Literature Review/Book Review

The role of genetic factors in the etiology of temporomandibular disorders: a review

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Objectives: To perform a review of the literature of published articles assessing the role of genetic factors in the etiology of temporomandibular disorders (TMDs).
Methods: A PubMed search was carried out by looking for all controlled clinical trials related to the topic and limiting the search to English language and humans. The references from the studies included and those from review articles were also examined for further relevant papers.
Results: A total of 1999 articles were first identified, 24 of which were considered relevant to the topic. Two other papers were found while searching the references. While TMD signs and symptoms' co-occurrence was not found in subjects within the same family, many gene polymorphisms were shown to be associated with a higher or lower risk of TMD. Such genes were mainly related to serotonin activity and metabolism, T-cell receptor pathway, catecholamine activity and metabolism, estrogen activity, folate metabolism, glutathione activity, ANKH gene, major histocompatibility complex, extracellular matrix metabolism, genes studied in the orofacial pain prospective evaluation risk and assessment (OPPERA) study, and related to cytokines activity and metabolism.
Discussion: This new understanding of the pathophysiology of TMD can lead to a different treatment approach by identifying the subjects at higher risk for this pathology, and possibly by creating new drugs targeted at interfering with the expression of the genes that enhance such risk.

Keywords: Genetic factors, Polymorphism, Temporomandibular disorders, Risk factors

Introduction

As defined by the American Academy of Orofacial Pain, temporomandibular disorders (TMDs) encompass a group of musculoskeletal and neuromuscular conditions that involve the temporomandibular joints (TMJs), the masticatory muscles, and all associated tissues.[1] The etiology of such disorders is still far from being clear, and identification of an evident cause is lacking. In the past, considerable attention was given to structural factors, such as dental occlusion, with the hypothesis that dental malocclusion could alter proper muscle and TMJ function, and therefore, lead to pain and dysfunction. However, more recent studies do not strongly support the etiologic role of dental occlusion in the genesis of TMD,[1–4] and the total contribution of occlusal variants was shown to explain only 10–25% of TMD specific diagnoses.[1]

Current studies put more emphasis on psychological and social factors defining the "biopsychosocial model" for the development of TMD;[5–8] nonetheless, such evaluation often needs to be carried out depending on the patient's history and clinical condition.[9]

Only recently, in the 2008 guidelines, the American Academy of Orofacial Pain introduced genetic factors in the section dedicated to the etiology of TMD,[10] in the light of a study highlighting the influence of gene polymorphism on pain sensitivity and development of myogenous TMD.[11] To explore such a hypothesis, the aim of this study was to carry out a review on the role of genetic factors in the etiology of TMD.

Materials and Methods

A review of the literature was performed by looking for all articles related to genetic features as etiologic factors for TMD, using PubMed. Key words to identify TMD were the following: *temporomandibular joint disorders, temporomandibular joint dysfunction syndrome, craniomandibular disorders, temporomandibular joint, myofascial pain syndromes, facial pain,*

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DOI 10.1179/2151090314Y.0000000027

temporomandibular disorders, TMD, TMJ, TMJDS, CMD, myofascial pain, myofascial pain dysfunction syndrome. Key words to identify genetic factors were the following: *genes, alleles, genetics, genetic polymorphism, genome, genomics, chromosomes, congenital, gene, genetic, polymorphism, polymorphisms, chromosome, inheritability, inheritable, inherited, hereditary, heritable.* The terms were searched as ''All Fields,'' the results were then combined and limited to humans and English language. Inclusion criteria were the following: original controlled studies including non-TMD subjects as control; however, review articles were obtained to examine their references. Exclusion criteria were the following: trials regarding systemic arthropathies, such as rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. Titles and abstracts were evaluated to identify relevant papers; references from those and review articles were also assessed to identify further pertinent papers.

Results

A total number of 1999 articles were found. Twenty-four articles were selected and the full- text was obtained. Two additional pertinent papers were identified from the references. The final number of articles that were included in the review was 26. A flow chart with all the details of the literature search is shown in Table 1.

