NUFFIELD DEPARTMENT OF
CLINICAL NEUROSCIENCES
Medical Sciences Division

Congenital lack of pain

David Bennett

Conflict of interest statement:

- I have undertaken consulting on behalf of Oxford innovation for Abide, Amgen, Mitsubishi Tanabe, Mundipharma, GSK, TEVA, Biogen, Lilly, Orion, Theranexus.

- I have an industrial partnership grant from BBSRC and Astra-Zeneca.

Congenital lack of pain

- Introduction to the clinical disorder and human genetics
- Disorders of nociceptor development
- Disorders of nociceptive function

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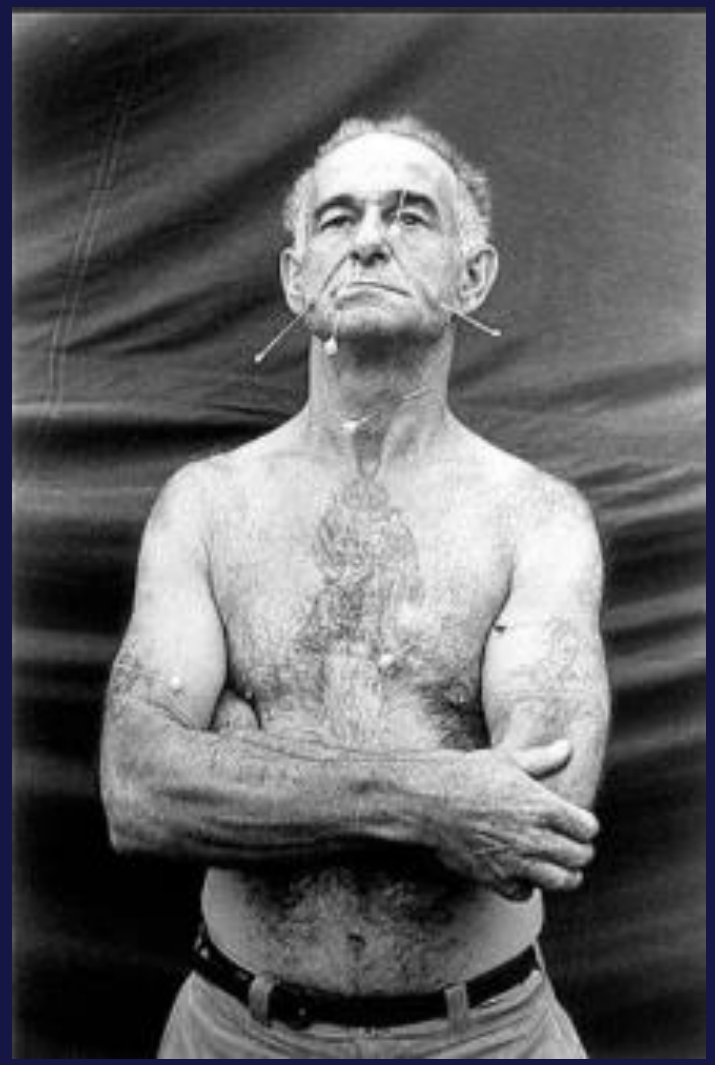
Individuals with extreme alterations in pain perception



A CASE OF CONGENITAL GENERAL PURE ANALGESIA*

By George Van Ness Dearborn, M.D., Ph.D.

UNITED STATES VETERANS HOSPITAL,
THE BRONX, NEW YORK CITY

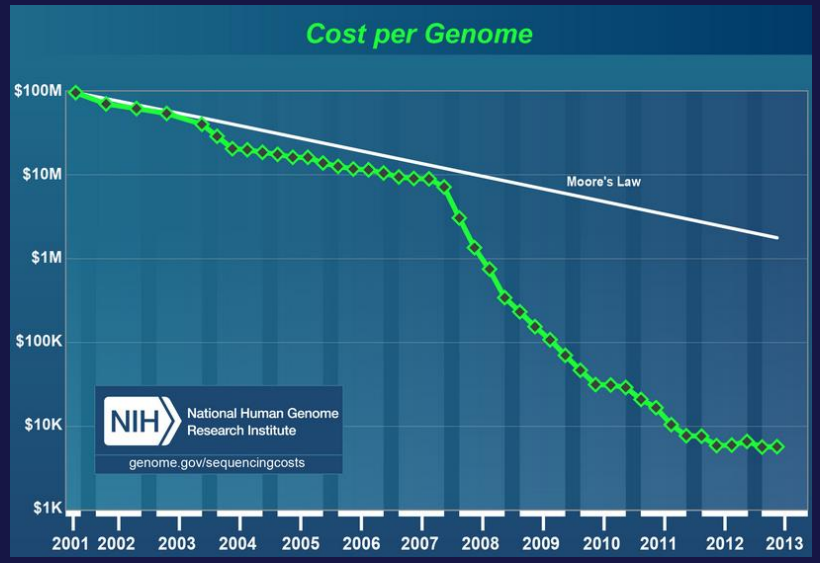
‘We know as yet far too little about the nervous system to warrant a single guess as to the neuropathology of such a case as this’

The Journal of Nervous and Mental Disease: June 1932 -

Genetic technology is moving fast

Sequencing:

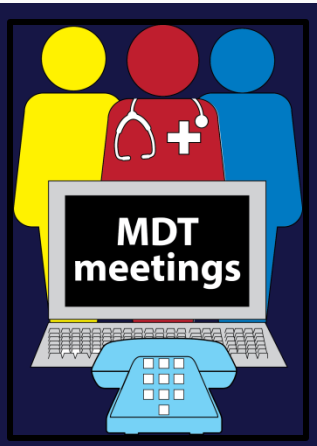
Gene discovery was originally dominated by linkage and candidate gene analysis. Whole exome and whole genome sequencing now readily available.



Interpretation:

Better bio-infomratics
more reference genomes
large databases of variants.

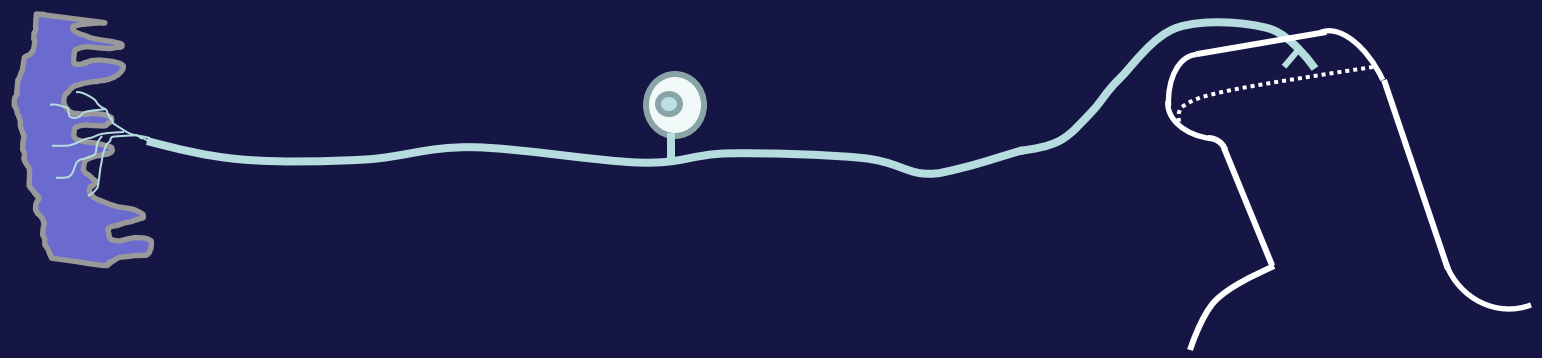
gnomAD
genome aggregation database

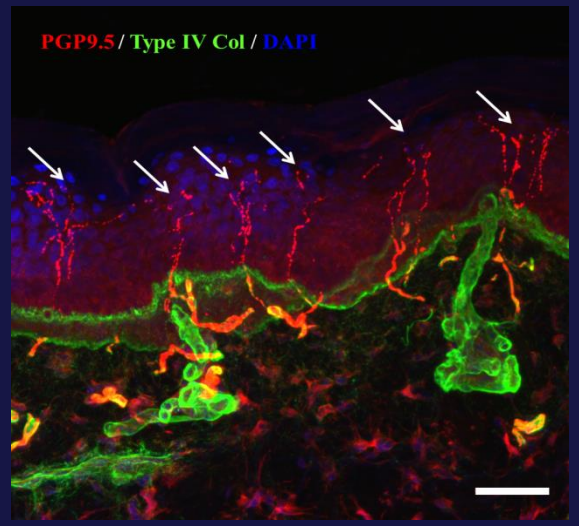


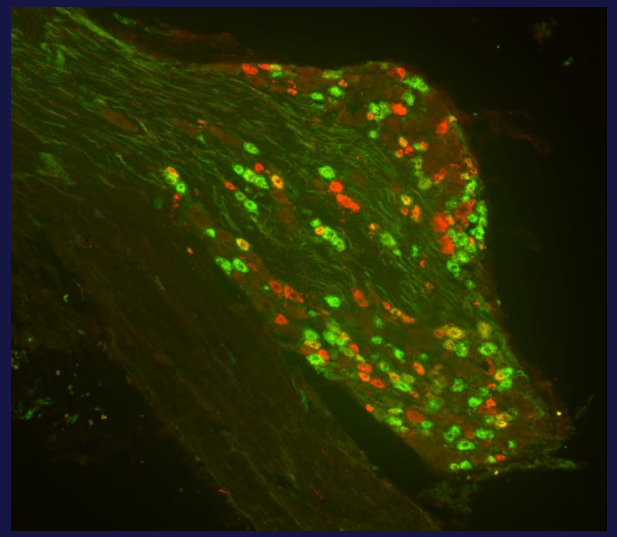
Healthcare delivery:

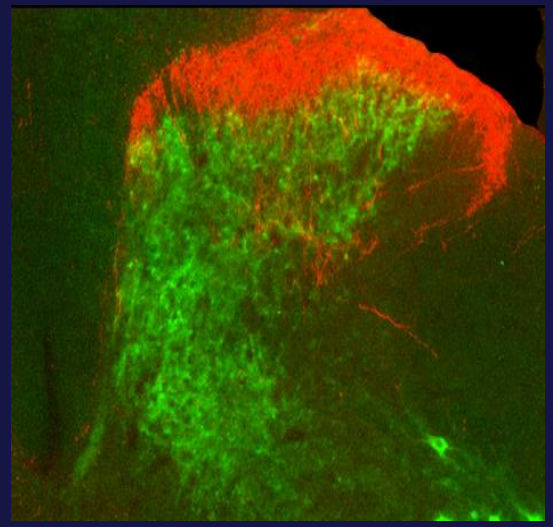
Integration into normal healthcare.

