Review Article

Genetics of musculoskeletal (TMD) and neuropathic orofacial pain: a narrative review

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Background and Objective: Orofacial pain is a debilitating condition affecting individuals' quality of life. Differences in pain perception and analgesia have been reported between individuals, suggesting genetics as a contributing factor. This genetic component of orofacial pain can be best defined as complex due to contributions from multiple genes, which interact with each other and additional environmental factors. The objective of this review was to provide a summary of the progress made in the field of musculoskeletal [temporomandibular disorders (TMD)] and neuropathic orofacial pain genetics.

Methods: PubMed database was searched using the following Medical Subject Headings: (("Facial Pain/genetics"[Mesh]) OR ("Trigeminal Neuralgia/genetics"[Mesh]) OR ("Trigeminal Nerve Diseases/genetics"[Mesh]) OR ("Temporomandibular Joint Disorders/genetics"[Mesh])). The search was limited to publications in English. No time-frame restriction was used.

Key Content and Findings: In this review, we discuss progress made in the field of orofacial pain genetics with the focus on non-malignant and non-odontogenic musculoskeletal, i.e., TMDs and forms of trigeminal neuropathic pain including post-traumatic trigeminal neuropathic pain (PTTN) and trigeminal neuralgia (TN). Available evidence supports the role of genetics in orofacial pain with variations in voltage gated ion channels, transient receptor potential channels, and GABA receptor-binding genes possessing the strongest support.

Conclusion: For most cases, orofacial pain conditions such as TMDs, TN, and PTTN follow a complex multifactorial pattern of inheritance with multiple compounding environmental and genetic factors. Under such conditions, the effect of individual genetic variation is modest. Defining the implications of individual genetic factors would thus require large samples of hundreds or thousands of carefully diagnosed patients and well-matched controls to provide sufficient statistical power. Rare damaging mutations that have a major effect on risk probably account for a small portion of cases due to aggregation in families, but nonetheless may be valuable for identifying pathophysiological mechanisms. Overall, the current evidence strongly suggests that inherited genetic differences among individuals make an important contribution to the development and severity of pain in conditions such as TMDs, TN, and PTTN. Future research should be aimed at identifying both the common variants with modest effects and rare damaging mutations with large effects on increasing patient risk. Such findings would offer promising avenues for development of novel therapeutic approaches to improve treatment for patients suffering from these debilitating conditions.

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Introduction

Orofacial pain is a debilitating condition affecting individual's quality of life. In the United States, the cost related to orofacial pain healthcare expense, disability and lost productivity is estimated to be over $4 billion annually (1). The exact pathophysiologies of orofacial pain conditions remain unclear. The challenge of studying the etiology of orofacial pain conditions may be attributed to their variable phenotype and treatment approaches aiming to alleviate symptoms rather than the underlying pathology. Understanding the complex biological mechanisms involved in the development and maintenance of chronic orofacial pain is of at most importance for the development of effective treatment approaches. In this review, we aimed to provide a summary of the progress made in the field of orofacial pain genetics with the focus on temporomandibular disorders (TMDs), post-traumatic trigeminal neuropathic pain (PTTN) and trigeminal neuralgia (TN).

There are two types of chronic pain: nociceptive/inflammatory pain and neuropathic/neurogenic pain. Nociceptive/inflammatory pain is associated with inflammation and is caused by tissue damage while neurogenic pain is caused by central and/or peripheral nerve damage (2). Both types of pain are thought to follow a complex or multifactorial mode of inheritance with multiple genetic and environmental factors as well as their interactions being implicated. This review focuses on genetic contributions to non-odontogenic orofacial pain in particular musculoskeletal pain of temporomandibular disorders (MS TMDs) and trigeminal neuropathic pain i.e., PTTN and TN.

Pain, including orofacial pain, is a highly personal, multidimensional somatosensory experience that can be affected by numerous biological, pharmacological, psychological, genetic, and environmental influences. The expression of such pain varies from one person to another. All individuals differ in their perception of pain and how they respond to painful and/or anxiety-provoking stimuli. Accumulating body of evidence supports the role of genetics in susceptibility to pain and in the variability in responses to having pain. Inter-individual differences in responses to experimental pain have been reported (3). Additionally, studies have shown that it may be possible to identify individuals susceptible to the development of painful conditions later on in life (4). However, the question remains "Of the genes relevant to pain, which ones when inherited in different forms (i.e. with different DNA sequences or 'alleles') are responsible for inherited variability?" (5). The vast majority of the identified genes do not code for well-known pain molecules, which suggests that they might be relevant to developing the pathology itself rather than pain within that pathology. Therefore, these pain molecules are related more to susceptibility of developing the painful disorder than to the pain levels within the disorder (6).

Majority of animal studies investigating genetics of neuropathic pain focused on spinal system. Cell bodies of the sensory neurons of the spinal system are located in the dorsal root ganglia (DRG) while sensory neurons of the trigeminal system are located in the trigeminal ganglion (TG). Although, DRG and TG are homologs of each other, differences between them exist. While nociceptors in these two tissues show a high degree of functional similarity, there are important differences in their development lineages and their functional connections to the CNS. The most prominent difference is the proximity of the trigeminal system to the CNS compared to relatively long trajectory of afferent axons in the spinal system. Trigeminal system has been shown to be more resistant than spinal to developing NP following injury (7). Moreover, sympathetic nerve sprouting around large ganglionic neurons have been reported in the DRB but not TG (8). Finally, genome-wide analyses of baseline gene expression in the TG and DRG of rats (9) and mice (10) suggest that they possess some unique genomic signatures. These differences between TG and DRG support the idea that different molecular mechanisms are involved in the baseline functional properties of the two systems and may partly explain differences in response to injury or disease such as NP.

