Review

Genomics and the new perspectives for temporomandibular disorders

Carolina B. Meloto a, Priscila O. Serrano a, Margarete C. Ribeiro-DaSilva b, Célia M. Rizzatti-Barbosa a,∗

a Department of Prosthesis and Periodontology, Dental College of Piracicaba, State University of Campinas, Avenida Limeira 901, 13414-903 Piracicaba, São Paulo, Brazil
b Department of Community Dentistry and Behavioral Science, College of Dentistry, University of Florida, Dental Tower Room D2-13, 32608-0404 Gainesville, FL, USA

A R T I C L E   I N F O

Article history:
Accepted 25 March 2011

Keywords:
Temporomandibular disorder
Genetic makers
Allelic variant
Polymorphisms
Genome/omics-based personalised care

A B S T R A C T

The field of temporomandibular disorders (TMD) is experiencing significant changes in terms of aetiology and treatment. Researchers and clinicians are becoming increasingly aware of the possibility that genetic variations may play a role in pain perception and onset of TMD. In this review, we purpose to briefly describe these allelic variants, how they may be involved in TMD pathophysiology and how they may affect TMD treatment. Studies have already pointed the association between TMD and genetic polymorphisms in the oestrogen receptor alpha, adrenergic receptor beta 2, serotonin receptor, serotonin transporter and catechol-O-methyltransferase genes, and other candidate genes continue to emerge. The main implication of these findings refers to the promising possibilities of "genome/omics-based personalised care", which consists of tailoring individual treatment based on personalised medication, depending on the individual genetic differences and early diagnosis and prognosis of the disorder, preventing acute pain conditions from becoming chronic. The following years of research shall focus on collecting and endorsing these findings if we are to provide patients in pain with efficient and successful TMD treatments.

© 2011 Elsevier Ltd. All rights reserved.

Contents

1. Introduction ............................................. 1182
   1.1. Oestrogen receptor alpha gene polymorphisms ............................................. 1182
   1.2. Catecholamine-O-methyltransferase gene polymorphisms .................................. 1183
   1.3. Adrenergic receptor beta 2 gene polymorphisms ............................................. 1185
   1.4. Serotonin transporter gene polymorphism ..................................................... 1185
2. Genome/omics-based personal care ............................................. 1186
3. Conclusions ............................................. 1187
   References ............................................. 1187

∗ Corresponding author. Fax: +55 19 21065211.
E-mail address: rizzatti@fop.unicamp.br (C.M. Rizzatti-Barbosa).
0003–9969/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.archoralbio.2011.03.012
1. Introduction

The field of temporomandibular disorders (TMD) has experienced significant changes in terms of etiology and treatment. For decades, it was believed that the etiology of TMD was mainly a result of problems of occlusal vertical dimension, condylar malposition, trapped mandibles, occlusal disharmony and neuromuscular imbalance, which led to treatments based on a variety of invasive and irreversible dental therapies, including bite-opening, occlusal adjustments, major restorative dentistry, orthodontics and even surgery. Nowadays, this point of view has largely been discredited.1

Studies2-4 have been consistently demonstrating that functional disturbances of the masticatory system, mainly driven by occlusion, orthodontic treatment and occlusal adjustments, can no longer be held as the only causes and solutions for TMD.

The most popular theory regarding TMD etiology today is based on the biopsychosocial model.5-8 Briefly, this refers to a biological problem (i.e., activation of pain pathways, with or without a demonstrable pathological condition) that may have psychological antecedents, as well as behavioural consequences; this situation exists in a social framework that includes interpersonal relationships with friends, families and healthcare providers, which almost always produces major negative experiences for the patients, as well as for their immediate families.9

These changes and new concepts are not purely the result of dental research, but of multidisciplinary researches, including orthopaedic principles, neurophysiological and neuroanatomical aspects of pain processing, molecular and cellular pathophysiology of muscle and joints, and behavioural aspects of chronic pain.

Researchers and clinicians are now becoming increasingly aware of the possibility that genetic variation may play a role in TMD onset and pain perception, as it does with clinical conditions that share common features with TMD. Many studies have been associating genetic polymorphisms with musculoskeletal conditions, such as fibromyalgia,20,21 and low back pain,12-14 strongly suggesting that TMD pathophysiology may also be importantly influenced by genetic conditions.