Genomics england









Bennett and Woods Lancet Neurology 2014

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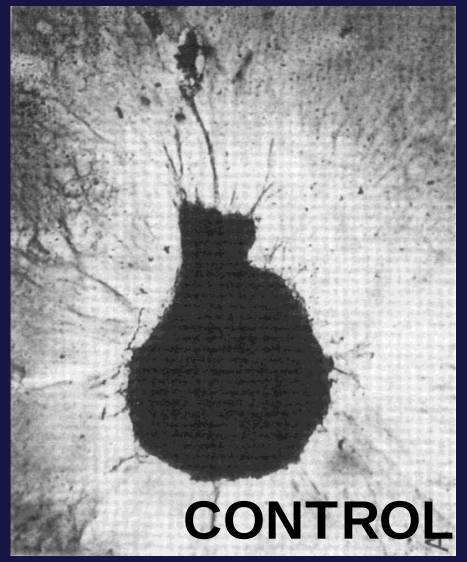
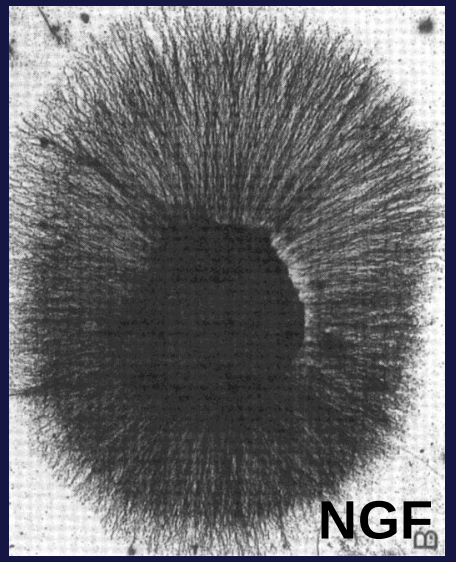
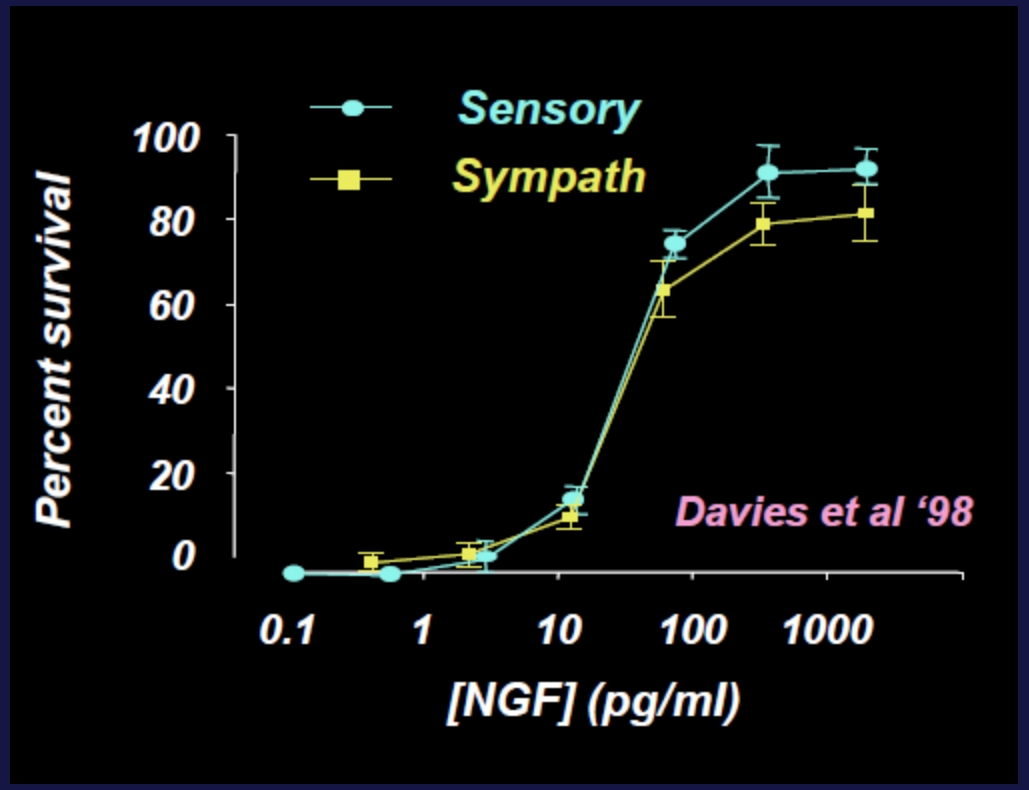
Failure of the normal development of the nociceptive system:

Lack of growth factors (bi-allelic loss of function in NGF and trkA)







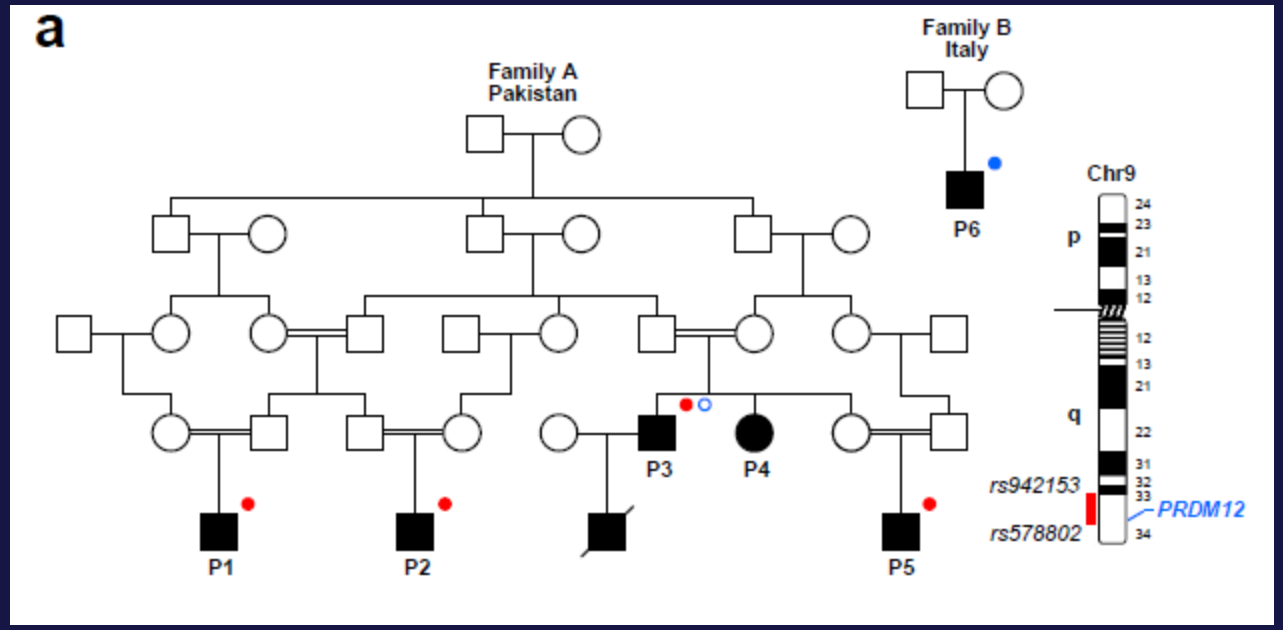
Mutations in the *TRKA*/NGF receptor gene in patients with congenital insensitivity to pain with anhidrosis

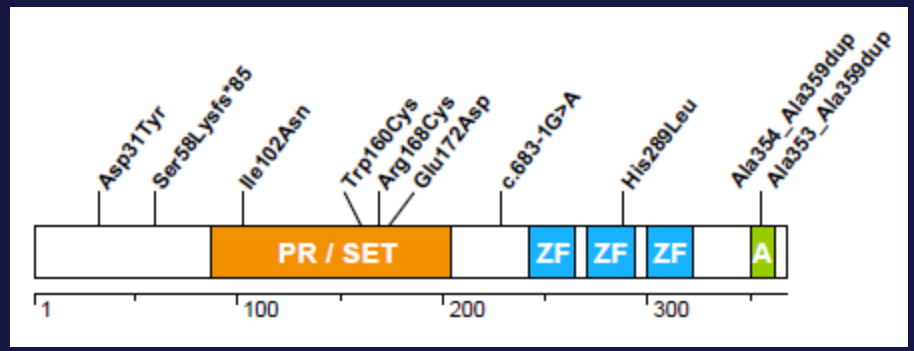
Yasuhiro Indo[1], Motoko Tsuruta[1], Yumi Hayashida[1], Mohammad Azharul Karim[1], Kohji Ohta[1], Tomoyasu Kawano[1], Hiroshi Mitsubuchi[1], Hidefumi Tonoki[2], Yutaka Awaya[3] & Ichiro Matsuda[1]

We examined three candidate genes initially: *NGF*, *p75* neurotrophin receptor (see below), and *TRKA*. To facilitate detection of putative *TRKA* mutations, we selected three unrelated CIPA patients who had consanguineous parents, and in which homozygous abnormalities could be expected (see Methods). Given the lack of information on the whole human *TRKA* gene, we determined part of the gene structure (Fig. 1). Preliminary data shows that *TRKA* is expressed in EB-virus transformed lymphoblastoid cells. Thus, RNA from these cell lines from CIPA-affected individuals could be used to assess this locus as a candidate for CIPA.

