Can the absence of pain make you a hero?

Do we need pain?

- *Pain is essential to minimize damage to the organism*
- *Pain leads to behaviour of damage avoidance and promotes tissue repair*

Do we need analgesics?

YES!!!!

What problems are associated with current pain killers?

Effectivity?

Unwanted effects (side effects) e.g.:

- *Respiratory suppression*
- *Drowsiness*
- *Itchiness*
- *Nausea/vomiting*
- *Constipation/gastrointestinal problems (e.g. ulcers)*

Can the absence of pain make you a hero?

nature

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ARTICLES

An *SCN9A* channelopathy causes congenital inability to experience pain

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Pain is essential to minimize damage to the organism

Pain leads to behaviour of damage avoidance and promotes tissue repair

Congenital indifference to pain (CIP)

Loss-of-function mutations in the $Na_v1.7$ gene

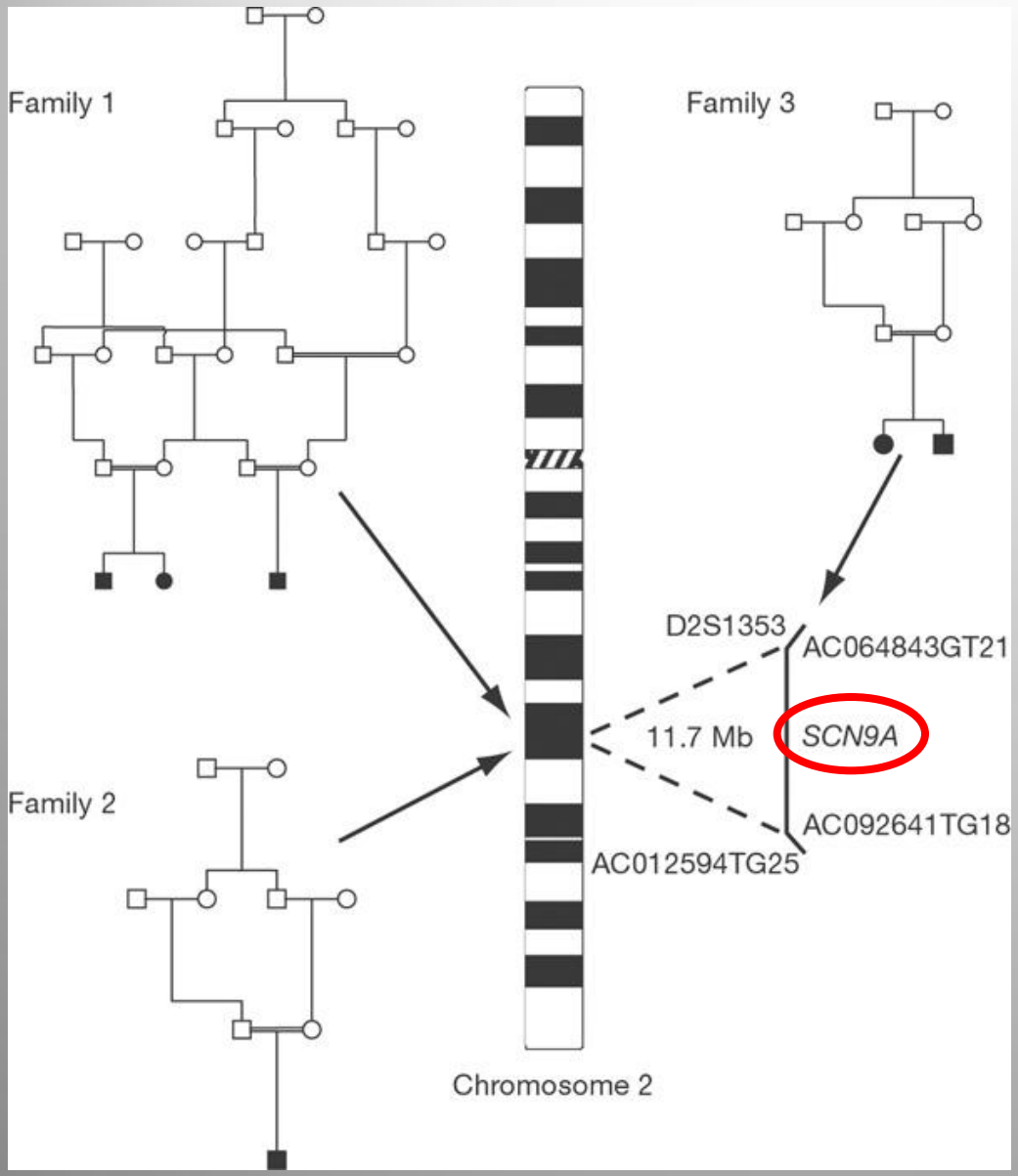
Table 1. Clinical features for CIP diagnosis

Clinical feature	CIP-14	CIP-10	CIP-8	CIP-32	CIP-5	CIP-26	CIP-33	CIP-38	CIP-102
Congenital onset and/or presenting in early childhood	Y	Y	Y	Y	Y	Y	Y	Y	Y
Lack of response to pain all over body on pinprick test	Y	Y	Y	Y	Y	Y	Y	Y	Y
Lack of response to visceral pain	Y	Y	Y	Y	Y	Y	Y	Y	Y
Other sensory modalities (tactile, thermal, vibratory) are normal	Y	Y	Y	Y	Y	Y	Y	Y	Y
Normal intelligence	Y	Y	Y	Y	Y	Y	Y	Y	Y
Normal deep tendon reflexes	UK	Y	ND	Y	Y	Y	Y	Y	Y
Normal nerve biopsy (myelinated and unmyelinated fibres)	Y	ND	Y	ND	ND	Y	Y	Y	ND
Normal motor and sensory nerve conduction velocities	Y	UK	UK	Y	Y	Y	Y	UK	Y
Normal autonomic function (e.g. tearing, blood pressure, sweating)	Y	Y	Y	Y	Y	Y	Y	Y	Y
Normal response to intradermal histamine injection	Y	ND	ND	ND	Y	UK	UK	Y	ND
Normal karyotype	ND	Y	Y	ND	ND	UK	UK	ND	UK

