Headache and Orofacial
Brief Report

OPEN

PAIN REPORTS®

Preliminary evidence for conserved transcriptional response to adversity in adults with temporomandibular disorder

Christopher D. King[a,b,c,*], Ian A. Boggero[d], Grant S. Schulert[d,e], Hannah M. Pickerill[a,b], Steve Cole[f]

Abstract

Introduction: Temporomandibular disorder (TMD) is one of the most common orofacial pain conditions. Alteration in immune functioning is one promising biological mechanism underlying pain in TMD. However, there is a gap in the understanding of molecular bases contributing to altered immune functioning in these patients.
Objectives: In the current study, we investigated whether individuals with TMD would exhibit differential activity of 3 specific transcription factors involved in inflammatory (nuclear factor-kappa B, NF-kB), antiviral (interferon-regulatory factors, IRF), and sympathetic (cAMP response element-binding protein, CREB) processes using a promoter-based bioinformatics analysis, which is characterized as the "Conserved Transcriptional Response to Adversity."
Methods: Adults with TMD (n = 19) and without (n = 17) underwent a standardized clinical examination for TMD. A blood sample was collected for genome-wide transcriptional RNA profiling. Bioinformatic analyses tested for differential prevalence of proinflammatory and antiviral transcription factor activity in core promoter sequences from all genes showing >1.2-fold differential expression in TMD vs controls.
Results: Promoter-based bioinformatic analyses of genome-wide transcriptome profiles confirmed upregulation of genes bearing response elements for proinflammatory transcription factor (NF-kB, $P = 0.002$) and downregulation of genes with response elements for IRF ($P = 0.037$) in patients with TMD relative to controls. Results also indicated upregulated activity of CREB in patients with TMD ($P = 0.08$), consistent with increased activity of the sympathetic nervous system.
Conclusion: These results provide initial support that the regulation of immune pathways is altered in individuals with TMD. A shift of transcriptional resources to a proinflammatory state may be driven by psychosocial stress and contributes to symptoms associated with TMD.

Keywords: Pain, Inflammation, TMD, Gene expression

1. Introduction

Chronic temporomandibular disorder (TMD), characterized by muscle and/or joint pain of the masticatory system lasting greater than 3 months, affects up to 5% of the population.[37,38] Although a number of psychobehavioral (somatic awareness, stress, and sleep[13,16,24,32,33,36,39]) stressors contribute to TMD, alterations in immune system has been proposed as a key biological mechanism in chronic pain and TMD.[7,29,31] However, there is a current gap in the understanding of molecular basis contributing to alterations in immune system in individuals with chronic pain. The "Conserved Transcriptional Response to Adversity" (CTRA) profile, characterized by an upregulation of genes bearing response elements for the proinflammatory transcription factor

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

[a] Center for Understanding Pediatric Pain (CUPP), Cincinnati Children's, Cincinnati, OH, USA, [b] Division of Behavioral Medicine and Clinical Psychology, Cincinnati Children's, Cincinnati, OH, USA, [c] Orofacial Pain Center, Department of Oral Health Science, University of Kentucky College of Dentistry, Kentucky, USA, [d] Department of Pediatrics, University of Cincinnati, College of Medicine, Cincinnati, OH, USA, [e] Division of Rheumatology, Cincinnati Children's, Cincinnati, OH, USA, [f] Psychiatry and Biobehavioral Sciences and Medicine, University of California, Los Angeles, CA, USA

**Corresponding author. Address: Department of Pediatrics, Division of Behavioral Medicine and Clinical Psychology, Cincinnati Children's, Department of Pediatrics, College of Medicine, University of Cincinnati, 3333 Burnet Ave, MLC2 7031 Pain Research Center, Cincinnati, OH 45229. Tel.: 513-803-2391. E-mail address: Christopher.King@cchmc.org (C.D. King).*

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.painrpts.com).

