Genetic studies of human neuropathic pain conditions: a review
Katerina Zorina-Lichtenwalter*, Marc Parisien, Luda Diatchenko

Abstract
Numerous studies have shown associations between genetic variants and neuropathic pain disorders. Rare monogenic disorders are caused by mutations of substantial effect size in a single gene, whereas common disorders are likely to have a contribution from multiple genetic variants of mild effect size, representing different biological pathways. In this review, we survey the reported genetic contributors to neuropathic pain and submit them for validation in a 150,000-participant sample of the U.K. Biobank cohort. Successfully replicated association with a neuropathic pain construct for 2 variants in IL10 underscores the importance of neuroimmune interactions, whereas genome-wide significant association with low back pain ($P = 1.3e-8$) and false discovery rate 5% significant associations with hip, knee, and neck pain for variant rs7734804 upstream of the MAT2B gene provide evidence of shared contributing mechanisms to overlapping pain conditions at the molecular genetic level.

Keywords: Neuropathic pain, Genetic association studies, Genetic variants, Single nucleotide polymorphisms, U.K. Biobank

1. Introduction
Neuropathic pain arises from a lesion or disease of the somatosensory system.6,6 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.6,21 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. In all these cases, susceptibility to chronic pain varies beyond what environmental factors can explain. Although twin studies for common neuropathic pain conditions have not been done, substantial heritability has been reported in multiple other chronic pain conditions105—including back and neck pain, which often have a neuropathic component. Animal models of neuropathic pain have likewise revealed a significant genetic contribution.106,107

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. In this review, we summarise these studies and present the current landscape of neuropathic pain molecular pathophysiology as it has been informed by them.

2. Methods
To obtain a list of original studies reporting genetic association or linkage analysis with neuropathic pain conditions, we used the search method described in Ref. 158. Briefly, after drawing the initial list from the Human Pain Genetics Database (https://humanpaingenetics.org/hpgdb), a search was conducted in Google Scholar using the name of each disorder and one of the following terms: “genetic association,” “variant,” or “polymorphism.” In addition, we performed a search in PubMed, using the string: ((gene OR variant OR polymorphism) AND neuropath*) AND pain”) under the category “Text Word.” Last, recent reviews of neuropathic pain genetics were perused for studies overlooked using the above methods. Studies reporting association with a multi-symptom condition were included if neuropathic pain was one of the described symptoms, using the rationale that pleiotropic genetic loci should be considered neuropathic pain modulators whether or not they affect other clinical phenotypes. Although publications were primarily screened by title and abstract, the text and relevant tables were perused if clarifications were necessary.

After compiling the list of genes containing variants with reported associations in common neuropathic pain conditions, we took all variants with a minimum minor allele frequency of 1% (except human leukocyte antigen [HLA]-region variants because of their complex haplotypic structure) and checked them for validation in the U.K. Biobank, UKBB (application no. 20802). This public repository of genotypic and phenotypic data for 500,000 U.K. individuals, aged 40 to 69 years, is a data set of unprecedented proportions in human genetic association studies.131 To construct a neuropathic pain phenotype, we grouped the following conditions (self-reported or determined by interview with a clinical nurse,
UKBB Data Field, hereafter DF, 20002): peripheral neuropathy (code 1255), diabetic neuropathy and ulcers (1468), shingles (1573), trigeminal neuralgia (1523), sciatica (1476), spinal stenosis (1536), peripheral nerve injury (1594), trapped or compressed nerve (1257), prolapsed or slipped disk (1312), variella zoster virus (1674), and peripheral nerve disorder (1254). Individuals self-reporting one or more of these conditions were classified as cases and those reporting no pain conditions (DF 6159) as controls. In addition to neuropathic pain, we checked the list of variants in Table 1 for association with 4 site-specific pain conditions (>3 months’ duration) in the UKBB: back (DF 3571), hip (DF 3414), knee (DF 3773), and neck (DF 3404). Controls were the same as in the neuropathic pain group (no pain under DF 6159). To test for association with these phenotypes, we ran regression analyses on the available sample of 150,000 individuals of predominantly Caucasian ancestry using SNPTEST, version 2.5.2.

