Big pain, small fibres

Personalising medicine in painful neuropathies

Giuseppe Lauria

IRCCS “Carlo Besta” Neurological Institute
University of Milan
Italy
Giuseppe Lauria, MD

- **Grants** - European Commission, Italian Ministry of Health, Lombardy Foundation for Biomedical Research (FRRB), Italian Foundation for the Research in ALS (AriSLA)
- **Scientific advisory** - CSL Behring, Biogen, Vertex, Chromocell, Johnsons & Johnsons, Grünenthal, GlaxoSmithKline, Chiesi Pharmaceuticals, Theraphath, Kedrion, Pfitzer, Mitsubishi Pharma, Shire
Carlo Besta e lo sviluppo delle Neuroscienze in Italia
History

1918  Legal body «Institute for Brain Wounds of War»
1923  Moral Body «Neurobiological Institute for Brain Wounds»
1932  «Vittorio Emanuele III Neurological Institute»
1950  «Carlo Besta Neurological Institute»
1952  Recognition of Specialized Institute with Scientific Character
1964  First Department of Child Neuropsychiatry in Italy
2006  Transformation into public foundation with legal body
2018  City of Science and Research
Topics

- Neuropathic pain: phenotype featuring
- Small fiber neuropathy: from unrecognized entity to a research model in neuropathic pain
- Towards precision medicine in neuropathic pain: sodium channel genes unraveling individual susceptibility in diabetic neuropathy
Challenges of chronic neuropathic pain

- 5% of the population
- 40% of patients with neurological diseases
- Major impact on patients’ quality of life and healthcare costs
- Need of tailored treatments
- Individual susceptibility to chronic pain
Anatomical pathways of nociception
Descending Pain Modulatory System
Pain pathway sensitization

Mediators released at various levels induce sensitization and tonic activation of pain signaling system

- **Peripheral sensitization** at nociceptors and DRG level
  - Cytokines/chemokines
  - NGF, BDNF

- **Central sensitization** at spinal cord level
  - Recruitment of NMDA receptors
Factors influencing pain experience

Irene Tracey¹,* and Patrick W. Mantyh²;
Neuron 55, August 2, 2007
Expectation modifies pain perception

Expectation of analgesia reduces the intensity of pain, and vice versa.

Response to placebo; efficacy and compliance of treatments
Painful diabetic neuropathy & Depression

- Painful DN is associated with a more than 4-fold increased risk of depression compared with painless DN.

Cinzia D'Amato, Roberto Morganti, Carla Greco, Federica Di Gennaro, Laura Cacciotti, Susanna Longo, Giorgia Mataluni, Davide Lauro, Girolama A Marfia and Vincenza Spallone

Diabetes & Vascular Disease Research
2016, Vol. 13(6) 418–428
Individual variability

- **Pain sensitivity**
  - Socioeconomic status
  - Trauma/stress exposure
  - Ethnicity → African American and non-Caucasian Hispanics have more pain than Caucasians within the same clinical populations
  - Gender → women report greater pain than men

- **Response to analgesics**
  - Pain relief in <50% of patients, without differences among drugs and irrespective of the underlying disease
  - 25% of patients withdraw treatments because of unpredictable side effects

- **Pain susceptibility in patients with similar risk exposure**
  - Painful form of diabetic neuropathy in ~20% of patients and not related to age, diabetes duration, metabolic control, or severity of neuropathy.
  - Other conditions (eg major joint surgery, cardiothoracic surgery, etc) show a similar frequency of chronic pain (15-20%) among homogeneous risk exposure
Microglia-to-neuron signaling is essential for chronic pain hypersensitivity.

However, microglia activation is not required for mechanical pain hypersensitivity in female mice, which use adaptive immune cells, likely T lymphocytes.

This sexual dimorphism suggests that male mice cannot be used as proxies for females in pain research.
Omic modulation: from animal models to humans

- Genetic
  - >10% of the transcriptome dysregulated in neuropathic pain
    - receptors expressed by nociceptors (TRPV, TRPA1, GABA-B1, 5-HT3A)
    - ion channels regulating nociceptor excitability (NaV, Kv, CaV)
    - central neurotransmitters (e.g. NMDA, SP, BDNF)
  - Twin studies → heritable factors explain 30-60% of pain response variability
  - Pain disorders with Mendelian inheritance

- Epigenetic
  - stable and/or heritable changes in gene function without concomitant DNA sequence changes, through proteins that can add (writers), remove (erasers) or be recruited (readers) by specific marks.
    - DNA methylation
    - histone modification
    - REST
  - Emerging “behavioural epigenetics”
Gene variants influencing analgesic response and pain sensitivity

- **Increased opioid analgesia**
  - Catechol- O-methyltransferase (COMT)
  - Melanocortin-1 receptor gene (MC1R)
  - Cytochrome P450 2D6
  - P-glicoprotein gene

- **Reduced pain sensitivity**
  - Catechol- O-methyltransferase (COMT)
  - µ-opioid receptor gene (OPRM1)
  - GPT cyclohydrolase (GCH1)

- **Increased pain sensitivity**
  - Potassium and sodium channel gene polymorphisms

- **Pain chronicization**
  - GFAP
  - β-arrestin-2
Markedly downregulated following nerve injury in rat DRG across three distinct neuropathic pain rodent models

Characterization in six cohorts of chronic pain patients

rs734784 “valine risk allele” → significantly associated with higher pain scores in lumbar radiculopathy, sciatica, phantom limb
  - not in post-mastectomy and post-surgery pain cohorts
  - additive risk profile → two copies confer the most, one intermediate and none the least risk

Allelic frequency 18–22% of the population homozygous, 50% heterozygous
SCN9A (Nav1.7) polymorphism can influence pain perception

- R1550W → Slow inactivation at more positive potentials than fast inactivation and reached only ~80%.
- Carriers more sensitive to C-fiber–mediated heat pain
- Minor allele frequency 17.8%