UK: unknown
ND: not tested

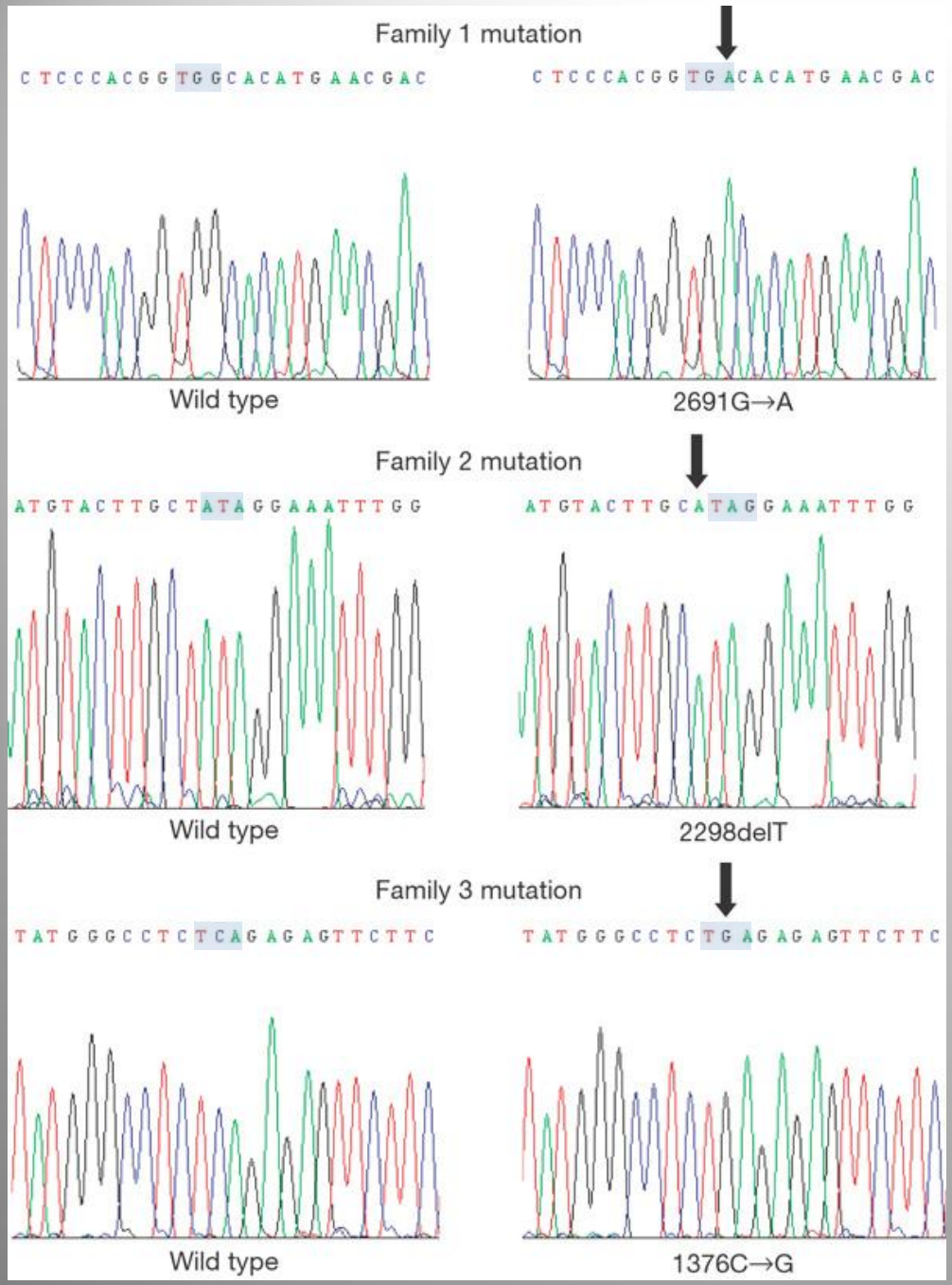
In four families affected patients were offspring of known consanguineous mating

Clin Genet (2007) **71**:311



The gene SCN9A encodes for the voltage-gated Na^+ channel $Na_V1.7$

Consanguineous family trees!