PR9 6 (2021) e874

http://dx.doi.org/10.1097/PR9.0000000000000874

nuclear factor-kappa B (NF-kB) and a downregulation of innate antiviral response genes bearing response elements for interferon-regulatory factors (IRF), is one molecular mechanism linking psychosocial and behavioral stress to negative health outcomes through alterations in the immune system.[9,10]

Using a promoter-based bioinformatics analyses of RNA from peripheral blood leukocytes, the CTRA profile can be assessed by quantifying the differential representation of "response elements," or a sequence of DNA within a promoter permitting binding of transcription factors, in a set of differentially expressed genes empirically associated with an outcome of interest (TMD). Studies have repeatedly found a shift to a more proinflammatory and less Type I interferon-regulated bias within the transcriptome of circulating leukocytes, which is driven by extended periods and high levels of psychosocial, behavioral, and/or environmental stress, and consequent increases in activity of the sympathetic nervous system (cAMP response element-binding protein, CREB). This proinflammatory/anti-interferon transcriptome bias, in turn, can contribute to negative health outcomes related to stress.[4,8,21,23,30]

For the current study, we investigate whether the activity of 3 specific CTRA-related transcription factors, as indicated by expression of genes bearing response elements for NF-kB, IRF, and CREB, differed as a function of TMD status. This is important for 3 reasons. First, little is known about the relationship of CTRA to chronic pain states because only one study to date has tested whether the CTRA profile is present in patients with irritable bowel syndrome.[19] Second, pain conditions such as TMD are highly sensitive to psychosocial stress, and it is possible that the relationship between stress and pain involves changes in proinflammatory gene regulation. Third, the CTRA profile may offer a unique window into the functioning of the cellular components of the immune system, which may not be readily observed with peripheral measurements of cytokines. The current study tested the hypothesis that individuals with TMD would exhibit elevated CTRA expression, which will be characterized by a differential expression of inflammation (upregulated) and antiviral (downregulated) genes bearing response elements for transcription factors, compared with controls. We also explored other aspect of the CTRA profile including differential expression of genes underlying the sympathetic nervous system (SNS)-responsive CREB signaling pathway because altered β-adrenergic signaling has been implicated in TMD.

2. Methods

Detailed information about participants and methods can be found in Supplementary Information (available at http://links.lww.com/PR9/A89).

2.1. Participants

After informed consent and health history review, all participants underwent a standardized clinical examination (DC-TMD) by a calibrated investigator for TMD.[5,34] In participants with TMD (n = 19) and pain-free healthy controls (HCs, n = 17), a blood sample was collected for gene expression profiling (**Fig. 1A**). Information about sex, age, and history of smoking and alcohol consumption were collected and used as covariates (**Table 1**).

2.2. Gene expression profiling and analysis

After RNA extraction (**Fig. 1B**), genome-wide transcriptional profiling of RNA samples was performed (**Fig. 1C**). For the gene expression analysis, we first excluded genes with minimal level (or variation) in expression and then identified a set of genes with a >1.2-fold differential expression in TMD vs controls (Supplemental Tables, available at http://links.lww.com/PR9/A89). Due to the limited size of the sample and the hypothesis-testing nature of this study, we did not perform any exploratory/discovery analysis or statistical testing of individual gene transcripts, but rather this gene set served as input to the Transcription Element Listening System (TELiS) promoter-based bioinformatic analyses[12] to explore associated transcription factor activity (**Fig. 1D**) and the CTRA profile (**Fig. 1E**). As in previous research, point estimates of differential expression served as input because previous research has found such lists to generate more reliable downstream bioinformatics results than gene lists derived from statistical *p*-/*q*-values.[17,35,47]

3. Results

3.1. Covariates

Sex ($\chi^2 = 0.56$, $P = 0.46$), history of alcohol use ($\chi^2 = 2.5$, $P = 0.11$), BMI ($t = 0.3$, $P = 0.79$), and age ($t = 1.9$, $P = 0.07$) were similar between the 2 groups. Differences were observed with race ($\chi^2 = 4.5$, $P = 0.03$) with a higher percentage of Whites in the TMD group. None of the participants reported a history of smoking (current or past), so this variable was not included as a covariate in the transcriptome analysis.

