Maastricht UMC+

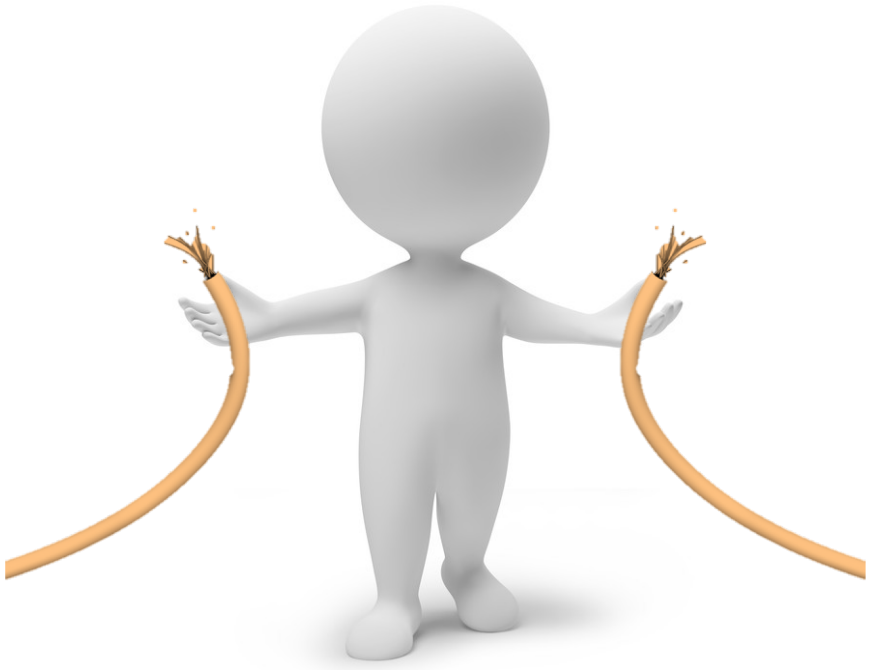
Genetics of small fiber neuropathy

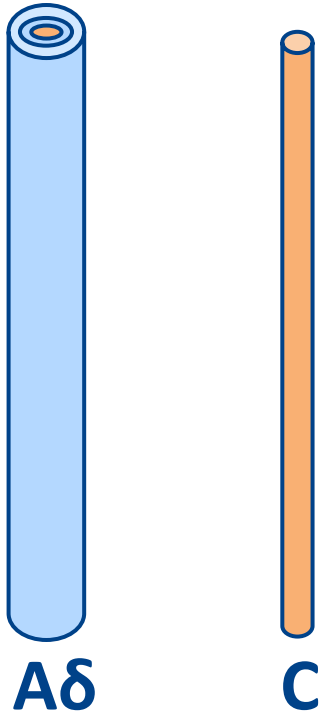
Catharina (Karin) Faber

Maastricht UMC+

Small fiber neuropathy

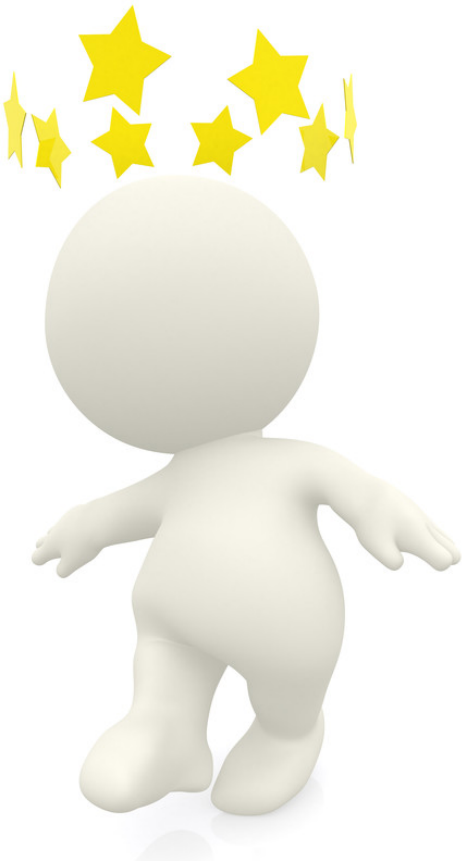
Small fiber neuropathy





Symptoms

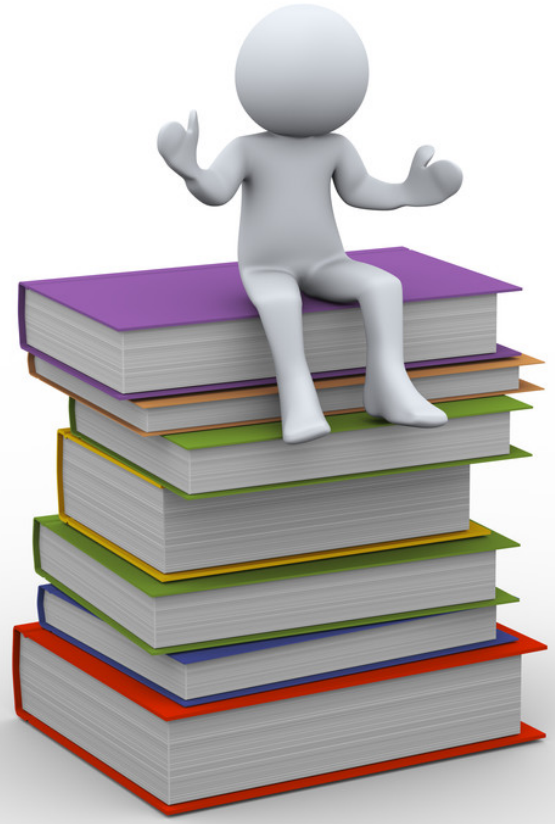
Symptoms



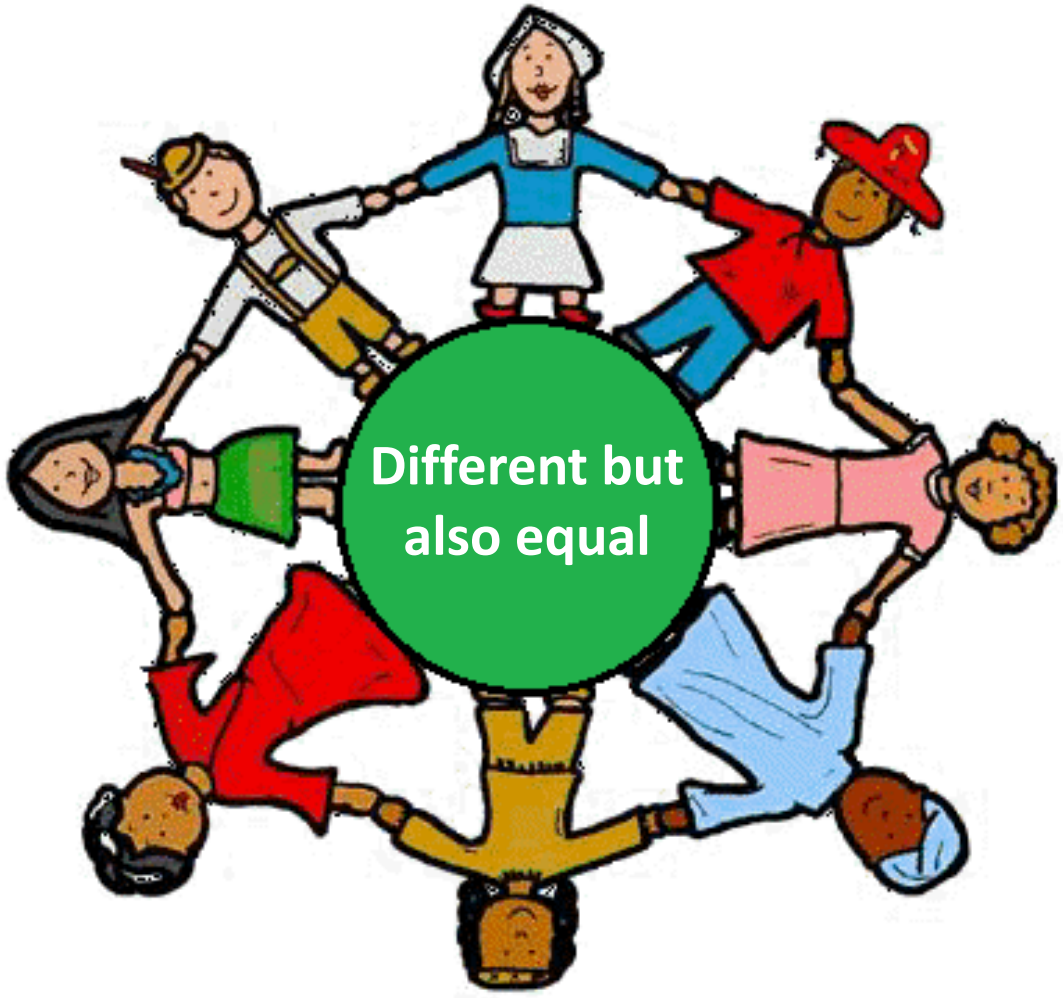
Maastricht UMC+

Associated conditions

Diabetes mellitus, glucose intolerance, alcohol abuse, antiretroviral drugs, chemotherapy, toxins, vitamin B6, HIV, Epstein Barr virus, Lepra, botulism, vasculitis, SLE, Sjögren, coeliac disease, sarcoidosis, monoclonal gammopathy, amyloidosis, paraneoplastic neuropathy, inflammatory bowel disease, Guillain Barré syndrome, M. Fabry, M. Tangier, familial amyloidosis, Charcot Marie Tooth 2B, erythromelalgia/erythermalgia, burning feet syndrome, idiopathic…..