3. Results

The literature review findings are divided into rare monogenic disorders and common disorders with multiple associated risk loci and a complex etiology. The 2 classes of disorders are studied using different approaches: while rare conditions require linkage analysis of multi-generation pedigrees, common conditions require association studies of large cohorts of unrelated individuals. Section 3.1 is devoted to findings from familial rare variant studies, and section 3.2 focuses on common disorders with neuropathic pain as a secondary attribute.

3.1. Monogenic disorders

As the name suggests, monogenic disorders are often caused by variants in a single gene. The effect of such a variant can either exacerbate nociception or annul it. Although not painful, the latter class of disorders is tied to genetic loci that directly participate in pain signalling or contribute to the vitality of sensory neurons and are therefore equally important to our understanding of pain processing. In fact, some of the same genes that harbour painful neuropathic variants also carry mutations leading to painless states.

3.1.1. Painful rare monogenic disorders

Erythromelalgia is marked by redness and painful swelling of hands and feet, symptoms that have been attributed to C-fibre hypersensitivity. Its hereditary form, primary erythromelalgia, has shown linkage to rare hyperfunctional variants in sodium channel Na\(_{v}1.7\) (SCN9A), discovered as causal\(^{53}\) and repeatedly replicated in Chinese\(^{59,79,84,85,157}\) and Caucasian\(^{53,55,36,97,121}\) individuals.

The implicated SCN9A variants have been reported to change the electrophysiological properties of dorsal root ganglion neurons, thereby affecting nociceptive signalling.\(^{26,35,99}\) The magnitude of effect on these functions seems to modulate the timing of disease onset. Thus, a variant with a smaller effect on hyperpolarization has been reported to be associated with later onset of erythromelalgia.\(^{47}\) An alternative theory posits that SCN9A variants affecting different electrophysiological properties translate to different neuropathic conditions.\(^{80,81}\) In cellular assays, this group has demonstrated that alleles responsible for erythromelalgia disrupted fast inactivation in nociceptors, whereas alleles that lower firing thresholds, slow deactivation, and potentiate currents result in paroxysmal extreme pain disorder.\(^{38}\) The latter is also a rare neuropathic disorder, which manifests as rectal, periorcular, and perimandibular pain, and affected individuals have been reported to carry gain-of-function variants in SCN9A.\(^{38,42,94}\) The genetic contribution of SCN9A variants to paroxysmal extreme pain disorder and their cellular phenotype has been also reported in Ref. 34. This gene’s variants have likewise been reported to be associated with unexplained chronic neuropathic pain.\(^{28}\)

Sodium channels Na\(_{v}1.7\), Na\(_{v}1.8\), and Na\(_{v}1.9\) (SCN9A, SCN10A, and SCN11A, respectively), have been found to harbour variants involved in a set of conditions collectively known as idopathic painful small fibre neuropathies. These conditions affect small-diameter A-delta and C fibres, and their clinical manifestations include sudden bouts of pain propagating inward from the extremities. Associations with SCN9A,\(^{29,40,46,48}\) SCN10A,\(^{27,41,57}\) and SCN11A\(^{30,56,81}\) are supported by their cellular phenotype—hyperexcitability in dorsal root ganglion neurons.\(^{40,41,48,50,56,57}\)

Aside from sodium channels, variants in 4 other genes have been reported in connection with painful peripheral neuropathies. \(\alpha\)-galactosidase A, GLA, has been reported in a small fibre neuropathy patient.\(^{31}\) Myelin protein zero, MPZ, has been reported in a family with debilitating neuropathic pain and demyelination. A variant in a subunit of kinesin, KIF5A, a protein involved in intracellular motility, has been reported to cause a form of hereditary spastic paraplegia with axonal neuropathy and pain.\(^{119}\) Individuals with a rare case of late-onset hereditary peripheral neuropathy have been reported to carry a variant in \(\alpha\)-N-acetyl-glucosaminidase, NAGLU.\(^{138}\)

3.1.2. Painless rare monogenic disorders

Among rare congenital sensory disorders, a class of conditions defined by insensitivity to pain has been linked to hypofunctional variants in SCN9A\(^{22,23,70,74,90,112,126}\) and hyperfunctional variants in SCN11A.\(^{80,113}\) These findings are consistent with the electrophysiological properties of the 2 sodium channels. Increased activity in Na\(_{v}1.9\) leads to longer neuronal depolarisation, which inhibits Na\(_{v}1.7\) and Na\(_{v}1.8\) activity in nociceptors, effectively shutting down pain signal transmission.

