Gene Mutations Associated with Temporomandibular Joint Disorders: A Systematic Review

Dhruvee Sangani, Akiko Suzuki, Helena VonVille, James E. Hixson, and Junichi Iwata

Department of Epidemiology, Human Genetics & Environmental Sciences, The University of Texas School of Public Health, Houston, TX, USA
Department of Diagnostic & Biomedical Sciences, The University of Texas Health Science Center at Houston School of Dentistry, Houston, TX, USA
Center for Craniofacial Research, The University of Texas Health Science Center at Houston School of Dentistry, Houston, TX, USA
The University of Texas School of Public Health Library, Houston, TX, USA
The University of Texas Graduate School of Biomedical Sciences at Houston, Houston, TX, USA

Abstract

Background—The temporomandibular joint (TMJ) is a bilateral synovial joint between the mandible and the temporal bone of the skull. TMJ disorders (TMDs) are a set of complicated and poorly understood clinical conditions, in which TMDs are associated with a number of symptoms including pain and limited jaw movement. The increasing scientific evidence suggests that genetic factors play a significant role in the pathology of TMDs. However, the underlying mechanism of TMDs remains largely unknown.

Objective—The study aimed to determine the associated genes to TMDs in humans and animals.

Methods—The literature search was conducted through databases including Medline (Ovid), EMBASE (Ovid), and PubMed (NLM) by using scientific terms for TMDs and genetics in March 2015. Additional studies were identified by searching bibliographies of highly relevant articles and Scopus (Elsevier).
Results—Our systematic analyses identified 31 articles through literature searches. A total of 112 genes were identified to be significantly and specifically associated with TMDs.

Conclusion—Our systematic review provides a list of accurate genes associated with TMDs and suggests a genetic contribution to the pathology of TMDs.

Keywords
Temporomandibular Joint; Temporomandibular Joint Disorders; Systematic Review

1. Introduction

The temporomandibular joint (TMJ; aka the jaw joint) is a bilateral synovial joint between the mandible and the temporal bone. The TMJ consists of an articular disc located in the articular cavity, the glenoid fossa of the temporal bone and the mandibular condyle, and is filled with synovial fluid. The TMJ is unique because it consists of two joints in one bone, which is required to work simultaneously, and it acquires two major movements of the mandibular condyles: hinge and sliding, which is important for smoothly opening/closing mouth and chewing. TMJ disorders (TMDs) are a sub-classification of musculoskeletal disorders that result from stomatognathic system defects, and affect the function of masticatory muscles, the TMJ, and its associated structures [1].

TMDs are a set of complicated and poorly understood clinical conditions, which are associated with a number of symptoms including pain and limited jaw movement. The estimated prevalence of TMDs ranges from 5% to 60% worldwide [2]. TMDs occur as an individual disorder or associated with other syndromes, and TMJ pain is the second most common musculoskeletal pain after chronic low back pain [3] [4]. Since the symptoms of TMDs include pain, inflammation, and limited jaw movements, the etiology of TMDs may be complex. In addition, the susceptibility to TMDs may not be equal; for example, it is known that women are more susceptible than men. Severe and/or chronic cases of TMDs often occur with pain, but in mild cases, pain may be resolved over time. The possible influence factors of TMDs are mechanical and/or psychic stresses, hormones, genes, ethnicity, social status, and gender [5]. It has been postulated that women and adolescents have a higher risk for TMDs, compared to men [6] [7]. TMJ osteoarthritis (OA) is also diagnosed at the later stages of severe cases of TMDs [8]. The extent of causative genes of TMDs has been of prime interest [9]. The increasing scientific evidence suggests that genetic factors may play a significant role in the pathology of TMDs [10] [11]. However, the underlying mechanism of TMDs remains largely unknown. In this study, we performed a systematic review to identify genes associated with TMDs.

Currently, there are a few dental experts trained to precisely diagnose and treat this complex disorder. The treatment of TMDs has been very broad and general, including medications such as non-steroidal anti-inflammatory drugs (NSAIDs), muscle relaxants, physiotherapy, splints, biofeedback, and cognitive behavioral therapy. This study aims to provide precise information and highlight scientific literatures identifying genes associated with specific TMD conditions. Since not much research has been done on humans, animal studies have
also been included in this systematic review. With knowledge of genetic studies, physicians and dentists can make diagnosis, tailor treatments, and predict susceptibility among people.

2. Methods and Materials

2.1. Eligibility Criteria for Systemic Review

The PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guideline and checklist was followed for this systematic review. Articles included in our systematic review met the following eligibility criteria: 1) described genes that are identified in TMDs; 2) were published as original articles (not as review articles, editorials, or comments); 3) were published in the English language; 4) were published between the years 2000 and 2015; and 5) specified TMD caused by gene mutations. Some articles were excluded from our systematic review because of one or more of the following reasons: a) gene mutations were not described in original articles; b) the type of TMDs (signs, symptoms, etc.) was not described or not diagnosed; c) the symptom was only pain, or the other symptoms and/or evaluations were not described; d) TMDs resulted from environmental factors; e) the studies had been done in other joints of the body; and f) others that include articles that failed to fit in any of the above criteria.

