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Review article

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

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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 it also evaluates their potential as a promising therapeutic target to treat both pathologies.
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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 features, 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

Abbreviations: COMT, catechol-O-methyltransferase; ESR1, estrogen receptor 1; GWAS, genome-wide association studies; MTHFR, methylenetetrahydrofolate reductase; PHD, primary headache disorders; PICOS, Population, Intervention, Comparison, Outcomes and Study design; PRISMA, Preferred Reporting Items for Systematic Review and Meta-analysis; TMD, temporomandibular disorders; TMJ, temporomandibular joint

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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 disorders" OR "temporomandibular disorder" OR "temporomandibular dysfunction" OR "temporomandibular dysfunctions" OR "craniomandibular dysfunction" OR "craniomandibular dysfunctions" OR "orofacial 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 (population, intervention, comparison, outcomes and study design) strategy applied to the current review.

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

Table 2
Eligibility criteria for this review.

Inclusion criteria	Exclusion criteria
• Clinical studies, case-controls, association study, Genome-wide association studies (GWAS), genetic expression studies that report genetic involvement in PHD, as migraine, cluster, and tension-type headaches; • Clinical studies, case-controls, association study, GWAS, genetic expression studies that report impairment of the jaw muscles, TMJ, and the nerves linked to chronic facial pain were included as TMD; • Studies published from 2015 to 2020; • Studies written in English.	• Family hemiplegic migraine studies; • Studies in which specific genes/alleles are not clearly described; • Studies that do not refer to the population size.

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 [29,48,51,66,72] 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.

4. Discussion

Unlike monogenic diseases (as in the case of family hemiplegic migraine in which there is only a gene responsible for the disease), PHD and TMD behave like complex disorders whose inheritance cannot be explained by the simple genetic segregation of a single gene and therefore it is not trivial to identify the associated genetic cause. Thus, this review reinforces the existence of a network of genes that interplay with each other, plus the environmental effects, which ultimately result in the phenotype of these diseases (Fig. 3).

4.1. Evaluation of the genetic overlap between PHD and TMD

After finding the overlap of three genes in the analyzed studies, the next methodological step was to thoroughly analyze the 19 works that drew conclusions about the impact of *MTHFR, COMT or ESR1* genes in the revised pathologies. *MTHFR* gene encodes an enzyme crucial for Homocysteine metabolism, necessary in the processing of vitamin B1, B6, B12, and folate. Some studies have shown that vitamin supplementation (folate, vitamin B6, and B12), decreasing homocysteine concentrations, improves migraine frequencies [109]. For this reason, the *MTHFR* gene has been highly investigated as a genetic risk factor for migraine, especially for the migraine with aura subform. Likewise, the nutritional deficiency of these vitamins can induce myofascial dysfunction and pain, and these efficiencies are relatively common in cases of TMD mechanical stress [110]. Although, for lack of solid evidence, it was concluded that the *MTHFR* gene was not linked to either TMD or PHD [41,104].

COMT gene's polymorphisms were proved to be a major influence in the studies focused on TMD, as all of them have drawn conclusions of its impact on the occurrence of the disease [81,83,86,89,90]. However, none of the reviewed PHD studies have associated this gene and the disease [48,51,66,72], except for Fernández-De-Las-Peñas et al. (2019) [29], who stated that *COMT* is associated with a lower widespread pressure pain thresholds in determined genotypes of their study population [29].

The most substantial results are definitely the ones concerning the *ESR1* gene. Of the four studies exploring this gene in the TMD, three of them observed a positive association between the *ESR1* gene and this pathological condition [84,95,108]. Among the two studies exploring the referred gene in PHD patients, both have stated positive associations between the *ESR1* gene and this pathology [52,56].

None of the revised GWAS has drawn any significant correlation between the genetic profile that it is sought and PHD and/or TMD incidence [39,40,79,111].

4.2. Understanding what is the function of the genes that constitute the genetic overlap between PHD and TMD

The *COMT* gene encodes an enzyme present in the metabolic degradation of numerous neurotransmitters, such as dopamine, norepinephrine, or epinephrine [112]. It is a primarily studied gene alongside the literature, considered as a potential genetic determinant in chronic pain syndromes. Distinct polymorphisms determine *COMT* activity, but the most investigated one is definitely the rs4680 [113]. In fact, the extracted data allow us to understand that, among

Table 3
Systematized information on genes and pathways associated with Primary Headache Disorders.

