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Temporomandibular disorders is associated with genetic factors: A review

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ABSTRACT

Background and Objectives: Pain is the most leading cause of visits to physicians and dentists. It is also a common symptom of diseases that can significantly undermine the quality of life and physical activities. This study aimed to review the existing literature for the causes of temporomandibular disorders (TMD) from the genetic point of view.

Materials and Methods: Four international scientific databases including Google Scholar, Biomed Central, PubMed, and ProQuest plus two Iranian databases including Magiran and SID. Then all articles published between 1980 and 2019 were searched using the following keywords: facial pain, genetic factors and temporomandibular disorders (TMDs). A total of 900 articles were found that 36 were review articles.

Results: Our review shows that genetic factors have an impact on the incidence and pathology of TMDs These factors include TSPAN9 polymorphism and the COMT gene.

Conclusion: There is growing evidence indicating that genetic factors play a key role in the pathology of temporomandibular disorders, however, the underlying mechanism of pain is still largely unknown.

Keywords: Facial pain; Genetic factors; Temporomandibular joint disorder (TMD).

Introduction

Chronic and acute orofacial pains are common problems with undeniable implications for public health and a large effect on the quality of life. It is sometimes difficult to determine the origin and cause of orofacial pain, especially when patients cannot properly communicate. The major intraoral causes of orofacial pains are neoplasia, infection, dental injury, tooth decay, and root sensitivity. The extraoral causes of these pains include headaches, TMD, masticatory muscle disorders, neuralgia, and facial pain syndromes [1].

TMD manifests a variety of common symptoms such as dental problems, earache, hearing loss, burning sensation in the tongue and throat, and tinnitus [2]. Evidence suggests that common diseases in adults are usually multifactorial. Some well-known examples of such multifactorial diseases are cleft lip, cleft palate, Alzheimer's disease, heart diseases, blood pressure, diabetes, cancers, etc. It is often difficult to understand how multifactorial disorders are inherited, because the incidence of such disorders may be affected by the environmental factors too. Another fact is that the contribution of environmental and genetic factors to the incidence of multifactorial diseases varies from person to person. While the risk of incidence of single-gene diseases in predisposed individuals is sometimes as high as 50%, it is 4-5% in first-degree relatives of the affected person among multifactorial diseases. Therefore, in comparison with other inherited conditions, it is really difficult to determine the inheritance pattern of multifactorial diseases and estimate the risk of recurrence in predisposed people [3]. From investigations, it can be found that chronic oral and maxillofacial disorders are the most common cause of visits to medical and dental centers that require multidisciplinary clinics for treatment and follow up [4]. Given the role of cumulative genetic risk factors in the causation of multifactorial diseases, assessing the independent effect of each of these risk factors would require extensive research to decipher a wide range of contributing hereditary factors. It should also be remembered that each factor, such as polymorphism, may play a very minor role in the whole scheme of genetic effects [5]. Due to the high prevalence of orofacial pains, it is worth identifying the genetic alterations associated with these disorders in terms of prevention, diagnosis, prognosis, and treatment of them. Therefore, identification of contributing genes in the pathology of a multifactorial condition like TMD provides an opportunity to prevent or at least reduce the severity of the diseases in future generations by therapeutic and preventive self-care measurements. The goal of this review study was to collect and categorize useful information published between the years 1980 and 2019 on the genetics of TMD. Four major international scientific databases, namely BioMed, ProQuest, PubMed, and Google Scholar, and two major Iranian databases including Magiran and SID were searched for relevant articles published between 1980 and 2019. The keywords used in this search were facial pain and temporomandibular disorder or TMD, and genetic factors. Then all duplicate or irrelevant articles were excluded. The inclusion criteria for the articles were: a) Research articles, original article, clinical studies, and animal studies. And b) articles only Published in English or Persian. The exclusion criteria were (a) reviews, abstracts, commentaries, letters to the editor, opinion articles b) Duplicate articles retrieved from different databases and c) Lack of access to the full text.