Causes of congenital insensitivity to pain:

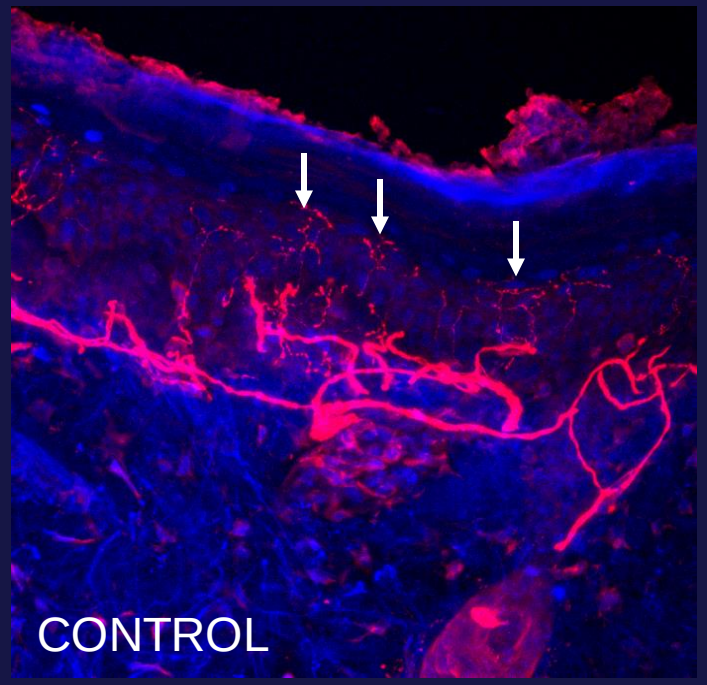
- Bi-allelic mutations in the transcriptional regulator: PRDM12.



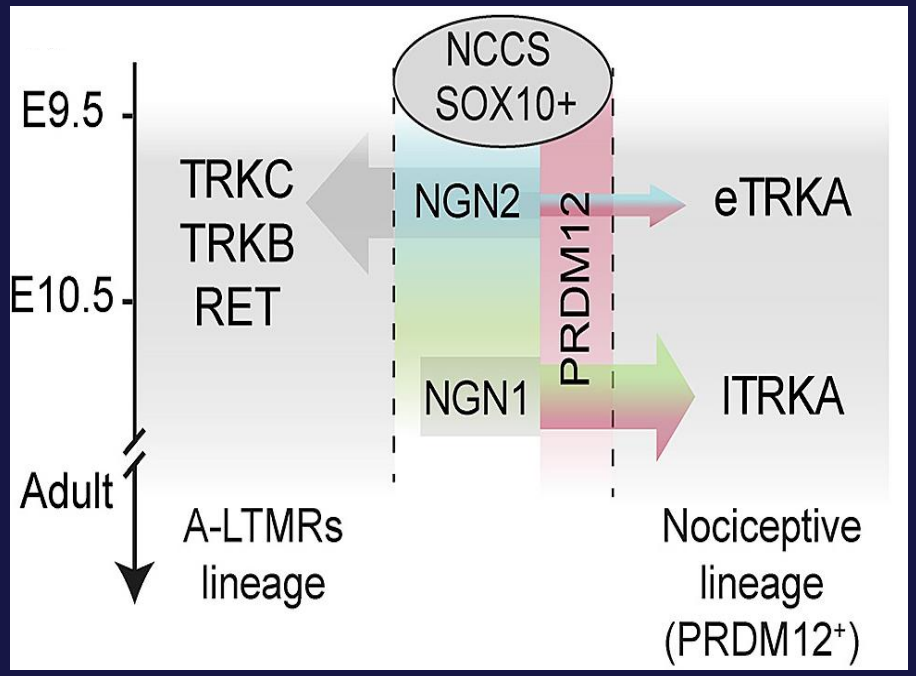


Chen et al., Nature Genetics 2015

PRDM12 is required for nociceptor development:



Chen et al., Nature Genetics 2015



Bartesaghi L et al., Cell Reports 2019
Desiderio S et al., Cell Reports 2019

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Case Hx: Congenital insensitivity to pain

