Genetic overlap between temporomandibular disorders and primary headaches: A systematic review

Diogo Cruz, Francisca Monteiro, Maria Paço, Manuel Vaz-Silva, Carolina Lemos, Miguel Alves-Ferreira, Teresa Pinho

Abstract

Primary headache disorders (PHD), specifically migraine, are strongly associated with temporomandibular disorders (TMD), sharing some patterns of orofacial pain. Both disorders have significant genetic contributions already studied. PRISMA guidelines were followed to conduct this systematic review, which comprehensively summarize and discuss the genetic overlap between TMD and PHD to aid future research in potential therapy targets. This review included eight original articles published between 2015 and 2020, written in English and related to either TMD and/or PHD. The genes simultaneously assessed in PHD and TMD studies were COMT, MTHFR, and ESR1. COMT was proved to play a critical role in TMD pathogenesis, as all studies have concluded about its impact on the occurrence of the disease, although no association with PHD was found. No proof on the impact of MTHFR gene regulation on either TMD or PHD was found. The most robust results are concerning the ESR1 gene, which is present in the genetic profile of both clinical conditions. This novel systematic review highlights not only the need for a clear understanding of the role of ESR1 and COMT genes in pain pathogenesis, but also it evaluates their potential as a promising therapeutic target to treat both pathologies.

1. Introduction

The expression ‘temporomandibular disorders’ (TMD) is an “umbrella term” that involves alterations of the temporomandibular joint (TMJ), masticatory muscles, and related structures. Among its most frequent muscles, we can find limitations in the mandible motion, regional pain in the face, and the preauricular zone [1]. It affects up to 31% of the adult population and approximately 11% of the children [2,3], but only a tiny portion of them seek treatment [4].

Although this condition may affect children and adolescents, its peak occurrence is between 20 and 50 years old, depending on the specific TMD condition [5,6]. It usually affects more women than men, with female-to-male ratios between 2:1–8:1 [7–9].

Many of the clinical aspects of these disorders overlap with other medical conditions in otology, neurology, and psychiatry [10]. Indeed, TMD and primary headache disorders (PHD), including migraine, cluster headache and tension-type headache, usually cause similar oral parafunctional behaviors and share some
pathophysiological mechanisms [11,12]. Both are highly prevalent and disabling [13–15]. Together, these disorders present a detrimental synergistic effect, and the presence of either disorder is considered a risk factor for the other [16–19], also increasing the probability of progression to a chronic condition [20–22].

The prevalence of headaches in the population with TMD is about 67%, while in the general population, the prevalence of headaches is around 46% [23,24]. Besides that, both disorders have a major genetic component associated with the pathophysiological mechanisms’ onset [25–27]. Thus, this evidence suggests that common genes may genetically predispose the development of TMD and PHD.

Gathering this information and knowing the high publication rate on the genetic of these two disorders lately, we considered it pertinent to conduct a systematic review comparing the genes involved in each of the referred pathologies in studies published thereafter. In this sense, we intended to analyze the recent advances on the genetic profile of PHD and TMD to comprehensively discuss the potential of overlapping genes to work as a therapeutic target. This will certainly aid the development of novel diagnostic and/or monitoring techniques needed to revolutionize the treatment of both disorders simultaneously in the early stages of these disorders.

2. Methods

2.1. Review guidelines and registration

This systematic review was elaborated following the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines [28]. The study protocol was registered in the PROSPERO database (CRD42020222922).

2.2. Eligibility criteria

The focused question was defined according to the Population characteristics, Intervention type, Comparison parameters, Outcomes and Study design (PICOS) strategy, as presented in Table 1.

Therefore, the following focused questions of this systematic review were defined as (i) “Is there a genetic overlap between primary headaches and temporomandibular disorders?” and (ii) “If so, what are the genetic factors involved?”. In this sense, the eligibility criteria for the studies to be included were defined accordingly with PICOS strategy and completed by the criteria described in Table 2.

2.3. Search strategy

A bibliographic search was conducted in three databases: PubMed, Scopus, and Web of Science, until December 2020. Articles published between 2015 and 2020 and written in English were selected. The following keywords and MeSH terms were employed in the search strategy:

i) For genes and pathways associated with PHD: (“primary headache disorder” OR “primary headache disorders” OR “migraine disorders” OR “tension type headaches” OR “cluster headache”) AND (“genetic analysis” OR “genes”) AND (“human” OR “humans”) AND (2015/01:01:2020/12/31).

ii) For genes and pathways associated with TMD: (“temporomandibular disorder” OR “temporomandibular disorder” OR “temporomandibular dysfunction” OR “temporomandibular dysfunctions” OR “craniofacial pain”) AND (“genetic analysis” OR “genes”) AND (“human” OR “humans”) AND (2015/01:01:2020/12/31).

2.4. Articles selection and data collection

An advanced search was performed using the search terms previously exposed. Duplicates were manually removed. The title and abstract of the identified and potentially relevant articles were submitted to a preliminary evaluation to determine whether they met the study's intended purpose. This task was carried out independently by two authors (DC and MAF) for genes and pathways associated with PHD, and by (DC and TP) for genes and pathways associated with TMD. The clinical studies that met the inclusion criteria were fully analyzed and evaluated for eligibility. Then, other eligible articles were identified from the reference list of all included articles (manual screening). Finally, data were extracted and chronologically organized in Table 3 (PHD) and Table 4 (TMD) among the full-text selected articles.

2.5. Quality assessment

Two authors (DC and MAF) independently assessed the quality of the selected articles based on six broad perspectives: selection bias; study design; cofounders; blinding; data collection method and withdraws; and dropouts. EPHPP Quality Assessment Tool was used for randomized controlled trials.

3. Results

From the included studies, a brief description of the study design and sample is provided, followed by identifying the genes involved in the pathophysiology of either PHD (Table 3) [29–80] or TMD (Table 4) [81–107] and their respective pathways. Then, the main findings and the associated conclusions are reported.

3.1. Articles’ selection

The electronic literature search resulted in 998 articles found for primary PHD and/or TMD. After duplicates removal, 948 articles remained. Titles and abstracts were assessed, and 804 articles were selected for further evaluation. These studies were thoroughly read and analyzed individually for eligibility, from which 79 articles were selected and included in this systematic review. Besides the articles selected from this procedure, a manual search was carried out in the bibliography of the included studies to identify and retrieve articles that were not found in the electronic search. This selection process is described in Fig. 1.

Table 1

| PICOS Categories | Applied Criteria |
|------------------|------------------|
| **Population**   | Human patients clinically diagnosed with primary headaches and/or temporomandibular disorders |
| **Intervention** | Genetic screening/sequencing/characterization |
| **Comparison**   | Healthy patients in whom the genetic study has been carried out that were compared to patients either having temporomandibular disorders and/or primary headaches |
| **Outcomes**     | Genetic profile of patients with primary headache and/or temporomandibular disorders |
| **Study design** | Randomized trials, cross-sectional studies, prospective and retrospective studies, case-control and case-studies |
3.2. Profile of the reviewed studies

Data from the included studies about genes and pathways associated with PHD and TMD was organized and systematized in Tables 3 and 4, respectively. The reported outcomes were considered significant for a significance level of 0.05, and a tendency for improvement was indicated as such.

The main features and findings of the 79 selected articles are systematized in Tables 3 and 4. Of these studies, 65 articles were case-control studies, being 51 of them related to PHD and 24 related to TMD. Also, four cohort studies were reviewed, of which three were related to TMD and one to PHD. Moreover, six genome-wide association studies (GWAS) studies were included (four PHD and two TMD studies). Finally, one PHD prospective-observational study was also revised.

From a genetic point of view, the catechol-O-methyltransferase (COMT) gene was the most frequent gene being investigated in the selected period. Indeed, four studies associated with PHD [29,48,51,67,72] and six studies in TMD patients [81,83,86,89,90] have reported the role of COMT in the onset/progression of the disease, resulting in a total of 10 articles. The estrogen receptor 1 (ESR1) gene was also evaluated in six studies (two and four associated with PHD [52,56] and TMD [84,87,95,108], respectively). At last, the methylenetetrahydrofolate reductase (MTHFR) gene was studied twice, once in each pathology.