The first report on the role of genetic factors in the etiology of TMD was published in 1980.[12]

The study compared the prevalence of myofascial pain (MP) in monozygotic and dizygotic twins obtaining similar results. Two almost identical trials were carried out by Michalowicz *et al.*,[13] who assessed the prevalence of arthrogenous TMD, and Matsuka *et al.*,[14] who evaluated the occurrence of TMD symptoms using a questionnaire, with the same findings. The authors of the mentioned studies concluded that no genetic predisposition was evident for TMD. Similar outcomes were reported by Raphael *et al.*[15] and Liljeström *et al.*[16] The former showed that first degree relatives of MP patients do not display higher rates of MP symptoms than first degree relatives of asymptomatic control subjects; the latter found no association between mother's and child's signs of TMD.

Later on, instead of looking for general familiar co-occurrence of signs and symptoms of TMD, several authors identified different polymorphic variants of gene regions that affect the onset of TMD. Those results are displayed in detail in Table 2.

Polymorphisms of genes related to the activity and metabolism of serotonin were associated with higher and lower risk of TMD.[17–23] A combination of 8 single nucleotide polymorphisms (SNPs) in the genes involved in the T-cell receptor pathway was a predictor of TMD with widespread pain.[22] Also polymorphisms of genes involved in the activity and metabolism of catecholamines were correlated with higher and lower risk of TMD.[11,21,24–26] Furthermore, polymorphism of the estrogen receptor-alpha and polymorphism of the genes' encoding enzymes involved in folate metabolism and glutathione activity were related to higher risk of TMD.[26–28]

Homozygous ANKH gene polymorphic variants were associated with higher risk of disc displacement without reduction.[29]

Human leukocyte antigen (HLA) class I alleles A1, A2, A3, B7, B14, B35, B44, and class II alleles DR1, DR4, DR7, and DR 52 were associated with greater occurrence of degenerative processes of the TMJ, with alleles DR4 and DR 52 exhibiting more aggressive form of articular degenerative processes.[30,31]

Table 1 Literature review search flow chart

	Key words	Selections
1	''Temporomandibular Joint Disorders'' OR ''Temporomandibular Joint Dysfunction Syndrome'' OR ''Craniomandibular Disorders'' OR ''Temporomandibular joint'' OR ''Myofascial Pain Syndromes'' OR ''Facial Pain'' OR ''Temporomandibular disorders'' OR ''TMD'' OR ''TMJ'' OR ''TMJDS'' OR ''CMD'' OR ''Myofascial pain'' OR ''Myofascial pain dysfunction syndrome''	47826
2	''Genes'' OR ''Alleles'' OR ''Genetics'' OR ''Genome'' OR ''Genomics'' OR ''Chromosomes'' OR ''Congenital'' OR ''Gene'' OR ''Genetic'' OR ''Polymorphism'' OR ''Polymorphisms'' OR ''Chromosome'' OR ''Inheritability'' OR ''Inheritable'' OR ''Inherited'' OR ''Hereditary'' OR ''Heritable''	3621633
3	Combining 1 and 2	3192
4	3 limited to English and humans	1999
5	Title and abstract based selection	24
6	5+Review articles references hand search	+2
7	Total articles selected	26

Table 2 List of gene polymorphisms related to the risk of temporomandibular disorders