3.2. Transcription factor activity

Genome-wide transcriptional profiling by RNA sequencing identified 1173 gene transcripts showing >1.2-fold differential expression in TMD vs HCs (80 upregulated and 1093 downregulated). TELiS bioinformatics analysis of transcription control pathways (**Fig. 2**) indicated significant upregulation of genes with response elements for the proinflammatory transcription factor NF-kB (2.138 log2 TFBM ratio ± 0.694 standard error, $P = 0.002$) and significant downregulation of genes with IRF response elements (-1.135 ± 0.541, $P = 0.037$) in adults with TMD compared with HCs. Results also indicated a nonsignificant trend toward upregulation of the SNS-responsive CREB signaling pathway in patients with TMD (1.092 ± 0.624, $P = 0.08$).

4. Conclusions

In this small pilot study, we found preliminary evidence that patients with TMD show a CTRA-characteristic shift in gene regulation within the basal leukocyte transcriptome including greater proinflammatory activity, reduced antiviral activity, and greater adrenergic signaling. These 3 transcription control pathways were targeted a priori based on previous hypotheses linking pain to stress biology and inflammation and were quantified by asymmetrical distribution of binding sites for the targeted transcription factors in upregulated vs downregulated genes.[4,8,21,23,30] Consistent with the classic CTRA profile, patients with TMD showed upregulation of genes bearing response elements for the proinflammatory transcription factor NF-kB, suggesting elevated levels of NF-kB activation and a propensity for proinflammatory responses. In addition, patients with TMD showed downregulation of genes bearing response elements for interferon regulatory factors (IRF), the primary inverse component of the CTRA profile.[9,10] These results were observed after controlling for demographic and behavioral factors that might otherwise confound relationships between TMD and gene expression.