In addition, insensitivity to pain is one of the defining symptoms in a group of disorders known collectively as hereditary sensory and autonomic neuropathies (HSANs). Primarily, variations in autonomic symptoms and genetic causes segregate these disorders into 8 major subtypes, 7 of which include insensitivity to pain. The different pathways leading to pain insensitivity are tagged by the 11 operative genes whose variants have been found in affected individuals: SPTLC1, DMNT1, WNK1, KIF1A, RETREG1, SCN9A, ELP1, NTRK1, NGF, SCN11A, and PRDM12. SPTLC1 encodes a subunit of serine palmitoyltransferase, whose variant-compromised activity contributes to neuronal toxicity and death. DMNT1 encodes a DNA methyltransferase, whose impaired function disrupts neuronal maintenance. Variants in these 2 genes have been reported as causal in HSAN, type I,\(^{3,5,6,9,50,66,150}\) WNK1 encodes WNK lysine deficient protein kinase 1, whose variants lead to a reduced number of sensory neurons, although the exact mechanism for this is unknown. KIF1A encodes kinesin family member 1A, an axonal transporter of synaptic vesicles, and variants in this gene lead to impaired neuronal function. RETREG1 encodes reticulophagy regulator 1, whose variants disrupt its physiological function in autophagy leading to neuronal toxicity and death. WNK1, KIF1A, and RETREG1 variants lead to different subtypes of HSAN, type II,\(^{29,76,77,102,120,125}\) variants in SCN9A have also been implicated in HSAN, type II,\(^{156}\) ELP1 encodes elongator complex protein 1, a scaffolding protein whose variants have been found in patients with HSAN, type III,\(^{5,127}\) HSAN, type IV, as its alternative name—
**Table 1**

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

| Gene   | SNP               | Function/pathway                  | Condition(s) | Citation           |
|--------|-------------------|-----------------------------------|--------------|--------------------|
| ABCB1  | rs1045642         | Pharmacokinetics                  | Cancer pain  | 149                |
| CACNG2 | rs4820242         | Neurotransmission                 | PSP          | 104                |
|        | rs2284015         | Neurotransmission                 | PSP          | 104                |
|        | rs2284017         | Neurotransmission                 | PSP          | 104                |
| CASP9  | rs4645978         | Apoptosis                         | Radicular pain | 46                |
| COL9A3 | rs61734651        | Structural                         | Radicular pain | 111               |
| COMT   | rs4680            | Neurotransmission                 | Cancer pain  | 149                |
|        |                   |                                   | Radicular pain | 63                |
| DDR2   | rs6277            | Neurotransmission                 | Neuropathic pain | 62                |
| GCH1   | rs8007267         | Metabolism/neurotransmission      | Cancer pain  | 87, 53, 146        |
|        |                   |                                   | HIV-SNP      | 9, 135             |
|        | rs8007201         | Metabolism/neurotransmission      | PSP          | 135                |
|        | rs4411417         | Metabolism/neurotransmission      | PSP          | 135                |
|        | rs752688          | Metabolism/neurotransmission      | PSP          | 135                |
|        | rs10483639        | Metabolism/neurotransmission      | Cancer pain  | 87, 53, 146        |
|        |                   |                                   | HIV-SNP      | 9, 135             |
|        | rs3783641         | Metabolism/neurotransmission      | Cancer pain  | 87, 53, 146        |
|        |                   |                                   | HIV-SNP      | 9, 135             |
| GFRA2  | rs17428041        | Immune response/development       | DNP          | 95                 |
| HMGB1P46 | rs6986153      | Unknown                           | DNP          | 96                 |
|        | rs3024505         | Immune response                   | Postoperative pain | 129               |
| IL10   | rs3024498         | Immune response                   | Postoperative pain | 129               |
| IL10   | rs3024406         | Immune response                   | Postoperative pain | 129               |
| IL10   | rs1878672         | Immune response                   | Postoperative pain | 129               |
| IL10   | rs1518111         | Immune response                   | Postoperative pain | 129               |
| IL10   | rs1518110         | Immune response                   | Postoperative pain | 129               |
| IL10   | rs3024491         | Immune response                   | Postoperative pain | 129               |
| IL10   | rs2834167         | Immune response                   | Cancer pain  | 117                |
| IL1A   | rs1800587         | Immune response                   | Radicular pain | 100, 123           |
| IL1B   | rs1143627         | Immune response                   | Cancer pain  | 117                |
| IL1B   | rs1143634         | Immune response                   | Cancer pain  | 107                |
| IL1R2  | rs11674595        | Immune response                   | Postoperative pain | 129               |
| IL1RN  | rs2234677         | Immune response                   | Radicular pain | 100                |
| IL6    | rs1800797         | Immune response                   | Radicular pain | 67, 105            |
| IL6    | rs1800796         | Immune response                   | Radicular pain | 67, 105            |
| IL6    | rs1800795         | Immune response                   | Radicular pain | 67, 105            |
| IL6    | rs13306435        | Immune response                   | Radicular pain | 67, 105            |
| KCNJ3  | rs7574878         | Neurotransmission                 | Cancer pain  | 78                 |
| KCNJ3  | rs2591168         | Neurotransmission                 | Cancer pain  | 78                 |
| KCNJ3  | rs2591172         | Neurotransmission                 | Cancer pain  | 78                 |
| KCNJ6  | rs2835914         | Neurotransmission                 | Cancer pain  | 78                 |
| KCNJ6  | rs8129919         | Neurotransmission                 | Cancer pain  | 78                 |
| KCNJ6  | rs2836050         | Neurotransmission                 | Cancer pain  | 78                 |
| KCNJ9  | rs3780039         | Neurotransmission                 | Cancer pain  | 78                 |
| KCNJ9  | rs11166921        | Neurotransmission                 | Cancer pain  | 78                 |