3.3. Overview of the included studies

A schematic representation of the collected data using the Venn diagram is depicted in Fig. 2. This illustration reveals that the reviewed studies present a genetic overlap for three specific genes (i.e., ESR1, MTHFR, and COMT) in the genetic profile of PHD and TMD patients. The possibility of these three genes being associated with the reviewed pathological conditions will be addressed during the discussion.

3.4. Quality assessment data

Concerning the methodological quality assessment, the Newcastle–Ottawa Quality Assessment Scale criteria was used to classify the reviewed studies: (i) a total of 54 studies (n_PHD = 35 and n_TMD = 20) were scored as having a “good quality” (case-control and three cohort studies), (ii) 15 studies were classified as “fair quality” (n_PHD = 10 and n_TMD = 5), and (iii) nine studies (n_PHD = 7 and n_TMD = 2) were considered to have “poor quality”. The majority of the included case-control studies presented a weak global rating due to blinding issues or because of the lack of a selection of controls, whereas some studies did not report the non-response rate. On the other hand, all the cohort studies fail in the definition of accurate follow-ups, while other issues in the selection of the non-exposed cohort and in the assessment methods of the outcomes were highlighted. These aspects should be addressed in future clinical trials in the field to guarantee transparency and reduce the risk of bias within the relevant assessments in each study. The complete quality assessment data can be consulted in Supplementary Tables 1 and 2.
### Table 3

Systematized information on genes and pathways associated with Primary Headache Disorders.

| Publication data | Study Design | Diagnosis of samples (n) | Gene/Allele | Under Results | Conclusions |
|------------------|--------------|-------------------------|-------------|---------------|-------------|
| *Fernández-De-Las-Peñas, C., et al.* (2019) | Case-control study | Women with: CTTH (50); & controls (50) | COMT Val158Met (rs4680) | - no significant difference between women with and without headache. | - trend for association between CH and the Met/Met genotype was lower in disease groups compared to controls. |
| *Fourrier, C. et al.* (2019) | Case-control study | MO (198); MA (99); & controls (204) | HCRTR2 | - the allele frequency was lower in diseased groups compared to controls. | - trend for association between CH and the Met/Met genotype was lower in disease groups compared to controls. |
| *Barbanti, P., et al.* (2019) | Case-control study | MO (199); MA (71); & controls (155) | DBH 19-bp I/D | - DBH 19-bp I/D SNP did not correlate with migraine susceptibility. | - two differentially expressed genes were found: NMNAT2 and RETN (not replicated in an independent cohort). |
| *Ramroodi, N., et al.* (2018) | Case-control study | MO (112); MA (78); & controls (200) | CD40 (rs1883832) | - CD40 rs1883832, TC genotype may have a role in migraine susceptibility. | - no clear distinct difference in gene expression profiles of peripheral blood mononuclear cells was found. |
| *Kaur, S., et al.* (2019) | Case-control study | MO (107); MA (43); & controls (150) | TRPM8 (rs1016699) | - a significantly significant difference in migraineurs was found in the response to the treatment of Chronische Tension-type Kopfschmerzen (CTTH) and CH. | - no significant difference was found at rs1016699 variant. |
| *Chen, S. P., et al.* (2018) | Case-control study | MO (52); MA (54); & controls (105) | TRPM8 (rs1016699) | - a statistically significant difference in migraineurs was found for rs1016699 variant. | - no significant difference was found at rs1016699 variant. |

(continued on next page)
| Publication data | Study Design | Diagnosis of samples (n) | Genes/Alleles Under Study | Conclusions |
|------------------|--------------|--------------------------|---------------------------|-------------|
| Bacchelli et al. (2016) | Case-control study | CH (77); MA (23); controls (100) | ABCAPRI, MME | Association between ABCAPRI and MME gene variants and migraine. |
| Kaur, S., et al. (2018) | Case-control study | MO (77); MA (23); controls (100) | F5, F8, F9, F10 | Association between F5, F8, F9, and F10 genes and migraine. |
| Garcia-Martín, E., et al. (2018) | Case-control study | MO (99); MA (98); controls (278) | GABRR1, GABRQ | Association between GABRR1 and GABRQ genes and migraine. |
| Ozan, B., et al. (2018) | Case-control study | CH (112); controls (92) | GABRQ | Association between GABRQ gene and migraine. |
| Ran, C., et al. (2017) | Case-control study | CH (542); controls (581) | ADCYAP1R1, MME | Association between ADCYAP1R1 and MME genes and migraine. |
| Sutherland, H. G., et al. (2017) | Case-control study | Menstrual related migraine (268); controls (142) | COMT, CYP19A1, CYP1A1 | Association between COMT and CYP19A1 genes and migraine. |
| Meza-Velázquez, R., et al. (2017) | Case-control study | CYP1A1 | Association between CYP1A1 gene and migraine. |
| Publication data | Study Design | Gene/Allele | Results | Conclusions |
|------------------|--------------|-------------|---------|-------------|
| An, X. K. et al. (2017) | Case-control study | MO (494); MA (87); Controls (533) | MEF2D (rs2274616) | - significant association between MO and migraine susceptibility; - ESR1 rs2234693 and rs9340799 are associated with menstrual-related migraine. |
| Takigawa, H. et al. (2017) | Case-control study | MO (152); MA (71); Tension-type headache (86); & controls (191) | COMT (rs4680, rs4633, rs6267, rs6270, rs74062) | - no significant differences were found in any of the five SNPs in COMT among the patient groups and controls. |
| An, X. et al. (2017) | Case-control study | MO (420); MA (74); Menstrual related migraine (126); & controls (533) | ESR1 (rs2234693, rs9340799) | - increased expression in rs2234693 and rs9340799 in ESR1 gene between diseased patients and controls; - haplotype analysis shows that rs2234693–rs9340799 TA haplotype is a risk haplotype for migraine; - rs2234693 in ESR1 alone to be a crucial candidate in migraine susceptibility. |
| Juhasz, G. et al. (2017) | Cross-sectional study | 2426 participants: migraine (144) or migraine-related symptoms (668) | CNR1 (rs806398, rs1004353, rs409356) | - association between the rs806398 in the CNR1 gene promoter region and migraine. |
| Sazci, A. et al. (2016) | Case-control study | Migraine (433); Controls (229) | NNMT (rs694539) | - significant association between NNMT gene rs694539 and female migraineurs; - NNMT gene rs694539 variant is a genetic risk factor for migraine. |
| Fuh, J. L. et al. (2016) | Case-control study | Migraine patients with Restless leg syndrome: MO (182); & MA (29). | MEIS1 (rs2300478) | - MEIS1 augmented the risk of restless leg syndrome only in the patients who experienced Episodic Migraine and not those experiencing Chronic Migraine. |
| CoŞkun, S. et al. (2016) | Case-control study | Migraine (142); & controls (141) | CYP1B1 (rs1010066) | - CYP1B1 gene interacts with life stress increases the risk of headache with nausea, - CYP1B1 gene interacts with RLE on headache. |
| Yuvel, Y. et al. (2016) | Case-control study | MO (122); MA (23); & controls (139) | 5-HTTR (rs131929) | - 5-HTTR (rs131929) can be a genetic risk factor for migraine in a Turkish population. |
| Publication data | Study Design | Diagnosis of samples (n) | Gene/Allele Under Study | Results | Conclusions |
|------------------|--------------|--------------------------|-------------------------|---------|-------------|
| **Sezer, S., et al. (2016)** [58] | Case-control study | MO (167); MA (33); & controls (267) | DBH (rs161115, rs6271, rs1108580) | the allele of rs3813929 was more common in the migraine group. - association for the allelic and genotypic frequency distribution between the rs6271 DBH and migraine. | - DBH gene rs6271 may be one of the many genetic factors for migraine susceptibility in the Turkish population. - U-II may play a role in migraine pathogenesis; - Th21Met SNP was associated with the risk of migraine disease; - association of several SNPs with migraine, suggesting that migraine susceptibility loci may be risk factors for severe migraine traits. |
| **Geyik, S., et al. (2016)** [59] | Case-control study | MO (186); Controls (171) | UTS2 Thr21Met, Ser89Asn, MDR1 C3435T | - plasma U-II levels were significantly higher in MO patients; - association between the Thr21Met SNP in the UTS2 gene and migraine. | |
| **Esserlind, A. L., et al. (2016)** [60] | Case-control study | MO (1010); MA (796); & controls (6415) | MEF2D (rs2274116), LRPI (rs1172113) | - association between gene expression (MEF2D and LRPI) and migraine; - two SNPs (rs2274116 and rs1172113) conferred risk of many lifetime attacks of migraine in the case-control analysis. | |
| **Fear, A. L., et al. (2016)** [61] | Case-control study | CH (65); & controls (263) | CHRNA3 | - analysis of the sequences did not evidence new mutations with a functional effect on the development of disease. | |
| **Gasparini, C. F., et al. (2015)** [62] | Case-control study | MO (219); medication overuse headache (130); & controls (209) | RAMP1 (rs7590387) | - RAMP1 rs7590387 showed a lower risk of episodic migraine transformation into medication overuse headache. - carriers of RAMP1 rs7590387 GG were found at lower risk of developing medication overuse headache. | - CH patients seem to have a stronger genetic predisposition to develop smoke dependence. - RAMP1 rs7590387 might have a role in the transformation of episodic migraine into medication overuse headache. |
| **Jia, S., et al. (2015)** [63] | Case-control study | MO (252); MA (17); & controls (374) | TNFSF10 (rs35975099) | - there were no significant relationships between allele or genotypic frequency and gene SNP rs35975099 in migraine. - DAO SNP rs10156191 is associated with the risk of developing migraine, mostly in females. - two SNPs (rs4379368 and rs13208321) are potential genetic markers for migraine in this population. | - no functional significance of the TNFSF10 gene SNP rs35975099 in migraine pathogenesis. - DAO genotypes and allelic variants are associated with the risk for migraine in Caucasian Spanish people. - rs4379368 and rs13208321 are potential genetic markers for migraine in this population. |
| **Lin, Q., et al. (2015)** [66] | Case-control study | MO (238); MA (62); & controls (300) | FHL5 (rs13208321), C3orf10 (rs4379368) | - CT and TT genotypes were more frequent in the migraine compared with the control groups; - these genotypes were also more common in women with migraines than women without migraines; - CC genotype of rs4379368 and AA or AG genotype of rs1320832 were associated with a reduced risk of migraine. | - no evidence to support the involvement of RNA editing genes in migraine susceptibility in an Australian Caucasian population. |
| **De Marchis, M. L., et al. (2015)** [66] | Case-control study | MO (189); MA (65); CM (126); & controls (132) | COMT (rs4818, rs4680) | - rs4680 and rs4618 genotypic frequencies did not correlate with clinical migraine features. | - no evidence to support the involvement of RNA editing genes in migraine susceptibility in an Australian Caucasian population. |
| **Gasparini, C. F., et al. (2015)** [67] | Case-control study | MO (64); MA (227); & controls (314) | ADARB1 | - no significant association between any of the SNPs tested in the ADARB1 and ADARB2 genes in this study and the development of migraine. | - no evidence to support the involvement of RNA editing genes in migraine susceptibility in an Australian Caucasian population. |
| **Fang, J., et al. (2015)** [68] | Case-control study | Women with: MO (284); MA (47); & controls (330) | ADARB2, GRIA1 (rs2195450, rs548294) | - allele frequency of GRIA1 rs2195450 was statistically significant; - association between the MA subtype and MO subtype. | - confirmed association between GRIA1 (rs2195450) and female migraine (with and without aura) susceptibility in the Chinese Han population. |
| **Ofte, H. K., et al. (2015)** [69] | Case-control study | CH (149); & controls (432) | GRIA3 (rs3761555), PER3 VNTR | - no association between PER3 VNTR SNP and CH. | - no association between CH, PER3 VNTR SNP and chronotype. (continued on next page)
Table 3 (continued)