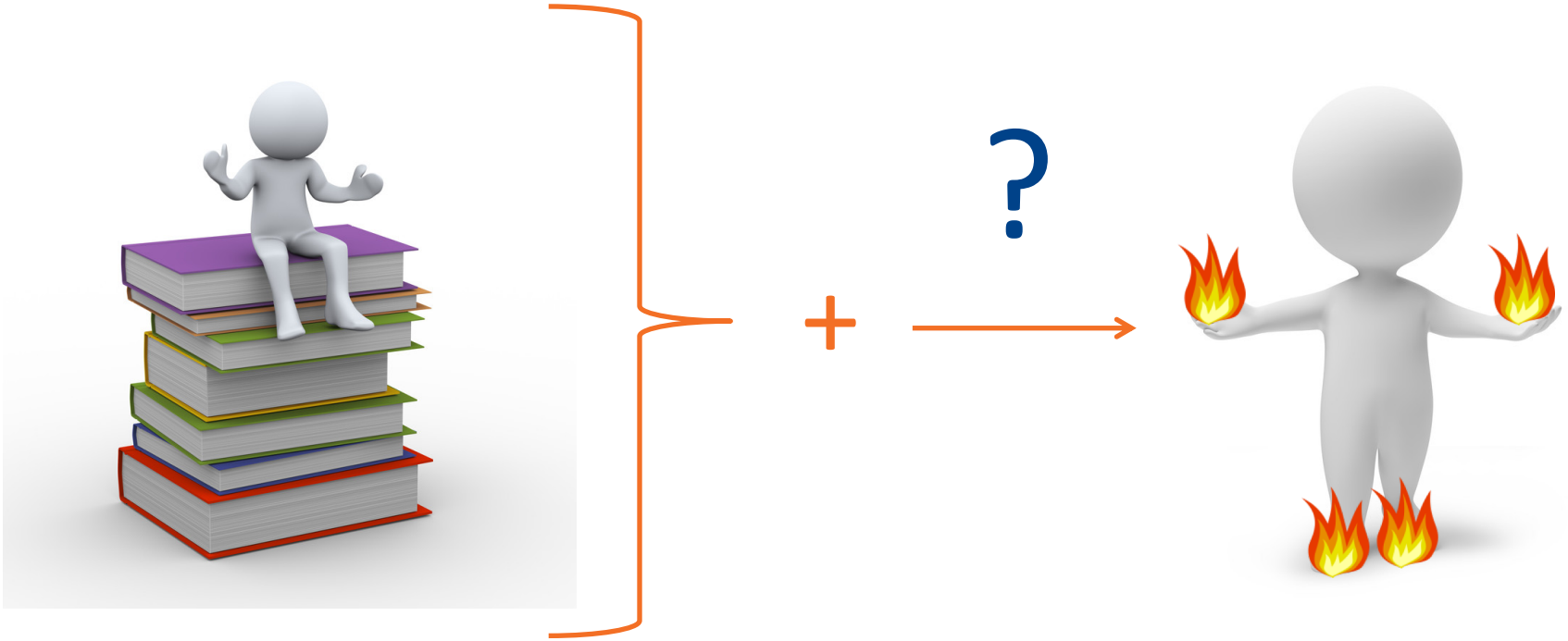


Clinical observation



Maastricht UMC+

Common pathophysiological pathway?



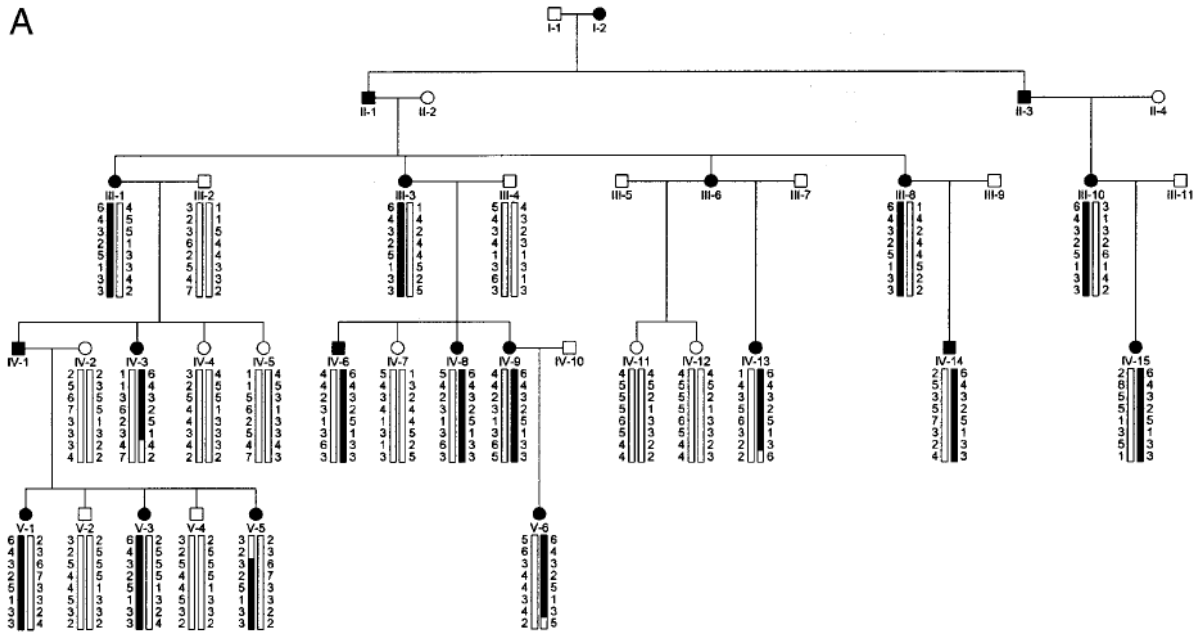
Maastricht UMC+

Sodium channels

The Primary Erythermalgia–Susceptibility Gene Is Located on Chromosome 2q31-32

Joost P. H. Drenth,[1] Wayne H. Finley,[2] Guido J. Breedveld,[3] Leon Testers,[4] Jan J. Michiels,[5,6] G. Guillet,[7] Alain Taieb,[8] R. Lee Kirby,[9] and Peter Heutink[3]

Am. J. Hum. Genet. 68:1277–1282, 2001



Genome screening with fluorescently labeled short tandem repeat polymorphisms (STRPs) → Chromosome 2q31-32 (7.94 cM)

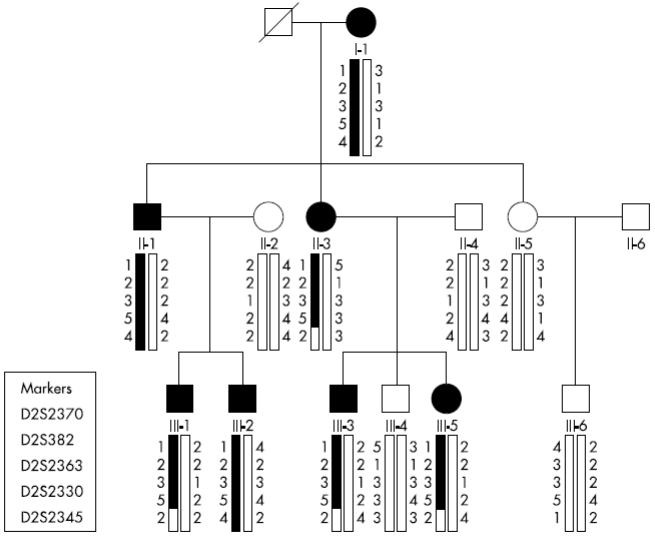
Maastricht UMC+

SHORT REPORT

Mutations in *SCN9A*, encoding a sodium channel alpha subunit, in patients with primary erythermalgia

Y Yang*, Y Wang*, S Li*, Z Xu, H Li, L Ma, J Fan, D Bu, B Liu, Z Fan, G Wu, J Jin, B Ding, X Zhu, Y Shen

J Med Genet 2004;**41**:171–174. doi: 10.1136/jmg.2003.012153



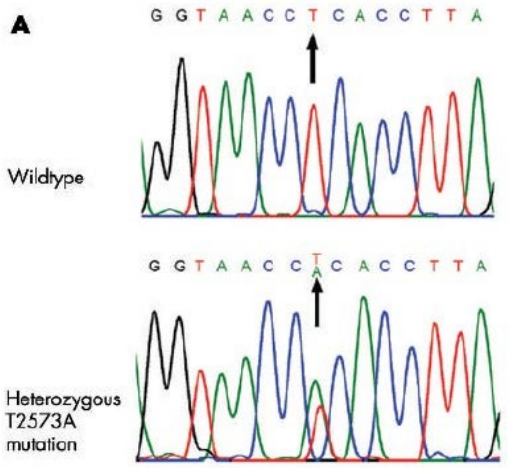


Figure 2 Pedigree of the family and haplotype analysis. Females are indicated by circles and males by squares. Blackened figures denote affected individuals. Recombinations occurred at marker D2S2345 in II-3 and III-1.

Maastricht UMC+

Brief Communication

Electrophysiological Properties of Mutant $Na_v1.7$ Sodium Channels in a Painful Inherited Neuropathy

Theodore R. Cummins,[1] Sulayman D. Dib-Hajj,[2,3,4] and Stephen G. Waxman[2,3,4]

8232 • The Journal of Neuroscience, September 22, 2004 • 24(38):8232–8236

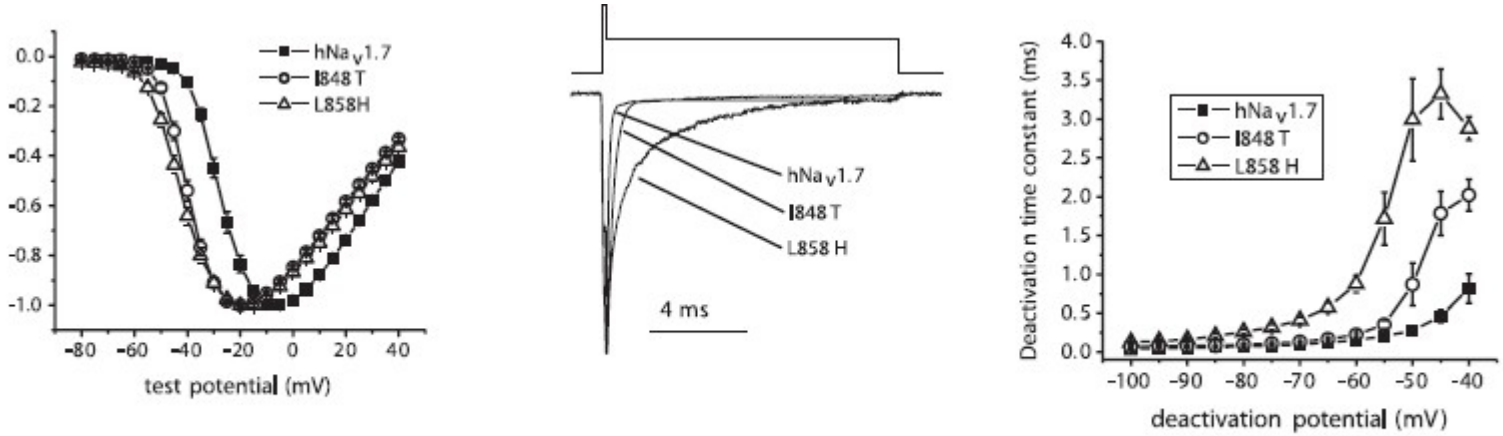


Figure 1. The I848T and L858H mutations of $hNa_v1.7$ alter activation and deactivation.