Gene	Polymorphic region	Allele	Risk of TMD
5-HTT[17,18]	VNTR	STin 2.10/10	Higher
		STin 2.12/12	Lower
	LPR	l and xl	Higher
		s	Lower
5-HT2A receptor[19–21]	T102C	C/C	Higher
		T/T	Lower
	rs9316233	minor G	Lower
5-HTT pathway[22]	rs9316233		Higher (1)
	rs4776783		
	RS12439516		
	rs2276008		
	RS6928		
	rs3813928		
TPH[23]	A218C	C/C	Higher
T-cell receptor pathway[22]	rs10500205		Higher (1)
	rs216535		
	rs306083		
	rs3797739		
	rs2070995		
	rs3756612		
	rs815815		
	rs790250		
COMT[11,21,24]	rs6269, rs4818	HPS, APS	Higher
		LPS	Lower
	rs165656		Higher
	rs4646310		Higher
ADRB2[25]		H2/H2	Higher
		H1/H1	Higher
		H1/H2, H1/H3	Lower
DRD4[26]	DRD4-48bptr	L	Higher
Estrogen receptor-alpha[27,28]	XbaI	GC	Higher
SHMT1[26]	rs1979277	G	Higher
	rs638416	C	Higher
MTHFD1[26]	rs2236225	T	Higher
MTRR[26]	rs1801394	A	Higher
GSTM1[26]	GSTM1del	null	Higher
ANKH[29]	ANKH-OR	Homozygotes	Higher
HLA[30,31]	Class I	A1	Higher
		A2	Higher
		A3	Higher
		B7	Higher
		B14	Higher
		B35	Higher
		B44	Higher
	Class II	DR1	Higher
		DR4	Higher
		DR7	Higher
		DR52	Higher
MMP1[32]	rs1799750	2G/2G	Higher
		1G/2G	Lower
		1G	Lower
NR3C1[21]	rs2963155	Minor G	Lower
	rs9324918	Minor C	Lower
	rs33389	Minor T	Lower
CHRM2[21]	rs7800170	Minor A	Lower
CAMK4[21]	rs3756612	Minor G	Higher
	rs10491334	Minor T	Lower
IFRD1[21]	rs728273	Minor G	Higher
GRK5[21]	rs12415832	Minor A	Higher
TGF-beta1[33] (2)	rs2241719	Minor T	
IL-8[33] (2)	rs4073	Major A	Higher
		Minor A	Lower

Note: TMD: temporomandibular disorders; 5-HTT: serotonin transporter; VNTR: variable-number-tandem-repeat; LPR: gene-linked polymorphic region; 5-HT2A: serotonin 2A; TPH: tryptophan H; COMT: catecholamine-*O*-methyltransferase; HPS: high pain sensitivity; APS: average pain sensitivity; LPS: lower pain sensitivity; ADRB2: adrenergic receptor beta2; DRD4: dopamine receptor D4; SHMT1: serine hydroxymethyl transferase 1; MTHFD1: methylenetetrahydrofolate dehydrogenase 1; MTRR: methionine synthase reductase;

Table 2 Continued

GSTM1: glutathione *S*-transferase mu-1; HLA: human leucocyte antigen; MMP1: matrix metalloproteinase 1; CHRM2: muscarinic cholinergic receptor 2; CAMK4: calcium/calmodulin-dependent protein kinase 4; IFRD1: interferon-related developmental regulator 1; GRK5: G protein-coupled receptor kinase 5; TGF-beta1: transforming growth factor beta1; IL-8: interleukin-8.
(1): combination of the single polymorphisms; (2): interaction between the two genes.

Higher risk of TMD was associated with the presence of homozygous 2G alleles in the polymorphic region rs1799750 of the matrix metalloproteinases 1 gene.[32] Conversely, the presence of the allele 1G, and consequently, the heterozygous 1G/2G genotype, showed a protective effect.[32]

Three polymorphisms of the glucocorticoid receptor NR3C1 gene were associated with a lower risk of TMD.[21] Also the polymorphism of the muscarinic cholinergic receptor 2 gene was related to lower risk of TMD.[21] Two polymorphic regions were detected in the calcium/calmodulin-dependent protein kinase 4 gene: rs3756612 and rs10491334. The presence of the minor allele G in the first region increased the risk of TMD. Conversely, the presence of a minor allele T in the second region decreased such risk.[21] Polymorphism of two other genes, interferon-related developmental regulator 1 and protein-coupled receptor kinase 5, were found to be correlated with higher risk of TMD.[21]