26 yr old male

Never experienced pain

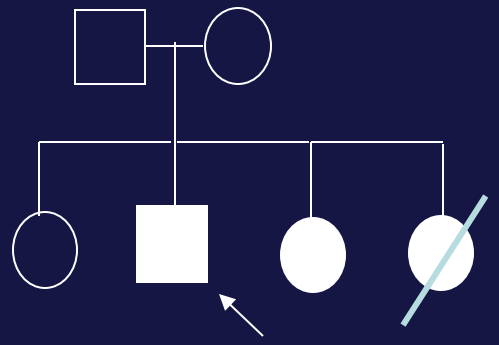
Over 20 fractures

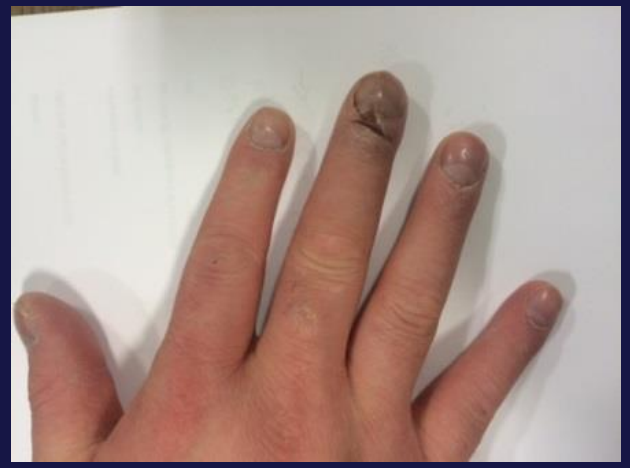
Multiple injuries to the mouth

Short stature

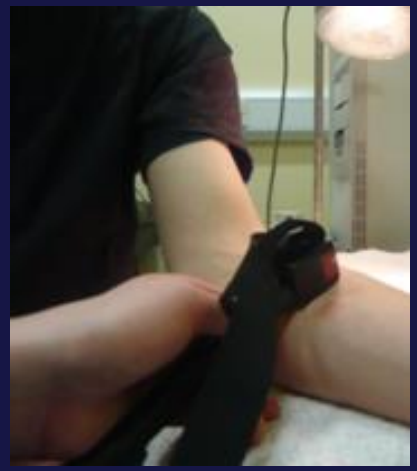
Anosmic

Normal sensorimotor function except no perception of pain



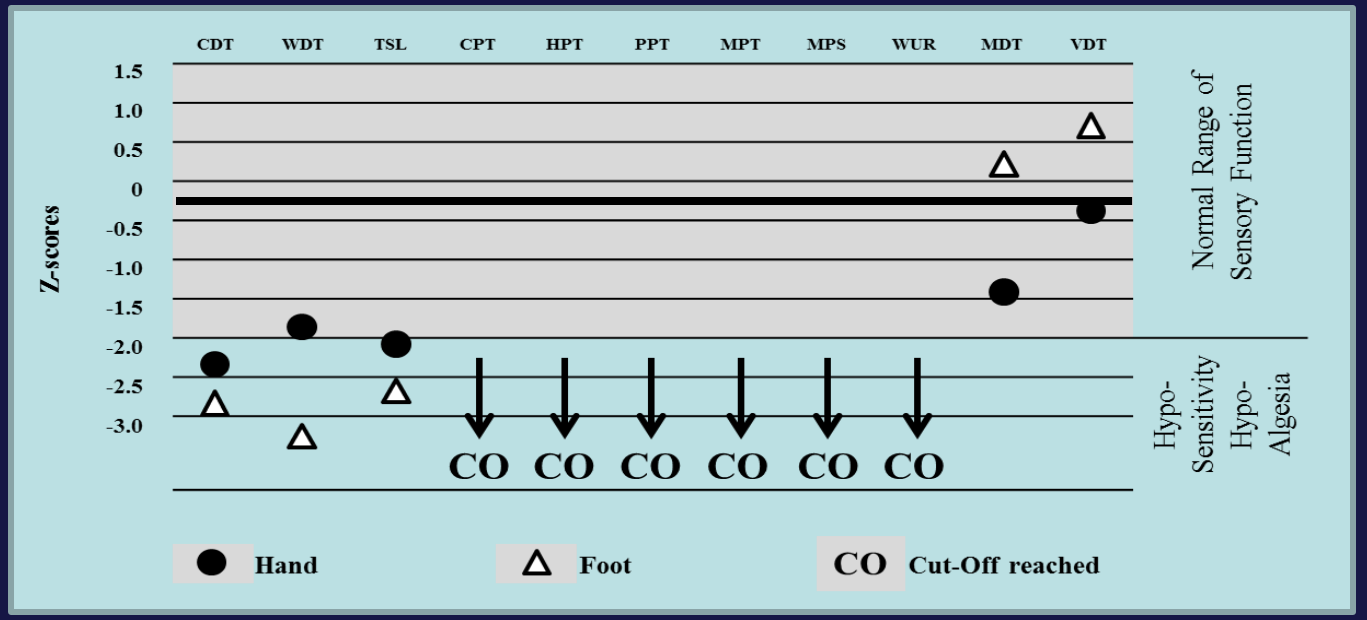


Case Hx: Sensory testing



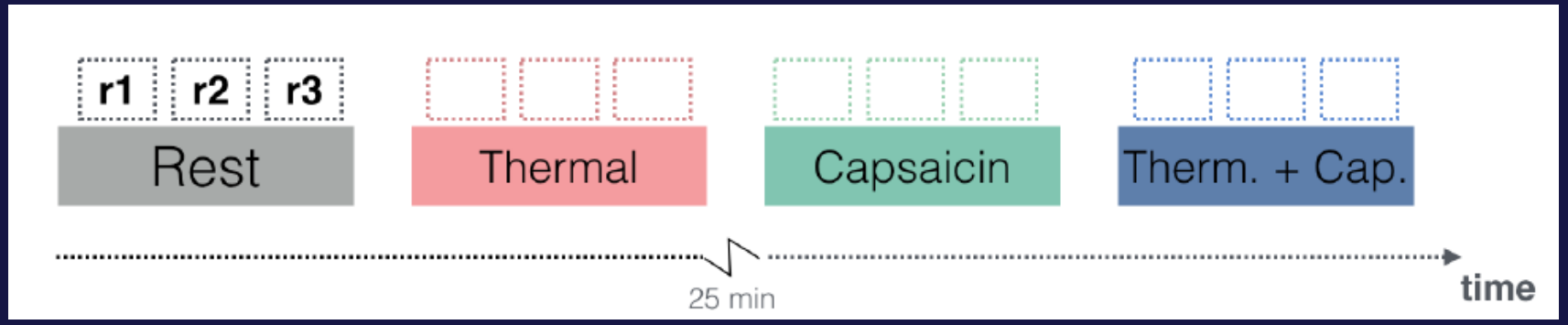
Hypersensitive

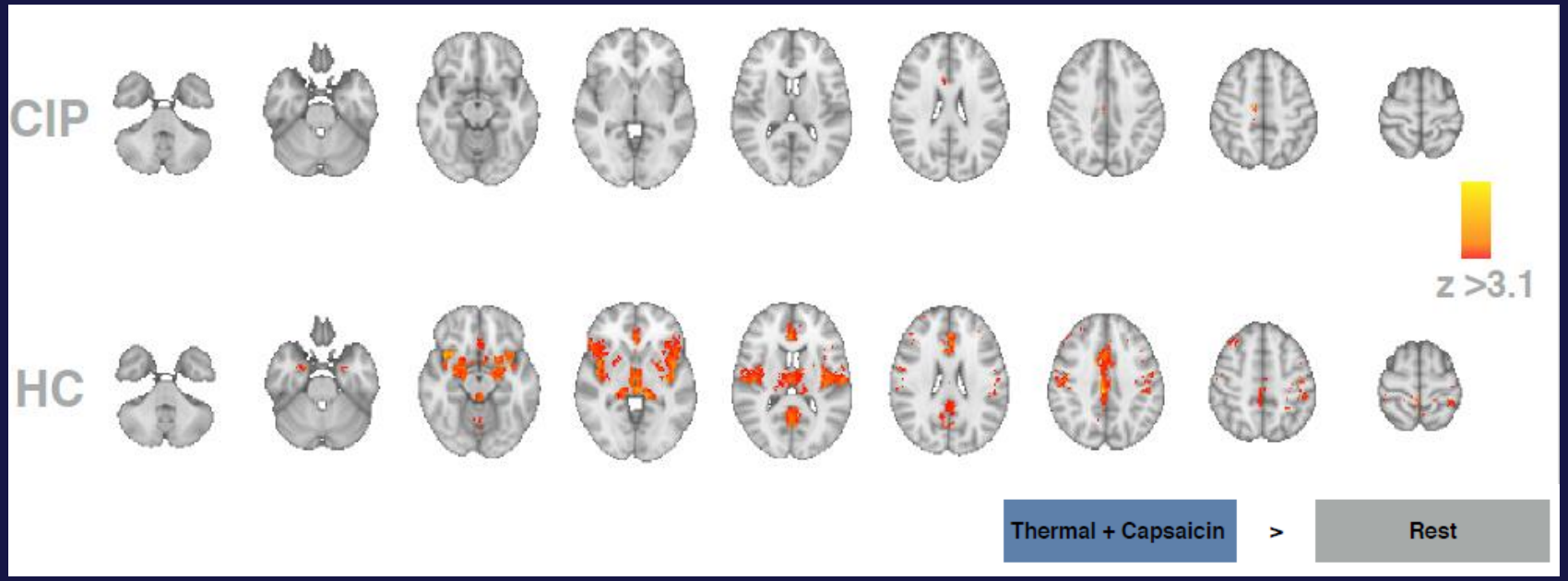
Hyposensitive



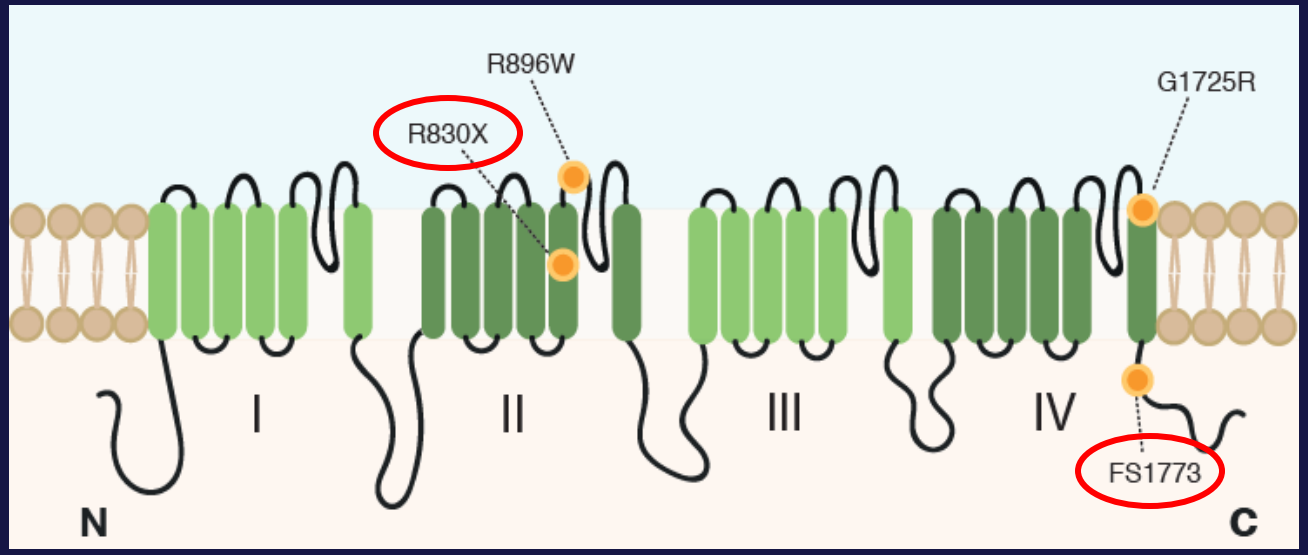
Congenital insesnitvity to pain: Brain imaging

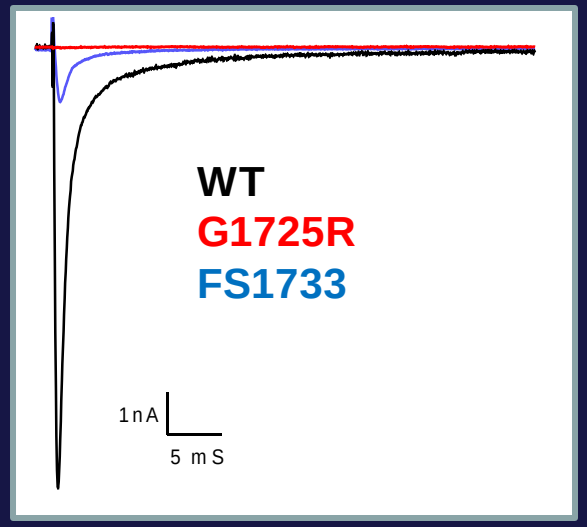
I Tracey, A Segerdahl (McDermott et al., Neuron 2019)