<table>
<thead>
<tr>
<th>Cohort</th>
<th>No. of affected individuals</th>
<th>rs6746030 allele for which most pain was felt</th>
<th>P value for A allele association</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Osteoarthritis</td>
<td>578</td>
<td>A</td>
<td>0.016*</td>
</tr>
<tr>
<td>2. Sciatica</td>
<td>195</td>
<td>A</td>
<td>0.039*</td>
</tr>
<tr>
<td>3. Postamputation</td>
<td>100</td>
<td>A</td>
<td>0.011*</td>
</tr>
<tr>
<td>4. Postdiscectomy</td>
<td>179</td>
<td>A</td>
<td>0.088</td>
</tr>
<tr>
<td>5. Chronic</td>
<td>205</td>
<td>A = G</td>
<td>0.732</td>
</tr>
<tr>
<td>6. Meta-analysis</td>
<td>1257</td>
<td>A</td>
<td>0.0001*</td>
</tr>
</tbody>
</table>
Unravelling individual susceptibility to neuropathic pain

- Animal models provided possible links between pain and channel dysregulation (altered expression; post-translational changes; trafficking)

- Unknown to what extent animal pain models reflect human pain

- Need of focused studies in humans
The model of Small Fiber Neuropathy

- Defined clinical condition
- Neuropathic pain common and severe
- Frequent in diabetes
SMALL FIBER NEUROPATHY

Spontaneous pain
- Burning
- Deep pain
- Paroxysmal pain
- Cold sensation
- Itch

Evoked pain
- Thermal alldynia (>warm)
- Dynamic mechanic alldynia
- Hyperalgia
- Aftersensation

Somatic
- Thermal hypoesthesia
- Pinprick hypoesthesia

Autonomic
- Cholinergic (xerofthalmia, xerostomia, impotence, constipation, blurred vision, altered sweating)
- Adrenergic (orthostatic hypotension, no heart frequency increase, skin vessel impairment, impaired ejaculation)

Normal large fiber function
- Deep tendon reflexes
- Tactile & proprioceptive sensation
- SNAP amplitude

Incidence 12/100,000
Prevalence 53/100,000
Small nerve fibers

- Aδ and C fibers are the largest class of nerves in mammals
  - provide information from somatic and autonomic organs
- Cannot be examined by routine NCS
  - Very slow conduction velocity leading to signal dispersion
DRG neurons

- Aδ and C fibers originate from small and medium-size neurons in DRG
- Most small-size DRG neurons are nociceptors (TRPV1 positive)

*TRPV1 staining in human DRG, spinal cord, roots*
DRG neuron segregation during development
• Neurogenesis → Neurogenin 1
• TrkA and Runx1 expression promote the differentiation

• Upper epidermal layer → high NGF → high Runx1 and Ret (non-peptidergic - IRet)
• Lower epidermal layer → low NGF → low Runx1 and high CGRP (peptidergic - ITrkA)
Genetic Control of the Segregation of Pain-Related Sensory Neurons Innervating the Cutaneous versus Deep Tissues

Fu-Chia Yang,1,2 Taralyn Tan,2 Tianwen Huang,1,2 Julie Christianson,3,4 Omar A. Samad,1,2,5 Yang Liu,1,2,6 David Roberson,2 Brian M. Davis,3 and Qiufu Ma1,2,6

Cell Reports 5, 1353–1364, December 12, 2013
Sensory endings in the skin

Karen Z. Rhoads, Benjamin R. Nelson, and John D. O'Leary

Introduction

The somatosensory system serves three major functions: cutaneous, proprioceptive, and interoceptive. The cutaneous system is responsible for the sensation of touch, pressure, temperature, and pain. It is composed of primary afferent neurons that transmit information from the skin, muscles, and tendons to the spinal cord and brain. The primary afferent neurons are categorized into four types based on their conduction velocities and response properties: slow-adapting (SA), rapid-adapting (RA), slowly adapting (SA), and rapidly adapting (RA). These neurons are responsible for conveying information about the world outside the body, including the location and intensity of tactile stimuli. The somatosensory system also plays a crucial role in the perception of pain, as it helps to distinguish between innocuous and noxious stimuli.

Sensory neurons called low-threshold mechanoreceptors (LTMRs) are responsible for conveying information about the tactile world. LTMRs are a subset of primary afferent neurons that are particularly sensitive to light touch and are associated with hair follicles. They are divided into three subtypes: Aβ-LTMRs, Aδ-LTMRs, and C-LTMRs based on their conduction velocities and response properties. Aβ-LTMRs are the fastest-conducting LTMRs and are particularly sensitive to gentle touch, while C-LTMRs are the slowest-conducting LTMRs and are particularly sensitive to noxious stimuli.

LTMRs are integrated and processed in somatotopically aligned mechanosensory columns of the spinal cord. The sensory information from LTMRs is transmitted to the brain, where it is further processed and integrated to allow for perception of the tactile world. This information is crucial for social exchange and the perception of objects, as it allows us to distinguish between different textures and surfaces. The somatosensory system also plays a crucial role in sensory-motor feedback, as it helps to coordinate movements and maintain balance.

The tactile world is rich, if not infinite. The flutter of an insect's wings, a warm breeze, a sudden pinch, or a mother's gentle caress all provide information about the environment and our body's interactions with it. The somatosensory system decodes a wide range of tactile stimuli and thus endows us with a remarkable capacity for object recognition, texture discrimination, sensory-motor feedback, and social exchange. Understanding the neurophysiological mechanisms underlying the processing of tactile information is crucial for developing effective treatments for disorders affecting the somatosensory system.
Sensory endings in the skin

- Lanceolate endings trigger TrkB; TH
- Lanceolate endings trigger TrkB; TH; Ret/MafA
- Lanceolate endings trigger Ret/MafA
- Circular nerve endings trigger TrkB; TrkA/CGRP
- Merkel cells trigger TrkB (?)
- Free nerve endings trigger TrkA/CGRP
- Pacinian corpuscle triggers Ret/MafA
- Free nerve endings trigger Ret/IB4/Runx1
- Meissner corpuscle triggers Ret/MafA
- Merkel cells trigger TrkB (?)

Innocuous touch information is processed by both glabrous (hairless, skin) and hairy skin (hairy skin) and are characterized by both A and C fibers. Zigzag hair follicles are the shortest and are innervated by both C- and A fibers. Guard hairs are short and sensitive to heat. Awl/Auchene hairs are triply circumferential lanceolate endings whose physiological properties remain unknown. The first step leading to perception of innocuous touch is activation of cutaneous endings in the skin. Merkel cells are specialized glabrous ending. Their well-recognized RAII-LTMR responses detect high frequency vibration. Pacinian corpuscles are located in the dermis of glabrous skin where its characteristic onion-shaped structure helps in reconstructing acute spatial images of tactile stimuli. Meissner corpuscles are localized in the sub-epidermal zone and respond best to skin stretch, though such correlations remain highly controversial. Lastly, hair mechanoreceptors respond best to skin stretch.