Relationships between genetic variants and disease can be investigated using family aggregation studies, in which clusters of disease within genetically related family members are analysed.15 To date, family-aggregation studies have failed to identify a genetic influence on TMD,16-18 but these studies have been greatly underpowered. Given the multifactorial nature and low prevalence of TMD coupled with the requirement for very large population sizes to detect levels of heritability below 0.5, it is not surprising that these studies have failed to identify a genetic influence on this disorder. Nonetheless, most pain conditions, including TMD, are best classified as complex, multifactorial disorders that are induced and influenced by both diverse environmental factors and a complex array of multiple genetic polymorphisms. These genetic factors consist of many highly prevalent polymorphic genes, rather than single rare mutations, and they therefore fail to follow traditional Mendelian modes of inheritance. It is more appropriate to search for allelic association using traditional epidemiological study designs in which the risk of disease is contrasted amongst sub-groups based on common allelic variants.19

In this respect, studies have investigated the association of allelic variants of some genes and temporomandibular disorders. This review briefly describes these allelic variants, how they may be involved in TMD pathophysiology and how they may affect TMD treatment in the short and long terms, as well as it indicates possible scientific inferences based on what is known to date.

In order to be considered eligible for this review, studies were firstly identified by performing a PubMed search using the search queries: temporomandibular disorder AND polymorphism, temporomandibular disorder AND genetic, temporomandibular joint AND polymorphism and temporomandibular joint AND genetic. This search has retrieved 105 articles, and only original articles written in English between the years of 1990 to 2010, with available abstracts, and aimed at investigating the association between previously described genetic polymorphisms and TMD were included in this review.

1.1. Oestrogen receptor alpha gene polymorphisms

The fact that women make up the majority of TMD patients is extensively documented in the literature,20-23 therefore it is reasonable to think that there is a link between TMD pathogenesis and the female hormonal axis.

Indeed, some studies have already implicated oestrogen in the pathophysiology of this condition: use of oral contraceptives by reproductive age women, or HRT by postmenopausal women, is associated with higher prevalence of TMD,24,25 and serum estradiol levels have been reported to be higher in luteal phase women and in men who have TMD compared to healthy controls.26

The human oestrogen receptor alpha (ERα) gene is located on chromosome 6 and several variations in the DNA sequence have been reported. Two common single nucleotide polymorphisms (SNP) are detected as PvuII and XbaI restriction fragment length polymorphisms (RFLP). They are located in intron 1, approximately 400 bp upstream from exon 2. The PvuII RFLP detects a T→C substitution at position −397 and the XbaI RFLP a G→A substitution at position −351.27 Alone or in combination, they have already been implicated in conditions such as low bone mineral density (BMD),28-32 osteoarthritis,33-36 rheumatoid arthritis,37 as well as painful temporomandibular joint disorders.38,39

Prior to understanding how these polymorphic sites may be implicated in the TMD pathophysiology, we have to consider that polymorphisms in introns are now known to affect mRNA production,40,41 and PvuII and XbaI alleles have been associated with transcription upregulation, resulting in overexpression of the ERα.

Specifically, the C allele may influence gene expression, as it has been shown to result in a potential binding site for myb transcription factors and augment in vitro transcription of a downstream reporter construct by 10-fold.42 Also, the C and A alleles (PvuII and XbaI restriction sites, respectively) may be in linkage disequilibrium (LD) with causal polymorphisms elsewhere in the gene, such as the upstream (TA), variable number of tandem repeats polymorphism in the promoter
region of the ERα gene, which can have a significant influence on transcriptional regulation. Consequently, individuals carrying these alleles would be more responsive to oestrogen. This is important because the human TMJ disc — whether from symptomatic or asymptomatic individuals, as well as the synoviocytes, stromal cells in the articular disc, and chondrocytes of the rat TMJ, express the ERα gene and, therefore, comprise a target tissue for oestrogen.

Studies conducted on animals have been demonstrating that the effects of oestrogen on the components of the TMJ may represent an important risk for those genetically more responsive to this hormone. For instance, the collagen content of the TMJ disc has been shown to be diminished in female rats and castrated males treated with oestrogen when compared to naive males. The proteoglycan content, quality of hypertrophic chondroblasts, and mandibular condyle articular cartilage thickness are also affected by the presence of oestrogen. Oestrogen also upregulates the expression of proinflammatory cytokines in mice mandibular chondroblasts, directly affecting TMJ inflammatory reaction, and indirectly causing degenerative changes, due to stimulation of the synthesis of various matrix metalloproteinases.

