GEPHE SUMMARY

Gephebase Gene
Na/K-ATPase alpha-subunit

GephelD
GP00000709

Entry Status
Published

Main curator
Courtier

PHENOTYPIC CHANGE

Trait Category
Physiology

Trait
Xenobiotic resistance (cardiac glycosides)

Trait State in Taxon A
Other insects

Trait State in Taxon B
Oncopeltus fasciatus and Lygaeus kalmii

Ancestral State
Taxon A

Taxonomic Status
Intergeneric or Higher

Taxon A

Latin Name
Insecta

Common Name
true insects

Synonyms
true insects

Rank
class

Lineage
cellular organisms; Eukaryota; Opisthokonta; Metazoa; Eumetazoa; Bilateria; Protostomia; Ecdysozoa; Panarthropoda; Arthropoda; Mandibulata; Pancrustacea; Hexapoda

Parent
Hexapoda (insects) - (Rank: subphylum)

NCBI Taxonomy ID
50557

is Taxon A an Infraspecies?
No

Taxon B #1

Latin Name
Oncopeltus fasciatus

Common Name
milkweed bug

Synonyms
milkweed bug; Oncopeltus fasciatus (Dallas, 1852)

Rank
species

Lineage
cellular organisms; Eukaryota; Opisthokonta; Metazoa; Eumetazoa; Bilateria; Protostomia; Ecdysozoa; Panarthropoda; Arthropoda; Mandibulata; Pancrustacea; Hexapoda; Insecta; Dicondylia; Pterygota; Neoptera; Paraneoptera; Hemiptera; Prosorrhyncha; Heteroptera; Euheteroptera; Neoheteroptera; Panheteroptera; Pentatomomorpha; Lygaeoidea; Lygaeidae; Lygaeinae; Oncopeltus

Parent
Oncopeltus () - (Rank: genus)

NCBI Taxonomy ID
7536

is Taxon B an Infraspecies?
No

Taxon B #2

Latin Name
Lygaeus kalmii

Common Name
-

Synonyms
Lygaeus kalmii Stal, 1874

Rank
species

Lineage
cellular organisms; Eukaryota; Opisthokonta; Metazoa; Eumetazoa; Bilateria; Protostomia; Ecdysozoa; Panarthropoda; Arthropoda; Mandibulata; Pancrustacea; Hexapoda; Insecta; Dicondylia; Pterygota; Neoptera; Paraneoptera; Hemiptera; Prosorrhyncha; Heteroptera; Euheteroptera; Neoheteroptera; Panheteroptera; Pentatomomorpha; Lygaeoidea; Lygaeidae; Lygaeinae; Lygaeus

Parent
Lygaeus () - (Rank: genus)

NCBI Taxonomy ID
683892

is Taxon B an Infraspecies?
No

GENOTYPIC CHANGE

Generic Gene Name
Atp1a1

Synonyms
Atpa-1; BC010319

String
10090.ENSMUSP00000039657

Sequence Similarities
Belongs to the cation transport ATPase (P-type) (TC 3.A.3) family. Type IIC subfamily.

GO - Molecular Function
GO:0005524 : ATP binding
GO:0043531 : ADP binding
GO:0019901 : protein kinase binding
GO:0043548 : phosphatidylinositol 3-kinase binding
GO:0005391 : sodium:potassium-exchanging ATPase activity
GO:0051087 : chaperone binding
GO:0019904 : protein domain specific binding
GO:0030506 : ankyrin binding
GO:0016791 : phosphatase activity
GO:0030955 : potassium ion binding
GO:0031402 : sodium ion binding
GO:1990239 : steroid hormone binding

GO - Biological Process
GO:0071383 : cellular response to steroid hormone stimulus
GO:0006813 : potassium ion transport
GO:0006814 : sodium ion transport
GO:0071260 : cellular response to mechanical stimulus
GO:0042493 : response to drug
GO:0008217 : regulation of blood pressure
GO:0015991 : ATP hydrolysis coupled proton transport
GO:0030007 : cellular potassium ion homeostasis
GO:0006883 : cellular sodium ion homeostasis
GO:1990573 : potassium ion import across plasma membrane
GO:0036376 : sodium ion export across plasma membrane
GO:0090662 : ATP hydrolysis coupled transmembrane transport
GO:0060081 : membrane hyperpolarization
GO:0086009 : membrane repolarization
GO:0031947 : negative regulation of glucocorticoid biosynthetic process
GO:0045822 : negative regulation of heart contraction
GO:0045823 : positive regulation of heart contraction
GO:0045989 : positive regulation of striated muscle contraction
GO:0086004 : regulation of cardiac muscle cell contraction
GO:0002028 : regulation of sodium ion transport
GO:0002026 : regulation of the force of heart contraction