Publication data	Study Design	Diagnosis of samples (*n*)	Gene/Allele Under Study	Results	Conclusions
Fernández-De-Las-Peñas, C., et al. (2019)[29]	Case-control study	Women with: CTTH (50); FETTH (50); & controls (50)	COMT Val158Met (rs4680)	- no significant differences between women with and without headache. - women with CTTH but not FETTH carrying the Met/Met genotype had lower widespread pressure pain thresholds than those with Val/Val or Val/Met genotype.	- COMT Val158Met (rs4680) was not proved to be significant in the presence of tension type headache but is associated with a lower widespread pressure pain thresholds in determined genotypes.
Fourier, C., et al. (2019)[30]	Case-control study	CH (517); & controls (581)	HCRTR2	- rs3122156, the allele frequency was lower in diseased groups compared to controls. - one haplotype was significantly less common in the diseased group.	- trend for association between CH and the HCRTR2 rs3122156, where the minor allele seems to be a protective factor.
Barbanti, P., et al. (2019)[31]	Case-control study	MO (199); MA (71); CM (130); & controls (204)	DBH 19-bp I/D	- DBH 19-bp I/D SNP did not correlate with migraine susceptibility.	- DBH 19-bp I/D SNP does not influence migraine susceptibility.
Moreno-Mayordomo, R., et al. (2019)[32]	Prospective, observational, multicenter study	Women CM (156)	CALCA (rs3781719) TRPV1 (rs222749)	- CALCA rs3781719 and TRPV1 rs222749 showed differences in the response to the treatment with OnabotulinumtoxinA.	- SNPs in CALCA and TRPV1 genes might have an impact as prognostic markers of efficacy of OnabotulinumtoxinA in chronic migraine female patients.
Kogelman, L. J., et al. (2019)[33]	Case-control study	Women with: MO (17); MA (9); & controls (20)	NMNAT2 RETN	- two differentially expressed genes were found: NMNAT2 and RETN (not replicated in an independent cohort); - no pathways or gene ontology terms were detected.	- no clear distinct difference in gene expression profiles of peripheral blood of migraineurs and controls were found.
Pollock, C. E., et al. (2018)[34]	Case-control study	Menstrual related migraine (235); & controls (140)	NRP1 (rs2506142)	- rs2506142 located near the *NRP1* gene was found to be significantly associated with menstrual related migraine.	- NRP1 may be important in the etiology of menstrual related migraine.
Ramroodi, N., et al. (2018)[35]	Case-control study	MO (112); MA (78); controls (200)	CD40 (rs1883832)	- CD40 rs1883832 was significantly associated with migraine; - increased concentration of soluble CD40L levels in rs1883832 patients compared to the control group.	- CD40 rs1883832, TC genotype may have a role in migraine susceptibility.
Ran, C., et al. (2018)[36]	Case-control study	CH (541); & controls (581)	MTDH (rs1835740)	- trend for association between rs1835740 (which affects MTDH mRNA levels) and CH. This association was stronger in a subgroup of patients suffering from both CH and migraine.	- rs1835740 is a potential risk factor for CH in Sweden; - rs1835740 and MTDH might be involved in neurovascular headaches in general, whilst rs2651899 is specifically related to migraine.
Kaur, S., et al. (2019)[37]	Case-control study	MO (107); MA (43); Controls (150)	PRDM16 (rs2651899) TRPM8 (rs10166942)	- a statistically significant difference in migraineurs with control for PRDM16 rs2651899 polymorphism and on subgroup in MO and female. - no significant difference was found at allelic level in both subgroup and gender analysis for rs10166942.	- rs2651899 is a potential genetic marker for migraine susceptibility in MO and female subgroup in the North Indian population; - rs10166942 variant may be a potential marker for MA and male subgroup.
Chang, X., et al. (2018)[38]	GWAS	Discovery study: 599 European American with migraine [MO (182) or MA (87)]; & controls (7327); 380 African-American with Migraine [MO (40) or MA (123)]; & controls (7327). Replication study: 233 African-Americans with Migraine [MO (54) or MA (23)].	ENSG 00000286749	- common variants at 5q33.1 associated with migraine risk in African-American children (rs72793414).	- a genomic locus at 5q33.1 is associated with migraine in African-American children and not associated with migraine in European-American children.
Chen, S. P., et al. (2018)[39]	GWAS	Discovery stage: MO (1005), & controls (1053).	DLG2 (rs655484) GFRA1 (rs3781545) TRPM8 (rs10166942)	- susceptibility loci were found (rs655484 in DLG2 and rs3781545i in GFRA1) that reached GWAS significance level for risk of	- DLG2 and GFRA1 novel migraine susceptibility genes, both of which had plausible pathogenic implications in