In humans, electron microscopy and immunohistochemical studies have shown that the synovial membrane consists of two kinds of synovial lining cells: macrophage-like type A and fibroblastic type B cells. Whilst evaluating the effect of oestrogen in human fibroblastic type B cells, Galal et al. have demonstrated a time-dependent increase in the expression of M-CSF/CSF-1 and c-fms. Based on previous studies reporting that M-CSF/CSF-1 regulates the proliferation and differentiation of haemopoietic progenitor cells into mature macrophages, their findings reinforce the hypothesis that oestrogen may exacerbate inflammatory reactions in the TMJ.

Anatomically, internal derangements of the TMJ are characterised by an abnormal positional relationship of the disc relative to the mandibular condyle and the articular eminence, which is suggested to precede the degradation of the articular surfaces. Although this displacement of the disc is common amongst non-patients and asymptomatic subjects, the pristine structures of the articular surfaces often deteriorate with ageing by internal derangement, and arthritis. Then they erode and become increasingly roughened, sometimes leading to pain and dysfunction. Thereby, those genetically more responsive to oestrogen may be affected by an exacerbation of the deterioration process, which may more easily progress into osteoarthritis.

Oestrogen is also known to play a critical role in pain modulation systems. In reproductive age women with TMD, TMJ pain is highest peri-menstrually, although in women not using oral contraceptives, an additional pain peak may occur in the peri-ovulatory period. These findings strongly suggest that ovarian hormones modulate pain in women with TMD, although this relationship is clearly not a simple one.

To determine how estrogens modulate TMD pain, rodent models have been very useful. The fact that trigeminal neurons contain ERα, provides a potential mechanism whereby oestrogen could affect neuronal function directly. Actually, the expression of galanin, neuropeptide Y, and ghrelin (peptides associated with modulation of pain) in the trigeminal ganglia is highest during the higher oestrogen stages of the oestrous cycle. Furthermore, TMJ inflammation induced by mustard oil injection produced greater fos-like immunoreactivity in proestrous compared to diestrous female rats at major terminal zone for sensory afferents innervating the TMJ, indicating that TMJ inflammation produces greater neural activation when ovarian hormones are higher. In women, this could mean that cycling females in higher hormone states may experience greater pain.

Oestadiol also dose-dependently increased trigeminal afferent discharge induced by NMDA after CFA injection into the masseter muscle or intra-TMJ in ovariecotomised rats, and increased NMDA receptor-mediated currents in cultured dorsal root ganglion neurons taken from female rats (more than in those taken from males).

Overall, replacement of oestadiol to levels found in normally cycling rats appears to enhance different pain neurotransmission systems, which may contribute to greater TMD pain observed in normally menstruating women at ovulation, or in post-menopausal women taking HRT. Therefore, it would be reasonable to imply that allele variants of the ERα gene associated with increased oestrogen responsiveness would represent a risk for painful TMD.

An important application of genetic studies on ER gene polymorphisms relates to the possibility of modulation of the activity via selective ER modulators in different target tissues. In particular, raloxifene and tamoxifen, two different selective ER modulators, might be indicated for TMD treatment according to prediction of the response of TMJ structures to oestrogen based on one’s genotype. Therefore, further studies are needed to investigate the influence of ER in pain and predisposition to TMD. An increase in the knowledge about the molecular role of these polymorphisms will certainly have important pharmacogenomic implications, giving better guidance regarding the therapeutic agents commonly used to treat oestrogen-related disorders, and it may serve as the basis for future treatment tailoring, which could enhance outcomes in these patients.

1.2. Catecholamine-O-methyltransferase gene polymorphisms

It is an enigma that individuals can vary considerably in their responses to clinical conditions that have an apparently similar potential to cause pain, a phenomenon that is frequently observed in TMD. Although the relative importance of genetic versus environmental factors in human pain perception remains unclear, the reported heritability for nociceptive and analgesic sensitivities in mice is estimated to range from 28 to 75%, and from the list of candidate ‘pain genes’, SNP in the catecholamine-O-methyltransferase (COMT) gene have been reported to contribute to differences in TMD pain perception. As early as 1965, Marbach and Levitt suggested a role for COMT in this persistent pain condition when they reported that patients with facial pain conditions comparable to TMD show increased urinary levels of catecholamine metabolites and express diminished erythrocytic COMT activity.
COMT is a ubiquitously expressed enzyme that metabolises catecholamines (epinephrine, noradrenaline, and dopamine), \(\text{L-dopa}\), catecholestrogens, ascorbic acid, and dihydroxyindolic intermediates of melanin.\(^6\) Abnormalities in the catecholamine physiology are associated with diminished COMT activity resulting in elevated levels of catecholamines that promote persistent pain states.\(^6\)

