REVIEW ARTICLE

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The many faces of the genetics contribution to temporomandibular joint disorder

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Structured Abstract

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Objectives – Review the literature on candidate genes for temporomandibular joint disorder (TMD).

Setting and Sample Population – Literature review.

Materials and Methods – Two basic approaches were used to obtain literature in any language regarding genes and TMD. First, Medline, Embase, and Science Citation Index databases were searched using the keywords 'temporomandibular joint disorder' and 'temporomandibular joint dysfunction' for studies published from 1966 to 2007. Then, the references list of the studies obtained in the database was also considered.

Results – Candidate genes for TMD include genes for individual variations in pain perception, gender and ethnicity, proinflammatory cytokines, female hormones, breakdown of extracellular matrix, and syndromic forms of TMD.

Conclusion – Most of the studies on genetic variation contributing to TMD are approaching the disease mainly from an immune-inflammatory perspective. Recent investigations of the genetic variables which may predict identifiable levels of pain perception may uncover new approaches to our traditional treatment modalities for the chronic pain patient.

Key words: myofascial pain dysfunction syndrome; pain; temporomandibular joint; temporomandibular joint dysfunction syndrome

Introduction

It is widely accepted in the healthcare environment that pain is one of the most common reasons why people seek professional advice and treatment. Chronic pain patients spend countless hours suffering while seeking advice from practitioner to practitioner experimenting from one therapy to the next. Chronic pain disorders are estimated to cost approximately $80 billion per year in health care costs and lost productivity in the United States (1, 2). These and other examples are compelling reasons why the management and relief of suffering should be the primary focus of the

healthcare professional. It is accepted that unrelieved pain can cause delayed healing, undue stress and potentially lead to autoimmune disorders and alterations of the peripheral and central nervous systems leading to chronic pain syndromes. Patients have reported countless psychosocial symptoms leading to real-life disruptions when experiencing various levels of pain. These symptoms include but are not limited to: loss of self-esteem, sleep disturbances, loss of libido, loss of appetite, fatigue, and depression. In short, pain can govern one's life (3).

It is accepted that there are two different kinds of chronic pain: nociceptive/inflammatory pain and neurophatic pain. The first, inflammation associated, is caused by tissue damage. Neurogenic pain syndromes arise as a consequence of central and peripheral nerve damage (4).

Pain is said to be a complex multidimensional experience as a result of a noxious stimulus which travels along nociceptive nerve pathways to the central nervous system. Pain perception is a multifaceted physioanatomical process. There are said to be multiple components of pain perception: the sensory-discriminative, affective-motivational, and autonomic. A patient may report sensory-discriminative properties of their pain when describing a severe dull ache in their right maxillary first molar over the past 24 h. He/she may include affective-motivational aspects of their pain perception by stating that due to this pain, sleep was not possible until a conventional therapeutic was administered. In the autonomic phase, this patient may also report being upset to the level he/she felt 'out-of-breath' during the entire encounter until the pain was relieved (5).

In 1959, Beecher (6) described a state of pain known as the *pain threshold*. The *pain threshold* can be described as the first perceptible pain produced by a noxious stimulation in the conscious subject. The variability from person to person in this area can be attributed to variables such as, but not limited to: age, sex, poor stimulus control, education, cultural background, fatigue, attention, suggestion, previous pain exposure and interpretation, genetics, etc. As a result, pain is an example of a highly complex biobehavioral health outcome that exhibits variability among individuals; that is, individuals differ in how they respond to painful and/or anxiety-provoking stimuli. Therefore, it is fundamentally established that the perception of pain is a multidimensional both sensory and emotional experience. But one cannot help but to ask as Mogil (2005) (7) did based on observations of his pain mouse model, '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?'.