Maastricht UMC+

Neuron 52, 767–774, December 7, 2006 ©2006 Elsevier Inc. DOI 10.1016/j.neuron.2006.10.006

SCN9A Mutations in Paroxysmal Extreme Pain Disorder: Allelic Variants Underlie Distinct Channel Defects and Phenotypes

Caroline R. Fertleman,[1] Mark D. Baker,[2,5]
Keith A. Parker,[1] Sarah Moffatt,[1] Frances V. Elmslie,[1]
Bjarke Abrahamsen,[2] Johan Ostman,[4]
Norbert Klugbauer,[3] John N. Wood,[2]
R. Mark Gardiner,[1,*] and Michele Rees[1]

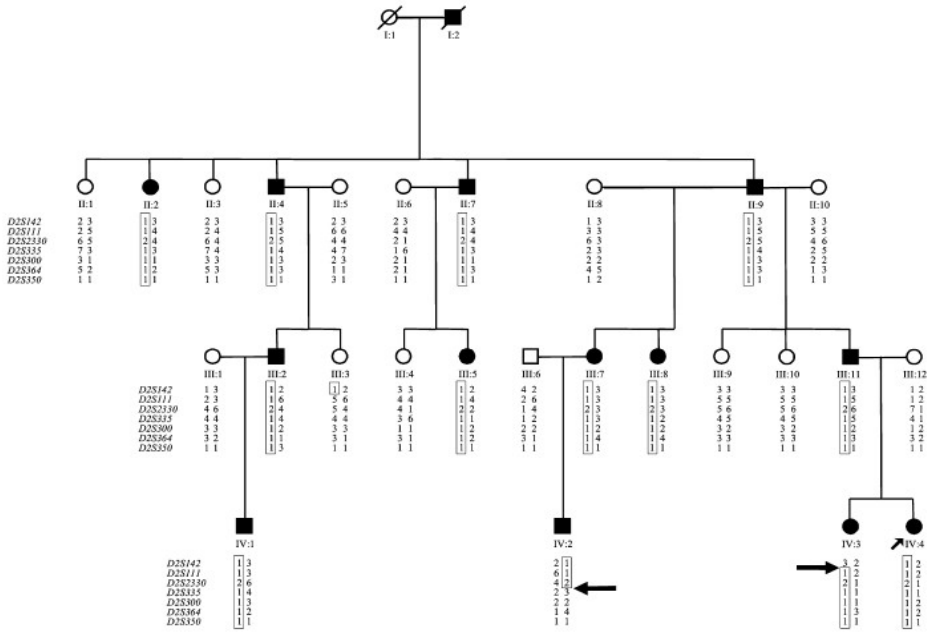
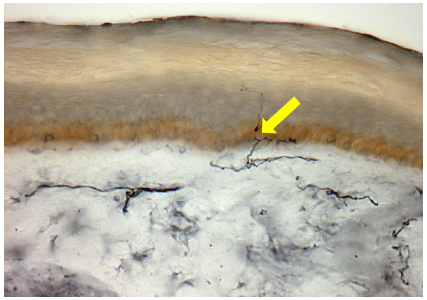


Figure 1. Familial Rectal Pain Maps to Chromosome 2q

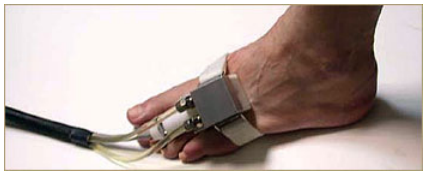
Maastricht UMC+

Idiopathic small fiber neuropathy

+



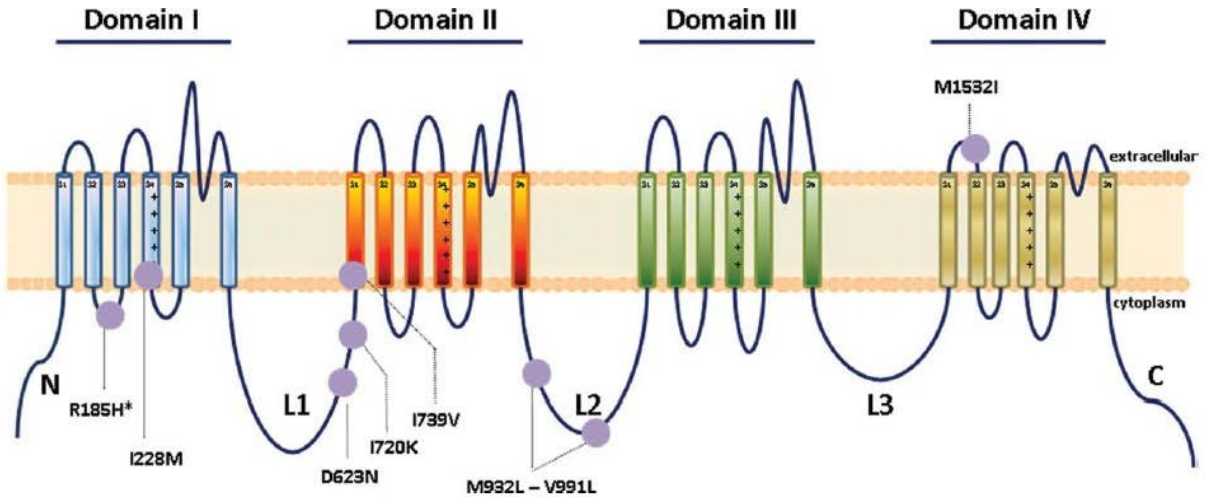
and



SCN9A

Gain of Function $Na_V1.7$ Mutations in Idiopathic Small Fiber Neuropathy

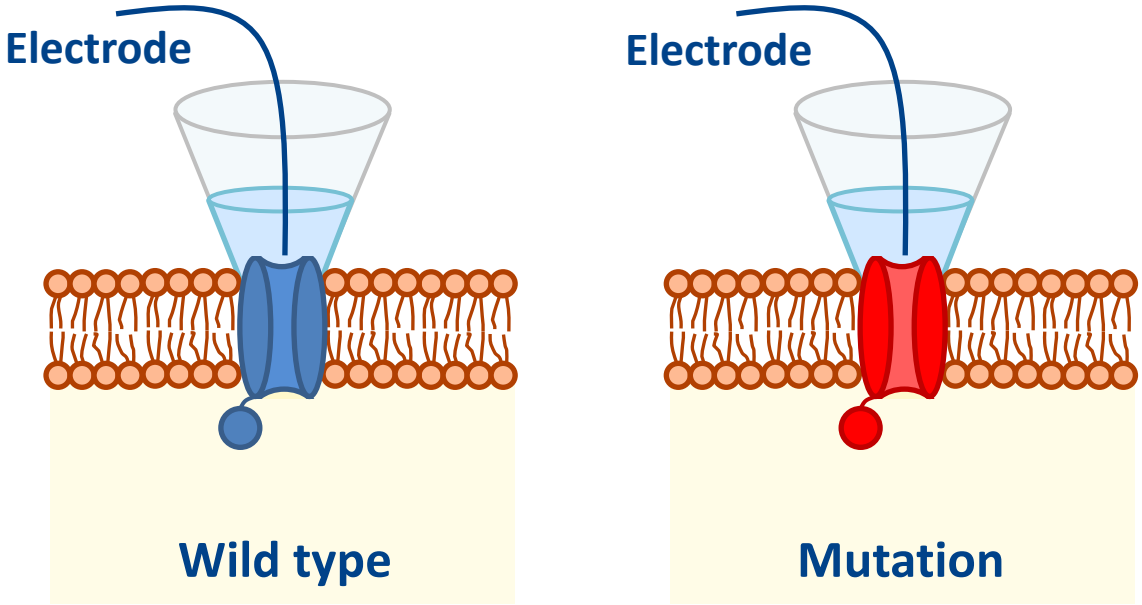
Catharina G. Faber, MD, PhD,[1] Janneke G. J. Hoeijmakers, MD,[1] Hye-Sook Ahn, PhD,[2,3] Xiaoyang Cheng, PhD,[2,3] Chongyang Han, PhD,[2,3] Jin-Sung Choi, PhD,[2,3]* Mark Estacion, PhD,[2,3] Giuseppe Lauria, MD, PhD,[4] Els K. Vanhoutte, MD,[1] Monique M. Gerrits, PhD,[5] Sulayman Dib-Hajj, PhD,[2,3] Joost P. H. Drenth, MD, PhD,[6] Stephen G. Waxman, MD, PhD,[2,3] and Ingemar S. J. Merkies, MD, PhD[1,7]