2.2. Information Sources and Search

The online databases that were searched included: Medline (Ovid), PubMed (National Library of Medicine), and EMBASE (Ovid). In addition, highly relevant citations were searched in Scopus (Elsevier) to determine if any unique studies were missed by the database searches. Bibliographies of highly relevant articles were also examined. The Primary Excel Workbook for Systematic Reviews was used to track all search strategies and results, as described previously [12]. All search strategies are listed in full in Table S1 and Table S2. The search was limited to studies from 2000 through 2015 as genetic studies have become more technologically advanced in recent years, and very few genetic studies on TMDs were conducted before the year 2000.

2.3. Study Selection and Data Collection

RefWorks (Proquest) was used to store all citations found during the entire search process. The Primary Excel Workbook for Systematic Reviews (VonVille, Helena M. Primary Excel Workbook for Systematic Reviews, http://libguides.sph.uth.tmc.edu/excel_SR_workbook) was used to screen titles and abstracts of items found through database search. Titles and abstracts were screened by the first author (DS). The full text of articles not excluded was retrieved and reviewed by the first and second authors (DS, AS) with all data related to both screening and reviewing recorded in the Primary Excel Workbook. The data collected were displayed as a descriptive narrative. A codebook for data extraction from eligible articles was developed. The data elements that were extracted for the codebook included citation information, study level information (characteristics and results), and quality level information.
3. Results and Discussions

Nearly 900 unique articles were identified using the search strategies described above (see Figure 1 and Supplemental Information, Tables S1 and S2 for the database search strategies). Approximately 61% of the articles included were published after 2010. Interestingly, most of the articles included were published in 2014. Among the articles included for review (n = 31), 10 studies were done on humans while 21 studies were conducted on animal models (Table 1 and Table 2). One study conducted research on both mouse and human subjects [13]. Out of 31 articles, 18 were conducted research on mice while 1 article studied in porcine, 2 articles in rats, and 1 article in rabbits. The articles from 2000–2015 covered most of the research related to genes in TMDs. Eight studies were conducted in 2014 and 2 studies were conducted in 2015. The demographic characteristics among the human studies were very different. Among the human studies, different ethnic groups such as Koreans, Japanese, Brazilian, Finnish, and Turkish populations were studied (Table 1). Three articles did not mention the ethnicity of the population studied [14] [15] [16]. One study indicated that in the miscegenetic Brazilian population, the age was significantly associated with TMDs [17]. Two studies were carried out only in women to determine the association of the estrogen receptor alpha (ESR1) gene with TMDs. One study [18] indicated the contribution of ESR1 on TMDs whereas another study [19] suggested no association of ESR1 with TMD symptoms such as clicks, crepitus, and bone erosion.

Females are more affected by TMJ pain and degeneration due to the effects of β-estradiol on the TMJ [18]. Three studies show no statistically significant changes in candidate TMD causative genes: MAOA (monoamine oxidase-A), ESR1 (estrogen receptor alpha), and TNF (tumor necrosis factor alpha) [16] [19] [20]. Several polymorphisms have been described in the promoter region of MMP genes, and these polymorphisms modify gene expression and function of the MMPs. MMP1 (matrix metalloproteinase 1) polymorphism, but not MMP3 and MMP9 polymorphisms, is associated with osteophyte and erosion of the mandibular condyle. In the Brazilian MMP1 2G/2G homozygous subjects, the probability of developing degeneration of the mandibular condyle is 2.47 times higher than that in the MMP1 1G/2G and 1G/1G individuals [17]. ADAMTS5 (a disintegrin and metalloproteinase with thrombospondin motif 5) is involved in deformation of the articular disc associated with internal derangement and osteoarthritis in the TMJ [14]. Thus, proteinases contribute to degrade the articular disc and the surface of the mandibular condyle during the progression of TMDs. Homozygous polymorphism in ANKH (a human homolog of the murine progressive ankylosis gene, ank) more likely develops TMJ closed lock compared to controls [13]. The human leukocyte antigen (HLA) complex is a major histocompatibility complex (MHC) which is present on the surface of immune cells. Polymorphism in HLA-DRB1 (MHC class II, DR beta 1) allele is associated with erosion of the mandibular condyle [21]. These findings suggest that inflammation and autoimmune diseases may affect the progression of TMDs. Polymorphism in the fibroblast growth factor 2 (FGF2) gene is involved in the pathogenesis of TMJ synovial chondromatosis that is a rare proliferative disorder characterized by the formation of cartilaginous or osteocartilaginous nodules in synovium and articular cavities [15]. A recent genome-wide association study (GWAS) identified 22 independent loci showing association with degeneration of the mandibular condyle in East Asian populations. Among them, TSPAN9 (tetraspanin 9) polymorphism
showed strongest association with TMD [22]. TSPAN9 mediates a signal transduction that plays a role in the regulation of cell development, activation, growth, and motility. Thus, some cell signaling pathways may be involved in the pathogenesis of TMDs. Although most of the studies have been done in small sample sizes, 28 out of 31 studies identified genes to be causal or associated with TMDs. This finding can lead us to believe that gene mutations are a causative factor for the incidence of TMDs.

