GEPHE SUMMARY

Gephebase Gene
Nav1.7 sodium channel (https://www.gephebase.org/search-criteria?/and+Gene Gephebase=^Nav1.7 sodium channel^#gephebase-summary-title)

Entry Status
Published

GepheID
GP00000736

Main curator
Courtier

PHENOTYPIC CHANGE

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

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

Trait State in Taxon A
Thamnophis sirtalis - sensitive

Trait State in Taxon B
Thamnophis sirtalis - resistant - Willow creek

Ancestral State
Taxon A

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

Taxon A

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

Common Name
-

Synonyms
FMNH 73660; FMNH:73660

Rank
species

Lineage
cellular organisms; Eukaryota; Opisthokonta; Metazoa; Eumetazoa; Bilateria; Deuterostomia; Chordata; Craniata; Vertebrata; Gnathostomata; Teleostomi; Euteleostomi; Sarcopterygii; Dipnotetrapodomorpha; Tetrapoda; Amniota; Sauropsida; Sauria; Lepidosauria; Squamata; Bifurcata; Unidentata; Episquamata; Toxicofera; Serpentes; Colubroidea; Colubridae; Natricinae; Thamnophis

Parent
Thamnophis () - (Rank: genus) (https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id= 34999)

NCBI Taxonomy ID
35019 (https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id= 35019)

is Taxon A an Infraspecies?
No

Taxon B

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

Common Name
-

Synonyms
FMNH 73660; FMNH:73660

Rank
species

Lineage
cellular organisms; Eukaryota; Opisthokonta; Metazoa; Eumetazoa; Bilateria; Deuterostomia; Chordata; Craniata; Vertebrata; Gnathostomata; Teleostomi; Euteleostomi; Sarcopterygii; Dipnotetrapodomorpha; Tetrapoda; Amniota; Sauropsida; Sauria; Lepidosauria; Squamata; Bifurcata; Unidentata; Episquamata; Toxicofera; Serpentes; Colubroidea; Colubridae; Natricinae; Thamnophis

Parent
Thamnophis () - (Rank: genus) (https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id= 34999)

NCBI Taxonomy ID
35019 (https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id= 35019)

is Taxon B an Infraspecies?
No

GENOTYPIC CHANGE

Generic Gene Name
SCN9A

Synonyms
PN1; ETHA; NENA; SFNP; FEB3B; NE-NA; GEFSP7; HSAN2D; Nav1.7

String
9606.ENSP00000386306 (http://string-db.org/newstring_cgi/show_network_section.pl?identifier= 9606.ENSP00000386306)

Sequence Similarities
Belongs to the sodium channel (TC 1.A.1.10) family. Nav1.7/SCN9A subfamily.

GO - Molecular Function
GO:0031402 : sodium ion binding (https://www.ebi.ac.uk/QuickGO/term/GO:0031402)
GO:0005244 : voltage-gated ion channel activity (https://www.ebi.ac.uk/QuickGO/term/GO:0005244)
GO:0005248 : voltage-gated sodium channel activity (https://www.ebi.ac.uk/QuickGO/term/GO:0005248)

GO - Biological Process

UniProtKB Homo sapiens
Q15858 (http://www.uniprot.org/uniprot/Q15858)

GenebankID or UniProtKB
()

GO:0006814 : sodium ion transport (https://www.ebi.ac.uk/QuickGO/term/GO:0006814)
GO:0006954 : inflammatory response
(https://www.ebi.ac.uk/QuickGO/term/GO:0006954)
GO:0019228 : neuronal action potential
(https://www.ebi.ac.uk/QuickGO/term/GO:0019228)
GO:0009791 : post-embryonic development
(https://www.ebi.ac.uk/QuickGO/term/GO:0009791)
GO:0019233 : sensory perception of pain
(https://www.ebi.ac.uk/QuickGO/term/GO:0019233)
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:0035725 : sodium ion transmembrane transport
(https://www.ebi.ac.uk/QuickGO/term/GO:0035725)
GO:0048266 : behavioral response to pain
(https://www.ebi.ac.uk/QuickGO/term/GO:0048266)
GO:0009636 : response to toxic substance
(https://www.ebi.ac.uk/QuickGO/term/GO:0009636)

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)

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

Asp1393Glu + Ala1681Gly + Asp1684Asn + Gly1685Tyr
The Aspâ€"Glu substitution has been previously described in Nav1.4 from two snake species, the resistant Th. atratus (Feldman et al. 2009) and the putatively resistant Amphiesma pryeri (Feldman et al. 2012) and replacements at this site lead to minor changes in TTX-binding affinity (Terlau et al. 1991; Choudhary et al. 2003) but this specific replacement has not been empirically tested for its effects on TTX binding.