Victoria E. Abraira and David D. Ginty
Neuron. 2013 August 21; 79(4)
Dorsal horn organization of functionally different sensory fibers
• Negatively regulate pain and touch pathways through both pre- and postsynaptic inhibition
• Reciprocal inhibition $\rightarrow$ switch between pain and touch pathways
Sural nerve biopsy

Remak bundle
Skin biopsy

- Unmyelinated axon
- Remak bundle
Epidermal nerve fibres (hairy and glabrous skin)

Naked axons *(no Schwann cell ensheathment)*
Epithelial nerve fibres (mucosae)

Naked axons (*no Schwann cell ensheathment*)

Pain 115 (2005) 332–337
Bulbar-like ending of Messner corpuscles for mechano-electric trasduction of tactile stimuli

Nolano et al, Ann Neurol 2003
The axon–cell network

Adapted from

Mechanisms of sensory transduction in the skin

Ellen A. Lumpkin¹ & Michael J. Caterina²

NATURE|Vol 445|22 February 2007
“Cold” fibers

- **Aδ fibers** have a primary role in conveying cold sensation.
  - activated by static innocuous temperature between 20° and 30°C and menthol
  - Adaptation to repetitive stimuli

- **C fibers** also respond to cold stimuli → after A-fiber block, menthol induces cold hyperalgesia, burning pain, and flare reaction.
  - might provide information for unconscious thermoregulation (e.g. warning for potentially dangerous temperatures)
  - inhibited by touch and Aδ cold fibers

- **Aβ fibers** innervating Merkel and Ruffini pressure mechanoceptors respond to cold stimuli down to 14.5°C
  - illusionary perception that an object is heavier when cold rather than warm

- **Cold becomes painful** when
  - hairy skin between 10 and 15°C
  - glabrous skin below 18°C
“Warm” fibers

• **C fibers** have a primary role in conveying warmth.
  – activated by static temperatures >30°C with maximal discharge rate at 40-43°C.
  – Adaptation to repetitive stimuli

• **Aδ fibers** involved in heat pain sensation are classified in:
  – **type I**: glabrous and hairy skin; respond to short lasting high temperatures (>53°C).
  – **type II**: hairy skin (lack of first sharp heat pain); lower threshold (47 °C); respond to long lasting stimulation with an adaptation during the response.

• **Noxious heat** → in glabrous skin instantaneous sharp and pricking pain followed by a later dull and burning sensation
  – Fast pain → Aδ fibers
  – Long latency pain → C fibers
Characterization of epidermal nerve fibers

Widely express the capsaicin (TRPV1) receptor (nociceptors)
IENF density at the distal leg: a worldwide normative reference study for clinical use

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Number of Subjects</th>
<th>Females (n=285)</th>
<th>Males (n=265)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.05 quantile IENFD values per age span</td>
<td>median IENFD values per age span</td>
</tr>
<tr>
<td>20 – 29</td>
<td>57</td>
<td>8.4</td>
<td>13.5</td>
</tr>
<tr>
<td>30 – 39</td>
<td>47</td>
<td>7.1</td>
<td>12.4</td>
</tr>
<tr>
<td>40 – 49</td>
<td>70</td>
<td>5.7</td>
<td>11.2</td>
</tr>
<tr>
<td>50 – 59</td>
<td>59</td>
<td>4.3</td>
<td>9.8</td>
</tr>
<tr>
<td>60 – 69</td>
<td>32</td>
<td>3.2</td>
<td>8.7</td>
</tr>
<tr>
<td>70 – 79</td>
<td>16</td>
<td>2.2</td>
<td>7.6</td>
</tr>
<tr>
<td>≥ 80</td>
<td>4</td>
<td>1.6</td>
<td>6.7</td>
</tr>
</tbody>
</table>

- Decrease 0.9 IENF/mm per decade
- Height does not influence IENFD densities in men or women
- Weight and BMI inversely correlate with IENF density in men
  - 12% variation (R²=0.12; p<0.001)
A multi-center, multinational age- and gender-adjusted normative dataset for immunofluorescent intraepidermal nerve fiber density at the distal leg

V. Provitera\textsuperscript{a}, C. H. Gibbons\textsuperscript{b}, G. Wendelschafer-Crabb\textsuperscript{c}, V. Donadio\textsuperscript{d}, D. F. Vitale\textsuperscript{a}, A. Stancanelli\textsuperscript{a}, G. Caporaso\textsuperscript{a}, R. Liguori\textsuperscript{d}, N. Wang\textsuperscript{b}, L. Santoro\textsuperscript{e}, W. R. Kennedy\textsuperscript{c} and M. Nolano\textsuperscript{a}

**Table 3.**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>18–29</th>
<th>30–39</th>
<th>40–49</th>
<th>50–59</th>
<th>60–69</th>
<th>&gt;70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>11.9 (11.1–12.7)</td>
<td>11.4 (10.8–12.0)</td>
<td>10.8 (10.3–11.4)</td>
<td>10.3 (9.8–10.8)</td>
<td>9.8 (9.2–10.3)</td>
<td>9.2 (8.5–9.9)</td>
</tr>
<tr>
<td>Male</td>
<td>10.9 (10.1–11.6)</td>
<td>10.3 (9.7–11.0)</td>
<td>9.8 (9.3–10.3)</td>
<td>9.3 (8.8–9.8)</td>
<td>8.7 (8.2–9.3)</td>
<td>8.2 (7.5–8.9)</td>
</tr>
</tbody>
</table>

Cutoffs are referred to the midpoint of each decade and their 95% CIs (in parentheses) are reported for male and female.

