Genetic and environmental influences on the transition from acute to chronic pain

Ze’ev Seltzer, DMD
Professor of Genetics
Canada Senior Research Chair
University of Toronto CTR for the Study of Pain
Pathophysiology of the transition from acute to chronic pain

Comparative pain genetics
  - Animal models

Heritability and genetic assays

Expected gains for pain medicine
Brief update

Pathophysiology of the transition from acute to chronic pain
What triggers the transition? - I

- Electrical signal ("Injury discharge"; online/msec)
Injury discharge

1. Noxious & nonnoxious stimuli

2. Electrical shock to determine fiber class: Aβ-δ; C

3. Cut

Recording from a single neuron
Injury discharge

33% of cut C-fibers
25% of cut A-fibers

Prolonged “saw tooth” type
12% of cut afferents
Lasts hours

Injury discharge triggers neuropathic pain - I

Preemptive analgesia

Efficacy of preemptive analgesia in humans is debated in the literature

Seltzer et al (1990a)
What triggers the transition? - II

- Chemical signal(s) (Neurotrophic factors: e.g., NGF; hrs/days)
Neuroplastic changes following nerve injury

PNS changes:
- Neuroma formation
Neuroplastic changes following nerve injury

PNS changes:
- Neuroma formation
- Spontaneous firing

Production of novel Na⁺ channels
Assembly in neuroma and DRG
Neuroplastic changes following nerve injury

PNS changes:
- Neuroma formation
- Spontaneous firing
- Firing induced by
  - chemical mediators (histamine, bradykinin…)
  - Mechanical stimuli (e.g., malfitting prosthesis)
  - electrical stimuli (cross-talk, ephapses)
Neuroplastic changes following nerve injury (cont.)

- DRGs
- Saphenous N
- Sciatic N
- Sympathetic-Sensory link Via NA & α2-AR
- Partially denervated limb
Neuroplastic changes following nerve injury (cont.)

CNS changes:
- Loss of I and II sensory neurons / microglia reaction / astroglia
- Loss of receptors (e.g., opioid rec.)
- Mediators + phenotypic switch (e.g., GABA depolarizes)
Neuroplastic changes following nerve injury (cont.)

CNS changes:
- Loss of I° & their terminals / microglia reaction / astroglia
- Loss of receptors (e.g., opioid rec.)
- Δ↑ mediators + phenotypic switch (e.g., GABA depolarizes)

REWIRING OF THE PAIN NETWORK:
- ⇔ tuning curves; novel modalities
- ⇔ RFs
- segmental disinhibition
- central sensitization
- reduced efficacy of descending inhibition
Comparative approach:
Animal models used in pain genetics
Genetic selection based on **spontaneous** neuropathic pain

Devor and Raper 1990, 2005

Currently generation 53

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**Neuropathic pain score**

- Wistar
- Sabra
- Lewis

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**Unselected Sabra**

- 0-2
- 3-5
- 6-8
- 9-11

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**BC (F1xHA)**

- 0-2
- 3-5
- 6-8
- 9-11

**BC (F1xLA)**

- 0-2
- 3-5
- 6-8
- 9-11

**F1(HAxAxLA)**

- 0-2
- 3-5
- 6-8
- 9-11

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**High Pain - HA**

- 0-2
- 3-5
- 6-8
- 9-11

**Low Pain - LA**

- 0-2
- 3-5
- 6-8
- 9-11
Neuropathic pain levels are strain specific / 2 species

Var \textsubscript{Pain} = Var \textsubscript{Gen} + Var \textsubscript{Env}

Seltzer & Shir (1998)

Mice (AXB-BXA Recombinant strains)

Parental strains

Seltzer et al (2001)
Stimulus-evoked chronic pain is also determined genetically.

PSL model
Partial Sciatic tight Ligation

~½ sciatic thickness trapped in a ligature

Seltzer, Dubner, Shir (1990)
Pain abnormalities in the PSL model - I

Tactile allodynia:

Shir & Seltzer (1998)
Pain abnormalities in the PSL model - II

Shir & Seltzer (1998)

Heat hyperalgesia:

![Graph showing heat hyperalgesia over time]

Intact
PSL
Response duration (sec)

Time (days)
Acute pain - Tactile allodynia - Heat hyperalgesia - Spontaneous pain

RATS (Mogil et al. in mice)

**Noxious heat**

- **Response duration (sec)**
  - FIS
  - LA
  - LEW
  - SD
  - HA
  - FSL
  - SAB
  - GEPR

**Heat hyperalgesia**

- **Response duration (sec)**
  - SD
  - SAB
  - LA
  - LEW
  - GEPR
  - HA
  - FSL

**Touch**

- **Withdrawal threshold (g)**
  - GEPR
  - HA
  - SAB
  - SD
  - FSL
  - LA
  - LEW
  - FIS

**Tactile allodynia**

- **Withdrawal threshold (g)**
  - HA
  - GEPR
  - FSL
  - LA
  - LEW
  - SAB
  - SD

**Spontaneous neuropathic pain**

- **Autotomy score on d63**
  - HA
  - FIS
  - GEPR
  - SD
  - SAB
  - FSL
  - LA
  - LEW

Moghul et al (2001)
Conclusions

1. **Acute** pain sensitivity does not predict levels of **chronic** pain (3 different chronic pain models, 2 stimulus modalities, 2 species, 2 research groups).