Pain in the facial region, including orofacial pain and craniofacial pain (excluding the traditional headache), accounts for a significant proportion of the approximately 10**%** of the Americans that suffer from chronic pain conditions. Sources of orofacial pain include caries, periodontal diseases, and neuropathic and musculoskeletal conditions (8). Orofacial pain is a major symptom of temporomandibular joint disorders (TMD) (9) and among the orofacial pain disorders, TMD comprise a relevant proportion of the total cases. The current treatments for these conditions could benefit from new approaches (10, 11) however, persistent pain among patients constitutes a public health concern that inflicts especially women between 20 and 40 years of age (2, 11–18). Studies concerning TMD have been limited because of the heterogeneous nature of symptoms leading to difficulties in diagnosis (19–21).

In 1996, the NIH Consensus Development Program targeted on TMD management consorted to develop the State of the Science Statements. This group was presented as a non-federal, non-advocate 15-member panel of leading clinicians and scientific researchers representing numerous topics in medicine and dentistry to include but not limited to: cellular and molecular biology, biostatistics, behavioral and social sciences, tissue engineering and surgical interventions. Their conference was dedicated to allow leading scientists the forum to present evidence-based information regarding subjects related to the diagnosis and management of TMD. The conference theme supported scientific evidence as opposed to giving preference to clinical and/or anecdotal experiences of the speakers (22). Among their nationally publicized guidelines was the literature's perspective related to the definition of TMD. It stated, 'Temporomandibular disorders (TMD) refer to a collection of medical and dental conditions affecting the temporomandibular joint (TMJ) and/or the muscles of mastication, as well as contiguous tissue components'. Their report continues to discuss the fact that the diagnosis and treatment of these disorders lacks research and significant

findings which can service the field of practitioners to adopt much needed universal guidelines.

What are the symptoms of TMD? According to the TMJ Association (2005; http://www.tmj.org), it is common for TMD sufferers to complain of symptoms such as but not limited to the following: a dull aching pain in the jaw, ear pain and/or ringing in the ears, inability to open the mouth comfortably, clicking, popping, or grating sounds in the jaw joint, locking of the jaw open, uncomfortable or 'off' bite. Although it is unknown as to what causes TMD disorders, contributing factors are thought to be related to trauma, bruxism (teeth grinding), or other destructive oral habits and growth abnormalities which can lead to malocclusion as excessive loads are placed on the joint (23).

There are a vast number of healthcare providers representing many fields of expertise who service TMD patients. Without universal guidelines related to classification, considerable variability exists as physicians depend upon their experience and philosophies to dictate treatment modalities rather than scientific evidence. It is widely accepted that these modalities can vary and may include: educational and behavioral counseling, pharmacological interventions, mechanical approaches, physical therapy, occlusal therapies and a variety of surgical approaches or even more so, a combination thereof. These variances in treatment modalities are likely to remain until a classification system is developed which relies on etiology rather than a detailed description of symptoms and underlying conditions.

As reported by the National Institute of Dental Craniofacial Research (NIDCR) of the National Institutes of Health (NIH), TMD is known to affect over 10 million people in the USA at any given time. This disorder afflicts both men and women, however, women in their childbearing years constitute approximately 90% of those seeking treatment. In a 20-year-long study, Magnusson et al. (24) revealed that TMD signs and symptoms were present in childhood and increased up to young adulthood, after which they appeared to level-out.

TMD is a collection of symptoms related to the muscles and joints of the masticatory system. They likely comprise a number of etiologically distinct conditions that lead to similar symptoms. For these reasons, it is not surprising genetics has not been considered as a main etiologic factor. For many years, a combination of stressors (environmental and/or nutritional) was believed to be the underlying cause of TMD, not genetics (25). Also, studies that attempt to find a segregation pattern in families of cases with TMD (26) or used twin models (27) have suggested that TMD is not a genetic disorder.

However, individuals are not equally susceptible to TMD. Women in their reproductive years represent the majority of those seeking care and the extent to which genetic and epigenetic factors contribute to TMD has become a point of high interest. Aside from familial risks, different genotypes can involve susceptibility to a particular clinical course of the disease and/or treatment response, including the development of complications (e.g. unfavorable response to environmental challenge, material, etc.). Therefore, the resulting symptoms of TMD should be understood as the person's complex response trait with specific complaints being either amplified or attenuated by the unique genetic makeup and/or prior experience (28). Hormonal milieus are believed to augment the inherent genetic vulnerability to TMD, explaining the greater likelihood of the condition among women in the childbearing age (29, 30).