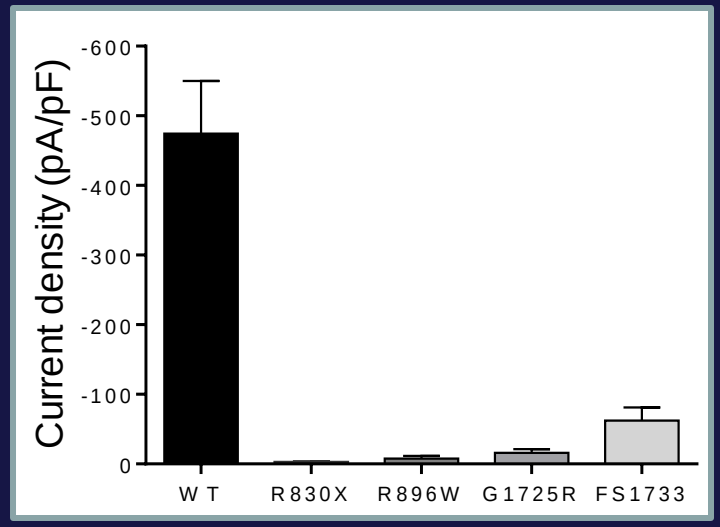




Genetic basis: LOF mutations in Nav1.7

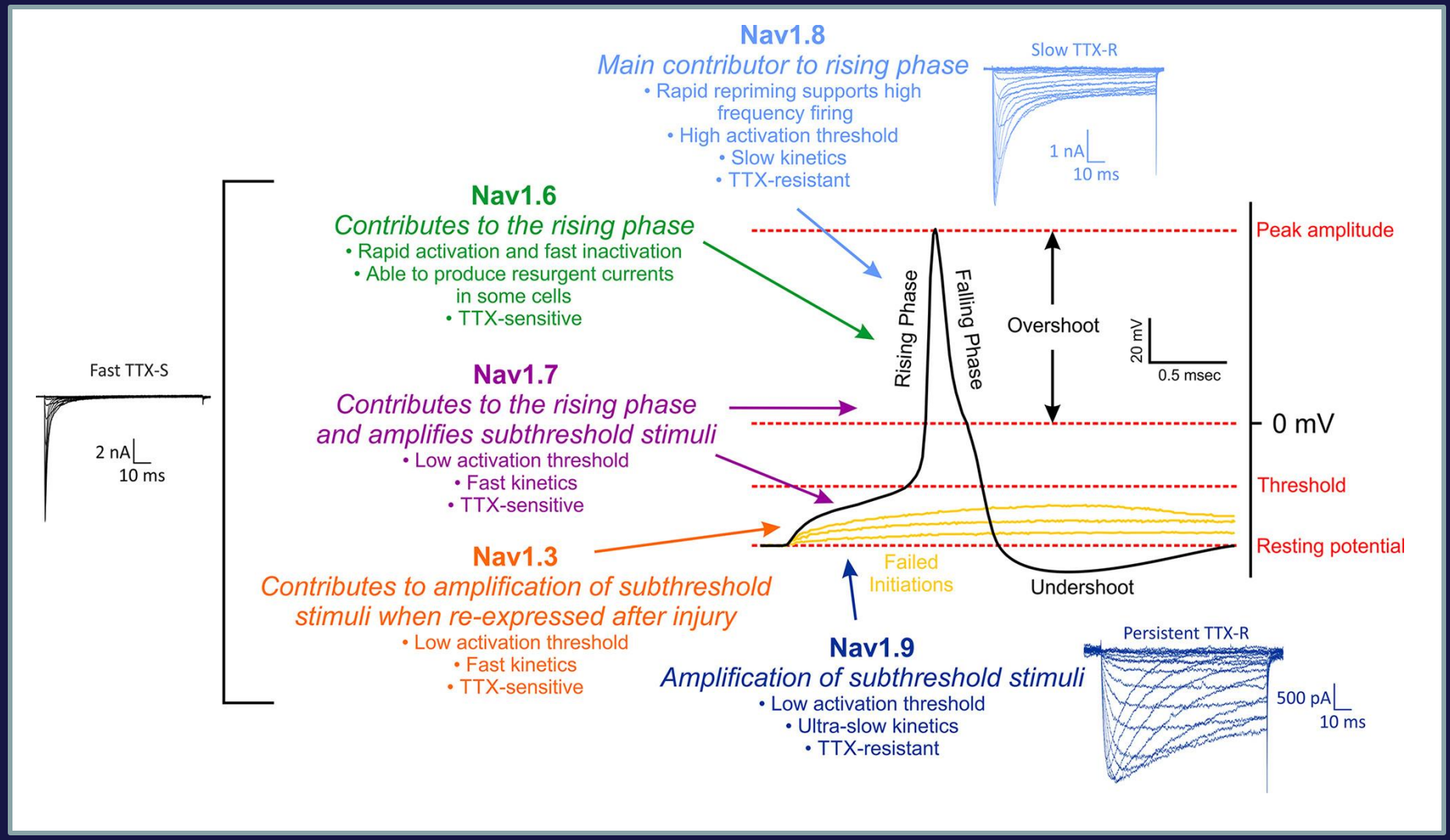






McDermott et al., Neuron 2019

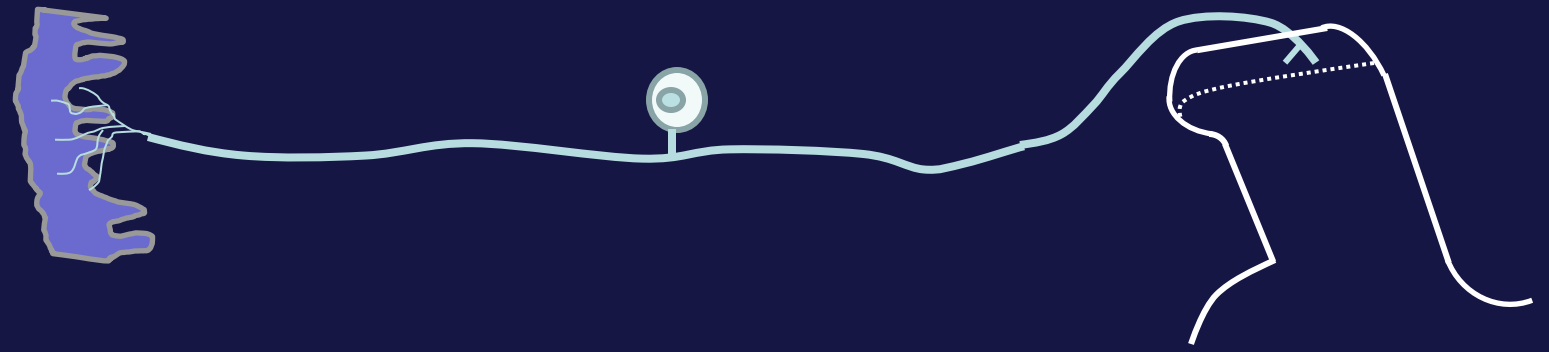
Genetic basis: LOF mutations in Nav1.7

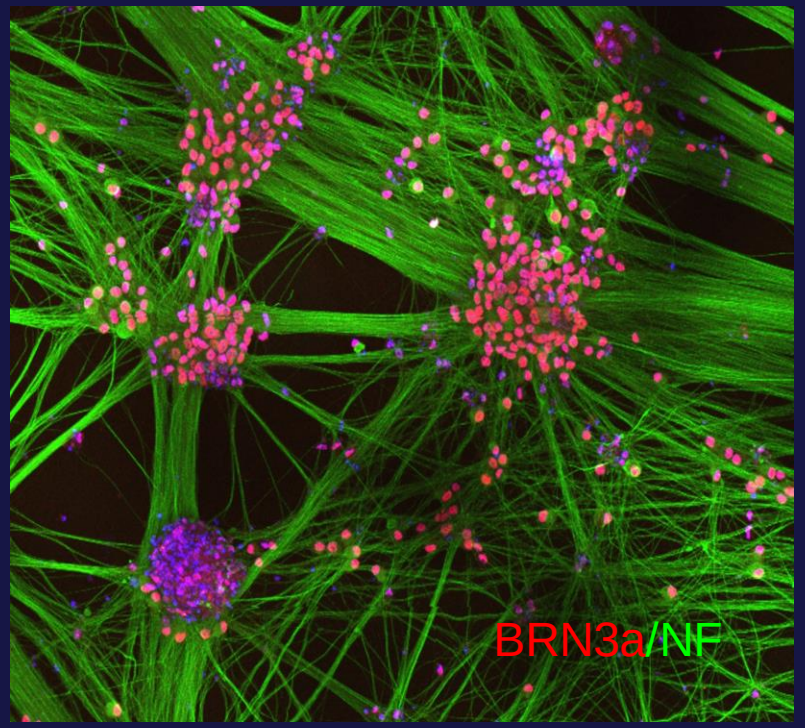


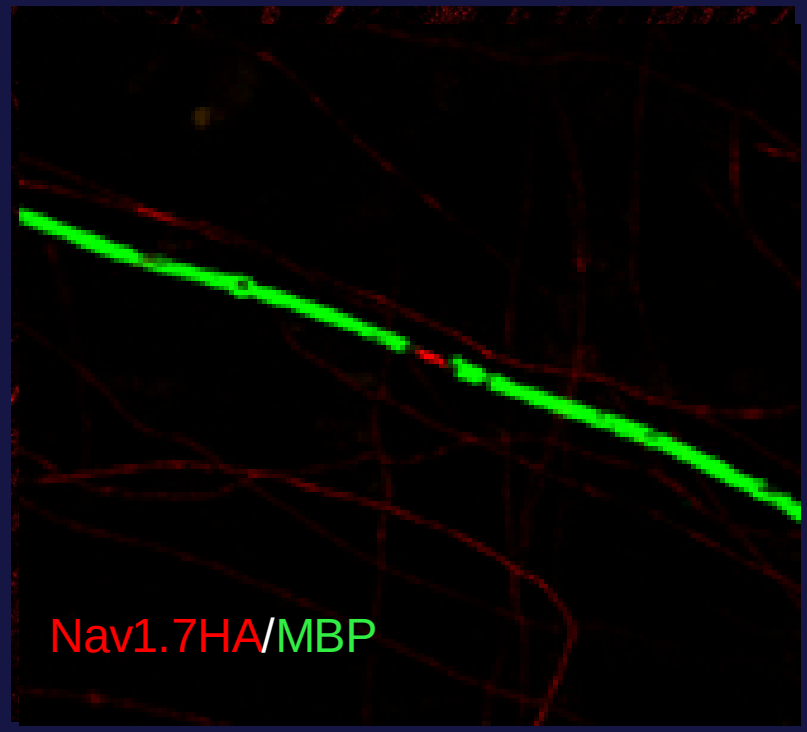
Bennett et al., physiological reviews 2019