The COMT gene locus (chromosome 22, band q11.21) spans 27.221 bases and codes for two major forms of the enzyme: membrane-bound and soluble COMT. Six SNP in the COMT gene that are found with high frequency in the human population (\(>\)40%) have been investigated for their association with TMD pain perception. The first SNP (rs2096792) is located at position –1217 in the oestrogen-sensitive portion of the MB-COMT promoter region, whereas the second SNP (rs6168) is located in the promoter region of S-COMT.\(^6\) The next three SNP (rs4623, rs4808 and rs4669) are located within the coding region for both S- and MB-COMT. Variations in SNPs rs4623 and rs4808 are synonymous whilst SNP rs4669, the most investigated SNP, is non-synonymous and codes for a substitution of valine (val) to methionine (met) at codon 158. This produces an enzyme with lower thermostability, resulting in decreased enzyme activity. It is generally accepted that genetic variability in codon 158 is the primary source of individual variation in COMT activity in humans.\(^6\) The last SNP (rs164139) is located at the end of the 3′-UTR of the gene.\(^6\)

Based on this, Diatchenko et al.\(^{64}\) investigated the association of COMT SNP with TMD, and identified three haplotypes of the gene that were designated as low pain sensitivity (LPS), average pain sensitivity (APS) and high pain sensitivity (HPS). The authors demonstrated that the presence of even a single LPS haplotype diminishes by as much as 2.3 times the risk of developing myogenous TMD. By transfecting human HEK 292 cells with S-COMT cDNA clones corresponding to the LPS, APS and HPS haplotypes, the authors have also demonstrated that the LPS produces higher levels of COMT enzymatic activity. In addition, inhibition of COMT in rats resulted in a profound increase in pain sensitivity. It was then suggested that the three major haplotypes determine COMT activity in humans and inversely correlate with the risk of developing myogenous TMD.

Because COMT genetic variants had also been previously associated to psychological characteristics that are consistent risk factors for TMD (e.g. depression and anxiety), the same research group explored whether COMT genetic variants interact with psychological factors in the risk of developing TMD, and such interaction was not found. This indicates that there are separate etiological mechanisms by which these psychological characteristics and genetic variants of the COMT gene influence the risk of a person developing TMD.\(^6\)

Besides psychological characteristics, orthodontic treatment may also be a harmful factor in TMD aetiology. Therefore, the relationship amongst COMT genotypes, orthodontic treatment, and the risk of developing TMD myalgia and/or arthralgia has also been examined. The relative risk of developing myalgia and/or arthralgia associated with a previous history of orthodontic treatment was dependent on a variant of the gene encoding COMT. This illustrates an example of the gene–environment interaction.\(^9\) Specifically, orthodontic treatment was not associated with an elevated risk of TMD amongst people with the pain-resistant haplotypes, whereas orthodontic treatment was associated with a marked elevation in risk for subjects with pain-sensitive haplotypes.

The precise molecular mechanisms whereby genomic variations in COMT gene result in diminished COMT activity and consequent sustained pain perception states, such as TMD and also fibromyalgia,\(^6\) are not completely known. It is likely that these genomic variations, which do not alter the amount of COMT mRNA, alter the secondary mRNA structure, which affects the efficacy of protein translation and produces differences in enzymatic activity. Still, functional genetic variants may affect not only the protein coded by the gene in question but may also have downstream effects, contributing to the overall system response.\(^6\)

In animal models, the chronic activation of dopaminergic neurotransmission and D2 receptors, a situation parallel to that encountered in met/met homozygotes (SNP rs4669), reduces the neuronal content of enkephalin peptides, which in turn induces compensatory increases in regional \(\mu\)-opioid receptor concentrations in various brain regions.\(^6\) Therefore, it was hypothesised that, also in humans, the low function met/met COMT enzyme would cause chronic overactivity of the dopaminergic system and a lower neuronal content of enkephalin, resulting in a reduced capacity to activate \(\mu\)-opioid neurotransmission.

