Molecular genetics and epigenetics of temporomandibular disorder

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Abstract. Temporomandibular joint (TMJ) has an important role in stomatognathic system. Its role during function is facilitated from rotation and translation movement. Any deviation from TMJ normal anatomy and movement could lead into either clicking, crepitus, or pain in preauricular area. These sign and symptoms, which are widely referred as TMJ Temporomandibular joint disorder (TMD), extremely common in world population. Several genes have been identified contribute in susceptibility towards TMD. Genetic polymorphism are a form of gene sequences variance that is found in more than 1% of world population. Epigenetics is an interaction between internal and external environments that leads to a change in chromatin structures that switches the gene expression on and off. There are several factors that possibly affect the genetic polymorphisms in TMD such as; serotonin, cathecolamine, estrogen, folate, human leukocyte antigen (HLA), extracellular matrix, transcription factors, transforming growth factor beta (TGFβ), epithelial growth factor, β-catenin, and discoidin. Epigenetic mechanisms such as DNA methylation, histone modification, and microRNA are found in chondrocyte of TMD patients. In a temporomandibular joint, miRNA-140 controls bone homeostasis especially on the articular remodeling. Genetic molecular and epigenetic study will benefit in diagnosis and treatment of TMD patient. The aim of this paper is author want to inform about molecular genetics and epigenetics of TMD.

1. Introduction
American Academy of Orofacial Pain refers Temporomandibular Disorders (TMD) as group of functional disturbance in stomatognathic systems. Most common clinical signs of this disorder are clicking during function, regional pain in the preauricular area, and limited mandibular movement. TMD signs and symptoms are well known and common to be found. Indeed, women of productive age would likely to suffer in a higher prevalence, compared to men [1],[2].

The multifactorial nature makes TMD difficult for a treatment. Studies within the last decade have proven the relationship between gene and temporomandibular joint condition [3],[4],[5]. This review will elaborate the role of genetic molecular and epigenetic mechanism as the risk factor of TMD.

2. Discussion

2.1. Temporomandibular Joint (TMJ)
In the stomatognathic system, temporomandibular joint consists of mandibular condyle and cranial temporal bone. These components are separated by articular disc, that is a fibrous tissue that contains blood vessel and innervation. Inferior, superior, and posterior areas of discal are surrounded by
retrodiscal tissue. The inferior retrodiscal tissue connects inferior surface of disc to condyle, meanwhile the superior retrodiscal tissue connects posterior surface of articular disc to cranial tympanic plate [1]. During function, TMJ movement is passively retained by ligament to protect the structure of the joint. Three functional ligaments in TMJ are collateral ligament, temporomandibular ligament, and capsular ligament. Capsular and discal ligaments divide joint cavity into two categories: superior and inferior. Space between lower surface of disc and mandibular condyle is called inferior joint cavity, meanwhile space between superior border disc and mandibular fossa is called superior joint cavity. A lining of endothelial cells in inner part of these cavities produces synovial fluid, which is not only the medium for metabolic exchange but also the TMJ’s lubricant during function [1].

Figure 1. Anatomy of Temporomandibular Joint: RT, retrodiscal tissues; SRL, superior retrodiscal lamina; IRL, inferior retrodiscal lamina; ACL, anterior capsular ligament; SLP and ILP, superior and inferior lateral pterygoid muscles; AS, articular surface; SC and IC, superior and inferior joint cavity.
(Source: Okeson, 2013) [1]

2.1.1. Biomechanics of TMJ Movement.
MJ has two movement systems. With centre in the inferior joint cavity, the first system consists of mandibular condyle and articular disc. This system accounts for TMJ rotational movement due to discal ligament restricted movement towards discs. The rotation occurs without any change of condyle position during first 20-25 mm of mandibular opening [1]. The second system consists of condyle-disc complex. This system permits mandible translation by disc sliding movement through articular surface. The condyle can freely slide from mandibular fossa to articular eminence during mandibular opening, and can slide back to original position during closure [1]. During mastication, the force of muscle is transmitted to temporomandibular joint and teeth. Thus, the centric relation term was introduced to maintain orthopaedic stability in patient. The most stable position of all stomatognathic system components is achieved by positioning condyle in the most posteroanterior to articular eminence with articular disc located between these twos [1]. However, the dentition stability is needed to keep a condyle in the most stable position. This is achieved by ensuring simultaneous contact of all teeth during function. Thus, the masticatory force could be divided equally, and also any damage could be avoided.

