

Haploinsufficiency of the brain-derived neurotrophic factor (*BDNF*) gene causes reduced pain sensitivity in an animal model and humans with the WAGR copy number variant.

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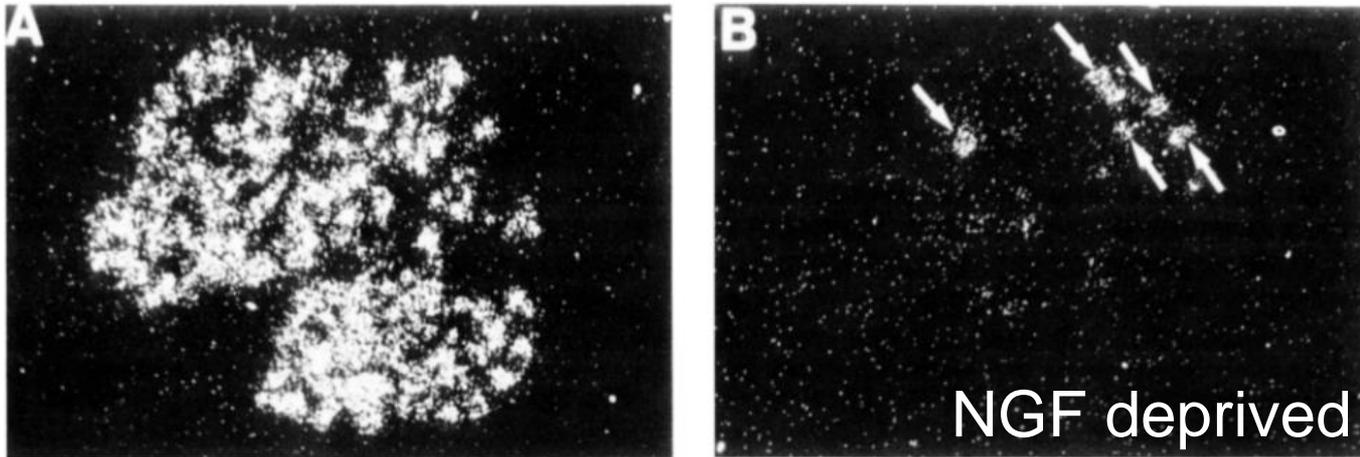
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Human genetics: Mutations in the NGF receptor, TrkA cause **profound** pain insensitivity due to loss of primary sensory afferents

TrkA probe



Mouse: Carroll, et al 1992: *in utero* NGF deprivation kills **93%** of TrkA-positive neurons in the dorsal root ganglia

