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.

Matthew Sapio, PhD
Department of Perioperative Medicine
NIH Clinical Center
May 31, 2016
Human genetics: Mutations in the NGF receptor, TrkA cause **profound** pain insensitivity due to loss of primary sensory afferents

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(Sapio, et al., unpublished data)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 Retardation**

![Deletion Boundaries Diagram](image-url)

- **BDNF**
- **PAX6**
- **WT1**

**Deletion Boundaries**
- Normal DNA
- Deleted DNA

**Chromosomal Position**
- Telomeric
- Centromeric

**Sex (% female)**
- Age 15: 67%
- Age 14: 50%
WAGR syndrome children have a variable genetic deletion on chromosome 11

**Wilms Tumor (kidney)**

**Aniridia (eye, iris)**

**Genitourinary anomalies**

**Mental Retardation**

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

(Sapió, 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 Unpublished data)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 \textit{Bdnf} +/- rats

\textbf{A} Radiant Heat Stimulation

\begin{itemize}
  \item Withdrawal Latency (s)
  \item \textbf{WT} vs. +/- \textit{Bdnf}
\end{itemize}

\textbf{B} Thermistor Curve for Radiant Heat

\begin{itemize}
  \item Temperature (°C)
  \item WT vs. +/- \textit{Bdnf}
\end{itemize}

\textbf{C} Cold Stimulation

\begin{itemize}
  \item Withdrawal Latency (s)
  \item \textbf{WT} vs. +/- \textit{Bdnf}
\end{itemize}

\textbf{D} Thermistor Curve for Cold

\begin{itemize}
  \item Temperature (°C)
  \item WT vs. +/- \textit{Bdnf}
\end{itemize}

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

**A**

**B**

**C**

**D**
Aversive behavior on the cold plate

Tail down

Tail lifted

Time (s)

Temperature (°C)

WT

+/- Bdnf

*
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 \textit{BDNF} +/-

Peripheral nerve ending

\textbf{PAIN}

\textbf{DRG}

\textbf{DRG central nerve terminal}

\textbf{Substance P}

\textbf{CGRP}

\textbf{nociception}

\textbf{ Tac1 | Calca}
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

**NIH Clinical Center**
Michael J. Iadarola
Andrew J. Mannes
Danielle M. LaPaglia
Samridhi C. Goswami
Jackyln R. Gross

**NICHD**
Joan C. Han
Jack A. Yanovski

**NCBI (MAGIC RNA-Seq pipeline)**
Jean Thierry-Mieg
Danielle Thierry-Mieg