

GEPHE SUMMARY

Gephebase Gene		GepheID
Na/K-ATPase alpha-subunit (https://www.gephebase.org/search-criteria?/and+Gene Gephebase="Na/K-ATPase alpha-subunit"#gephebase-summary-title)		GP00000707
Entry Status		Courtier
Published		Main curator

PHENOTYPIC CHANGE

Trait Category		Trait	
Physiology (https://www.gephebase.org/search-criteria?/and+Trait Category="Physiology"#gephebase-summary-title)		Xenobiotic resistance (cardiac glycosides; ouabaine) (https://www.gephebase.org/search-criteria?/and+Trait=Xenobiotic+resistance+(cardiac+glycosides;+ouabaine)#gephebase-summary-title)	
Trait State in Taxon A		Trait State in Taxon B	
Other butterflies		Danaus plexippus and Danaus eresimus - highly resistant	
Ancestral State		Taxonomic Status	
Taxon A		Interspecific (https://www.gephebase.org/search-criteria?/and+Taxonomic Status="Interspecific"#gephebase-summary-title)	
Taxon A		Taxon B #1	
Latin Name		Latin Name	
Nymphalidae (https://www.gephebase.org/search-criteria?/and+Taxon+and+Synonyms=Nymphalidae#gephebase-summary-title)		Danaus plexippus (https://www.gephebase.org/search-criteria?/and+Taxon+and+Synonyms=Danaus+plexippus#gephebase-summary-title)	
Common Name		Common Name	
brushfoots		monarch butterfly	
Synonyms		Synonyms	
brushfoots; brush-footed butterflies		Danaus (Danaus) plexippus; monarch butterfly; American monarch; Danaus plexippus (Linnaeus, 1758)	
Rank		Rank	
family		species	
Lineage		Lineage	
cellular organisms; Eukaryota; Opisthokonta; Metazoa; Eumetazoa; Bilateria; Protostomia; Ecdysozoa; Panarthropoda; Arthropoda; Mandibulata; Pancrustacea; Hexapoda; Insecta; Dicondylia; Pterygota; Neoptera; Holometabola; Amphiesmenoptera; Lepidoptera; Glossata; Neolepidoptera; Heteroneura; Ditrysia; Obtectomera; Papilionoidea		cellular organisms; Eukaryota; Opisthokonta; Metazoa; Eumetazoa; Bilateria; Protostomia; Ecdysozoa; Panarthropoda; Arthropoda; Mandibulata; Pancrustacea; Hexapoda; Insecta; Dicondylia; Pterygota; Neoptera; Holometabola; Amphiesmenoptera; Lepidoptera; Glossata; Neolepidoptera; Heteroneura; Ditrysia; Obtectomera; Papilionoidea; Nymphalidae; Danainae; Danaini; Danaina; Danaus; Danaus	
Parent		Parent	
Papilionoidea (butterflies) - (Rank: superfamily) (https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id=37572)		Danaus () - (Rank: subgenus) (https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id=151542)	
NCBI Taxonomy ID		NCBI Taxonomy ID	
33415 (https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id=33415)		13037 (https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id=13037)	
is Taxon A an Intraspecies?		is Taxon B an Intraspecies?	
No		No	
Taxon B #2		Latin Name	
-		Common Name	
-		Synonyms	
-		Rank	
-		Lineage	
-		Parent	
-		NCBI Taxonomy ID	
165861 (https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id=165861)		is Taxon B an Intraspecies?	
No			

Taxon B #3	
Danaus erippus (<a +danaus="" erippus^#gephebase-summary-title"="" href="https://www.gephebase.org/search-criteria?/and+Taxon and Synonyms=">https://www.gephebase.org/search-criteria?/and+Taxon and Synonyms="+Danaus erippus^#gephebase-summary-title)	Latin Name
-	Common Name
Danaus (Danaus) erippus	Synonyms
species	Rank
cellular organisms; Eukaryota; Opisthokonta; Metazoa; Eumetazoa; Bilateria; Protostomia; Ecdysozoa; Panarthropoda; Arthropoda; Mandibulata; Pancrustacea; Hexapoda; Insecta; Dicondylia; Pterygota; Neoptera; Holometabola; Amphimesenoptera; Lepidoptera; Glossata; Neolepidoptera; Heteroneura; Ditrysia; Obtectomera; Papilionoidea; Nymphalidae; Danainae; Danaini; Danaina; Danaus;	Lineage
Danaus () - (Rank: subgenus) (https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id=151542)	Parent
166451 (https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id=166451)	NCBI Taxonomy ID
is Taxon B an Intraspecies?	
No	

