Genetics of pain: From rare Mendelian disorders to genetic predisposition to pain

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Abstract. Background and aim of the work: Pain is defined by the International Association for the Study of Pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”. In this mini-review, we focused on the Mendelian disorders with chronic pain as the main characteristic or where pain perception is disrupted, and on the polymorphisms that can impart susceptibility to chronic pain. Methods: We searched PubMed and Online Mendelian Inheritance in Man (OMIM) databases and selected only syndromes in which pain or insensitivity to pain were among the main characteristics. Polymorphisms were selected from the database GWAS catalog (https://www.ebi.ac.uk/gwas/home). Results: We retrieved a total of 28 genes associated with Mendelian inheritance in which pain or insensitivity to pain were the main characteristics and 70 polymorphisms associated with modulation of pain perception. Conclusions: This mini-review highlights the importance of genetics in phenotypes characterized by chronic pain or pain insensitivity. We think that an effective genetic test should analyze all genes associated with Mendelian pain disorders and all SNPs that can increase the risk of pain. (www.actabiomedica.it)

Key words: chronic pain; pain insensitivity; genetic predisposition; polymorphism

Introduction

Pain is defined by the International Association for the Study of Pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (1). In physiological conditions, pain is necessary as a warning of potential harm or of disease or damage requiring appropriate behavior or measures (2). Pain perception is termed nociception. The neurons (nociceptors) that detect noxious stimuli (extreme heat or cold, mechanical and chemical signals) and transmit them to the spinal cord are located in the dorsal root ganglia and are connected by nerve fibers to nerve terminals in the skin and soft tissue (3). Nociception occurs through transmembrane receptors in nerve terminals. The stimuli are converted into action potentials and transmitted to the dorsal horn of the spinal cord (4).

Although the role of pain is universal, its perception can vary greatly between individuals on the basis of environmental and genetic factors (5). Pain sensitivity, susceptibility to chronic pain and response to pain treatment may differ between populations and genders (6,7).

In this mini-review, we focused on the genetic basis of pain. We describe Mendelian genetic disorders with chronic pain as the main characteristic or
where pain perception is disrupted. Finally, we focused on polymorphisms that can impart susceptibility to chronic pain.

Methods

We searched PubMed for articles in English using the following keywords: (((genetic pain[Title/Abstract]) AND pain syndrome[Title/Abstract]) OR insensitivity to pain[Title/Abstract]) OR chronic pain predisposition[Title/Abstract]. We only considered articles regarding human subjects and for which the full text was available. The articles retrieved were filtered to obtain only articles on the genetics of pain. The reference lists were checked to find other relevant publications. We also searched the Online Mendelian Inheritance in Man (OMIM) database for the word “pain” among records that included a clinical synopsis. We only selected syndromes in which pain or insensitivity to pain were among the main characteristics. Polymorphisms were selected from the database GWAS catalog (https://www.ebi.ac.uk/gwas/home) by using “pain” as keyword.

Mendelian disorders with chronic pain or pain insensitivity

We retrieved a total of 384 articles, 215 specifically dealing with pain. From these 215 articles, we selected those that described the genetics of pain. In OMIM, we found a total of 522 entries regarding disorders that featured the word pain in the clinical description; 423 mentioned an associated gene, but only 25 were disorders with Mendelian inheritance in which pain or insensitivity to pain were the main characteristics (Table 1).

Genetic predisposition to chronic pain

Individual sensitivity to chronic pain and the severity of chronic pain after neural injury and inflammation may be attributed to polymorphisms in specific genes (Table 2). Single nucleotide polymorphisms (SNPs), found in >1% of the population, modulate susceptibility to chronic pain and often exert their effects under specific environmental conditions. For instance, the minor allele of SNP Arg1150Trp; rs6746030 in SCN9A (encoding the Na.1.7 sodium channel) en-