- Decrease 0.54 IENF/mm per decade
- **BMI and ethnicity** do not influence IENF densities

**Figure 3.** Gender-specific cutoffs greater than males.

**Figure 2.** Gender-specific cutoffs greater than females.
Epidermal innervation morphometry by immunofluorescence and bright-field microscopy

<table>
<thead>
<tr>
<th></th>
<th>Age (years)</th>
<th>Sex (M/F)</th>
<th>IENF/mm IF</th>
<th>IENF/mm BFI</th>
</tr>
</thead>
<tbody>
<tr>
<td>SFN</td>
<td>58.7 ± 13</td>
<td>31/32</td>
<td>9.4 ± 4.8</td>
<td>4.6 ± 2.8</td>
</tr>
<tr>
<td>Healthy subject</td>
<td>42.6 ± 14</td>
<td>28/27</td>
<td>13.2 ± 4.2</td>
<td>6.9 ± 2.6</td>
</tr>
</tbody>
</table>

BFI/IF ratio = 1:2

Diagnostic agreement = 93.3%

(<1 IENF from 5th cut-off tolerated)
Side and time variability of intraepidermal nerve fiber density

40 SFN patients and 17 healthy subjects → bilateral biopsies
15 SFN patients and 8 healthy subjects → 20-day follow-up biopsies

Unilateral skin biopsy can reliably diagnose SFN and IENFD is not expected to vary within 3 weeks
QST vs IENF density

- QST WDT+CDT (Levels)
  - Sens. 85.8
  - Spec. 77.8

- IENF density DL
  - Sens. 92.2
  - Spec. 90.1
QST individual sensory profile

Subgroup 1
DPN 13%
PHN 34%

Subgroup 2
DPN 16%
PHN 11%

Subgroup 3
DPN 37%
PHN 25%

Subgroup 4
DPN 9%
PHN 24%

Subgroup 5
DPN 26%
PHN 5%

Not related to the etiology
Normative Values for Corneal Nerve Morphology Assessed Using Corneal Confocal Microscopy: A Multinational Normative Data Set

Mitra Tavakoli,1 Maryam Ferdousi,1 Ioannis N. Petropoulos,1 Julie Morris,2 Nicola Pritchard,3 Andrey Zhivot,4 Dan Ziegler,5,6 Danièle Pacaud,7 Kenneth Romanchuk,2 Bruce A. Perkins,8 Leif E. Lovblom,8 Vera Bril,9 J. Robinson Singleton,10 Gordon Smith,10 Andrew J.M. Boulton,1 Nathan Efron,3 and Rayaz A. Malik1,11

Diabetes Care 2015;38:838–843 | DOI: 10.2337/dc14-2311

Table 3—Corneal nerve parameter cutoff points for clinical use

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Female subjects</th>
<th>Male subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.05th quantile</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CNFD (no./mm²)</td>
<td>CNBD (no./mm²)</td>
</tr>
<tr>
<td>&lt;16</td>
<td>23.98</td>
<td>46.52</td>
</tr>
<tr>
<td>16–25</td>
<td>20.07</td>
<td>34.01</td>
</tr>
<tr>
<td>46–55</td>
<td>13.91</td>
<td>16.47</td>
</tr>
</tbody>
</table>
Small Nerve Fiber Quantification in the Diagnosis of Diabetic Sensorimotor Polyneuropathy: Comparing Corneal Confocal Microscopy With Intraepidermal Nerve Fiber Density

Diabetes Care 2015;38:1138–1144 | DOI: 10.2337/dc14-2422

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control subjects ( n = 26 )</th>
<th>DSPN(−) ( n = 46 )</th>
<th>DSPN(+) ( n = 17 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>44 ± 15</td>
<td>44 ± 13</td>
<td>59 ± 11</td>
</tr>
</tbody>
</table>

Table 2—AUC, 95% CI values, and sensitivity-specificity for manual and automated CCM and IENFD for the diagnosis of DSPN

<table>
<thead>
<tr>
<th></th>
<th>Manual</th>
<th>Automated</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUC</td>
<td>95% CI</td>
<td>Sensitivity-specificity at equal-error rate</td>
</tr>
<tr>
<td>Manual</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNFD</td>
<td>0.82</td>
<td>0.68–0.95</td>
<td>0.76</td>
</tr>
<tr>
<td>CNFL</td>
<td>0.70</td>
<td>0.54–0.85</td>
<td>0.71</td>
</tr>
<tr>
<td>CNBD</td>
<td>0.59</td>
<td>0.43–0.75</td>
<td>0.53</td>
</tr>
<tr>
<td>Automated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNFD</td>
<td>0.80</td>
<td>0.66–0.93</td>
<td>0.70</td>
</tr>
<tr>
<td>CNFL</td>
<td>0.77</td>
<td>0.63–0.91</td>
<td>0.70</td>
</tr>
<tr>
<td>CNBD</td>
<td>0.70</td>
<td>0.55–0.86</td>
<td>0.59</td>
</tr>
<tr>
<td>IENFD</td>
<td>0.66</td>
<td>0.50–0.82</td>
<td>0.65</td>
</tr>
</tbody>
</table>

Readers may use this article as long as the work is correctly cited, and the work is not altered.
Greater corneal nerve loss at the inferior whorl is related to the presence of diabetic neuropathy and painful diabetic neuropathy

Alise Kalteniece¹, Maryam Ferdousi¹, Ioannis Petropoulos², Shazli Azmi¹, Safwaan Adam¹, Hassan Fadavi¹, Andrew Marshall¹, Andrew J. M. Boulton¹, Nathan Efron³, Catharina G. Faber¹, Giuseppe Lauria⁵,⁶, Handrean Soran¹ & Rayaz A. Malik¹,²
Small fibre neuropathy: role in the diagnosis of diabetic sensorimotor polyneuropathy


Criteria for the diagnosis of SFN

1. Possible
   Symptoms or clinical signs

2. Probable
   Symptoms + clinical signs + normal sural NCS

3. Definite
   Symptoms + clinical signs + normal sural NCS + decreased IENF at the ankle and/or abnormal QST at the foot
SFN etiology