Therefore, ideally the musculoskeletal stability of either condyle or centric relation position must coincide with the maximum intercuspal position of dentition. Although this ideal occlusion is rarely found [1].

2.2. Temporomandibular Disorder (TMD)
Temporomandibular disorder (TMD) is a term used to describe any functional disturbance in masticatory systems. Signs and symptoms of TMD are commonly found. In cross-sectional studies, 41% of the population has at least one symptom of TMD, meanwhile, 56% of the population shows at least one sign of TMD. The prevalence is higher in women with ratio 2:1 compared to men, especially in productive age (20-40 years old) [1].
The epidemiological study in Indonesia shows similar occurrence of TMD. Maulina et al. (2016) claims that 69.9% of total population in West Java suffers from orofacial pain, with 44.1% from those pain is due to TMD [6]. Marpaung, Maurit, and Frank (2018) claims that 23.4% (95% CI=20-27) of children with age range 7-12 y.o. and 36.9% (95% CI=33-41) of adolescents with age range 13-18 y.o. in Jakarta shows TMD signs [7]. Another study of Himawan (2007) states that 69% of geriatric patient with age range 60-91 y.o. suffers TMD [8].

2.2.1. Classification. In 1992, Leresche (1992) introduced Research Diagnostic Criteria for Temporomandibular Disorder (RDC/TD) as the most effective method for diagnosing TMD. TMD is classified into 3 main groups: group I is for myofascial pain, group II is for disc displacement, and group III is for inflammatory or degenerative disorder. This classification latter is modified into Diagnostic Criteria for Temporomandibular Disorder (DC/TD) that divides TMD into four main sub-classifications: TMJ disorder, masticatory muscle disorder, headache, and associated structures. Smaller groups of TMJ disorder are then classified again based on clinical sign similarities: joint pain (arthralgia, arthritis), joint disorder (disc displacement, hypomobility & hypermobility disorder), joint disease, fracture, and congenital or developmental disorder [9].

This Temporomandibular Joint disorder classification is similar to the proposed classification by Okeson (2013), that consists of condyle-disc complex derangement, incompatibility of articular surface, and inflammation of TMJ component. Condyle and discal complex derangements are induced by direction change during rotational and translation TMJ movement. They show clinical signs of either disc displacement or disc dislocation in temporomandibular joint. History of either jaw direct trauma (macrotrauma) or musculoskeletal instability induced trauma (microtrauma) is the most common etiology of this category. Incompatibility of articular surface occurs due to the change of articular surface, that deteriorates smooth sliding movement during function. The disorder can also be in a deviation of articular surface, adherence/adhesion, subluxation, or spontaneous dislocation (open lock). Inflammatory joint disease is classified according to affected joint areas such as retrodiscitis, synovitis, and osteoarthritis. A patient with this category mostly seeks care due to an increase of pain intensity during function [1].

2.3. Genetic in temporomandibular disorder

The multifactorial nature of TMD encourages to research and find genetic association as risk factors of TMD. In earlier study to investigate relationship between TMD and hereditary, Raphael (1999) failed to establish a connection between myofascial pain in TMD patients and their first-degree relatives [10]. Several earlier study also state that there is no statistical difference in the prevalence of myofascial pain and temporomandibular disorder between monozygotic and dizygotic twin. However, these study has a caveat due to a small number of sample that could affect research validity before be able to be generalized in a bigger number of population sample [11],[12].

On the other hand, advanced study that used a bigger sample by Plesh et. Al (2012), discovers that TMD pain is indeed inherited for the likelihood of 27% for twin siblings [13]. Genello (2017) also supports that there is a genetic influence in TMD by showing the finding of TMD signs and symptoms were inherited in three generations of family [14]. Therefore in recent study, gene variations in TMD patients and controls were compared to examine genetic association from either genetic polymorphisms or gene mutation as risk factors of TMD.

2.3.1. Genetic Polymorphisms in TMD. Genetic polymorphism are a form of gene sequences variance that is found in more than 1% of world population. Polymorphism could result in a phenotype change, which in this manner contributes to increase the risk of temporomandibular disorder [15].