| Publication data | Study Design | Diagnosis of samples (n) | Gene/Allele Under Study | Results | Conclusions |
|------------------|--------------|--------------------------|-------------------------|---------|-------------|
| García-Martín, E., et al. (2015) [70] | Case-control study | MO (99); MA (98); & controls (308) | NOS1 (rs7977109, rs693534) | - the frequencies of rs7977109 and rs693534 genotypes and allelic variants were not associated with the risk for migraine. - genotype, allele and haplotype frequencies were not statistically different between chronic migraineurs and non-migraineurs. | - NOS1 rs7977109 and rs693534 variants are not linked with the risk for migraine in Caucasian Spanish people. - lack of association between oxidative stress-related genes SNPs and chronic migraine. |
| Gentile, G., et al. (2015) [71] | Case-control study | CM (96); & controls (45) | GSTT1, GSTM1, GSTP1, SOD2, CAT, eNOS, PON1, CYBA | - eight SNPs were significantly associated with Chronic Migraine and High Frequency Migraine in the two-stage phase; - none survived replication in the third stage. | - there were no significant findings for migraine chronification. |
| Louter, M. A., et al. (2015) [72] | Case-control study | Discovery stage: CM (262); & controls (2879). Second stage: HFM (226); & controls (2879). Third stage: CM or HFM (531); & controls (2491). | SCNNIA (rs5742912), CLOCK (rs3792803), Intergenic (rs21769), CALCA (rs9256), CALCRL (rs858746), RAMP1 (rs302680), ADCYAPI (rs267730, rs2299908) | - c.0.51 G>A [p.Val191Met] was linked with the ATPIA2 gene that showed co-segregation with the phenotype in the family. - allele and genotype frequency of the 2 ADH4 mutations was significantly between sporadic CH and controls; - the same mutations were homozygous in CH patients from two families; - 2 novel rearrangements that require the intron regions of TM6D and NRXN3 genes found in some sporadic and familial CH cases. | - confirmation the genetic heterogeneity of CH, proposing that mutations in the ADH4 gene and a novel rearrangement involving NRXN3 gene might be related to CH. |
| Oh, S. K., et al. (2015) [73] | Family study | Hearing loss and MO (12) | ATP1A2 | - a variant in Na+/K+-ATPase can be involved in both migraine and hearing loss. | - polygenic contribution to migraine risk in an isolated population; - specific SNPs (including rs171251) that regulate the expression of USMG5 are critical for mitochondrial function. - DNA methylation at RAMP1 promoter might play a role in migraine; - lower methylation level may be a risk of migraine in females. |
| Zarrilli, F., et al. (2015) [74] | Case-control study | CH (54); & controls (200) | ADH4, NRXN3 | - confirmation the genetic heterogeneity of CH, proposing that mutations in the ADH4 gene and a novel rearrangement involving NRXN3 gene might be related to CH. | - confirmation the genetic heterogeneity of CH, proposing that mutations in the ADH4 gene and a novel rearrangement involving NRXN3 gene might be related to CH. |
| Rodriguez-Acevedo, A. J., et al. (2015) [75] | Case-control study | Migraine (74); & controls (211) | USMG5 (rs171251) | - migraine polygenic risk score was associated with migraine case-control status in this population; - four genes were associated with the expression of the USMG5 gene. - no significant differences in CpG sites or units at RAMP1 promoter region between the migraine and control groups; - stratification analysis showed that methylation level related to the transcription start site CpG unit was higher in migraineurs with migraine family history compared to controls; - methylation level was lower in migraine female than that in healthy female. | - no evidence for association between rs2653349 and CH was found. |
| Wan, D. et al. (2015) [76] | Case-control study | MO (21); MA (5); & controls (25) | RAMP1 | - no significant association with CH was found. - genotype frequency of PTX3 was significantly different between the migraine patients and the control subjects; - CC variant homozygote genotype was | - no evidence for association between rs2653349 and CH was found. - association between the PTX3 rs3816527 gene with susceptibility to migraine only in men migraineurs. |
| Weller, C. M., et al. (2015) [77] | Case-control study | CH (575); & controls (874) | HCRTR2 (rs2653349) | - no significant association with CH was found. - no evidence for association between rs2653349 and CH was found. - association between the PTX3 rs3816527 gene with susceptibility to migraine only in men migraineurs. |
| Zandifar, A., et al. (2015) [78] | Case-control study | Migraine (103); & controls (148) | PTX3 (rs3816527) | - no evidence for association between rs2653349 and CH was found. - association between the PTX3 rs3816527 gene with susceptibility to migraine only in men migraineurs. | - no evidence for association between rs2653349 and CH was found. - association between the PTX3 rs3816527 gene with susceptibility to migraine only in men migraineurs. |