**Curr Opin Neurol 2017, 30:490–499**

<table>
<thead>
<tr>
<th><strong>ACQUIRED</strong></th>
<th>Diabetes and IGT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td></td>
<td>Folate deficiency</td>
</tr>
<tr>
<td></td>
<td>Vitamin B₁₂ deficiency</td>
</tr>
<tr>
<td></td>
<td>Treatment-induced in diabetes</td>
</tr>
<tr>
<td></td>
<td>Metabolic syndrome</td>
</tr>
<tr>
<td><strong>Infectious</strong></td>
<td>HIV</td>
</tr>
<tr>
<td></td>
<td>Hepatitis C</td>
</tr>
<tr>
<td></td>
<td>Chagas disease</td>
</tr>
<tr>
<td><strong>Drugs and toxins</strong></td>
<td>Metronidazole</td>
</tr>
<tr>
<td></td>
<td>Nitrofurantoin</td>
</tr>
<tr>
<td></td>
<td>Linezolid</td>
</tr>
<tr>
<td></td>
<td>Statins</td>
</tr>
<tr>
<td></td>
<td>Bortezomib</td>
</tr>
<tr>
<td></td>
<td>TNF inhibitor</td>
</tr>
<tr>
<td></td>
<td>Alcohol</td>
</tr>
<tr>
<td></td>
<td>Thallium</td>
</tr>
<tr>
<td><strong>Immune-mediated</strong></td>
<td>Sjogren’s syndrome</td>
</tr>
<tr>
<td></td>
<td>Celiac disease</td>
</tr>
<tr>
<td></td>
<td>Sarcoïdosis</td>
</tr>
<tr>
<td></td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td></td>
<td>Inflammatory bowel diseases</td>
</tr>
<tr>
<td></td>
<td>Monoclonal gammopathy</td>
</tr>
<tr>
<td><strong>HEREDITARY</strong></td>
<td>Sodium channelopathies (SCN9A; SCN10A; SCN11A)</td>
</tr>
<tr>
<td></td>
<td>Familial amyloidosis</td>
</tr>
<tr>
<td></td>
<td>Fabry disease</td>
</tr>
<tr>
<td></td>
<td>COL6A5 mutations</td>
</tr>
<tr>
<td><strong>SYNDROMIC</strong></td>
<td>Fibromyalgia</td>
</tr>
<tr>
<td></td>
<td>Ehlers–Danlos syndrome</td>
</tr>
<tr>
<td></td>
<td>Parkinson’s disease</td>
</tr>
<tr>
<td></td>
<td>Amyotrophic lateral sclerosis</td>
</tr>
<tr>
<td></td>
<td>Pompe disease</td>
</tr>
<tr>
<td><strong>IDIOPATHIC</strong></td>
<td>Unknown</td>
</tr>
</tbody>
</table>
Unraveling neuropathic pain susceptibility using the model of Small Fiber Neuropathy

Neuropathic pain occurs in 20% of diabetic neuropathy

Research hypotheses

• Stratification by diagnosis irrespective of pain features
• Genotype-phenotype in painful vs painless diabetic neuropathy
### “Peripheral” Sodium Channel alfa-subunits

<table>
<thead>
<tr>
<th>Name</th>
<th>Further Names</th>
<th>Gene</th>
<th>TTX Sensitive?</th>
<th>Localisation</th>
<th>Inactivation Rate</th>
<th>Disease link</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nav1.1</td>
<td>Type 1</td>
<td>SCN1A</td>
<td>Yes</td>
<td>CNS, DRG</td>
<td>Fast</td>
<td>Epilepsy</td>
</tr>
<tr>
<td>Nav1.2</td>
<td>Type 2</td>
<td>SCN2A2</td>
<td>Yes</td>
<td>CNS</td>
<td>Fast</td>
<td>Epilepsy</td>
</tr>
<tr>
<td>Nav1.3</td>
<td>Type 3</td>
<td>SCN3A</td>
<td>Yes</td>
<td>Embryonic CNS, injured DRG</td>
<td>Fast</td>
<td>Ectopic discharge in neuropathic pain</td>
</tr>
<tr>
<td>Nav1.4</td>
<td>Skm1</td>
<td>SCN4A</td>
<td>Yes</td>
<td>Skeletal muscle</td>
<td>Fast</td>
<td>Contractility problems</td>
</tr>
<tr>
<td>Nav1.5</td>
<td>H1, Skm2</td>
<td>SCN5A</td>
<td>Moderate</td>
<td>Heart, embryonic CNS</td>
<td>Slow</td>
<td>Cardiac arrhythmias</td>
</tr>
<tr>
<td>Nav1.6</td>
<td>PN4, CerIII</td>
<td>SCN8A</td>
<td>Yes</td>
<td>DRG, motor neurons</td>
<td>Fast</td>
<td>Neurological dysfunction</td>
</tr>
<tr>
<td>Nav1.7</td>
<td>PN1, hNe, NaS</td>
<td>SCN9A</td>
<td>Yes</td>
<td>DRG, low levels in CNS</td>
<td>Fast</td>
<td>Peripheral transmission</td>
</tr>
<tr>
<td>Nav1.8</td>
<td>PN3, SNS</td>
<td>SCN10A</td>
<td>No</td>
<td>DRG</td>
<td>Slow</td>
<td>Sensory hypersensitivity</td>
</tr>
<tr>
<td>Nav1.9</td>
<td>PN5, NaN, SNS-2</td>
<td>SCN11A</td>
<td>No</td>
<td>DRG, low levels in hippocampus</td>
<td>Slow</td>
<td>Modulates resting potential in DRG, linked to hyperalgesia</td>
</tr>
</tbody>
</table>
Sodium channel subtypes in the electrogenesis

Major: $Na_v^{1.8}$
Minor: $Na_v^{1.1/1.6/1.7}$

Threshold

$Na_v^{1.7}$
$Na_v^{1.6}$
$Na_v^{1.9}$
Sodium channels and transient currents: distinct subunits, different properties

Nav_1.1, 1.2, 1.3
1.4, 1.6, 1.7

Nav_1.8

Nav_1.5

Nav_1.9

Current-voltage relationship

Steady-state inactivation

MODIFIED FROM DIB-HAJJ ET AL., 2002, TINS
Nav1.7 mutations in the spectrum of pain disorders

Gain-of-function missense mutations

Loss-of-function nonsense mutations
Congenital insensitivity to pain

- **HSAN IV (NTRK) and HSAN V (NGF)**
  - Anhidrosis
  - Cognitive impairment

  - Anosmia
  - No dysautonomia
  - Normal large sensory fibers and CNS (normal intelligence)

  - Congenital or adolescent-onset
  - Variable anosmia
  - Anhidrosis
  - Large sensory fibre loss (reduced SNAP amplitudes)

- **Nav1.9** Leipold E et al. Nat Genet 2013; 45: 1399–404.
  - Congenital onset
  - No neuropathy; impaired nociceptive transmission into CNS
  - No anosmia
  - Normal cognitive development
  - Mild muscular weakness
  - Hyperhidrosis (no cardiovascular autonomic dysfunction)
  - Severe gastrointestinal dysfunction
Inherited Erythromelalgia

- Nav1.7 mutations induce abnormal channel activation and increase response to small depolarizing stimuli

- Nav1.7 mutations have divergent effects on neurons
  - hyperexcitability of DRG neurons
  - hypoexcitability of sympathetic ganglion neurons

