

Na/K-ATPase alpha-subunit (https://www.gephebase.org/search-criteria?/and+Gene)	Gephebase Gene	GP00000714	GepheID
Gephebase="Na/K-ATPase alpha-subunit" #gephebase-summary-title)	Entry Status	Courtier	Main curator
Published			

	Trait Category
Physiology (https://www.gephebase.org/search-criteria?/and+TraitCategory=^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 rodents ; Jerboas spp.	
	Trait State in Taxon B
Murinae	
	Ancestral State
Taxon A	
	Taxonomic Status
Intergeneric or Higher (https://www.gephebase.org/search-criteria?/and+TaxonomicStatus=^Intergeneric or Higher^#gephebase-summary-title)	

GENOTYPIC CHANGE

Generic Gene Name	UniProtKB Mus musculus
Atp1a1	Q8VDN2 (http://www.uniprot.org/uniprot/Q8VDN2)
Atpa-1; BC010319	GenebankID or UniProtKB
String	NP_659149 (https://www.ncbi.nlm.nih.gov/nuccore/NP_659149)
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=))

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

Q111R+ N122D

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	Arg	111

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

Ujvari B; Casewell NR; Sunagar K; Arbuckle K; WÄ¼ster W; Lo N; O'Meally D; Beckmann C; King GF; Deplazes E; Madsen T

Main Reference

Authors

Abstract

The question about whether evolution is unpredictable and stochastic or intermittently constrained along predictable pathways is the subject of a fundamental debate in biology, in which understanding convergent evolution plays a central role. At the molecular level, documented examples of convergence are rare and limited to occurring within specific taxonomic groups. Here we provide evidence of constrained convergent molecular evolution across the metazoan tree of life. We show that resistance to toxic cardiac glycosides produced by plants and bufonid toads is mediated by similar molecular changes to the sodium-potassium-pump (Na(+)/K(+)-ATPase) in insects, amphibians, reptiles, and mammals. In toad-feeding reptiles, resistance is conferred by two point mutations that have evolved convergently on four occasions, whereas evidence of a molecular reversal back to the susceptible state in varanid lizards migrating to toad-free areas suggests that toxin resistance is maladaptive in the absence of selection. Importantly, resistance in all taxa is mediated by replacements of 2 of the 12 amino acids comprising the Na(+)/K(+)-ATPase H1-H2 extracellular domain that constitutes a core part of the cardiac glycoside binding site. We provide mechanistic insight into the basis of resistance by showing that these alterations perturb the interaction between the cardiac glycoside bufalin and the Na(+)/K(+)-ATPase. Thus, similar selection pressures have resulted in convergent evolution of the same molecular solution across the breadth of the animal kingdom, demonstrating how a scarcity of possible solutions to a selective challenge can lead to highly predictable evolutionary responses.

Additional References

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

Q111R+ N122D

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	Asn	Asp	122

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

Ujvari B; Casewell NR; Sunagar K; Arbuckle K; WÄ¼ster W; Lo N; O'Meally D; Beckmann C; King GF; Deplazes E; Madsen T

Main Reference

Authors

Abstract

The question about whether evolution is unpredictable and stochastic or intermittently constrained along predictable pathways is the subject of a fundamental debate in biology, in which understanding convergent evolution plays a central role. At the molecular level, documented examples of convergence are rare and limited to occurring within specific taxonomic groups. Here we provide evidence of constrained convergent molecular evolution across the metazoan tree of life. We show that resistance to toxic cardiac glycosides produced by plants and bufonid toads is mediated by similar molecular changes to the sodium-potassium-pump (Na(+)/K(+)-ATPase) in insects, amphibians, reptiles, and mammals. In toad-feeding reptiles, resistance is conferred by two point mutations that have evolved convergently on four occasions, whereas evidence of a molecular reversal back to the susceptible state in varanid lizards migrating to toad-free areas suggests that toxin resistance is maladaptive in the absence of selection. Importantly, resistance in all taxa is mediated by replacements of 2 of the 12 amino acids comprising the Na(+)/K(+)-ATPase H1-H2 extracellular domain that constitutes a core part of the cardiac glycoside binding site. We provide mechanistic insight into the basis of resistance by showing that these alterations perturb the interaction between the cardiac glycoside bufalin and the Na(+)/K(+)-ATPase. Thus, similar selection pressures have resulted in convergent evolution of the same molecular solution across the breadth of the animal kingdom, demonstrating how a scarcity of possible solutions to a selective challenge can lead to highly predictable evolutionary responses.

Additional References

RELATED GEPHE

Related Genes

2 (AHR, Vkorc1) (<https://www.gephebase.org/search-criteria?/or+Taxon ID=~9989~/and+Trait=Xenobiotic resistance/or+Taxon ID=~39107~/and+Trait=Xenobiotic resistance/and+groupHaplotypes=true#gephebase-summary-title>)

Related Haplotypes

1 (<https://www.gephebase.org/search-criteria?/or+Gene Gephebase=~Na/K-ATPase alpha-subunit~/and+Taxon ID=~9989~/or+Gene Gephebase=~Na/K-ATPase alpha-subunit~/and+Taxon ID=~39107~#gephebase-summary-title>)

EXTERNAL LINKS

COMMENTS

Resistance acquired in the alpha 1 chain paralog @SeveralMutationsWithEffect