NGF antibodies for pain control

Pre-validated from human genetic pain insensitivity

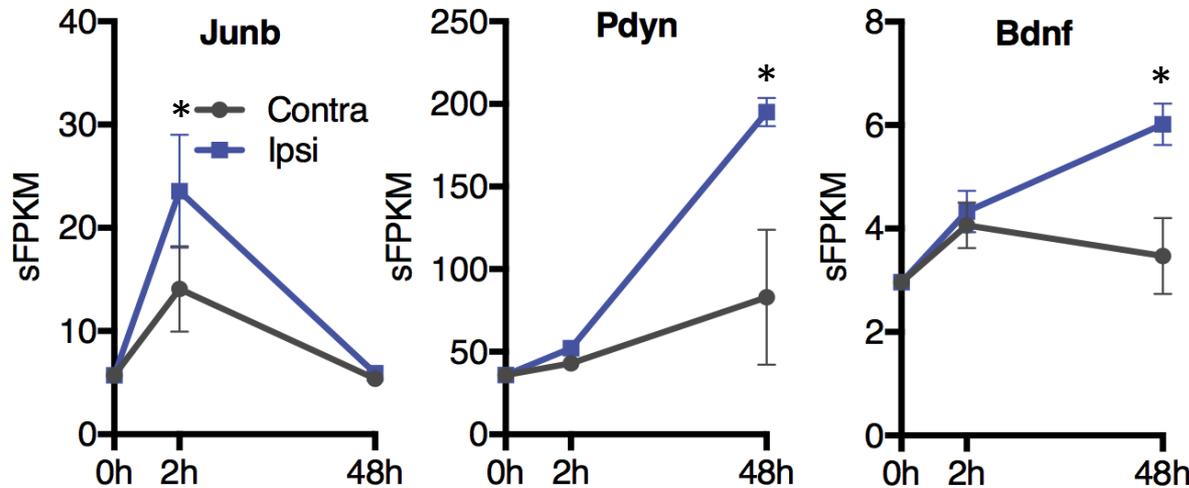
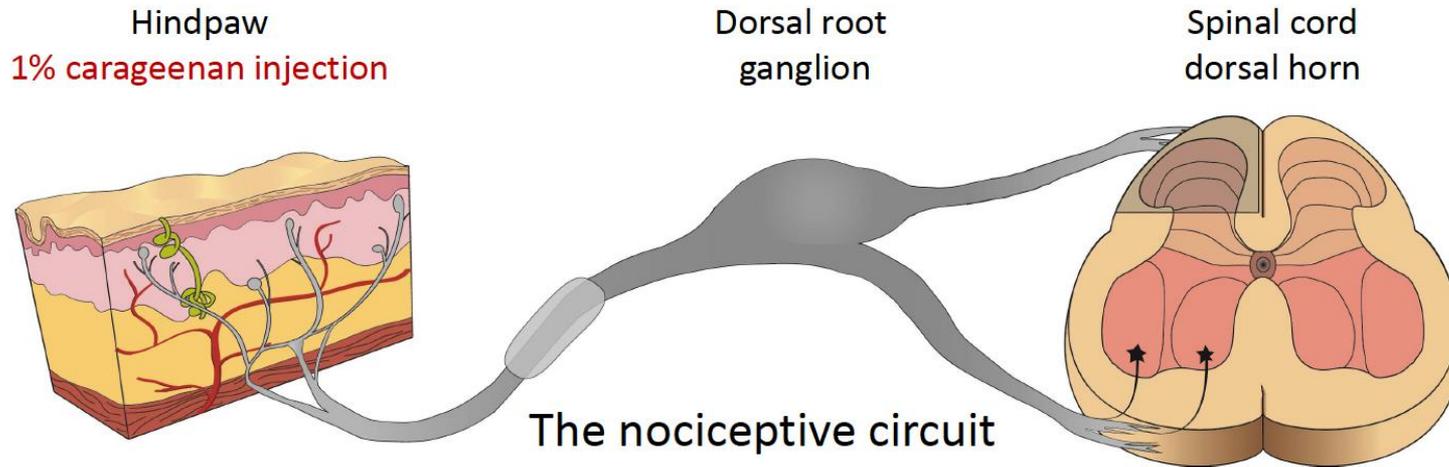
Tanezumab, Fasinumab, Fulranumab, ABT-110

Good efficacy for pain control in osteoarthritis

TRKB is the other receptor on sensory neurons

BDNF is the ligand for TRKB and has been linked to pain

Persistent pain induces gene regulation in the spinal cord

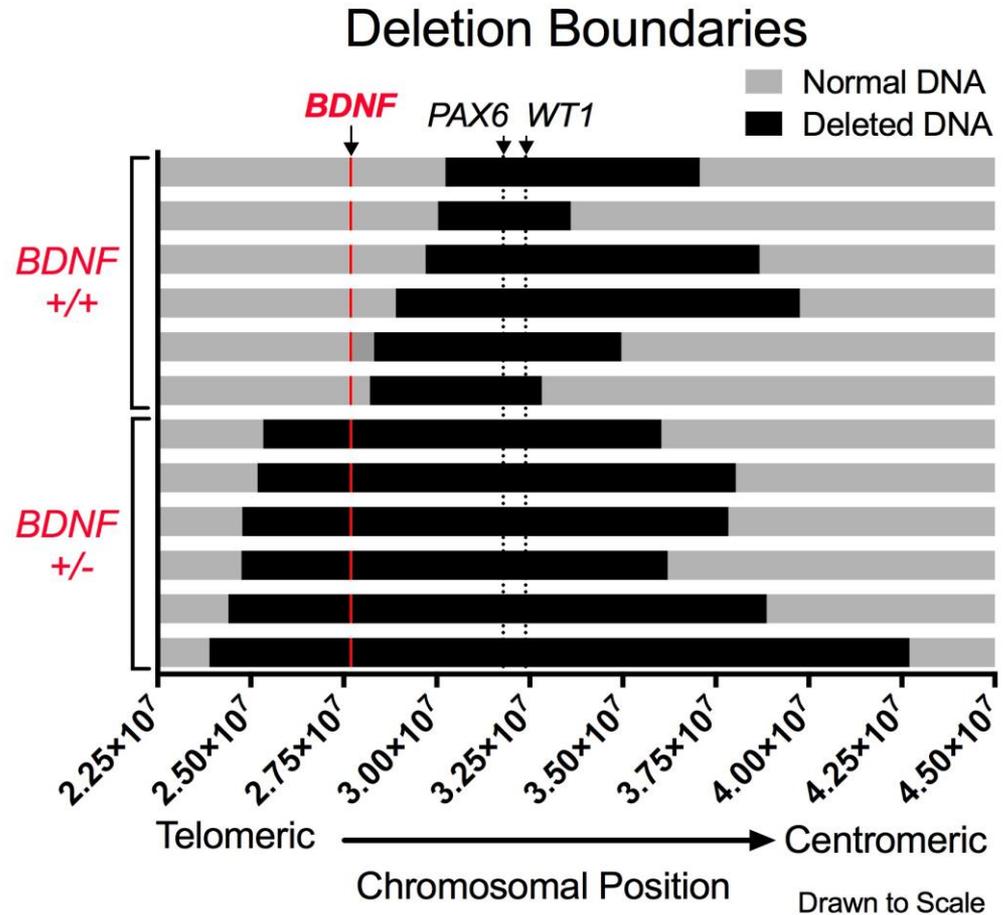


Bdnf is transcriptionally regulated in the dorsal spinal cord after peripheral inflammation

