

GEPHE SUMMARY

SCN4A (Nav1.4) (https://www.gephebase.org/search-criteria?/and+Gene Gephebase= [^] SCN4A (Nav1.4) [^] #gephebase-summary-title)	Gephebase Gene	GP00001584	GepheID
Published	Entry Status	Prigent	Main curator

PHENOTYPIC CHANGE

Physiology (https://www.gephebase.org/search-criteria?/and+Trait Category= [^] Physiology [^] #gephebase-summary-title)	Trait Category		
Xenobiotic resistance (poison frog alkaloids) (<a href="https://www.gephebase.org/search-criteria?/and+Trait=<sup>^</sup>Xenobiotic resistance (poison frog alkaloids)<sup>^</sup>#gephebase-summary-title">https://www.gephebase.org/search-criteria?/and+Trait=[^]Xenobiotic resistance (poison frog alkaloids)[^]#gephebase-summary-title)	Trait		
Frogs susceptible to alkaloids	Trait State in Taxon A		
Poison frog <i>Dendrobates tinctorius</i> (Dendrobatidae) resistant to toxin	Trait State in Taxon B		
Taxon A	Ancestral State		
Intergeneric or Higher (https://www.gephebase.org/search-criteria?/and+Taxonomic Status= [^] Intergeneric or Higher [^] #gephebase-summary-title)	Taxonomic Status		
		Taxon A	Taxon B
Anura (<a href="https://www.gephebase.org/search-criteria?/and+Taxon and Synonyms=<sup>^</sup>Anura<sup>^</sup>#gephebase-summary-title">https://www.gephebase.org/search-criteria?/and+Taxon and Synonyms=[^]Anura[^]#gephebase-summary-title)	Latin Name	<i>Dendrobates tinctorius</i> (<a href="https://www.gephebase.org/search-criteria?/and+Taxon and Synonyms=<sup>^</sup>Dendrobates tinctorius<sup>^</sup>#gephebase-summary-title">https://www.gephebase.org/search-criteria?/and+Taxon and Synonyms=[^]Dendrobates tinctorius[^]#gephebase-summary-title)	Latin Name
frogs and toads	Common Name	dyeing poison frog	Common Name
Salientia; frogs and toads; anurans; frogs	Synonyms	Calamita tinctorius; Hyla tinctoria; Hylaplesia tinctoria; Rana tinctoria; dyeing poison frog; blue poison-arrow frog; dyeing poison-arrow frog; <i>Dendrobates tinctorius</i> (Cuvier, 1797)	Synonyms
order	Rank	species	Rank
cellular organisms; Eukaryota; Opisthokonta; Metazoa; Eumetazoa; Bilateria; Deuterostomia; Chordata; Craniata; Vertebrata; Gnathostomata; Teleostomi; Euteleostomi; Sarcopterygii; Dipnotetrapodomorpha; Tetrapoda; Amphibia; Batrachia	Lineage	cellular organisms; Eukaryota; Opisthokonta; Metazoa; Eumetazoa; Bilateria; Deuterostomia; Chordata; Craniata; Vertebrata; Gnathostomata; Teleostomi; Euteleostomi; Sarcopterygii; Dipnotetrapodomorpha; Tetrapoda; Amphibia; Batrachia; Anura; Neobatrachia; Hyloidea; Dendrobatidae; Dendrobatinae; <i>Dendrobates</i>	Lineage
Batrachia () - (Rank: superorder) (https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id= 41666)	Parent	<i>Dendrobates</i> () - (Rank: genus) (https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id= 43470)	Parent
8342 (https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id= 8342)	NCBI Taxonomy ID	92724 (https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id= 92724)	NCBI Taxonomy ID
No	is Taxon A an Intraspecies?	No	is Taxon B an Intraspecies?

GENOTYPIC CHANGE

SCN4A	Generic Gene Name	P35499 (http://www.uniprot.org/uniprot/P35499)	UniProtKB Homo sapiens
HYPP; SkM1; CMS16; HYKPP; NAC1A; HOKPP2; Nav1.4; Na(V)1.4	Synonyms	()	GenebankID or UniProtKB
9606.ENSPO0000396320 (http://string-db.org/newstring_cgi/show_network_section.pl?identifier=9606.ENSPO0000396320)	String		
Belongs to the sodium channel (TC.1.A.1.10) family. Nav1.4/SCN4A subfamily.	Sequence Similarities		
GO:0005244 : voltage-gated ion channel activity (https://www.ebi.ac.uk/QuickGO/term/GO:0005244)	GO - Molecular Function		
GO:0005248 : voltage-gated sodium channel activity (https://www.ebi.ac.uk/QuickGO/term/GO:0005248)	GO - Biological Process		