(continued on next page)
congenital insensitivity to pain with anhidrosis—suggests, is defined by insensitivity to pain as its primary symptom. Variants in NTRK1, which encodes neurotrophic receptor tyrosine kinase 1, disrupt its role in neuronal cell maintenance, thereby leading to congenital insensitivity to pain with anhidrosis.\textsuperscript{1,12,13,45,58,60,61,75,82,86,88,98,124,134,141,147,148,154} NGF encodes nerve growth factor beta, the binding partner of NTRK1. Its variants lead to HSAN, type V.\textsuperscript{14,37} HSAN subtypes VII and VIII were characterised more recently, and their genetic causes have been determined to be variants in SCN11A\textsuperscript{80,113,152} and PRDM12,\textsuperscript{15} respectively. A recent study showed variants in FLVCR1, a heme transporter, in a patient with an unclassified HSAN.\textsuperscript{17} All of these genes, in their pathological variant form, abolish pain sensitivity by depleting the number of viable sensory neurons.

### Table 1 (continued)

| Gene   | SNP          | Function/pathway      | Condition(s)       | Citation |
|--------|--------------|-----------------------|--------------------|----------|
| KONJ9  | rs2014612    | Neurotransmission     | Cancer pain        | 78       |
| KON1   | rs734784     | Neurotransmission     | PSP                | 20       |
| KON1   | rs13043825   | Neurotransmission     | PSP                | 20       |
| KON1   | rs6017486    | Neurotransmission     | HIV-SN             | 53       |
| KON1   | rs6073643    | Neurotransmission     | HIV-SN             | 53       |
| KON1   | rs4499491    | Neurotransmission     | HIV-SN             | 53       |
| LTA    | rs1799964    | Immune response       | Cancer pain        | 114      |
| MAPK1  | rs8136667    | Wide range            | Cancer pain        | 118      |
| MAT2B/TENM2 | rs7734804 | Metabolism/unknown    | PSP                | 150      |
| MMP1   | rs1799750    | Tissue remodelling    | Radicular pain     | 64       |
| NFKB1  | rs8904       | Immune response       | Cancer pain        | 116      |
| NOS3   | rs1800783    | Neurotransmission     | Cancer pain        | 117      |
| OPRM1  | rs1799971    | Neurotransmission     | DNP, Postoperative pain, Neuropathic pain | 16, 72, 108 |
| P2RX7  | rs1718119    | Immune system         | DNP                | 143      |
| P2RX7  | rs208294     | Immune system         | DNP, PSP           | 143, 128 |
| P2RX7  | rs7958311    | Immune system         | PSP                | 128      |
| PRKCA  | rs887797     | Cell signalling       | PSP                | 150      |
| PTGS2  | rs5275       | Immune response/metabolism | Cancer pain   | 116, 117 |
| PTGS2  | rs5277       | Immune response/metabolism | Cancer pain    | 114      |
| SCN9A  | rs6746030    | Neurotransmission     | Peripheral neuropathy | 52       |
| SCN9A  | rs6746030    | Neurotransmission     | Radicular pain     | 115      |
| SCN9A  | rs3750904    | Neurotransmission     | DNP                | 83       |
| SCN9A  | rs4369876    | Neurotransmission     | DNP                | 83       |
| SCN9A  | rs200139913  | Neurotransmission     | DNP                | 83       |
| SCN9A  | rs74449889   | Neurotransmission     | DNP                | 83       |
| TNF    | rs28445017   | Immune system         | HIV-SN             | 54       |
| TNFRSF18 | rs1061622   | Immune response       | Cancer pain        | 116      |
| ZSCAN20 | rs35260355   | Unknown               | DNP                | 95       |
| ZSCAN20 | rs71647933   | Unknown               | DNP                | 95       |