Results and Discussion

The literature selection process was showed in Fig 1. By searching the mentioned databases studies were found 900 articles, almost 61% of articles were published after 2010, and, interestingly, most articles were published in 2014. Of the articles selected for the study (36 cases), 15 studies were performed on humans, while 21 studies were performed on animal models. A study of mice and human studies has been conducted. Eighteen out of 36 studies were done on mice while 1 on pigs, 2 on rats and 1 on rabbits. Articles from 1990 to 2019 covered much of the research on TMD genes. The demographic characteristics of human studies have varied widely. Among human studies, various ethnic groups such as Korean, Japanese, Brazilian, Finnish and Turkish have been studied. Three articles did not mention the ethnicity of the study population. The most prominent etiological hypothesis for TMD is a biopsychosocial model that incorporates biological factors such as activation of pain pathways with or without pathological evidence [6]. It has been predicted that the causative factors of TMD are multidimensional and influenced by not only environmental conditions but also by several genetic factors,which appear to be more in the form of genetic polymorphisms rather than single mutations [7]. Several gene polymorphisms association have been investigated for TMD. These were mainly related to serotonin activity [8], Tcell receptors [8], catecholamine activity and metabolism [9,10], estrogen activity [11], folate metabolism[12], glutathione activity [12], ankh gene [13], major histocompatibility complex [14], extracellular matrix metabolism [15], cytokines activity and metabolism [16]. It is believed that temporomandibular joint degradation is a common cause of TMD. Matrix metalloproteinases (MMPs) have been shown to play an important role in temporomandibular joint degradation by reducing extracellular matrix components. MMP1 gene polymorphism is associated with osteopetrosis and condylar erosion. In a study on Brazilian population, homozygosity for MMP1 2G/2G was 2.47 times more likely to be associated with mandibular condylar degradation than people with genotypes of MMP1 1G/2G and 1G/1G.