The genetic component of orofacial pain can be best defined as complex, in most cases due to modest

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contributions from multiple genes, their interactions as well as interactions with environmental factors. Genes themselves can be a risk factor for orofacial pain conditions, they can amplify an existing polygenic risk, or they can exacerbate the effects of environmental risk factors. In recent years, genetic research has focused on identifying "signature" genes, i.e., genes that are either significantly up- or downregulated with respect to background measures or genes in which genetic variations are significantly associated with various orofacial pain conditions, to arrive at a possible molecular explanation for these diseases. Additionally, when investigating genetics of clinical pain conditions, it is important to differentiate between genetic contributions to a condition itself from the genetic contribution to pain processing.

The objective of this review was to provide a summary of the progress made in the field of orofacial pain genetics with the focus on non-malignant and non-odontogenic musculoskeletal pain conditions, i.e., TMDs, forms of trigeminal neuropathic pain including PTTN and TN.

We present the following article in accordance with the narrative review reporting checklist (available at https://fomm.amegroups.com/article/view/10.21037/fomm-22-12/rc).

Methods

This is a narrative review of genetic factors contributing to musculoskeletal (TMDs) and neuropathic orofacial pain conditions including PTTN and TN. Relevant research was identified using a search of PubMed database. The search was limited to publications in English. We did not specify restrictions on the year of the publications. Only full text articles were considered. An electronic PubMed search was performed on February 14, 2022. The following MeSH (Medical Subject Headings) database terms were used in the search: (("Facial Pain/genetics"[Mesh]) OR ("Trigeminal Neuralgia/genetics"[Mesh]) OR ("Trigeminal Nerve Diseases/genetics"[Mesh]) OR ("Temporomandibular Joint Disorders/genetics"[Mesh])). Two hundred forty nine articles were identified using these search terms. The resulting publication list (title and abstract) was examined for eligibility. Original research studies pertaining to genetics of musculoskeletal pain in the face (TMDs) and trigeminal neuropathic pain (TN and PTTN) were considered. Relevant publications were retrieved electronically. References in the included articles were checked and relevant studies that were missed by the electronic search were added. Studies were cited as deemed relevant by the authors (*Table 1*).

Discussion/summary

TMDs

Orofacial pain is a major symptom of TMDs (11) and TMDs comprise a significant proportion of the total orofacial pain cases. The prevalence of temporomandibular joint disorders has been estimated to be 31.1% among adults/elderly and 11.3% among children/adolescents (12). The incidence of first-onset of TMDs has been estimated to be approximately 3.5% per year (13). The exact causes of TMDs are largely unknown. For many people symptoms start without an obvious triggering event. It has been postulated that sex-genotype dependent susceptibility involving multiple genes, with the additive or multiplicative effects, together with environmental exposures, including the effect of risk-conferring behaviors, and not the mutation in a single gene, form the basis of TMDs phenotypes and treatment response (14). Therefore, TMDs are believed to be a complex, multifactorial condition, in which multiple genes and factors such as mechanical, and/or psychic stresses, hormones, ethnicity, social status, and gender as well as the interactions between them contribute to the disease susceptibility and phenotype (15). It is possible that genetic factors contribute to the clinical heterogeneity observed among patients with TMDs and influence the extent to which environmental factors and risk-conferring behaviors manifest their effects. Heritability of TMDs has been estimated to be approximately 0.35 (95% confidence interval: 0.17 to 0.51). This indicates that 35% of the individual differences observed in TMDs may be attributed to genetic differences between individuals (16). The heterogeneity of TMD phenotypes has made identification of genetic contributions challenging.

Limited number of clinical and animal studies that investigated genetic contributions to TMDs identified number of genes associated with an increased risk of various TMD manifestations (17). Structural function genes such as *ACTN3* (alpha-actinin-3), *GSTM1* (glutathione S-transferase mu 1), *MTHFD* (C-1-tetrahydrofolate synthase, cytoplasmic), and *MTRR* (methionine synthase reductase) have been associated with increased risk of temporomandibular dysfunction (18-20). *HLA-DRB1* (21) genes have been associated with osteophyte formation, erosion of the mandibular condyle, closed lock, clicks,

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Table 1 The search summary strategy

Items	Specification
Date of Search	02/14/2022
Databases and other sources searched	PubMed
Search terms used	"Facial Pain/genetics"[Mesh]) OR ("Trigeminal Neuralgia/genetics"[Mesh]) OR ("Trigeminal Nerve Diseases/genetics"[Mesh]) OR ("Temporomandibular Joint Disorders/genetics"[Mesh])
Timeframe	None
Inclusion and exclusion criteria	Inclusion: • Original research articles relevant to the topic of interests were included in the study • Articles published in English language • Full text articles Exclusion: • Articles published in languages other than English • Conference papers • Review articles
Selection process	Articles relevant to the topic of interest were selected

crepitus, and bone erosion. Additional gene associations include: HLA-DRB1*01 (human leucocyte antigen) *DRB1* allele with joint erosions, *DR54* and *DR11* alleles with higher susceptibility to degenerative process, and *DR54* and *DR52* alleles with a higher severity of degenerative process. These identified alleles are all associated with risk factors for developing TMDs (21,22). Contrarily, other variants including DRB1*12:01, DQB1*03:01, DRB1*06, DQA1*05:01, and HLA-B27 have been shown to be protective against temporomandibular joint (TMJ) arthritis (21,22).