Results from GWAS are in boldface. DNP, diabetic neuropathic pain; FDR, false discovery rate; HIV-SN, HIV-sensory neuropathy; PSP, postoperative pain; SNP, single nucleotide polymorphism.

3.2. Common disorders

Genetic studies of common neuropathic pain conditions suffer from a lack of clearly defined phenotyping.\textsuperscript{144} Despite the recently updated definition and grading system published by the neuropathic pain task force,\textsuperscript{43,66,140} this type of pain remains resistant to accurate diagnosis. Although diabetic neuropathy, radicular pain, trigeminal neuralgia, and viral infection-related sensory neuropathies are among the more clearly defined neuropathic pain conditions, cancer pain and postoperative pain display mixed phenotypes of neuropathic and nociceptive pain. Many genetic reports do not adhere to standardised terminology and diagnostic procedures,\textsuperscript{10} and some studies report an association with chronic pain in cancer or postsurgery patients without characterising it. Nevertheless, given the substantial neuropathic component of these conditions, we include these studies in our review.
Common neuropathic pain conditions, in which suspected genetic contribution derives from many different loci, benefit from studies in large cohorts with hypothesis-free scans of the entire genome. Thus, the publication of 3 genome-wide association studies (GWAS) in neuropathic pain during the past 3 years is an exciting recent development, even if the top findings in these studies are just below the threshold of genome-wide significance.\textsuperscript{95,96,150} Aside from these GWAS, studies done in patients genotyped or sequenced at targeted gene panels have been informative about loci that may modulate susceptibility to developing neuropathic pain after a traumatic event, physical injury, or the onset of another disease. Variants identified in this disease category are listed in Table 1. The most frequently investigated gene with variants reported to be associated with common neuropathic pain is GCH1.

3.2.1. Diabetic neuropathy

Diabetic neuropathy is a condition of polar extremes, characterised by pain at one extreme and insensitivity at the other, and its prevalence is up to 50\% in diabetes patients.\textsuperscript{136} Prolonged glycemic mismanagement and disruption of nerve microvasculature are the putative disease-associated risk factors.\textsuperscript{136,137} However, given the incomplete penetrance of neuropathic pain in diabetic patients, the search for genetic contributors is ongoing. The first GWAS in the domain of painful neuropathies to be published was on diabetic neuropathic pain.\textsuperscript{95} Closely following came a second report from the same group.\textsuperscript{96} Both studies were conducted with the same cohort of almost 7000 genotyped diabetic patients. In the first study, cases of neuropathic pain were defined as individuals with a history of at least 1 specified diabetic peripheral neuropathy drug prescription and a positive monofilament test indicative of sensory neuropathy. In the second study, the monofilament test requirement was dropped, but cases had to have at least 2 prescriptions. The results in the first study showed a nearly genome-wide significant association for glial cell-derived neurotrophic factor family receptor alpha 2, encoded by GFRA2. In the second study, the same level of significance was reported for a wide region in women on chr1p35.1, gated by zinc-finger and SCAN domain-encoding ZSCAN20 on one end and toll-like receptor 12 pseudogene TLR12P on the other, and in men a high-mobility group box 1 pseudogene 46, HMGB1P46, on chr8p23.1.