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Table 3 (*continued*)

Publication data	Study Design	Diagnosis of samples (*n*)	Gene/Allele Under Study	Results	Conclusions
		Replication stage: MO (1120); & controls (604).	LRP1 (rs1172113)	developing migraine; - tendency to an association between rs10166942 in TRPM8 and rs1172113 in LRP1 and migraine in Caucasian.	migraine; - positive association signals between TRPM8 and LRP1 and migraine.
Bacchelli et al. (2016)[40]	GWAS	CH (99); & controls (360)	ADCYAP1R1 MME	- suggestive association was identified with a common variant ADCYAP1R1; - significant evidence of association of missense variant in the MME gene.	- results implicate ADCYAP1R1 and MME gene variants in CH susceptibility and point to a role for genes involved in pain processing.
Kaur, S., et al. (2018)[41]	Case-control study	MO (77); MA (23); & controls (100)	MTHFR (rs1801133; rs1801131)	- rs1801131was found to be a risk factor in migraine patients than controls; - rs1801133 influences susceptibility to MA but not to MO. - rs1801131could be a risk factor for migraine patients without aura.	- MTHFR SNPs are not significantly associated with a risk for the development of migraine in this study; - CC genotype in rs1801131 may be a marker for susceptibility to MO.
Fan, Z., et al. (2018)[42]	Case-control study	CH (112); & controls (192)	HCRTR2 (rs2653349) ADH4 (rs1126671, rs1800759) CLOCK	- tendency of the HCRTR2 SNP rs3800539 in patients rather than in controls. - one HCRTR2 haplotype was linked to a reduced CH risk.	- association between HCRTR2, ADH4, CLOCK gene polymorphisms and CH was not significant in this study, - HCRTR2 gene was linked to CH.
García-Martín, E., et al. (2018)[43]	Case-control study	MO (99); MA (98); & controls (394)	GABRA4 GABRE GABRQ	- triggering of migraine by ethanol showed a tendency with GABRA4 rs2229940 and with GABRQ 3810651; - GABRE rs1139916 also showed a tendency in the female migraine group; - the age of onset of migraine was significantly lower in patients with GABRQ rs3810651AA as compared with the other two genotypes.	- GABRQ rs3810651 could play a role on the modification of the age of onset of migraine.
Ozan, B., et al. (2017)[44]	Case-control study	MO (132); MA (14); & controls (154)	UTS2 (Thr21Met, Ser89Asn)	- no significant differences were observed for Thr21Met and Ser89Asn SNPs between the diseased patients and control group and between MA and MO and control group; - no association between UTS2 gene haplotypes and migraine.	-Thr21Met and Ser89Asn SNPs of the UTS2 gene are not risk factors for migraine in this sample of Turkish migraine patients.
Ran, C., et al. (2017)[45]	Case-control study	CH (542); Controls (581)	ADCYAP1R1 (rs12668955) 14q21 (rs1006417) MME (rs147564881)	- rs12668955 and rs1006417 were not associated with CH. - the MME mutation was investigated in patients, of whom all were wild-type.	- rs12668955 and rs1006417 do not impact the risk of developing CH in this study's population.
Ambrosini, A., et al. (2017)[46]	Case-control study	MO (24); MA (55); complex neurological auras (38); & controls (102)	CACNA1E (Asp859Glu)	- Asp859Glu was present in 12.7% of control subjects and in 20.4% of the total migraine group. - no significant difference between migraine with typical aura (10.9%) and controls.	- Asp859Glu is more prevalent in FHM and brain stem aura migraine.
García-Martín, E., et al. (2017)[47]	Case-control association study	MO (99); MA (98); & controls (278)	GABRR1 (rs1186902) GABRR2 (rs282129) GABRR3 (rs832032)	- no differences in genotypes and allelic frequencies of the 4 SNPs; - carriers of the minor allele of the rs1186902 SNP showed a trend towards later onset of migraine.	- the most common SNPs in the GABRR genes seemed to be not associated with the risk for migraine in Caucasian Spanish people; - GABRR1 rs1186902 shows a statistically significant association with the age of onset of migraine.
Sutherland, H. G., et al. (2017)[48]	Case-control association study	Menstrual related migraine (268); & controls (142)	COMT (rs4680) CYP1A1 (rs4646903) rs1048943) CYP19A1 (rs700519)	- neither genotype nor allele frequencies for the COMT and CYP SNPs genotyped were found to be significantly different between menstrual related migraineurs and controls.	- no association between functional SNPs in the estrogen metabolism genes COMT, CYP1A1 or CYP19A1 and menstrual related migraine.
Meza-Velázquez, R., et al. (2017)[49]	Case-control study		C314T HNMT		