There are several factors that possibly affect the genetic polymorphisms in TMD such as; serotonin, cathecolamine, estrogen, folate, and human leukocyte antigen (HLA).
- Serotonin activities and metabolism
Serotonin (5-hydroxytryptamine) is one of neurotransmitters as a pain reception of temporomandibular disorder. The serotonin transporter gene (HTR2A) regulates serotonin activities that is located in chromosome 17q11.1-q12. Past study shows that polymorphisms in serotonin transporter gene appear in Variable Number Tandem Repeat (VNTR) and Gene-linked Polymorphic Region (LPR). In VNTR, a TMD’s risk is higher in homozygous Stin 2.10 allele, compared to Stin2.12 allele [16]. In LPR, a gene with long allele have higher risk of TMD than short allele. This could relate to a lower extracellular serotonin level and higher level of serotonin uptake by transcription activity in long allele gene. As the result, it increases TMD susceptibility [17]. Another gene polymorphism related to serotonin activity is a polymorphism of serotonin receptor 2A in T102C. Subjects with a homozygous C allele shows higher risk of TMD, than homozygous T allele. Conversely, an appearance of G allele in rs9316233 gives protective effect towards TMD [18],[19].

- **Cathecolamine activity**
  Cathecolamine has a role as an adrenergic receptor that increases pain intensity in Temporomandibular Disorder. Cathecolamine neurotransmitter is degraded by Cathecolamine-O-Methyltransferase enzyme (COMT). COMT gene locus is located in chromosome 22 (q11.21). By reducing the COMT level, it may result in a higher level of cathecolamine that leads to intense and persistent pain level [20]. There are three variations of coding agent in COMT enzyme that are classified based on their sensitivity towards pain. A lower pain sensitivity allele (LPS) is known to increase COMT enzyme and diminish TMD’s risk. On the contrary, high and moderate pain sensitivity alleles increase TMD’s risk [20]. Michelotti, et.al finds another correlation between TMD and variants of COMT enzyme such as rs4646310 and rs65656. These polymorphisms related to the higher risk of temporomandibular disorder [21].

- **Estrogen activity**
  A higher prevalence of TMD in women, encourages researchers to investigate possibilities of sexual hormone estrogen as TMD’s risk factor [22],[23]. An estrogen activation is through receptors, either alpha or beta. Estrogen alpha receptor (ESR1) that is located on chromosome 6, has a role as an intercellular mediator. A receptors sequence variance is commonly seen as single nucleotide polymorphisms (SNP) of PvuII (T-397C) and XbaI (A-351G) restriction fragment length polymorphisms (RFLP). These variants are located in intron1, 400 bp upstream from exon 2. Polymorphisms in intron affect mRNA production, resulting overproduction of ESR1 that is suspected to induce the hyperactivity of estrogen towards inflammatory mediators and increase Temporomandibular Disorder’s risk [22],[23],[24],[25].

- **Folate metabolism**
  Folate plays an important role in DNA regulation and protein methylation, and to synthesize acid nucleic during tissue formation. A reduce of folic acid contributes to an increase in pain intensity and myofascial dysfunction that lead to mechanical stress induced TMD [26]. Several enzymes degrade and disrupt folic acids’ synthetize, such as Serine Hydroxymethyl Transferase 1 gene (SHMT1), Methylenetetrahydrofolate Dehydrogenase 1 gene (MTHFD1), and Methionine Synthase Reductase gene (MTRR). Polymorphics in alleles of these enzymes, such as G allele in rs1979277, T allele in rs638416, T allele in rs2236255, and A allele in rs1801394 lead to a sensitivity increase towards pain induction and TMD [27].