In fact, Zubieta et al. found that the magnitude of \(\mu\)-opioid system activation in response to pain challenge was lower in low COMT function met/met individuals, and that the \(\mu\)-opioid receptor binding potential was increased. These results confirmed that the varying levels of catecholamine metabolism induced by the COMT met158val polymorphism are associated with downstream alterations in the functional responses of the \(\mu\)-opioid neurotransmitter system.\(^6\) These findings were further validated by Jensen et al., who demonstrated increased pain sensitivity in met/met individu-
auls over time, as well as following the administration of exogenous opioids.\(^6\)

Another possible mechanism is that reduced COMT activity and the resulting elevated levels of catecholamines such as epinephrine, promotes the production of persistent pain states via the stimulation of \(\beta\)-adrenergic receptors (\(\beta\AR)). Nackley et al. reported that COMT-dependent increases in pain sensitivity were completely blocked by the non-selective \(\beta\)-adrenergic antagonist propranolol, or by the combined administration of selective \(\beta_2\)- and \(\beta_3\)-adrenergic antagonists, suggesting that COMT-dependent pain sensitivity is mediated through coincident \(\beta_2/3\)-adrenergic signalling processes. Thus, it may be suggested that elevated catecholamine levels, resulting from depressed COMT activity, activate \(\beta_2/3\)-AR to produce heightened pain sensitivity.\(^6\)

Endorsing the involvement of the \(\beta_2/3\)-adrenergic sympathetic pathway in human pain perception, \(\beta\AR\) antagonists have been shown to provide significant pain relief for patients with temporomandibular joint disorder and fibromyalgia,\(^7\) suggesting that carriers of the APS and HPS haplotypes suffering pain conditions resulting from low COMT activity may be favoured by pharmacological treatment with agents that block the \(\beta\)-adrenergic system.

However, further studies are necessary to provide sufficient information on the efficacy of this treatment modality.
For instance, elevated levels of catecholamines are generally associated with descending inhibition of pain in the spinal dorsal horn,71 and the antidepressants used to treat persistent pain conditions are thought to act by increasing the synaptic level of catecholamines at the spinal level.72

In sum, catecholamines seem to exert divergent influences on nociception as a function of localisation and the net influence on neuronal excitability, and further studies are needed to clarify whether pain patients will benefit from βAR antagonist treatment.

1.3 Adrenergic receptor beta 2 gene polymorphisms

It is well known that inflammatory pain has a sympathetic component3,74 that may predominate in pain that is less sensitive to non-steroidal anti-inflammatory drugs and in regions receiving rich sympathetic innervation, such as the TMJ.75 In a recent study, the injection of epinephrine, the major endogenous ligand for the beta-adrenergic receptor, into the TMJ of the rat produced a significant increase in spontaneous nociceptive behaviour.76

Therefore, genetic polymorphisms that influence beta-2 adrenergic receptor (ADRβ2) mediated responses, especially when coupled with environmental factors, may produce a clinical phenotype that is vulnerable to TMD pain.

Alterations in ADRβ2 function have already been widely implicated in psychiatric diseases and psychological disorders, including those associated with chronic pain conditions.77–79 Furthermore, ADRβ2 activity regulates resting arterial blood pressure and it has been shown that individuals with a higher resting arterial pressure show a lower prevalence of chronic musculoskeletal pain complaints.80

The human ADRβ2 is an intronless gene that spans approximately 5500 kb on chromosome 5q31–32.81 Amongst the ADRβ2 SNP, eight occur with a high frequency in the population (>-20%) and form three major haplotypes (H1, H2 and H3): G-702TA, rs11948840, rs1432612, rs1432613 and rs2400696, located in the promoter region of the gene; and rs1042703, rs1042704 and rs1042707, located within the coding region. The variants Arg16Gly (rs1042703) and Gln27Glu (rs1042704) are well-studied common nonsynonymous polymorphisms. SNP Leu83Leu (rs1042707) is a synonymous polymorphism.81