(Sapio, et al., unpublished data)

WAGR syndrome children have a variable genetic deletion on chromosome 11 (*BDNF* +/-)

Wilms Tumor (kidney)
Aniridia (eye, iris)
Genitourinary anomalies
Mental **R**etardation



WAGR syndrome children have a variable genetic deletion on chromosome 11

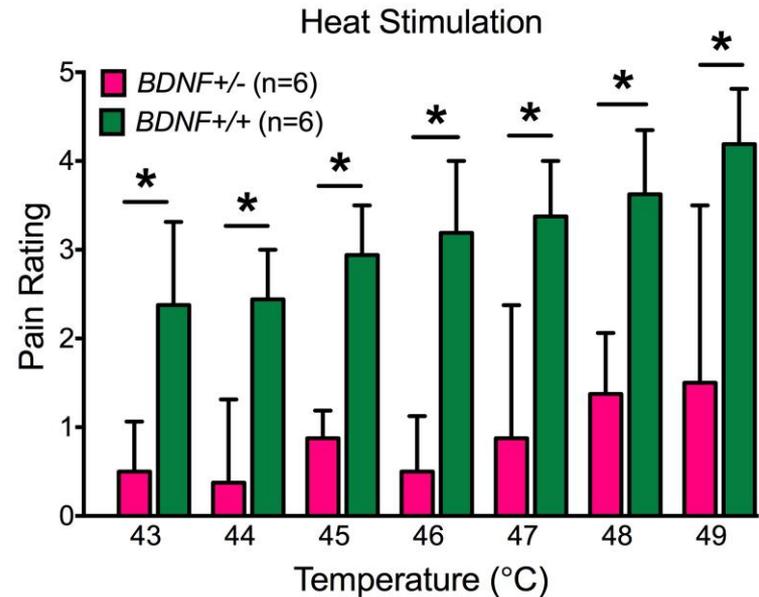
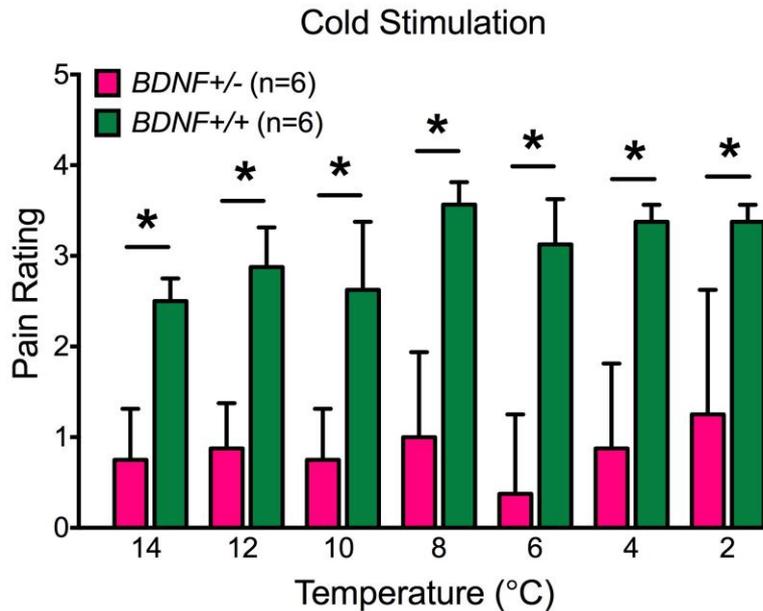
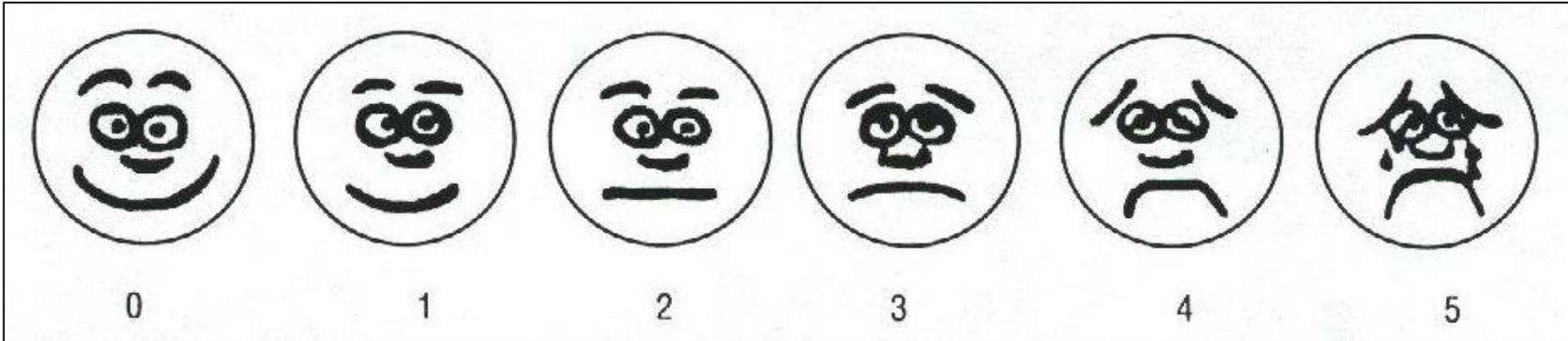
Wilms Tumor (kidney)
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Parental reports

