GEPHE SUMMARY

Gephebase Gene

Na/K-ATPase alpha-subunit (https://www.gephebase.org/search-criteria?/and+Gene Gephebase=^Na/K-ATPase alpha-subunit^#gephebase-summary-title)

Entry Status

Published

GepheID

GP00000709

Main curator

Courtier

PHENOTYPIC CHANGE

Trait Category

Physiology (https://www.gephebase.org/search-criteria?/and+Trait Category=^Physiology^#gephebase-summary-title)

Trait

Xenobiotic resistance (cardiac glycosides) (https://www.gephebase.org/search-criteria?/and+Trait=^Xenobiotic resistance (cardiac glycosides)^#gephebase-summary-title)

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 (https://www.gephebase.org/search-criteria?/and+Taxonomic Status=^Intergeneric or Higher^#gephebase-summary-title)

Taxon A

Latin Name

Insecta (https://www.gephebase.org/search-criteria?/and+Taxon and Synonyms=^Insecta^#gephebase-summary-title)

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) (https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id= 6960)

NCBI Taxonomy ID

50557 (https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id= 50557)

is Taxon A an Infraspecies?

No

Taxon B #1

Latin Name

Oncopeltus fasciatus (https://www.gephebase.org/search-criteria?/and+Taxon and Synonyms=^Oncopeltus fasciatus^#gephebase-summary-title)

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) (https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id= 7535)

NCBI Taxonomy ID

7536 (https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id= 7536)

is Taxon B an Infraspecies?

No

Taxon B #2

Latin Name

Lygaeus kalmii (https://www.gephebase.org/search-criteria?/and+Taxon and Synonyms=^Lygaeus kalmii^#gephebase-summary-title)

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) (https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id= 683891)

NCBI Taxonomy ID

683892
(https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id= 683892)

is Taxon B an Infraspecies?

No

GENOTYPIC CHANGE

Generic Gene Name

Atp1a1

Synonyms

Atpa-1; BC010319

String

10090.ENSMUSP00000039657
(http://string-db.org/newstring_cgi/show_network_section.pl?identifier= 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 (https://www.ebi.ac.uk/QuickGO/term/GO:0005524)
GO:0043531 : ADP binding (https://www.ebi.ac.uk/QuickGO/term/GO:0043531)
GO:0019901 : protein kinase binding (https://www.ebi.ac.uk/QuickGO/term/GO:0019901)
GO:0043548 : phosphatidylinositol 3-kinase binding (https://www.ebi.ac.uk/QuickGO/term/GO:0043548)
GO:0005391 : sodium:potassium-exchanging ATPase activity (https://www.ebi.ac.uk/QuickGO/term/GO:0005391)
GO:0051087 : chaperone binding (https://www.ebi.ac.uk/QuickGO/term/GO:0051087)
GO:0019904 : protein domain specific binding (https://www.ebi.ac.uk/QuickGO/term/GO:0019904)
GO:0030506 : ankyrin binding (https://www.ebi.ac.uk/QuickGO/term/GO:0030506)
GO:0016791 : phosphatase activity (https://www.ebi.ac.uk/QuickGO/term/GO:0016791)
GO:0030955 : potassium ion binding (https://www.ebi.ac.uk/QuickGO/term/GO:0030955)
GO:0031402 : sodium ion binding (https://www.ebi.ac.uk/QuickGO/term/GO:0031402)
GO:1990239 : steroid hormone binding (https://www.ebi.ac.uk/QuickGO/term/GO:1990239)

GO - Biological Process

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

GO - Cellular Component

GO:0016021 : integral component of membrane

UniProtKB Mus musculus

Q8VDN2 (http://www.uniprot.org/uniprot/Q8VDN2)

GenebankID or UniProtKB

()

(https://www.ebi.ac.uk/QuickGO/term/GO:0016021)
GO:0005886 : plasma membrane (https://www.ebi.ac.uk/QuickGO/term/GO:0005886)
GO:0016324 : apical plasma membrane (https://www.ebi.ac.uk/QuickGO/term/GO:0016324)
GO:0016020 : membrane (https://www.ebi.ac.uk/QuickGO/term/GO:0016020)
GO:0045121 : membrane raft (https://www.ebi.ac.uk/QuickGO/term/GO:0045121)
GO:0005794 : Golgi apparatus (https://www.ebi.ac.uk/QuickGO/term/GO:0005794)
GO:0032991 : protein-containing complex
(https://www.ebi.ac.uk/QuickGO/term/GO:0032991)
GO:0005783 : endoplasmic reticulum (https://www.ebi.ac.uk/QuickGO/term/GO:0005783)
GO:0005768 : endosome (https://www.ebi.ac.uk/QuickGO/term/GO:0005768)
GO:0016323 : basolateral plasma membrane
(https://www.ebi.ac.uk/QuickGO/term/GO:0016323)
GO:0005901 : caveola (https://www.ebi.ac.uk/QuickGO/term/GO:0005901)
GO:0030315 : T-tubule (https://www.ebi.ac.uk/QuickGO/term/GO:0030315)
GO:0014069 : postsynaptic density (https://www.ebi.ac.uk/QuickGO/term/GO:0014069)
GO:0014704 : intercalated disc (https://www.ebi.ac.uk/QuickGO/term/GO:0014704)
GO:0043209 : myelin sheath (https://www.ebi.ac.uk/QuickGO/term/GO:0043209)
GO:0042383 : sarcolemma (https://www.ebi.ac.uk/QuickGO/term/GO:0042383)
GO:0005890 : sodium:potassium-exchanging ATPase complex
(https://www.ebi.ac.uk/QuickGO/term/GO:0005890)

Mutation #1

Presumptive Null

No (https://www.gephebase.org/search-criteria?/and+Presumptive Null=^No^#gephebase-summary-title)