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Table 3 (*continued*)

Publication data	Study Design	Diagnosis of samples (*n*)	Gene/Allele Under Study	Results	Conclusions
		162 mothers with allergic children (80 with migraine)	C2029G DAO	- increased frequency of C2029G DAO SNP in disease women than in controls; - both mutated alleles were associated with migraine-related disability; - haplotypes containing both mutated alleles showed a strong association with migraine.	- possible synergistic association between HNMT and DAO functional SNPs and migraine.
An, X. K., et al. (2017)[50]	Case-control study	MO (494); MA (87); Controls (533)	MEF2D (rs2274316) ASTN2 (rs6478241) PRDM16	- significant associations of SNPs in the MEF2D and ASTN2 genes with migraine susceptibility; - MEF2D, PRDM16 and ASTN2 were also found to be associated with MO and migraine with family history. - MEF2D and ASTN2 also served as genetic risk factors for the migraine without family history.	- MEF2D, PRDM16 and ASTN2 genes from GWAS are associated with migraine susceptibility, especially MO, among Chinese patients.
Takigawa, H., et al. (2017)[51]	Case-control study	MO (152); MA (71); Tension-type headache (86); & controls (191)	COMT (rs4680, rs4633, rs6267, rs6270, rs740602)	- no significant differences were found in any genotypes, allele frequencies, or haplotypes among the patient groups and controls.	- the five SNPs in COMT have no association with migraineurs in Western Japan.
An, X., et al. (2017)[52]	Case-control association 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; - rs2234693 in ESR1 gene is found associated with menstrual related migraine. - haplotypic 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.	- ESR1 rs2234693 and rs9340799 are risk factors for migraine - ESR1 rs2234693 plays a potential role in migraine susceptibility in a Chinese population, especially for Menstrual Related migraine.
Juhasz, G., et al. (2017)[53]	Cross-sectional study	2426 participants: migraine (144) or migraine related symptoms (668)	CNR1 (rs806369, rs1049353, rs4707436, rs806366, rs7766029)	- five SNPs showed nominally significant interaction with RLE on headache with nausea; - the effect of rs806366 remained significant after replicated in the subpopulations.	- CNR1 gene in interaction with life stress increases the risk of headache with nausea, suggesting a specific pathological mechanism to develop migraine.
Sazci, A., et al. (2016)[54]	Case-control study	Migraine (433); Controls (229)	NNMT (rs694539)	- association between NNMT gene rs694539 variant and female migraineurs;	- NNMT gene rs694539 variant is a genetic risk factor for migraine.
Fuh, J. L., et al. (2016)[55]	Case-control study	Migraine patients with Restless leg syndrome: MO (182); & MA (29). Migraine patients without Restless leg syndrome: MO (690); & MA (91)	MEIS1 (rs2300478)	-MEIS1 augmented the risk of restless leg syndrome only in the patients who experienced Episodic Migraine and not those experiencing Chronic Migraine. - an increase expression rs2300478 in MEIS1 of restless leg syndrome in migraine.	- MEIS1 variants were associated with an increased risk of restless leg syndrome in migraine patients.
CoŞKun, S., et al. (2016)[56]	Case-control study	Migraine (142); & controls (141)	CYP19A1 (rs10046) FSHR (rs6166) ESR1 (rs726281) NRIP1 (rs2229741)	- significant gene–gene interaction among CYP19A1, FSHR, ESR1 and NRIP1 in migraine patients; - significant association between rs10046 and rs2229741 and migraine susceptibility; - rs726281 was significantly associated with migraine related to menstruation; - rs2229741 may reduce the risk of migraine in Turkish women.	- CYP19A1 plays a potential role in migraine susceptibility in a Turkish population; - rs2229741 in NRIP1 strikingly reduced the risk of migraine in Turkish women; - ESR1 rs726281 appears to influence susceptibility in a recessive manner in Menstrual Related Migraine subgroup;
Yücel, Y., et al. (2016)[57]	Case-control study	MO (112); MA (23); & controls (139)	5-HTR2C (rs3813929)	- association between the rs3813929 in the promoter region of 5-HTR2C gene and migraine;	- 5-HTR2C rs3813929 can be a genetic risk factor for migraine in a Turkish population.