Finally, the association of transforming growth factor beta1 gene polymorphic variant minor T and interleukin-8 polymorphic gene homozygous alleles major A were shown to increase the risk of TMD. However, when the transforming growth factor beta1 gene polymorphic variant minor T was associated with at least one interleukin-8 polymorphic gene allele minor A, the risk of TMD was reduced.[33]

One study did not find any association between different polymorphic variants of the G308A region of the tumor necrosis factor-alpha gene and the risk of TMD.[34] Another study by Kim *et al.* could not show any risk of TMD correlated with different polymorphisms of the regions *Pvu*II and *Xba*I of the estrogen receptor-alpha gene.[35] Also, no correlation was found between gene polymorphisms and new cases of TMD in a population of asymptomatic subjects.[36]

Discussion

The first reports on the role of genetic factors in the etiology of TMD were carried out by assessing the co-occurrence of signs and symptoms of TMD in monozygotic versus dizygotic twins,[12–14] and in subjects within the same family.[15,16] Those studies failed to confirm any relationship between the two variables, leading the authors to conclude that no genetic predisposition was evident for TMD. However, those trials had insufficient statistical power to identify genetic factors for common disorders.[21,37] Therefore, more recent studies identified different polymorphic variants of gene regions that were related to the onset of TMD.

Serotonin activity and metabolism

Some studies investigated the role of serotonin activity and metabolism through the assessment of the genes involved. The activity of serotonin is regulated by the serotonin transporter gene, which has two polymorphic regions: the variable-number-tandem-repeat (VNTR), and the gene-linked polymorphic region (LPR). Subjects homozygous for allele STin 2.10 in the polymorphic region VNTR had increased risk of TMD; conversely, the presence of the alleles STin 2.12 in the same region reduced such risk.[17] The polymorphic region LPR of the same gene can be characterized by the presence of either long (l or xl) or short (s) alleles. The long alleles are supposed to have higher transcriptional activity than short alleles. As a consequence, this causes an increased uptake of serotonin, which leads to lower extracellular concentration of serotonin.[37] The presence of a long allele increases the risk of TMD, while the presence of a short allele reduces such risk.[18] However, this outcome is not confirmed by another study, where no difference was found between TMD patients and controls regarding the presence of s and l alleles.[17]

The polymorphism of another gene related to the action of serotonin, the serotonin 2A receptor gene, in the region T102C can affect the risk of TMD, with higher risk in subjects homozygous for the C allele, and lower risk in subjects homozygous for the T allele.[19,20]

Furthermore, in the region rs9316233 of the same gene, the presence of the allele minor G showed a protective effect against the risk of TMD.[21] Another study highlighted the different effect of SNPs when combined together.[22] A combination of six SNPs in the genes involved in serotonin receptor pathway was a predictor of localized TMD.[22]

Tryptophan is a precursor of serotonin, and is transformed into serotonin by the enzyme tryptophan hydroxylase. The presence of the alleles C/C in the polymorphic region A218C of the gene tryptophan hydroxylase was shown to raise the risk of TMD.[23]

The results are supported by Kopp's studies, which have demonstrated the role of serotonin in the genesis of TMJ symptoms, specifically TMJ pain on mandibular movement, restricted mandibular mobility, TMJ hyperalgesia and allodynia.[38,39]

T-cell receptor pathway

Recent studies suggest that T cells can be mediators in the mechanisms of pain by contributing to the development of pain response. A more appreciable T-cell infiltration and activation in the dorsal horn of the spinal chord has been shown after peripheral nerve injury;[40] also, in a previous animal study, T-cell infiltration in injured sciatic nerves was related to neuropathic pain.[41] Slade *et al.*'s findings on the association between the combined effect of eight SNPs from the T-cell receptor pathway and greater odds of TMD with widespread pain seems to confirm such hypothesis.[22]