(continued on next page)
| Publication data | Study Design | Diagnosis of samples (n) | Gene/Allele Under Study | Results | Conclusions |
|------------------|--------------|--------------------------|-------------------------|---------|-------------|
| Jacobsen, K. K., et al. (2015)[79] GWAS | Bipolar patients having migraine (460); & bipolar patients without migraine (914) | NBEA (rs1160720) | statistically more frequent in the patients than in the controls; - C allele was not significantly more frequent in the patients. - one genome-wide significant association of rs1160720, an intronic SNP in the NBEA gene, although this was not replicated in a smaller sample of 289 migraine cases. - polygenic scores for schizophrenia was inversely associated with migraine, which could be attributed to rs4523957 in SRR encoding serine-racemase; - expression quantitative trait loci analyses of functional variants in SRR and gene-gene interaction analyses further supported the validity of this finding. | - no proof of association was found, suggesting that the association might be specific to migraine co-morbid with bipolar disorder. - a decreased versus increased activation of NMDA receptors may play a role in the etiology of schizophrenia, as well as in migraine. |
| Van der Auwer a, S., et al. (2015)[80] Polygenic scores study | Migraine and schizophrenia patients (3973) | SRR | | |

**Abbreviations:** 14q21: chromosome 14q deletion; 5-HTR2C: 5-hydroxytryptamine receptor 2C; ADARB1: adenosine deaminase RNA specific B1; ADARB2: adenosine deaminase RNA specific B2; ADCYAP1R1: ADCYAP receptor type 1; ADH4: alcohol dehydrogenase 4; ASTN2: astrotactin 2; ATP1A2: ATPase Na+/K+ transporting subunit alpha 2; C7orf10: succinate-hydroxymethylglutamate CoA-transferase; CALCA: calcitonin related polypeptide alpha; CAT: catalase; CH: Cluster Headache; CHRNA3: cholinergic receptor nicotinic alpha 3 subunit; CLOCK: clock circadian regulator; CM: Chronic Migraine; CNR1: cannabinoid receptor 1; COMT: catechol-O-methyltransferase; CTTH: Chronic Tension Type Headache; CYBA: cytochrome B-245 alpha chain; CYP: cytochrome P450; DDAO: D-amino acid oxidase; DBH: dopamine beta-hydroxylase; DLG2: discs large MAGUK scaffold protein 2; eNOS: endothelial nitric oxide synthase; ESR1: estrogen receptor 1; FETTH: Frequent Episodic Tension-Type Headache; FHLS: four and a half UM domains 5; FSHR: follicle stimulating hormone receptor; GABRA: gamma-aminobutyric acid type A receptor subunit s; GABBR: gamma-aminobutyric acid type B receptor subunit epsilon; GABRB: gamma-aminobutyric acid type B receptor subunit beta; GABBR2: gamma-aminobutyric acid type 2 receptor subunit rho-2; GABRR3: gamma-aminobutyric acid type A receptor subunit rho-3; GFRα1: GDNF family receptor alpha 1; GRIA: glutamate ionotropic receptor AMPA type subunit 1; GRIK2: glutamate receptor ionotropic kainate 2; GT1: glutatione S-transferase 1; GSTM1: glutatione S-transferase M1; GSTR1: glutatione S-transferase pi 1; GWAS: genome-wide association study; HCRTR2: hypocretin receptor 2; HCRTR2: hypocretin receptor 2; HCRTR2: hypocretin receptor 2; HFM: High Frequency Migraine; LRP1: low density lipoprotein receptor-related protein 1; MA: migraine with aura; MDR1: multidrug resistance mutation; MEF2D: myocyte enhancer factor 2D; MEIS1: Meis homeobox 1; MEME: membrane metalloendopeptidase; MOC: migraine without aura; mRNA: messenger RNA; MTHF: methylene tetrahydrofolate reductase; NBEA: neurobeachin; MNAT2: nicotinamide nucleotide adenyllytransferase 2; NNNMT: nicotinamide N-methyltransferase; NOS1: nitric oxide synthase 1; NRI1: nuclear receptor interacting protein 1; NRP1: neuropilin 1; NRXN3: neurexin 3; PER3: period circadian regulator 3; PON1: paraoxonase 1; PRDM16: PR domain containing 16; PTX3: pentraxin 3; RAMP1: receptor activity modifying protein 1; RELN: resistin; RLE: Recent Negative Life events; SCNN1A: sodium channel epithelial 1 subunit alpha; SNP: single-nucleotide polymorphism; SOD2: superoxide dismutase 2; SRR: serine racemase; - TNSF10: TNF superfamily member 10; TRPM8: transient receptor potential channel subfamily M member 8; TRPV1: transient receptor potential cation channel subfamily V member 1; USMG5: up-regulated during skeletal muscle growth 5 homolog; UTS2: urotensin 2; VNTR: variable number tandem repeat.
| Publication data | Study Design | Diagnosis of samples (n) | Gene/Allele Under Study | Results | Conclusions |
|------------------|--------------|--------------------------|-------------------------|---------|-------------|
| de Souza Tesch, R., et al. (2020)[81] | Case-control study | Muscular TMD (49); articular TMD (49); & controls (154) | COMT (rs9332377) ADRB2 (rs1042713) | - rs9332377 in the COMT gene was highly linked with the presence of muscular TMD; - rs1042713 in the ADRB2 gene was more frequent in the articular TMD group than in the muscular TMD group. | - Alterations in the COMT and ADRB2 genes are associated with the presence of chronic masticatory myofascial. |
| Nicot et al. (2020)[82] | Case-control study | Individuals with dentofacial deformities (128) with: normal condyle modeling (43) & abnormal condyle modeling (68) | ACTN3 (rs1671064, rs1815739, rs678397) | - Two significant genotype interrelations for ACTN3 rs1671064 (Q523R missense), rs678397 (intrinsic SNP) and one significant allele association rs1815739 (R977X nonsense). | - ACTN3 genotypes can influence ENP1 expression, as can changes in cartilage mechanical strain environments. |
| Slade et al. (2020)[83] | Case-control study | TMD patients with anterior disc displacement without reduction (124); & controls (126) | ESR1 (rs1643821) TNF-α (rs1800629) | - ESR1 rs1643821 was more expressed in patients with anterior disc displacement without reduction; - No significant differences in TNF-α rs1800629 in TMD patients compared to controls. | - Cumulative response curves proved higher efficacy for G-G homozygotes than for A:A homozygotes. |
| Dalewski et al. (2020)[84] | Case-control study | TMD patients with anterior disc displacement without reduction (124); & controls (126) | MMP1 (1G/2G, 2G/2G, 1G/1G) | - An association between the 2G allele of the 1607 1G/2G SNP of MMP1 gene and the presence of anterior disc displacement with reduction in Western Mexico patients; - The presence of the 2G allele could be considered as a risk factor for the development of anterior disc displacement with reduction. | - Patients with a genotype of ESR1 rs1643821 exhibited a decreased probability against anterior disc displacement without reduction; - rs1643821 is associated with susceptibility to the anterior disc displacement without a decrease in European Caucasians. |
| Rosales et al. (2020)[85] | Case-control study | TMD patients with anterior disc displacement with reduction (67); & controls (90) | COMT (rs4680) | - TNF A-308 was associated with TMD and SNP Val158Met influenced pain sensitivity of patients with TMD. | - TNFA-308 was associated with TMD and SNP I16-174 and SNP Val158Met influenced pain sensitivity of patients with TMD. |
| Pinto Fiamengui, L. M. S., et al. (2020)[86] | Cross-sectional study | TMD patients including myofascial pain, arthralgia and mixed diagnosis encompassing these ones and disc displacement (131); & controls (137) | IL6–174 COMT Val158Met TNF-α-308 | - SNP I16-174 envisioned higher pain sensitivity in the TMJ and in anterior temporals muscle; - SNP Val158Met influenced increase pain sensibility in the masseter muscle. | - SNP I16-174 was associated with TMD and SNP I16-174 and SNP Val158Met influenced pain sensitivity of patients with TMD. |
| Küchler, E. C., et al. (2020)[87] | Cross-sectional study | TMD teenager patients, 10–14 years old (139); & adults, 18–50 years old (93) | ESR1 (rs2234693, rs9340799) ESR2 (rs1256049) | - SNP Val158Met influenced increase pain sensibility in the masseter muscle. | - ESR2 is linked with TMD and may be a genetic marker for this condition in adult females. |
| Carpio Horta, K., et al. (2019)[88] | Cross-sectional study | Orthognathic surgery patients, class I, II and III (113) with: myofascial pain; disc displacement; or other TMD condition (number of participants in each group not described) | FGF3 (rs1893047, rs7932320) FGF3 (rs9332320) FGF10 (rs900379) FGF13 (rs931572) FGF13 (rs9074804) | - rs1206049 in ESR2 was associated with disc displacement and arthralgia in adults. - rs7932320 in FGF3 and rs900379 in FGF10 were associated with the presence of muscle disorder; - rs1893047 in FGF3, rs900379 in FGF10, and rs9074804 in FGF13 were linked with the presence of disk displacement; - rs1893047 and rs7932320 in FGF3, rs900379 in FGF10, and rs9074804 in FGF13 were associated with other TMD conditions. | - SNPs in FGF3, FGF10, and FGF13 genes were associated with temporomandibular disorders in a population with dentofacial deformities. |