For that reason, it has been suggested that a better understanding of the genetics modulating TMD is a necessary step that will lead to innovative therapies related to these conditions (31). Also, there is strong recent evidence from the literature of the importance of genes on how pain is perceived and manifested (32). Having a genetic marker that would predict treatment efficacy with a high degree of success would add a very powerful approach toward improving the treatment of TMD and potentially other painful conditions.

In this literature review, the myriad of possibilities for a genetic contribution to TMD is presented to provide the scope of opportunities for future research. The aim of this explorative review was to identify the genes that have been proposed as suitable candidates for contributing to TMD.

Search strategy

Two basic approaches were used to obtain literature in any language regarding genes and temporomandibular joint disorder. First, Medline, Embase, and Science Citation Index databases were searched by two abstractors using the keywords 'temporomandibular joint disorder' and 'temporomandibular joint dysfunction'

for studies published from 1966 to 2007. A total of 82 articles were identified after cross-referencing with the keyword 'genetics.' Both human and animal studies were considered. The references list of the studies obtained in the database was also considered. Finally, text books describing the etiology of TMJ conditions were identified and pertinent reference lists of the related book chapters were also considered. All studies dealing with gene identification in TMD were cited in the review.

Candidate genes for temporomandibular joint disorder

How genes may contribute to TMD could be described as follows: (1) individual pain perception; (2) gender and ethnicity; (3) proinflammatory cytokines; (4) breakdown of extracellular matrix; (5) other genes expressed in the TMJ; and (6) syndromes. Table 1 summarizes the candidate genes described in this section. Table 2 describes syndromic forms of TMD.

Genes for individual variations in pain perception

Animal studies have provided a list of candidate 'pain genes' (33) but identification of genes associated with human pathologies in which pain is the defining symptom provides a good source of candidate genes for TMD. Those conditions include: (1) experimental pain (34–37) [*COMT* (catechol-O-methyltransferase), *MC1R* (melanocortin 1 receptor), and *OPRM1* (opioid receptor mu 1)]; (2) fibromyalgia (38–40) [*COMT*, *HTR2A* (5-hydroxytryptamine – serotonin-receptor 2A), and *SLC6A4* (solute carrier family 6 – neurotransmitter transporter, serotonin-member 4)]; (3) irritable bowel syndrome (41) (*HTR2A*); (4) low back pain (42) [*IL1A* (interleukin 1 alpha) and *IL1RN* (interleukin 1 receptor antagonist)]; (5) idiopathic migraine (43) [*CACNA1A* (calcium channel, voltage dependent, P/Q type, alpha 1A subunit), *ATP1A2* (ATPase, Na^+/K^+ transporting alpha 2 (+) polypeptide), *INSR* (insulin receptor), and loci 4q24, 6p12.2–21.1, 11q24, and 14q21.2–q22.3]; (6) pelvic pain syndrome (44) (*IL10*; interleukin 10); and (7) vulvar vestibulitis (45–47) [*IL1RN*, *MBL2* (mannose-binding lectin 2), and *MC1R*].

In addition, *MC1R* and neuronal cytochrome P450 2D6 (*CYP2D6*) are associated with alterations in opioid analgesia in humans (48, 49). Also, congenital insensitivity to pain (CIP) type I has been linked to the gene encoding a subunit of serine palmitoyltransferase, and CIP type IV has been linked to the gene encoding for a nerve growth factor-specific tyrosine kinase receptor (48–50).