Catecholamine activity and metabolism

Three genetic variants of the gene encoding catecholamine-*O*-methyltransferase (COMT) enzyme have been identified, with different sensitivity to experimental pain. These alleles are designated as lower pain sensitivity (LPS), average pain sensitivity (APS), and high pain sensitivity (HPS). The presence of at least one LPS allele diminishes significantly the risk of myogenous TMD. Since the LPS allele produces higher levels of COMT, such enzyme seems to be involved in the pathogenesis of TMD.[11,21] Two other polymorphic regions were shown to be associated with higher risk of TMD.[24] These polymorphisms were located in the promoter region of the gene, which could exert a regulatory role in the COMT gene, and be predisposed to TMD by affecting DNA transcription, RNA splicing, mRNA stability, and mRNA transport and translation.[24]

The adrenergic receptor beta$_2$ is a primary target for epinephrine, and its expression is dependent on the corresponding gene. Three different polymorphic alleles, H1, H2, and H3 have been identified, H1 codes for low receptor expression, while H2 and H3 code for high receptor expression. Subjects homozygous for H2 had the highest risk of TMD, followed by the subjects homozygous for H1.[25] On the other hand, the lowest risk was represented by the subjects heterozygous for H1 (H1/H2 and H1/H3). These findings suggest that either positive or negative imbalances of the adrenergic receptor beta$_2$ function increase the vulnerability to TMD.[25] The polymorphisms of the COMT gene and beta$_2$ receptor gene seem to act together. In fact, the higher pain intensity caused by the absence of the LPS allele in the COMT gene can be reduced by administration of the beta-adrenergic receptor antagonist medication propranolol, demonstrating that COMT inhibition increases pain sensitivity through activation of beta-adrenergic receptors.[42,43]

One study showed that dopamine activity might be related to higher risk of TMD. A polymorphism of the dopamine receptor D4 in the 48-bptr region is characterized by the presence of a short allele or a long allele. Increase of the long allele, when compared to the short allele, was found in TMD patients.[26] There are no studies correlating dopamine activity to TMD; however, a role of dopamine has been hypothesized in the development of bruxism,[44] which is considered a risk factor for TMD. Nevertheless, a direct cause-and-effect relationship between bruxism and TMD has not been demonstrated.[45]

Estrogen activity

TMD are significantly more prevalent in women than in men, and sexual hormones, especially estrogen, may contribute to female predominance.[46] The estrogen receptor has two configurations: alpha and beta. The alpha-receptor is present in intra-articular cartilage, osteocytes, and many other cells. It also plays a role as a regulator of intracellular mediators.[35] Two common polymorphisms of the estrogen receptor-alpha gene are in the *Pvu*II and *Xba*I sites, and the presence of GC haplotype in the polymorphic region *Xba*I has been shown to increase the risk of TMD.[27,28] The authors hypothesized that such a genotype can affect the level or the function of the estrogen receptor-alpha, or the activity of estrogen on inflammatory mediators.[27]

However, another study by Kim *et al.*[35] could not show any risk of TMD correlated to different polymorphisms of the regions *Pvu*II and *Xba*I of the estrogen receptor-alpha gene.

Folate metabolism

Folate metabolism has an impact on the formation of any growing tissue because of its participation in the synthesis of nucleic acid, and its role in regulating DNA and protein methylation. Nutritional deficiency of folic acid is considered a perpetuating factor for myofascial pain and dysfunction, and these deficiencies are frequent in cases of mechanical stress of the TMJ.[26]

Four polymorphic variants of three genes related to folate metabolism have been found to be associated with a higher risk of TMD.[26] The first of these genes is the serine hydroxymethyl transferase 1 gene, encoding the homonymous enzyme that intervenes in the folate synthesis. The presence of the allele

G in the polymorphic region rs1979277, and the presence of the allele C in the polymorphic region rs638416 of this gene have been related to a higher risk of TMD. A second gene is the methylenetetrahydrofolate dehydrogenase 1, encoding another enzyme involved in folate synthesis. In this case the presence of an allele T in the region rs2236225 was more frequent in TMD patients than in controls. The polymorphism of the gene of another enzyme, the methionine synthase reductase, has been related to higher risk of TMD. The presence of an allele A in the polymorphic region rs1801394 of this gene raises the affinity of the enzyme for the substrate. The allele A was prevalent in the TMD group. The metabolic effect of all these variants is similar, causing the final result of augmenting folate levels.