A genome-wide association study identified 22 independent loci showing association with degeneration of the mandibular condyle (23). Among the identified loci polymorphisms in *TSPAN9* (tetraspanin 9) were strongly associated with development of TMDs (23). Articular disc alterations have also been linked to genetic variations in the *ADAMTs* (a disintegrin and metalloproteinase with thrombospondin motifs) gene family. This is due to the fact that when major degenerative conditions are present, collagen synthesis related genes, particularly *ADAMTs5*, is associated with a disc destruction (24,25). Additionally, matrix metalloproteinases (MMPs) play a role in cartilage degradation (26) and have been implicated in internal derangements of TMJ (20,27-29). Variations in the *MMP-1* gene have been associated with disc displacement without reduction (30). Additionally, variations in *MMP-1* (31), *ANKH* (32), *ESR1* (33), and *ADAMTS-5* (25) genes have been associated with osteophyte formation, erosion of the mandibular condyle, closed lock, clicks, crepitus, bone erosion. Finally, inflammatory response genes such as *IL17A* (interleukin 17A), *IL1B*, and *IL6* have been implicated in increasing individuals' risk of TMDs (34-37) as these genes encode proinflammatory cytokines that can accumulate in synovial liquid and lead to bone destruction. For a systematic review of genes showing evidence of association with TMD please refer to Sangani *et al.* 2015 (38) and Scariot *et al.* 2018 (39).

Among different TMDs, the ones associated with chronic pain are the most challenging to manage. Data from a large number of adult female twins with TMDs, showed that variation in TMD related pain could in part be attributed to genetics (16). Several genes responsible for neuromodulation and neurotransmission of pain including *CAMK4* (calcium/calmodulin-dependent protein kinase type IV), *COMT* (catechol-O-methyltransferase), *DRD4* (dopamine D2-like G protein-coupled receptor 4), *HTR2A* (5-hydroxytryptamine receptor 2A), and *HTR2C* have been implicated in increased risk of painful TMDs (17,28,40,41). COMT enzyme activity has been inversely correlated to pain sensitivity and the development of TMDs. Nearly a third of new TMD cases reported have been suggested to

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be attributed to such variation in the *COMT* gene (26). Additionally, variations in five genes: *NR3C1*, *CAMK4*, *CHRM2*, *IFRD1*, *and GRK5* have been identified as potential risk factors for pain associated with TMDs (17). Variation in *NR3C1*, specifically, has been associated with increased risk of TMDs (17) and pain intensity in TMD patients (42). *NR3C1* encodes the glucocorticoid receptor, which serves as a binding site for cortisol and plays a major role in the hypothalamic-pituitary-adrenal (HPA) system (a primary stress axis in humans). The increased daytime cortisol levels observed in TMD patients (43) has been attributed to an increased activation of the HPA axis through conscious pain perception by the TMD patients. The role of *CAMK4*, *CHRM2*, *IFRD1*, and *GRK5* genes in pain associated with TMD remains unclear. The *CAMK4* (calcium/calmodulin-dependent protein kinase type IV) encodes for a multifunctional serine/threonine protein kinase with limited tissue distribution that has been implicated in transcriptional regulation in neurons. Its activity affects learning, memory (44), and development of opioid analgesic tolerance (45). The *CHRM2* gene encodes for muscarinic cholinergic receptor 2 that binds acetylcholine and controls cellular responses such as adenylate cyclase inhibition, phosphoinositide degeneration, and potassium channel mediation in both the central and peripheral nervous system. *IFRD1* is a histone-deacetylase-dependent transcriptional co-regulator. It controls inflammation, the growth and differentiation of specific cell types during embryonic development, and tissue regeneration. Mutations in *IFRD1* gene have been associated with sensory/motor neuropathy and ataxia (46). The *GRK5* gene regulates the activity of G protein-coupled receptors, including those implicated in chronic pain (adrenergic receptor B2, *ADRB2*) (47,48). One such G protein-coupled receptor implicated in the chronic pain process, ADRB2, is a primary target for epinephrine. Individuals carrying one haplotype encoding high and the other low *ADRB2* expression were shown to be 10 times less likely to develop TMDs, suggesting that imbalances in ADRB2 function increases the risk of TMD development (49). Furthermore, the TNFA-308 polymorphism has been shown to be positively associated with TMD, such that TMD subjects had 2.87 times greater chance of having the GA genotype than did healthy controls (50). In addition, individuals homozygous for the rare A-allele demonstrated deceased pain sensitivity for temporomandibular joint and anterior fascicle of the temporal muscle in the pressure pain threshold tests compared with G-allele homozygotes (50). Finally, hormones have been implicated in increased risk and severity of TMDs, which could explain higher incidences of TMD, as well as chronic pain, in woman compared to men (51). The variations in the estrogen receptor-α (ESR1) that have been associated with TMD related pain and temporomandibular joint osteoarthritis in females supports this (33,52,53). The summary of genes showing evidence of association with painful TMDs is provided in *Table 2*.