In spite of extensive attempts, the molecular mechanism of TMDs is largely unknown because of the complex interaction of genes with other confounding factors like hormones, age, ethnicity, and environment. The presence of more than one symptom may be interdependent and act as a confounding factor [19]. Due to heterogeneity of symptoms, there are a lot of variations in diagnosis of TMDs worldwide. The appropriate treatments for TMD can only be initiated with a precise diagnosis. A number of imaging techniques including ultrasonography, computed tomography (CT), arthrography, and magnetic resonance imaging (MRI) have been adopted to confirm the diagnosis made by history taking and clinical examination. In 1992, The Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) was proposed as the basis for diagnosis of these complicated disorders [23]. In 2004, RDC/TMD has been replaced with Diagnostic Criteria for TMD (DC/TMD) because the validity of RDC/TMD was not sufficient enough in clinic [24]. Only 2 studies used the RDC/TMD diagnostic criteria, and none of the clinical studies have used the latest DC/TMD criteria yet.

This systematic review has much strength in identifying causative genes and their genetic interactions; however, it has a few limitations such as the year range of 2000–2015 and the English language. All the human studies had more number of females participating in the study. The participation of unequal numbers of gender might affect the validity of the results that women are more susceptible to TMDs. In addition, due to a broad classification and diagnostic criteria of TMDs, a potent detection bias cannot be ignored. Publication bias also can be the reason for limited literature being published. Future research with larger sample sizes will enable us to better understand genetic association with TMDs. Recent advances have introduced new techniques like GWAS that can help us discover genes associated with TMDs.

4. Conclusion

From a public health perspective, there is an urgent need to address TMDs and determine their causative factors. Despite different diagnostic criteria used, most of the included studies find associations between genes and TMDs. Future studies should incorporate objective diagnostic methods such as DC/TMD for TMD diagnosis to yield consistent results. Understanding the molecular mechanism is important to individualize treatment for TMDs in order to alleviate the overall burden of TMDs. Further studies to identify genes associated with TMDs will enable us to specifically diagnose TMDs and improve the quality of treatment. These findings will also help us understand why there is a gender disparity in TMDs and who may be more likely to suffer from TMDs.
Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study was supported by start-up fund to J.I.

Abbreviations

| Abbreviation | Description |
|--------------|-------------|
| DC/TMD | Diagnostic Criteria for TMD |
| ESR1 | Estrogen Receptor Alpha |
| GWAS | Genome-Wide Association Study |
| MAOA | Monoamine Oxidase-A |
| NSAIDs | Non-Steroidal Anti-Inflammatory Drugs |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| RDC/TMD | Research Diagnostic Criteria for Temporomandibular Disorders |
| TMDs | Temporomandibular Joint Disorders |
| TMJ | Temporomandibular Joint |
| TNF | Tumor Necrosis Factor Alpha |

References

1. Tanaka E, Detamore MS, Mercuri LG. Degenerative Disorders of the Temporomandibular Joint: Etiology, Diagnosis, and Treatment. Journal of Dental Research. 2008; 87:296–307. http://dx.doi.org/10.1177/154405910808700406. [PubMed: 18362309]

2. Shaffer SM, Brismee JM, Sizer PS, Courtney CA. Temporomandibular Disorders. Part 1: Anatomy and Examination/Diagnosis. The Journal of Manual & Manipulative Therapy. 2014; 22:2–12. http://dx.doi.org/10.1179/2042618613Y.0000000060. [PubMed: 24976743]

3. Mundt T, Mack F, Schwahn C, Bernhardt O, Kocher T, et al. Association between Sociodemographic, Behavioral, and Medical Conditions and Signs of Temporomandibular Disorders across Gender: Results of the Study of Health in Pomerania (SHIP-0). The International Journal of Prosthodontics. 2008; 21:141–148. [PubMed: 18546769]

4. Leboeuf-Yde C, Nielsen J, Kyvik KO, Fejer R, Hartvigsen J. Pain in the Lumbar, Thoracic or Cervical Regions: Do Age and Gender Matter? A Population-Based Study of 34,902 Danish Twins 20–71 Years of Age. BMC Musculoskeletal Disorders. 2009; 10:39. http://dx.doi.org/10.1186/1471-2474-10-39. [PubMed: 19379477]

5. Magalhaes BG, de-Sousa ST, de Mello VV, da-Silva-Barbosa AC, de-Assis-Morais MP, et al. Risk Factors for Temporomandibular Disorder: Binary Logistic Regression Analysis. Medicina Oral Patologia Oral y Cirugia Bucal. 2014; 19:e232–e236. http://dx.doi.org/10.4317/medoral.19434.

6. Dworkin SF, Huggins KH, LeResche L, Von Korff M, Howard J, et al. Epidemiology of Signs and Symptoms in Temporomandibular Disorders: Clinical Signs in Cases and Controls. The Journal of the American Dental Association. 1990; 120:273–281. http://dx.doi.org/10.14219/jada.archive.1990.0043. [PubMed: 2312947]

7. Bagis B, Ayaz EA, Turgut S, Durkan R, Ozcan M. Gender Difference in Prevalence of Signs and Symptoms of Temporomandibular Joint Disorders: A Retrospective Study on 243 Consecutive
8. Wadhwa S, Embree M, Ameye L, Young MF. Mice Deficient in Biglycan and Fibromodulin as A Model for Temporomandibular Joint Osteoarthritis. Cells Tissues Organs. 2005; 181:136–143. http://dx.doi.org/10.1159/000091375. [PubMed: 16612079]