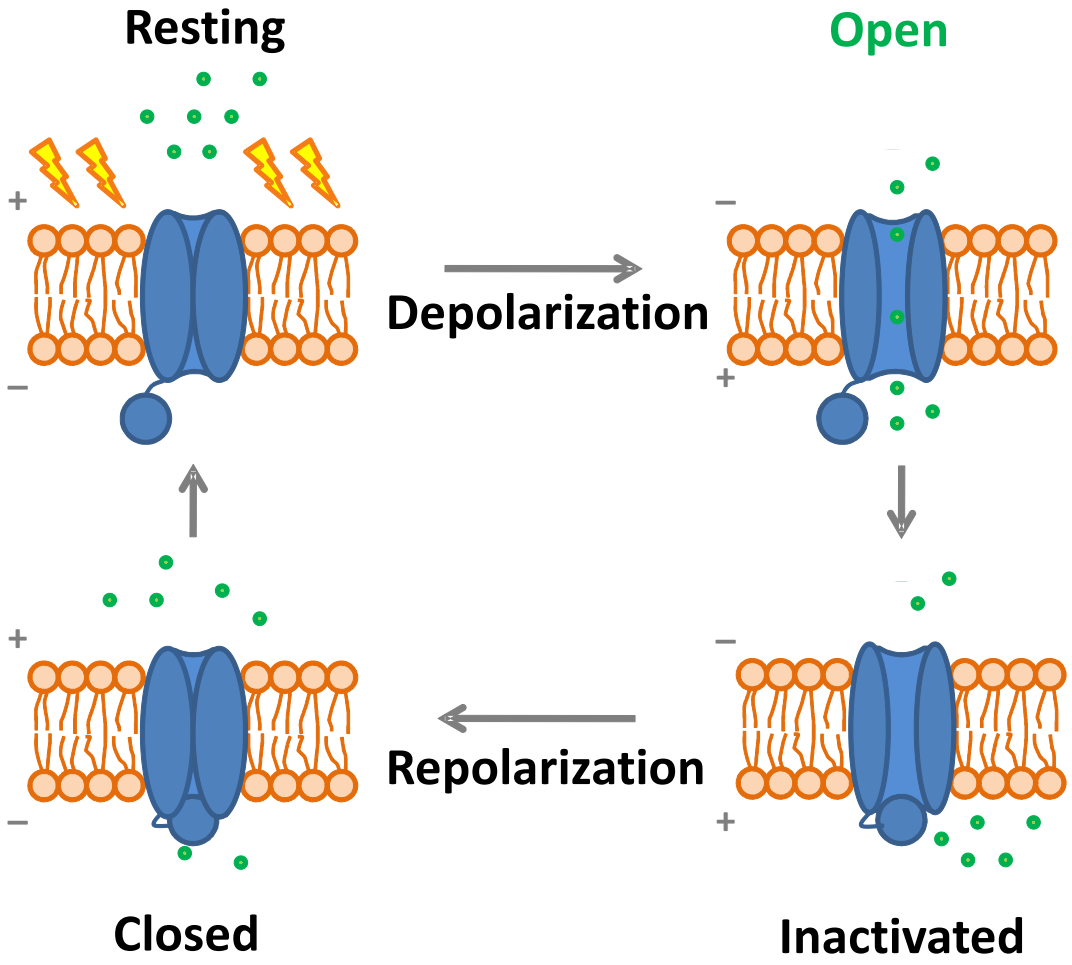
Maastricht UMC+

Faber, Ann Neurol 2012

Patch clamp analyses



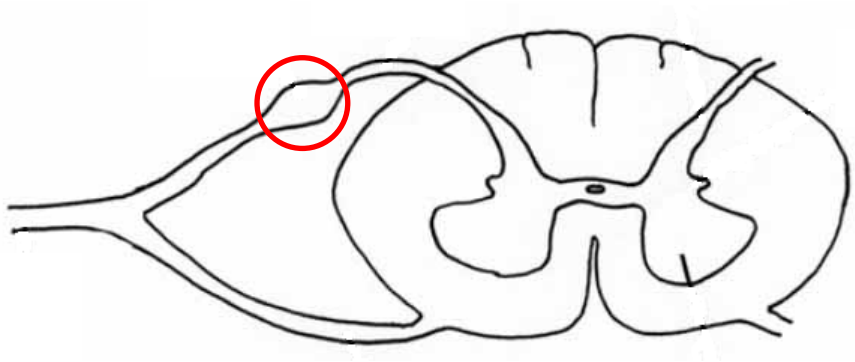
Voltage clamp - channel function



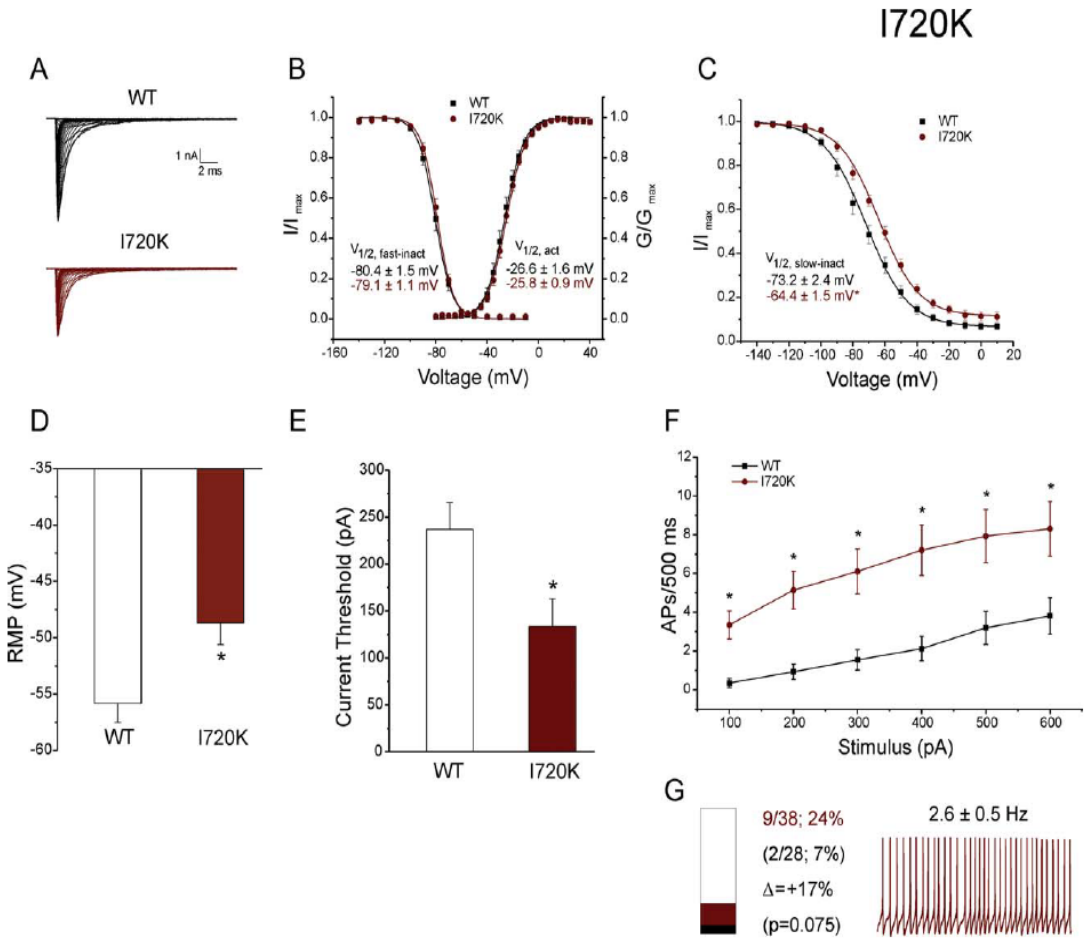
Maastricht UMC+

Current clamp - channel excitability

- Resting membrane potential
- Current threshold
- Spontaneous firing
- Firing frequency



Patch clamp analyses



C. Impaired 'slow inactivation'

D. RMP DRG depolarized

E. 43% ↓ current threshold

F. Firing frequency ↑

G. Spontaneous firing

Maastricht UMC+

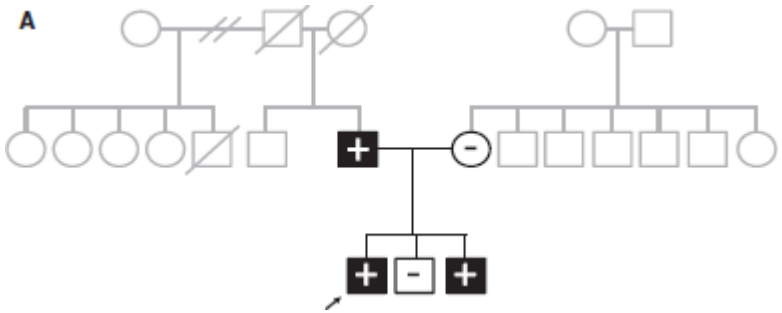
Faber et al. Annals Neurol. 2012;71:26-39.

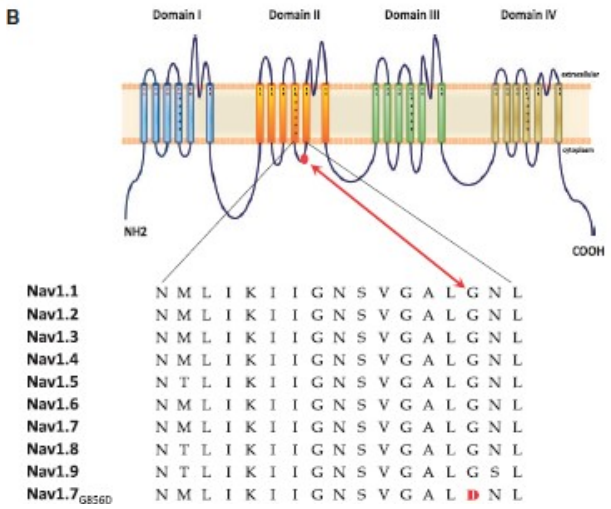
doi:10.1093/brain/awr349 Brain 2012: 135; 345–358 | 345

BRAIN
A JOURNAL OF NEUROLOGY

Small nerve fibres, small hands and small feet: a new syndrome of pain, dysautonomia and acromesomelia in a kindred with a novel $Na_V1.7$ mutation

Janneke G. J. Hoeijmakers,[1,*] Chongyang Han,[2,3,*] Ingemar S. J. Merkies,[1,4] Lawrence J. Macala,[2,3] Giuseppe Lauria,[5] Monique M. Gerrits,[6] Sulayman D. Dib-Hajj,[2,3] Catharina G. Faber[1,†] and Stephen G. Waxman[2,3,†]



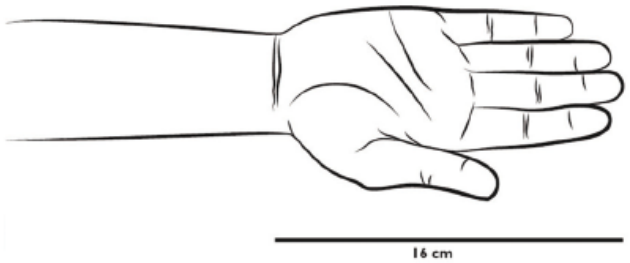


Maastricht UMC+

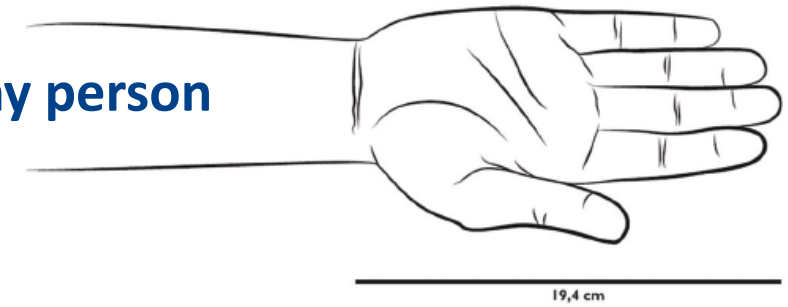
Hoeijmakers et al. Brain. 2012;135:345-58.

