

GEPHE SUMMARY

	Gephebase Gene		GepheID
Na/K-ATPase alpha-subunit ( <a href="https://www.gephebase.org/search-criteria?/and+Gene">https://www.gephebase.org/search-criteria?/and+Gene</a> Gephebase="Na/K-ATPase alpha-subunit"#gephebase-summary-title)		GP00000704	
	Entry Status	Courtier	Main curator
Published			

PHENOTYPIC CHANGE

	Trait Category		
Physiology ( <a href="https://www.gephebase.org/search-criteria?/and+Trait">https://www.gephebase.org/search-criteria?/and+Trait</a> Category="Physiology"#gephebase-summary-title)			
	Trait		
Xenobiotic resistance (cardiac glycosides) ( <a (cardiac="" glycosides)"#gephebase-summary-title"="" href="https://www.gephebase.org/search-criteria?/and+Trait=" resistance="" xenobiotic="">https://www.gephebase.org/search-criteria?/and+Trait="Xenobiotic resistance (cardiac glycosides)"#gephebase-summary-title</a> )			
	Trait State in Taxon A		
Other beetles			
	Trait State in Taxon B		
Chrysochus auratus			
	Ancestral State		
Taxon A			
	Taxonomic Status		
Interspecific ( <a href="https://www.gephebase.org/search-criteria?/and+Taxonomic">https://www.gephebase.org/search-criteria?/and+Taxonomic</a> Status="Interspecific"#gephebase-summary-title)			
		Taxon B	
	Latin Name		Latin Name
Coleoptera ( <a href="https://www.gephebase.org/search-criteria?/and+Taxon and">https://www.gephebase.org/search-criteria?/and+Taxon and</a> Synonyms="Coleoptera"#gephebase-summary-title)		Chrysochus auratus ( <a href="https://www.gephebase.org/search-criteria?/and+Taxon and">https://www.gephebase.org/search-criteria?/and+Taxon and</a> Synonyms="Chrysochus auratus"#gephebase-summary-title)	
	Common Name		Common Name
beetles		dogbane beetle	
	Synonyms		Synonyms
beetles		dogbane beetle	
	Rank		Rank
order		species	
	Lineage		Lineage
cellular organisms; Eukaryota; Opisthokonta; Metazoa; Eumetazoa; Bilateria; Protostomia; Ecdysozoa; Panarthropoda; Arthropoda; Mandibulata; Pancrustacea; Hexapoda; Insecta; Dicondylia; Pterygota; Neoptera; Holometabola		cellular organisms; Eukaryota; Opisthokonta; Metazoa; Eumetazoa; Bilateria; Protostomia; Ecdysozoa; Panarthropoda; Arthropoda; Mandibulata; Pancrustacea; Hexapoda; Insecta; Dicondylia; Pterygota; Neoptera; Holometabola; Coleoptera; Polyphaga; Cucujiformia; Chrysomeloidea; Chrysomelidae; Eumolpinae; Chrysochus	
	Parent		Parent
Holometabola () - (Rank: cohort) ( <a href="https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id= 33392">https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id= 33392</a> )		Chrysochus () - (Rank: genus) ( <a href="https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id= 131618">https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id= 131618</a> )	
	NCBI Taxonomy ID		NCBI Taxonomy ID
7041 ( <a href="https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id= 7041">https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id= 7041</a> )		131619 ( <a href="https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id= 131619">https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id= 131619</a> )	
	is Taxon A an Intraspecies?		is Taxon B an Intraspecies?
No		No	

GENOTYPIC CHANGE

	Generic Gene Name		UniProtKB Mus musculus
Atp1a1		Q8VDN2 ( <a href="http://www.uniprot.org/uniprot/Q8VDN2">http://www.uniprot.org/uniprot/Q8VDN2</a> )	
	Synonyms		GenebankID or UniProtKB
Atpa-1; BC010319		()	
	String		
10090.ENSMUSP00000039657 ( <a href="http://string-db.org/newstring.cgi/show_network_section.pl?identifier=10090.ENSMUSP00000039657">http://string-db.org/newstring.cgi/show_network_section.pl?identifier=10090.ENSMUSP00000039657</a> )			
	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 ( <a href="https://www.ebi.ac.uk/QuickGO/term/GO:0005524">https://www.ebi.ac.uk/QuickGO/term/GO:0005524</a> )			
GO:0043531 : ADP binding ( <a href="https://www.ebi.ac.uk/QuickGO/term/GO:0043531">https://www.ebi.ac.uk/QuickGO/term/GO:0043531</a> )			
GO:0019901 : protein kinase binding ( <a href="https://www.ebi.ac.uk/QuickGO/term/GO:0019901">https://www.ebi.ac.uk/QuickGO/term/GO:0019901</a> )			
GO:0043548 : phosphatidylinositol 3-kinase binding ( <a href="https://www.ebi.ac.uk/QuickGO/term/GO:0043548">https://www.ebi.ac.uk/QuickGO/term/GO:0043548</a> )			
GO:0005391 : sodium:potassium-exchanging ATPase activity ( <a href="https://www.ebi.ac.uk/QuickGO/term/GO:0005391">https://www.ebi.ac.uk/QuickGO/term/GO:0005391</a> )			

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=))

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

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

Nonsynonymous

Q111L then L111V + N122H +I315L on one recent gene copy

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

Molecular Type

Aberration Type

SNP Coding Change

Molecular Details of the Mutation

Experimental Evidence

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

Main Reference

The evolution of cardenolide-resistant forms of Na<sup>+</sup>,K<sup>+</sup>-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†’â†’L111Vâ†’â†’N122H) has also occurred in Chrysochus 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>)

Mutation #2

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

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

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

Nonsynonymous

Q111L then L111V + N122H +I315L on one recent gene copy

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

Presumptive Null

Molecular Type

Aberration Type

SNP Coding Change

Molecular Details of the Mutation

Experimental Evidence

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

Main Reference

The evolution of cardenolide-resistant forms of Na<sup>+</sup>,K<sup>+</sup>-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](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 then L111V + N122H +I315L on one recent gene copy

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	-	-	-
Amino-acid	Asn	His	122

Main Reference

The evolution of cardenolide-resistant forms of Na<sup>+</sup>, K<sup>+</sup> -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](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 then L111V + N122H +I315L on one recent gene copy

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	-	-	-
Amino-acid	Ile	Leu	315

Main Reference

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

Authors

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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  $\alpha$  subunit of Na(+) , K(+) -ATPase (ATP1 $\alpha$ ) that reduces this enzyme's sensitivity to cardenolides. More recently, it has been suggested that at ATP1 $\alpha$  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 ATP1 $\alpha$  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 (Q111L→L111V→N122H) has also occurred in Chrysomelid 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

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RELATED GEPHE

Related Genes

6 (ABCB1, Acetylcholinesterase (Ace-2), Acetylcholinesterase (Ace), para (kdr), nAChR, resistance to dieldrin) (<https://www.gephebase.org/search-criteria?/or+TaxonID=~7041~/and+Trait=Xenobiotic+resistance/or+TaxonID=~131619~/and+Trait=Xenobiotic+resistance/and+groupHaplotypes=true#gephebase-summary-title>)

Related Haplotypes

3 (<https://www.gephebase.org/search-criteria?/or+GeneGephebase=~Na/K-ATPase+alpha-subunit~/and+TaxonID=~7041~/or+GeneGephebase=~Na/K-ATPase+alpha-subunit~/and+TaxonID=~131619~/#gephebase-summary-title>)

EXTERNAL LINKS

COMMENTS

@SeveralMutationsWithEffect @SuccessiveMutationsAtSameCodon