(continued on next page)
| Publication data            | Study Design       | Diagnosis of samples (n)                                                                 | Gene/Allele Under Study                      | Results                                                                                                                                                                                                 | Conclusions                                                                                       |
|-----------------------------|--------------------|----------------------------------------------------------------------------------------|---------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|
| Brancher et al. (2019)[89]  | Case-control study | TMD adolescent patients, including myofascial pain, arthralgia and mixed diagnosis encompassing these ones and disc displacement (149); & controls (149) | 5HTT (rs3813024 & rs1042173) COMT (rs4633 & rs6269) | 5HTT rs1042173 was associated with painful TMD (arthralgia and myofascial pain); rs4633 and rs6269 were linked with myofascial pain and were borderline for painful TMD and disc displacement; COMT rs6269 had a borderline association for myofascial and disc displacement. | - SNPs in 5HTT and COMT are linked with TMD in adolescents.                                      |
| Nascimento et al. (2019)[90]| Case-control study | TMD patients having chronic myofascial pain (12); & controls (12)                      | COMT (rs6269, rs4633, rs4818, rs4680)         | TMD patients with the COMT 158Met substitution had higher pain sensitivity and longer pain chronicity.                                                                                                    | - COMT 158Met substitution concurrently influences pain sensitivity, chronicity, and dysfunctional µ-opioid receptor-mediated pathways in chronic TMD patients. |
| Bonato, L. L., et al. (2019)[91]| Case-control study | Patients with: myofascial pain and chronic arthralgia (42); TMJ disorders and chronic arthralgia (16); combined myofascial pain, TMJ disorders and chronic arthralgia (69); any TMD subgroup and without some other arthralgia (16); TMD-free and chronic arthralgia in any other joint (82); & controls (72) | COMT (rs9312377 ADRB2 (rs1042713) | rs9312377 in COMT gene and rs1042713 in ADRB2 gene was associated with the absence of myofascial pain.                                                                                                  | - Variations in the COMT, ADRB2, and HTR1A genes influence the presence of chronic pain and TMD.     |
| Smith et al. (2019)[92]    | Case-control study (GWAS) | TMD patients (999); & controls (2031)                                                | MRAS (rs5862730, rs1078661, rs10092633, rs34612513, rs2865059) | rs1078661 was significantly linked with TMD in men only; this association was nominally reproduced in a meta-analysis of 7 independent orofacial pain cohorts including 160,194 participants.                                                                 | - Genetic and behavioral data support a novel pathway by which genetically determined MRAS expression moderates the resiliency to chronic pain; this effect is male-specific and may contribute to the lower rates of painful TMD in males. |
| Yerliyurt et al. (2019)[93]| Case-control study | TMD patients (104); & controls (126)                                                  | TNF-β-252A/G (rs909253)                      | A trend was found for the TNF-β-252A/G variant in TMD patients compared to healthy controls.                                                                                                        | - TNF-β-252A/G variant may contribute to TMD development in a Turkish cohort.                      |
| Franco et al. (2019)[94]   | Case-control study | TMD adolescent patients including myofascial pain, arthralgia and disc displacement (152); & controls (104) | DRD2 - ANKK1                                | rs6275 was associated in a recessive model for disc displacement patients; rs6276 and rs1800497 presented only a borderline association between recessive and dominant models, respectively. | - rs6275 in DRD2 was associated with disc displacement in Brazilian adolescents.                 |
| Quinelato, V., et al. (2018)[95]| Case-control study | Patients with muscular TMD and chronic pain in other joint (42); TMJ disorders and chronic pain in other joint (16); TMD-free and chronic pain in other joint (82); & controls (72) | ESR1 (rs22273206, ESRR (rs1676303), ENPP1 (rs8538393) ESR1 (rs1643221, rs3020318) | rs22273206 in ESR1 gene was strongly associated with the risk of developing muscle TMDs and TMJ pain; rs1676303 in ESRR gene was associated with the presence of articular TMDs related with other chronic arthralgia. | - ESR1 and ESRR genes influence the presence of TMDs associated with chronic joint pain.           |
| Tümer et al. (2018)[96]    | Case-control study | TMD patients (100); & controls (110) (different subgroups not discriminated)          | IL-1Ra VNTR                                 | - IL-1Ra genotype distribution and allele were more common in TMD patients, than controls; frequency of alleles 1 and 4 was higher in diseased patients, whereas alleles 2 and 3 had a lower frequency in patients with TMD. | - VNTR variant related to IL-1Ra gene showed a strong pattern of association with TMD.           |
| Publication data | Study Design | Diagnosis of samples (n) | Gene/Allele Under Study | Results | Conclusions |
|------------------|--------------|--------------------------|-------------------------|---------|-------------|
| Tumer et al. (2017)[97] | Case-control study | TMD patients including masticatory muscle disorders, TMJ pain, alone or combined with each other and also combined with headache (100); & controls (105) | NR3C1 gene Bcl1 (rs41423247) | - No significant difference in genotype and allele frequencies between patients and controls; Genotypes in rs41423247 were associated with pain rating scale. - OPG gene showed an association between specific genotypes and an increased risk of presenting chronic arthralgia associated with articular TMD; - NR3C1 Bcl1 variant did not show any variation between the TMD and the control groups, but it could be correlated with pain intensity in patients. |
| Bonato et al. (2017)[98] | Case-control study | Patients with: articular TMD and systemic arthralgia (85); no articular TMD and systemic arthralgia (82); articular TMD and no systemic arthralgia (21); & controls (72) | OPG (rs11573919, rs11573875, rs11573854, rs11573838, rs11573817, and rs11573816) RANK (rs474369, rs9498322, rs904762, rs6920383, and rs237033) RANKL (rs492956, rs13215304, and rs12660731) | - OPG gene showed an association between specific genotypes and an increased risk of presenting chronic arthralgia associated with articular TMD; - A propensity towards an association of the OPG gene haplotype with an increased risk of developing chronic joint pain, even in the absence of TMD; - For the RANK gene, one haplotype was associated with the lowest risk of presenting chronic joint pain in people without TMD. - Changes in the OPG and RANK genes influence the presence of chronic joint pain in individuals with and without TMD. |
| Sanders et al. (2017)[99] | Case-control study (GWAS) | TMD patients (769); & controls (9384) | SGCA (rs4794106) RXP2 (rs60249166, rs1531554) DMD (rs73460075) SP4 (rs73271865) | - SGCA rs4794106 was suggestive in the discovery analysis and replicated in the Brazilian cohort; - RXP2 rs60249166 - replicated among females in the meta-analysis; - RXP2, rs1531554 - replicated among females, as well as replicated in meta-analysis of both sexes; - DMD rs73460075, SP4 rs73271865 were identified in the discovery cohort, but neither of these was replicated. - Several of these variants reside in loci that regulate processes relevant to TMD pathological processes. |
| Furquim et al. (2016)[100] | Case-control study | TMD patients including articular disc displacement (with and without reduction), inflammatory articular disease and masticatory muscle disorders (152); & controls (91) | TNFA-308 (rs1800629) | - TNFA-308 SNP is positively correlated with TMD; - Subjects with TMD had a 2.87 times greater chance of having the GA genotype than did the control group; - Rare A-allele homozygotes demonstrated decreased pain sensitivity for the TMJ and anterior fascicle of the temporal muscle in the pressure pain threshold test. | - Association between the TNFA-308 (rs1800629) and TMD. |
| Nicot R et al. (2016)[101] | Case-control study | Orthognathic surgery patients: pre-operative TMD including myalgia, arthralgia and articular disc displacement (27); & controls (74) | ENPP1 (rs858339) ESRI (rs1643821) | - ESRI rs1643821 is a risk factor for dysfunctional worsening after orthognathic surgery; - TT genotype of ENPP1 gene rs858339 is a protective factor against TMD in a population of patients with dentofacial deformities; - AF genotype was identified as a risk factor of TMD with respect to the rest of our population. | - ESRI rs1643821 is a risk factor for dysfunctional worsening after orthognathic surgery; - ENPP1 rs858339 is a protective or risk factor against TMD in patients with dentofacial deformities or in rest of our population, respectively. |
| Table 4 (continued) |
|---------------------|
| Study Design        | Diagnosis of samples (n) | Gene/Allele Under Study | Results |
| Renaldo et al. (2006) | Case-control study       | Patients with: RCD and TMD-free (16); RCD and TMD (49); & controls (30) | MMP-1 SNP genotypes and allele frequencies in TMD patients compared to controls. |
| Luo, S., et al. (2015) | Case-control study       | Patients with: unilater al anterior disc displacement with reduction (141); with or without TMJO A. | MMP-1 - The susceptibility of 2G2G genotype carriers to ADDWOR with or without TMJO A was considerably higher than that of other genotype carriers. |
| Milosevic, N., et al. (2015) | Case-control study       | Patients with: anterior disc displacement with reduction (18); osteoarthritis (12); & controls (7) | MMP-1 - C-1562T SNP in the promoter region of the MMP-1 gene, the GSTM1 null, as well as the GSTT1 null genotype and lower muscle activity were associated with TMD. |
| Xiao, J. L., et al. (2015) | Case-control study       | Patients with: TMJO A; & controls (20) | MMP-1 - Increased expression levels of DKK-1 and VEGF in synovial fluid from patients with TMJO A. |
| Huang et al. (2015) | Case-control study       | Patients with: TMJ clicking (21); & controls (20) | MMP-1 - ANKH (ANKH-OR allele 1 and ANKH-TR allele 1) SNPs were associated with TMJ clicking and asymptomatic individuals. |