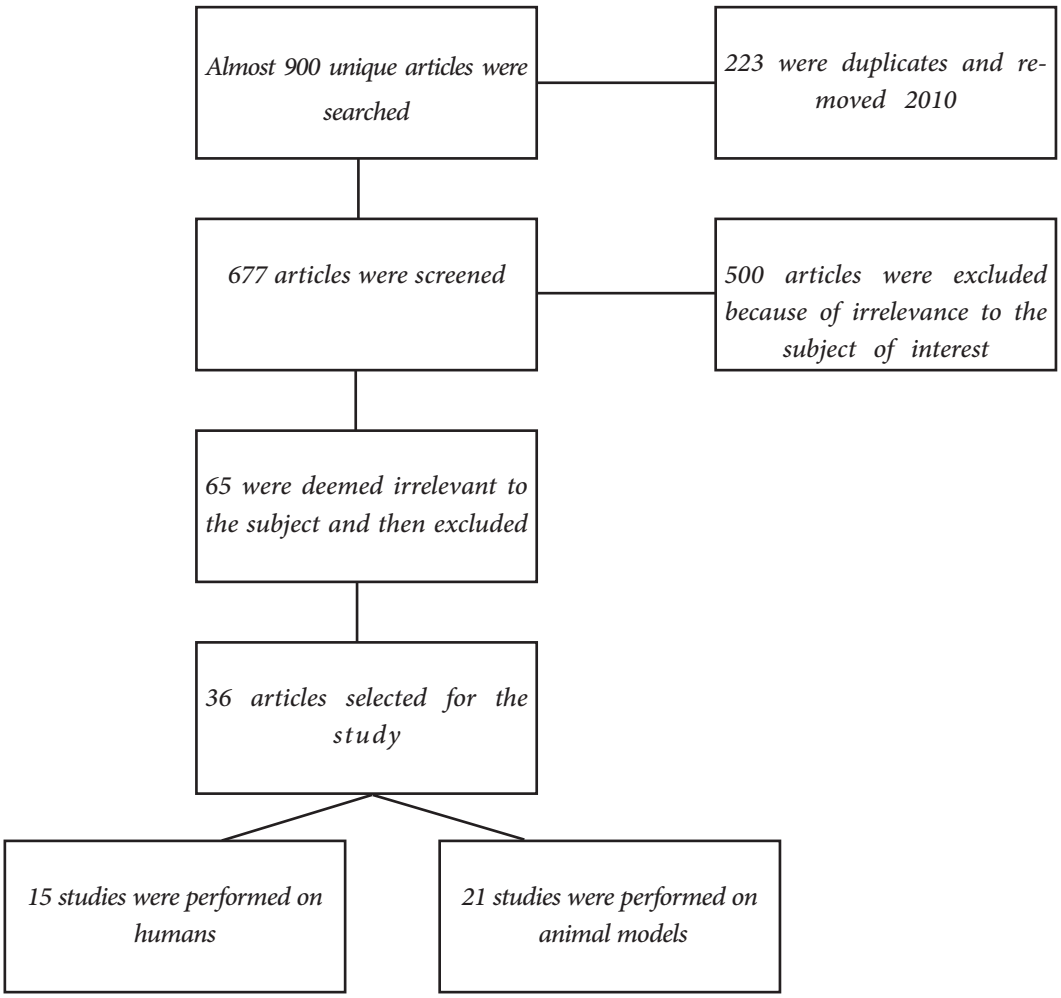

Fig 1. Flow diagram of patient selectiom.

These findings are indicative of the role of MMP1 polymorphisms in the exacerbation of temporomandibular joint degradation [17]. Also, a study on the expression of disintegrin and metalloproteinase with thrombospondin motifs 5 (ADAMTS-5) in cell tissue samples from deformed temporomandibular joints, has shown that ADAMTS-5 was associated with the deformation and degradation of discs in temporomandibular joints [18].

A clear association between SMAD1 and TMD pain has not been confirmed, other SMAD pathway genes have been related to acute inflammatory (but not neuropathic) and excitability of neurons as well as osteoarthritis of the temporomandibular joint [19]. In a case-control study on the temporomandibular joints of mutant mice, which was designed to identify human ANKH gene polymorphism, among TMD cases, jaw locking was found to be more prevalentin subjects with ANKH homozygosity (p=0.011, OR=7.7, 95% CI 1.6-36.5 and p=0.005, OR=2.4, 95% CI 1.3-4.3 in older subjects) [18]. Our findings suggest that males and females may develop TMD through different pathophysiological pathways [20]. Given the higher prevalence of TMD among women, sex hormones are also suspected to play a role in causation of TMD. It is believed that women experience more inflammation, pain, and tenderness in masticatory muscles and temporomandibular joint than men, so stronger inflammatory responses in women can accelerate the degradation of articular cartilage. Since estrogen acts through its receptors, some researchers have examined the polymorphisms of certain genes to identify any association between different variants of the estrogen receptor gene and the symptoms of TMD such as joint muscle pain, jaw movement restriction, and condylar head bone alteration.

From these studies, two have shown no association between thealleles of estrogen receptor alpha and TMD symptoms including clicking noise, crepitus, and bone erosion [21][22], however one study suggests that estrogen receptor polymorphisms may increase the risk of TMD in females [21]. The human leukocyte antigen (HLA) complex is a major histocompatibility factor (MHC) and its main function within the immune

system is to differentiate between self antigens from non-self antigens to stimulate the immune response. Epidemiological studies have shown that some polymorphisms in HLA-DRB1 alleles (MHC class II, DR beta 1) cause the representing receptors on the surface of immune cells to be associated with erosions of the mandibular condyle [23]. It has been reported that the average annual prevalence of TMD (4%) is highly or partially affected by a wide range of phenotypic factors including socio-demographic characteristics, general health conditions, clinical orofacial factors, physiological function, pain threshold, and cardiac autonomic responses. Among these factors, the general health condition have the highest association with the prevalence of TMD followed by physiological and clinical orofacial factors while low pain threshold and autonomic function have the lowest association with the prevalence.

Also, the prevalence of TMD is completely independent of age and location even after adjusting for other phenotypes. An analysis of 358 pain-regulating genes has found several genes with confounding phenotypes that are potential contributors to TMD [24]. Genetic factors are involved in the etiology of chronic pain through the regulation of processes such as nociceptive sensitivity, psychological well-being, inflammation, and autonomic responses. studies on those 358 genes corroborate the previous reports of existing a link between TMD and HTR2A and COMT genes. Other genes that have been discovered as potential genetic factors for TMD are NR3C1, CAMK4, CHRM2, IFRD1, and GRK5 [25]. The COMT gene plays an important role in the development of TMD [5].