9. Oakley M, Vieira AR. The Many Faces of the Genetics Contribution to Temporomandibular Joint Disorder. Orthodontics & Craniofacial Research. 2008; 11:125–135. http://dx.doi.org/10.1111/j.1601-6434.2008.00426.x. [PubMed: 22991492]

10. Fillingim RB, Wallace MR, Herbstman DM, Ribeiro-Dasilva M, Staud R. Genetic Contributions to Pain: A Review Of Findings in Humans. Oral Diseases. 2008; 14:673–682. http://dx.doi.org/10.1111/j.1601-0825.2008.01458.x. [PubMed: 19193196]

11. Smith SB, Mir E, Bair E, Slade GD, Dubner R, et al. Genetic Variants Associated with Development of TMD and Its Intermediate Phenotypes: The Genetic Architecture of TMD in the OPPERA Prospective Cohort Study. Journal of Pain. 2013; 14:T91–T101.e3. http://dx.doi.org/10.1016/j.jpain.2013.09.004. [PubMed: 24275226]

12. Davlin SL, VonVille HM. Canine Rabies Vaccination and Domestic Dog Population Characteristics in the Developing World: A Systematic Review. Vaccine. 2012; 30:3492–3502. http://dx.doi.org/10.1016/j.vaccine.2012.03.069. [PubMed: 22480924]

13. Huang B, Takahashi K, Sakata T, Kiso H, Sugai M, et al. Increased Risk of Temporomandibular Joint Closed Lock: A Case-Control Study of ANKH Polymorphisms. PLoS ONE. 2011; 6:e25503. http://dx.doi.org/10.1371/journal.pone.0025503. [PubMed: 22003394]

14. Matsumoto T, Tojyo I, Kiga N, Hiraishi Y, Fujita S. Expression of ADAMTS-5 in Deformed Human Temporomandibular Joint Discs. Histology and Histopathology. 2008; 23:1485–1493. [PubMed: 18830934]

15. Li YJ, Cai HX, Fang W, Meng QG, Li J, et al. Fibroblast Growth Factor 2 Involved in the Pathogenesis of Synovial Chondromatosis of Temporomandibular Joint. Journal of Oral Pathology & Medicine. 2014; 43:388–394. http://dx.doi.org/10.1111/j.1601-0825.2014.01345.x. [PubMed: 24372705]

16. Mutlu N, Erdal ME, Herken H, Ozkaya M, Erdal N, Oz G, et al. Monoamine Oxidase-A Gene Promoter Polymorphism in Temporomandibular Joint Pain and Dysfunction. Pain Clinics. 2005; 17:39–44.

17. Planello AC, Campos MI, Meloto CB, Secolin R, Rizatti-Barbosa CM, et al. Association of Matrix Metalloproteinase Gene Polymorphism with Temporomandibular Joint Degeneration. European Journal of Oral Sciences. 2011; 119:1–6. http://dx.doi.org/10.1111/j.1600-0722.2010.00803.x. [PubMed: 21244504]

18. Ribeiro-Dasilva MC, Peres Line SR, dos Santos MCLG, Arturhi MT, Hou W, Fillingim RB, et al. Estrogen Receptor-α Polymorphisms and Predisposition to TMJ Disorder. Journal of Pain. 2009; 10:527–533. http://dx.doi.org/10.1111/j.1601-0825.2008.01102.x. [PubMed: 19410160]

19. Kim BS, Kim YK, Yun PY, Lee E, Bae J. The Effects of Estrogen Receptor α Polymorphism on the Prevalence of Symptomatic Temporomandibular Disorders. Journal of Oral and Maxillofacial Surgery. 2010; 68:2975–2979. http://dx.doi.org/10.1016/j.joms.2010.02.023. [PubMed: 20656393]

20. Etoz OA, Erdal ME, Herken H, Bayazit YA, Mutlu MN. Lack of Association between the 308GA Polymorphism of the Tumor Necrosis Factor α Gene and Temporomandibular Dysfunction. Pain Clinics. 2006; 18:175–180.

21. Helenius LM, Hallikainen D, Helenius I, Meurman JH, Koskimies S, et al. HLA-DRB1* Alleles and Temporomandibular Joint Erosion in Patients with Various Rheumatic Diseases. Scandinavian Journal of Rheumatology. 2004; 33:24–29. http://dx.doi.org/10.1080/03009740310004603. [PubMed: 15124939]

22. Yamaguchi T, Nakaoka H, Yamamoto K, Fujikawa T, Kim YI, et al. Genome-Wide Association Study of Degenerative Bony Changes of the Temporomandibular Joint. Oral Diseases. 2014; 20:409–415. http://dx.doi.org/10.1111/odi.12141. [PubMed: 23746317]

23. Ahmad M, Hollender L, Anderson Q, Kartha K, Ohrbach R, et al. Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD): Development of Image Analysis Criteria and Examiner Reliability for Image Analysis. Oral Surgery, Oral Medicine, Oral Pathology, Oral
Radiology, and Endodontontology. 2009; 107:844–860. http://dx.doi.org/10.1016/j.tripleo.2009.02.023.