Other groups have conducted association studies to examine the effects of a priori determined genetic variants, based on their roles in other related diseases. Among them, 1 has reported an association for the well-known A188G hypofunctional variant in µ-opioid receptor, OPRM1, with foot ulcer pain in diabetic patients.\textsuperscript{136} Another reported 2 hyperfunctional variants in purinergic receptor P2, P2RX7, to be associated with higher pain in women diagnosed with diabetic neuropathy.\textsuperscript{143} Interleukin-4 receptor, encoded by IL4R, has been reported to have its variable number of tandem repeats associated with diabetic neuropathy.\textsuperscript{7} Last, several hyperfunctional variants in sodium channel Na\textsubscript{v}1.7 (SCN9A), were found in a cohort of nearly 1000 individuals with diabetes to be associated with neuropathic pain.\textsuperscript{93}

3.2.2. Radicular pain

Spinal disk herniation or prolapse leads to neuropathic pain through a combination of inflammation and nerve compression.\textsuperscript{69} Accompanying pain intensity and duration vary, and several studies have reported genetic variants as risk modifiers. Inflammatory mediators have shown association with herniated disk-related pain intensity, namely IL1A\textsuperscript{100,123}, IL1RN\textsuperscript{102}; and IL6\textsuperscript{67,105} In addition, associations have been published for variants in OPORM1,\textsuperscript{106} COMT,\textsuperscript{93} COL9A3 (encoding a chain of type IX collagen),\textsuperscript{111} MMP1 (encoding matrix metalloproteinase 1),\textsuperscript{64} and CASP9 (encoding caspase-9).\textsuperscript{54}

3.2.3. Trigeminal neuralgia

Trigeminal neuralgia manifests as paroxysmal bursts of pain along the innervation pathway of the trigeminal nerve.\textsuperscript{73} According to recently proposed diagnostic criteria, its onset may be: (1) idiopathic, (2) caused by an underlying condition, or (3) accompanying pressure exerted on the trigeminal nerve root by the surrounding blood vessels.\textsuperscript{24} Genetic studies of trigeminal neuralgia have been scarce, with 1 report suggesting a variant in serotonin transporter, SLC6A4,\textsuperscript{25} and a recent study suggesting sodium channel Na\textsubscript{v}1.6, encoded by SCN8A.\textsuperscript{123} Both proteins are involved in neurotransmission and are suggestive of the nociceptive pathway. The finding of Na\textsubscript{v}1.6 is unique, because this is the first report of this channel’s involvement in pain. Given its distribution in high-frequency firing neurons, it had previously been studied for its role in epilepsy.\textsuperscript{153}

3.2.4. Viral infection–related sensory neuropathies

Painful neuropathy as a sequel of HIV infection is common and has been investigated by several groups in the recent years. An excellent review of the genetics of HIV-associated painful neuropathy on the African continent has just been published.\textsuperscript{93} Two genes harbouring variants associated with pain intensity in HIV-infected Southern Africans are KCNS1\textsuperscript{153} and TNF.\textsuperscript{54,145} Two groups have also investigated the involvement of GCH1 in HIV-associated neuropathic pain in Africans but found no association.\textsuperscript{53,146}

Postherpetic neuralgia is a condition characterised by persistent spontaneous or innocuous stimulus-evoked pain. Several studies in Japanese patients have examined the role of genetic variants in the HLA region.\textsuperscript{18,110,122,123} Associations have been found for both class I molecules: HLA-A, HLA-B, and HLA-C\textsuperscript{18,110,122,123}; and class II HLA-DRB1\textsuperscript{122,123}. The proposed mechanism whereby HLA-complex variants contribute to postherpetic neuropathic pain is nerve damage permitted by inadequate immune system response to the initial viral infection.\textsuperscript{132}

3.2.5. Cancer pain

Up to 40\% of all cancer pain has a neuropathic component.\textsuperscript{10} Aside from cancer-related surgery and chemotherapy, the cancer itself leads to neuropathic pain either by tumour invasion of nociceptors or by inflammatory cytokine leakage from cancerous cells.\textsuperscript{142} Given the protracted inflammation, a sustained level of nociceptor activation could lead to persistent changes in neuronal connectivity, changing the response thresholds and intensities and transmitting innocuous stimuli as painful.\textsuperscript{116}