He also broke a bone in his hand while riding a bike, we didn't notice until the next day

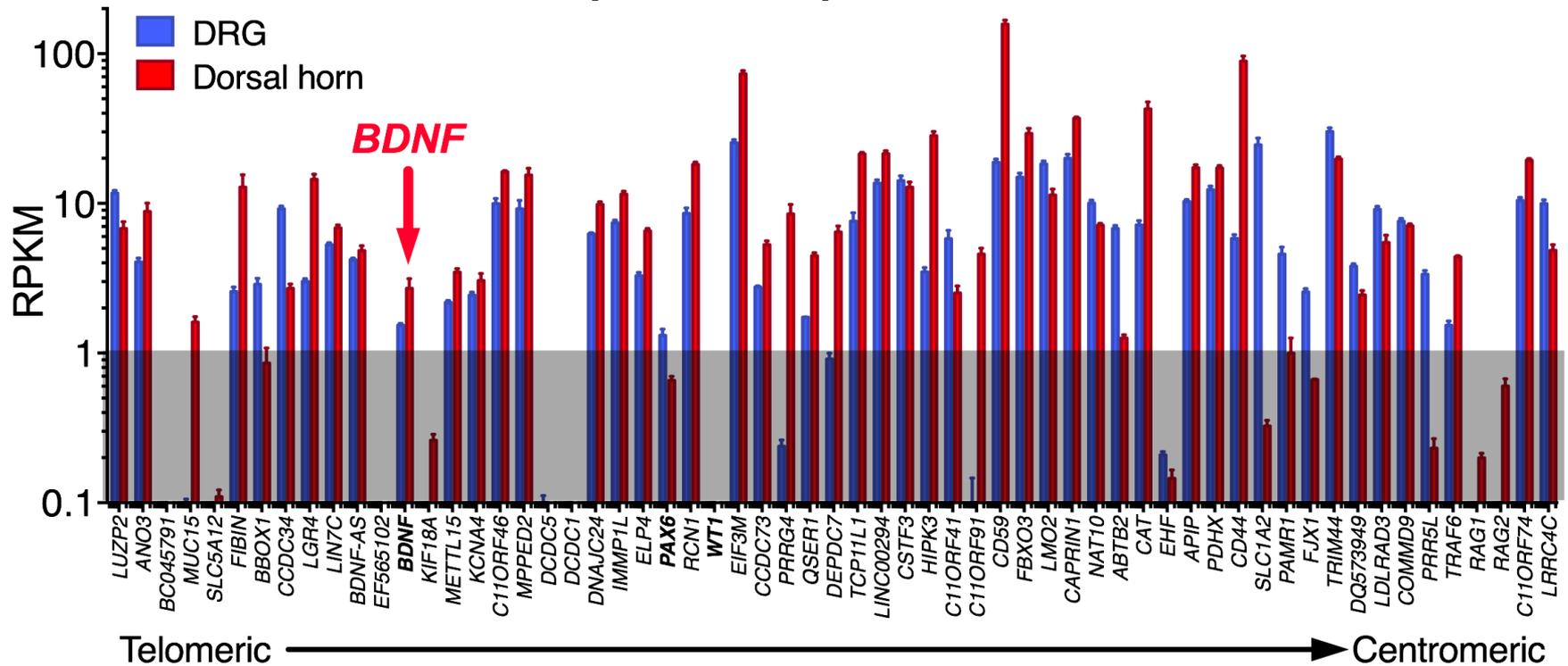
I believe there are many times when I know nothing. She had a punctured ear drum once that I only discovered from the discharge coming out. Asked her if her ear hurt and she said, "not really."