Preliminary work on the serotonin 5-HT transporter gene (*SLC6A4*) suggested that this gene may have a role in the genetic predisposition of TMD (51, 52). Of particular interest is the catecholamine-*O*-methyltransferase (*COMT*), in which activity has been inversely correlated with pain sensitivity and the risk of developing TMD (36). The presence of even a single high *COMT* activity haplotype was shown to diminish the risk of developing TMD by as much as 2.3 times. The risk ratio of 2.3 is of a magnitude comparable to other predictors of TMD, such as history for chronic pain at other body sites (53, 54). The measure of population attributable fraction for having the 'high pain sensitivity' haplotype and/or the 'intermediate pain sensitivity' haplotype was 29**%** of the cohort of women studied, indicating that nearly one-third of new TMD cases can be attributed to *COMT* genotypes (36).

Individuals that carry one haplotype coding for high and one coding for low adrenergic receptor B2 (*ADRB2*) expression, which is a primary target for epinephrine, were shown to be 10 times less likely to develop TMD, suggesting that either positive or negative imbalances in ADRB2 function increase the vulnerability to TMD (55).

Gender and ethnicity

It is believed that besides the individuals' genetic constitution, sensory input is filtered through a number of socio-cultural aspects. There is evidence that women exhibit higher response to cold and thermal stimuli than men, including variation depending on the ethnic background (56). European American males appear to be more tolerant to pain generated by cold stimulus, while females appear to be less tolerant to hot stimulus. *OPRD1* (delta opioid receptor subtype 1) genotypes appear to modify hot stimulus sensation (57). Although these results come from experimentally induced pain, they may provide a useful surrogate measure for clinical pain.

Gender differences in TMD incidence are quite remarkable. The role of female hormones is suggested

Table 1. **Summary of candidate genes for TMD**

Gene	Locus	Protein function*
OPRD1	1p35.3	Opioid receptor
ATP1A2	1q23.3	Responsible for establishing and maintaining the electrochemical gradients of Na and K ions across the plasma membrane
PTGS2	1q25.2–q25.3	Involved in prostaglandin biosynthesis
IL10	1q32.1	Involved in immunoregulation and inflammation
IL1B	2q13	Mediator of the inflammatory response, and is involved in a variety of cellular activities, including cell proliferation, differentiation, and apoptosis
IL1A	2q13	Involved in various immune responses, inflammatory processes, and hematopoiesis
IL1RN	2q13	Inhibits the activity of IL1A
IHH	2q35	Defines a variety of patterning events during development by intercellular signaling
CCL20	2q36.3	Regulates mitogenic signaling
SPP2	2q37.1	May coordinate an aspect of bone turnover
CXCL3	4q13.3	Chemokine ligand that has chemotactic activity for neutrophils
CXCL2	4q13.3	Suppresses hematopoietic progenitor cell proliferation
IL8	4q13.3	Mediator of inflammatory response
ADRB2	5q33.1	Beta-2-adrenergic receptor
OPRM1	6q25.2	Opioid receptor
IL6	7p15.3	Plays an essential role in the final differentiation of B-cells
NOV	8q24.12	Likely plays a role in cell growth regulation
AQP3	9p13.3	Water channel protein
MBL2	10q21.1	Activates the classical complement pathway and recognizes mannose and *N*-acetylglucosamine on bacterial pathogens
DKK3	11p15.3	Inhibitor of the Wnt signaling pathway
HTR2A	13q14.2	Serotonin receptor
EGLN3	14q13.1	Catalyzes the post-translational formation of 4-hydroxyproline in hypoxia-inducible factor alpha proteins
CYP19A1	15q21.1	Catalyzes many reactions involved in drug metabolism and synthesis of cholesterol, steroids, and other lipids
BCL2A1	15q25.1	Reduces the release of pro-apoptotic cytochrome *c* from mitochondria and block caspase activation
MC1R	16q24.3	Receptor protein for melanocyte-stimulating hormone
SLC6A4	17q11.2	Integral membrane protein that transports serotonin from synaptic spaces into pre-synaptic neurons
CCL7	17q12	Attracts macrophages during inflammation and metastasis
CSF3	17q21.1	Controls the production, differentiation, and function of granulocytes
BCL2	18q21.33	Blocks apoptotic death of some cells such as lymphocytes
CACNA1A	19p13.13	Mediates the entry of calcium ions into excitable cells of the neuronal tissue
INSR	19p13.2	Insulin receptor
BAX	19q33.3	Apoptotic activator
CYP2D6	22q13.1	Catalyzes many reactions involved in drug metabolism and synthesis of cholesterol, steroids, and other lipids
MMPs	–	Collectively they are capable of degrading all kinds of extracellular matrix proteins
ADAMTs	–	Collectively they contribute to inflammation and cancer

*Information obtained from the UCSC Genome Bioinformatics (http://genome.ucsc.edu) and National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov).

as a risk factor by the strong female prevalence and by the effects of physiologic and therapeutic modification of estrogen levels in patients with TMD (10).