The genotype with two 'T' alleles (TT) for the COMT gene rs9332377 was highly associated with the presence of muscular TMD [26]. COMT is anenzyme with a unique expression that maintains cells' basic biological functions via deactivating a large group of catechol substrates such as catecholamines and estrogens. For example, although the low activity of COMT is not associated with migraine or musculoskeletal pain, it may increase the risk of fibromyalgia or widespread pain [27]. In another study they founded that TGFb1 regulation of cytokines such as MCP-1 and IL-8, which is mediated by SMAD protein activation, is consistently inhibited in the plasma of TMD cases relative to controls (1In this study they examind whether whole blood mRNA levels of MRAS varied according to TMD case status. they found a statistically significant association at the gene level (beta520.04, P54.83 1022) in males and females [19]. Genetic association and eQTL analyses both suggested MRAS expression level influenced chronic pain in males; genome-wide significant associations with chronic TMD were found for 3 loci, including an association in males-only at 3 linked SNPs on chromosome 3 (rs28865059, rs13078961, and rs34612513 [19]. Regarding the ADRB2 gene, the non-polymorphic AA genotype in the rs1042713 region was more prevalent in the control group with exclusive painful joint TMD than in the group with muscular TMD.

Alterations in the ADRB2 gene may also modify the pain sensitivity of individuals, also being related to symptoms of somatization, depression, anxiety, and low blood pressure, which are phenotypic characteristics commonly found in individuals with generalized chronic pain, including TMD it is, therefore, believed that the risk of phenotypic changes resulting from polymorphisms in the ADRB2 gene is substantially greater than that associated with other risk factors, such as fluctuations in oestrogen levels, prior history of chronic pain, and even genetic variations in the COMT gene consistent with the formulated hypothesis, the results observed demonstrated that polymorphisms in the COMT and ADRB2 genes are associated with the presence of chronic masticatory myofascial pain, among patients with TMDs and controls. In relation to TMD, polymorphisms in the COMT gene substantially influence orofacial pain sen- sitivity, given that the activity of this en zyme is inversely correlated with pain sensitivity thresholds and the increased risk of developing TMD.Although the stability of messenger RNA was higher for COMTb transcriptions carrying the A allele, the expression levels of the protein and its enzymatic activity proved to be lower.

This provides an excellent example of how allelic variants can have opposite effects on messenger RNA stability and protein expression. In improving pain symptoms. In summary, gene polymorphisms related to the catecholaminergic system are associated with the presence of chronic masticatory myofascial pain, possibly through the influence exerted on the neu-ronal pain thresholds, peripheral and cen-tral. Pain thresholds are decreased in patients with chronic masticatory myofas-cial pain, even at sites remote from the trigeminal innervation regions, suggesting that this hyperexcitability is generalized and related to central sensitization states. Knowledge of the genetic characteristics of a patient with chronic pain could help the professional in relation to the patient's prognosis, thus influencing the entire ther-apeutic approach [26]. In another study wich was about effects of COMT and 5HTT, it

was concluded that In 5HTT, the rs1042173 was associated with painful TMD (arthralgia and myofascial pain) [28]. Polymorphisms in COMT rs4818 were significantly associated with myofascial pain (ORc=2.15; CI 95%: 1.08□]4.29; P=0.02) and were borderline for painful TMD (ORc=1.85; CI 95%: 0.97□]3.51; P=0.06) and disc displacement (ORc=2.42; CI 95%: 1.00□]5.87; P=0.05). The rs6269 was borderline for myofascial pain (ORc=1.82; CI 95%: 0.92□]3.59; P= 0.08) and disc displacement (ORc= 2.38; CI 95% 0.95□]5.97; P = 0.06) and also was associated with anxiety (ORa=2.34; CI 95% 1.04□]5.25; P=0.03).