Case Hx 1: A painless channelopathy

McDermott et al., Neuron 2019

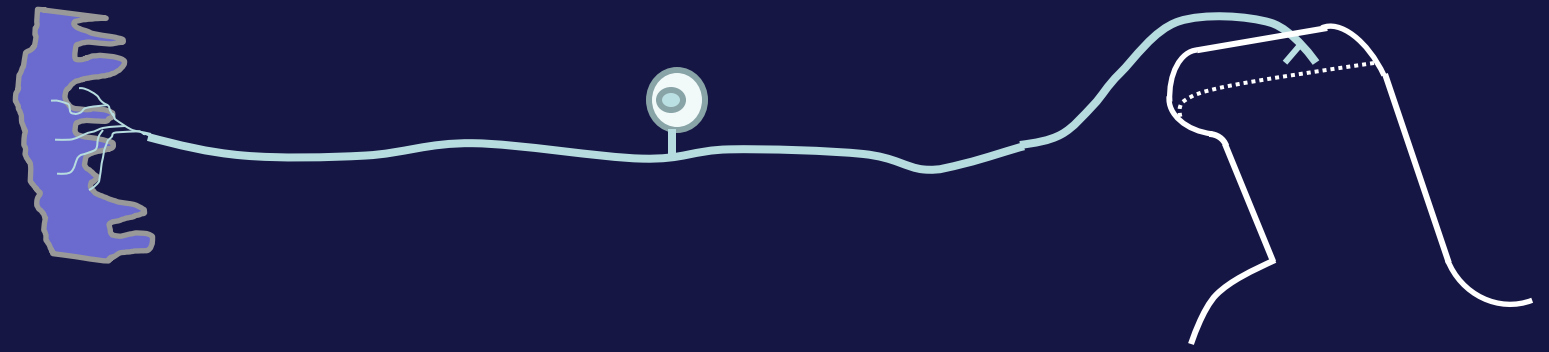


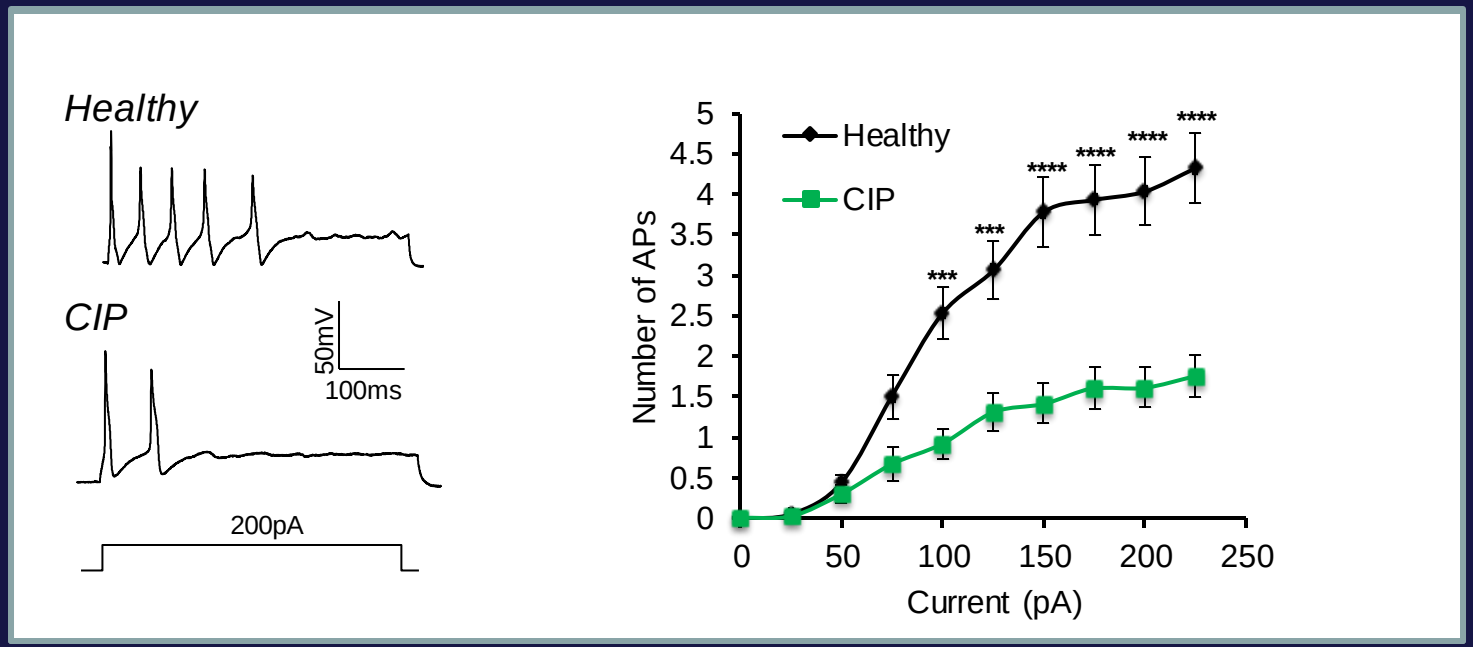




Case Hx 1: A painless channelopathy

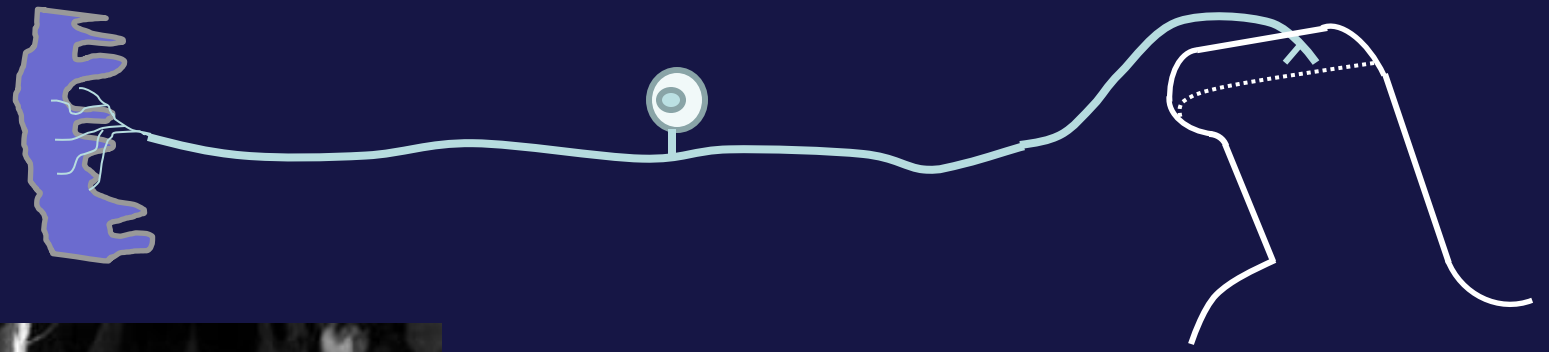
McDermott et al., Neuron 2019

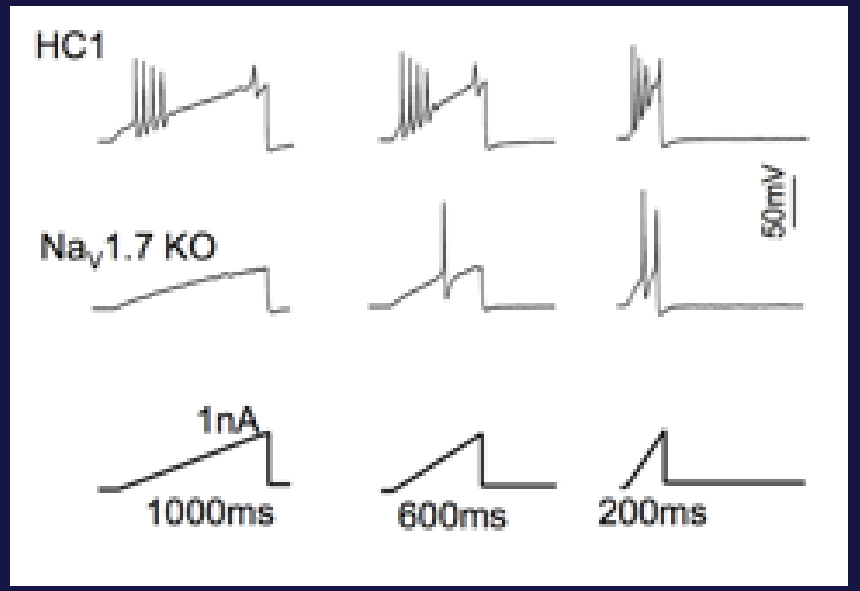




Case Hx 1: A painless channelopathy

McDermott et al., Neuron 2019





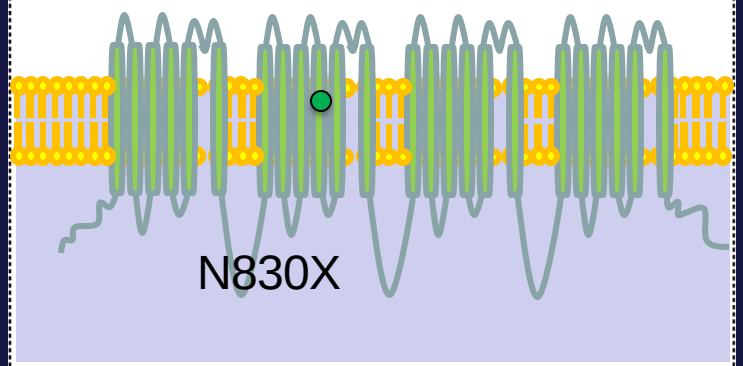
Genome editing using CRISPR-Cas9

Lucy McDermott and Greg Weir

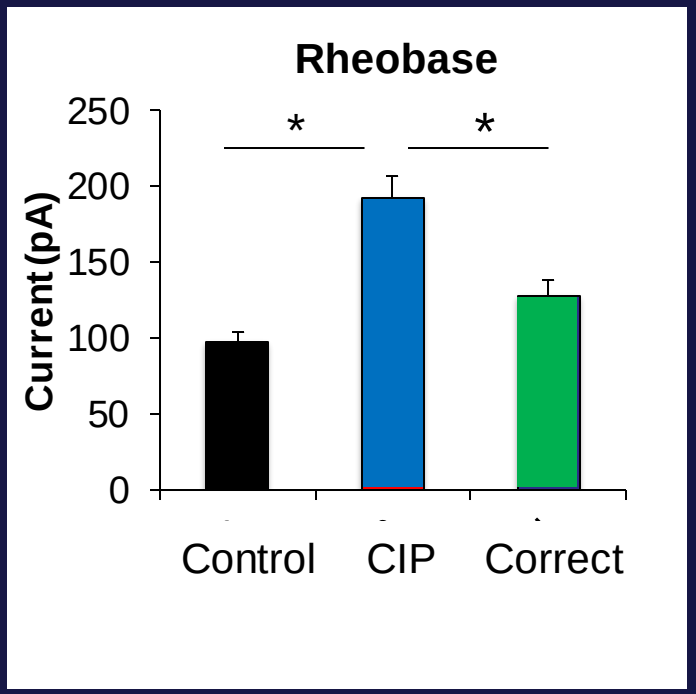
Genomic correction of a CIP patient line

