Neuropathological and genetic diathesis of neuropathic pain: A current genomic perspective

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ABSTRACT

Humans of all ages manifest neuropathic pain with long-lasting consequences. The influence of this condition comprises biological, socioeconomic, environmental, lifestyle, and personal factors. Therefore, scientists have undertaken various researches to determine this neurological pain over the past few decades by using genetic markers. As a result, nearly 50% of all people have the heritability of neuropathic phenotypes and identified that the selected genes were linked to the relevant pathways. All types of neurological disorders are associated with dopaminergic, serotonergic, adrenaline, and noradrenaline genes. By gathering the information from the previous records, it is found that the genes play a crucial role in the influence of neuropathy, and it is also reported as many neurological/psychiatric diseases are associated with this condition. With modern technology's arrival, novel selected genes are investigated and might be used as early biomarkers for diagnosing and developing drug targets for therapeutics. Overcoming obstacles, advances in our knowledge of the mechanism of nerve pain are stimulating the emergence of new screening methods and customised therapies, emphasising the importance of a holistic strategy to neuropathological management.

BACKGROUND

- Neuropathic pain arises from a lesion or disease of the somatosensory system.
- Although some conditions have a known genetic cause, others develop as part of disease sequelae or posttraumatic complications.
- The defining feature is an aberrant nociceptive network manifesting as pain occurring spontaneously or without adequate stimulation.
- In the case of rare familial disorders, abnormal nociceptive signalling is genetically encoded, and many causal variants are known.
- Acquired neuropathic pain may develop secondarily to another condition, such as diabetes or cancer, in which nerve damage is often a consequence of disease progression.
- Alternatively, nerve damage or lesion may occur during physical trauma or surgery and result in a neuropathic pain condition.
- During the past decade, the number of studies aiming to identify genetic factors in neuropathic pain conditions has grown in the hope of elucidating the molecular risk factors and identifying treatment targets.

OBJECTIVES

- This study aims to identify the relationship between candidate genes and neuropathic pain in humans by combining genetic association studies.
- In this review, we summarise these studies and present the current landscape of neuropathic pain molecular pathophysiology as it has been informed by them.

METHODS

- The NCBI gene database for neurotransmitter genes with a collection of 127 genes were updated for neuropathic pain.
- The genes discussed in this study are detected from Web of Science, PubMed, and several other databases such as PsycINFO over the past 30 years, and only a few researches have been done using GWAS approaches.

GENES ASSOCIATED WITH NP

Table 1. Genetic variants reported in association studies of common neuropathic pain conditions.