W897X

W=Trp=tryptophane

X=stop codon

Frameshift I767X

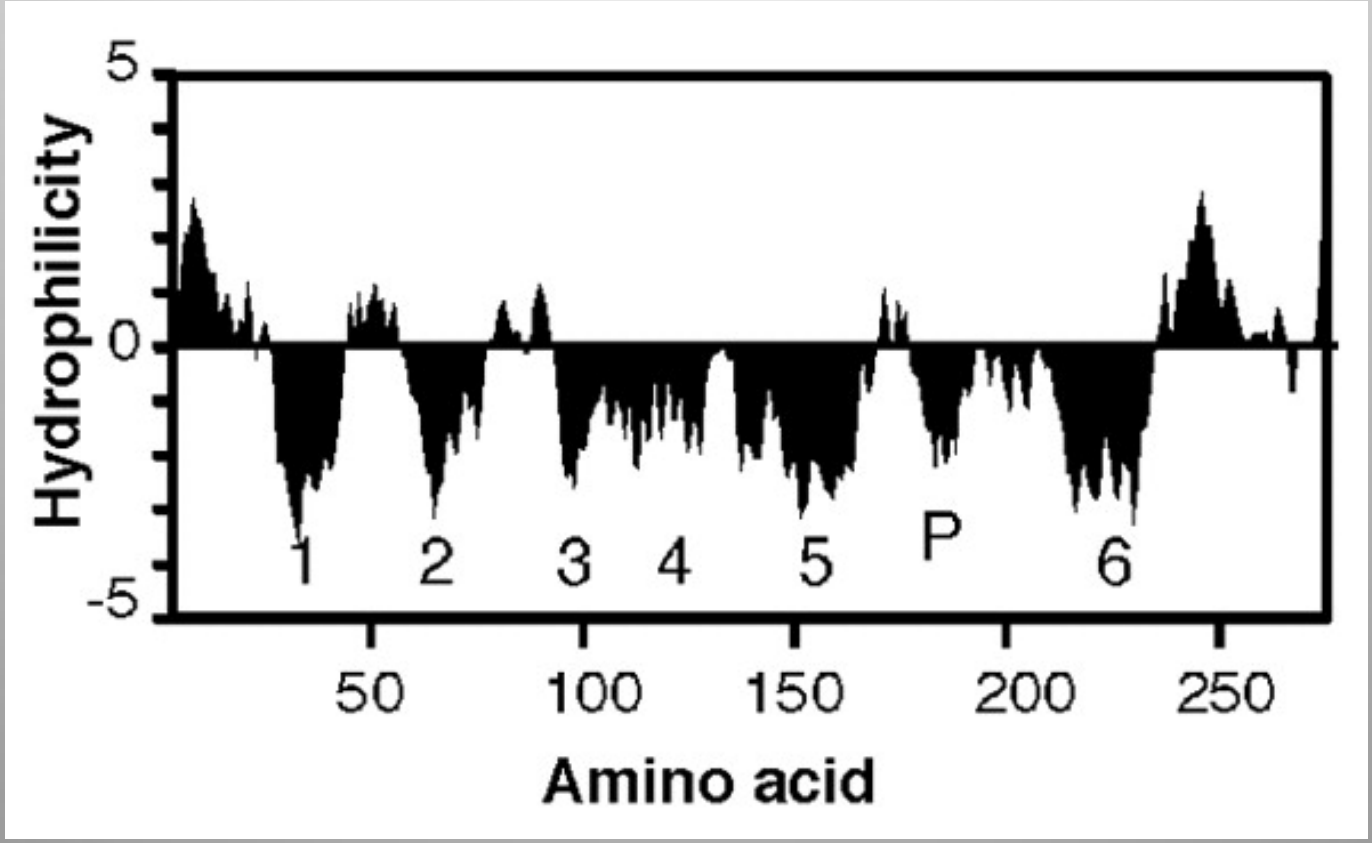
I=Ile=isoleucine

S=Ser=serine

S459X

Affected individuals are homozygous for mutation!

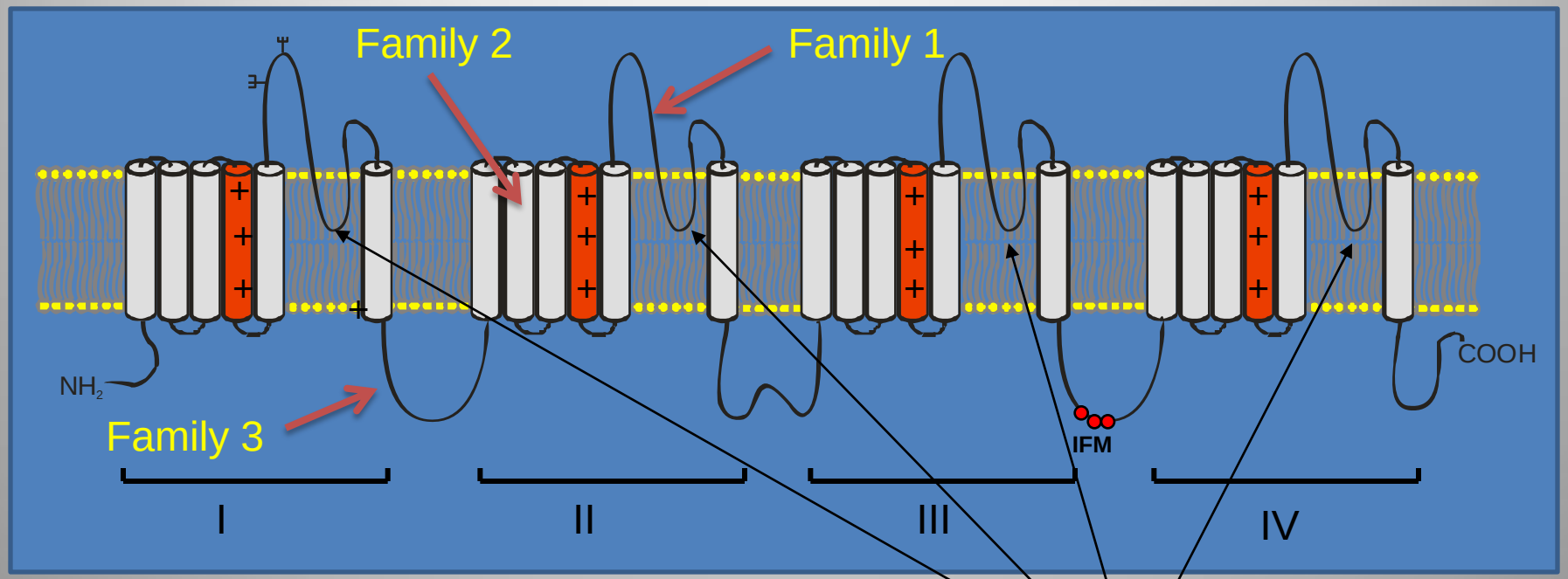
A hydropathy plot allows to predict transmembrane segments of a membrane protein