CIP line correction

C.2488C>T → C.2488T>C

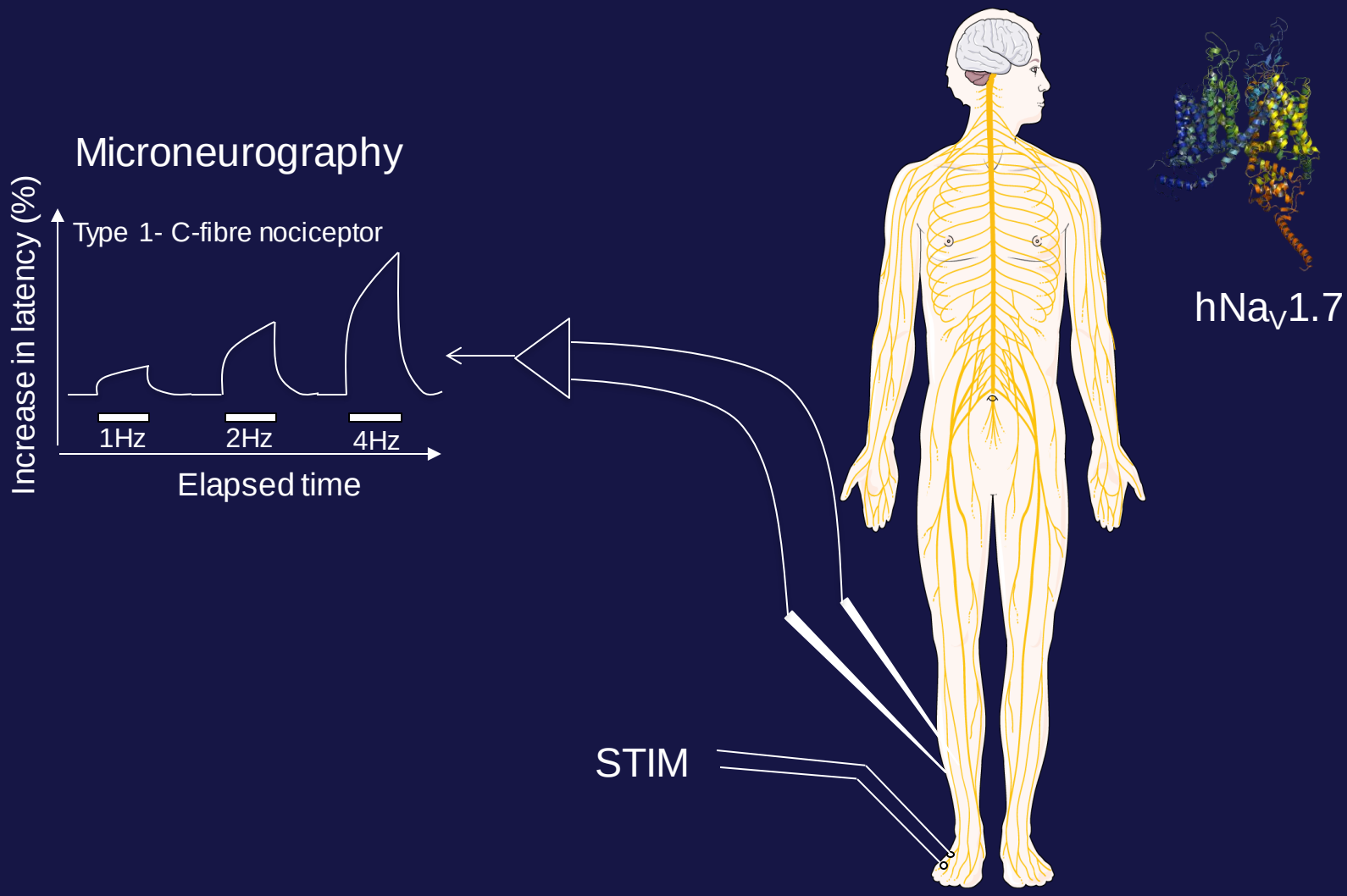


Successful correction of SCN9A CIP line. Reversal of C.2488C>T mutation



Lack of nociceptors *in vivo*

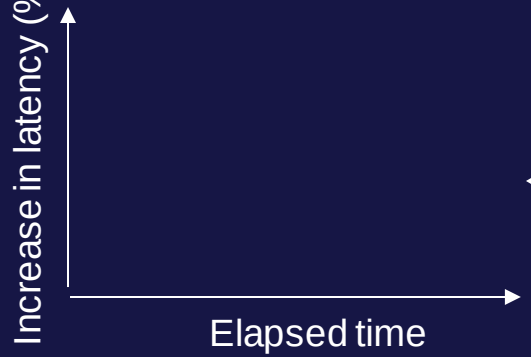
J Serra

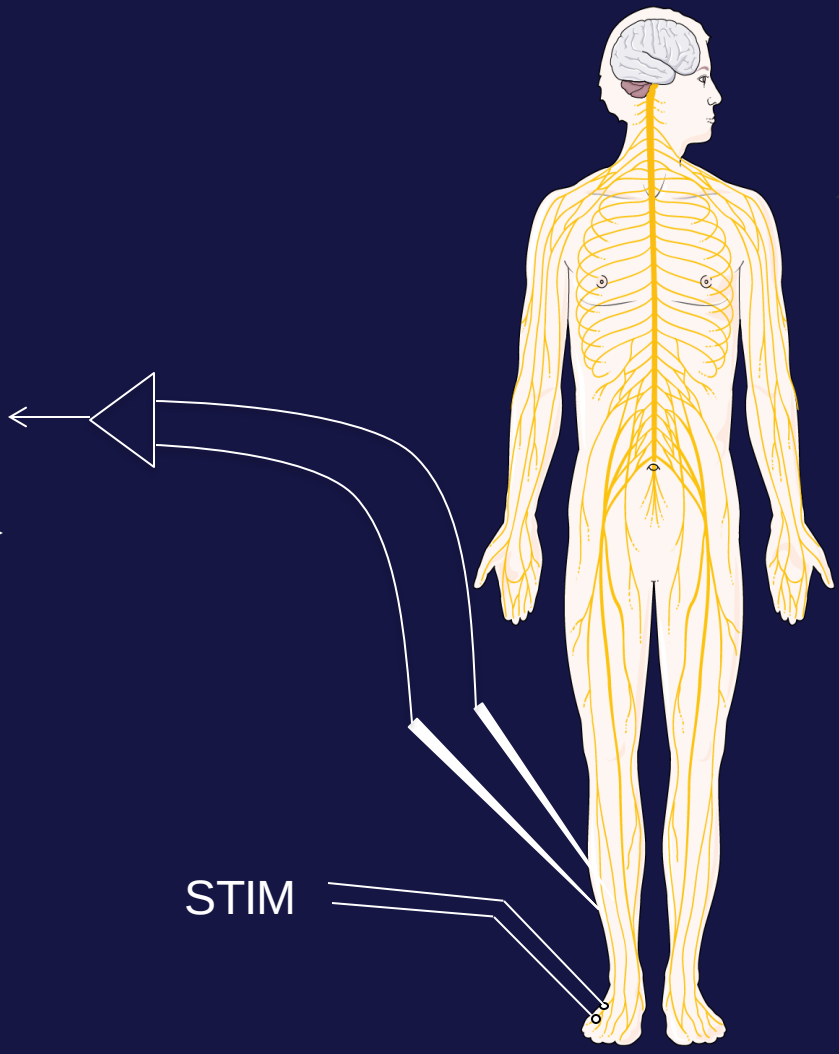


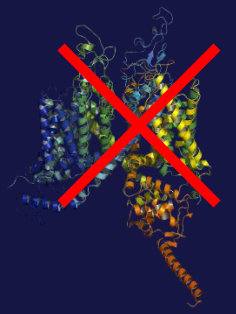
Lack of nociceptors *in vivo*

J Serra

Microneurography







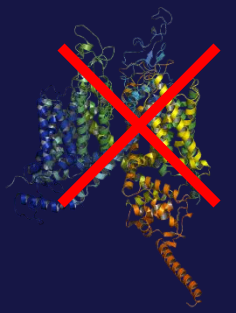
$hNa_V1.7$

Cellular models to test pharmacology:

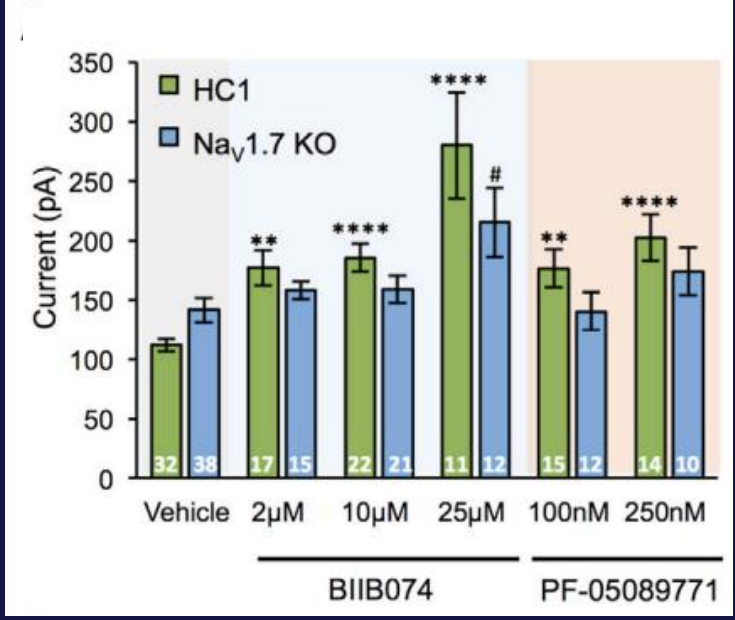
Safety and efficacy of a Nav1.7 selective sodium channel blocker in patients with trigeminal neuralgia: a double-blind, placebo-controlled, randomised withdrawal phase 2a trial