Variants in prostaglandin-endoperoxide synthase 2, PTGS2, tumour necrosis factor, TNF, and NFkB inhibitor-α, NFKBIA, genotyped in Ref. 116, and tumour necrosis factor-β, LTA, genotyped in Ref. 114, have been reported to be associated with severe cancer pain. In another study, an aggregate of phenotypes that includes high pain intensity has been reported to be associated with the cumulative effect of variants in nitric oxide synthase-3, NOS3; interleukin-1β, IL1B; tumor necrosis factor receptor superfamily member 1B, TNFRSF1B; PTGS2; and
interleukin-10 receptor-β, IL10RB. In addition, pain-protective variants in GCH1-encoded GTP cyclohydrolase, also involved in nitric oxide production, have been reported in patients with advanced cancer. These studies converge on a suggestive role for the immune system in modulating the extent of neuropathic pain accompanying cancer.

On the other hand, several studies have shown association with mediators of neurotransmission and even members of the pain-inhibition pathway. Variants in voltage-gated potassium ion channel encoding KCNS1, KCNJ3, KCNJ6, and KCNK9 have been reported in women with breast cancer pain before surgery, and variants in catechol-O-methyltransferase (COMT) and membrane-bounded P-glycoprotein (ABCB1) in charge of clearing exogenous opioids have also been reported to be associated with pain in cancer patients.

Last, mitogen-activated protein kinase 1 (MAPK1)—a broad-spectrum regulator—has also been implicated in cancer pain.

### 3.2.6. Postoperative pain

Persistent postoperative pain is generally defined by the lower duration boundary of 2 to 6 months. Among putative causal mechanisms are nerve damage, which recruits immune cells and a prolonged state of inflammation during the acute period. In either case, inflammatory cytokine barrage leads to sustained nociceptor activity, which may result in a rewired pain transmission system.

Two studies of postmastectomy patients, in whom neuropathic pain prevalence has been estimated to be up to 68%, reported associations between persistent breast pain and variants in interleukin-1 receptor type 2, IL1R2, interleukin-10, IL10, and purinergic receptor 7, P2RX7.

Several variants in genes directly involved in neurotransmission have also been reported as risk modifiers in persistent postoperative pain, specifically μ-opioid receptor (OPRM1) in a postabdominal surgery cohort, voltage-gated potassium channel subunit (KCNS1) in 2 limb amputation cohorts and 1 postmastectomy cohort, and stargazin (CACNG2)—involved in the trafficking of AMPA receptors—in a postmastectomy cohort. Variants in GTP hydrolase, encoded by GCH1, have been reported to modulate postoperative pain in 2 studies.

The first genome-wide scan in a postoperative pain cohort (individuals with knee and hip replacement surgery) was published this year. The strongest associated variant, just shy of genome-wide significance (rs887797, P = 1.29 × 10e-7), lies in PRKCA, which encodes protein kinase C alpha, and the next best association is for a variant in MAT2B (rs7734804, P = 5.25 × 10e-6). Both of these associations were confirmed in one of their 2 replication joint-related neuropathic pain cohorts.

### 3.2.7. Other conditions

In several studies, neuropathic pain conditions were grouped into 1 phenotype, such that an association would indicate a link to condition-agnostic neuropathic pain. In 1 such study, a variant in dopamine receptor DRD2 has been shown to be associated with susceptibility to pain, given one of the following primary conditions:

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**Table 2**

| SNP ID  | Gene | Minor allele | Effect (OR) | P      | FDR    |
|---------|------|--------------|-------------|--------|--------|
| rs1518110 | IL10 | C            | 1.1023      | 0.0013 | 0.0615 |
| rs1518111 | IL10 | C            | 1.1005      | 0.0017 | 0.0615 |

FDR, false discovery rate; OR, odds ratio; SNP, single nucleotide polymorphism.

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Figure 1. Results of association analysis for genetic variants reported for common neuropathic pain conditions (Table 1) with pain in different body sites (A-D) and neuropathic pain (E) in the UKBB cohort. In each quantile-quantile plot, the P values smaller than expected by chance surpass at least 3 of the fixed thresholds of statistical significance (false discovery rate = 5%, 10%, and 20%).
In addition, transient receptor potential channels, TRPA1 and TRPV1, have been reported to affect somatosensory sensitivity in patients with neuropathic pain who had a variety of neuropathic conditions. A variant in SCN9A has also been reported to have association with pain by a group that examined 5 different cohorts with neuropathic pain.