- **Histocompatibility complex**
  Human Leukocyte Antigen (HLA) is the main histocompatibility complex of immune system in human body that differentiates between self and non-self antigen. A change in HLA that is caused by polymorphisms increases HLA’s sensitivity towards infectious agent and also escalates inflammatory reaction. This theory is supported by Learetta’s experiment (2011) that found common changes in the TMJ of subject with polymorphisms HLA in allele DR4 and allele DR52. The findings of degenerative joint signs include thinning and tearing of TMJ discal, irregularity of condyle, and flattening of glenoid fossa. Thus, it can be concluded that HLA polymorphisms contribute to a risk increase towards TMJ degenerative disease [28].
2.3.2. Genetic Mutation in TMD. Genetic mutation is the DNA variants acquired with prevalence lower than 1% in world population [15]. Several experimental studies have succeeded to correlate gene mutation contribution towards temporomandibular disorder, especially degenerative joint disorders. There are several factors that possibly affect the genetic mutation in TMD such as; extracellular matrix, transcription factors, transforming growth factor beta (TGFβ), epithelial growth factor, β-catenin, and discoidin.

- **Extracellular matrix**
  Extracellular matrix maintains biomechanical function of organs, such as rigidity and resistance of compression and shear force. In mandibular condyle, the matrix consists of superficial, middle, and deep layers. The superficial layer is mainly composed of type I collagen (Col1), meanwhile middle and deep layers are mainly composed with type II collagen (Col2). An excessive increase of metalloproteinase matrix production by chondrocyte and synovial cell will escalate destruction of extracellular matrix. In temporomandibular joint, this could lead to degenerative joint disorder such as osteoarthritis [29]. As a result of disproporitate micromelia mutation (dmm), a deletion of col2a1 causes growth disturbance in TMJ [29]. Both loss of Col9a1 (Col9a1/-/-) or type IX Collagen deficient and cho/+ or type XI collagen-haploinsufficient relates to an increase of proteoglican level. This increase induces chondrocyte to release matrix-degrading enzyme (MMP) in order to degrade the proteoglican and also result in an increase of Discoidin Domain Receptor 2 (Ddr2) signaling. This will induce the expression of MMP-13, that latter will cleave to the type II collagen, and increase more Ddr2’s expression at the same time. The breakdown of type II collagen will continue until no more proteoglican in extracellular matrix. A fragment from collagen breakdown (α2β1) activates the signal to synthesize MMPT that aggravates the destruction [30].

- **Transcription factor**
  Enzyme 1α-hydroxylase [1α(OH)ase] transforms 25-hydroxyvitamin D into 1,25 dihydroxyvitamin D (1,25(OH)2D). A loss of 1,25(OH)2D, due to deletion of 1α(OH)ase/-/- accelerates a production of inflammatory mediators such as IL-1α, IL-1β, IL-6, MMP-3, MMP-13, Adamts-5 and Cathepsin K. In addition, a reduce of 1α(OH)ase/-/- causes a reduction of bone density, reduction of subchondral bone volume in condyle, reduction of cartilage thickness, and articular surface erosion. Therefore this transcription factor mutation may lead to a degenerative change in temporomandibular joint [31].

- **Transforming growth factor beta (TGFβ) signaling**
  Transforming growth factor is one of the main regulators of collagen synthesis. TGF-β1 is active in bone remodeling and stimulates osteoclast to initiate the resorption. TGF-β1 cleaves into latency-associated protein (LAP) and detaches bone matrix into bone marrow. An increase of TGF-β1 incites abnormality of bone remodeling and could amplify the degradation of cartilage in temporomandibular joint [32].

- **Epithelial growth factor signaling**
  Mitogen-inducible gene 6 (Mig-6) or gene 33, is a negative inhibitor feedback of EGF receptor signaling. An absence of Mig-6 leads to osteophyte formation that is one of the markers in osteoarthritis. Hence, it will cause a phenotype of degenerative joint disorder [33],[34].

- **WNT/β-catenin signaling**
  β-catenin (CTNNB1) induces temporomandibular joint cartilage degeneration through Wnt signaling pathway. At the cellular level, an increase in β-catenin level causes hypertrophy. This will be followed by apoptosis and destruction in tissue levels, such as subchondral bone sclerosis and osteophyte formation. Meanwhile in the molecular level, Col 2 matrix and aggrecan will be reduced but the biomarker of chondrocyte hypertrophy, such as Runx2 and Col10, and cartilage degeneration gene, such as Mmp13, Adamrs4, Adamts5, will be increased. Consequently it will exaggerate a destruction in cartilage of temporomandibular joint [35].