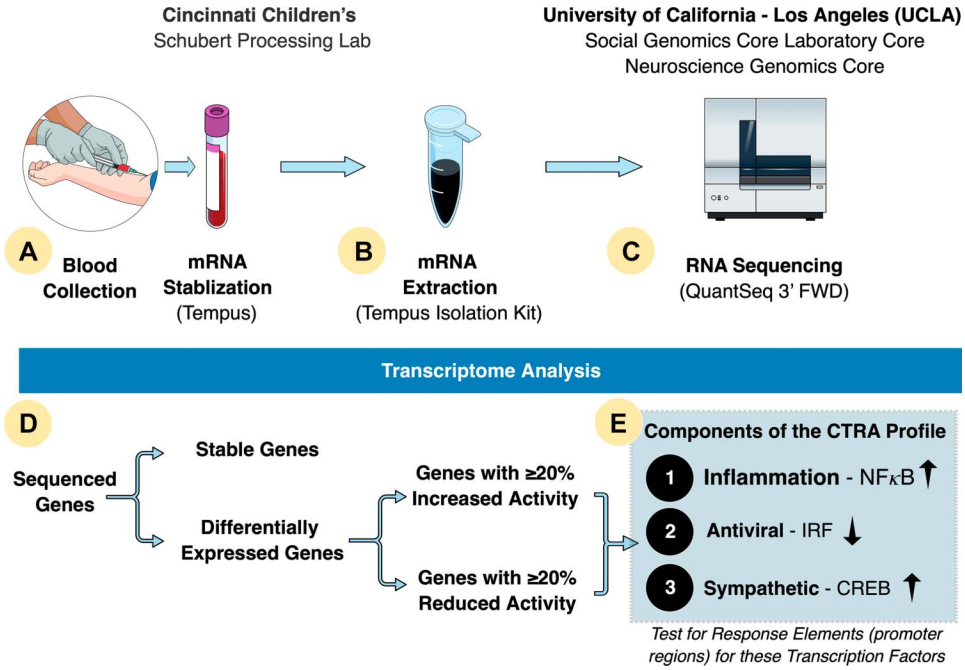

Figure 1. Collection, processing, and bioinformatic analysis of transcriptome outcomes between adults with and without DC-TMD confirmed diagnosis of TMD. (A) Blood samples were collected with Tempus Blood RNA Tube. (B) When all samples were collected, RNA was extracted and isolated with Tempus Spin RNA Isolation Kit. (C) Genome-wide mRNA profiling using a high-efficiency 3′ mRNA-targeted transcript counting assay (Lexogen QuantSeq 3′ FWD) with multiplex cDNA sequencing on an Illumina HiSeq 4000 instrument in the UCLA Neuroscience Genomics Core Laboratory. (D) Gene expression was quantified and screened to exclude transcripts showing minimal variation in expression (SD < 0.5 log2 unit). All genes showing 1.2-fold differential expression in TMD vs Controls (adjusted by covariates) served as input into Transcription Element Listening System (TELiS) promoter-based bioinformatic analyses. (E) The components of the CTRA profile were explored based on empirical differences in genes attributed to differential activity of inflammatory-, interferon-, and sympathetic-related transcription factors using TELiS. TMD, temporomandibular disorder.

Evidence for proinflammatory shift in our current sample is supportive of a growing literature about the presence of low-grade inflammation (eg, basal inflammation and exaggerated inflammatory activity)[1–3,40,41] in chronic pain. Although some of this literature is conflicting,[1] low-grade inflammation can be driven by toll-like receptor-4 (TLR4) signaling,[6,18] which induces the transcription factor NF-kB. Our preliminary data support the presence of low-grade inflammation, as reflected by NF-kB, in TMD. Also, limited evidence suggests that interferon signaling pathways can distinguish individuals with pain,[27] and infections have been shown to be predictive of widespread pain.[22] Finally, these CTRA-characteristic shifts may be related to altered β-adrenergic signaling due to chronic activation of the SNS by psychobehavioral stressors[11,14,15,20,39,48]. Recent studies have highlighted favorable impacts of β-adrenergic antagonist medication in TMD.[42,43] Our preliminary data found directional evidence for CREB activation in TMD, which would be consistent with increased SNS activity in TMD.

Although findings provide initial support for the hypothesis of altered inflammatory and antiviral pathway activity in individuals with TMD, the study is preliminary and has several limitations. First, our current study was not large enough to support any hypothesis-free genome-wide discovery analysis. Consequently, any attempts to interpret the role of specific, differentially expressed genes will require a larger sample size. Second, our gene expression was measured in peripheral blood samples. Although the observed transcriptional shift occurred in total blood leukocytes, future studies should collect information about the leukocyte subset composition of peripheral blood (eg, by flow cytometry) and clarify whether other tissues associated with TMD also show similar transcriptional shifts.

Overall, a shift of transcriptional resources of immune cells in individuals with TMD to a proinflammatory state may contribute to somatic symptoms (pain and fatigue), although it is also possible that chronic pain causes SNS activation (through stressful experience). In addition to limiting healing of damaged tissue of the temporomandibular joint and muscle,[26] this shift to a proinflammatory state of peripheral immune cells in individuals with TMD may result in a direct[45,48] and/or indirect (eg, synovial fluid of the temporomandibular joint[25]) enhancement of neuronal sensory processing. Preclinical evidence suggests that elevated levels of peripheral inflammation lead to activation of glial cells in peripheral (eg, trigeminal ganglia) and central nervous systems,[46] which can increase release of inflammatory mediators and amplify neuronal excitability, which in turn leads to an increased hypersensitivity to painful stimuli within these neuronal structures.[28,44] Future research blocking the pathways identified here and/or manipulating pain or distress may help clarify the causal

Table 1

Participant characteristics.

Mean (SD) or %	TMD* (n = 19)	HCs (n = 17)	Cohen's *d*
Study covariates†			
Age (Years)	31.2 (6.4)	27.4 (6.1)	0.62
BMI (kg/m^2)	25.8 (7.7)	25.2 (5.1)	0.09
Sex (% female)	78.9%	88.2%	—
Race (% NHW)‡	89.5%	58.8%	—
Alcohol consumption (%yes)	42.1%	17.6%	—

* All participants with TMD meet criteria for mixed facial pain diagnosis (myofascial and arthralgia).
† Although the study did not restrict enrollment into the study for smoking, none of the enrolled participants report a history of smoking.
‡ Significant group differences: $P < 0.05$.
TMD, temporomandibular disorder.