It is important to recognize that pain perception genes may be responsible for inter-individual difference in how TMDs are perceived and that they may not necessarily be involved in the actual disease development and progression. Due to very heterogeneous manifestations of TMDs, identification of genes contributing to TMDs and specifically contributing to pain due to TMDs has proven challenging. Additionally, heterogeneity in studies' populations and limited sample sizes further hinders the ability of research to identify genes with subtle effects and may explain the lack of replication of the findings. Therefore, despite extensive efforts, the molecular mechanisms of painful TMDs remains largely unknown. Genes involved in the development of TMJ structures, as well as immune-inflammatory responses may predispose some individual to TMD development. Variations in genes involved in pain perception and modulation are likely to be important for the development of chronic pain conditions such as TMDs. Better understanding of genetic factors modulating TMDs is necessary for the development of more effective, innovative therapies.

TN

TN is a rare, debilitating condition characterized by mostly unilateral facial pain within the innervation of trigeminal nerve that lasts from seconds to a few minutes. The pain is excruciating, short-lasting, usually described as 'electric-like' or 'sharp,' and is oftentimes triggered by light touch in the affected area, however, the pain can also occur spontaneously without an obvious trigger (54). Four types of TN have been described: classical TN that is purely paroxysmal (TN developing without apparent cause other than neurovascular compression), classical TN with concomitant continuous pain (TN developing without apparent cause other than neurovascular compression), secondary TN (TN due to an underlying disease), and idiopathic TN (TN with neither electrophysiological tests nor MRI showing significant abnormalities) (55). In this

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Table 2 Summary of positive associations of genetic variations and painful TMDs. For systematic review of investigated genes please refer to Sangani *et al.* 2015 (38) and Scariot *et al.* 2018 (39)

Gene ID	Protein encoded	Population	Change associated with NP	References
COMT	Catechol-O-methyltransferase	Combined OPPERA and UNC Cohort	rs174697 minor allele A—increased risk against TMD; enzyme activity inversely correlated with pain sensitivity and development of TMD; HPS haplotype—increased risk of TMD	(17)
DRD4	Dopamine D2-like G protein-coupled receptor 4	86 TMD cases and 143 healthy controls	Long allele (48 bp-repeat)—increased risk of TMD	(40)
HTR2A	Serotonin 2A receptor	Combined OPPERA and UNC Cohort	rs9316233 minor allele G—protective effect against TMD	(17)
NR3C1	Glucocorticoid receptor	Combined OPPERA and UNC Cohort	Minor alleles at 3 SNPs (rs2963155, rs9324918 and rs33389) identified in this gene showed protective effect against TMD	(17)
CAMK4	Calcium/calmodulin-dependent protein kinase 4	Combined OPPERA and UNC Cohort	rs3756612 minor allele G—increased risk of TMD; rs10491334 minor allele T—protective effect of TMD	(17)
CHRM2	Muscarinic cholinergic receptor 2	Combined OPPERA and UNC Cohort	rs7800170 minor allele A—protective effect against TMD	(17)
IFRD1	Interferon-related developmental regulator 1	Combined OPPERA and UNC Cohort	rs728273 minor allele G—increased risk against TMD	(17)
GRK5	G protein-coupled receptor kinase 5	Combined OPPERA and UNC Cohort	rs12415832 minor allele A—increased risk of TMD	(17)
ESR1	Estrogen receptor-α	100 women with painful TMJD, 100 women with TMJD and no pain and 100 women without TMJD	GC haplotype of the XbaI locus more prevalent in painful TMJD	(33)
		TMJ OA patients	PX haplotype at Pvu II and XbaI restriction fragment polymorphisms associated with significantly higher risk of moderate or severe pain	(53)

OPPERA, Orofacial Pain: Prospective Evaluation and Risk Assessment cohort study; UNC, University of North Carolina Pain Clinic cohort; SNP, Single nucleotide polymorphism; HPS, high pain sensitivity haplotype; TMJD, temporomandibular joint disorders; OA, osteoarthritis; TNP, trigeminal neuropathic pain.

review, we will focus on classical and idiopathic TN.

The incidence of TN has been estimated to range from (12.6–27)/100,000 (56). Incidence begins at 50–60 years and has been known to increase with age: in 60 to 69-year-old the incidence is 17.5/100,000, whereas in >80-year-old, it is 25.9/100,000 (57,58). There is a significant burden of the disease and decrease in patients' quality of life, as patients suffer considerable pain and disability, even when they are prescribed the most optimal drug regimens currently available (59).

The pathophysiology of TN is not fully understood, however, both peripheral and central mechanisms have been implicated (60). Peripherally, demyelination of the trigeminal nerve at the root entry zone may lead to hyperexcitability of the primary trigeminal afferents (60) with sodium and potassium channels being implicated in this ectopic activity (61). The ectopic impulses may cause ephaptic cross talk between fibers mediating light touch and those involved in generation of pain, which would explain the pain attacks following light stimulation of trigger zones sustained by TN patients (60). Central mechanisms contributing to TN also may involve hyperexcitability of 2nd order neurons within the trigeminal brainstem sensory nuclei or 3rd order neurons in thalamus projecting to the cortical gray matter.