- **Discoidin signaling**
  Discoidin domain receptor is a modulator of cell proliferations and metalloproteinase matrix expressions. Deletion of discoidin domain receptor tyrosine kinase 1 (Ddr1/-/-) by genetic mutation results in following actions degradation of articular surface, loss of proteoglycans, and chondrocyte
formation. Moreover, a loss of Ddr1 reduces an expression of Col2a1, Col3a1, Col9a1, Aggrecan (Acan). On the other hand, it increases Sox9 and nidogen-2 (nid2), runx2 [36].

2.4. Epigenetics Mechanism of TMD
Epigenetics is an interaction between internal and external environments that leads to a change in chromatin structures that switches the gene expression on and off [37]. DNA methylation is one of epigenetic mechanisms that caused silencing gene expression. In a normal situation, CpG island is unmethylated. DNA methyltransferase (DNMT) enzymes induce additional methyl attachment in citocyne, mainly in C5 of CpG shores. This inhibits transcription factor to start processing protein synthesis. Oppositely, hypomethylation of DNA enhances the transcription activities and results in gene expression [37].

In the chromatin complex, histone regulates DNA by tightening and loosening the complex that influences both initiation and silencing transcriptions. Modification of histone tail includes acetylation, methylation, ubiquitination, and sumoylation. Either the addition of acetyl or the release of methyl in histone tails will result in gene overexpression [37].

Epigenetic mechanisms such as DNA methylation, histone modification, and microRNA are found in chondrocyte of TMD patients. Epigenetic mediates gene expression of extracellular matrix (COL2A1, COL9A1, ACAN), inflammatory mediator (IL-1B, TNF-alpha), and proteinase or matrix-degrading enzymes (ADAMTS4, ADAMTS5). Any disturbance in the homeostasis of these genes will affect bone remodeling and deposition in temporomandibular joint that could lead to a TMJ destruction [38], [39], [40], [41], [42].

| Table 1. Degenerative joint disorder in TMJ induced by epigenetic mechanism |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Category**    | **Gene**        | **Expression**  | **Epigenetic regulation** | **References** |
| ECM             | COL2A1          | ↓               | DNA methylation | V               | v               | [39-41] |
|                 | COL9A1          | ↓               |                   | V               | [40,41] |
|                 | ACAN            | ↓               |                   | V               | v               | [41] |
|                 | Chad            | ↓               |                   | V               | [42] |
| Cytokines       | IL-1B           | ↑               |                   | V               | v               | [41] |
|                 | TNF-alpha       | ↑               |                   | V               | v               | [41-42] |
| Proteinases     | ADAMTS4         | ↑               |                   | V               | v               | [41] |
|                 | ADAMTS5         | ↑               |                   | V               | v               | [41-42] |
|                 | MMP 3           | ↑               |                   | V               | v               | [41] |
|                 | MMP 9           | ↑               |                   | v               | [41] |
|                 | MMP 13          | ↑               |                   | v               | [41] |

2.4.1. MicroRNA (miRNA). MicroRNA (miRNA) is one of short noncoding agents that inhibits post-transcription mRNA to translate and bind with tRNA. miRNA affects catabolic and anabolic genes with transcription and epigenetic factors [43].
Figure 2. Mechanism of miRNAs: 1. Polymerase II induces transcription of miRNAs; 2A-2C type III RNase Drosha processes pri-miRNAs; 3 Pre-miRNAs leaves nucleus through NPC; 4-6 maturation of miRNA creates miRNA:miRNA duplex and miRSC:miRSC complex; 7. Attachment of mRNA and miRSC; 8A-8B Translational repression of mRNA that leads to mRNA decay. (Source: Araldi, 2010) [44]

In a temporomandibular joint, miRNA-140 controls bone homeostasis especially on the articular remodeling. A loss of miR-140 increases susceptibility to the TMD. IL-1β, a osteoarthritis TMJ marker suppresses gene expression of miR-140 [45]. Past study by Miyaki (2010) finds that miR-140 reduces the ADAMT5S level, that is an aggrecanase that induces osteoarthritis in knee [46].

3. Conclusion

As a multifactorial disease, genetic factors exhibit as TMD risk factors. Genetic polymorphisms and genetic mutation may lead to any activity change in inflammation mediator, sexual hormones, matrix-degrading enzyme, immune system that influences the homeostasis of bone remodeling in temporomandibular joint. Moreover, an activity change is also found in neurotransmitter and pain receptor that results in a relatively high sensitivity towards pain. Thus, this condition also increases susceptibility with subject to the TMD.