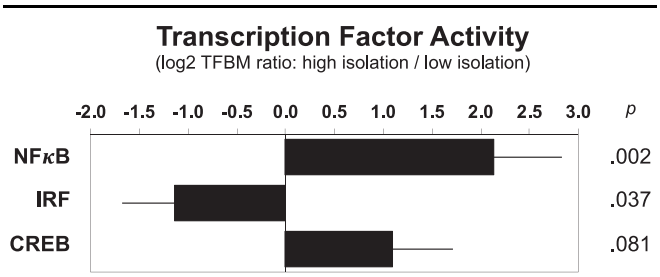

Figure 2. Gene expression profiling of components of the CTRA Profile in adults with and without TMD. Data are represented as log^2-transformed ratios of transcription factor binding motifs (TFMB) for proinflammatory (nuclear factor-kappa B, NF-kB), antiviral (interferon-regulatory factor, IRF), and sympathetic (cAMP response element-binding protein, CREB) transcription factors of differentially expression genes, which showed a >1.2-fold difference in average transcript abundance between adults with TMD and controls. Because the study was interested in differences in molecular mechanisms (eg, transcription factors), we did not explore if individual genes were different between TMD and HCs. IRF, interferon response factor; TMD, temporomandibular disorder.

mechanisms involved. Despite these limitations, our results identify new candidate molecular pathways that can be targeted in future research examining pathogenesis of TMD pain.

Disclosures

G. Schulert has received consulting fees from Novartis and SOBI. The remaining authors have no conflicts of interest to declare.

Acknowledgment

Supported by the National Institute of Dental and Craniofacial Research of the National Institutes of Health (R00DE022368). The authors would like to acknowledge Duong Do for her technical assistance with RNA extraction and Victor Schneider for recruiting, screening, and collecting outcomes from the study participants.

Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PR9/A89.

Article history:
Received 1 May 2020
Received in revised form 25 September 2020
Accepted 21 October 2020
Available online 8 January 2021

