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Review

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 $Na_v1.7$ 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	#615551	AD	Episodic burning pain affecting distal lower extremities and hands; Hyperalgesia
SCN11A	*604385	FEPS3	#615552	AD	Episodic pain localized to the distal extremities
		HSAN7	#615548	AD	Insensitivity to pain
SCN9A	*603415	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]
CTNNA2	rs4852567; A>G,T (A)	Multisite chronic pain	[16]
DCC	rs4384683; G>A,C,T (G)	Chronic back pain	[17]
	rs62098013; G>A (G)	Multisite chronic pain	[16]
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)	Acute post-radiotherapy pain in breast cancer	[20]
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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Table 2 ***(continued)*****.** Polymorphisms associated with modulation of pain perception

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, AMIGO3	rs7628207; T>A,C,G (T)	Multisite chronic pain	[16]
RORA	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 $K_v9.1$, 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 $Na_v1.8$, 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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