The results of this study showed that polymorphisms in both genes, independent of gender, or anxiety were associated with TMD symptoms: COMT rs4818 was significantly associated with myofacial pain and was effective for disk and TMD displacement, whereas rs1042173 5HTT was significantly associated with TMD. Painful TMD polymorphism in COMT was also associated with anxiety in the model adjusted using logistic regression. The rs6269 polymorphism was associated with a higher probability of moderate/high anxiety [28].

Synovial chondromatosis (SC) is a rare proliferative disorder, which is characterized by formation of cartilaginous or osteocartilaginous nodules in the synovium and articular space. FGF-2 gene polymorphism is also believed to be involved in the pathogenesis of synovial temporomandibular joint [29,30]. Identification of 22 independent loci associated with the gradual degeneration of mandibular condyle in the East Asian population was performed in a study, among which TSPAN9 polymorphism showed the strongest association with TMD. TSPAN9 is a mediator of cellular signaling pathways that plays an important role in regulating cell growth, activation, growth and motility, this finding can lead us to believe that gene mutations are an important factor in the development of TMD.

Thus, some cellular signaling pathways may be involved in the pathogenesis of TMD [30]. An investigation on the relationship of TMD with monoamine oxidase A gene, showed no significant difference between patients and controls in terms of MAO-LPR gene polymorphism and its findings suggested that only the presence of high-activity alleles might play a role in the clinical manifestation of TMD [31]. There are several studies showing a significant prevalence of three serotonin-dependent genetic polymorphisms among TMD patients in comparison with control groups, indicating the effect of serotonin receptors in the pathogenesis of TMD [32]. A Turkish study on interleukin-1 receptor antagonist (IL-1Ra), which is an important anti-inflammatory molecule competing with other IL-1 molecules, showed a correlation between IL-1Ra VNTR gene and TMD. This study reported that the VNTR variant of IL-1Ra had a strong pattern of association with TMD whichmight have a potential impact on disease management andcounseling. This study believes thatlarger studies on different ethnicities are necessary to confirm the real effect of VNTR IL-1Ra on the risk of developing TMD [33].

Ribeiro-DaSilva et al. (2008) conducted a study on the relationship of alpha estrogen receptor polymorphism and susceptibility to TMD. They collected DNA from 200 women,of whom 100 had chronic pain and 100 weresuffering from pain-free TMD, so theyusedthe DNA of 100 women without TMD as controls. This study found that the presence of alpha estrogen receptor polymorphism might play an explicit role in increasing risk of TMD [34]. In cohort study by Smith SB and et al. (2019) a genome-wide association study performed assuming an additive genetic model of TMD and showed that genetically determined MRAS expression moderates the resiliency to chronic pain. Also they reported that males and females may developTMD through different pathophysiological pathways [35].

In a cross-sectional study by de Freitas LV and et al findings supported that the 102T-C polymorphism in the HTR2A gene is associated with TMD in the Brazilian population [36]. In this study, we reviewed the current literature to find the causative genes for TMD and the effect of genetic interactions on the molecular mechanism of TMD. However, there are severe limitations, which need to be acknowledged in this review study. First, it was limited to articles published between 2000 and 2019 in English or Persian. Second, all studies we reviewed had significantly a great number of female subjects causing unequal gender distribution, which might affect the validity of the results that indicated higher susceptibility for women. Given the broad classification and diagnostic criteria for TMDs, the chance of diagnostic bias must be also considered.

Table 1. Results from human studies.