24. Schiffman E, Ohrbach R, Truelove E, Look J, Anderson G, et al. 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 Group. Journal of Oral & Facial Pain and Headache. 2014; 28:6–27. http://dx.doi.org/10.11607/jop.1151. [PubMed: 24482784]

25. Jing J, Hinton RJ, Jing Y, Liu Y, Zhou X, Feng JQ. Osterix Couples Chondrogenesis and Osteogenesis in Post-Natal Condylar Growth. Journal of Dental Research. 2014; 93:1014–1021. http://dx.doi.org/10.1177/0022034514549379. [PubMed: 25192899]

26. Ishizuka Y, Shibukawa Y, Nagayama M, Decker R, Kinumatsu T, Saito A, et al. TMJ Degeneration in SAMP8 Mice Is Accompanied by Deranged Ihh Signaling. Journal of Dental Research. 2014; 93:281–287. http://dx.doi.org/10.1177/0022034513519649. [PubMed: 24453178]

27. Li XH, Liang WN, Ye HZ, Weng XP, Liu FY, Liu XX. Overexpression of Shox2 Leads to Congenital Dysplasia of the Temporomandibular Joint in Mice. International Journal of Molecular Sciences. 2014; 15:13135–13150. http://dx.doi.org/10.3390/ijms150813135. [PubMed: 25062834]

28. Jiao K, Zhang M, Niu L, Yu S, Zhen G, Xian L, et al. Overexpressed TGF-β in Subchondral Bone Leads to Mandibular Condyle Degradation. Journal of Dental Research. 2014; 93:140–147. http://dx.doi.org/10.1177/0022034513513034. [PubMed: 24309371]

29. Inman KE, Purcell P, Kume T, Trainor PA. Interaction between Foxc1 and Fgf8 during Mammalian Jaw Patterning and in the Pathogenesis of Synagnathia. PLoS Genetics. 2013; 9:e1003949. http://dx.doi.org/10.1371/journal.pgen.1003949. [PubMed: 24385915]

30. Ricks ML, Farrell JT, Falk DJ, Holt DW, Rees M, Carr J, et al. Osteoarthritis in Temporomandibular Joint of Col2a1 Mutant Mice. Archives of Oral Biology. 2013; 58:1092–1099. http://dx.doi.org/10.1016/j.archoralbio.2013.02.008. [PubMed: 23518238]

31. Yasuda T, Nah HD, Laurita J, Kinumatsu T, Shibukawa Y, Shibutani T, et al. Muenke Syndrome Mutation, FgfR3P244R, Causes TMJ Defects. Journal of Dental Research. 2012; 91:683–689. http://dx.doi.org/10.1177/0022034512449170. [PubMed: 22622662]

32. Purcell P, Jheon A, Vivero MP, Rahimi H, Joo A, Klein OD. Spry1 and Spry2 Are Essential for Development of the Temporomandibular Joint. Journal of Dental Research. 2012; 91:387–393. http://dx.doi.org/10.1177/0022034512438401. [PubMed: 22385787]

33. Embree M, Ono M, Kilts T, Walker D, Langguth J, Mao J, et al. Role of Subchondral Bone during Early-Stage Experimental TMJ Osteoarthritis. Journal of Dental Research. 2011; 90:1331–1338. http://dx.doi.org/10.1177/0022034511421930. [PubMed: 21917603]

34. Purcell P, Joo BW, Hu JK, Tran PV, Calicchio ML, O’Connell DJ, et al. Temporomandibular Joint Formation Requires Two Distinct Hedgehog-Dependent Steps. Proceedings of the National Academy of Sciences of the United States of America. 2009; 106:18297–18302. http://dx.doi.org/10.1073/pnas.0908836106. [PubMed: 19815519]

35. Gu SP, Wei N, Yu L, Fei J, Chen YP. Shox2-Deficiency Leads to Dysplasia and Ankylosis of the Temporomandibular Joint in Mice. Developmental Dynamics. 2008; 236:426–434. http://dx.doi.org/10.1002/dvdy.21036. [PubMed: 17191253]

36. Shibukawa Y, Young B, Wu CS, Yamada S, Long FX, Pacifici M, et al. Temporomandibular Joint Formation and Condyle Growth Require Indian Hedgehog Signaling. Developmental Dynamics. 2007; 236:426–434. http://dx.doi.org/10.1002/dvdy.21036. [PubMed: 15905105]

37. Meng JH, Ma XC, Ma DL, Xu CM. Microarray Analysis of Differential Gene Expression in Temporomandibular Joint Condylar Cartilage after Experimentally Induced Osteoarthritis. Osteoarthritis & Cartilage. 2005; 13:1115–1125. http://dx.doi.org/10.1016/j.joca.2005.03.010. [PubMed: 15905105]

38. Xu L, Flahiff CM, Waldman BA, Wu D, Olsen BR, Setton LA, et al. Osteoarthritis-Like Changes and Decreased Mechanical Function of Articular Cartilage in the Joints of Mice with the Chondrodysplasia Gene (Cho). Arthritis & Rheumatism. 2003; 48:2509–2518. http://dx.doi.org/10.1002/art.11233. [PubMed: 13130470]
39. Gu SP, Wu WJ, Liu C, Yang L, Sun C, Ye WD, et al. BMPRIA Mediated Signaling Is Essential for Temporomandibular Joint Development in Mice. PLoS ONE. 2014; 9:e101000. http://dx.doi.org/10.1371/journal.pone.0101000. [PubMed: 25093411]