Therefore, polymorphisms in genes encoding enzymes involved in estrogen metabolism would be suitable candidates for TMD. Among them, *COMT*

Table 2. **OMIM TMD syndromes**

Syndrome	Main clinical characteristics	Gene (locus)
Auriculocondylar syndrome (%602483)	Bilateral external ear malformations and hypoplastic mandible	–
Ehlers-Danlos syndrome type III (#130020)	Benign joint hypermobility without skeletal deformity	*COL3A1* (collagen type III alpha 1; 6p21.3) and *TNXB* (tenascin XB; 2q31)
Ehlers-Danlos syndrome type VIII (%130080)	Skin lesions in association with periodontal disease leading to early loss of teeth	–
Fibrodysplasia Ossificans Progressiva (#135100)	Intermittently progressive ectopic ossification and malformed big toes	*ACVR1* (activin A receptor type I; 2q23–q24)
Ophthalmomandibulomelic Dysplasia (%164900)	Eye, mandible, and limb anomalies	–
Schwartz-Jampel syndrome type I (#255800)	Short stature, myotonic myophaty, dystrophy of epiphyseal cartilages, joint contractures, eye anomalies	*HSPG2* (heparin sulfate proteoglycan 2; 1p36.1)
Tight Skin Contracture syndrome, Lethal (#275210)	Restrictive dermopathy	*LMNA* and *ZMPSTE24* (lamin A/C and zinc metallopeptidase STE24 homolog of *Saccharaomyces cerevisiae*, respectively; 1p34)

appears to be a likely candidate (36). Another estrogen-related gene, *CYP19A1* (aromatase), is expressed intensely in condylar cartilage of rats, which suggests that it may play an important role in pathophysiological mechanisms in condylar cartilage (58).

Proinflammatory cytokines

Initial studies on immune-related markers explored the possibility of human leukocyte antigens (HLA) (major histocompatibility complex) being associated to TMD with inconclusive results (59). In patients with various rheumatic diseases, HLA antigens were associated with TMD (60, 61). More recently, immune-inflammatory response genes became a matter of interest. Cytokines normally confer a survival advantage to the host by mediating immune responses, limiting tissue damage, and promoting tissue remodeling (62–64). However, slight or persistent elevations in the local level cytokines can alter immune and accessory immune cell function *in vivo* and result in tissue pathology (63). Cytokines present in the superior joint space of the TMJ may be directly responsible for such pathologic changes leading to TMD. Preliminary work has shown that the presence of *IL6* (interleukin 6) correlated with the degree of acute synovitis in humans, however *IL1B* (interleukin 1B) and *TNFA* (tumor necrosis factor alpha) were not found in significant levels within the superior joint space in cases with TMJ internal derangements (63). In addition, animal models have shown that the induction of *ILIB* expression in the TMJ of adult mice leads to pathologic development and related pain in the joints (64). Gene expression profiles of synovial fibroblasts stimulated with *IL1B* were studied in TMJ of rats and the results show that 121 genes had a greater than threefold change in their expression when compared with *ILB1* untreated synovial fibroblasts (65). The most upregulated gene was *Ccl20* [chemokine (C–C motif) ligand 20] that presented a 413.6-fold change. Other nine genes presented between 19.9- and 60.8-fold increase in expression: *Cxcl3* [chemokine (C-X-C motif) ligand 3], *Bcl2a1* (BCL2-related protein A1), *Ptgs2* (prostaglandin-endoperoxide synthase 2), *Cxcl2* [chemokine (C-X-C motif) ligand 2)], *Il8* (interleukin 8), *Csf3* [colony-stimulating factor 3 (granulocyte)], *Ccl7* [chemokine (C–C motif) ligand 7], *Il1b* (interleukin 1 beta), and *Il6* (interleukin 6) (66).