2. Levels of **spontaneous** chronic pain are not correlated with levels of **stimulus-evoked** chronic pain.

3. If these results are translatable to humans, **genes are ‘syndrome-specific’**. Pharmaco-genetic solutions will have to be tailored per syndrome.
Heritability of chronic pain

How much of the variance is accountable by genetics?
Heritability in rodents

- Nociception: 30-76% mean ~ 53%
- Anti-nociception / analgesia: 23-68% mean ~ 45%
- Neuropathic pain (SNL, Autotomy, PSL): ~ 30-70% mean ~50%

Mogil et al (2002)
Heritability of pain in humans

Pedigree analyses / twins studies: \( h^2 \sim 0.2-0.7 \) (mean \( \sim 50\% \))

- Sciatica
- Diabetic neuropathy
- Carpal tunnel syndrome
- “Burning feet” syndrome
- Post-herpetic neuralgia (HLA)
- CRPS (HLA)
- Fibromyalgia (HLA; \( 5HTTP1 \))
- Low back pain / Sciatica (\( GCH1; BDNF \))
- Migraine (\( Cacna1a, ATP1A2, \ldots \))
- TMD - Temporo-Mandibular Pain Disorder (\( COMT \))
- Phantom limb pain / stump pain (HLA, \( GCH1, GDNF \))
- Post-Mastectomy Pain Syndrome (\( COMT, GCH1 \))
Phenomics of chronic pain as a complex trait
Chronic pain

Sensory discriminative

- Intensity
- Spatial
- Temporal

Type

Catastrophizing

Cognitive

- Beliefs about pain
- Other

Education

Impact on QoL

Affective / motivational

Aggravating / Relieving factors

Past painful experiences

Different genes for different phenotypes

Different genes for different phenotypes
Chronic pain phenomics

Choosing the right phenotypes for genetics:

- Clinical relevance
- Mechanism-based
- N traits vs. multiple comparisons ("Bonferroni correction")
- Pooling / Indexing / Loosing resolution
- Endophenotypes
The Human Pain Phenome Project

- Detailed registry of previous chronic pain episodes
- Aetiology and medical history
- Detailed phenotypes
- Tests (QST, electrodiagnosis, imaging, biochemistry)
- Treatment effects
- Additional traits: life style, personality / character
- Bioinformatics / data mining
Expected gains in pain genetics
- Diagnostic kits
- Prognostic kits
- Preventive pain medicine
- Novel painkillers
- New mechanisms
- Gene therapy
- Better animal models
- Faster / cheaper clinical trials
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United States Congress declared:
2001-2010: The Decade of Pain Control and Research

The Human Genome Project has developed methodological templates that can be transposed immediately to pain genetics.

This is the time to:

- Establish new research teams
- Support the collections of DNA samples / multicenter approach
- Finance genome-wide screens using microarray chips (1,000 samples X $ 500/sample = $ 0.5 million / syndrome)

**Proposed goal for 2010:** First draft listing all major chronic pain genes in humans and mice. Given the right support – this is achievable!
Injury discharge triggers neuropathic pain - II

Electrical tetanization

Neuropathic pain score vs. Postoperative time (days)

- C-fibers “Wind-up” (0.5Hz)
- C-fibers (0.1Hz)
- A-fibers
- CON
- Local anesthetic

Seltzer et al (1990b)
Neuroplastic changes following nerve injury (cont.)

Spontaneous firing in intact DRGs

Partially denervated limb
Activity in neuroma and DRG causes pain

Resection / RF / neurolysis of painful neuroma & GG - sometime successful

Devor et al (1999)
Chronic pain

Sensory discriminative
- Intensity
- Temporal
- Spatial
- Type

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Acute pain - Tactile allodynia - Heat hyperalgesia - Spontaneous pain

MICE

Tactile Alloodynia

Heat Hyperalgesia

% Allodynic Mice

% Hyperalgesic Mice

Disorder B

Disorder A

Neuropathic pain score

Spontaneous pain (self-mutilation)

R² = 0.002
R² = 0.09
R² = 0.005

Aut X HH
Aut X TA
HH X TA

Mogil et al (1999)
Thousands/~25K genes in the human genome encode the chronic pain network.

- Sensory-discriminative
- Affective
- Cognitive

“Social” pain genes

Nocifension / reflexive
Shall we need to control thousands to treat pain?

No

• Most genes have been fixed throughout evolution
  (e.g., “Painless” for noxious heat in the fly larva)

• While many have Single Nucleotide Polymorphisms (SNPs)

• Only a small fraction are functional, even fewer clinically relevant

• So how many will have to treated to treat a given pain syndrome?

  Not known as of yet
  
  Guess: ~5 ‘major’ and up to ~15 ‘modifiers’ per syndrome
How many genes would have to be pharmaco-genetically controlled to provide solutions for a pain syndrome?
Neuroplastic changes following nerve injury (cont.)

Aδ-fibers

DRGs

Saphenous N

Sciatic N

Collateral sprouting

Aδ-fibers
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The case of Roni A. (male, age 44, contractor)

- 1995 - suffered an accident at work
  - L. brachial plexus avulsion
  - L. hand numb and painful
  - L. hand paralysed at an awkward position
• 1997 – surgical relocation of the arm
• 2002 – amputation of the hand
  – Telescoping
  – Triggering the phantom from the face/arm
  – Exacerbation of pain
    – When symp system aroused
    – Changing weather
    – When attempting to move phantom
No therapy has helped Roni get rid of the pain.