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	Glu	1393

Main Reference

Parallel evolution of tetrodotoxin resistance in three voltage-gated sodium channel genes in the garter snake Thamnophis sirtalis. (2014) (https://pubmed.ncbi.nlm.nih.gov/25135948)

Authors

McGlothlin JW; Chuckalovcak JP; Janes DE; Edwards SV; Feldman CR; Brodie ED; Pfrender ME; Brodie ED

Abstract

Members of a gene family expressed in a single species often experience common selection pressures. Consequently, the molecular basis of complex adaptations may be expected to involve parallel evolutionary changes in multiple paralogs. Here, we use bacterial artificial chromosome library scans to investigate the evolution of the voltage-gated sodium channel (Nav) family in the garter snake Thamnophis sirtalis, a predator of highly toxic Taricha newts. Newts possess tetrodotoxin (TTX), which blocks Nav's, arresting action potentials in nerves and muscle. Some Thamnophis populations have evolved resistance to extremely high levels of TTX. Previous work has identified amino acid sites in the skeletal muscle sodium channel Nav1.4 that confer resistance to TTX and vary across populations. We identify parallel evolution of TTX resistance in two additional Nav paralogs, Nav1.6 and 1.7, which are known to be expressed in the peripheral nervous system and should thus be exposed to ingested TTX. Each paralog contains at least one TTX-resistant substitution identical to a substitution previously identified in Nav1.4. These sites are fixed across populations, suggesting that the resistant peripheral nerves antedate resistant muscle. In contrast, three sodium channels expressed solely in the central nervous system (Nav1.1-1.3) showed no evidence of TTX resistance, consistent with protection from toxins by the blood-brain barrier. We also report the exon-intron structure of six Nav paralogs, the first such analysis for snake genes. Our results demonstrate that the molecular basis of adaptation may be both repeatable across members of a gene family and predictable based on functional considerations.

Additional References

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

Asp1393Glu + Ala1681Gly + Asp1684Asn + Gly1685Tyr
- The Alaâ€"Gly substitution occurs at the channelâ€™s selectivity filter, and is also found in four different paralogs in TTX-bearing pufferfishes, where it provides 1.5-fold resistance to TTX and 11-fold resistance to saxitoxin (Jost et al. 2008). Despite its location, this substitution does not affect ion selectivity, but delays recovery from slow inactivation (Wu et al. 2013), suggesting the possibility that it evolved to compensate for other changes to the channelâ€™s pore.

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	Ala	Gly	1681

Main Reference

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Additional References

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

Asp1393Glu + Ala1681Gly + Asp1684Asn + Gly1685Tyr
- The Aspâ€"Asn substitution occurs in a highly TTX-resistant (600X) isoform of Nav1.4 found in California Th. sirtalis (Geffeney et al. 2005) and on its own should confer approximately 30- to 40-fold resistance to TTX (Penzotti et al. 1998; Choudhary et al. 2003).

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	1684

Main Reference

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Additional References

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

Asp1393Glu + Ala1681Gly + Asp1684Asn + Gly1685Tyr
- The Glyâ€“Tyr substitution is previously undescribed and untested but substitutions in this location are often found in TTX-resistant species (Geffeney et al. 2005; Jost et al. 2008; Feldman et al. 2012). This residue is located in the outer portion of the pore, and the replacement of glycineâ€™s hydrogen with tyrosineâ€™s large aromatic side chain may conceivably interfere with the ability of TTX to access its binding site in the pore.

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	Gly	Tyr	1685

Main Reference

Parallel evolution of tetrodotoxin resistance in three voltage-gated sodium channel genes in the garter snake Thamnophis sirtalis. (2014) (https://pubmed.ncbi.nlm.nih.gov/25135948)

Authors

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Additional References

RELATED GEPHE

Related Genes

2 (Nav1.6 sodium channel, SCN4A (Nav1.4)) (https://www.gephebase.org/search-criteria?/or+Taxon ID=^35019^/and+Trait=Xenobiotic resistance/and+groupHaplotypes=true#gephebase-summary-title)

Related Haplotypes

No matches found.

EXTERNAL LINKS

COMMENTS

@SeveralMutationsWithEffect