40. Li XH, Liu HB, Gu SP, Liu C, Sun C, Zheng YQ, et al. Replacing Shox2 with Human SHOX Leads to Congenital Disc Degeneration of the Temporomandibular Joint in Mice. Cell & Tissue Research. 2014; 355:345–354. http://dx.doi.org/10.1007/s00441-013-1743-2. [PubMed: 24248941]

41. Wang M, Li S, Xie W, Shen J, Im HJ, Holz JD, et al. Activation of β-Catenin Signalling Leads to Temporomandibular Joint Defects. European Cells & Materials. 2014; 28:223–235. [PubMed: 25340802]

42. Meng JH, Ma XC, Li ZM, Wu DC. Aquaporin-1 and Aquaporin-3 Expressions in the Temporomandibular joint Condylar Cartilage after an Experimentally Induced Osteoarthritis. Chinese Medical Journal. 2007; 120:2191–2194. [PubMed: 18167200]

43. Yu S, Sun L, Liu L, Jiao K, Wang M. Differential Expression of IGF1, IGFR1 and IGFBP3 in Mandibular Condylar Cartilage between Male and Female Rats Applied with Malocclusion. Journal of Oral Rehabilitation. 2012; 39:727–736. [PubMed: 22758598]

44. Asakawa-Tanne Y, Su S, Kunimatsu R, Hirose N, Mitsuyoshi T, Okamoto Y, et al. Effects of Enzymatic Degradation after Loading in Temporomandibular Joint. Journal of Dental Research. 2015; 94:337–343. http://dx.doi.org/10.1177/0022034514560588. [PubMed: 25503611]

45. Ge XP, Ma XC, Meng JH, Zhang CG, Ma KT, Zhou CY. Role of Wnt-5A in Interleukin-1β-Induced Matrix Metalloproteinase Expression in Rabbit Temporomandibular Joint Condylar Chondrocytes. Arthritis & Rheumatism. 2009; 60:2714–2722. http://dx.doi.org/10.1002/art.24779. [PubMed: 19714632]
Figure 1.
Prisma flowchart for selection of articles.
Table 1

Human studies.

| Author publication year country of study | Study population characteristics | Diagnosis diagnostic criteria | Gene(s) studied | Results | Study limitations |
|-----------------------------------------|---------------------------------|------------------------------|----------------|---------|-----------------|
| Planello, 2011 Brazil                   | Mean Age of Cases 42.82 ± 14.96 | Osteophytes, erosion, avascular necrosis, subchondral cyst, loose bodies, OA CT, Interview, MRI | MMP1, MMP3, MMP9 | Only MMP1 2G/2G genotype was found to be significant (P < 0.003). Effect of age on TMJ degeneration was significant (P < 0.002) | Small sample size to detect association of MMP3 gene |
| Huang, 2011 Japan                      | Mean Age of Cases 15.5 to 69.7  | TMJ clicking (disc displacement with reduction) or closed lock (disc displacement without reduction) and not having previous history of trauma, neoplasm and/or surgery in the TMJ; TMJ clicking used as controls Clinical evaluation, MRI | ANKH | Two alleles of ANKH-OR polymorphism were identified. ANKH-OR homozygotes were more likely to develop closed lock compared to controls (P = 0.011) | Calculation of minimal sample size was unattainable. Low response rate could have resulted in sampling bias. Application of cohort study would have explored the influence of age on TMD. High percentage of patients were unwilling to take a blood test for assessment. Study failed to indicate equivalence between fibrous ankylosis in mice and closed lock in humans |
| Kim, 2010 South Korea                  | Mean Age of Cases 31.45 ± 15.25 years | MPDS, IDD with reduction, IDD without reduction, OA. Osteoarthrosis RDC/TMD | ESR1 | No statistical difference between study group and control group (P > 0.5) | Small sample size |
| Ribeiro-Dasilva, 2009 Brazil           | Mean Age of Cases 31.1 ± 8.36 | Disc displacement with and without reduction, with limited mouth opening, without reduction and without limited mouth opening RDC/TMD | ESR1 | Presence of [GC] haplotype in ERα gene was higher in TMD with pain compared to control group (P = 0.0028) | Small sample size, admixed Brazilian population limits generalizability of data. Only data from articular pain included and not muscular pain |
| Matsumoto, 2008 Japan                  | Mean Age of Cases 50.11 | ID, OA NR | ADAMTS-5 | ADAMTS-5 is involved in deformation of the TMJ discs with ID and OA (P < 0.01) | Small sample size, limited use of TMJ disc cells |
| Helenius, 2004 Finland                 | Mean Age of Cases 43.57 | RA, MCTD, AS, SPA ARA 1987 for RA, Alarcon-Segovia for MCTD, MNYC for AS, ESSG for SPA | HLA-DRB1 | In the whole patient population, HLA-DRB1 allele was significantly associated with TMJ erosions (P = 0.0014) | Controls were not clinically or radiologically examined |
| Study population characteristics | Diagnosis diagnostic criteria | Gene(s) studied | Results | Study limitations |
|----------------------------------|------------------------------|----------------|---------|------------------|
| Ethnic status: Finnish           |                               | FGF2           | NR      |                  |
| Mean Age of Cases NR             | Synovial chondromatosis for cases; Open Reduction for controls NR |               |         |                  |
| N = 3: F = NR, M = NR            |                              |                |         |                  |
| Mean Age of Controls NR          |                              |                |         |                  |
| N = 3: F = NR, M = NR            |                              |                |         |                  |
| Ethnic status: Finnish           |                              |                |         |                  |
| Mean Age of Cases                 |                              |                |         |                  |
| Japanese 25.6                    |                              |                |         |                  |
| Koreans 28.5                     |                              |                |         |                  |
| N of Japanese = 105: F = 93, M = 12|                              |                |         |                  |
| N of Koreans = 41: F = 23, M = 18 |                              |                |         |                  |
| Ethnic status: East Asian        |                              |                |         |                  |
| Mean Age of Controls Japanese 25.6|                              |                |         |                  |
| Koreans 28.5                     |                              |                |         |                  |
| F = 141, M = 53                  |                              |                |         |                  |
| N of Koreans = 181: F = 70, M = 111 |                              |                |         |                  |
| Ethnic status: East Asian        |                              |                |         |                  |
| Mean Age of Cases 21.1 ± 12.1    | Difficulty or pain while opening mouth, locking of jaw, pain, noises, unusual bite, frequent headache, MRI findings- | TNF             | NR      | No radiological diagnosis |
| N = 98: F = 75, M = 23           | Anamnestic Questionnaire clinical investigation, MRI |                |         |                  |
| Mean Age of Controls 22.9 ± 10.1 |                               |                |         |                  |
| N = 132: F = 104, M = 28        |                               |                |         |                  |
| Ethnic Status: Turkish           |                               |                |         |                  |
| Mean Age of Cases: 22.8 ± 3.6 years; |                               |                |         |                  |
| N = 93: F = 73, M = 20          |                               |                |         |                  |
| Mean Age of Controls 21.10 ± 3.7 |                               |                |         |                  |
| N = 91: F = 61, M = 30          |                               |                |         |                  |
| Ethnic Status: Turkish           |                               |                |         |                  |