Genetic analysis and biomarkers of temporomandibular disorder could improve sensitivity and specificity metrics when diagnosing and treating TMD patient. Therefore, further research is suggested before genetic molecular reaches their full potential in any clinical application. Acknowledgments

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References
[1] Okeson JP 2013 Management of Temporomandibular Disorders and Occlusion 7th edition (Missouri: Elsevier)
[2] Cobourne M, DiBiase A 2015 Handbook of Orthodontics 2nd Edition (Amsterdam: Elsevier)
[3] Visscher CM, Lobbezoo F 2015 J Oral Rehabil. 42 5 386-399
[4] Smith S B, Mir E, Bair E, Slad G D, Dubner R, Fillingim R B, Greenspan J D, Ohrbach R, Knott C, Weir B, Maixner W, Diatchenko L. 2013 J Pain. 14 12 SUPPL T91-T101

[5] Melis M, Di Giosis M. 2016 J Craniofacial Sleep Pract. 34 1 43-51

[6] Maulina T, Yubuliana G, Rachmi CN, Wulansari D, Rikmasari R. 2016 Int J Clin Dent. 9 3 1-12

[7] Marpaung C, Selms MKA Van, Lobbezoo F. 2018 Community Dent Oral Epidemiol. 1-7

[8] Himawan LS, Kusdhanly LS, Ariani N. 2007 Med J Indones. 16 4 237-240

[9] Schifman E, Ohrbach R, Truelove E, Look J, Anderson G, Goulet J P, List T, Svensson P, Gonzalez Y, Lobbezoo F, Michelotti A, Brooks S L, Ceusters W, Drangsholt M, Ettlin D, Gaul C, Goldberg L J, Haythornthwaite J A, Hollender L, Jensen R, John MT, De Laat A, de Leeuw R, Maixner W, van der Meulen M, Murray G M, Nixdorf D R, Palla S, Peterssson A, Pionchon P, Smith B, Visscher C M, Zakrzewska J, Dworkin SF. 2014 J Oral Facial Pain Headache 28 1 6-27

[10] Raphael KG, Marbach JJ, Gallagher RM, Dohrenwend BP. 1999 Pain. 80 1-2 15-22

[11] Matsuka Y, Nagamatsu C, Itoh S, Tomonari T, Makki A, Minakuchi H, Maekawa K, Kanyama M and Kuboki T. 2007 Cranio 25 1 23-29

[12] Michalowicz BS, Philstrom BL, Hodges J, Bouchard Jr. 2000 J Dent Res. 79 1573-1578

[13] Plesh O, Noonan C, Buchwald DS, Goldberg J, Afari N. 2012 J Orofac Pain. 26 91-98

[14] Genello M. 2017 Dent 300 51

[15] Kirk R, Pandya D, Elston RC, Ferlini C. 2015 BMC Med Genomics. 8 1 1-7

[16] Herken H, Erdal E, Mutlu N, Barlas O, Cataloluk O, Oz F, Gumery E. 2001 Am J Orthod Dentofac Orthop. 120 3 308-313

[17] Ojima K, Watanabe N, Narita M, Narita M. 2007 Biopsychosoc Med. 1 1-4

[18] De Freitas L V S, Lopes A C P, Piatto V B, Maniglia J V. 2013 Arch Med Sci. 9 6 1013-1018

[19] Mutlu N, Erdal M, Herken H, Oz G, Bayazit Y. 2004 Oral Dis. 10 6 349-352

[20] Diatchenko L, Slade G D, Nackley A G, Bhalang K, Sigurdsson A, Belfer I, Goldman D, Xu K, Shabalina S A, Shagin D, Max M B, Makarov S S, Maixner W. 2005 Hum Mol Genet. 14 1 135-143

[21] Michelotti A, Liguori R, Torriolo M, Sacchetti L. 2014 Clin J Pain. 30 2 129-133

[22] Patil S, Yadav N, Mousa M A, Alzwiri A, Kassab M, Sahu R, Chuggani S. 2015 J Oral Res Rev. 7 2 41