- Nav1.7 mutants display greater biophysics changes at higher temperature
  - extreme sensitivity to pain and warm stimuli

- Mexiletine is effective in most patients
Paroxysmal extreme pain disorder

- Described in 1959 as familial rectal pain
- NAV1.7 mutations impair channel inactivation
- Paroxysmal episodes of severe perineal and rectal, ocular and mandibular pain presenting at birth or in infancy
- Autonomic dysfunctions
  - flushing, lacrimation, rhinorrhea, tonic attacks with apnoea and bradycardia
- Mechanical triggers
  - Defecation, urination, eating, strong emotions
- Frequency of rectal pain episodes falls with increasing age, while ocular and mandibular pain becomes more common
- Carbamazepine is effective in most patients.
Sodium channel-related SFN
a new syndrome in the spectrum of pain disorders

Gain of Function Na\textsubscript{v}1.7 Mutations in Idiopathic Small Fiber Neuropathy
ANN NEUROL 2012;71:26–39

Gain-of-function Na\textsubscript{v}1.8 mutations in painful neuropathy
PNAS | November 20, 2012 | vol. 109 | no. 47

Gain-of-function mutations in sodium channel Na\textsubscript{v}1.9 in painful neuropathy
Brain 2014: 137; 1627–1642
Sodium channel-related painful neuropathies

- Most sporadic, some familial
- Variable age onset (<15 to >70 y/o)

- Idiopathic and diabetic neuropathies

- Painful symptoms
  - Length-dependent pure SFN or small and large neuropathy
  - New phenotypes (proximal pain; episodic pain; itch)

- Dysautonomia in some patients
  - Skin vascular changes, orthostatic dizziness, gastrointestinal disturbances, cardiac dysrhythmias; blood pressure fluctuations, diarrhoea, urge incontinence, abdominal discomfort, hot flashes, hyperhidrosis

- Biophysics-genotype-phenotype correlation for some mutations
5 patients with severe painful SFN

- 3 patients with I739V $\rightarrow$ dysautonomia
- 2 patients with R185H $\rightarrow$ no dysautonomia

- R185H and I739V $\rightarrow$ hyperexcitable DRG neurons $\rightarrow$ pain

- I739V $\rightarrow$ hypoexcitable sympathetic neurons $\rightarrow$ dysautonomia
Patients with small fibre neuropathy typically manifest pain in distal extremities and severe autonomic dysfunction. However, occasionally patients present with minimal autonomic symptoms. The basis for this phenotypic difference is not understood. Sodium channel Nav1.7, encoded by the SCN9A gene, is preferentially expressed in the peripheral nervous system within sensory dorsal root ganglion and sympathetic ganglion neurons and their small diameter peripheral axons. We recently reported missense substitutions in SCN9A that encode functional Nav1.7 variants in 28% of patients with biopsy-confirmed small fibre neuropathy. Two patients with biopsy-confirmed small fibre neuropathy manifested minimal autonomic dysfunction unlike the other six patients in this series, and both of these patients carry the Nav1.7/R185H variant, presenting the opportunity to compare variants associated with extreme ends of a spectrum from minimal to severe autonomic dysfunction. Herein, we show by voltage-clamp that R185H variant channels enhance resurgent currents within dorsal root ganglion neurons and show by current-clamp that R185H renders dorsal root ganglion neurons hyperexcitable. We also show that in contrast, R185H variant channels do not produce detectable changes when studied by voltage-clamp within sympathetic neurons of the superior cervical ganglion, and have no effect on the excitability of these cells. As a comparator, we studied the Nav1.7 variant I739V, identified in three patients with small fibre neuropathy characterized by severe autonomic dysfunction as well as neuropathic pain, and show that this variant impairs channel slow inactivation within both dorsal root ganglion and superior cervical ganglion neurons, and renders dorsal root ganglion neurons hyperexcitable and superior cervical ganglion neurons hypoexcitable. Thus, we show that R185H, from patients with minimal autonomic dysfunction, does not produce detectable changes in the properties of sympathetic ganglion neurons, while I739V, from patients with severe autonomic dysfunction, has a profound effect on excitability of sympathetic ganglion neurons.
COL6A5 variants in familial neuropathic chronic itch

Filippo Martinelli-Boneschi,¹,* Marina Colombi,²,* Marco Castori,³ Grazia Devigli,⁴ Roberto Eleopra,⁴ Rayaz A. Malik,⁵ Marco Ritelli,² Nicoletta Zoppi,² Chiara Dordoni,² Melissa Sorosina,¹ Paola Grammatico,³ Hassan Fadavi,⁷ Monique M. Gerrits,⁶,⁷ Rowida Almomanii,⁶,⁷ Catharina G. Faber,⁶,⁷ Ingemar S. J. Merkies,⁶,⁷ Daniela Toniolo, for the INGI Network⁸ Massimiliano Cocca,⁹ Claudio Doglioni,¹⁰ Stephen G. Waxman,¹¹,¹² Sulayman D. Dib-Hajji,¹¹,¹² Michela M. Taiana,¹³ Jenny Sassone,¹³ Raffaella Lombardi,¹³ Daniele Cazzato,¹³ Andrea Zauli,¹ Silvia Santoro,¹ Margherita Marchi¹³ and Giuseppe Lauria¹³

Family 1

Family 2

Family 3

R2162

Homo sapiens
Mus musculus
Rattus norvegicus
Myotis lucifugus
Carassius auratus
Alligator mississippiensis
Mustela putorius furo
Peromyscus maniculatus
Sus scrofa
Ovis aries
Pan troglodytes
Gorilla gorilla
Nomascus leucogenys
Gallus gallus
Ovis aries
Cavia porcellus
Ornithorhynchus anatinus