Breakdown of extracellular matrix

Extracellular matrix of collagen and proteoglycans have different roles for mechanical stress to articular cartilage in the TMJ. Collagen type II resists forces, and proteoglycan as aggrecan provides compressibility and elasticity in the articulating surface (67). Two major families of enzymes are responsible for cartilage degradation: matrix metalloproteinases (MMPs) and aggrecanases (68). MMPs are zinc-dependent endopeptidases with a wide spectrum of substrate specificities and consist of at least 19 different members. On the other hand, aggrecanase is classified as a member of the disintegrin and metalloproteinase domain with thrombospondin (ADAMTS) family. Preliminary work with MMP2, MMP9, and aggrecanase suggests that expression of aggrecanase in the TMJ of patients with internal derangement could be a potential biochemical marker for this articular degradation (68, 69).

Other genes expressed in the temporomandibular joint

Hereditary and mechanical modulations of growth and development share a common pathway via genes. Cells are influenced by genes and environmental cues to migrate, proliferate, differentiate, and synthetize extracellular matrix in specific directions and magnitudes, ultimately resulting in macroscopic shapes such as the condylar aspect. Mechanical forces readily modulate bone and cartilage growth (29). Apoptosis (programmed cell death) appears to be an important mechanism in pre-natal and post-natal TMJ development. *Bcl2* (B-cell leukemia/lymphoma 2) and *Bax* (Bcl2-associated X protein) are the genes that have been associated with apoptosis at the condylar cartilage. In addition, *Bcl2* appears to have an important role in maintaining survival of chondrocytes during their proliferation, differentiation, and maturation (70, 71).

Wild-type mouse embryos strongly express *Ihh* (Indian hedgehog) in condylar cartilage by embryonic day (E) 15.5. In *Ihh*-null embryos, TMJ development is severely compromised. These defects were partially corrected in double *Ihh*-null and *Gli3* (Greig cephalopolysyndactyly syndrome)-null mutants, indicating that *Ihh* action is normally modulated and delimited by *Gli3*. Both single and double mutants failed to form normal articular disc and joint cavities (72).

Gene expression profiles of mandibular condylar cartilage after experimentally induced osteoarthritis in rats show that 138 genes and expressed sequence tags were up- or down-regulated at least two-fold. Among these, five genes that were never reported to be related to osteoarthritis were consistently observed to be up-regulated in this study, suggesting they may be involved in osteoarthritis progression (73). These genes are *AQP3* (aquaporin 3), *SPP2* (secreated phosphoprotein 2), *NOV* (nephroblastoma overexpressed gene), *DKK3* [dickkopf homolog 3 (*Xenopus laevis*)] and *EGLN3* [egl nine homolg 3 (*Caenorhabditis elegans*)].

Syndromic forms of TMD

Humans

Syndromes that present TMD as part of the phenotype could serve as models for isolated forms of TMD. This approach has been used in other craniofacial complex traits, such as cleft lip and palate (74) and tooth agenesis (75). The OMIM (Online Mendelian Inheritance in Man) database displays seven syndromes that present with TMD (Table 1). Among those, four syndromes have genes mapped.

One common finding in many TMD cases with no definable cause is anterior displacement of the disk. It might occur in persons with hypermobile joint syndrome (hypermobility of muscular, articular, and ligamentous tissues) and may lead to joint disease (23, 76). Hypermobility syndrome has been reported in 0.6%–31.5% of adults without joint pain, depending on age, ethnicity, and criteria for assessing hypermobility (77).