NR: Not Reported; RA: Rheumatoid Arthritis; MCTD: Mixed Connective Tissue disease; AS: Ankylosing Spondylitis; SPA: Spondyloarthropathy; ARA: American Rheumatism Association; MNYC: Modified New York Criteria; ESSG: European Spondyloarthropathy Study Group; ID: Internal Derangement; OA: Osteoarthritis; MPDS: Myofacial Pain Dysfunction Syndrome; MRI: Magnetic Resonance Imaging; CT: Computed Tomography.
| Author publication year | Animal studies | TMD condition method of inducing | Gene studied | Results | Study limitations |
|-------------------------|----------------|-------------------------------|--------------|---------|------------------|
| Jing [25] 2014          | Mice           | TMD Mutant condylar cartilage  | Oxx          | Defect in coupling chondrogenesis and osteogenesis in cKO mice, calcified cartilage in hypertrophic zone, few signs of endochondral bone formation, disorganized intramembranous bone | NR |
| Ishizuka [26] 2014      | Mice           | OA-like changes               | Samp8        | Abnormal condylar organization, condylar degeneration, decreased chondroprogenitor cell proliferation and increased cell death | NR |
| Li [27] 2014            | Mice           | Knock-in mouse line with replacement of mouse Shox2 by the human SHOX coding sequence | Shox2        | Genetic association with congenital articular disc degeneration, suggesting that SHOX2 represents a susceptible locus for OA of the TMJ | NR |
| Jiao [28] 2014          | Mice           | Cartilage degradation         | Tgfb1        | Abnormalities in the subchondral bone which induced cartilage degradation | Small sample size |
| Inman [29] 2013         | Mice           | Syngnathi, agenesis of TMJ    | Foxc1        | Foxc1−/− mutant mice exhibit bilateral fusion of the upper jaw zygomatic complex to the dentary bone (syngnathia) | NR |
| Ricks [30] 2013         | Mice           | Heterozygous mice (Dmm+/−) of a C3H strain were crossed to produce wildtype(+/+) and Dmm+/− mice | Col2a1       | TMJ in Dmm+/− mice displayed premature articular cartilage and greater defects in chondrocyte arrangement, known biomarkers of OA were significantly expressed (P < 0.01) | NR |
| Yasuda [31] 2012        | Mice           | Abnormal endochondral ossification and Class 3 dental malocclusion, shortening of cranial base | Fgfr3        | Articular disc fused with temporal bone, articular surface developed fissures, defects in endochondral ossification, abnormal gelenoid fossa, defective trabecular bone formation | NR |
| Purcell [32] 2012       | Mice           | NR Inactivation of genes Spry1, Spry2 | Spry1, Spry2 | Combined inactivation of Spry1 and Spry2 genes leads to absence of gelenoid fossa and overgrowth of lateral pterygoid and temporalis muscles | NR |
| Huang [13] 2011         | Mice           | Internal derangement Commercially bred ank/ank mutant mice were purchased | Ank          | Fibrous ankylosis, narrower and/or ankylosed superior and inferior synovial cavities filled with fibrous connective tissue throughout the entire joint space | Utilization of 3-to-5 month old mice in this study might be responsible for the absence of erosive changes in the TMJ |
| Embree [33] 2011        | Mice           | OA Differential gene expression analysis was performed with RNA extracted from 3-week old WT and bgn−/+; fmod−/− mice | 483346E15Rik Aebp1, Ahsp Angpt1, Arsk Bace1, Bgn Cartp, Col2a1 Col9a1, Col9a3 Fmod, Hapln1 | The microarray analysis discovered 22 genes differentially expressed in bgn−/+; fmod−/− mouse model that could be involved in disease initiation. 5 genes (Cartpt,Shp1, Arsk, Stc4a1, Ptprv) changed in the mouse models and are related to osteoclast function/differentiation and bone turnover | NR |
| Author publication year | Animal studies | TMD condition method of inducing | Gene studied | Results | Study limitations |
|-------------------------|----------------|---------------------------------|-------------|---------|------------------|
| Purcell [34] 2009       | Mice           | Targeted disruption of the Gli2 zinc finger domain (Gli2\textsuperscript{zfd/zfd}) Crossbreeding | LOC 344564, Matn3, Mrpl30, Pfl1, Pprv, Rps19, Sfrp1, Slc4a1, Tspan33 | TMJ disk was missing, small condyle, cellular organization of growth plate was lost | NR |
