CPIJ009170 CPIJ012755	CPIJ019704	CPIJ000925	CPIJ009170		CPIJ012755		
CPIJ019751 CPIJ000929 1 CPIJ015233	CPIJ019751	CPIJ000929	1		CPIJ015233		
55 5	55				5		

Table 2a: Comparative distribution of various gene families or classes of cytochrome p450s, glutathione-S-transferases, and carboxylesterases from sequenced dipteran species. The enzyme data for the *Drosophila, Aedes*, and *Anopheles* were retrieved from Claudianos *et. al.* [25] And for *Culex* freshly analyzed data is used.

Species	D. melanogaster	A. gambiae	A. aegypti	Cx. quinquefasciatus
Cytosolic GSTs				
Delta	11	12	9	14
Epsilon	14	8	8	9
Ōmega	4	1	1	1
Sigma	1	1	1	1
Theta	4	2	4	6
Zeta	2	1	1	0
Iota	0	1	1	1
Others (unclassified)	0	3	2	3
Microsomal	0	4	3	4
Total GSTs	36	33	30	39
Cytochrome P450s				
CYP4	32	45	59	66
CYP3	36	42	84	77
CYP2	6	10	11	13
Mitochondrial CYPs	11	9	10	10
P450 total	85	106	164	166
CCEs				
Mitochondrial & secretedµsomal	13	16	22	28
Hormone/semiochemical processing				
D clade/ integument esterases	3	0	0	0
E clade/ beta esterases	2	4	2	8
F clade/ juvenile hormone esterases	3	10	12	13
Neuro/developmental				
H clade/glutactin	5	10	7	5
I clade/ uncharacterized	1	1	1	1
J clade/ acetylcholinesterases	1	2	2	2
K clade/ gliotactins	1	1	1	1
L clade/ neuroligins	4	5	5	3
M clade/ neurotactins	2	2	2	1
CCEs total	35	51	54	62

Table 2b: Comparative distribution of various IR gene families or classes of cytochrome P450s, glutathione-S-transferases, and carboxylesterases from the sequenced dipteran species

	Culex quinquefasciatus	Anopheles gambiae	Aedes aegypti	Drosophila melanogaster
P450s	166	105	160	85
CYP3 Clan	77	36	82	36
CYP4 Clan	66	32	57	32
Percent contribution	143 (86%)	68 (64%)	139 (87%)	68 (80%)
GSTs	40	31	29	38
Delta	14	12	8	11
Epsilon	9	8	8	14
Percent contribution	23 (57%)	20 (66%)	16 (55%)	25 (66%)
Esterases	62	51	49	35
Alpha class	28 (50%)	16 (30%)	22 (40%)	13 (40%)