Quantitative sensory testing in WAGR children with intellectual disability



The WAGR locus includes many genes expressed in pain circuit tissues

Transcriptomics of pain circuit tissues



(Sapio, et al. Unpublished data)

An animal model with a single gene deletion

Bdnf +/- rats



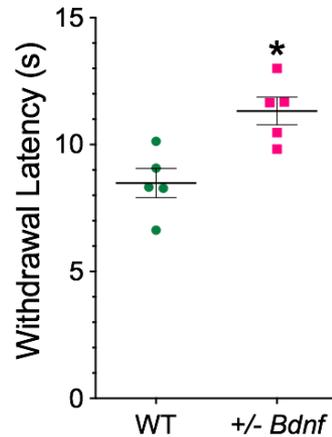
Zinc finger targeted 7bp deletion
in *Bdnf* (early stop codon)

Testing of multiple pain modalities

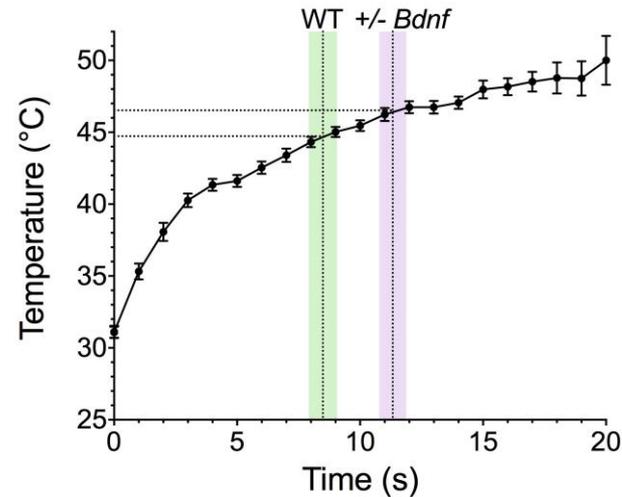
C-fiber mediated nociceptive responses in *Bdnf* +/- rats