Table 1. Genes found mutated in patients with syndromes characterized by painful manifestations or painlessness

| Gene   | OMIM gene ID | Disease                  | OMIM disease ID | Inheritance | Pain-related manifestation                                      |
|--------|--------------|--------------------------|-----------------|-------------|----------------------------------------------------------------|
| CSNK1D | *600864      | FASPS2                   | #615224         | AD          | Migraine with/without aura                                      |
| TRPA1  | *604775      | FEPS1                    | #615040         | AD          | Episodic pain in the upper body                                 |
| SCN10A | *604427      | FEPS2                    | #61551          | AD          | Episodic burning pain affecting distal lower extremities and hands; Hyperalgesia |
| SCN11A | *604385      | HSAN7                    | #61552          | AD          | Episodic pain localized to the distal extremities               |
|        |              |                          | #615548         | AD          | Insensitivity to pain                                           |
|        |              | Primary erythermalgia    | #133020         | AD          | Painful episodic reddish skin discoloration; Myalgia; Episodic burning pain in the hands and feet; itching |
|        |              | CIP                      | #243000         | AR          | Painless fractures; Distal painless ulcers; Isolated absence of pain sensation |
|        |              | Paroxysmal extreme pain disorder | #167400     | AD          | Episodic mandibular and submandibular pain triggered by eating and yawning; Episodic ocular pain; Episodico rectal pain triggered by defecation; Painful micturition; Episodic reddish discoloration associated with pain; Episodic skin flushing associated with pain; Episodic burning pain |

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Table 1 (continued). Genes found mutated in patients with syndromes characterized by painful manifestations or painlessness

| Gene    | OMIM gene ID | Disease | OMIM disease ID | Inheritance | Pain-related manifestation                                                                 |
|---------|--------------|---------|-----------------|-------------|------------------------------------------------------------------------------------------|
| NLRP3   | *606416      | FCAS1   | #120100         | AD          | Episodic arthralgia; Episodic myalgia; Episodic headache                                   |
| NLRP12  | *609648      | FCAS2   | #611762         | AD          | Episodic abdominal pain; Episodic arthralgias; Episodic arthritis; Episodic myalgia; Episodic headache |
| NLRC4   | *606831      | FCAS4   | #616115         | AD          | Episodic arthralgia                                                                      |
| NTRK1   | *191315      | CIPA    | #256800         | AR          | Diffuse pain insensitivity (including visceral pain)                                      |
| ZFHX2   | *617828      | MARSIS  | #147430         | AD          | Painless fractures; Painless cutaneous thermal burns; Pain insensitivity                  |
| SPTLC1  | *605712      | HSAN1A  | #162400         | AD          | Distal painless ulcers due to sensory neuropathy; Distal sensory loss of pain; Sharp, lightning-like pain |
| SPTLC2  | *605713      | HSAN1C  | #613640         | AD          | Distal painless ulcers due to sensory neuropathy; Distal sensory loss of pain              |
| WNK1    | *605232      | HSAN2A  | #201300         | AR          | Painless fractures due to injury; Impaired pain sensation in distal extremities           |
| FAM134B | *613114      | HSAN2B  | #613115         | AR          | Impaired pain sensation in distal extremities                                            |
| ELP1    | *603722      | HSAN3   | #223900         | AR          | Decreased pain perception                                                                |
| NGF     | *162030      | HSAN5   | #608654         | AR          | Distal pain insensitivity                                                                |
| DST     | *113810      | HSAN6   | #614653         | AR          | Decreased pain response                                                                 |
| PRDM12  | *616458      | HSAN8   | #616488         | AR          | Recurrent infections due to painless trauma and ulceration; Ulcerating painless lesions of distal extremities, tongue, lips; Insensitivity to pain |
| ATL1    | *606439      | HSN1D   | #613708         | AD          | Distal painless ulcers due to sensory neuropathy; Distal sensory loss of pain; Occasional lancinating pain |
| DNMT1   | *126375      | HSN1E   | #614116         | AD          | Sensory neuropathy affecting pain sensation in the lower/upper limbs; Occasional lancinating pain |
| ATL3    | *609369      | HSN1F   | #615632         | AD          | Distal painless ulcers due to sensory neuropathy; Distal sensory impairment to pain       |
| KIF1A   | *601255      | HSN2C   | #614213         | AR          | Ulceration and amputation of fingers and toes due to sensory loss; Panmodal distal sensory loss; Spontaneous pain |
| ATP1A2  | *182340      | FHM2    | #602481         | AD          | Migraine with/without aura                                                               |
| CACNA1A  | *601011     | FHM1    | #141500         | AD          | Migraine with/without aura                                                               |
| KCNK18  | *613655      | MGR13   | #613656         | AD          | Migraine headache with/without visual aura, lateralized or holocranial headache          |
| PRRT2   | *614386      | BFIS2   | #605751         | AD          | Migraine                                                                                 |
| SCN1A   | *182389      | FHM3    | #609634         | AD          | Migraine with/without aura                                                               |
| SLC2A1  | *138140      | DYT9    | #601042         | AD          | Migraine, headache                                                                       |