Abbreviations: 5HTT: sodium-dependent serotonin transporter; ACTN3: actinin alpha-3; AKT: protein kinase B; ADRB2: beta-2 adrenergic receptor; ANKH: ANKH inorganic pyrophosphate transporter; ANKK1: ankyrin repeat and kinase domain 1; ESR: estrogen receptor; ESR1: estrogen receptor alpha; ESRRB: estrogen related receptor beta; FGF: fibroblast growth factor; GDF5: growth differentiation factor 5; GSTM1: glutathione S-transferase mu 1; GSTT1: glutathione S-transferase theta 1; HIF-1 alpha: hypoxia inducible factor 1 alpha; IL: interleukin; MMP: matrix metalloproteinase; MRAS: muscle RAS oncogene homolog; MTHFR: methylenetetrahydrofolate reductase; NR3C1: nuclear receptor subfamily 3 group C member 1; RANK: receptor activator of nuclear factor kappa-B; RANKL: receptor activator of nuclear factor kappa-B ligand; RCD: rotator cuff disease; RGP2: relaxin family peptide receptor 2; SMAD3: SMAD family member 3; RUNX2: runt-related transcription factor 2; SGCA: sarcoglycan alpha; SNP: single nucleotide polymorphism; TMJ: temporomandibular joint; TMD: temporomandibular disorder; TNF: tumor necrosis factor; VEGF: vascular endothelial growth factor; VNTR: variable number tandem repeat. |
the 11 studies that explored the COMT gene expression, the rs4689 (Val158Met) polymorphism was searched seven times [29,48,51,66,83,86,90], confirming the upwards information. The ESR1 gene is responsible for encoding the estrogen receptor alpha, which regulates numerous physiological activities such as cell growth, reproduction, differentiation, and development. The
intracellular pathway begins with the activation of receptor alpha and estrogen receptor beta \[114\]. The estrogen receptor alpha acts as a regulator of intracellular mediators, being found in intra-articular osteocytes, cartilage tissue \[115,116\], and in mandibular condylar fibrocartilage \[117,118\]. Besides that, the estrogen receptor alpha is also highly expressed in the human brain \[119\], explaining why this...
gene was a recurrent candidate gene found during the data extraction. We discovered that ESR1 is one of the keys to the core question of this systematic review, as it was often observed in the genetic profile of PHD and TMD patients.

4.3. Hypothesis for the reasons behind this genetic overlap

Regarding the COMT gene, although no significant differences were found in women suffering from headaches, women with chronic tension-type headaches carrying the Met/Met genotype for rs4680 had lower widespread pain thresholds than those carrying the other genotypes [29]. Pathophysiologically, this makes sense as the COMT gene codifies the COMT enzyme, which degrades numerous neurotransmitters and is highly associated with chronic pain syndromes. Nevertheless, this study's results highlight that the COMT gene should not be considered as part of the genetic overlap between PHD and TMD.

Although there are several pathways that TMD and PHD patients share, the data extracted in the present systematic review only reveals one common gene among the genetic profile of these pathologies, the ESR1 gene. From an epidemiological point of view, both PHD and TMD incidence is higher among women, and the included studies showed that this gene is obviously more expressed in this demographic group [52,56,87].

Estrogen's role in the occurrence of TMD and PHD has been long investigated [52,56,84,87,101]. Regarding the TMD, its prevalence presumes the role of sex hormones, particularly estrogen, in the TMJ alterations through time [9,120]. Indeed, the severity of pain seems higher in females for many body regions, one of them being the TMJ [121]. Moreover, the menstrual cycle seems to worsen the TMD's pain. Its severity in many women has its peak during the phase of rapid estrogen fluctuations [122]. Corroborating all this information, we know that either hormone replacement therapy or the use of hormonal contraceptives is associated with a higher chance of developing TMD among women [121,122].

The same goes for PHD, as there is evidence that a late luteal decrease in estrogen is both a trigger [123,124] and an aggravating factor [125] in the migraine's pain intensity. There are studies in which, similarly to the TMD, between 20% and 60% of females report relation to menstruation [126,127]. The evidence of the estrogen relationship was strong enough to originate the sub-classification of Menstrual Migraine credited by the International Classification of Headache Disorders (ICHD-3) [128].

4.4. Possible pathophysiological relationship between genes and pain

What is the possible pathophysiological relationship between the results found in this study (i.e., different expressions of the COMT, MTHFR and ESR1 genes), in patients with various types of headaches (e.g., migraine, tension-type, trigeminal autonomic cephalalgias) and pain related to temporomandibular joint pathology? A possible explanation has to do with the most primary afferent nociceptive neurons that innervate the head and neck region, which are located in the trigeminal ganglion (TG). Also, the processing of the painful information of the two entities may also take place in a common encephalic system [129]. Temporomandibular disorders are also linked to the V3 branch of the trigeminal system [130].

Clinical evidence suggests that ESR1 expression may be influenced by 17β-estradiol, which activates two types of receptors, namely ERα and ERβ [130]. ERα was found throughout the whole brain and in several migraine-related structures [130]. In the TG, ERα was found in the nucleus of neurons where there could be a modulatory role on the trigeminal neuron function, which is very sensitive to variations in the levels of this hormone [130]. Interestingly, the number of ERα- and ERβ-expressing cells are significantly higher in female TG compared to male TG [130].

Also, a functional polymorphism (Val158met) of the gene coding for the COMT has been demonstrated to be associated with pain regulation in healthy subjects, being also observed in several pain-processing brain regions, including dorso-ventral frontal cortex, posterior parietal cortex, lateral globus pallidus, as well as anterior and posterior insula [131].