References

[1] Andres-Rodriguez L, Borras X, Feliu-Soler A, Perez-Aranda A, Angarita-Osorio N, Moreno-Peral P, Montero-Marin J, Garcia-Campayo J, Carvalho AF, Maes M, Luciano JV. Peripheral immune aberrations in fibromyalgia: a systematic review, meta-analysis and meta-regression. Brain Behav Immun 2020;87:881–9.
[2] Andres-Rodriguez L, Borras X, Feliu-Soler A, Perez-Aranda A, Rozadilla-Sacanell A, Arranz B, Montero-Marin J, Garcia-Campayo J, Angarita-Osorio N, Maes M, Luciano JV. Machine learning to understand the immune-inflammatory pathways in fibromyalgia. Int J Mol Sci 2019;20:4231.
[3] Andres-Rodriguez L, Borras X, Feliu-Soler A, Perez-Aranda A, Rozadilla-Sacanell A, Montero-Marin J, Maes M, Luciano JV. Immune-inflammatory pathways and clinical changes in fibromyalgia patients treated with Mindfulness-Based Stress Reduction (MBSR): a randomized, controlled clinical trial. Brain Behav Immun 2019;80:109–19.
[4] Antoni MH, Bouchard LC, Jacobs JM, Lechner SC, Jutagir DR, Gudenkauf LM, Carver CS, Lutgendorf S, Cole SW, Lippman M, Blomberg BB. Stress management, leukocyte transcriptional changes and breast cancer recurrence in a randomized trial: an exploratory analysis. Psychoneuroendocrinology 2016;74:269–77.
[5] Boggero IA, Schneider VJ, II, Thomas PL, Nahman-Averbuch H, King CD. Associations of self-report and actigraphy sleep measures with experimental pain outcomes in patients with temporomandibular disorder and healthy controls. J Psychosom Res 2019;123:109730.
[6] Bruno K, Woller SA, Miller YI, Yaksh TL, Wallace M, Beaton G, Chakravarthy K. Targeting toll-like receptor-4 (TLR4)-an emerging therapeutic target for persistent pain states. PAIN 2018;159:1908–15.
[7] Chen H, Nackley A, Miller V, Diatchenko L, Maixner W. Multisystem dysregulation in painful temporomandibular disorders. J Pain 2013;14:983–96.
[8] Chiang JJ, Cole SW, Bower JE, Irwin MR, Taylor SE, Arevalo J, Fuligni AJ. Daily interpersonal stress, sleep duration, and gene regulation during late adolescence. Psychoneuroendocrinology 2019;103:147–55.
[9] Cole SW. Human social genomics. PLoS Genet 2014;10:e1004601.
[10] Cole SW. The conserved transcriptional response to adversity. Curr Opin Behav Sci 2019;28:31–7.
[11] Cole SW, Hawkley LC, Arevalo JM, Cacioppo JT. Transcript origin analysis identifies antigen-presenting cells as primary targets of socially regulated gene expression in leukocytes. Proc Natl Acad Sci U S A 2011;108:3080–5.
[12] Cole SW, Yan W, Galic Z, Arevalo J, Zack JA. Expression-based monitoring of transcription factor activity: the TELiS database. Bioinformatics 2005;21:803–10.
[13] Diatchenko L, Anderson AD, Slade GD, Fillingim RB, Shabalina SA, Higgins TJ, Sama S, Belfer I, Goldman D, Max MB, Weir BS, Maixner W. Three major haplotypes of the beta2 adrenergic receptor define psychological profile, blood pressure, and the risk for development of a common musculoskeletal pain disorder. Am J Med Genet B Neuropsychiatr Genet 2006;141B:449–62.