Voltage-gated K channel

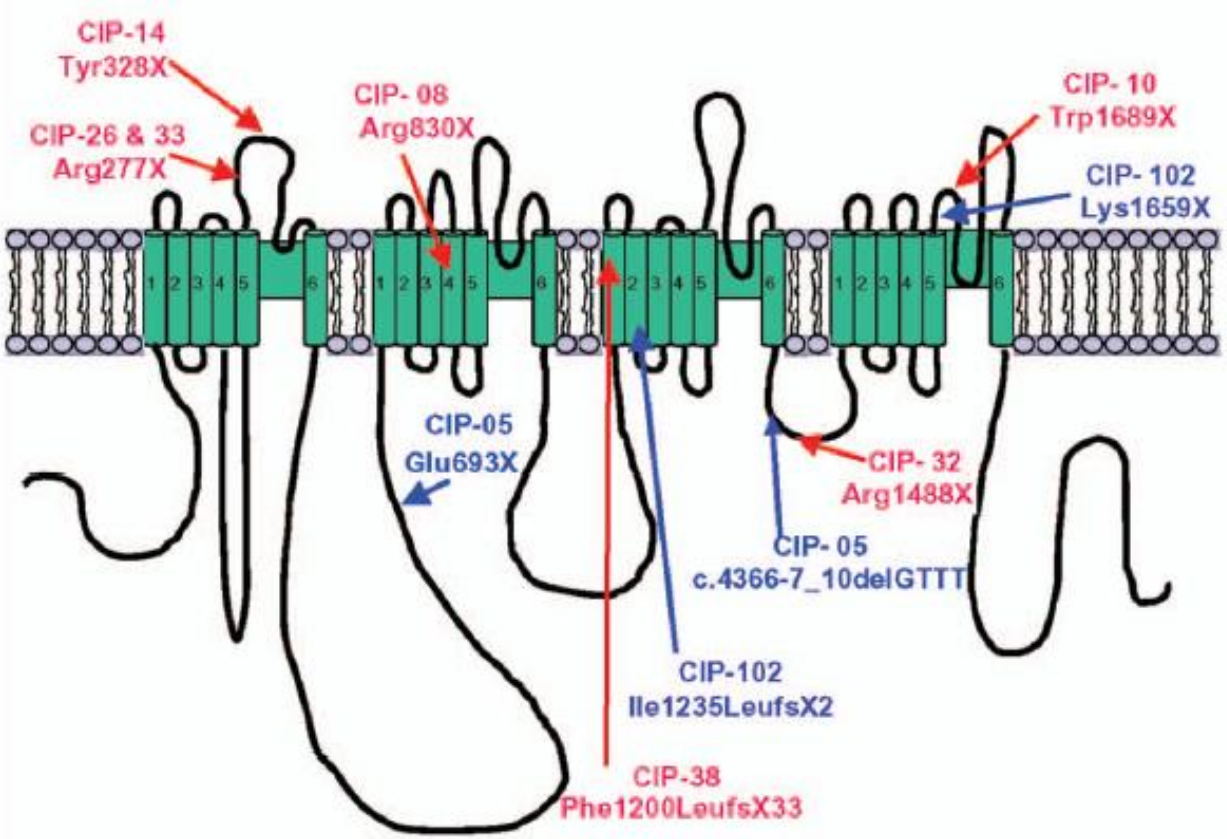
Voltage-gated Na^+ channel topology

(α-subunit)



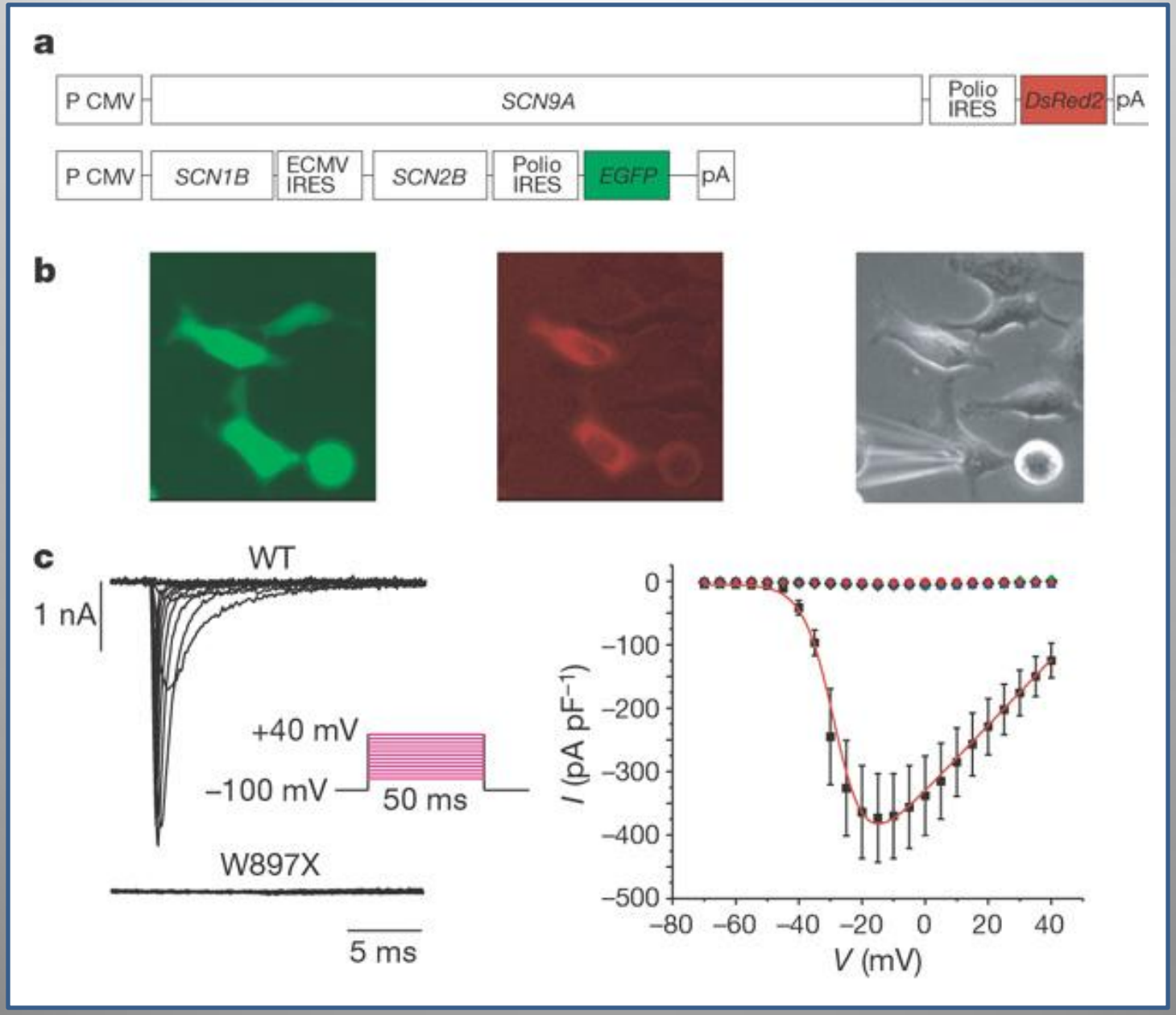
- Approx 2000 amino acid residues
- 4 repeats (I-IV)
- Extracellular glycosylation sites
- TM4: voltage sensor
- inactivation loop with IFM sequence