Moreover, MTHFR expression may be different in the pathologies addressed here, which is reflected in homocysteine plasma concentrations, which could elicit an increase of the spontaneous trigeminal cell firing, leading to inflammation in the meninges and dilation of cerebral vessels [132]. These and other data, which require a more detailed investigation regarding molecular and functional features (for instance, by functional magnetic resonance imaging) may explain the different but common expression of the ESR1, COMT and MTHFR genes in the studied pathologies.

4.5. Limitations of the study

As previously explained, we decided to narrow the limit to five years only (i.e., 2015–2020) as this systematic review focus on the last achievements (after the period of significant publication in the topic) on the genetic overlap between these two pathologies. Nevertheless, this could be a limitation, and it would be important that further studies would enlarge the time frame before 2015, probably finding other common genes between TMD and PHD. Also, it could be interesting if future studies could focus on the incidence and severity of the disease. Taking that into account, in these reviews, the authors could stratify the findings and deepen the genetic associations found. Another limitation of most genetic association studies is the attention given to rare variants with larger effect sizes and, therefore, the omission of genes with common variants whose effect sizes fell under significance thresholds.

5. Conclusions

PHD and TMD are extremely complex clinical conditions that have numerous genes involved in their etiology. The most remarkable result emerging from the data extracted in this systematic review was the association of the ESR1 gene in both disorders. This is in complete agreement with the current literature that highlights the multifactorial role of estrogen, ranging from cellular and genetic modifications to pain perception. By narrowing the shared pathways of these disorders and the evidence of common genes involved will lead to a better understanding of the pathophysiological mechanisms and may in the future help in developing better therapeutic approaches. Recent and forthcoming advances of the ‘omics era, namely genomics, will certainly contribute to further discoveries in candidate pathways and mechanisms involved in the pathophysiology of these two diseases.

Authors’ contributions

The literature review, studies selection, quality assessment and initial manuscript writing were done by DC and FM, while MAF, MP, CL, MVS and TP provided guidance throughout the preparation of the manuscript. MAF, MP, MVS and TP revised and finalized the manuscript.

Conflict of Interest

none.

Acknowledgments

This systematic review was supported by FCT (Fundação para a Ciência e Tecnologia, Portugal), through the grants SFRH/BD/09375/
Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jdst.2022.02.002.

References

[1] List T, Jensen RH. Temporomandibular disorders: old ideas and new concepts. Cephalalgia 2017;37(7):692–704.
[2] Valesan L, Da-Cas C, Conti Réus J, Denardin A, Garanhani R, Bonotto D, et al. Prevalence of temporomandibular joint disorders: a systematic review and meta-analysis. Clinical Relevance 2021:251–57.
[3] Colombo J, Slade GD, Fillingim RB, Ohrbach R, Maixner W. Experimental pain sensitivity in subjects with temporomandibular disorders and multiple other chronic pain conditions: the OPPERA prospective cohort study. J Oral Facial Pain Headache 2020;34:43–56.
[4] D’Urso A, Serritella E, Tolevski Meshkova D, Falisi G, Di Paolo C. Headache and temporomandibular disorders: epidemiological assessment. Minerva Stomatol 2016;65(3–4):85–92.
[5] Tovar L, Hagen K, Jensen R, Katsarava Z, Lipton R, Scher A, et al. The global burden of headache: a documentation of headache prevalence and disability worldwide. Cephalalgia 2007;27(3):193–210.
[6] Goncalves D A, Bigal ME, Jales LC, Camparis CM, Speciali JG. Headache and Migraine. Cephalalgia 2023;43(1):21–32.
[7] Russell MB, Andersen P, Olesen J. Familial occurrence of cluster headache. J Neurology Neurosurgery Psychiatry 1995;58(3):341–2.
[8] Moreira DS, Libarici A, Tezilij AF, Passos M, et al. Prevalence and risk factors in women. Cephalalgia 2015;35(4):345–52.
[9] Russell MB, Andersen P, Olesen J. Familial occurrence of cluster headache. J Neurology Neurosurgery Psychiatry 1995;58(3):341–2.
[10] Bigal ME, Ashina S, Burstein R, Reed ML, Buse D, Serrano D, et al. Prevalence and risk factors in women. Cephalalgia 2015;35(4):345–52.
[11] Russell MB, Andersen P, Olesen J. Familial occurrence of cluster headache. J Neurology Neurosurgery Psychiatry 1995;58(3):341–2.
[12] Russell MB, Andersen P, Olesen J. Familial occurrence of cluster headache. J Neurology Neurosurgery Psychiatry 1995;58(3):341–2.
[13] Russell MB, Andersen P, Olesen J. Familial occurrence of cluster headache. J Neurology Neurosurgery Psychiatry 1995;58(3):341–2.
[14] Russell MB, Andersen P, Olesen J. Familial occurrence of cluster headache. J Neurology Neurosurgery Psychiatry 1995;58(3):341–2.
[15] Russell MB, Andersen P, Olesen J. Familial occurrence of cluster headache. J Neurology Neurosurgery Psychiatry 1995;58(3):341–2.
[16] Russell MB, Andersen P, Olesen J. Familial occurrence of cluster headache. J Neurology Neurosurgery Psychiatry 1995;58(3):341–2.
[17] Russell MB, Andersen P, Olesen J. Familial occurrence of cluster headache. J Neurology Neurosurgery Psychiatry 1995;58(3):341–2.
[18] Russell MB, Andersen P, Olesen J. Familial occurrence of cluster headache. J Neurology Neurosurgery Psychiatry 1995;58(3):341–2.
[19] Russell MB, Andersen P, Olesen J. Familial occurrence of cluster headache. J Neurology Neurosurgery Psychiatry 1995;58(3):341–2.
[20] Russell MB, Andersen P, Olesen J. Familial occurrence of cluster headache. J Neurology Neurosurgery Psychiatry 1995;58(3):341–2.
[21] Russell MB, Andersen P, Olesen J. Familial occurrence of cluster headache. J Neurology Neurosurgery Psychiatry 1995;58(3):341–2.
[22] Russell MB, Andersen P, Olesen J. Familial occurrence of cluster headache. J Neurology Neurosurgery Psychiatry 1995;58(3):341–2.
[23] Russell MB, Andersen P, Olesen J. Familial occurrence of cluster headache. J Neurology Neurosurgery Psychiatry 1995;58(3):341–2.
[24] Russell MB, Andersen P, Olesen J. Familial occurrence of cluster headache. J Neurology Neurosurgery Psychiatry 1995;58(3):341–2.
[25] Russell MB, Andersen P, Olesen J. Familial occurrence of cluster headache. J Neurology Neurosurgery Psychiatry 1995;58(3):341–2.
[26] Russell MB, Andersen P, Olesen J. Familial occurrence of cluster headache. J Neurology Neurosurgery Psychiatry 1995;58(3):341–2.
[27] Russell MB, Andersen P, Olesen J. Familial occurrence of cluster headache. J Neurology Neurosurgery Psychiatry 1995;58(3):341–2.
[28] Russell MB, Andersen P, Olesen J. Familial occurrence of cluster headache. J Neurology Neurosurgery Psychiatry 1995;58(3):341–2.
[29] Russell MB, Andersen P, Olesen J. Familial occurrence of cluster headache. J Neurology Neurosurgery Psychiatry 1995;58(3):341–2.
[30] Russell MB, Andersen P, Olesen J. Familial occurrence of cluster headache. J Neurology Neurosurgery Psychiatry 1995;58(3):341–2.
[31] Russell MB, Andersen P, Olesen J. Familial occurrence of cluster headache. J Neurology Neurosurgery Psychiatry 1995;58(3):341–2.
[32] Russell MB, Andersen P, Olesen J. Familial occurrence of cluster headache. J Neurology Neurosurgery Psychiatry 1995;58(3):341–2.
[33] Russell MB, Andersen P, Olesen J. Familial occurrence of cluster headache. J Neurology Neurosurgery Psychiatry 1995;58(3):341–2.
[34] Russell MB, Andersen P, Olesen J. Familial occurrence of cluster headache. J Neurology Neurosurgery Psychiatry 1995;58(3):341–2.
[35] Russell MB, Andersen P, Olesen J. Familial occurrence of cluster headache. J Neurology Neurosurgery Psychiatry 1995;58(3):341–2.
[36] Russell MB, Andersen P, Olesen J. Familial occurrence of cluster headache. J Neurology Neurosurgery Psychiatry 1995;58(3):341–2.
[37] Russell MB, Andersen P, Olesen J. Familial occurrence of cluster headache. J Neurology Neurosurgery Psychiatry 1995;58(3):341–2.
[38] Russell MB, Andersen P, Olesen J. Familial occurrence of cluster headache. J Neurology Neurosurgery Psychiatry 1995;58(3):341–2.
[39] Russell MB, Andersen P, Olesen J. Familial occurrence of cluster headache. J Neurology Neurosurgery Psychiatry 1995;58(3):341–2.
[40] Russell MB, Andersen P, Olesen J. Familial occurrence of cluster headache. J Neurology Neurosurgery Psychiatry 1995;58(3):341–2.
[41] Russell MB, Andersen P, Olesen J. Familial occurrence of cluster headache. J Neurology Neurosurgery Psychiatry 1995;58(3):341–2.
[42] Russell MB, Andersen P, Olesen J. Familial occurrence of cluster headache. J Neurology Neurosurgery Psychiatry 1995;58(3):341–2.
[43] Russell MB, Andersen P, Olesen J. Familial occurrence of cluster headache. J Neurology Neurosurgery Psychiatry 1995;58(3):341–2.
[44] Russell MB, Andersen P, Olesen J. Familial occurrence of cluster headache. J Neurology Neurosurgery Psychiatry 1995;58(3):341–2.
[45] Russell MB, Andersen P, Olesen J. Familial occurrence of cluster headache. J Neurology Neurosurgery Psychiatry 1995;58(3):341–2.
[46] Russell MB, Andersen P, Olesen J. Familial occurrence of cluster headache. J Neurology Neurosurgery Psychiatry 1995;58(3):341–2.
[47] Russell MB, Andersen P, Olesen J. Familial occurrence of cluster headache. J Neurology Neurosurgery Psychiatry 1995;58(3):341–2.
[48] Russell MB, Andersen P, Olesen J. Familial occurrence of cluster headache. J Neurology Neurosurgery Psychiatry 1995;58(3):341–2.
[49] Russell MB, Andersen P, Olesen J. Familial occurrence of cluster headache. J Neurology Neurosurgery Psychiatry 1995;58(3):341–2.
[50] Russell MB, Andersen P, Olesen J. Familial occurrence of cluster headache. J Neurology Neurosurgery Psychiatry 1995;58(3):341–2.
[51] Russell MB, Andersen P, Olesen J. Familial occurrence of cluster headache. J Neurology Neurosurgery Psychiatry 1995;58(3):341–2.
[52] Russell MB, Andersen P, Olesen J. Familial occurrence of cluster headache. J Neurology Neurosurgery Psychiatry 1995;58(3):341–2.
[53] Russell MB, Andersen P, Olesen J. Familial occurrence of cluster headache. J Neurology Neurosurgery Psychiatry 1995;58(3):341–2.
[54] Russell MB, Andersen P, Olesen J. Familial occurrence of cluster headache. J Neurology Neurosurgery Psychiatry 1995;58(3):341–2.
[55] Russell MB, Andersen P, Olesen J. Familial occurrence of cluster headache. J Neurology Neurosurgery Psychiatry 1995;58(3):341–2.
[105] Xiao JL, Meng JH, Gan YH, Zhou CY, Ma XC. Association of GDF5, SMAD3 and RUNX2 polymorphisms with temporomandibular joint osteoarthritis in female Han Chinese. J Oral Rehabil 2015;42(7):529–36.