### Table 3

| Type of pain | SNP ID   | Gene     | Minor allele | Effect (OR) | P     | FDR   |
|--------------|----------|----------|--------------|-------------|-------|-------|
| **Back**     | rs7734804 | MAT2B    | T            | 1.20        | 1.3e-8 | 9.5e-7 |
|              | rs1800796 | IL6      | C            | 1.09        | 2.0e-4 | 6.0e-3 |
|              | rs6277    | DRD2     | A            | 0.96        | 2.4e-4 | 6.0e-3 |
|              | rs2591168 | KCNJ3    | A            | 0.96        | 8.7e-4 | 1.6e-2 |
| **Hip**      | rs7734804 | MAT2B    | T            | 1.16        | 2.0e-4 | 1.4e-2 |
|              | rs6277    | DRD2     | A            | 0.96        | 3.9e-4 | 1.4e-2 |
| **Knee**     | rs2591168 | KCNJ3    | A            | 0.96        | 1.4e-4 | 8.4e-3 |
|              | rs6277    | DRD2     | A            | 0.97        | 4.3e-4 | 8.4e-3 |
|              | rs7734804 | MAT2B    | T            | 1.11        | 4.5e-4 | 8.4e-3 |
|              | rs2836050 | KCNJ6    | T            | 1.04        | 1.8e-3 | 2.0e-2 |
| **Neck**     | rs2591168 | KCNJ3    | A            | 0.95        | 4.3e-5 | 3.2e-3 |
|              | rs2836050 | KCNJ6    | T            | 1.05        | 3.7e-4 | 1.4e-2 |
|              | rs7734804 | MAT2B    | T            | 1.12        | 6.6e-4 | 1.6e-2 |
|              | rs1800796 | IL6      | C            | 1.08        | 9.7e-4 | 1.8e-2 |
|              | rs4411417 | GCH1     | C            | 0.97        | 1.4e-3 | 2.1e-2 |
|              | rs7529886 | GCH1     | T            | 0.97        | 3.2e-3 | 4.0e-2 |

Associations with rs7734804 (upstream of MAT2B), highlighted in boldface, are in the same direction as in the original study. FDR, false discovery rate; OR, odds ratio; SNP, single nucleotide polymorphism.

3.3. Replication in UKBB

We analysed the list of variants reported in association studies of common neuropathic pain conditions (Table 1) for replication with neuropathic pain in UKBB. Associations for 2 single nucleotide polymorphisms (SNPs) on 1 haploblock of IL10 pass correction for multiple testing at false discovery rate 20% (Table 2). Previously reported in a postoperative pain cohort, these replicated associations, albeit nominal, give us increased confidence in the contribution of inflammatory mediators to neuropathic pain in a condition-agnostic manner, underscoring the importance of neuroimmune interactions already suspected to contribute to neuropathic pain.

In addition, we tested the list of variants in Table 1 for association with pain in 4 body sites—back, hip, knee, and neck—in all of which chronic pain may indicate neuropathy. Results of these association analyses are shown in quantile-quantile plots (Fig. 1), which are a statistical tool to visualise the deviation of the observed distribution of association P values (log transformed) from the one expected by chance, given uniform sampling in the P-value space. Notably, although in all 4 sites several SNPs are associated with P values passing the false discovery rate 5% threshold, SNP rs7734804, whose minor allele was originally reported as risk-conferring in a neuropathic pain cohort, whose direction of effect in all 4 sites and with back pain with genome-wide significance (P = 1.3e-8, odds ratio = 1.2; Table 3).

4. Conclusion

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. Nevertheless, neuroimmune interactions have emerged with a central role in neuropathic pain pathophysiology, supported by additional evidence from the UKBB study. 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.

Conflict of interest statement

L. Diatchenko declares a potential conflict of interest as a co-inventor of the patent-pending application on genetic variants of the COMT enzyme contributing to pain phenotypes. L. Diatchenko is also a board member, consultant, and shareholder of Algynomics, Inc and Proove Biosciences. The other authors have no conflict of interest to declare.

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