Hypermobile joint syndrome is a benign disorder of increased joint laxity that is often hereditary. It has been reported that between 5 and 10 percent of Caucasians are hypermobile, and the condition is more commonly associated with the female population (78). Hypermobile joint syndrome has also shown to be prevalent in high percentages across ethnicities such as Iraqi, African and Asian Indian populations (23). In 1991, Buckingham et al. (23) suggested that anterior displacement of the temporomandibular disk may occur in people who have a laxity (hypermobility) of muscular, articular, and ligamentous tissues which can contribute to joint disease. They hypothesized that excess movements in the TMJ of these patients may cause accelerated disk destruction and degenerative disease.

Besides being associated with TMD, excessive joint laxity is associated with a variety of rheumatic conditions (79). It is not uncommon to identify both parents of a child with marked laxity showing some evidence of joint laxity as well (80). Ehlers-Danlos patients present with hypermobility and are typically symptomatic for the TMJ, reporting recurrent temporomandibular joint dislocations (81, 82).

Hallermann-Streiff syndrome (OMIM 234100), for which features are bird-like facies with hypoplastic mandible and beaked nose, proportionate dwarfism, hypotrichosis, microphthalmia, and congenital cataract, can also include some TMD signals. Patterson et al.(31) described a case with normal vertical, transverse, and anteroposterior functional movements of the TMJ except for partial inability to open the mouth because of the mandibular hypodevelopment and cervical soft tissue restriction.

It has been shown that the TMJ is frequently affected by juvenile idiopathic arthritis, and this degenerative disease, which may occur during facial growth, results in severe mandibular dysfunction (83, 84). Mitochondrial myopathy was also identified as the cause of facial pain in three cases originally diagnosed as TMD cases (85). Finally, mitral valve prolapse patients have also shown similar TMD findings when compared with the population that is affected by TMD (77).

Transgenic mice

A small number of hemifacial microsomia (HFM) transgenic mice have the development of the TMJ affected. These animals appear to be a useful model for the HFM-microtia spectrum and support the hypothesis that a proportion of HFM anomalies have a genetic causation mediated via mesenchymal disruptions and possibly embryonic hemorrhages (86). The HFM locus maps in mouse B1 to B3 chromosome 10, which corresponds to human 14q32. Hemifacial microsomia (OMIM 164210) is a common birth defect involving first and second branchial arch derivatives. The phenotype is highly variable. In addition to craniofacial anomalies, there may be cardiac, vertebral, and central nervous system defects. Most cases are sporadic, but there are rare familial cases that exhibit autosomal dominant inheritance. To the best of our knowledge, HFM has not been associated with TMD in humans.

Final remarks

Genes that regulate pain perception are likely responsible for how TMD is perceived by the patient but not necessarily are involved in how the disease develops. The genetics of TMD can be thought of being twofold. It is suggested that a better understanding of the genetics behind why one person perceives pain differently than others may allow us to provide more customized therapeutic options to control pain. The traditional chronic pain patient who may present with identifiable gene alleles may indeed be relieved of their discomfort more quickly and efficiently, should their healthcare team impart a protocol of targeted care individualized to their genetic characteristics. TMD surgical patients may have the ability to be screened prior to surgery, alerting their doctors of a predetermined propensity of possessing a lower pain threshold than the average patient. Looking closely at genetic factors may also shed some light on TMD development. Genes involved in TMJ structures development and immune-inflammatory responses are likely to play a role in who may be more likely to suffer from TMD. Research should also focus on understanding why there is such a gender disparity in TMD. The fact that women are by in large more affected by TMD justifies TMD as one of the many public health concerns that requires attention of future research initiatives.

The investigation of the genetic variables which may predict identifiable levels of pain perception or contribute to development of the TMJ may uncover new approaches to our traditional treatment modalities for the chronic TMD patient.

Clinical relevance

Temporomandibular joint disorder is a collection of symptoms related to the muscles and joints of the masticatory system. They likely comprise a number of etiologically distinct conditions that lead to similar symptoms. As individuals are not equally susceptible to TMD, this condition appears to be the result of the person's unique genetic makeup. For that reason, it has been suggested that a better understanding of the genetics modulating TMD is a necessary step that will lead to innovative therapies related to these conditions.

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