[106] Jiang SJ, Li W, Li YJ, Fang W, Long X. Dickkopf-related protein 1 induces angiogenesis by upregulating vascular endothelial growth factor in the synovial fibroblasts of patients with temporomandibular joint disorders. Mol Med Rep 2015;12(4):4959–66.

[107] Huang B, Takahashi K, Goto T, Kiso H, Sugai M, Shimizu A, et al. ANKH polymorphisms and clicking of the temporomandibular joint in dental residents. J Maxillofac Oral Surg 2015;14(2):247–51.

[108] Chung K, Richards T, Nicot R, Vieira AR, Cruz CV, Raoul G, et al. ENPP1 and ESR1 genotypes associated with sub classifications of craniofacial asymmetry and severity of temporomandibular disorders. Am J Orthod Dentofac Orthop 2017;152(5):631–45.

[109] Rainero I, Vacca A, Rovera F, Govone F, Gai A, Rubino E. Targeting MTHFR for the treatment of migraines. Expert Opin Ther Targets 2019;23(1):29–37.

[110] Milosevic N, Nikolic N, Djordjevic I, Todorovic A, Lazic V, Milasin J. Association of functional polymorphisms in matrix metalloproteinase-9 and glutathione S-transferase T1 genes with temporomandibular disorders. J Oral Facial Pain Headache 2015;29(3):279–85.

[111] Chang X, Pellegrino R, Garifallou J, March M, Snyder J, Mentch F, et al. Common variants at 5q33.1 predispose to migraine in African-American children. J Med Genet 2018;55(12):831–6.

[112] Mannisto PT, Kaakkola S. Catechol-O-methyltransferase gene polymorphism and functional aspects. J Oral Maxillofac Surg 2010;68(12):2975–9.

[113] Yamada K, Nozawa-Inoue K, Kawano Y, Kohno S, Amizuka N, Iwanaga T, et al. Expression of estrogen receptor alpha (ER alpha) in the rat temporomandibular joint. Anat Rec A Discov Mol Cell Evol Biol 2003;274(2):534–41.

[114] Robinson JL, Gupta V, Soria P, Clanaman E, Gurbarg S, Xu M, et al. Estrogen receptor alpha mediates mandibular condylar cartilage growth in male mice. Orthod Craniofac Res 2017;20 Suppl 1:167–71. Suppl 1.

[115] Almej A, Milner TA, Brake WG. Estrogen receptors in the central nervous system and their implication for dopamine-dependent cognition in females. Horm Behav 2015;74:125–38.

[116] Arnett GW, Milam SB, Gottesman L. Progressive mandibular retrusion-idio pathic condylar resorption. Part I. Am J Orthod Dentofac Orthop 1999;110(1):8–15.

[117] Fillingim RB, King CD, Ribeiro-Dasila MC, Rahim-Williams B, Riley 3rd JL, Sex, gender, and pain: a review of recent clinical and experimental findings. J Pain 2009;10(5):447–85.

[118] LeResche L, Manci L, Sherman JJ, Gandara B, Dworkin SF. Changes in temporomandibular pain and other symptoms across the menstrual cycle. Pain 2003;106(3):253–61.

[119] Somerville BW. The role of estradiol withdrawal in the etiology of menstrual migraine. Neurology 1972;22(4):355–65.

[120] MacGregor EA, Firth A, Ellis J, Aspinall L, Hackshaw A. Incidence of migraine relative to menstrual cycle phases of rising and falling estrogen. Neurology 2006;67(12):2154–8.

[121] Martin VT, Behbehani M. Ovarian hormones and migraine headache: understanding mechanisms and pathogenesis—part I. Headache 2006;46(1):3–23.

[122] E.A. MacGregor Migraine Management During Menstruation and Menopause. Continuum (Minneapolis), 2015, 21(4 Headache). 990–1003.

[123] Jedynak B, Jaworska-Zaremba M, Grzechocińska B, Chmurska M, Janicka J, Krotszewa-Janicka J. TMD in females with menstrual disorders. Int J Environ Res Public Health 2021;18(14).

[124] The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 2013;33(9):629–808.

[125] Edvinsson JCA, Vigano A, Aleeva A, Arruda R, De Luca C, et al. The fifth cranial nerve in headaches. J Headache Pain 2020;21(1):65.

[126] Fillingim RB, King CD, Ribeiro-Dasilva MC, Rahim-Williams B, Riley 3rd JL. Sex, gender, and pain: a review of recent clinical and experimental findings. J Pain 2009;10(5):447–85.

[127] Somerville BW. The role of estradiol withdrawal in the etiology of menstrual migraine. Neurology 1972;22(4):355–65.