Novel Methods to Identify Pain Targets: Genomic/Genetic Approaches

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The National Academies of SCIENCE ENGINEERING MEDICINE
Advancing Therapeutic Development for Pain and Opioid Use Disorders through Public-Private Partnerships: A Workshop
Washington, DC, October 11–12, 2017
Translation of Genetic Information into Clinical Practice

- Associated variants
  - Novel biological insights
    - Clinical applications
      - Therapeutic targets
      - Biomarkers
      - Prevention
  - Measures for improved treatment
    - Personalized medicine
      - Diagnostics
      - Prognostics
      - Therapeutic optimization

How are genomes of individuals different?

DNA contains 99.9% of identical sequence in all the individuals with only 0.1% difference. Out of this 0.1% variation, over 80% are single nucleotide polymorphisms (SNPs).
# Genes Responsible for Monogenic Pain Disorders

<table>
<thead>
<tr>
<th>Type</th>
<th>Gene</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSN Type I</td>
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<td>HSN Type V</td>
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<td><em>TRPA1</em></td>
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<td>FHM Type II</td>
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“**The Human Pincushion** (congenital insensitivity to pain with anhidrosis; HSN Type IV)

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FEPS: familial episodic pain syndrome; HSN: hereditary sensory neuropathy; PE: primary erythromelalgia; PEPD: paroxysmal extreme pain disorder; FHM: familial hereditary migraine

Courtesy from Dr. Mogil
Drug Development Based on Monogenic Pan Disorders -

Anti-NGF attenuates knee pain while walking in osteoarthritis patients

Mantyh et al., Anesthesiology, 2011
Drug Development Based on Monogenic Pan Disorders – Sodium Channel blockers

Active compounds
- AstraZeneca
- Bayer
- Eli Lilly
- Janssen
- Johnson & Johnson
- Novartis
- Others

Preclinical
- Renovis-Pfizer
  - Sanofi-Aventis
    - SAR-115740

Phase I
- Amgen
  - AMG517

- Abbott
  - ABT102

Phase II
- Glenmark
  - GRC 6211

- GSK
  - SB-705498

Phase III
- Merck-Neurogen
  - MK-2295
Common Persistent Pain Conditions

- High Psychological Distress
  - Mood
  - Anxiety
  - Depression
  - Stress Response
  - Somatization
- High State of Pain Amplification
  - Tissue Injury
  - Blood Pressure
  - Impaired Pain Regulatory Systems
  - Pro-inflammatory State

Development of Pain Genetics Field

Questioning genetic component of human pain

Single gene association studies

COMT

OPRM1

Genome-wide analysis

Needs for integration of multiple genome-wide datasets

2000

2017

We are here
To create a database that aggregates relevant and up-to-date human pain genetics data and complementary resources in one centralized location to be used as a resource for clinicians and pain researchers.

<table>
<thead>
<tr>
<th>Loci</th>
<th>Variants</th>
<th>Alleles</th>
<th>Direction</th>
<th>Phenotype</th>
<th>Publication</th>
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<td>Cancer Pain</td>
<td>Wang 2015</td>
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</tbody>
</table>
Genetic Loci Associated With
Quantified By The Number Of Genetic Association Studies

Migraine

- MTHFR
- ACE
- PRDM16
- TNF
- ESR1
- AJAP1
- C7orf10
- DBH
- FHL5
- LRP1
- LTA
- MMP16
- TRPM8
- Other

Musculoskeletal Pain Disorders

- COMT
- HTR2A
- ESR1
- ADRB2
- II1A

Zorina-Lichtenwalter et al, Neuroscience, 2016
The Translational Research Clock – closing the circle

Association study results, *HMG*, 2005
(942 citations)

(607 citations)

Clinical trial – *Pharmacogenet Genomics*, 2010
(83 citations)

(198 citations)
Epiregulin and EGFR interactions are involved in pain processing

Phenotypes categories included in the HPGdb

- **Analgesia** (78) - 25%
- **Migraine** (68) - 22%
- **Nociception** (34)
- **Neuraxial Pain** (25)
- **Musculoskeletal pain** (30)
- **Fibromyalgia** (19)
- **Post-operative Pain** (18)
- **Non-musculoskeletal pain** (15)
- **Cancer Pain** (13)
- **Neuropathic Pain** (9)
Multiple Roads to Migraine

Freilinger et al Nature Genetics 2012
Heterogeneity of patient population

patients subgroup 1

patients subgroup 2
QQ plots for SNPs replication in the UK BioBank. Ratios are number of SNPs better than 20% FDR to the total number of SNPs in respective SNP groups (SNPs from GWAS in orange).
Non-organ specific approach to treatment cancer

Personalized Cancer Therapy

1. Molecular Profiling
2. Prognostic Markers
   - Markers predictive of drug sensitivity/resistance
   - Markers predictive of adverse events

Targeted therapies:
- PIK3CA target
- HER2 target
- FGFR target
- EGFR target
- KRAS target
Non-organ specific approach to treatment pain

Personalized pain treatment

Neuropathic pain patients
Low back pain patients
Osteoarthritis patients

Molecular Profiling

Prognostic Markers
Markers predictive of drug sensitivity/resistance
Markers predictive of adverse events

NGFR target
ADRB2 target
Ca++ channels target
NE target
5TH target
Welcome to the Human Pain Genetics Lab
Thank You