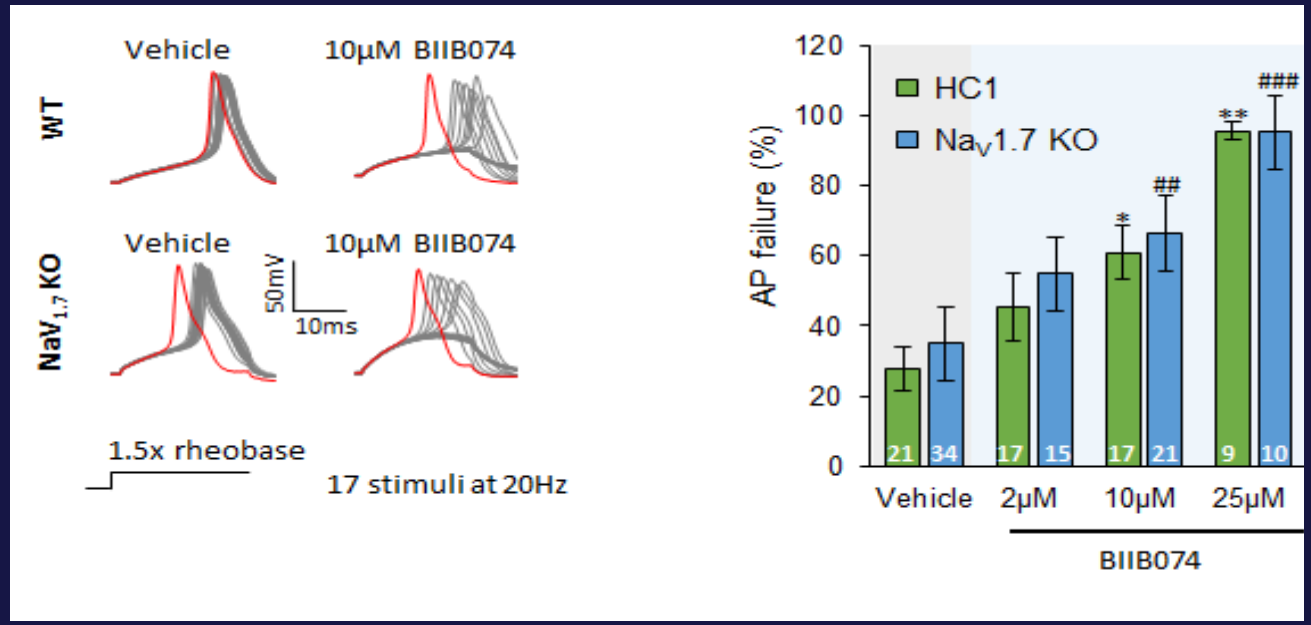
Joanna M Zakrzewska, Joanne Palmer, Valerie Morisset, Gerard MP Giblin, Mark Obermann, Dominik A Ettlin, Giorgio Cruccu, Lars Bendtsen, Mark Estacion, Dominique Derjean, Stephen G Waxman, Gary Layton, Kevin Gunn, Simon Tate, for the study investigators

Lancet Neurol 2017; 16: 291–300
Published Online
February 16, 2017
http://dx.doi.org/10.1016/
S1474-4422(17)30005-4



$hNa_V1.7$

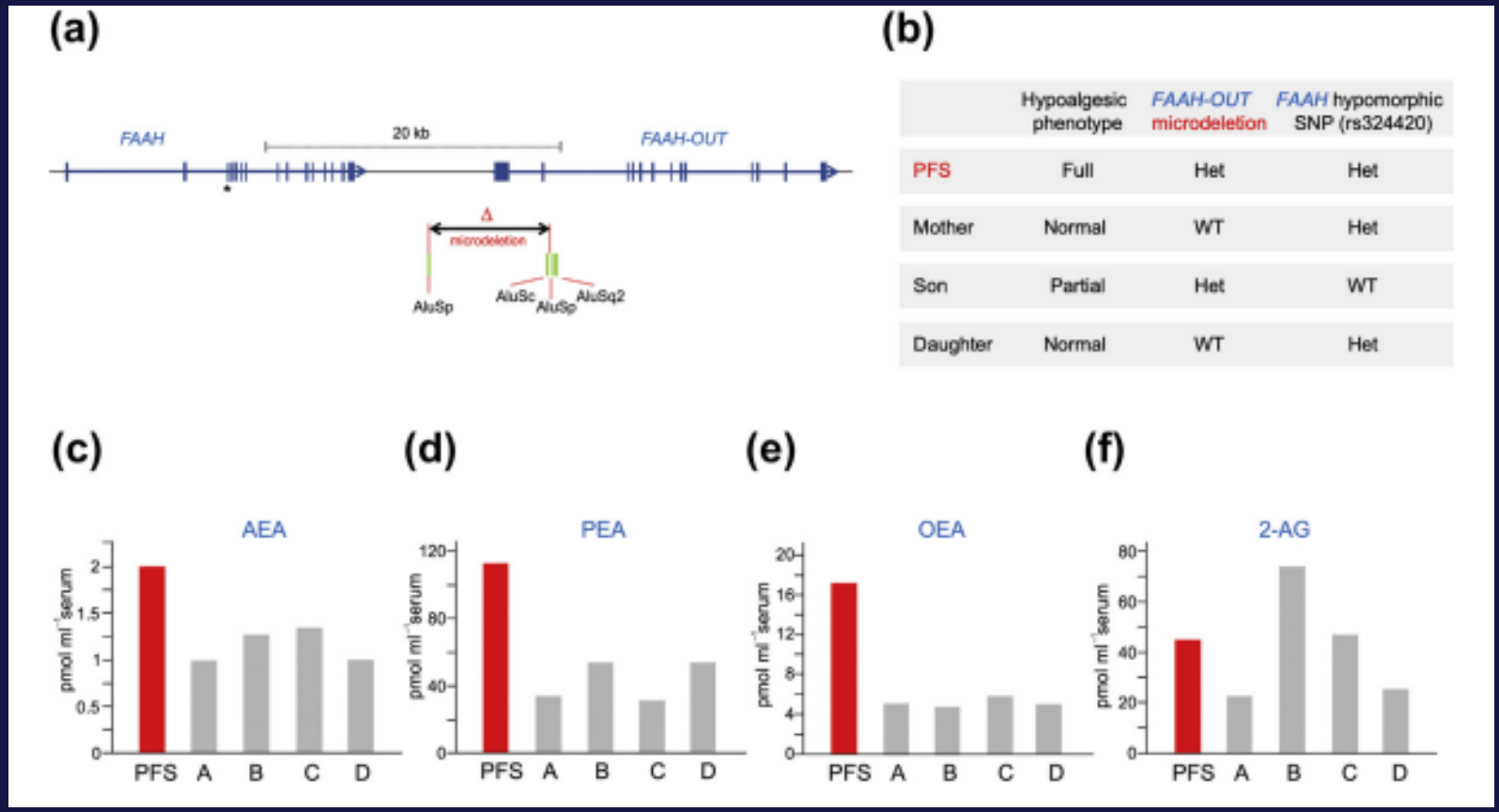




Novel mechanisms of pain insensitivity

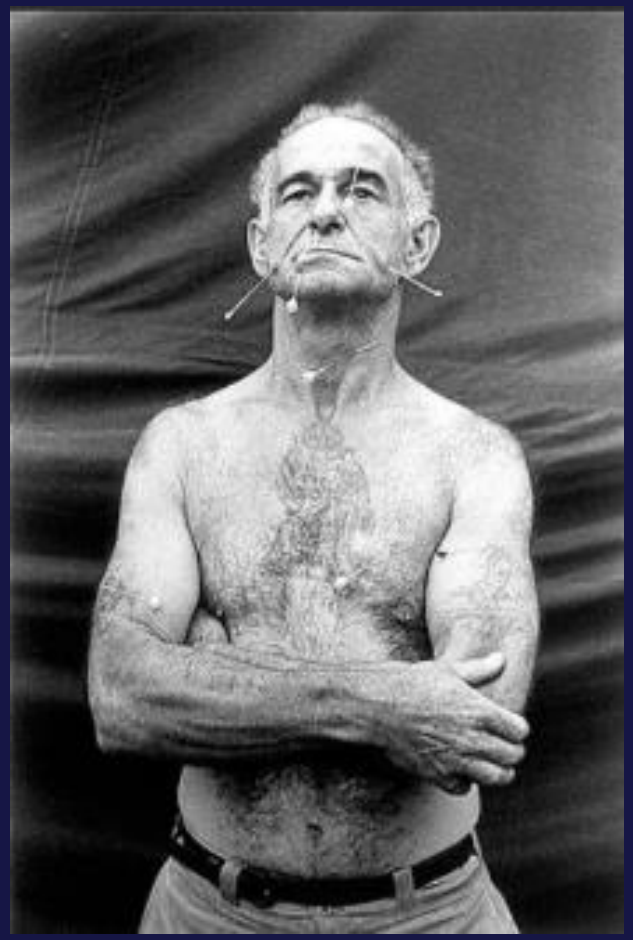
Microdeletion in a *FAAH* pseudogene identified in a patient with high anandamide concentrations and pain insensitivity

Abdella M. Habib[1,2], Andrei L. Okorokov[1], Matthew N. Hill[3], Jose T. Bras[4,5], Man-Cheung Lee[1,6,7], Shengnan Li[1], Samuel J. Gossage[1], Marie van Drimmelen[8], Maria Morena[3], Henry Houlden[5], Juan D. Ramirez[9], David L. H. Bennett[9], Devjit Srivastava[10,*] and James J. Cox[1,*]



BJA
123 (2): e249ee253 (2019)

Conclusions:



- Congenital disorders of pain perception are rare but have been highly informative regarding how the nociceptive system develops and functions.
- So far almost all of the genes identified have been specific to the peripheral nervous system.
- Studying these patients helps develop new model systems and test biomarkers to facilitate drug development.

My group:

Collaborators

Oxford
A Segerdahl, I Tracey
M Mccarthy
KCL
SB McMahon
UCL
JN Wood, A Dickenson, C Orengo
Imperial
A Rice
Sheffield
S Tesfaye
Yale
S Dib-Hajj, S Waxman
Cambridge
Geoff Woods

Lack of epidermal innervation *in vivo*