Selectivity filter



	Family	Exon	Allele WT	Allele MT	DNA sequence variation	Genotype	Description
Homozygote	CIP-26	E6	C	T	c.829C>T	T, T	Nonsense mutation p.Arg277X
	CIP-33	E6	C	T	c.829C>T	T, T	Nonsense mutation p.Arg277X
	CIP-14	E8	C	A	c.984C>A	A, A	Nonsense mutation p.Tyr328X
	CIP-08	E15	C	T	c.2486C>T	T, T	Nonsense mutation p.Arg830X
	CIP-38	E19	A	–	c.3600delT	del T, del T	Frameshift causing p.Phe1200LeufsX33
	CIP-32	E24	C	T	c.4462C>T	T, T	Nonsense mutation p.Arg1488X
	CIP-10	E26	G	A	c.5067G>A	A, A	Nonsense mutation p.Trp1689X
Compound Heterozygote	CIP-05	E13	–	T	c.2076_2077insT	–, insT	Frameshift causing immediate STOP p.Glu693X
		Intron 23-24	–	–	c.4366-7_10delGTTT	–, del 4 bp	Splice–junction mutation
	CIP-102	E19	–	–	c.3703_3713del	–, del 11 bp	Frameshift causing p.Ile1235LeufsX2
		E26	A	T	c.4975A>T	A, T	Nonsense mutation p.Lys1659X.

Mutant analysis in heterologous expression system



Loss-of-Function mutation causes loss of pain sensation

What does a Gain-of-Function mutation do?

Table $Na_v1.7$ channelopathies

Disorder	Inheritance	Mutation	Clinical phenotype
Inherited erythromelalgia	Autosomal dominant	Missense mutations	Attacks of burning pain and redness in distal extremities; triggered by mild warmth and exercise
Paroxysmal extreme pain disorder	Autosomal dominant	Missense mutations	Episodic perirectal, ocular, and jaw pain accompanied by flushing and other autonomic abnormalities
Channelopathy-associated insensitivity to pain	Autosomal recessive	Nonsense mutations	Inability to sense pain

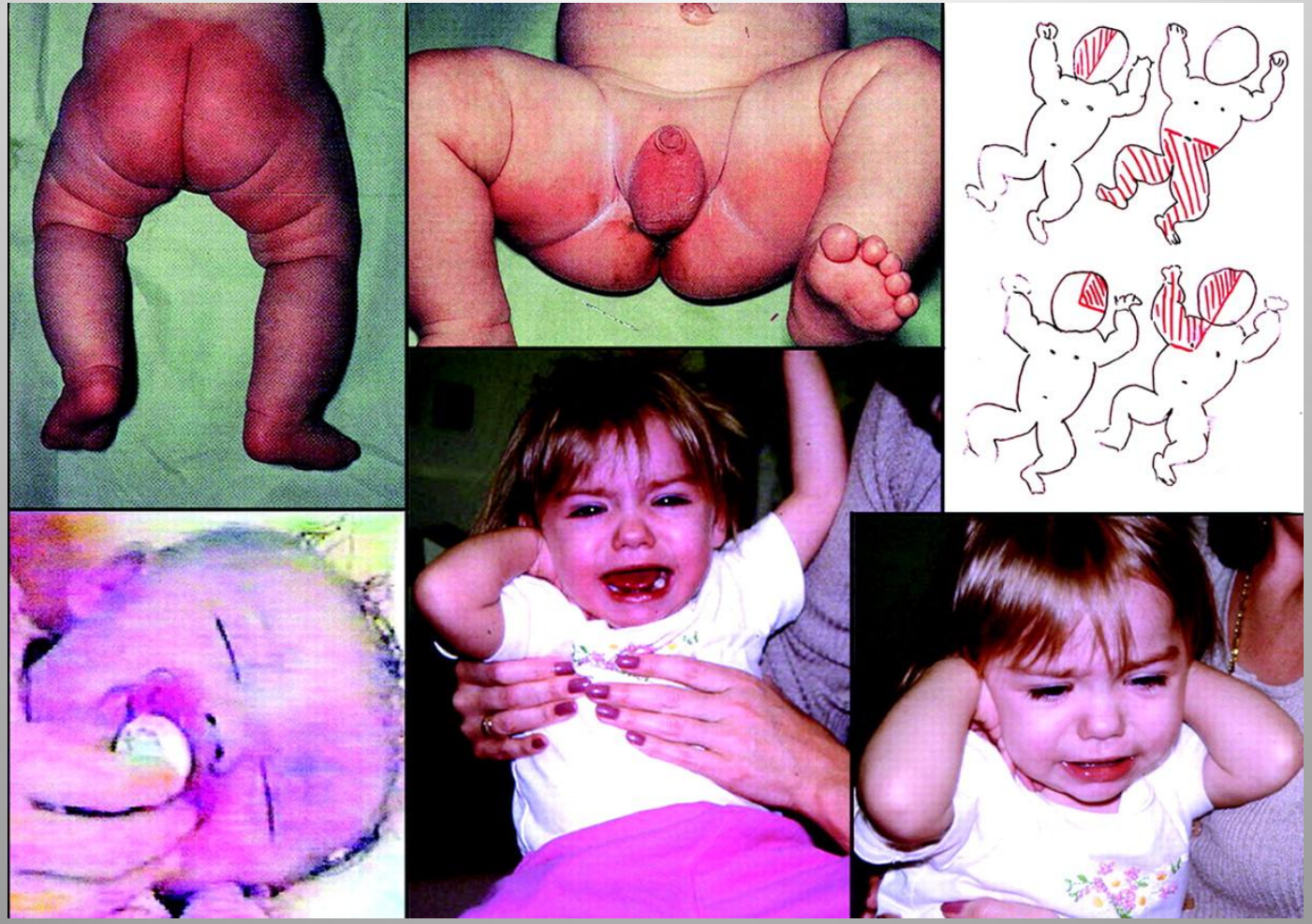
Waxman, S. G. Neurology 2007;69:505-507

NEUROLOGY

Paroxysmal extreme pain disorder (previously familial rectal pain syndrome)