These haplotypes have been investigated for their contribution to the risk of developing myogenous TMD, and their relative expression levels of ADRβ2 mRNA were estimated on the basis of the relative abundance of EST (expressed sequence tags). The amounts of H2- and H3-specific EST relative to H1 were 1.8 and 4.4, respectively. Since the allelic combination of H1 in the promoter region of the gene and Gln27Glu SNP is the opposite of the allelic combination associated with H2 and H3 (haplotype AAAGG versus TGGAC for rs11948840, rs1432612, rs1432613, and rs2400696, Gln27Glu, respectively), it was suggested that H1 codes for a lower efficiency of transcription whilst H2 and H3 code for a high efficiency of transcription.82

Furthermore, it has been previously observed that the Arg16Gly (rs1042703) polymorphism is associated with agonist-induced internalisation of the receptor, with the G allele (Gly16) coding for rapid internalisation,83 and haplotypes H1 and H3, but not H2, being considered to be associated with efficient internalisation of the receptor. With regard to the association with myogenous TMD onset, its incidence was highest amongst H2/H2 homozygotes and lowest amongst H1/H2 and H1/H3 heterozygotes, suggesting that the presence of one copy of H1 is protective against TMD onset.82

These subjects showed also high somatisation score and low blood pressure, which are factors that appear to contribute to painful TMD via, at least in part, an impairment in central pain regulatory systems.84,85

Homozygotes for low ADRβ2 function also showed an increased risk for TMD development, suggesting that either positive or negative imbalances in ADRβ2 function increase vulnerability to myogenous TMD pain via different etiological pathways.82

Thus, these findings have potentially important treatment implications. If ADRβ2 hyperfunction contributes to TMD pain, then a relatively high percentage of these patients (60–70%) should respond to treatment with an ADRβ2 antagonist such as propranolol.82 In contrast, approximately 25–30% of TMD cases should have a hypofunction of ADRβ2 (H1/H1) and should not respond to treatment with an ADRβ2 antagonist. In fact, treatment of this group with such an agent may actually worsen their signs and symptoms. Thus, it may be possible to predict treatment outcomes to ADRβ2 blockade by determining the specific haplotype profile of patients with TMD and related disorders.83

1.4 Serotonin transporter gene polymorphism

TMD is often comorbid and considered to be part of a range of psychosomatic symptoms, such as sleep disorder, headache, fatigue, and depression, which are characterised as functional somatic syndromes (FSS).84,85

A substantial body of evidence indicates that TMD, as well as pain associated with other FSS, such as irritable bowel syndrome and fibromyalgia, involves dysfunction in pain and sensory processing systems.86 Therefore, it has been hypothesised that abnormal pain processing is an important factor in the dysfunction of descending neuronal pathways.

Serotonin (5-hydroxytryptamine, 5-HT) is one of the key neurotransmitters involved in enhancing endogenous analgesic mechanisms via the descending nociceptive modulatory pathways in the brain and spinal cord.87

Polymorphic studies within 5-HT-related genes have reported associations with numerous FSS, suggesting the relevance of 5-HT neuronal dysfunction to such conditions.88–92

The human serotonin transporter gene (5-HTT), located on chromosome 17q11.1–q12, is a candidate for involvement in the pathogenesis of painful disorders, such as TMD. The 5-HTT gene has a 44-bp insertion/deletion polymorphism within the promoter region, the so-called 5-HTT gene-linked polymorphic region (5HTTLPR). It has two allelic forms: the long (l) variant and the short (s) variant, which has lower transcriptional activity than the l allele in vitro.93 The 5HTTLPR genotypes also correlate with different rates of uptake of serotonin into lymphoblastoid cells in culture. The s variant appears to exert a dominant influence, as 5-HTT expression and serotonin uptake were indistinguishable between cultured cells with either one or two copies of the s allele.95–97 The −1438G/A SNP is also found within the promoter region of the gene and may affect its transcription.98
A variable number of tandem repeats (VNTR) polymorphism is found in intron 2 of the 5-HTT gene (5HTT-intron2VNTR), consisting of varying lengths of a repetitive sequence comprising 20–23 bp-long repeat elements, and has been shown to act as a transcriptional regulator in an allele-dependent fashion.104,105

The 5-HTT gene polymorphisms have been investigated in one association study for their relation with TMD myalgia.96 Only the 5HTTLPR analysis revealed that the l allele was more frequent amongst TMD patients. This allele is suggested to retain higher transcriptional activity than the s allele, and this may result in a lower concentration of 5-HT in the extracellular space, namely, active 5-HT.