limitations	Results	Studied gene	Author and Year of Publication
Small sample size to detect MMP3 gene association	Only MMP1 2G/2G genotype was significant (P<0.003). The effect of age on TMJ destruction was significant (P<0.002)	Studied gene MMP1 MMP3 MMP9	Planello-2011 [66]
Calculating the minimum sample size was unattainable.	Two alleles of ANKH-OR polymorphism were identified. The ANKH-OR homozygote is more likely to be locked than the control group. (P=0.011)	ANKH	Huang-2011 [67]
Small sample size	There was no statistical difference between case and control groups (P>0.05).	ESR1	Kim-2010 [76]
The small sample size and population of Brazilians limit the definitions of the data, only data from joint pain have been examined and do not include muscle pain.	The presence of haplotype [GC] in the ERα gene in TMD with pain was higher than in the control group (P=0.0028)	ESR1	Ribeiro-Dasilva-2009 [75]
Small sample size, limited use of TMJ disk cells	ADAMTS-5 is associated with ID and osteoarthritis in TMJ disk reshaping (P<0.01).	ADAMTS-5	Matsumoto-2008 [72]
Controls were not clinically or radiologically evaluated.	In the whole patient population, HLA-DRB1 allele was significantly associated with TMJ ablation (P=0.0014).	HLA-DRB1	Helenius-2004 [78]
Unknown	FGF2 is involved in the pathogenesis of synovial chondromatosis (P<0.01)	FGF2	Li-2014 [73]
Unknown	TNFα-308GA polymorphism is not associated with TMD.	TNF	Etoz -2006 [77]
Unknown	There is no evidence to support the involvement of the MAOA gene in TMD.	MAOA	Mutlu -2005 [74]
Small sample size, age, and gender differ between Japanese and Korean datasets.	All genes were significantly related and effective. TSPAN 9 showed the strongest association.	APOL3 APP CCDC81 EXT2 FRMD4A FSTL4 LOC100506 274 MRC2 N4BP1 OXR1 PCSK5 SLC24A4 THRB TPSAN9 ULK4 ZNF618	Yamaguchi-2014 [65]
Unknown	The mean infusion rate in patients with TMD/HC decreased with COMT 158 Met replacement.	COMT	Nascimento-2019 [116]

Animal Studies

In order to examine more accurately the function and genetic impact of TMD in many articles, model animals have been used in one or more mutant candidate genes, because the description of methods such as the methods used to construct model animals is beyond the scope of this study. In the following table, we review the findings of 21 articles from animal model studies. Healthy female animals with high susceptibility to the pain haplotype presented the COMT enzyme more than 10-fold less than the animals with "low susceptibility to the haplotype" [26].

Table 2. Results of animal models studies.

limitations	*Results*	*Studied gene*	*Study animal*	*Author and Year of Publication*
Unknown	*Drastogenesis defects in knockout mice in the target gene, calcified cartilage in the hypertrophy region, few signs of endochondral bone formation, abnormal intracranial bone*	*Osx*	*Mice*	
Unknown	*Abnormal condylar organization, condylar degradation, reduced proliferation of preconditioning cells, and increased cell death*	*Samp8*	*Mice*	*Ishizuka-2014 [83]*
Unknown	*Congenital disc degeneration indicates SHOX2 genetic association with TMJ osteoarthritis*	*Shox2*	*Mice*	*Li-2014 [84]*
Small sample size	*Abnormalities in the subconductive bone that cause cartilage destruction*	*Tgfb1*	*Mice*	*Jiao-2014 [85]*
Unknown	*Bilateral Syngnathia (Upper and Lower Jaw Fusion) in Foxc1 Mutant Mice.*	*Foxc1*	*Mice*	*Inman-2013 [86]*
Unknown	*TMJ in Dmm/+ mice showed immature articular cartilage and and further defects in chondrocyte accumulation, known biomarkers of osteoarthritis were significantly expressed (P<0.01).*	*Col2a1*	*Mice*	*Ricks-2013 [87]*
Unknown	*Articular disk fusion with temporal bone, defect in endochondral bone formation, fractured articular surface with cleft, defect in trabecular bone formation and lack of glenoid curvature*	*Fgfr3*	*Mice*	*Yasuda-2012 [88]*
Unknown	*Spry 1 and Spry 2 resulted in simultaneous inactivation of genes lacking glenoid curvature and overgrowth of lateral pterygoid muscles and temporal muscles*	*Spry1, Spry2*	*Mice*	*Purcell-2012 [89]*
The use of 3- to 5-month-old mice in this study may be responsible for the lack of erosive changes in the temporomandibular joint..	*Narrow joint space*	*Ank*	*Mice*	*Huang-2011 [67]*