Genes	SNP	Functional pathways	Conditions
ABCB1	rs1045642	Pharmacokinetics	Cancer pain
CACNG2	rs4820242	Neurotransmission	Post-operative pain
	rs2284015	Neurotransmission	Post-operative pain
	rs2284015	Neurotransmission	Post-operative pain
CASP9	rs4645978	Apoptosis	Radicular pain
COL9A3	rs61734651	Structural	Radicular pain
COMT	rs4680	Neurotransmission	Cancer pain, Radicular pain
DRD2	rs6277	Neurotransmission	Neuropathic pain
GCH1	rs8007267	Metabolism/Neurotransmission	Cancer pain, HIV SNP, Post-operative pain
GFRA2	rs17428041	Immune response/Development	Diabetic neuropathic pain
IL10	rs3024505	Immune response	Postoperative pain
	rs3024498	Immune response	Postoperative pain
	rs3024496	Immune response	Postoperative pain
	rs1878672	Immune response	Postoperative pain
	rs1518111	Immune response	Postoperative pain
	rs1518110	Immune response	Postoperative pain
IL10RB	rs2834167	Immune response	Cancer pain
IL1A	rs1800587	Immune response	Radicular pain
IL1B	rs1143627	Immune response	Cancer pain
	rs1143634	Immune response	Cancer pain
IL1R2	rs11674595	Immune response	Postoperative pain
IL1RN	rs2234677	Immune response	Radicular pain
IL6	rs1800797	Immune response	Radicular pain
	rs1800796	Immune response	Radicular pain
	rs1800795	Immune response	Radicular pain
	rs13306435	Immune response	Radicular pain
KCNJ3	rs7574878	Neurotransmission	Cancer pain
	rs2591168	Neurotransmission	Cancer pain
	rs2591172	Neurotransmission	Cancer pain
KCNJ6	rs2835914	Neurotransmission	Cancer pain
	rs8129919	Neurotransmission	Cancer pain
	rs2836050	Neurotransmission	Cancer pain
KCNJ9	rs3780039	Neurotransmission	Cancer pain
	rs11166921	Neurotransmission	Cancer pain
	rs2014612	Neurotransmission	Cancer pain
KCNS1	rs734784	Neurotransmission	Postoperative pain
	rs13043825	Neurotransmission	Postoperative pain
	rs6017486	Neurotransmission	HIV-SNP
	rs6073643	Neurotransmission	HIV-SNP
	rs4499491	Neurotransmission	HIV-SNP
LTA	rs1799964	Immune response	Cancer pain
MAPK1	rs8136867	Wide range	Cancer pain
MAT2B/TENM2	rs7734804	Metabolism/Unknown	Postoperative pain
MMP1	rs1799750	Tissue remodelling	Radicular pain
NFKBIA	rs8904	Immune response	Cancer pain
NOS3	rs1800783	Neurotransmission	Cancer pain
OPRM1	rs1799971	Neurotransmission	Diabetic neuropathic pain
P2RX7	rs1718119	Immune system	Diabetic neuropathic pain
	rs208294	Immune system	Postoperative pain
	rs7958311	Immune system	Postoperative pain
PRKCA	rs887797	Cell signalling	Postoperative pain

Table 1. Continue

PTGS2	**rs5275**	**Immune response/metabolism**	**Cancer pain**
	rs5277	**Immune response/metabolism**	**Cancer pain**
SCN9A	rs6746030	Neurotransmission	Peripheral neuropathy
	rs3750904	Neurotransmission	Diabetic neuropathic pain
	rs4369876	Neurotransmission	Diabetic neuropathic pain
	rs200139913	Neurotransmission	Diabetic neuropathic pain
	rs74449889	Neurotransmission	Diabetic neuropathic pain
TNF	rs28445017	System	HIV-SN
	rs1800629	Immune system	Cancer pain
TNFRSF1B	rs1061622	Immune response	Cancer pain

SIGNIFICANCE OF THIS REVIEW

- This survey of literature provides an overview of genetic variants implicated in a variety of neuropathic pain conditions. Rare monogenic painful conditions are firmly rooted in the ion channel—specifically sodium channel—mutations, underscoring the critical role of these channels in pain processing.
- Among painless monogenic conditions, mutations disrupting nociceptive neuron maintenance are overrepresented.
- In common nonfamilial neuropathic pain conditions, the landscape of implicated molecules is more varied; the effect of genetic variants is considerably smaller and often harder to demonstrate.

CONCLUSIONS

- Although further studies are needed, this evidence supports the hypothesis that timely treatment targeting the immune system could be helpful in mitigating neuropathic pain.
- In addition, the involvement of neuropathic pain genetic variants in other pain conditions with a neuropathic pain component—in particular, a variant upstream of *MAT2B* whose association is prominent in back, hip, knee, and neck pain—provides preliminary evidence of shared contributing mechanisms at the genetic-molecular level.
- Diagnosing pain and confirming it as neuropathic in origin remains a challenge.
- The difficulty of identifying a nerve lesion or disease is exacerbated by other pain comorbidities and by the fact that diagnosis relies heavily on verbal interpretation of pain, far removed from the pathophysiological mechanisms that engender it.
- Thus, it is our hope that genetic studies will enable a more comprehensive assessment of patients presenting with painful conditions and become a powerful tool in diagnosing and treating these conditions with requisite specificity.

ACKNOWLEDGEMENT

The authors thank Chettinad Academy of Research and Education for constant support and encouragement.

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