FASPS = familial advanced sleep phase syndrome; FEPS = familial episodic pain syndrome; FCAS = familial cold autoinflammatory syndrome; CIP = congenital autosomal recessive indifference to pain; CIPA = congenital insensitivity to pain with anhidrosis; MARSIS = Marsili syndrome; HSAN = hereditary sensory and autonomic neuropathy; HSN = hereditary sensory neuropathy.
Table 2. Polymorphisms associated with modulation of pain perception

| Gene  | Polymorphism; alleles (risk allele) | Pain-related manifestation                                           | Reference |
|-------|------------------------------------|---------------------------------------------------------------------|-----------|
| ABCC4 | rs4584690; T>A,C,G (T)             | Acute post-radiotherapy pain in breast cancer                       | [15]      |
| Intergenic | rs11786084; G>A (G)              | Multisite chronic pain                                               | [16]      |
| Intergenic | rs1443914; T>C (T)                | Multisite chronic pain                                               | [16]      |
| ANAPC4 | rs34811474; G>A,T (G)             | Multisite chronic pain                                               | [16]      |
| ASTN2  | rs6478241; A>G,T (A)              | Multisite chronic pain                                               | [16]      |
| BBX    | rs28428925; G>A (G)               | Multisite chronic pain                                               | [16]      |
| ILRUN  | rs6907508; A/G (A)                | Multisite chronic pain                                               | [16]      |
| GSDMC  | rs7833174; T>C,G (T)              | Chronic back pain                                                    | [17]      |
| Intergenic | rs13361160; T>C (C)              | Pain                                                                | [18]      |
| CEP120 | rs17474406; G>A (G)               | Multisite chronic pain                                               | [16]      |
| Intergenic | rs2006281; C>G,T (C)             | Multisite chronic pain                                               | [16]      |
| CTNN4L2| rs4852567; A>G,T (A)              | Multisite chronic pain                                               | [16]      |
| DCC    | rs4384683; G>A,C,T (G)            | Chronic back pain                                                    | [17]      |
| DIS3L2 | rs1453867; C,G,T (C)              | Chronic back pain                                                    | [17]      |
| Intergenic | rs17428041; T>C (T)              | Neuropathic pain in type 2 diabetes                                   | [19]      |
| DYNC1I1| rs6966540; T>A,C,G (T)            | Multisite chronic pain                                               | [16]      |
| Intergenic | rs73633565; A>G (G)              | Multisite chronic pain                                               | [16]      |
| FAF1   | rs10888692; C>G (C)               | Multisite chronic pain                                               | [16]      |
| Intergenic | rs12596162; C>A,T (A)            | Possible neuropathic pain in post total joint replacement surgery for osteoarthritis | [21] |
| FOXP2  | rs12537376; A>G,T (A)             | Multisite chronic pain                                               | [16]      |
| GABRB2 | rs1946247; T>G (T)                | Multisite chronic pain                                               | [16]      |
| GDF5   | rs143384; G>A (A)                 | Knee pain                                                            | [22]      |
|        | rs6120946; A>T (A)                | Knee pain                                                            | [22]      |
| GPD2   | rs298235; A>C,G,T (A)             | Possible neuropathic pain in post total joint replacement surgery for osteoarthritis | [21] |
| Intergenic | rs6986153; G>A,C,T (G)           | Neuropathic pain in type 2 diabetes                                   | [23]      |
| KCND3  | rs197422; C>A,G (C)               | Multisite chronic pain                                               | [16]      |
| KNDC1  | rs12765185; T>A (T)               | Multisite chronic pain                                               | [16]      |
| Intergenic | rs59898460; T>C,G (T)            | Multisite chronic pain                                               | [16]      |
| Intergenic | rs919642; A>T (A)                | Knee pain                                                            | [22]      |
| Intergenic | rs2808772; A>G,T (A)             | Knee pain                                                            | [22]      |
| MAML3  | rs13136239; G>A,T (G)             | Multisite chronic pain                                               | [16]      |
| MLLT10 | rs2183271; T>C (T)                | Multisite chronic pain                                               | [16]      |
| MLN    | rs11751591; G>A,T (G)             | Multisite chronic pain                                               | [16]      |
| Intergenic | rs285026; G>A,C,T (G)            | Multisite chronic pain                                               | [16]      |
| NMT1   | rs11871043; T>C (T)               | Multisite chronic pain                                               | [16]      |