GENOTYPIC CHANGE

Accession	Gene Name	UniProtKB Mus musculus
Atp1a1	Generic Gene Name	Q8VDN2 (http://www.uniprot.org/uniprot/Q8VDN2)
	Synonyms	GenebankID or UniProtKB
Atpa-1; BC010319		HF945454 (https://www.ncbi.nlm.nih.gov/nuccore/HF945454)
	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
(<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`](https://www.gephebase.org/search-criteria?/and+Presumptive Null=))

Molecular Type

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

Aberration Type

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

SNP Coding Change

Nonsynonymous

Molecular Details of the Mutation

Q111L

Experimental Evidence

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

	Taxon A	Taxon B	Position
Codon	CAG	CTG	-
Amino-acid	Gln	Leu	111

Main Reference

The evolution of cardenolide-resistant forms of Na⁺,K⁺ -ATPase in Danainae butterflies. (2012) (<https://pubmed.ncbi.nlm.nih.gov/22126595>)

Authors

Aardema ML; Zhen Y; Andolfatto P

Abstract

Cardenolides are a class of plant secondary compounds that inhibit the proper functioning of the Na⁽⁺⁾ , K⁽⁺⁾ -ATPase enzyme in susceptible animals. Nonetheless, many insect species are able to sequester cardenolides for their own defence. These include butterflies in the subfamily Danainae (Family: Nymphalidae) such as the monarch (*Danaus plexippus*). Previous studies demonstrated that monarchs harbour an asparagine (N) to histidine (H) substitution (N122H) in the Î± subunit of Na⁽⁺⁾ , K⁽⁺⁾ -ATPase (ATPÎ±) that reduces this enzyme’s sensitivity to cardenolides. More recently, it has been suggested that at ATPÎ± position 111, monarchs may also harbour a leucine (L)/glutamine (Q) polymorphism. This later amino acid could also contribute to cardenolide insensitivity. However, here we find that incorrect annotation of the initially reported DNA sequence for ATPÎ± has led to several erroneous conclusions. Using a population genetic and phylogenetic analysis of monarchs and their close relatives, we show that an ancient Q111L substitution occurred prior to the radiation of all Danainae, followed by a second substitution at the same site to valine (V), which arose before the diversification of the *Danaus* genus. In contrast, N122H appears to be a recent substitution specific to monarchs. Surprisingly, examination of a broader insect phylogeny reveals that the same progression of amino acid substitutions (Q111Lâ†’fâ†’â†’fL111Vâ†’f+â†’fN122H) has also occurred in

Chyrsochus beetles (Family: Chrysomelidae, Subfamily: Eumolpinae) that feed on cardenolide-containing host plants. The parallel pattern of amino acid substitution in these two distantly related lineages is consistent with an adaptive role for these substitutions in reducing cardenolide sensitivity and suggests that their temporal order may be limited by epistatic interactions.

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Additional References

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>)

Adaptive substitutions underlying cardiac glycoside insensitivity in insects exhibit epistasis in vivo. (2019) (<https://pubmed.ncbi.nlm.nih.gov/31453806>)

Genome editing retraces the evolution of toxin resistance in the monarch butterfly. (2019) (<https://pubmed.ncbi.nlm.nih.gov/31578524>)

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

A119S

Experimental Evidence

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

	Taxon A	Taxon B	Position
Codon	GCC	TCC	-
Amino-acid	Ala	Ser	119

Main Reference

The evolution of cardenolide-resistant forms of Na⁺,K⁺ -ATPase in Danainae butterflies. (2012) (<https://pubmed.ncbi.nlm.nih.gov/22126595>)

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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

L111V

Experimental Evidence

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

	Taxon A	Taxon B	Position
Codon	CTG	GTG	-
Amino-acid	Leu	Val	111

Main Reference

The evolution of cardenolide-resistant forms of Na⁺,K⁺ -ATPase in Danainae butterflies. (2012) (<https://pubmed.ncbi.nlm.nih.gov/22126595>)

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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

N122H

Experimental Evidence

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

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

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Main Reference

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RELATED GEPHE

2 (CYP6B1, CYP6B4) (<https://www.gephebase.org/search-criteria?/or+Taxon ID+33415+and+Trait=Xenobiotic resistance/or+Taxon ID+13037+and+Trait=Xenobiotic resistance/or+Taxon ID+165861+and+Trait=Xenobiotic resistance/or+Taxon ID+166451+and+Trait=Xenobiotic resistance+and+groupHaplotypes=true#gephebase-summary-title>)

Related Genes

No matches found.

Related Haplotypes

EXTERNAL LINKS

COMMENTS

@SeveralMutationsWithEffect @Epistasis @& taxon 165861 Danaus eresimus in Taxon B is not indicated