GO - Cellular Component
GO:0016021 : integral component of membrane
GO:0005886 : plasma membrane
GO:0016324 : apical plasma membrane
GO:0016020 : membrane
GO:0045121 : membrane raft
GO:0005794 : Golgi apparatus
GO:0032991 : protein-containing complex
GO:0005783 : endoplasmic reticulum
GO:0005768 : endosome
GO:0016323 : basolateral plasma membrane
GO:0005901 : caveola
GO:0030315 : T-tubule
GO:0014069 : postsynaptic density
GO:0014704 : intercalated disc
GO:0043209 : myelin sheath
GO:0042383 : sarcolemma
GO:0005890 : sodium:potassium-exchanging ATPase complex

UniProtKB Mus musculus
Q8VDN2

GenebankID or UniProtKB

Mutation #1
Presumptive Null
No

Molecular Type
Coding

Aberration Type
SNP

SNP Coding Change
Nonsynonymous

Molecular Details of the Mutation

Q111T + D121N + N122H +F786N + T797A on one gene copy
D121N, F786N and T797A have been shown to increase resistance to cardiac glucosides

Experimental Evidence
Candidate Gene

	Taxon A	Taxon B	Position
Codon	-	-	-
Amino-acid	Asp	Asn	121

Main Reference
Community-wide convergent evolution in insect adaptation to toxic cardenolides by substitutions in the Na,K-ATPase. (2012)

Authors
Dobler S; Dalla S; Wagschal V; Agrawal AA

Abstract
The extent of convergent molecular evolution is largely unknown, yet is critical to understanding the genetics of adaptation. Target site insensitivity to cardenolides is a prime candidate for studying molecular convergence because herbivores in six orders of insects have specialized on these plant poisons, which gain their toxicity by blocking an essential transmembrane carrier, the sodium pump (Na,K-ATPase). We investigated gene sequences of the Na,K-ATPase Î±-subunit in 18 insects feeding on cardenolide-containing plants (spanning 15 genera and four orders) to screen for amino acid substitutions that might lower sensitivity to cardenolides. The replacement N122H that was previously shown to confer resistance in the monarch butterfly (Danaus plexippus) and Chrysochus leaf beetles was found in four additional species, Oncopeltus fasciatus and Lygaeus kalmii (Heteroptera, Lygaeidae), Labidomera clivicollis (Coleoptera, Chrysomelidae), and Liriomyza asclepiadis (Diptera, Agromyzidae). Thus, across 300 Myr of insect divergence, specialization on cardenolide-containing plants resulted in molecular convergence for an adaptation likely involved in coevolution. Our screen revealed a number of other substitutions connected to cardenolide binding in mammals. We confirmed that some of the particular substitutions provide resistance to cardenolides by introducing five distinct constructs of the Drosophila melanogaster gene into susceptible eucaryotic cells under an ouabain selection regime. These functional assays demonstrate that combined substitutions of Q(111) and N(122) are synergistic, with greater than twofold higher resistance than either substitution alone and >12-fold resistance over the wild type. Thus, even across deep phylogenetic branches, evolutionary degrees of freedom seem to be limited by physiological constraints, such that the same molecular substitutions confer adaptation.

Additional References
Parallel molecular evolution in an herbivore community. (2012)

Mutation #2
Presumptive Null
No

Molecular Type
Coding

Aberration Type
SNP

SNP Coding Change
Nonsynonymous

Molecular Details of the Mutation
Q111T + D121N + N122H +F786N + T797A on one gene copy
D121N, F786N and T797A have been shown to increase resistance to cardiac glucosides

Experimental Evidence
Candidate Gene

	Taxon A	Taxon B	Position
Codon	-	-	-
Amino-acid	Phe	Asn	786

Main Reference
Community-wide convergent evolution in insect adaptation to toxic cardenolides by substitutions in the Na,K-ATPase. (2012)

Authors
Dobler S; Dalla S; Wagschal V; Agrawal AA

Abstract
The extent of convergent molecular evolution is largely unknown, yet is critical to understanding the genetics of adaptation. Target site insensitivity to cardenolides is a prime candidate for studying molecular convergence because herbivores in six orders of insects have specialized on these plant poisons, which gain their toxicity by blocking an essential transmembrane carrier, the sodium pump (Na,K-ATPase). We investigated gene sequences of the Na,K-ATPase Î±-subunit in 18 insects feeding on cardenolide-containing plants (spanning 15 genera and four orders) to screen for amino acid substitutions that might lower sensitivity to cardenolides. The replacement N122H that was previously shown to confer resistance in the monarch butterfly (Danaus plexippus) and Chrysochus leaf beetles was found in four additional species, Oncopeltus fasciatus and Lygaeus kalmii (Heteroptera, Lygaeidae), Labidomera clivicollis (Coleoptera, Chrysomelidae), and Liriomyza asclepiadis (Diptera, Agromyzidae). Thus, across 300 Myr of insect divergence, specialization on cardenolide-containing plants resulted in molecular convergence for an adaptation likely involved in coevolution. Our screen revealed a number of other substitutions connected to cardenolide binding in mammals. We confirmed that some of the particular substitutions provide resistance to cardenolides by introducing five distinct constructs of the Drosophila melanogaster gene into susceptible eucaryotic cells under an ouabain selection regime. These functional assays demonstrate that combined substitutions of Q(111) and N(122) are synergistic, with greater than twofold higher resistance than either substitution alone and >12-fold resistance over the wild type. Thus, even across deep phylogenetic branches, evolutionary degrees of freedom seem to be limited by physiological constraints, such that the same molecular substitutions confer adaptation.