Glutathione activity

Oxidative stress, which results in the production of nitric oxide and peroxynitrite, is detrimental to DNA in response to the excessive mechanical overload, which consequently contributes to synovial hyperplasia of the TMJ.[47] Also TMJ inflammation is intimately related to oxidative stress.[47,48] This suggests that a reduced detoxification capacity would make one more susceptible to TMD.

The function of the enzyme mu-class glutathione *S*-transferase is the detoxification of electrophilic compounds, such as carcinogens, medications, toxins, and products of oxidative stress. This result is accomplished by the conjugation with glutathione. A deletion in the related gene (null variant) has been associated with higher risk of TMD, possibly due to a reduced capacity of detoxification.[26]

ANKH gene

The murine *ank* gene and the human homolog ANKH gene have been associated with arthritis in mice and ankylosing spondylitis in humans. In the ANKH-OR polymorphic region of the ANKH gene, two alleles were identified: the 1-allele and the 2-allele. The homozygote genotypes, both 1/1 and 2/2, were associated with higher risk of a particular TMD diagnosis, disc displacement without reduction (closed lock).[29] Since fibrous ankylosis of the TMJ of *ank* mutant mice was detected in the same study, it can be hypothesized that the formation of fibrous adhesions might predispose for the development of disc displacement without reduction in humans.[29]

Major histocompatibility complex

The HLA is the human major histocompatibility complex. Its function in the immune system is to distinguish between self and non-self antigens to evoke an immune response to defend the organism from pathogens. HLA specific alleles have been associated with spondyloarthropathies involving the peripheral and axial joints and can also affect the TMJ.[30] In two studies, the presence of HLA class I alleles A1, A2, A3, B7, B14, B35, B44, and class II alleles DR1, DR4, DR7, and DR52 was associated with greater occurrence of degenerative processes of the TMJ.[30,31] Among the patients with such a disorder, the subjects with alleles DR4 and DR52 exhibited a more aggressive form of degenerative processes of the TMJ, with serious thinning and tearing of the articular disc, irregularity of the mandibular condyle, flattening of the glenoid fossa, severe osseous erosion, and reduced mouth opening.[31]

Subjects with these alleles may have higher risk for the progression of degenerative processes of the TMJ as a result of the presence of infectious agents with consequent host interactions and the resulting inflammatory response being influenced by their HLA phenotype.[30]

Extracellular matrix metabolism (MMP)

MMPs are a family of enzymes that degrades the components of the extracellular matrix, such as collagen, fibronectin, and proteoglycans. These enzymes are produced by fibroblasts and chondrocytes, and could play a role in TMJ degeneration. In fact, an imbalance between the synthesis and the destruction of diverse types of extracellular matrix in favor of proteolysis is characteristic of degenerative changes in the TMJ.[32] Two polymorphisms have been identified in the region rs1799750 of the MMP1 gene: the 1G and 2G variants. Higher risk of TMD was associated with the presence of homozygous 2G alleles.[32]

Conversely, the presence of the allele 1G, and consequently, the heterozygous 1G/2G genotype showed a protective effect.[32] The presence of the 2G allele is associated with higher gene transcription, which, in turn, causes higher levels of the enzyme, intensifying degradation of the extracellular matrix in the TMJ.