limitations	Results	Studied gene	Study animal	Author and Year of Publication
Unknown	Microbial analysis identified 22 different expression genes in mouse models that could interfere with the onset of the disease; 5 genes (Cartpt, Sfrp1, Arsk, Slc4a1, Ptprv) were altered in mouse models and with osteoclast differentiation/function and bone changes it›s related to	Studied gene 4833416E15Rik Aebp1, Ahsp Angptl7, Arsk Bace1, Bgn Cartpt, Col2a1 Col9a1, Col9a3 Fmod, Hapln1 LOC 344564 Matn3, Mrpl30 Pfn1, Ptprv Rps19, Sfrp1 Slc4a1, Tspan33	Mice	Embree-2011 [90]
Unknown	Temporomandibular articular disc loss, small condyle, loss of growth plate cell organization	Gli2	Mice	Purcell-2009 [91]
Unknown	Glenoid curvature dysplasia, congenital hardening of the temporomandibular joint	Shox2	Mice	Gu-2008 [92]
Small sample size	Incomplete development of jaw, anomalous condylar angle, complete absence of functional disc and articular cavity	Ihh	Mice	Shibukawa-2006 [93]
Unknown	Swelling, superficial fibrillation, early changes in osteoarthritis	Angpt12, Aqp3 Baalc, Casr, Cav, Chad, Cldn11, Cls Clu, Crabp2 Csrp2, Dkk3 Dpt, Egln3 Eln, Gda, Gda, Hig1 Hspca, Htr2a Igfbp5, Igfbp6 Il11ra1, Lg11 Lg11, Lib Meox2, Mmp3 Nb11, Nov Nr1d1, Nt5 Octnl, Plat Prelp, Prrx2 Pthlh, Scrg1 Serpina1, Sfrp4 Sod3, Spin2c Spp2, Tgfbi Thbs4, Tnfrsf11b Tnmd	Mice	Meng-2005 [94]
Unknown	At age 6 months, severe osteoarthritis-like changes were seen, including flattening of the candidal head, loss of proteoglucins, and decreased hypertrophy	cho	Mice	Xu-2003 [95]
Unknown	Lack of functional fibro-optic layer formation, lack of disc separation from the condyle	Bmpr1a	Mice	Gu-2014 [96]

limitations	Results	Studied gene	Study animal	Author and Year of Publication
Unknown	Increased number of apoptotic cells in glenoid curvature causes glenoid curvature dysplasia, condylar dysplasia	Shox2	Mice	Li-2014 [97]
Unknown	Significant decrease in temporomandibular joint space, cartilage thickness decreased significantly, increased cartilage degradation enzymes, osteoarthritis-like phenotype	Ctnnb1	Mice	Wang-2014 [98]
Unknown	There was no significant difference between OA and normal controls	Aqp1, Aqp3	Rats	Meng-2007 [99]
Unknown	Osteoarthritis-like changes in the 2-week female experimental group compared to the control (P<0.01) and the two-week male experimental group (P<0.05), IGF1 expression was lower in the 2-week female subjects (P<0.01). IGFR1) was significantly decreased in female 2 weeks (P<0.05), but in male 2-week experimental group IGFBP3 was significantly lower in all female subgroups than in male counterparts.	Igf1 Gfr1 Igfbp3	Rats	Yu-2012 [100]
Differences in the type of jaw lock between rats	The cartilage surface coating with cartilage affects the friction rate of the jaw lock	Cox2 Il1b Mmp1 Mmp3 Mmp9	Porcine	Asakawa-Tanne-2015 [101]
The amount and nature of the samples used in this study do not reflect the true dynamics of TMJ in vivo	WNT5A is associated with cartilage destruction with decreased expression of MMP1, MMP3, MMP9, MMP13	Wnt5a	Rabbit	Ge-2009 [102]
Unknown	Healthy female animals with high susceptibility to the pain haplotype presented the COMT enzyme more than 10-fold less than the animals with "low susceptibility to the haplotype."	COMT	Mice	de Souza Tesch-2019 [115]

Conclusion

However the genetic risk factors are supposed to play a role, future studies with larger samples are required to understand the genetic mechanisms behind the association of TMD and trigeminal neuralgia. Recent advances have led to the introduction of new techniques such as GWAS, which can help us identify the genes involved in the development of TMD and trigeminal neuralgia.

Conflict of Interest

There is no conflict of interest to declare.

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