K  P  F  L  Y  S  V  R  G  F  N  Q  Y  P
K  P  F  I  Y  S  V  R  G  F  N  Q  Y  P
K  P  F  V  Y  S  V  R  G  F  N  Q  Y  P
K  P  F  V  Y  S  V  R  G  F  N  Q  Y  P
K  P  L  Y  Y  I  R  G  F  N  Q  Y  P
K  P  V  Y  S  V  R  G  F  N  Q  Y  P
K  P  L  Y  Y  I  R  G  F  N  Q  Y  P
K  P  F  I  Y  S  V  R  G  F  N  Q  Y  P
K  P  F  I  Y  S  V  R  G  F  N  Q  Y  P
K  P  F  I  Y  S  V  R  G  F  N  Q  Y  P
K  P  F  I  Y  S  V  R  G  F  N  Q  Y  P
K  P  F  I  Y  S  V  R  G  F  N  Q  Y  P
K  P  F  I  Y  S  V  R  G  F  N  Q  Y  P
K  P  F  I  Y  S  V  R  G  F  N  Q  Y  P
K  P  F  I  Y  S  V  R  G  F  N  Q  Y  P
K  P  F  I  Y  S  V  R  G  F  N  Q  Y  P
Genetic profiling of voltage-gated sodium channels in painful and painless diabetic and idiopathic neuropathy
Inclusion criteria

- **Diabetic** small fiber neuropathy
- **Idiopathic** small fiber neuropathy

- **Painful** neuropathy → neuropathic pain for more than 1 year and PI-NRS ≥4 despite analgesic or before starting treatment
- **Painless** neuropathy → PI-NRS ≤3 and no need of treatment
Study population

Total sequenced samples: 1,217

Etiology and phenotype

<table>
<thead>
<tr>
<th></th>
<th>Painful</th>
<th>Painless</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic neuropathy</td>
<td>650</td>
<td>20</td>
</tr>
<tr>
<td>Diabetic neuropathy</td>
<td>230</td>
<td>317</td>
</tr>
</tbody>
</table>
VGSC variant rate

Diabetic

- 22% Mutated
- 78% Non mutated

Idiopathic

- 22% Mutated
- 78% Non mutated

Painful

- 22% Mutated
- 78% Non mutated

Painless

- 22% Mutated
- 78% Non mutated
Variant distribution according to etiology and phenotype

Total variants
N=302

Diabetic vs Idiopathic

Painful vs Painless
Diabetic N=79
Idiopathic N=93
## Painful variants distribution between phenotypes

<table>
<thead>
<tr>
<th>Subunit</th>
<th>Painful</th>
<th>Painless</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCN3A</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>SCN8A</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td>SCN9A</td>
<td>25%</td>
<td>8%</td>
</tr>
<tr>
<td>SCN10A</td>
<td>20%</td>
<td>38%</td>
</tr>
<tr>
<td>SCN11A</td>
<td>20%</td>
<td>19%</td>
</tr>
<tr>
<td>SCN7A</td>
<td>14%</td>
<td>11%</td>
</tr>
</tbody>
</table>

- **Painful N=142**
- **Painless N=37**
Variants distribution between aetiologies according to topological regions

<table>
<thead>
<tr>
<th></th>
<th>Diabetic</th>
<th>Idiopathic</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-terminus</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>Transmembrane</td>
<td>20%</td>
<td>24%</td>
</tr>
<tr>
<td>Loops</td>
<td>11%</td>
<td>18%</td>
</tr>
<tr>
<td>Voltage-sensor</td>
<td>5%</td>
<td>7%</td>
</tr>
<tr>
<td>Pore-forming</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Domain linkers</td>
<td>23%</td>
<td>29%</td>
</tr>
<tr>
<td>C-terminus</td>
<td>8%</td>
<td>7%</td>
</tr>
<tr>
<td>Beta-subunits</td>
<td>24%</td>
<td>7%</td>
</tr>
</tbody>
</table>
Variants distribution between phenotypes according to topological regions

<table>
<thead>
<tr>
<th>Region</th>
<th>Painful</th>
<th>Painless</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-terminus</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Transmembrane</td>
<td>18%</td>
<td>22%</td>
</tr>
<tr>
<td>Loops</td>
<td>19%</td>
<td>14%</td>
</tr>
<tr>
<td>Voltage-sensor</td>
<td>8%</td>
<td>11%</td>
</tr>
<tr>
<td>Pore-forming</td>
<td>2%</td>
<td>5%</td>
</tr>
<tr>
<td>Domain linkers</td>
<td>32%</td>
<td>11%</td>
</tr>
<tr>
<td>C-terminus</td>
<td>6%</td>
<td>16%</td>
</tr>
<tr>
<td>β-subunits</td>
<td>10%</td>
<td>16%</td>
</tr>
</tbody>
</table>
Plurimutated samples between Aetiologies

<table>
<thead>
<tr>
<th>Subunits</th>
<th>Diabetics</th>
<th>Idiopathics</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCN3A</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>SCN8A</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>SCN9A</td>
<td>8</td>
<td>19</td>
</tr>
<tr>
<td>SCN10A</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>SCN11A</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>SCN7A</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>β-subunits</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>
Plurimutated samples between phenotypes

<table>
<thead>
<tr>
<th>Subunit</th>
<th>Painful</th>
<th>Painless</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCN3A</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>SCN8A</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>SCN9A</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td>SCN10A</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>SCN11A</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>SCN7A</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>β-subunits</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>
Prediction of pathogenicity

Classification according to Wallis et al.
(conservation among mammal Nav-channels and Nav-paralogues, predictive algorithms, HGMD and SNP databases)
Class 1-5 system

Functional analyses  Co-segregation

Classification according to Waxman et al.
Categories: Pathogenic variant, Probably pathogenic variant, Possibly pathogenic variant, Variant with uncertain clinical significance, Variant unlikely to be pathogenic
Scoring system according to Wallis et al.

- **Class 1** = Clearly not pathogenic
- **Class 2** = Unlikely to be pathogenic
- **Class 3** = Unknown significance (VUS)
- **Class 4** = Likely to be pathogenic
- **Class 5** = Clearly pathogenic
Scoring system according to Waxman et al.