Molecular Type

Coding (https://www.gephebase.org/search-criteria?/and+Molecular Type=^Coding^#gephebase-summary-title)

Aberration Type

SNP (https://www.gephebase.org/search-criteria?/and+Aberration Type=^SNP^#gephebase-summary-title)

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 (https://www.gephebase.org/search-criteria?/and+Experimental Evidence=^Candidate Gene^#gephebase-summary-title)

	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) (https://pubmed.ncbi.nlm.nih.gov/22826239)

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) (https://pubmed.ncbi.nlm.nih.gov/23019645)

Mutation #2

Presumptive Null

No (https://www.gephebase.org/search-criteria?/and+Presumptive Null=^No^#gephebase-summary-title)

Molecular Type

Coding (https://www.gephebase.org/search-criteria?/and+Molecular Type=^Coding^#gephebase-summary-title)

Aberration Type

SNP (https://www.gephebase.org/search-criteria?/and+Aberration Type=^SNP^#gephebase-summary-title)

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 (https://www.gephebase.org/search-criteria?/and+Experimental Evidence=^Candidate Gene^#gephebase-summary-title)

	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) (https://pubmed.ncbi.nlm.nih.gov/22826239)

Authors

Dobler S; Dalla S; Wagschal V; Agrawal AA

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Additional References

Parallel molecular evolution in an herbivore community. (2012) (https://pubmed.ncbi.nlm.nih.gov/23019645)

Mutation #3

Presumptive Null

No (https://www.gephebase.org/search-criteria?/and+Presumptive Null=^No^#gephebase-summary-title)

Molecular Type

Coding (https://www.gephebase.org/search-criteria?/and+Molecular Type=^Coding^#gephebase-summary-title)

Aberration Type

SNP (https://www.gephebase.org/search-criteria?/and+Aberration Type=^SNP^#gephebase-summary-title)

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 (https://www.gephebase.org/search-criteria?/and+Experimental Evidence=^Candidate Gene^#gephebase-summary-title)

	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) (https://pubmed.ncbi.nlm.nih.gov/22826239)

Authors

Dobler S; Dalla S; Wagschal V; Agrawal AA

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Additional References

Parallel molecular evolution in an herbivore community. (2012) (https://pubmed.ncbi.nlm.nih.gov/23019645)

Mutation #4

Presumptive Null

No (https://www.gephebase.org/search-criteria?/and+Presumptive Null=^No^#gephebase-summary-title)

Molecular Type

Coding (https://www.gephebase.org/search-criteria?/and+Molecular Type=^Coding^#gephebase-summary-title)

Aberration Type

SNP (https://www.gephebase.org/search-criteria?/and+Aberration Type=^SNP^#gephebase-summary-title)

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 (https://www.gephebase.org/search-criteria?/and+Experimental Evidence=^Candidate Gene^#gephebase-summary-title)

	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) (https://pubmed.ncbi.nlm.nih.gov/22826239)

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) (https://pubmed.ncbi.nlm.nih.gov/23019645)
Widespread convergence in toxin resistance by predictable molecular evolution. (2015) (https://pubmed.ncbi.nlm.nih.gov/26372961)

RELATED GEPHE

Related Genes

73 (ABCA2, Aminopeptidase N (APN), cadherin, CYP337B3, Ha_BtR, para (kdr), tetraspanin, ABCC2, ABCB1, ABCB4, CYP9J26, CYP9M6, resistance to dieldrin, Acetylcholinesterase (Ace-1), Chitin synthase 1 (CHS1), CYP6BG1, FMO2, glutamate-gated chloride channel (GluCl), MAP4K4, nAChR, RYR, CYP321A8, CYP9A186, GSTe, CYP9A, acetyl-CoA carboxylase (ACC), Acetylcholinesterase (Ace-2), CYP6CM1, CYP6CY3, CYP6CY3-CYP6CY4, esterase E4, esterase FE4, SAP-2, Cpm1, esterase A8 and B8, esterase B4, esterase B5, esterase B1, CYP6AY1, CYP6ER1, esterase NI-EST1, GST, CYP6FU1, Acetylcholinesterase (Ace), CYP6D1, esterase isozyme E7 = E3, alcohol dehydrogenase (Adh), Aldehyde dehydrogenase (Aldh), CG11699, Cyp12d1, Cyp28d1, Cyp28d1-Cyp28d2, cyp6d2, cyp6g1, GSS (glutathione synthetase), GSTE1-E10 cluster, kin of irre (kire), PHGPx, RnrS, SOD1, Ugt86Dd, esterase isozyme E3, esterase B1 + esterase A, esterase B1 = esterase beta1, CYP6AB3, CYP6P9 cluster (CYP6P9a and CYP6P9b), CYP6P9; CYP6P4 cluster, esterase type I, Nav1 sodium channel, CHKov1, CYP6B1, CYP6B4, FMO1) (https://www.gephebase.org/search-criteria?/or+Taxon ID=^50557^/and+Trait=Xenobiotic resistance/or+Taxon ID=^7536^/and+Trait=Xenobiotic resistance/or+Taxon ID=^683892^/and+Trait=Xenobiotic resistance/and+groupHaplotypes=true#gephebase-summary-title)

Related Haplotypes

11 (https://www.gephebase.org/search-criteria?/or+Gene Gephebase=^Na/K-ATPase alpha-subunit^/and+Taxon ID=^50557^/or+Gene Gephebase=^Na/K-ATPase alpha-subunit^/and+Taxon ID=^7536^/or+Gene Gephebase=^Na/K-ATPase alpha-subunit^/and+Taxon ID=^683892^#gephebase-summary-title)

EXTERNAL LINKS

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