| Gu [35] 2008            | Mice           | Inactivation of Shox2 Shox2 conventional knock out mice and mice with floxed Shox2 allele were generated. Wnt1-Cre;Shox2\textsuperscript{f/f} obtained by mating | Shox2 | Dysplasia of glenoid fossa, congenital TMJ ankylosis | NR |
| Shibukawa [36] 2006     | Mice           | Absence of articular disc Absence of joint cavities Crossbreeding and induced mutation | Ihh | Mandible development was defective, condyle zonal architecture was abnormal, complete absence of functional disc and joint cavity | NR |
| Meng [37] 2005          | Mice           | Surgical lesion on discs, gene expression profile | Angpt1, Aqp3, Baalc, Casr, Cav, Chad, Cldn11, Cis, Ctx, Crabp2, Cspg2, Dkk3, Dpt, Egln3, Eln, Gda, Gda, Hg1, Hspca, Htr2a, Igfbp5, Igfbp6, Il1ra1, Lg11, Lg11, Lib, Meox2, Mmp3, Nb11, Nol, Nrd11, Ns, Ocm1, Plat, Prelp, Prx2, Pthlh, Sgcn, Serpin1, Sfrp4, Sod3, Spin2c, Spp2, Tgb1, Thbs4, T11frs1, Tmn1, Tmn2 | Swelling, superficial fibrillation, early osteoarthritic changes | NR |
| Xu [38] 2003            | Mice           | Cartilage Degeneration Heterozygous cho+/− mutant mice | cho | At age 6 months OA-like changes became more severe, including flattening of the condylar head, loss of proteoglycans, and a reduced hypertrophic zone | NR |
| Gu [39] 2014            | Mice           | Apoptotic cells Wnt1-Cre; Bmpr1a\textsuperscript{−/−} embryos obtained by crossing Wnt1-Cre; Bmpr1a\textsuperscript{−/−} with Bmpr1a\textsuperscript{f/f} line | Bmpr1a | Agenesis Failed formation of functional fibrocartilage layer, failure of disc separation from hypoplastic condyle | NR |
| Li [40] 2014            | Mice           | Dysplasia Cross of Wnt-Cre mice with pMesShox2 mice | Shox2 | Increased number of apoptotic cells in the glenoid fossa causing glenoid fossa dysplasia, dysplasia of condyle | NR |
| Author publication year | Animal studies | TMD condition method of inducing | Gene studied | Results | Study limitations |
|-------------------------|----------------|--------------------------------|--------------|---------|------------------|
| Wang [41] 2014          | Mice           | TMJ Cartilage Degeneration Crossbreeding to generate β-catenin (ex3), Gq/ER, Tamoxifen administered | Ctnnb1 | Significant reduction in TMJ joint space, cartilage thickness was significantly decreased, increase in cartilage degrading enzymes, OA-like phenotype | NR |
| Meng [42] 2007          | Rats           | OA Surgically, lesions created in discs | Aqp1, Aqp3 | High expression and different localization of AQP3 in OA cartilage. No significant difference between OA and normal controls | NR |
| Yu [43] 2012            | Rats           | Condyle cartilage Degeneration Occlusal treatment carried out to induce degenerative changes in the mandibular condylar cartilage | Igf1, Gfr1, Igfbp3 | Obvious OA-like changes were observed in 2 week female experimental group than those in control group (P < 0.01) and 2 week male experimental group (P < 0.05), Expression of IGF1 in the 2 week females was lower than males (P < 0.01), IGFR1 was significantly lower in 2 week female (P < 0.05) but increased in 2 week male experimental group, IGFBP3 in all female subgroups was significantly lower than that in their male counterparts | Differences in occlusion between rats and humans |
| Asakawa-Tanne [44] 2015 | Porcine        | Disc indentation Porcine cranial heads were subjected to cyclic loading | Cox2, Il1b, Mnp1, Mnp3, Mnp9 | Compromised lubrication in TMJ is associated with altered frictional properties and surface wear of condylar cartilage | Amount and nature of loading used in the study do not represent the actual TMJ dynamics in vivo |
| Ge [45] 2009            | Rabbit         | Cartilage destruction Primary rabbit condylar chondrocytes were treated with IL-β, purified WNT5A protein, or both and transfected with Wnt5a expression vector | Wnt5a | WNT5A is associated with cartilage destruction by promoting expression of MMP1, MMP3, MMP9, MMP13 | NR |

NR: Not reported; OA: Osteoarthritis.