Etiology of the classical TN has been largely attributed

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to trigeminal nerve damage caused by vascular compression of the nerve near its entry to the brain (the root entry zone). However, up to 15% of the general population have such neurovascular compression, but only very few develop TN. This implies that other factors, such as genetics, contribute to the etiology of TN. Mutations in the *MPZ* (myelin protein zero) gene (62,63) and voltage gated ion channel coding genes (64) have been implicated. Additionally, inherited anatomical abnormalities (64-67) and familial neuropathic disease, such as Charcot-Marie Tooth (67), are also believed to contribute to TN. Summary of positive associations of genetic variations and TN are presented in *Table 3*.

Familial clustering of TN has been observed. The prevalence of familial TN among individuals diagnosed with TN has been estimated to about 1–2% (68,69,75), implying that genetic factors may contribute to the development of the disease (69,76-78). Most of the studies of familial TN suggest an autosomal dominant inheritance (62,64-66,78-80) with potentially variable penetrance [28]; however, the genetic basis of TN remains largely unknown. A whole-exome sequencing study of 11 TN patients (69) identified 41 variants in ion channels including sodium channels [6], potassium channels [10], chloride channels [5], calcium channels [7], transient receptor potential channels [12], and gap junction channels [1]. Additionally, a previously identified gain-of-function mutation (Nav1.8 p.Ala1304Thr) in the *SCN10A* gene encoding sodium channel Nav1.8 was identified in one TN patient and was not found in unaffected siblings (69). Another study suggested that a novel missense mutation (c.A406G; p.Met136Val) in *SCN8A* gene (encoding sodium channel $Na_V1.6$) reduces the threshold for action potential in the trigeminal ganglion (TRG) neurons and potentiates both transient and resurgent sodium currents, causing increased excitability in TRG neurons which has been suggested to play a role in TN (70). The authors suggested that this gain-of-function mutation in the $Na_V1.6$ channel might also exacerbate the pathophysiology of vascular compression and therefore additionally contributing to TN (70). Additionally, mRNA levels of *Nav1.7* were found to be downregulated and mRNA levels of *Nav1.3* were found to be upregulated in the gingival tissue of TN patients (71). These findings suggest that TN might be a channelopathy where demyelination could induce injury to the membrane of small myelinated (Aδ) fibers resulting in upregulation of Nav1.3 and downregulation of Nav1.7 in injured nerve endings as in traumatic neuropathic pain (81-83). Furthermore, another whole exome-sequencing study implicated impairment of GABA signaling and neuronal ion transport in the pathophysiology of TN (72). The analyses of 290 TN probands, including 20 multiplex kindreds and 70 parent-offspring trios, identified higher frequency of rare damaging variants in GABA receptor-binding genes, as well as in sodium and calcium ion channel genes, in TN cases. In particular, a variation in the α-1H subunit of the voltage-gated Ca^{2+} channel Cav3.2 encoded by *CACNA1H* gene was found to be associated with TN (72). Additionally, a reduction in calcium dependent inactivation of the Cav2.1 channel has been implicated in TN (84). A missense mutation (Pro2455His) in the *CACNA1A* gene encoding Cav2.1 alters the channel's gating properties leading to changes in $Ca_v2.1$ dependent synaptic communications in the trigeminal system (68,84). This results in a depolarizing shift in the voltage-dependence of activation and deactivation of the Cav2.1 channel that has been implicated in the etiology of TN (84). Furthermore, a G163T mutation in the *MPZ* (myelin protein zero) gene has been associated with Charcot-Marie-Tooth (CMT) disorder and therefore is indirectly associated with TN (63). Variations in *SLC6A4* gene, coding for 5-HTTLPR (a serotonin transporter), in particular polymorphism rs25531, has been associated with susceptibility to TN, pain severity of TN, and treatment response to carbamazepine (73). Finally, changes in serum micro RNA (miRNAs) profile, specifically changes in serum levels of miR-132-3p, mir-146-5p, miR-155-5p and miR-384, have been linked to increased occurrence and development of TN (74). These miRNA target genes involved in the proliferation and migration of Schwann cells, as well as nerve regeneration and apoptosis (74). Reduction in proliferation and migration of Schwann cells as well as inhibition of regeneration and apoptosis of nerve cells has been suggested to play a role in TN, however the exact mechanisms by which differential miRNA expression contributes to TN development remains unclear.

In summary, despite the relatively few clinical studies on the role of genetic factors in TN, emerging bodies of evidence suggests a significant genetic component in the signal transduction channels involved in the disorder's pathophysiology. Based on the reported findings, TN like other neuropathic pain conditions, is proposed to follow a complex, multifactorial pattern of inheritance with multiple genes of small effects and their subsequent interactions

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Table 3 Summary of positive associations of genetic variations and trigeminal neuralgia (TN). For a systematic review of investigated genes please refer to Mannerak *et al.* 2021 (68)