C. R. Fertleman, C. D. Ferrie, J. Aicardi, N.A.F. Bednarek, O. Eeg-Olofsson, F. V. Elmslie, D. A. Griesemer, F. Goutières, M. Kirkpatrick, I. N.O. Malmros, M. Pollitzer, M. Rossiter, E. Roulet-Perez, R. Schubert, V. V. Smith, H. Testard, V. Wong and J. B.P. Stephenson

Neurology 2007;69;586-595
DOI: 10.1212/01.wnl.0000268065.16865.5f

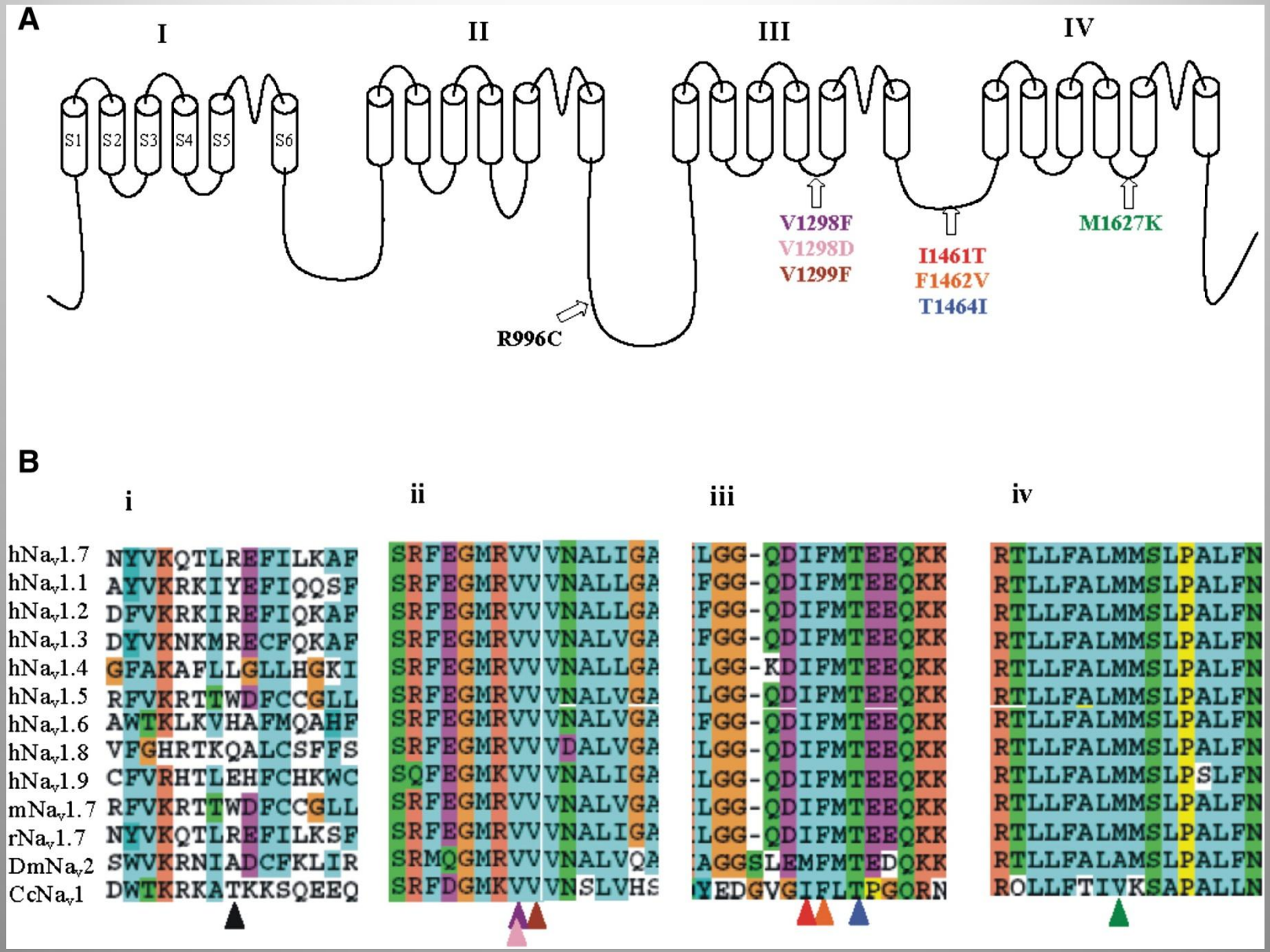


Fertleman, C. R. et al. Neurology 2007;69:586-595

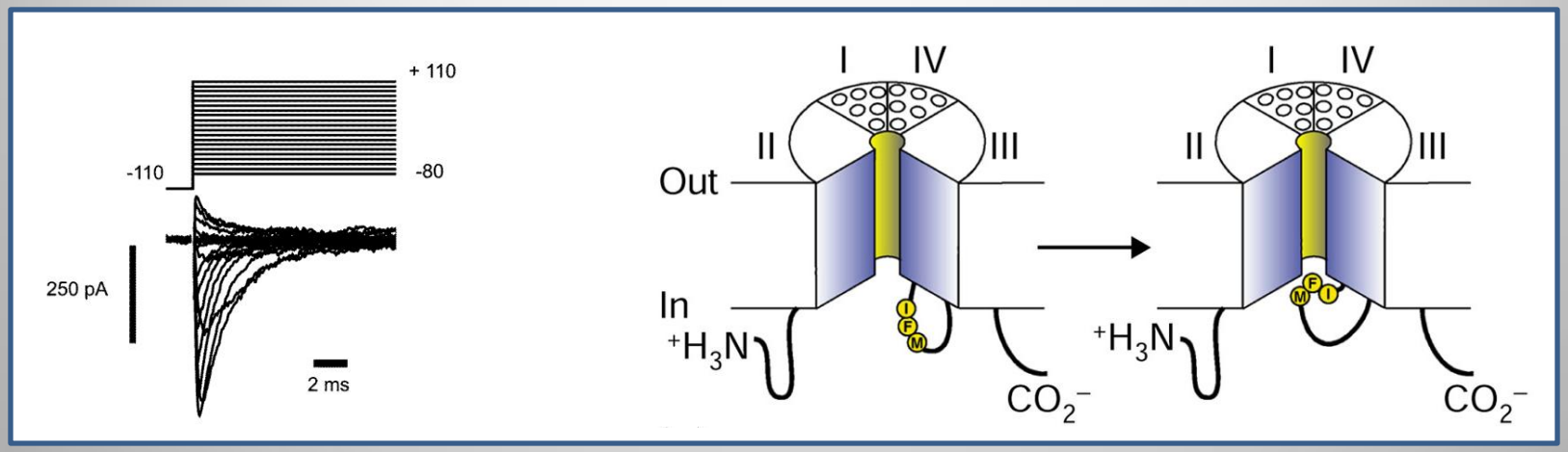
NEUROLOGY

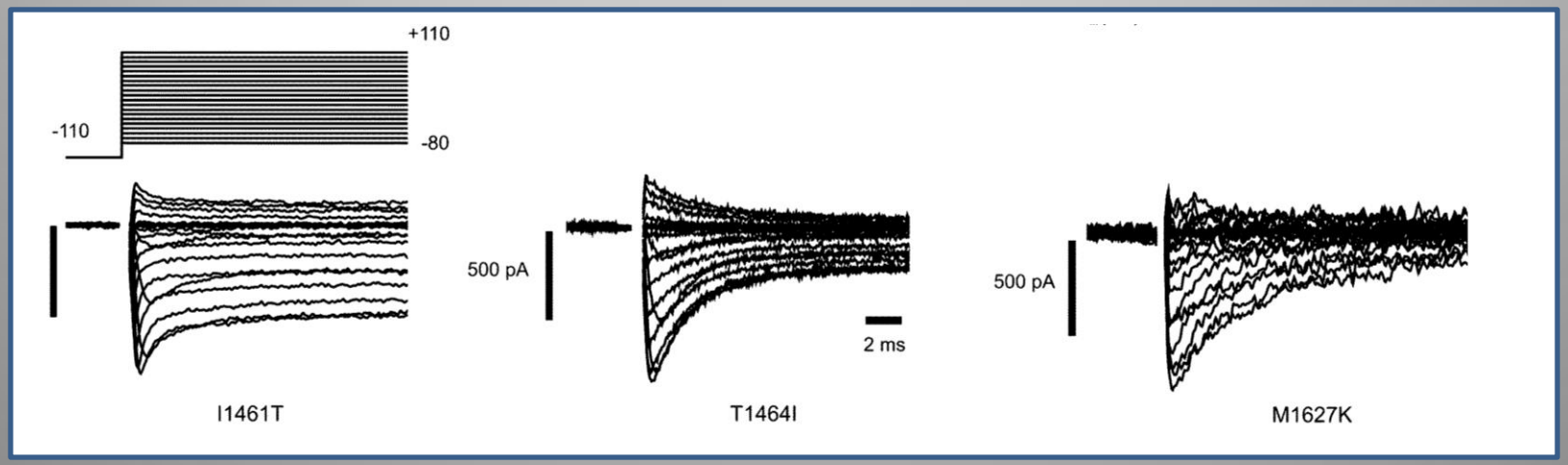
AMERICAN ACADEMY OF NEUROLOGY

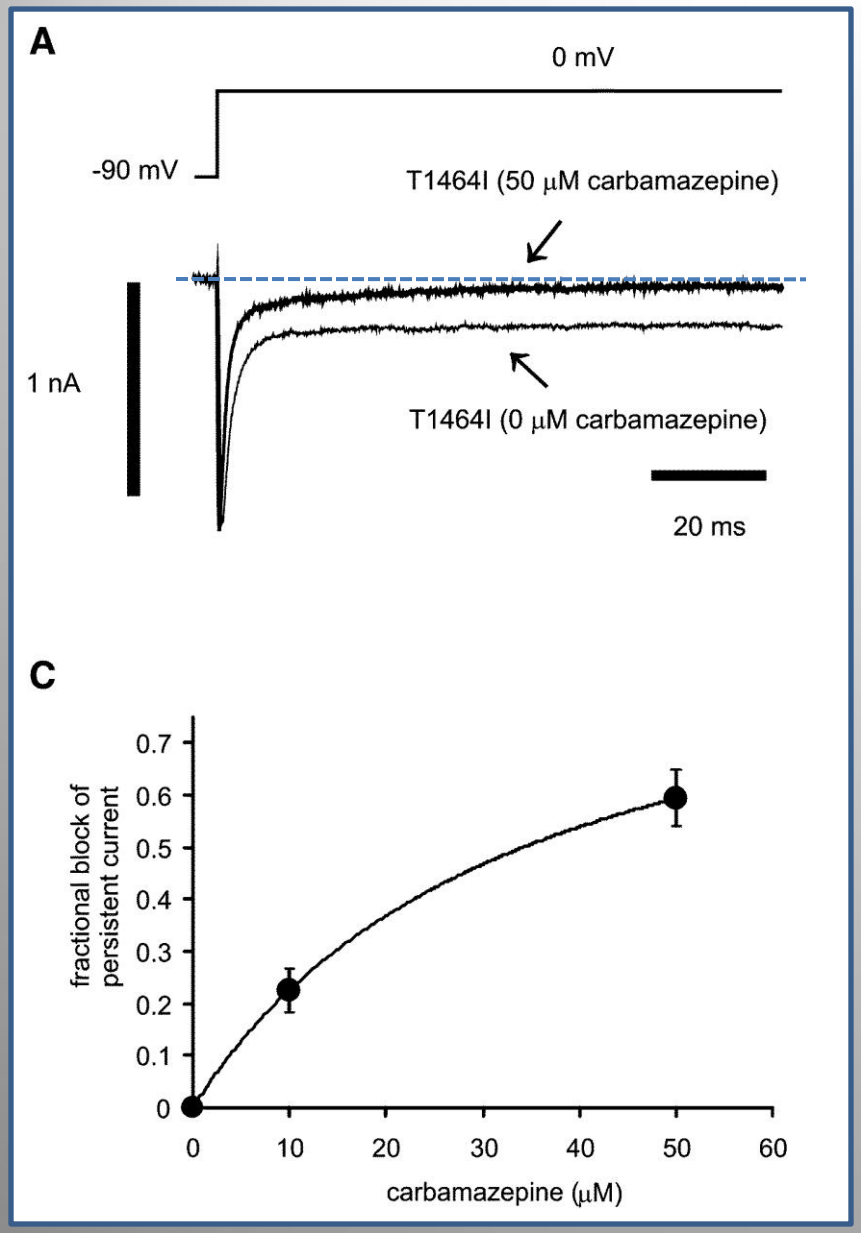
SCN9A mutations causing paroxysmal extreme pain disorder (PEPD)