A Radiant Heat Stimulation



B Thermistor Curve for Radiant Heat

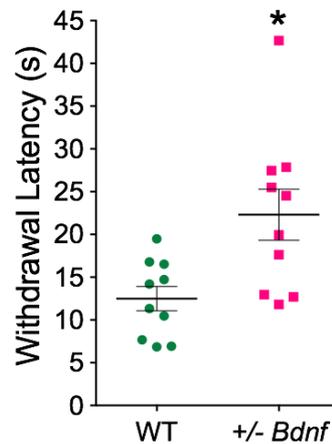


47°C *Bdnf* +/-

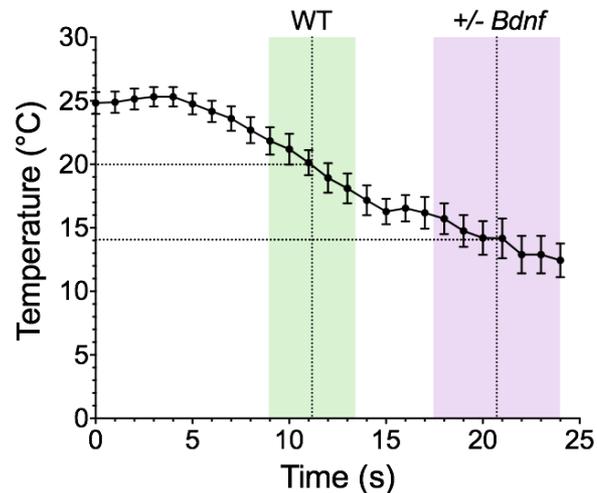


45°C WT

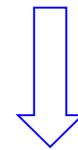
C Cold Stimulation



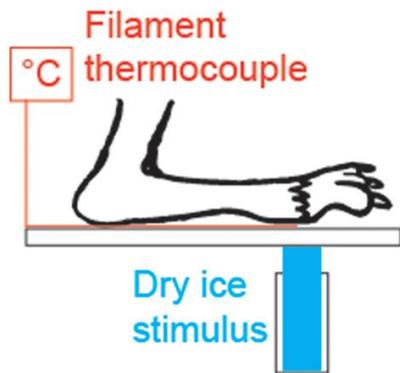
D Thermistor Curve for Cold



20°C WT

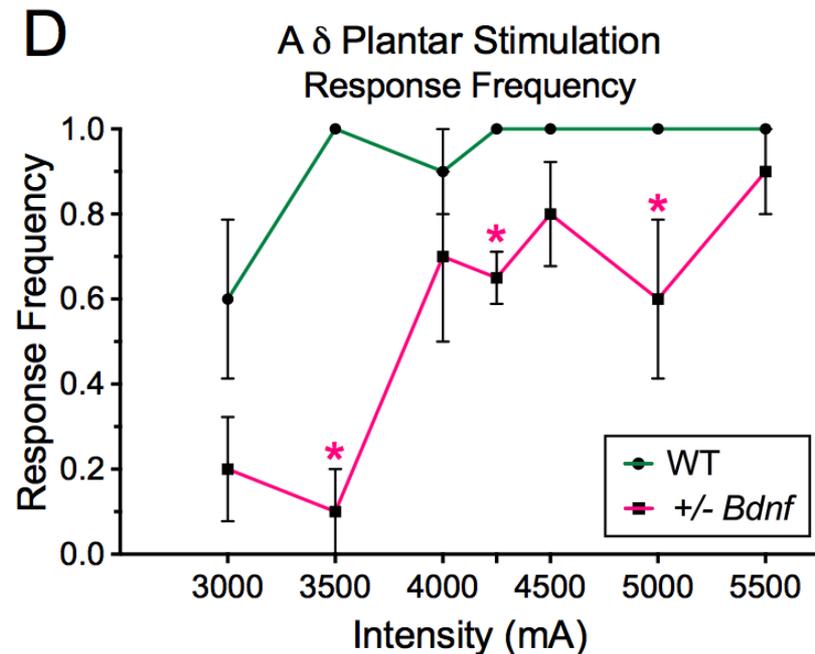
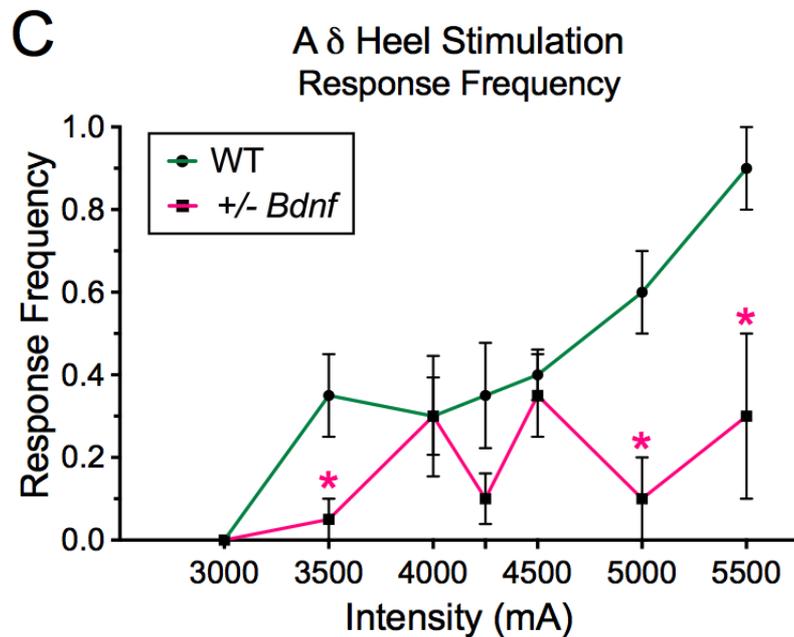