Hence, 5HTTLPR could be further exploited as a diagnostic tool for TMD versus other orofacial pain diseases. Also, these data together convey that the pathogenesis of TMD is associated with serotonergic neuronal dysfunction, just as it happens for other FSS disorders.96

Although exciting, this hypothesis has to be very carefully examined. The study cited presented a small sample size and, although significance was reached, further studies are warranted to confirm this association.

In terms of treatment, confirming the involvement of the serotonergic system in TMD pathophysiology may lead to some promising clinical applications. Although no data have been obtained from TMD studies, a number of aspects and new treatment possibilities have emerged from FSS and fibromyalgia and may soon benefit TMD patients.

Because serotonin and noradrenaline are both important modulators in pain perception, sleep, fatigue, cognition, and mood in normal subjects, it is reasonable to suspect that disturbances in these functions may be consequences of abnormalities in serotonin and noradrenaline metabolism and transmission.

In this context, dual reuptake inhibitors appear to be potentially useful in the treatment of pain patients, since they enhance noradrenaline and serotonin neurotransmission in the descending inhibitory pain pathways, by inhibiting the reuptake of both serotonin and noradrenaline, resulting in a reduction in pain.97

Animal studies and clinical trials have shown that dual reuptake inhibitors of serotonin and noradrenaline are effective in the treatment of fibromyalgia.98–103 Furthermore, these studies demonstrated that drugs acting on noradrenergic (e.g., nisoxetine, nortriptyline) or both noradrenergic and serotonergic systems (e.g., imipramine, duloxetine, and milnacipran) are more effective analgesics than those acting on the serotonergic system alone (e.g., fluvoxamine, fluoxetine).104,105

Documented clinical use of dual serotonin and noradrenaline reuptake inhibitors in the treatment of TMD is limited to one case report.106 Although it presents a favourable view of the use of minalcipran, no substantial claims about efficacy can be made currently.

In the meantime, drugs acting on noradrenergic and serotonergic systems are potentially useful drugs of choice for the treatment of patients in pain. Alongside this, the identification of individuals more prone to suffering from a specific disorder based on their genetic make-up may be helpful in successfully treating these patients.

2. Genome/omics-based personal care

The term genome/omics-based personal care, or its synonymous terms, such as personalised medicine or personalised genomic medicine, can be used generally to refer to a more holistic vision of individualised or humanistic patient care, and consists of the utilisation of genome technology to assess individual risk and ensure the delivery of the “right treatment for the right patient at the right time”.107

Ultimately, genomic technologies could lead to therapies targeted to groups of patients with specific genetic variants.108 Specific applications include the use of genomic information to classify individuals according to disease susceptibility or expected responsiveness to a pharmacologic treatment and to provide targeted interventions.109

In fact, some companies already offer genome-wide tests directly to consumers and physicians, in which single nucleotide polymorphisms at more than 500,000 locations across the genome are sequenced.110 However, the ability of this technology to actually achieve the goal of genome/omics-based personal care is constrained by our limited understanding of the functional significance of human genetic variation.111,112

Thus, genome/omics-based personal care is a promising modality for the treatment of clinical conditions with an underlying content of genetic make up, such as TMD, but these still require translational research.

Translational research is necessary to apply the results of basic research on the human genome to clinical practices that improve individual and population health. Four phases of translational research in genome/omics-based personal care have been distinguished: phase 1 (T1) and phase 2 (T2) translational research informs the development of clinical interventions and evidence-based guidelines; phase 3 (T3) assesses the implementation of guidelines in health practice; and phase 4 (T4) evaluates the health outcomes of changes in practice following the implementation of guidelines.113

Although the bulk of research funding is still in T1 research, including randomised control trials,114 and molecular medicine using whole genome sequencing is only beginning to be integrated into clinical care, recent advances in pharmacogenomics have generated much excitement about the promises of genome/omics-based personal care.107

For instance, pharmacogenomic studies of tamoxifen – used to treat breast cancer – have shown that women with the CYP2D6 genotype tend to have a higher risk of disease relapse, a lower incidence of hot flashes and generally poorer clinical outcomes because of the gene’s impact on metabolism. Similarly, research on warfarin – an anticoagulant – has shown that two genes (CYP2C9 and VKORC1) impact the optimal dosing of warfarin. These genetic factors account for 30–35% of the variability in warfarin dosing, whilst clinical factors are responsible for only 17–21% of the variability.107 Therefore, it is possible to glimpse how TMD treatment might be affected by the outcomes of genome/omics-based personal care.