Panel: Classification of variants of SCN9A, SCN10A, and SCN11A

**Pathogenic**
- Multigenerational segregation with the disease in a family spanning more than three generations, and predictive algorithms unequivocally suggesting pathogenicity
- Multigenerational segregation with the disease in a family spanning more than three generations, and the variant displays gain-of-function changes by voltage-clamp or current-clamp studies, or both
- Segregation with the disease in a nuclear, single-generation family, and predictive algorithms unequivocally suggesting pathogenicity, and the variant displays gain-of-function changes by voltage-clamp and current-clamp studies
- A patient with insensitivity to pain has a homozygous nonsense variant or substitutions that disrupt the consensus splice sites (noting that voltage-gated sodium channel genes also have non-canonically spliced introns), or compound heterozygous mutations of nonsense or splicing-disrupting substitutions, with missense mutations shown as non-functional after voltage-clamp studies

**Probably pathogenic**
- Segregation with the disease in a nuclear, single-generation family and predictive algorithms unequivocally suggesting pathogenicity
- Segregation with the disease in a nuclear, single-generation family and the variant displays gain-of-function changes by voltage-clamp or current clamp studies
- Only one family member and the variant displays gain-of-function changes through voltage-clamp and current-clamp studies

**Possibly pathogenic**
- Predictive algorithms unequivocally suggest pathogenicity, but segregation cannot be tested or is unclear (eg, sporadic cases, with possible incomplete penetrance) and no functional studies are available
- Only one family member and the variant displays gain-of-function changes through voltage-clamp or current-clamp studies

**Variants with uncertain clinical significance**
- Variants for which predictive algorithms suggest pathogenicity, that do not belong to any of the previous categories should, in our opinion, be listed as having unknown clinical significance

Sodium channel genes in pain-related disorders: phenotype-genotype associations and recommendations for clinical use

Wallis – 3 in class 2 variants, 36 in class 3, 8 in class 4, none in class 1 or class 5.

Waxman - 36 are VUS, none clearly pathogenic, 6 possibly pathogenic, none was unlikely pathogenic, and 5 could not be classified for lack of voltage clamp and patch clamp data
Conclusions

• **Small fiber neuropathy** can be considered a reliable **model** to investigate individual **susceptibility** to neuropathic **pain**

• We identified **272 variants** in 5 VGSC α-subunits.

• **22% of patients carrying at least one variant in VGSC genes** regardless of either etiological or pain phenotype stratification.

• Higher frequency of **SCN9A variants in idiopathic** neuropathy patients and of **SCN10A variants in diabetic** neuropathy patients.

• Higher prevalence of **SCN10A variants in painless** neuropathy and of **SCN9A variants in painful** neuropathy.

• Data confirmed at the analysis of plurimutated patients.
Conclusions

- Variants in the **cytoplasmic linkers** between domains were the most represented in **painful** neuropathy, while variants in the **C-terminus** were more frequent in **painless** neuropathies.

- **Cytoplasmic linkers** are implicated in the **regulation of channel activity** being the preferential sites of phosphorylation by kinases, while the **C-terminus** contains sequences for **membrane localization**.

**To be done:**

- New pain-related genes & gene families

- Validation studies to correlate genotype-phenotype with best response to available drugs
Acknowledgements

University of Maastricht (NL)
- Catharina G. Faber
- Ingemar S.J. Merkies
- Monique Gerrits

University of Yale (USA)
- Stephen G. Waxman
- Sulayman Dib-Hajj

Weill Cornell Medicine-Qatar, &
University of Manchester, UK
- Rayaz Malik

German Diabetes Center, Heinrich Heine University
- Dan Ziegler

San Raffaele Scientific Institute,
Milan
- Filippo Martinelli Boneschi
- Silvia Santoro
- Andrea Zauli

IRCCS
Istituto Neurologico “Carlo Besta”
Milan, Italy

The Skin Biopsy Lab

- Raffaella Lombardi
- Francesca Caravello
- Matilde Paolini
- Daniele Cazzato
- Patrizia Dacci
- Laura Piccolo
- Eleonora Dalla Bella
- Roberto Bianchi
- Daniele Cartelli
- Margherita Marchi
- Ilaria D’Amico
January 21-25, 2019
STRUCTURE, DEVELOPMENT, FUNCTION
Neuroanatomy - Neurobiology

March 18-22, 2019
DIAGNOSTICS
Clinical Neurophysiology - Autonomic nervous system
Neuroimaging - Neuropathology and related techniques

May 13-17, 2019
PATHOPHYSIOLOGY, DIAGNOSIS, THERAPY, PROGNOSIS OF NEUROPATHIES
Metabolic and systemic disease-related neuropathies - Traumatic nerve injuries and nerve tumors Immune-mediated neuropathies - Amyloid-related neuropathies - Inherited neuropathies

May 13-17, 2019
FUNCTIONAL ASSESSMENT AND REHABILITATION
Rehabilitation

November 11-15, 2019
PAIN
Neuropathic pain - Brain plasticity - Headaches and other cranial pain disorders - Cancer pain

January 20-24, 2020
PATHOPHYSIOLOGY, DIAGNOSIS, THERAPY, PROGNOSIS OF MOTOR NEURON AND NMJ DISEASES
Amyotrophic lateral sclerosis and related diseases - Spinal muscular atrophy
Neuromuscular junction diseases
Tomorrow belongs to those who can hear it coming.  

David Bowie

FACULTY

Adriano Chiò
Ahmet Hoke
Alberto Priori
Alberto Proietti
Alessandra Bolino
Alessandro Furlan
Angelo Maravita
Angelo Poletti
Angelo Quararone
Antonio Uncini
Augusto Caraceni
Carla Taveggia
Carlo Antozzi
Caterina Bendotti
Catharina Faber
Chiara Briani
Christian Lettieri
Christoph Neuwirth
Daniele Ghezzi
David Vodusek
Davide Pareyson
Domenico D’Amico
Eduardo Nobile-Orazio
Elior Peles
Enrico Alfonsi
Ernesta Magistroni
Fiore Manganelli
Gabriele Mora
Giacomo Comi
Gianpaolo Merlini
Giampietro Schiavo
Giandomenico Iannetti
Giovanni Baranello
Giuseppe Lauria
Grazia Devigili

Guido Cavaletti
Hugh Willison
Ingemar Merkies
Ivano Dones
Jordi Serra
Kai Rössler
Licia Grazzi
Lorenzo Maggi
Luca Padua
Luigi Tesio
Marco Sinisi
Maria Saraiva
Mary Reilly
Massimiliano Valeriani
Massimo Leone
Matilde Laurà
Mingdong Zhang
Paolo Confalonieri
Paolo Girlanda
Peter Brophy
Pieter van Doorn
Pietro Cortelli
Rayaz Malik
Renato Mantegazza
Roberto Eleopra
Roberto Gasparotti
Rocco Quatrale
Roy Freeman
Stefano Previtali
Stephen Waxman
Susanna Usai
Tiziana Cavallaro
Valeria Tugnoli
Vidmer Scaioli
Vincenzo Silani

SPONSOR

CSL Behring
Biotherapies for Life™

KEDRION
BIOPHARMA

BiOMARIN

GRUNENTHAL

David Bowie