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| Gene        | Polymorphism; alleles (risk allele) | Pain-related manifestation                                                                 | Reference |
|------------|-------------------------------------|-------------------------------------------------------------------------------------------|-----------|
| Intergenic | rs12464483; G>A,C (A)               | Pre-treatment pain in head and neck squamous cell carcinoma                                 | [24]      |
| Intergenic | rs1834077; C>A,T (A)                | Pre-treatment pain in head and neck squamous cell carcinoma                                 | [24]      |
| NUMB       | rs12435797; G>A,C,T (G)             | Multisite chronic pain                                                                      | [16]      |
| PRC1       | rs2386584; T>A,C,G (T)              | Multisite chronic pain                                                                      | [16]      |
| PRKCA      | rs887797; G>A,T (A)                 | Possible neuropathic pain in post total joint replacement surgery for osteoarthritis        | [21]      |
| RFFL       | rs16970540; C>T (T)                 | Acute post-radiotherapy pain in breast cancer                                              | [20]      |
| RNF123,    | rs7628207; T>A,C,G (T)              | Multisite chronic pain                                                                      | [16]      |
| AMIGO3     | rs4775319; G>A (G)                  | Neuropathic pain in head and neck cancer                                                   | [25]      |
| Intergenic | rs11615866; C>T (T)                 | Neuropathic pain in type 2 diabetes                                                        | [19]      |
| Intergenic | rs12071912; C>G,T (C)               | Multisite chronic pain                                                                      | [16]      |
| Intergenic | rs6869446; T>A,C,G (T)              | Multisite chronic pain                                                                      | [16]      |
| Intergenic | rs1976423; A>C (A)                  | Multisite chronic pain                                                                      | [16]      |
| SDK1       | rs10259354; G>A,C (G)               | Multisite chronic pain                                                                      | [16]      |
| SLC24A3    | rs2424248; G>A,T (G)                | Multisite chronic pain                                                                      | [16]      |
| SLC39A8    | rs13135092; A>G (A)                 | Multisite chronic pain                                                                      | [16]      |
| Intergenic | rs11079993; G>A,T (G)               | Multisite chronic pain                                                                      | [16]      |
| SNX8       | rs10950641; G>A (A)                 | Neuropathic pain in head and neck cancer                                                   | [25]      |
| SORCS3     | rs11599236; T>A,C,G (T)             | Multisite chronic pain                                                                      | [16]      |
| SOX5       | rs12310519; C>T (T)                 | Chronic back pain                                                                          | [17]      |
| SOX6       | rs61883178; C>A (C)                 | Multisite chronic pain                                                                      | [16]      |
| SP4        | rs7798894; A>C,G,T (A)              | Multisite chronic pain                                                                      | [16]      |
| STAG1      | rs6770476; C>T (C)                  | Multisite chronic pain                                                                      | [16]      |
| UTRN       | rs6926377; A>C (A)                  | Multisite chronic pain                                                                      | [16]      |
| Intergenic | rs10992729; C>G,T (C)               | Multisite chronic pain                                                                      | [16]      |
| ZSCAN20    | rs35260355; C>A,G,T (T)             | Neuropathic pain in type 2 diabetes                                                        | [23]      |
|            | rs71647933; A>G,T (G)               | Neuropathic pain in type 2 diabetes                                                        | [23]      |
| SCN9A      | rs6746030; A>C,G (A)                | Increased pain in patients with osteoarthritis, sciatica and phantom limb syndrome        | [8]       |
| CACNA2D3   | rs6777055; A>C (C)                  | Reduced acute thermal pain and diminished chronic pain after lumbar discectomy            | [9]       |
| KCNS1      | rs734784; T>C (C)                   | Increased acute pain in patients with neuropathic pain after radiculopathy or amputation  | [10]      |
| CACNG2     | rs4820242; G>A,C,T (A)              | Increased susceptibility to chronic pain after nerve injury in mastectomy patients.        | [11]      |
|            | rs2284015; C>G (G)                  |                                                                                           | [11]      |
|            | rs2284017; T>C (C)                  |                                                                                           | [11]      |
| P2RX7      | rs7958311; G>A,C (A)                | Reduction of chronic pain                                                                  | [12]      |
| SCN10A     | rs6795970; A>G,T (T)                | Anticipated onset of pain                                                                  | [13]      |
hances excitation of dorsal root ganglia. It is associated with increased pain in patients with osteoarthritis, sciatica and phantom limb syndrome (8).