Small fibers, small hands, small feet

Patient



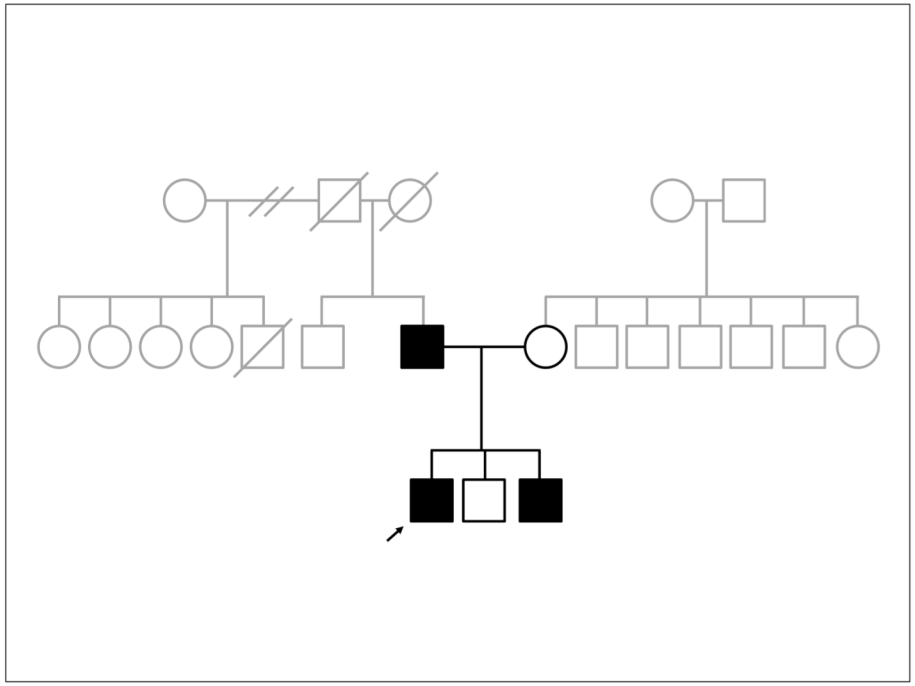
Healthy person

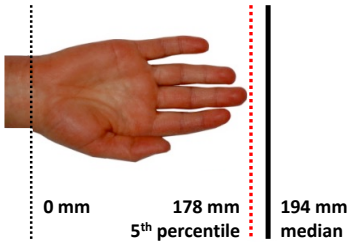


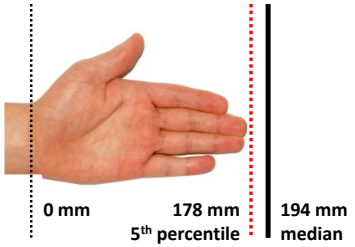
Maastricht UMC+

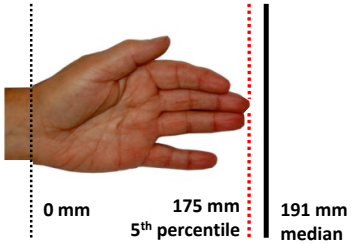
Hoeijmakers et al. Brain. 2012;135:345-58.

Small fibers, small hands, small feet





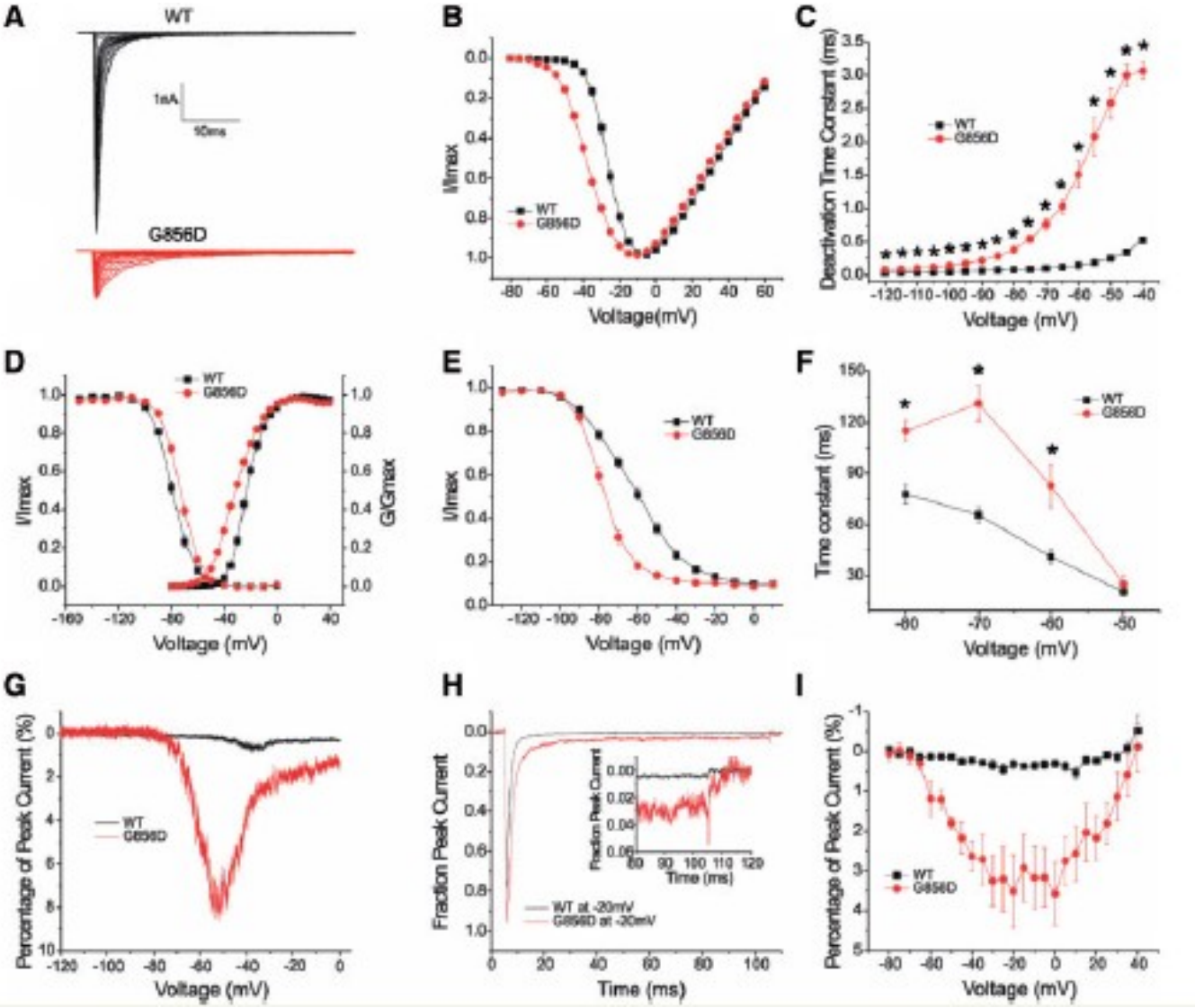




Mutation G856D

Maastricht UMC+

Hoeijmakers et al. Brain. 2012;135:345-58.

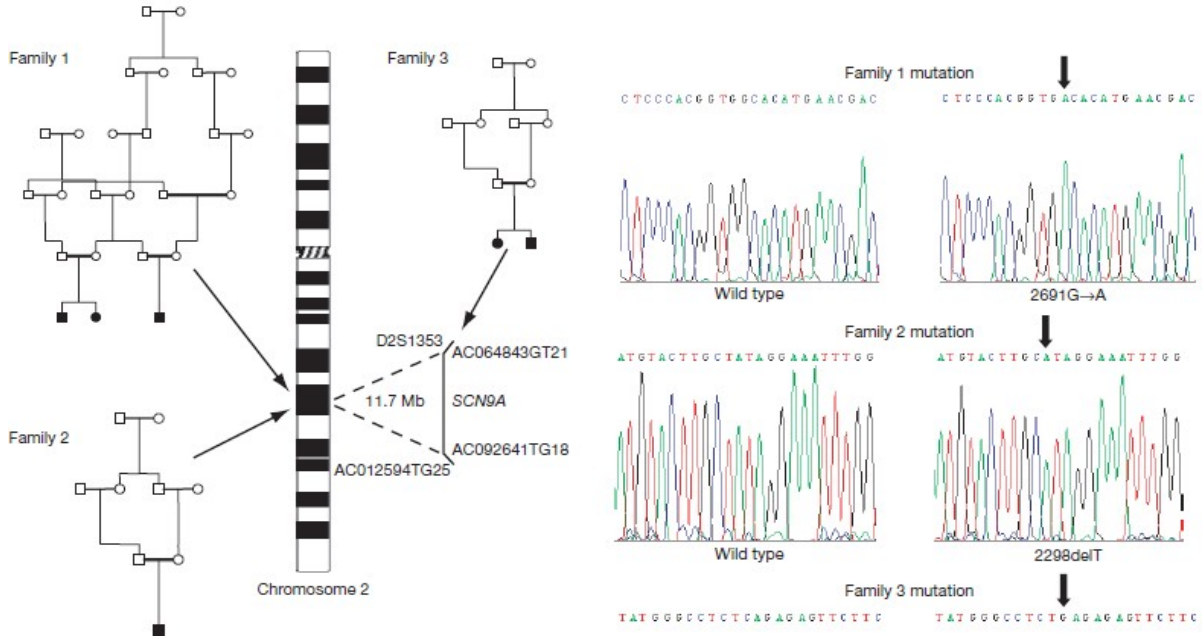


Maastricht UMC+

nature Vol 444|14 December 2006|doi:10.1038/nature05413

An *SCN9A* channelopathy causes congenital inability to experience pain

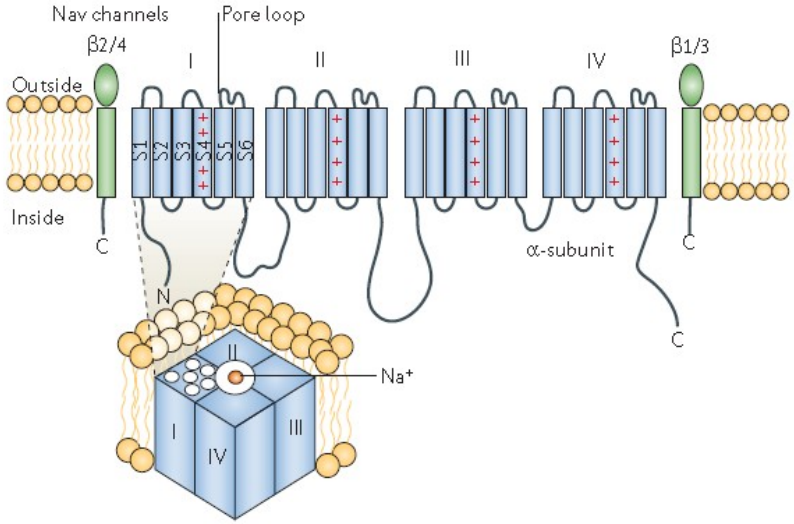
James J. Cox[1]*, Frank Reimann[2]*, Adeline K. Nicholas[1], Gemma Thornton[1], Emma Roberts[3], Kelly Springell[3], Gulshan Karbani[4], Hussain Jafri[5], Jovaria Mannan[6], Yasmin Raashid[7], Lihadh Al-Gazali[8], Henan Hamamy[9], Enza Maria Valente[10], Shaun Gorman[11], Richard Williams[12], Duncan P. McHale[12], John N. Wood[13], Fiona M. Gribble[2] & C. Geoffrey Woods[1]