Orofacial pain prospective evaluation risk and assessment (OPPERA) study

OPPERA is a wide prospective study intended to assess and determine biopsychosocial, environmental, and genetic elements that can represent precipitating and perpetuating factors for TMD. To achieve these goals, a group of internationally recognized scientists started a 7-year prospective cohort study and evaluated the results. Regarding the role of genetic factors, seven genes were found to be related to TMD. The role of two of these genes was discussed

previously;[21] in addition, five other genes were involved. Three polymorphisms of the glucocorticoid receptor NR3C1 gene were associated with a lower risk of TMD. The receptor is the binding site of cortisol and a major element of the hypothalamic–pituitary–adrenal system, which has been correlated with the pathophysiology of TMD. Also the polymorphisms of the muscarinic cholinergic receptor 2 gene, the calcium/calmodulin-dependent protein kinase 4 gene, the interferon-related developmental regulator 1 gene, and protein-coupled receptor kinase 5 gene were correlated with the risk of TMD.[21] It is difficult to establish the interaction between the activity of these genes and TMD because little data are available. Nonetheless, it can be due to the role of those genes at the cellular level on adenylate cyclase inhibition, phosphoinositide degeneration, potassium channel mediation in the central and peripheral system, transcriptional regulation in neurons, control on inflammation, the growth and differentiation of specific cells during embryonic development and tissue regeneration, phosphorylation, and regulation of activation of G protein-coupled receptors.[21] However, it has been hypothesized that more heterogeneous causes, like environmental factors, can be involved in acute-onset TMD, while compared to chronic TMD. In fact, when evaluating new TMD cases in a 2737 people population, no correlation was found between gene polymorphisms and the development of the disease.[36]

Cytokine activity and metabolism

One recent study showed how distinct genes can act differently by interacting with each other. In fact, the minor T variant of the transforming growth factor beta1 gene increased the risk of TMD when associated with the homozygous allele major A of the interleukin-8 polymorphic gene, but such risk was reduced when it was associated with at least one minor A allele of the interleukin-8 polymorphic gene.[33] This risk was specifically accompanied with widespread tenderness to palpation, probably because genetic polymorphisms can affect cytokine synthesis and release. In turn, pro-inflammatory cytokines may operate the progression from acute to chronic pain by activating transcription of genes controlling biological pathways that regulate pain.[33] Surprisingly, in the same study, tumor necrosis factor-alpha and interleukin 1beta were not found to be significantly different between the groups, despite the fact that those pro-inflammatory cytokines can stimulate interleukin-8 gene expression in synovial cells of the human TMJ.[33,49,50]

General considerations

The study of genetic factors is frequently hampered by false-negative associations when SNPs are evaluated independently. This is due to the fact that the contribution of each polymorphism can be of little weight when evaluating complex diseases characterized by multiple risk factors, such as TMD. To reach statistical significance, trials should involve large populations. However, when assessing metabolic pathways instead of SNPs independently, the results can be different, because SNPs occurring in different genes of the same metabolic pathway can act in combination, amplifying the effect.[22] In addition, different neurological mechanisms of pain processing can be affected by different genes. TMD with widespread pain, when compared to localized TMD, are characterized by sensitization of peripheral neurons and disturbances of descending inhibitory control.[51] This is probably the reason different genes regulate and affect TMD development with such different features.[22]

Conclusions

The evaluation of the role of genetic factors, especially specific polymorphisms, in the etiology of TMD is relatively recent. The present review summarizes and outlines the results of numerous studies that identified the genes associated with a higher or lower risk of TMD. Such new understanding of the pathophysiology of TMD can lead to a different treatment approach, specifically focused on the patient. First, this could be accomplished by recognizing earlier the subjects at risk for TMD, which can be stringently followed up. Secondly, this information can possibly be used to create new drugs targeted at interfering with the expression of the genes related to the risk of TMD.

Disclaimer Statements

Contributors Both authors participated in the review process by searching, selecting, and reading the articles, and in writing and reviewing the final article.

Funding None.

Conflicts of interest The authors declare no conflicts of interest.

Ethics approval None.

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