[14] Fernandez-de-Las-Penas C, Ambite-Quesada S, Gil-Crujera A, Cigaran-Mendez M, Penacoba-Puente C. Catechol-O-methyltransferase Val158Met polymorphism influences anxiety, depression, and disability, but not pressure pain sensitivity, in women with fibromyalgia syndrome. J Pain 2012;13:1068–74.
[15] Fernandez-de-las-Penas C, Penacoba-Puente C, Cigaran-Mendez M, Diaz-Rodriguez L, Rubio-Ruiz B, Arroyo-Morales M. Has catechol-O-methyltransferase genotype (Val158Met) an influence on endocrine, sympathetic nervous and humoral immune systems in women with fibromyalgia syndrome? Clin J Pain 2014;30:199–204.
[16] Fillingim RB, Ohrbach R, Greenspan JD, Knott C, Diatchenko L, Dubner R, Bair E, Baraian C, Mack N, Slade GD, Maixner W. Psychological factors associated with development of TMD: the OPPERA prospective cohort study. J Pain 2013;14(12 suppl):T75–90.
[17] Fredrickson BL, Grewen KM, Coffey KA, Algoe SB, Firestine AM, Arevalo JM, Ma J, Cole SW. A functional genomic perspective on human well-being. Proc Natl Acad Sci U S A 2013;110:13684–9.
[18] Generaal E, Vogelzangs N, Macfarlane GJ, Geenen R, Smit JH, Dekker J, Penninx BW. Basal inflammation and innate immune response in chronic multisite musculoskeletal pain. PAIN 2014;155:1605–12.
[19] Gupta A, Cole S, Labus JS, Joshi S, Nguyen TJ, Kilpatrick LA, Tillisch K, Naliboff BD, Chang L, Mayer EA. Gene expression profiles in peripheral blood mononuclear cells correlate with salience network activity in chronic visceral pain: a pilot study. Neurogastroenterol Motil 2017;29:10.
[20] Irwin MR, Cole SW. Reciprocal regulation of the neural and innate immune systems. Nat Rev Immunol 2011;11:625–32.
[21] Irwin MR, Wang M, Ribeiro D, Cho HJ, Olmstead R, Breen EC, Martinez-Maza O, Cole S. Sleep loss activates cellular inflammatory signaling. Biol Psychiatry 2008;64:538–40.
[22] Jiao J, Vincent A, Cha SS, Luedtke CA, Kim CH, Oh TH. Physical trauma and infection as precipitating factors in patients with fibromyalgia. Am J Phys Med Rehabil 2015;94:1075–82.
[23] Knight JM, Rizzo JD, Logan BR, Wang T, Arevalo JM, Ma J, Cole SW. Low socioeconomic status, adverse gene expression profiles, and clinical outcomes in hematopoietic stem cell transplant recipients. Clin Cancer Res 2016;22:69–78.
[24] Lambert CA, Sanders A, Wilder RS, Slade GD, Van Uum S, Russell E, Koren G, Maixner W. Chronic HPA axis response to stress in temporomandibular disorder. J Dent Hyg 2014;88(suppl 1):5–12.
[25] Lee JK, Cho YS, Song SI. Relationship of synovial tumor necrosis factor alpha and interleukin 6 to temporomandibular disorder. J Oral Maxillofac Surg 2010;68:1064–8.
[26] Lee YH, Park HK, Auh QS, Nah H, Lee JS, Moon HJ, Heo DN, Kim IS, Kwon IK. Emerging potential of exosomes in regenerative medicine for temporomandibular joint osteoarthritis. Int J Mol Sci 2020;21:1541.
[27] Lukkahatai N, Majors B, Reddy S, Walitt B, Saligan LN. Gene expression profiles of fatigued fibromyalgia patients with different categories of pain