Maastricht UMC+

$Na_V1.7$ channel

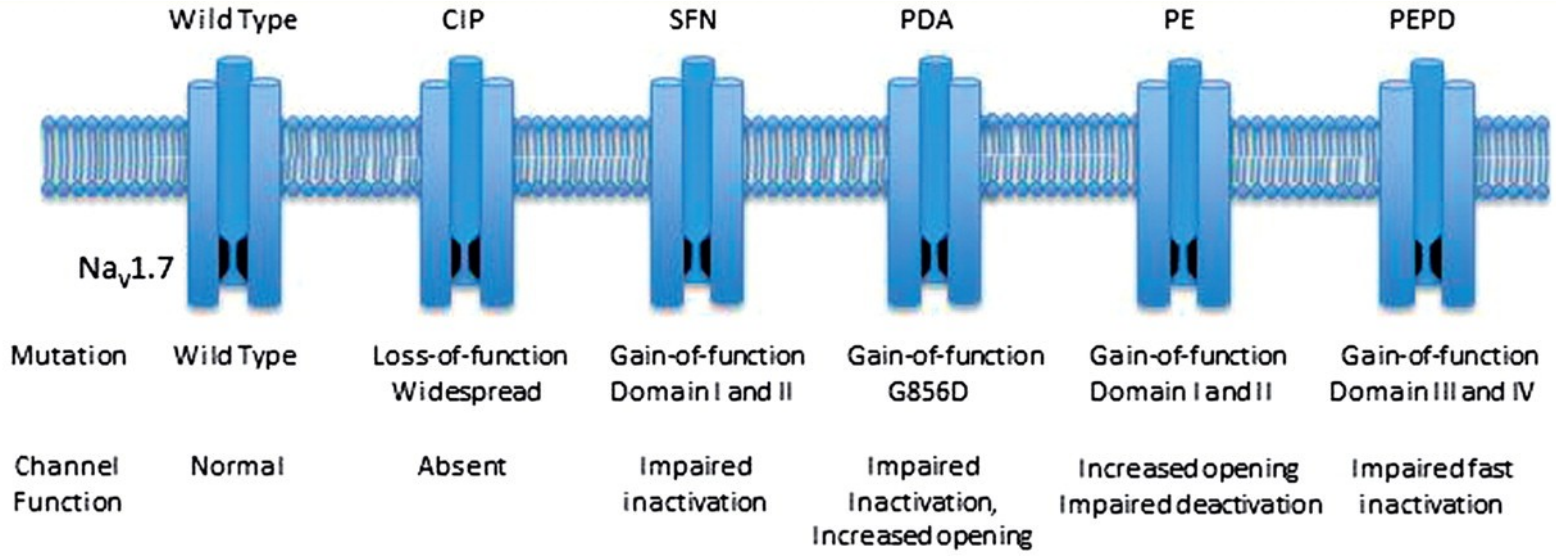
- $Na_v1.7$ consist of an α subunit and one or more β subunits



- $Na_v1.7$ is preferentially expressed in dorsal root ganglion (DRG) and sympathetic ganglion neurons and their axons
- *SCN9A* encodes the α subunit of the $Na_v1.7$

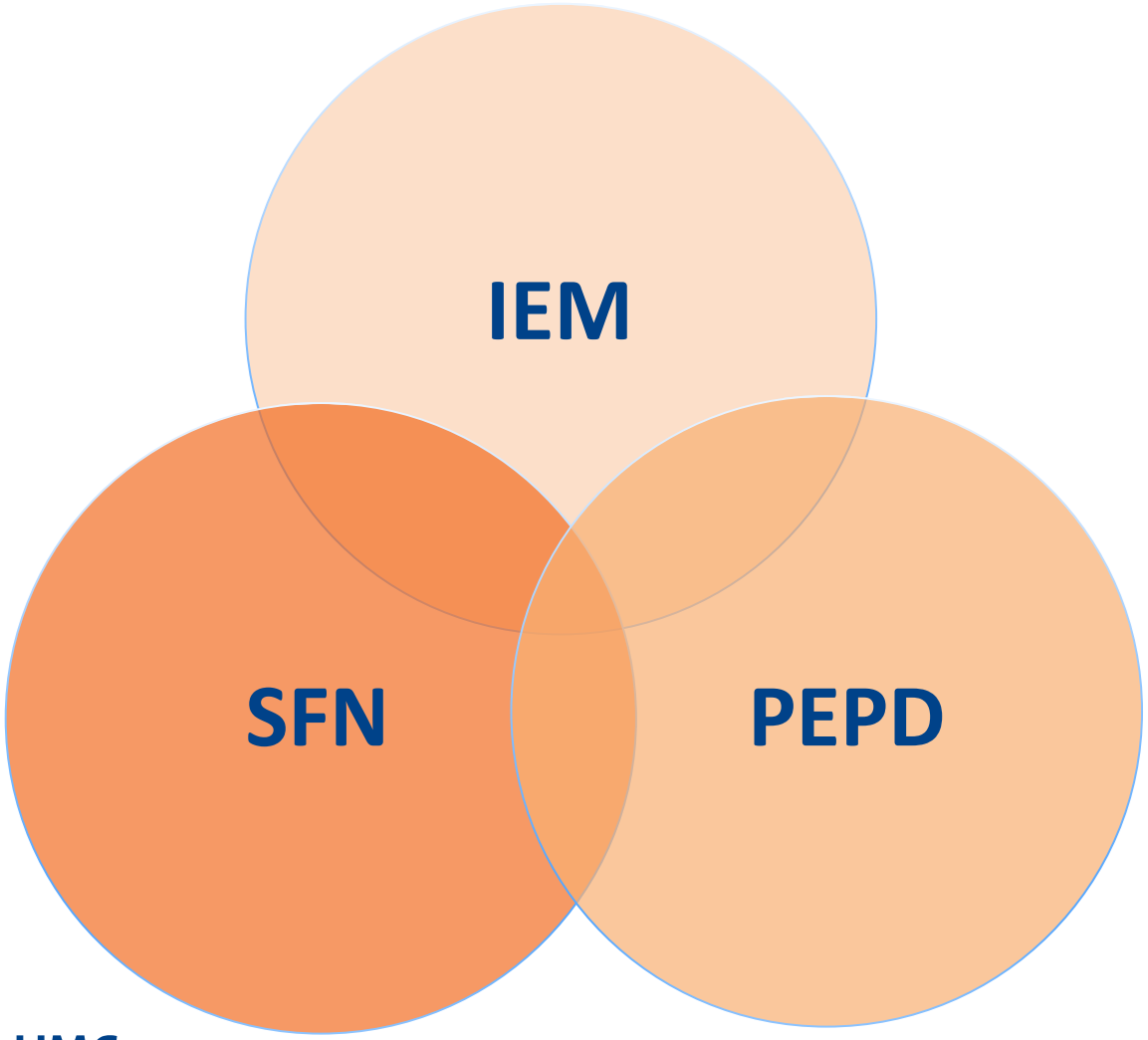
Maastricht UMC+

$Na_V1.7$ channelopathies



CIP = congenital indifference to pain
SFN = small fiber neuropathy
PDA = pain, dysautonomia and acromesomelia
PE = primary erythromelalgia
PEPD = paroxysmal extreme pain disorder

Spectrum



Maastricht UMC+

Gain/Loss of function mutations

Gain-of-function mutations:

- PE, PEPD, SFN, …
- Missense mutations
- Autosomal dominant inheritance

Loss-of-function mutations:

- CIP
- Nonsense, frame shift, splice site mutations
- Autosomal recessive inheritance

Phenotypic diversity

SCN9A p.Ile228Met

- Severe facial pain *
- Distal pain *
- Scalp discomfort

* Brother and sister

Maastricht UMC+

Estacion et al. *Mol Pain* 2011;**7**:92

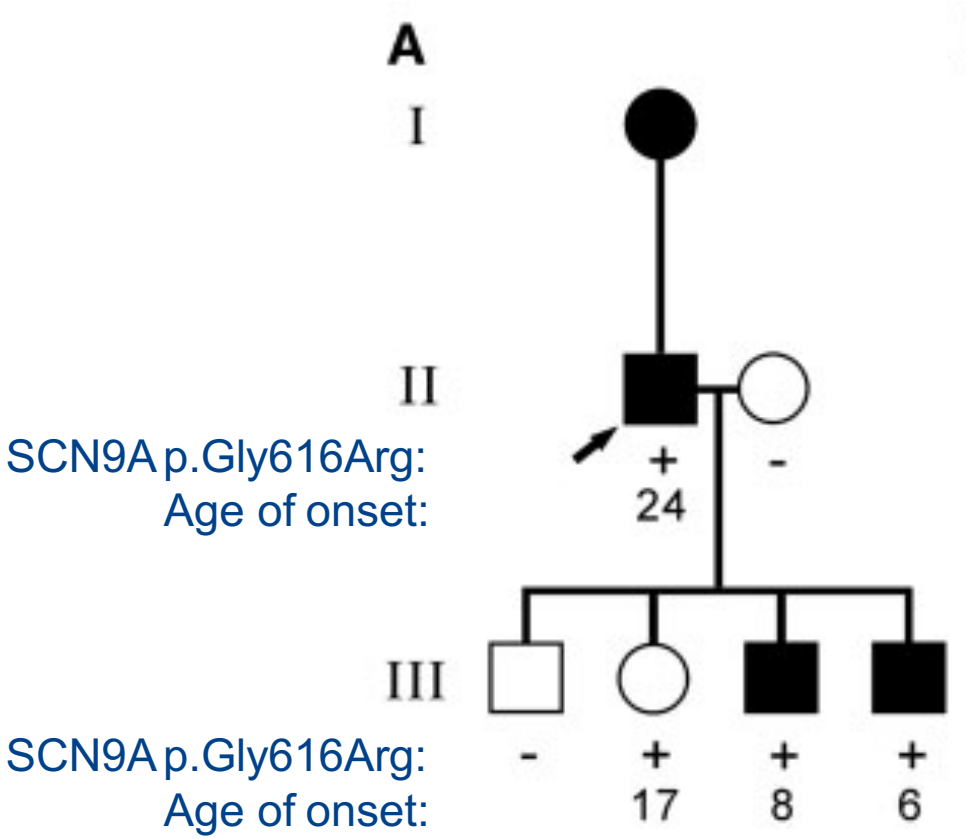
Variably expressed

- Mutation *SCN9A* p.Arg185His → no autonomic symptoms
- Mutation *SCN9A* p.Ile739Val → severe autonomic symptoms

Maastricht UMC+

Han et al. *Brain* 2012;**135**:2613-28

Partly penetrant



■/● = Affected individual

Maastricht UMC+

Choi et al. *Brain* 2010;**133**:1823-35

Disease-contributing variants - risk factors

Variant	MAF * General population (%) #	Frequency SFN-cohort Maastricht (%)
SCN9A p.Arg185His	0.3-0.6	0.1
SCN9A p.Ile739Val	0.1-0.9	1.5