14°C *Bdnf* +/-



Brenner, et al 2012

A-delta mediated nociceptive responses in *Bdnf* +/- rats by 100ms laser pulse



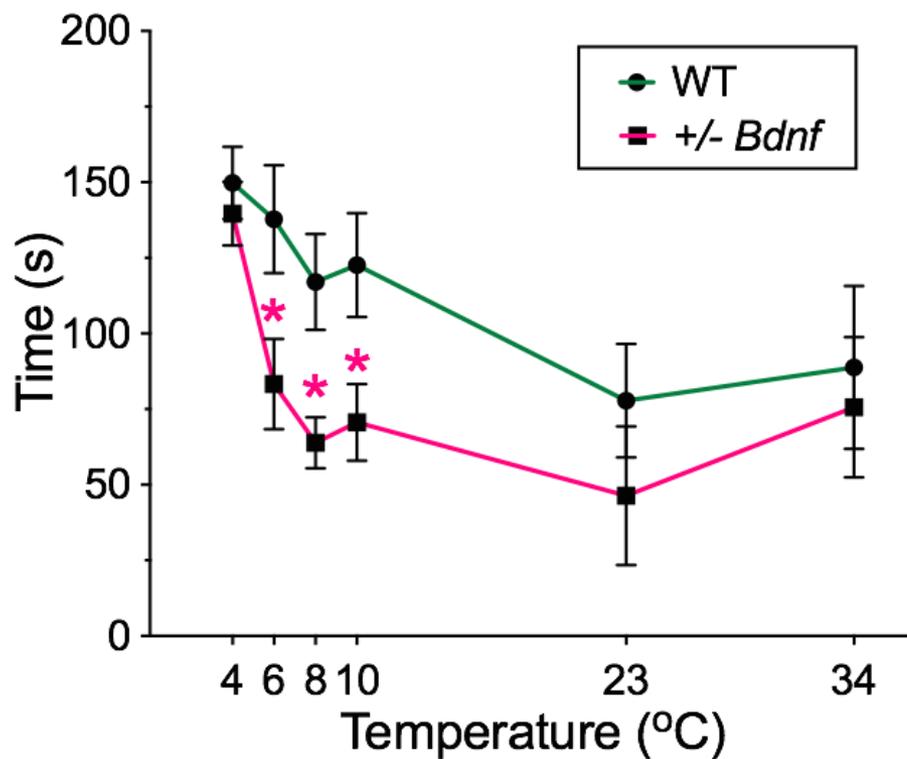
Aversive behavior on the cold plate



Tail down



Tail lifted



Towards molecular underpinnings

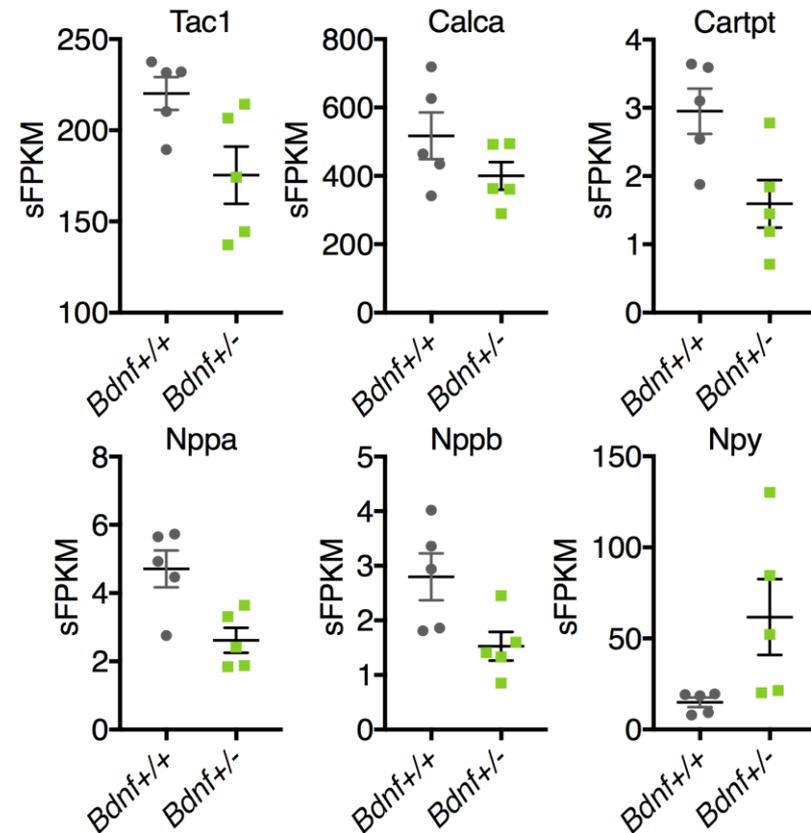
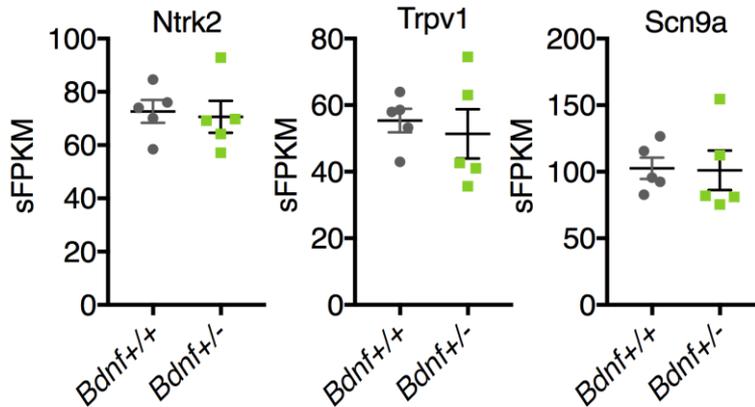
We know the quantitative gene expression for every gene in the pain circuit