Similarly, the minor allele of SNP rs6777055, located in an intron region of CACNA2D3, is associated with reduced acute thermal pain and diminished chronic pain after lumbar discectomy. CACNA2D3 encodes the alpha-2/delta 3 subunit of a voltage-dependent calcium channel complex (9).

Reduced expression of KCNS1, encoding the voltage-gated potassium channel subunit K.9.1, due to the minor allele of the SNP (Ile488Val; rs734784), results in neuronal hyperexcitability. This variation substantially increases acute pain in patients with neuropathic pain after radiculopathy or amputation (10).

Variations in three intron SNPs (rs4820242, rs2284015, and rs2284017) in the CACNG2 gene, which encodes a type 1 transmembrane α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) regulatory peptide, increase susceptibility to chronic pain after nerve injury in mastectomy patients (11).

Other SNPs are associated with a significant reduction in chronic pain. The minor allele of SNP Arg270His; rs7958311 in the P2RX7 gene, which encodes an ATP-gated ionotropic receptor, leads to impaired pore formation (12).

The minor allele of the SNP Ala1073Val; rs6795970 in SCN10A is significantly involved in visceral pain perception and results in changes in electrophysiological function of the encoded channel Na1.8, corresponding to anticipated onset of pain (13). However, the same minor allele causes a shift in channel activation, thus reducing repetitive firing of dorsal root ganglion neurons and attenuating mechanical pain sensitivity (14).

Conclusion

This mini-review highlights the importance of genetics in the onset of pain and in phenotypes characterized by chronic pain or pain insensitivity. We therefore think that an extensive genetic test could be very important for understanding the basis of pain (or insensitivity to it). This is important not only for monogenic disorders with Mendelian inheritance. In fact, analysis of polymorphisms that increase the risk of chronic pain could help formulate better and more personalized treatments. The genetic test should encompass all genes associated with monogenic Mendelian disorders associated with pain perception and all SNPs that can increase the risk of pain-related manifestations.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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