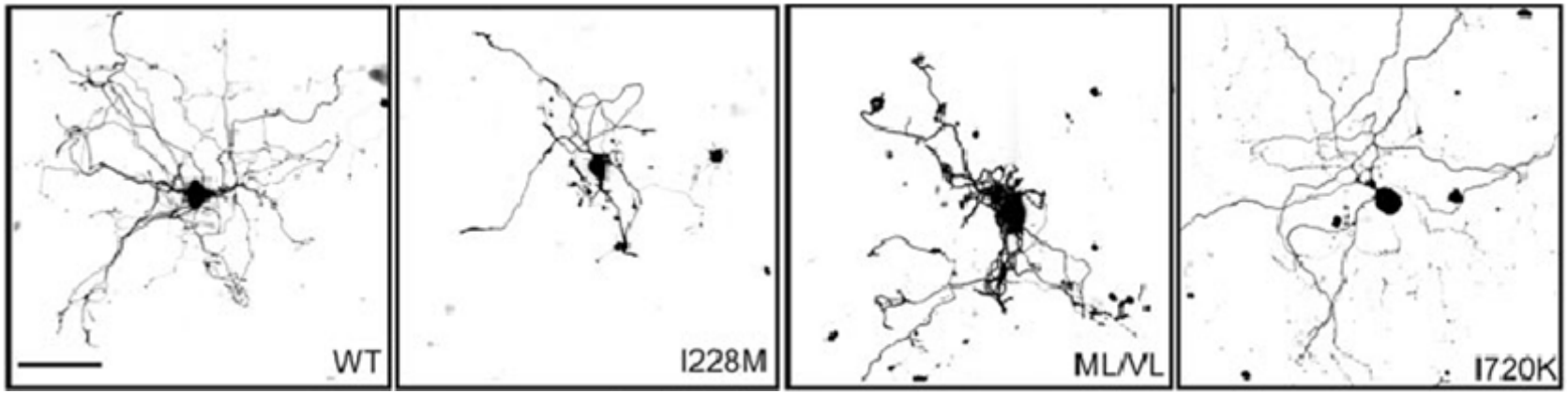
* MAF, minor allele frequency

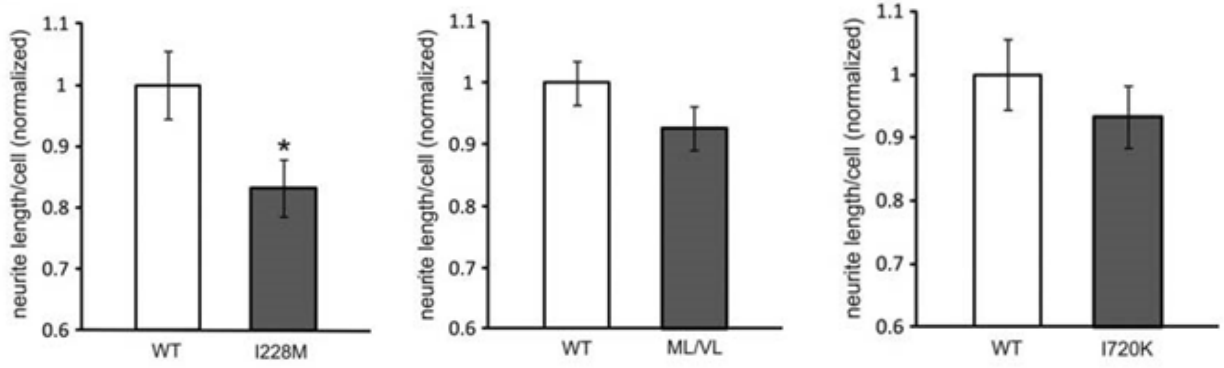
Used SNP databases: dbSNP, ExAC, ESP, GoNL