GO:0006814 : sodium ion transport (<https://www.ebi.ac.uk/QuickGO/term/GO:0006814>)
 GO:0019228 : neuronal action potential (<https://www.ebi.ac.uk/QuickGO/term/GO:0019228>)
 GO:0034765 : regulation of ion transmembrane transport (<https://www.ebi.ac.uk/QuickGO/term/GO:0034765>)
 GO:0086010 : membrane depolarization during action potential (<https://www.ebi.ac.uk/QuickGO/term/GO:0086010>)
 GO:0006936 : muscle contraction (<https://www.ebi.ac.uk/QuickGO/term/GO:0006936>)
 GO:0035725 : sodium ion transmembrane transport (<https://www.ebi.ac.uk/QuickGO/term/GO:0035725>)

GO - Cellular Component

GO:0005886 : plasma membrane (<https://www.ebi.ac.uk/QuickGO/term/GO:0005886>)
 GO:0005887 : integral component of plasma membrane (<https://www.ebi.ac.uk/QuickGO/term/GO:0005887>)
 GO:0030424 : axon (<https://www.ebi.ac.uk/QuickGO/term/GO:0030424>)
 GO:0001518 : voltage-gated sodium channel complex (<https://www.ebi.ac.uk/QuickGO/term/GO:0001518>)

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

G>A p.V1583I in DIV-S6 domain

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	-	-	-

Main Reference

Convergent Substitutions in a Sodium Channel Suggest Multiple Origins of Toxin Resistance in Poison Frogs. (2016) (<https://pubmed.ncbi.nlm.nih.gov/26782998>)

Authors

Tarvin RD; Santos JC; O'Connell LA; Zakon HH; Cannatella DC

Abstract

Complex phenotypes typically have a correspondingly multifaceted genetic component. However, the genotype-phenotype association between chemical defense and resistance is often simple: genetic changes in the binding site of a toxin alter how it affects its target. Some toxic organisms, such as poison frogs (*Anura: Dendrobatidae*), have defensive alkaloids that disrupt the function of ion channels, proteins that are crucial for nerve and muscle activity. Using protein-docking models, we predict that three major classes of poison frog alkaloids (histrionicotoxins, pumiliotoxins, and batrachotoxins) bind to similar sites in the highly conserved inner pore of the muscle voltage-gated sodium channel, Nav1.4. We predict that poison frogs are somewhat resistant to these compounds because they have six types of amino acid replacements in the Nav1.4 inner pore that are absent in all other frogs except for a distantly related alkaloid-defended frog from Madagascar, *Mantella aurantiaca*. Protein-docking models and comparative phylogenetics support the role of these replacements in alkaloid resistance. Taking into account the four independent origins of chemical defense in *Dendrobatidae*, phylogenetic patterns of the amino acid replacements suggest that 1) alkaloid resistance in Nav1.4 evolved independently at least seven times in these frogs, 2) variation in resistance-conferring replacements is likely a result of differences in alkaloid exposure across species, and 3) functional constraint shapes the evolution of the Nav1.4 inner pore. Our study is the first to demonstrate the genetic basis of autoresistance in frogs with alkaloid defenses.

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Additional References

RELATED GEPHE

Related Genes

1 (Na/K-ATPase alpha-subunit) (<https://www.gephebase.org/search-criteria?/or+Taxon+ID=~8342^/and+Trait=Xenobiotic+resistance/or+Taxon+ID=~92724^/and+Trait=Xenobiotic+resistance/and+groupHaplotypes=true#gephebase-summary-title>)

Related Haplotypes

15 ([https://www.gephebase.org/search-criteria?/or+Gene+Gephebase=~SCN4A+\(Nav1.4\)^/and+Taxon+ID=~8342^/or+Gene+Gephebase=~SCN4A+\(Nav1.4\)^/and+Taxon+ID=~92724^#gephebase-summary-title](https://www.gephebase.org/search-criteria?/or+Gene+Gephebase=~SCN4A+(Nav1.4)^/and+Taxon+ID=~8342^/or+Gene+Gephebase=~SCN4A+(Nav1.4)^/and+Taxon+ID=~92724^#gephebase-summary-title))

EXTERNAL LINKS

COMMENTS