and catastrophizing: a preliminary report. Nurs Outlook 2013;61:216–24 e212.
[28] Malcangio M. Role of the immune system in neuropathic pain. Scand J Pain 2019;20:33–7.
[29] Park JW, Chung JW. Inflammatory cytokines and sleep disturbance in patients with temporomandibular disorders. J Oral Facial Pain Headache 2016;30:27–33.
[30] Powell ND, Sloan EK, Bailey MT, Arevalo JM, Miller GE, Chen E, Kobor MS, Reader BF, Sheridan JF, Cole SW. Social stress up-regulates inflammatory gene expression in the leukocyte transcriptome via beta-adrenergic induction of myelopoiesis. Proc Natl Acad Sci U S A 2013;110: 16574–9.
[31] Ribeiro-Dasilva MC, Fillingim RB, Wallet SM. Estrogen-induced monocytic response correlates with TMD pain: a case control study. J Dent Res 2017;96:285–91.
[32] Sanders AE, Akinkugbe AA, Bair E, Fillingim RB, Greenspan JD, Ohrbach R, Dubner R, Maixner W, Slade GD. Subjective sleep quality deteriorates before development of painful temporomandibular disorder. J Pain 2016; 17:669–77.
[33] Sanders AE, Akinkugbe AA, Fillingim RB, Ohrbach R, Greenspan JD, Maixner W, Bair E, Slade GD. Causal mediation in the development of painful temporomandibular disorder. J Pain 2017;18:428–36.
[34] Schiffman E, Ohrbach R, Truelove E, Look J, Anderson G, Goulet JP, List T, Svensson P, Gonzalez Y, Lobbezoo F, Michelotti A, Brooks SL, Ceusters W, Drangsholt M, Ettlin D, Gaul C, Goldberg LJ, Haythornthwaite JA, Hollender L, Jensen R, John MT, De Laat A, de Leeuw R, Maixner W, van der Meulen M, Murray GM, Nixdorf DR, Palla S, Petersson A, Pionchon P, Smith B, Visscher CM, Zakrzewska J, Dworkin SF. International Rdc/Tmd consortium network IafDR, orofacial pain special interest group IAftSoP. Diagnostic criteria for temporomandibular disorders (DC/TMD) for clinical and research applications: recommendations of the international RDC/TMD consortium network* and orofacial pain special interest groupdagger. J Oral Facial Pain Headache 2014;28:6–27.
[35] Shi L, Jones WD, Jensen RV, Harris SC, Perkins RG, Goodsaid FM, Guo L, Croner LJ, Boysen C, Fang H, Qian F, Amur S, Bao W, Barbacioru CC, Bertholet V, Cao XM, Chu TM, Collins PJ, Fan XH, Frueh FW, Fuscoe JC, Guo X, Han J, Herman D, Hong H, Kawasaki ES, Li QZ, Luo Y, Ma Y, Mei N, Peterson RL, Puri RK, Shippy R, Su Z, Sun YA, Sun H, Thorn B, Turpaz Y, Wang C, Wang SJ, Warrington JA, Willey JC, Wu J, Xie Q, Zhang L, Zhang L, Zhong S, Wolfinger RD, Tong W. The balance of reproducibility, sensitivity, and specificity of lists of differentially expressed genes in microarray studies. BMC Bioinformatics 2008;9(suppl 9):S10.
[36] Slade GD, Diatchenko L, Bhalang K, Sigurdsson A, Fillingim RB, Belfer I, Max MB, Goldman D, Maixner W. Influence of psychological factors on risk of temporomandibular disorders. J Dent Res 2007;86:1120–5.
[37] Slade GD, Fillingim RB, Sanders AE, Bair E, Greenspan JD, Ohrbach R, Dubner R, Diatchenko L, Smith SB, Knott C, Maixner W. Summary of findings from the OPPERA prospective cohort study of incidence of first-onset temporomandibular disorder: implications and future directions. J Pain 2013;14(12 suppl):T116–124.
[38] Slade GD, Ohrbach R, Greenspan JD, Fillingim RB, Bair E, Sanders AE, Dubner R, Diatchenko L, Meloto CB, Smith S, Maixner W. Painful temporomandibular disorder: decade of discovery from OPPERA studies. J Dent Res 2016;95:1084–92.
[39] Slade GD, Sanders AE, Ohrbach R, Bair E, Maixner W, Greenspan JD, Fillingim RB, Smith S, Diatchenko L. COMT diplotype Amplifies effect of stress on risk of temporomandibular pain. J Dent Res 2015;94:1187–95.
[40] Staud R. Cytokine and immune system abnormalities in fibromyalgia and other central sensitivity syndromes. Curr Rheumatol Rev 2015;11: 109–15.
[41] Taylor AG, Fischer-White TG, Anderson JG, Adelstein KE, Murugesan M, Lewis JE, Scott MM, Gaykema RP, Goehler LE. Stress, inflammation and pain: a potential role for monocytes in fibromyalgia-related symptom severity. Stress Health 2016;32:503–13.
[42] Tchivileva IE, Hadgraft H, Lim PF, Di Giosia M, Ribeiro-Dasilva M, Campbell JH, Willis J, James R, Herman-Giddens M, Fillingim RB, Ohrbach R, Arbes SJ, Jr, Slade GD. Efficacy and safety of propranolol for treatment of TMD pain: a randomized, placebo-controlled clinical trial. PAIN 2020;161:1755–67.
[43] Tchivileva IE, Lim PF, Smith SB, Slade GD, Diatchenko L, McLean SA, Maixner W. Effect of catechol-O-methyltransferase polymorphism on response to propranolol therapy in chronic musculoskeletal pain: a randomized, double-blind, placebo-controlled, crossover pilot study. Pharmacogenet Genomics 2010;20:239–48.
[44] Totsch SK, Sorge RE. Immune system involvement in specific pain conditions. Mol Pain 2017;13:1744806917724559.
[45] Uceyler N, Schafers M, Sommer C. Mode of action of cytokines on nociceptive neurons. Exp Brain Res 2009;196:67–78.
[46] Villa G, Ceruti S, Zanardelli M, Magni G, Jasmin L, Ohara PT, Abbracchio MP. Temporomandibular joint inflammation activates glial and immune cells in both the trigeminal ganglia and in the spinal trigeminal nucleus. Mol Pain 2010;6:89.
[47] Witten DM, Tibshirani R. A comparison of fold-change and the t-statistic for microarray data analysis. Stanford: Stanford University Technical Report, 2007. pp. 1–17.
[48] Zhang X, Hartung JE, Bortsov AV, Kim S, O'Buckley SC, Kozlowski J, Nackley AG. Sustained stimulation of beta2- and beta3-adrenergic receptors leads to persistent functional pain and neuroinflammation. Brain Behav Immun 2018;73:520–32.