SCN9A mutations causing PEPD affect inactivation





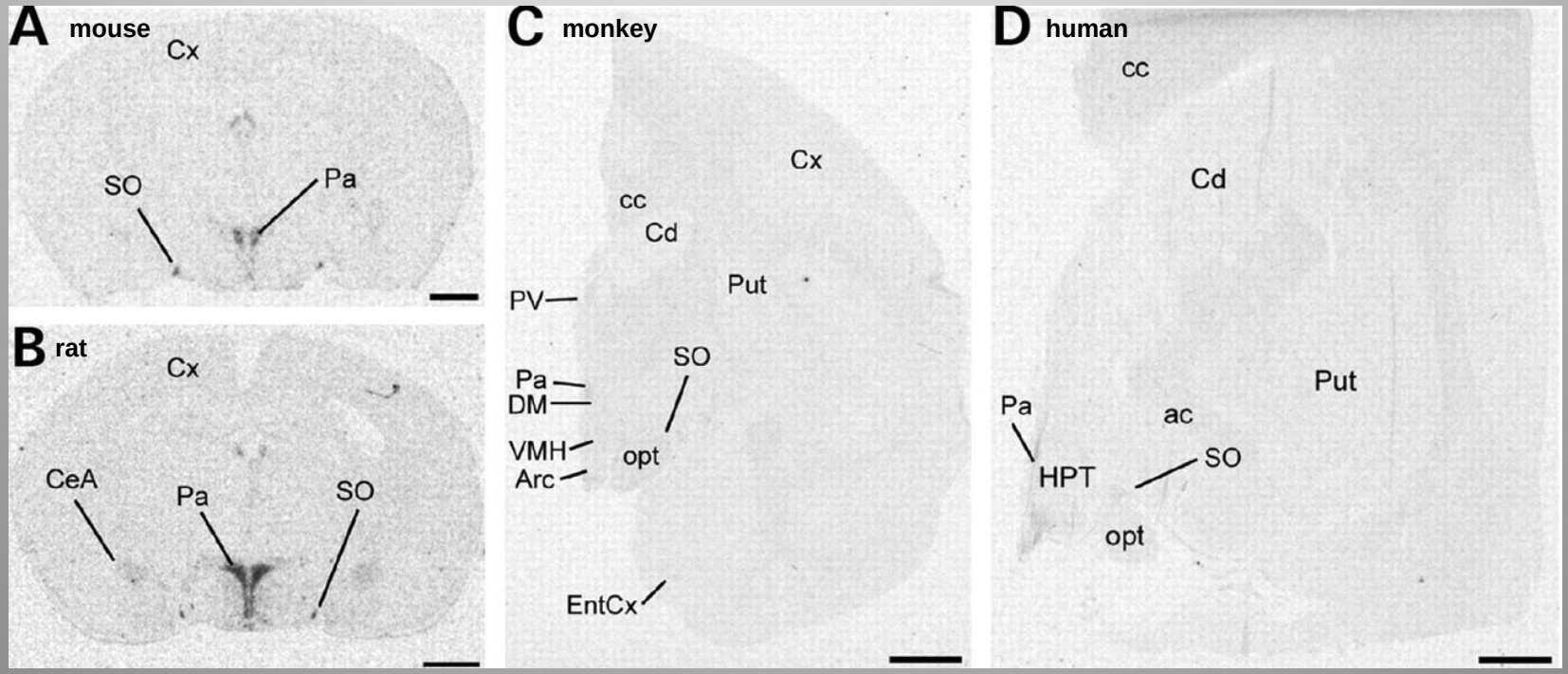


The anti-epileptic drug carbamazepine blocks the persistant current of the PEPD mutation T1461I

Problems with animal models of SCNA9A loss of function

A global knockout in mice is lethal(animals do not feed)

- In rodents, but not primates, prominent *in situ* labelling in hypothalamus, pituitary and adrenal glands



Ahmad S et al. Hum. Mol. Genet. 2007;16:2114-2121

Table $Na_v1.7$ channelopathies

Disorder	Inheritance	Mutation	Effects on channel
Inherited erythromelalgia	Autosomal dominant	Missense mutations	Lower threshold for activation; slow deactivation; enhanced response to subthreshold stimuli
Paroxysmal extreme pain disorder	Autosomal dominant	Missense mutations	Impaired inactivation; enhanced persistent current
Channelopathy-associated insensitivity to pain	Autosomal recessive	Nonsense mutations	Loss of function of $Na_v1.7$

Now we know that SCN9A is essential for pain perception in humans.
So what!

What benefit do you see in the information gained from these studies?

Further Reading

Original Articles and Reviews

Cox et al. (2006) An SCN9A channelopathy causes congenital inability to experience pain. Nature. 444:894-8.

Goldberg et al. (2007) Loss-of-function mutations in the Nav1.7 gene underlie congenital indifference to pain in multiple human populations. Clin Genet. 71:311-9.

Ahmad et al. (2007) A stop codon mutation in SCN9A causes lack of pain sensation. Hum Mol Genet. 16:2114-21.

Waxman SG. (2007) Nav1.7, its mutations, and the syndromes that they cause. Neurology. 69:505-7.

Fertleman et al. (2007) Paroxysmal extreme pain disorder (previously familial rectal pain syndrome). Neurology. 69:586-95.

Fertleman et al. (2006) SCN9A mutations in paroxysmal extreme pain disorder: allelic variants underlie distinct channel defects and phenotypes. Neuron 52:767-774.

Jurkat-Rott, K. & Lehmann-Horn, F. (2005). Muscle channelopathies and critical points in functional and genetic studies. The Journal of Clinical Investigation 115:2000.

Textbooks

Human Molecular Genetics 2. Strachan & Read. BIOS Scientific Publishers Ltd. Oxford

Ion Channels and Disease. Ashcroft, F.M. 2000. Academic Press, London