Gene ID	Protein encoded	Population	Change associated with NP	References
SCN2A, *SCN3A*, *SCN5N*, *SCN7A*, *SCN9A*, *SCN10A*	Sodium channels	11 cases with familial TN	Variants in sodium channels identified in familial TN	(69)
TRPA1, *TRPC6*, *TRPM2*, *TRPM3*, *TRPM4*, *TRPM7*, *TRPM8*, *TRPS1*, *TRPV4*, *TRPV5*, *TRPV6*	Transient receptor potential cation channels	11 cases with familial TN	Variants in transient receptor potential cation channels identified in familial TN	(69)
KCNA5, *KCNC3*, *KCND2*, *KCNH2*, *KCNH7*, *KCNJ6*, *KCNK17*, *KCNS2*, *KCNV1*	Potassium voltage-gated channels	11 cases with familial TN	Variants in potassium voltage-gated channels identified in familial TN	(69)
CACNA1A, *CACNA1D*, *CACNA1G*, *CACNA1I*, *CACNA1S*, *CACNB1*	Calcium voltage-gated channels	11 cases with familial TN	Variants in calcium voltage-gated channels identified in familial TN	(69)
CLCN1, *CLCN2*	Chloride voltage-gated channels	11 cases with familial TN	Variants in chloride voltage-gated channels identified in familial TN	(69)
CLIC5	Chloride intracellular channel 5	11 cases with familial TN	Variants in CLIC5 identified in familial TN	(69)
GJB5	Gap junction protein beta 5	11 cases with familial TN	Variants in this gene identified in familial TN	(69)
SCN10A	Sodium voltage-gated channel alpha subunit 10	11 cases with familial TN	Gain-of-function mutation (Nav1.8 p.Ala1304Thr) identified in familial TN	(69)
SCN8A	Sodium voltage-gated channel alpha subunit 8	TN case	Missense mutation (c.A406G; p.Met136Val) identified in familial TN	(70)
SCN9A	Nav1.7	10 patients with TN	mRNA downregulated in gingival tissue of TN patients	(71)
SCN3A	Nav1.3	10 patients with TN	mRNA upregulated in gingival tissue of TN patients	(71)
GABA	Gamma-Aminobutyric Acid	290 TN probands	Higher frequency of rare damaging variants in GABA receptor-binding genes	(72)
CACNA1H	Calcium voltage-gated channels subunit alpha 1H	290 TN probands	Variation in CACNA1H associated with TN	(72)
SLC6A4	5-HTTLPR (a serotonin transporter)	244 TN patients and 280 age and sex matched healthy volunteers	rs25531 associated with susceptibility to TN, pain severity of TN and response to carbamazepine	(73)
miR-132-3p, mir-146-5p, miR-155-5p and miR-384	Micro RNAs	28 TN patients and 31 healthy controls	Changes in serum micro RNA levels linked to increased occurrence and development of TN	(74)

being implicated. The variations in voltage gated ion channels (sodium, potassium, calcium, and chloride) and transient receptor potential channels that lead to increased neuronal excitability and increased sensitivity of trigeminal ganglion neurons, have been suggested to play a role in the development of TN. Additionally, mutations in GABA receptor-binding genes resulting in impaired GABA signaling and neuronal ion transport has been suggested to contribute to TN phenotype. Variations in the serotonin transporter gene have been associated with TN pain

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severity and response to carbamazepine. Finally, changes in serum micro-RNA profile that affects expression of the target genes has also been implicated in TN (74).

PTTN

Painful PTTN is a known complication that may occur following either major craniofacial/oral trauma or may be subsequent to relatively minor dental treatments. A wide variety of nerve injuries, ranging from mild to severe, can lead to PTTN. These include external trauma, iatrogenic injuries from dental interventions such as root canal therapies, extractions, oral surgery, dental implants, orthognathic surgery, local anesthetic injections, or other invasive procedures (85). Painful neuropathies may present with a clinical phenotype involving combinations of spontaneous and evoked pain of positive (e.g., dysesthesia) and negative (e.g., numbness) symptomatology (86). Thus, wide inter-individual differences in the onset and presentation of PTTN following identical injuries exist. Research suggests that this variability is due to a combination of environmental, psychosocial, and genetic factors (87).

Traumatic injuries to the trigeminal nerve largely result in either no residual deficit or in a non-painful neuropathy, as only a minority of cases develop into a painful neuropathy. Estimates of the prevalence of PTTN are lacking, which is partly due to changing diagnostic terms and criteria. In general, approximately 3% of patients with trigeminal nerve injuries develop PTTN (88). This entity can have a negative effect on patients' quality of life and wellbeing as it interferes with a variety of social functions and daily activities (89). Therefore, PTTN is associated with a substantial psychosocial burden (90). PTTN patients with severe pain demonstrate elevated levels of depression, pain catastrophizing, and substantially reduced quality of life and coping efficacy levels (89).

Neural damage can induce many facets of pain which can be generated by injury or changes originating in peripheral nerves (peripheral neuropathy), in a ganglion (ganglionopathy), in a dorsal root (radiculopathy), or from the central nervous system (central neuropathy). PTTN shares many pathophysiological mechanisms with other peripheral neuropathic pain conditions. A cascade of events occurs in the nervous system following traumatic injuries common to the conditions. Such events are time dependent and progress from the peripheral to the central nervous system. These include alterations in functional, biochemical, and physical characteristics of neurons and glia which inherently vary based on individual genetic makeup (87,91-93). These changes lead to hyperexcitability of primary trigeminal afferent. Peripheral sensitization as well as hyperexcitability of second order neurons of the medullary dorsal horn are an expression of that hypersensitivity and contribute to the development and maintenance of neuropathic pain.