Investigating the pain circuit transcriptome in *Bdnf*^{+/-}

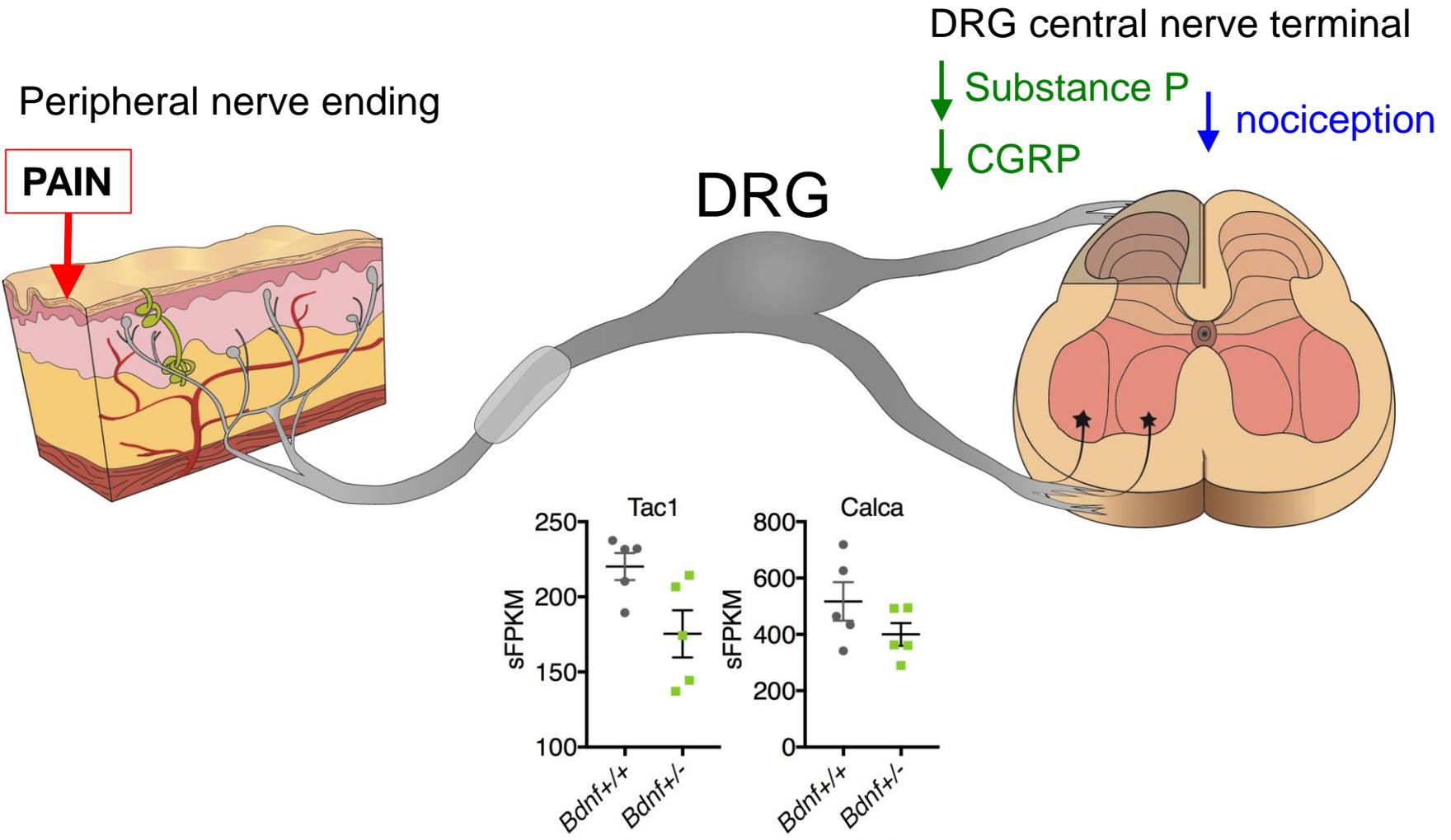
But something may be going on with how they signal...

RNA-Seq of DRG

TrkB⁺ cells are not lost



A working model for *BDNF* +/-



Conclusions

BDNF +/- WAGR syndrome children have reduced pain ratings to hot and cold

This has been overlooked because of the complex genotype/phenotype

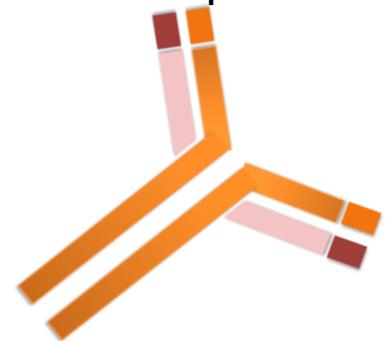
Bdnf +/- rats have reduced sensitivity to pain:

- A-delta
- C-fiber (hot and cold)
- Cold aversion
- Hot plate
- Mechanical pain

The rat is a good model of the human, and explains the clinical presentation

Strongly supports an underappreciated role of BDNF in basal nociceptive tone

Supports BDNF sequestration strategies for pain control



Acknowledgements

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