Maastricht UMC+

Waxman et al. *Lancet Neurol.* 2014;**13**(11):1152-1160

Reduction neurite outgrow

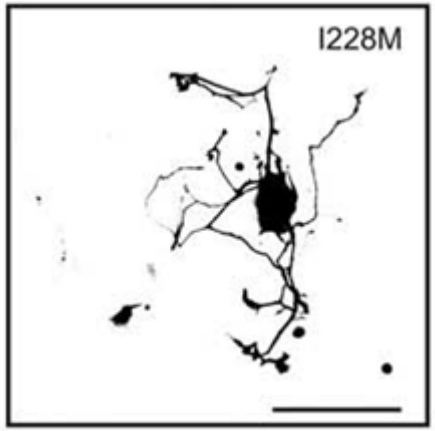


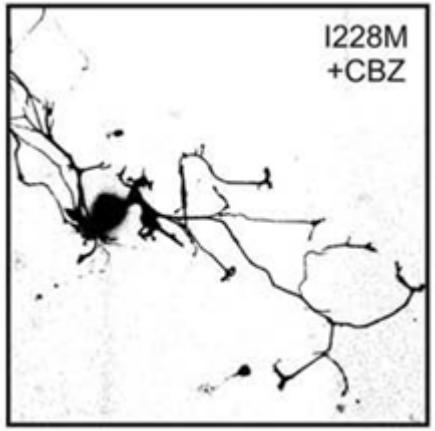


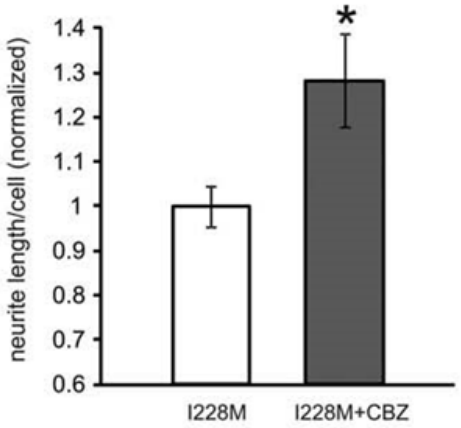
Maastricht UMC+

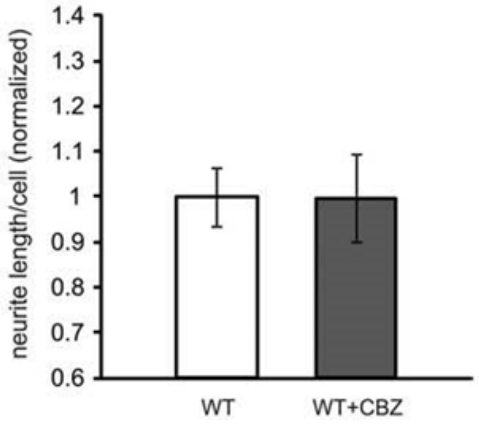
Persson et al. Ann Neurol 2013;73:140–5

Sodium channel blocker





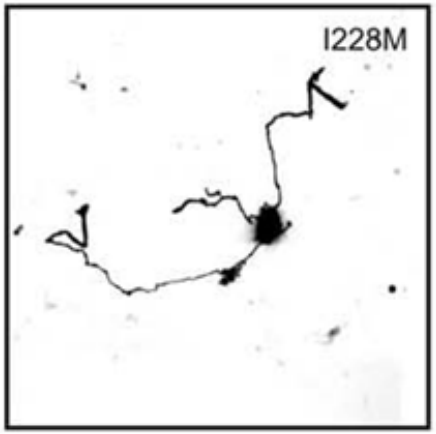


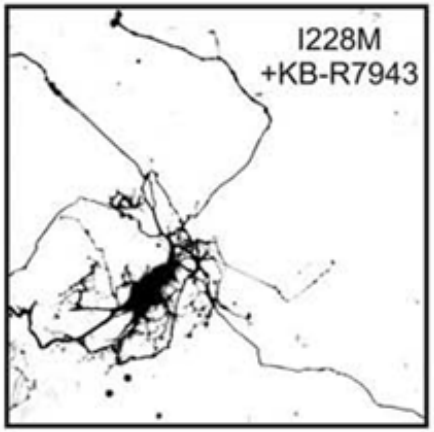


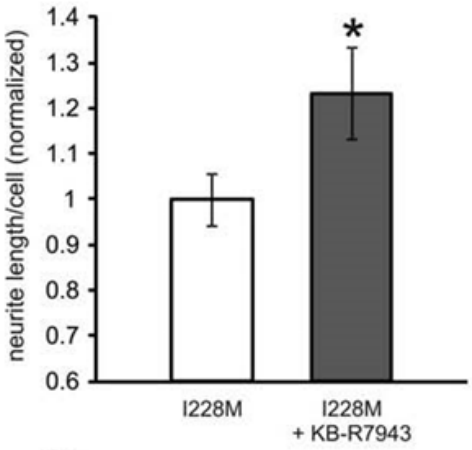
Maastricht UMC+

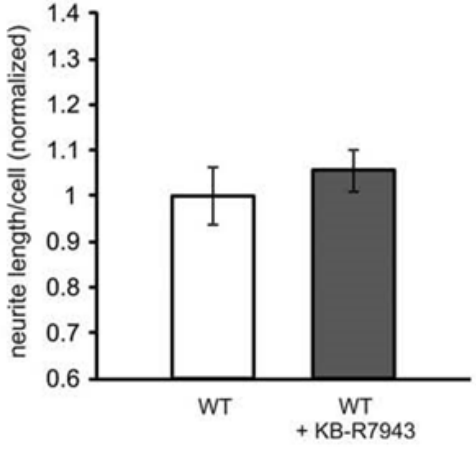
Persson et al. Ann Neurol 2013;73:140–5

Inhibition Na^{+}- Ca^{2+} exchanger





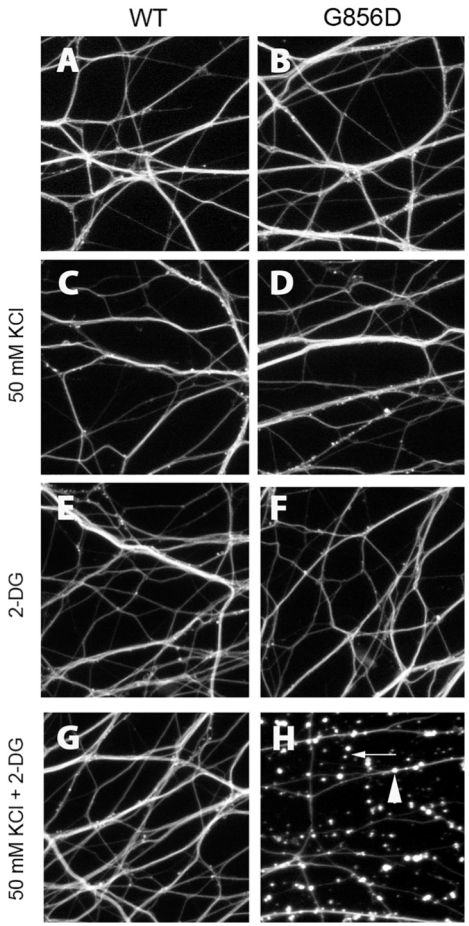


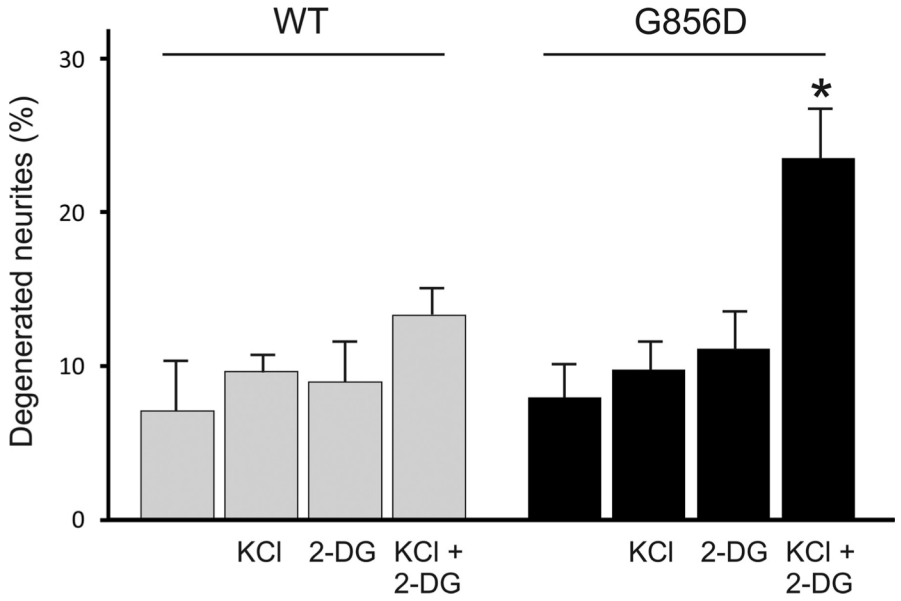


Maastricht UMC+

Persson et al. Ann Neurol 2013;73:140–5

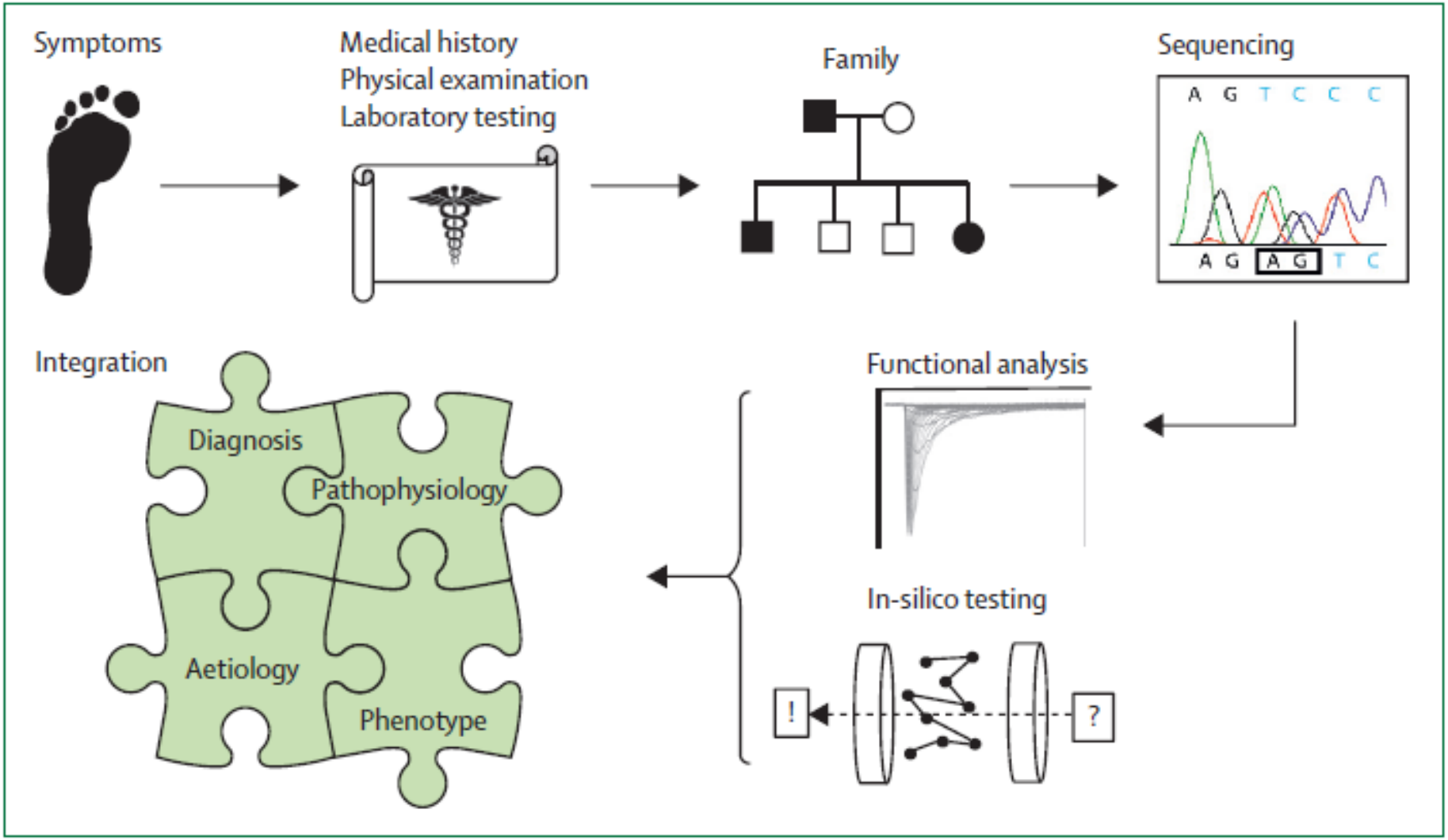
Metabolic stress and depolarization





Maastricht UMC+

Diagnostic process



Maastricht UMC+

Waxman et al. Lancet Neurol 2014; 13:1152-60

SCN9A polymorphism p.Arg1550Trp can influence pain perception

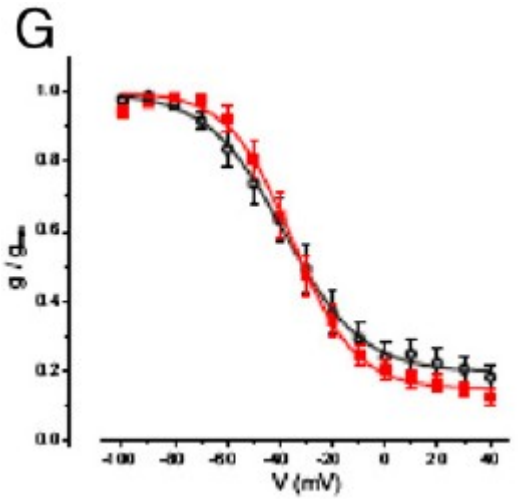
Cohort	No. of affected individuals	rs6746030 allele for which most pain was felt	*P* value for A allele association
1. Osteoarthritis	578	A	0.016*
2. Sciatica	195	A	0.039*
3. Postamputation	100	A	0.011*
4. Postdiscectomy	179	A	0.088
5. Chronic pancreatitis	205	A = G	0.732
6. Meta-analysis	1257	A	0.0001*

*Cohort results reached statistical significance.

MAF= 11.9% (gnomAD)

Nav1.7-1150W vs. Nav1.7-WT:

- Slow inactivation occurred at more positive potentials than fast inactivation
- Slow inactivation reached only ~80%
- Extent of slow inactivation was similar
- Voltage-dependence of Nav1.7 was steeper



Maastricht UMC+

Reimann et al., *PNAS* 2010;**107**(11):5148-53

Role of other sodium channels

PNAS

Gain-of-function $Na_V1.8$ mutations in painful neuropathy

Catharina G. Faber[a,1], Giuseppe Lauria[b,1], Ingemar S. J. Merkies[a,c,1], Xiaoyang Cheng[d,e], Chongyang Han[d,e], Hye-Sook Ahn[d,e], Anna-Karin Persson[d,e], Janneke G. J. Hoeijmakers[a], Monique M. Gerrits[f], Tiziana Pierro[b], Raffaella Lombardi[b], Dimos Kapetis[b,g], Sulayman D. Dib-Hajj[d,e], and Stephen G. Waxman[d,e,2]

Departments of [a]Neurology and [f]Clinical Genomics, University Medical Centre Maastricht, 6202 AZ Maastricht, The Netherlands; [b]Neuromuscular Diseases Unit and [g]Bioinformatics Unit, Istituto di Ricovero e Cura a Carattere Scientifico Foundation, "Carlo Besta," 20133 Milan, Italy; [c]Department of Neurology, Spaarne Hospital, 2130 AT Hoofddorp, The Netherlands; [d]Department of Neurology, Yale University School of Medicine, New Haven, CT 06510; and [e]Center for Neuroscience and Regeneration Research, Veterans Affairs Medical Center, West Haven, CT 06516

Edited* by David Julius, University of California, San Francisco, CA, and approved October 3, 2012 (received for review September 20, 2012)

doi:10.1093/brain/awu079 Brain 2014: 137; 1627–1642 | 1627

BRAIN
A JOURNAL OF NEUROLOGY

Gain-of-function mutations in sodium channel $Na_V1.9$ in painful neuropathy

Jianying Huang,[1,*] Chongyang Han,[1,*] Mark Estacion,[1,*] Dymtro Vasylyev,[1,*] Janneke G. J. Hoeijmakers,[2] Monique M. Gerrits,[3] Lynda Tyrrell,[1] Giuseppe Lauria,[4] Catharina G. Faber,[2] Sulayman D. Dib-Hajj,[1] Ingemar S. J. Merkies[2,5] and Stephen G. Waxman[1] on behalf of the PROPANE Study Group

Maastricht UMC+

Na_V channel variants in patients with painful and nonpainful peripheral neuropathy

OPEN

278 idiopathic neuropathy (67% painful)
179 diabetic neuropathy (77% painful

GOF mutations ≤ 3%
No differences between painful and non-painful group in previously reported GOF mutations

Meaning: Painful neuropathy ≠ diabetic neuropathy ≠ SFN

Maastricht UMC+

Wadhawan, Neurol Genet 2017;3:e207

Questions

- Penetrance
- Causes/contributor/risk factors
- Mutations in other genes/ genetic background
- Role of sodium channels in other painful neuropathies
- Therapeutic options

Conclusions

Sodium channel mutations

- Role in painful small fiber neuropathy
- Diagnosis based on integrated approach

- Possible role for other genes/ genetic background

- Key to targeted treatment

Trial design

1. Strict criteria for SFN (not all painful neuropathies are SFN)

2. Include gene mutations in trial design?
   - Depending on drugs tested (sodium channel blockers, other)
   - Secondary/ subgroup analysis for sodium channel mutations