Summary of positive associations of PTTN and genetic contributions is presented in *Table 4*. Most of the data on genetic contributions to PTTN come from animal studies of nerve injuries. These studies propose a wide range of genes associated with PTTN development and maintenance. Infraorbital nerve injury has been associated with time dependent changes in the levels of proinflammatory cytokines including IL-6, IL-1β, TNF-α (94), as well as brain derived neurotrophic factor (BDNF) (95), and its receptor, tyrosine kinase beta (TrkB). All of these factors contribute to peripheral sensitization associated with neuropathic pain. Additionally, genes coding for sodium channels (*SCN3A* (Nav1.3), *SCN8A* (Nav1.6), *SCN9A* (Nav1.7), *SCN10A* (Nav1.8) and *SCN11A* (Nav1.9) (96,108), potassium channels (Kcnip3, Kcnj6, Kcnq2 and Kcnq3 (98), Kcnj10 (99) and Kcnk18 (coding for TRESK) (100,101), TRP channels, purinoceptors, and tachykinin proteins have been shown to play a role in PTTN. An increase in *Trpa1 and Trpv1* mRNA was observed in rats' ipsilateral TG, cervical spinal cord and in medulla after chronic constriction injury to the infraorbital nerve (CCI-ION). Administration of TRPA1 antagonist has been shown to attenuate upregulation of TRPA1 and TRPV1 in the same areas following nerve injury (102). Additionally, lingual nerve injury in ferrets resulted in an initial increase in TRPV1 expression at the injured nerve and decrease in the TG; however, at 3 weeks following lingual nerve injury the TRPV1 levels were upregulated at nerve injury site as well as in the TG (103). These findings suggest that following a nerve injury there is an initial transport of TRPV1 from the TG to the damaged axons, which is then followed by an increase in synthesis of TRPV1 in the ganglion. Finally, TRPV1 antagonist was shown to reduce the level of spontaneous activity initiated in some axons following lingual nerve injury in ferrets (109). These findings support the hypothesis that TRPA1 and TRPV1 channels are involved in experimental trigeminal pain (102). Trpa1 positive mice have been shown to have a lower pain threshold after CCI-ION and deletion of Trpa1 reduced pain in CCI-ION mice (110). Furthermore, infraorbital

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Table 4 Summary of positive associations of post-traumatic trigeminal neuropathy (PTTN) and genetic contributions

Gene ID	Protein encoded	Population	Change associated with NP	References
IL-6, *IL-1β*, *TNF-α*	Proinflammatory cytokines	ION-CCI exposed Sprague-Dawley rats	Contribute to peripheral sensitization associated with NP	(94)
BDNF	Brain derived neurotrophic factor	ION-CCI exposed Sprague-Dawley rats	Contribute to peripheral sensitization associated with NP	(95)
TrkB	Receptor for brain-derived neurotrophic factor	ION-CCI exposed Sprague-Dawley rats	Contribute to peripheral sensitization associated with NP	(95)
SCN3A, *SCN8A*, *SCN9A*, *SCN10A*, *SCN11A*	Sodium channels	C57Bl/6 mice with ION-CCI, ferrets with IAN injury	Changes in mRNA expression in the TG associated with TNP	(96,97)
Kcnip3, *Kcnj6*, *Kcnq2*, *Kcnq3*	Potassium channels	ION-CCI exposed Sprague-Dawley rats	Changes in mRNA expression in the TG associated with TNP	(98)
Kcnj10	Potassium channel	ION-CCI exposed Sprague-Dawley rats	Changes in expression of Kir4.1 in TG contribute to TNP	(99)
Kcnk18	Potassium channel	ION-CCI exposed Sprague-Dawley rats	mRNA and protein levels downregulated in TG of ION-CCI rats	(100,101)
Trpa1, *Trpv1*	Transient receptor potential cation channels	ION-CCI exposed Sprague-Dawley rats	Increase in mRNA in TG, cervical spinal cord and medulla in ION-CCI rats	(102)
TRPV1	Transient receptor potential cation channels	Ferrets with lingual nerve injury	Increase in TRPV1 in TG and the injured nerve at 3 weeks post injury	(103)
P2X3	Purinoceptor 3	ION-CCI exposed Sprague-Dawley rats	Increase in density of P2X3 in astrocytes in the brain in ION-CCI rats	(104)
Tacr3	Tachykinin receptor 3	Partial transection of ION	Downregulated in lateral habenula of mice exposed to nerve injury	(105)
CGRP, *SP*, *VIP*, *GAL*, *ENK*	Neuropeptides	Lingual nerve injury in ferrets	Accumulation of these neuropeptides in the portion of the nerve immediately distal to the ligature associated with the increase in spontaneous activity in that region	(106)
rno-miRNA-138	Micro RNA	Rats with lingual nerve injury	Upregulated in lingual nerve following injury	(107)
has-miR-29a	Micro RNA	Humans with painful lingual nerve neuromas	Downregulated in lingual nerve neuromas of patients with higher pain VAS scores	(107)

ION, infraorbital nerve; CCI, chronic constriction injury; IAN, inferior alveolar nerve.

nerve injury (CCI-ION) resulted in an upregulation of *Calca*, *PPT-A*, *IL-1beta*, *IL-6*, and *TNF-alpha* mRNA expression in the ipsilateral TG, cervical spinal cord and in medulla in rats (102). These findings support the role of pro-inflammatory mediators released in the tissues surrounding the damaged nerve and glial cell in the pathophysiology of neuropathic pain (111,112) including trigeminal neuropathic pain (102).