Additional References
Parallel molecular evolution in an herbivore community. (2012)

Mutation #3
Presumptive Null

No

Molecular Type
Coding

Aberration Type
SNP

SNP Coding Change
Nonsynonymous

Molecular Details of the Mutation
Q111T + D121N + N122H +F786N + T797A on one gene copy
D121N, F786N and T797A have been shown to increase resistance to cardiac glucosides

Experimental Evidence
Candidate Gene

	Taxon A	Taxon B	Position
Codon	-	-	-
Amino-acid	Thr	Ala	797

Main Reference
Community-wide convergent evolution in insect adaptation to toxic cardenolides by substitutions in the Na,K-ATPase. (2012)

Authors
Dobler S; Dalla S; Wagschal V; Agrawal AA

Abstract
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Additional References
Parallel molecular evolution in an herbivore community. (2012)

Mutation #4
Presumptive Null
No

Molecular Type
Coding

Aberration Type
SNP

SNP Coding Change
Nonsynonymous

Molecular Details of the Mutation
Q111T + D121N + N122H +F786N + T797A on one gene copy
D121N, F786N and T797A have been shown to increase resistance to cardiac glucosides

Experimental Evidence
Candidate Gene

	Taxon A	Taxon B	Position
Codon	-	-	-
Amino-acid	Asn	His	122

Main Reference
Community-wide convergent evolution in insect adaptation to toxic cardenolides by substitutions in the Na,K-ATPase. (2012)

Authors
Dobler S; Dalla S; Wagschal V; Agrawal AA

Abstract
The extent of convergent molecular evolution is largely unknown, yet is critical to understanding the genetics of adaptation. Target site insensitivity to cardenolides is a prime candidate for studying molecular convergence because herbivores in six orders of insects have specialized on these plant poisons, which gain their toxicity by blocking an essential transmembrane carrier, the sodium pump (Na,K-ATPase). We investigated gene sequences of the Na,K-ATPase Î±-subunit in 18 insects feeding on cardenolide-containing plants (spanning 15 genera and four orders) to screen for amino acid substitutions that might lower sensitivity to cardenolides. The replacement N122H that was previously shown to confer resistance in the monarch butterfly (Danaus plexippus) and Chrysochus leaf beetles was found in four additional species, Oncopeltus fasciatus and Lygaeus kalmii (Heteroptera, Lygaeidae), Labidomera clivicollis (Coleoptera, Chrysomelidae), and Liriomyza asclepiadis (Diptera, Agromyzidae). Thus, across 300 Myr of insect divergence, specialization on cardenolide-containing plants resulted in molecular convergence for an adaptation likely involved in coevolution. Our screen revealed a number of other substitutions connected to cardenolide binding in mammals. We confirmed that some of the particular substitutions provide resistance to cardenolides by introducing five distinct constructs of the Drosophila melanogaster gene into susceptible eucaryotic cells under an ouabain selection regime. These functional assays demonstrate that combined substitutions of Q(111) and N(122) are synergistic, with greater than twofold higher resistance than either substitution alone and >12-fold resistance over the wild type.

Thus, even across deep phylogenetic branches, evolutionary degrees of freedom seem to be limited by physiological constraints, such that the same molecular substitutions confer adaptation.

Additional References

Parallel molecular evolution in an herbivore community. (2012)

Widespread convergence in toxin resistance by predictable molecular evolution. (2015)

RELATED GEPHE

Related Genes

39 (ABCA2, BTR1- Cadherin-like protein, Ha_BtR, ABCC2, cadherin, para (kdr), Chitin synthase 1 (CHS1), MAP4K4, Acetylcholinesterase (Ace-1), resistance to dieldrin, esterase B1, Acetylcholinesterase (Ace-2), alcohol dehydrogenase (Adh), Aldehyde dehydrogenase (Aldh), CG11699, Cyp12d1, Cyp28d1, cyp6d2, cyp6g1, GSTE1-E10 cluster, kin of irre (kire), PHGPx, RnrS, SOD1, Ugt86Dd, Acetylcholinesterase (Ace), esterase isozyme E7 = E3, esterase E4, CYP6AB3, CYP6P9 cluster (CYP6P9a and CYP6P9b), CYP6P9; CYP6P4 cluster, esterase B1 + esterase A, esterase B1 = esterase beta1, esterase isozyme E3, CHKov1, CYP6B1, CYP6B4, FMO1, CYP6CY3)

Related Haplotypes

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COMMENTS

@SeveralMutationsWithEffect - The mutation Q111T occurred in the branch leading to Oncopeltus and not to Lygaeus (see Figure S6 of Ujvari et al 2015) see other Gephebase entry for this mutation