[23] Torres-Chvez K E, Sanfins J M, Clemente-Napimoga J T, Pellegrini-Da-Silva A, Parada C A, Fischer L, Tambeli C H. 2012 Eur J Pain. 16 204-216

[24] Ribeiro-Dasilva M C, Peres S R L, LemGodoy dos Santos M C L, Arthur M T, Hou W, Fillingim B R, Barbosa C M R. 2009 J Pain. 10 5 527-533

[25] Kang SC, Lee DG, Choi JH, Kim ST, Kim YK, Ahn HJ. 2007 Int J Oral Maxillofac Surg. 36 5 391-394

[26] Mehra P, Wolford LM. 2008 Proc (Baylor Univ Med Cent). 21 3 243-247

[27] Anieiros-Guerrero A, Lendinez A M, Palomares A R, Perez-Nevot B, Aguado L, Mayor-Olea A, Ruiz-Galdon M, Reyes-Engel A. 2011 BMC Med Genet. 12 1-9

[28] Learreta JA, Bono AE, Durst AC. 2011 Craniomandib Sleep Pract. 29 1 32-37

[29] 2Rintala M, Metsänta M, Säämänen AM, Vuorio E, Rönning O. 1997 J Anat. 190 2 201-208

[30] Lam N P, Li Y, Waldman A B, Brussiat J, Lee P L, Olsen B R, Xu L. 2012 Arch Oral Biol. 40 6 1301-1315

[31] Shen M, Luo Y, Niu Y, Chen L, Yuan X, Goltzman D, Chen N, Miao D. 2013 Bone. 55 2 400-409

[32] Jiao K, Zhang M, Niu L, Yu S, Zhen G, Xian L, Yu B, Yang K, Liu P, Cao X, Wang M. 2014 J Dent Res. 93 2 140-147

[33] Zhang Y-W, Su Y, Lanning N, Swiatek P J, Bronson R T, Sigler R, Martin R W, Vande Woude GF. 2005 Proc Natl Acad Sci. 102 33 11740-11745

[34] Staal B, Williams B O, Beter F, Vande Woude G F, Zhang Y-W. 2014 Proc Natl Acad Sci. 111 7 2590-2595
[35] Wang M, Li S, Xie W, Shen J, Im H J, Holz J D, Wang M, Diekwisch T G H and Chen D 2014 *Eur Cells Mater*. 28 223-235
[36] Schminke B, Muhammad H, Bode C, Sadowski B 2014 *Cell Mol Life Sci.* 71 6 1081-1096
[37] Graber L w, Vanarsdall R L, Vig K W L, Huang G J 2017 *Orthodontics Current Principles and Techniques* (Missouri: Elsevier)
[38] Zhang M, Wang J 2015 *Genes Dis*. 2 1 69-75
[39] Oppenheimer H, Kumar A, Meir H, Schwartz I, Zini A, Haze A, Kandel L, Mattan Y, Liebergall M, Dvir-Ginzberg M 2014 *J Bone Miner Res*. 29 2 348-360
[40] Imagawa K, de Andrés M C, Hashimoto K, Itoi E, Otero M, Roach H I, Goldring M B, Oreffeo R O C 2014 *Arthritis Rheumatol* 66 11 3040-3051
[41] Rushton M D, Reynard L N, Barter M J, Refaie R, Rankin K S, Young D A and Loughlin J 2014 *Arthritis Rheumatol* 66 9 2450-2460
[42] Xiao J L, Meng J H, Gan Y H, Li Y L, Zhou C Y and Ma X C 2016 *Arch Oral Biol*. 68 105-115
[43] Zhang M, Lygrissea K and Wanga J 2017 *J Arthritis*. 6 2
[44] Araldi E and Schipani E 2010 *Genes Dev*. 24 11 1075-1080
[45] Miyaki S, Nakasa T, Otsuki S, Grogan P S, Higashiyama R, Inoue A, Kato Y, Sato T, Lotz M K, Asahara H 2009 *Arthritis Rheum*. 60 9 2723-2730
[46] Miyaki S, Sato T, Inoue A, Otsuki S, Ito Y, Yokoyama S, Kato Y, Takemoto F, Nakasa T, Yamashita S, Takada S, Lotz M K, Ueno-Kudo H, Asahara H 2010 *Genes Dev*. 24 11 1173-1185