Additionally, purinergic receptors have been implicated in the development of PTTN. Nerve injury leads to activation of spinal cord microglia that undergo a series of changes including transition to hypertrophic morphology, increase in numbers, and altered gene expression (113-115). These changes directly affect development of neuropathic pain. Activated microglia induce or enhance expression of various genes including neurotransmitter receptors such as purinergic P2 receptors (116) which include ionotropic receptors (P2XRs) and metabotropic receptors (P2YRs). Infraorbital nerve injury (ION-CCI) has been shown to induce a significant increase in the number of P2X3-positive fine astrocytic processes and a significant increase in the density of P2X3 in these processes in the brainstem of rats

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exposed to ION-CCI (104). Additionally, administration of a specific glutamate metabotropic receptor 5 (mGluR5) antagonist has been shown to alleviate the mechanical allodynia and abolished the increase in density of P2X3 in the fine astrocytic processes in the brainstem of ION-CCI exposed rats (104). These findings suggest that P2X3 plays a role in the mechanism of craniofacial neuropathic pain and that the peripheral nerve injury induced expression of astrocytic P2X3 may be regulated by astrocytic mGluR5. PTTN induced by ION-CCI has also been associated with an upregulation of complement component C1q expression in the subnucleus caudalis (Vc) of ION-CCI exposed rats (117). The observed upregulation of C1q in the Vc of ION-CCI rats was linked to astrocytic activation, which in turn induced mechanical hypersensitivity in the orofacial region (117). These findings suggest that astrocytic activation via the signaling of C1q released from activated microglia in the Vc of ION-CCI exposed rats leads to the enhanced excitability of Vc nociceptors which results in persistent orofacial neuropathic pain. Furthermore, tachykinins, a family of neurotransmitter-encoding genes, have been implicated in PTTN. Tachykinins are active peptides that excite neurons, induce behavioral responses, and are potent vasodilators. Infraorbital nerve injury resulted in a downregulation of the *Tacr3* gene encoding for the neurokinin 3 receptor (NK3R) in mice (105) supporting the role of the tachykinins in trigeminal neuropathic pain.

Furthermore, neuropeptides such as calcitonin gene-related peptide (CGRP), substance P (SP), vasoactive intestinal polypeptide (VIP), galanin (GAL), encephalin (ENK) and neuropeptide Y (NYP) have been suggested to play a role in the etiology of PTTN. Elevated immunoreactivity of these peptides was observed at 3 days following lingual nerve injury in ferrets, which then decreased by 3 weeks. However, by 3 months levels of CGRP, SP, VIP and GAL increased slightly in the nerve proximal to the injury. This increase was accompanied by an accumulation of all of the neuropeptides except NPY in the portion of nerve immediately distal to the ligature which coincided with the increase in spontaneous activity in that region (106). These findings imply the role of neuropeptides in the etiology of sensory disorders after nerve injury as observed in PTTN. Additionally, accumulation of neuronal nitric oxide (nNOS) at the site of injury has been associated with ectopic activity following inferior alveolar nerve injury (IAN) in ferrets (118) suggesting that nNOS may contribute to PTTN. IAN injury has also been shown to induce changes in levels of sodium channels (Nav1.3, Nav1.7, Nav1.8 and Nav1.9) in the injured nerves and in the ganglia (97). Levels of Nav1.8 and Nav1.9 were found to be significantly elevated in the injured IAN compared to contralateral and control nerves. However, levels of Nav1.3, Nav1.7 and Nav1.9 were significantly lower in the TG following IAN damage (97). These findings suggest that together with the findings reported in infraorbital nerve injury support the role of sodium channel expression in nerve injury induced trigeminal pain (PTTN). Finally, changes in lingual nerve micro-RNA profile that affects expression of the target genes has also been implicated in PTTN induced by lingual nerve injuries in rats and humans (107). In rats, rno-miR-138 was shown to be upregulated in lingual nerve of injured rats compared to sham controls and expression of rno-miR-138 and rno-miR-667 was negatively and positively correlated with behavioral changes at 3 days post nerve injury, respectively (107). In humans, has-miR-29a was downregulated in lingual nerve neuromas of patients with higher pain VAS scores compared to patients with lower pain VAS scores. Hsa-miR-29a and hsa-miR-500a were negatively correlated with pain VAS scores in lingual nerve neuromas patients. The suggested targets for the identified miRNAs targets included genes related to interleukin and chemokine receptors and potassium channels (107).

Conclusion

For most cases, orofacial pain conditions such as TMDs, TN, and PTTN follow a complex multifactorial pattern of inheritance with multiple environmental and genetic factors and their subsequent interactions being implicated. In such conditions, the effect of individual genetic variation is modest. Thus, large sample sizes of hundreds or thousands of carefully diagnosed patients and well-matched controls are required to provide sufficient statistical power to generate conclusive results. Rare damaging mutations that aggregate in families have a major effect on risk. Although they account for a small portion of cases, they may be valuable for identifying pathophysiological mechanisms of the conditions. Nevertheless, available evidence supports the role of genetics in orofacial pain conditions with variations in voltage gated ion channels, transient receptor potential channels, and GABA receptor-binding genes providing strongest support. Overall, the current evidence strongly suggests that inherited genetic differences among individuals make an important contribution to the development and severity of pain. Future research aimed

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at identifying both the common variants of modest effect on risk and rare damaging mutations of large effect on risk offer promising avenues for development of novel therapeutic approaches to improve treatment for patients suffering from these conditions.

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