In this review, we have presented an overview of the state-of-the-art to date with regard to genetics and TMD, and discussed the apparent involvement of the oestrogen receptor
alpha gene in TMD pathophysiology. Thus, it is reasonable to suppose that knowledge of the patient’s genomic profile will allow a more tailored treatment, in which oestrogen receptor selective modulators – such as raloxifene and tamoxifen – may be indicated to benefit estrogenic actions on TMJ structures and in particular, the oestrogen-related modulation of pain.

Another specific target for tailored TMD treatment is the COMT gene. As previously discussed, catecholamines seem to exert divergent influences on TMD nociception as a function of localisation and net influence on neuronal excitation, and treatment with β-adrenergic antagonists – such as propranolol – has been shown to block COMT-dependent increases in pain sensitivity in rats and to provide significant pain relief for patients with temporomandibular joint disorder and fibromyalgia.60,68

In addition, ADRβ2 has also been found to be involved in TMD pain, and patients whose genetic make-up points in the direction of an ADRβ2 hyperfunction should benefit from treatment with an ADRβ2 antagonist, such as propranolol. On the other hand, those carrying ADRβ2 haplotypes encoding for gene hypofunction may even have their symptoms worsened by treatment with an ADRβ2 antagonist. Hence, knowing the patient’s genetic profile will allow us to better treat TMD patients based on their individual responses to specific drugs, achieving one of the goals of genome/omics-based personal care.

Despite the small sample size used in the study that identified the involvement of the SHTTLPR allele of the 5-HTT gene in TMD myalgia, emerging information from FSS and fibromyalgia studies may soon benefit TMD patients. Animal studies and clinical trials have shown the effectiveness of dual reuptake inhibitors of serotonin and noradrenaline in the treatment of fibromyalgia and these drugs appear to be more effective than those acting on the serotonergic system alone.99–106 Whether these drugs will be able to benefit TMD patients as well as they have been shown to benefit fibromyalgia patients remains to be clarified, but the one case report available that treated a TMD patient with a dual reuptake inhibitor presented a favourable view.106

In general, it is presumed that the new genome sequencing technologies will improve individual risk assessment, which will lead to disease prevention or at least early diagnosis and more tailored treatments for patients, preventing acute symptoms from becoming chronic. For instance, once a patient’s genetic profile is known, care providers will be able to predict how that patient will respond to a stressor event based on information that will point in the direction of genes that are up- or downregulated. Based on this knowledge, specific drugs can be prescribed aiming to reestablish balance in the microenvironment affected, thus preventing localised and circumstantial events from becoming a permanent harmful afferent pathway.

With this aim in mind, we can begin to count on systems biology, which uses engineering and computational approaches and physics combined with biological and medical inputs in an iterative manner to develop representations of the network of interactions within a cell that regulate cellular, organ, and organisational behaviour. As opposed to the traditional reductionist approaches focusing on the manipulation of one gene or protein, systems biology attempts to integrate important information from reductionist approaches with multidimensional data into a comprehensive map of the way components of a biological system integrate with external inputs to optimally predict the behaviour of the system and how it is regulated. This map will ultimately describe the behaviour of the cells and thus predict the natural course of a condition and its response to specific treatments.315

Therefore, the field of genome/omics-based personal care is just beginning to be implemented. In all different health areas information is still being gathered and evidence-based guidelines are being determined to allow further evaluation of their outcomes. With regard to TMD, studies continue to emerge relating genetic markers to its various subtypes, but no evidence-based guidelines are available to date, opening new and promising possibilities for translational research applied to TMD treatment.

3. Conclusions

Based on the information reviewed, it is reasonable to conceive that the fields of genetic and temporomandibular disorders can no longer be independently considered. We are only now beginning to identify genes that may be involved in the pathophysiology of this disorder and to interpret the impact that these new findings might have on preventing and treating TMD. Despite this newly born interaction, it points in the direction of “genome/omics-based personalised care”, in which individuals will be diagnosed and treated according to their genetic make-up in order to achieve maximal efficiency and minimum side effects.

Funding: None.

Competing interests: None declared.

Ethical approval: Not required.

References


110. Vanier V. National physician group MDVIP partners with Navigenics. The Navigator [accessed 23.08.10].