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Table 3 (*continued*)

Publication data	Study Design	Diagnosis of samples (*n*)	Gene/Allele Under Study	Results	Conclusions
				- the allele of rs3813929 was more common in the migraine group.	
Sezer, S., et al. (2016)[58]	Case-control study	MO (167); MA (33); & controls (267)	DBH (rs1611115, rs6271, rs1108580)	- 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.
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.	- U-II may play a role in migraine pathogenesis; - Thr21Met SNP was associated with the risk of migraine disease.
Esserlind, A. L., et al. (2016)[60]	Case-control study	MO (1010); MA (796); & controls (6415)	MEF2D (rs2274316) LRP1 (rs1172113)	- association between gene expression (MEF2D and LRP1) and all migraine and MO patients; - two SNPs (rs2274316 and rs1172113) conferred risk of many lifetime attacks of migraine in the case-control analysis.	- association of several SNPs with migraine, suggesting that migraine susceptibility loci may be risk factors for severe migraine traits.
Cainazzo, M. M., et al. (2015)[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.	- CH patients seem to have a stronger genetic predisposition to develop smoke dependence.
Cargnin, S., 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.	- 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 genotype frequency and migraine.	- no functional significance of the TNFSF10 gene SNP rs35975099 in migraine pathogenesis.
García-Martín, E., et al. (2015)[64]	Case-control study	MO (99); MA (98); & controls (245)	DAO (rs10156191)	- the DAO SNP rs10156191 is associated with the risk of developing migraine, mostly in females.	- DAO genotypes and allelic variants are associated with the risk for migraine in Caucasian Spanish people.
Lin, Q. F., et al. (2015)[65]	Case-control study	MO (238); MA (62); & controls (300)	FHL5 (rs13208321) C7orf10 (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.	- rs4379368 and rs13208321 are potential genetic markers for migraine in this 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 rs4818 genotypic frequencies did not correlate with clinical migraine features.	- COMT genotype does not impact migraine susceptibility or phenotype.
Gasparini, C. F., et al. (2015)[67]	Case-control study	MO (64); MA (227); & controls (314)	ADARB1 ADARB2	- 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)	GRIA1 (rs2195450, rs548294) GRIA3 (rs3761555)	- 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)	PER3 VNTR	- no association between PER3 VNTR SNP and CH.	- no association between CH, PER3 VNTR SNP and chronotype.

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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.	- NOS1 rs7977109 and rs693534 variants are not linked with the risk for migraine in Caucasian Spanish people.
Gentile, G., et al. (2015)[71]	Case-control study	CM (96); & controls (45)	GST1 GSTM1 GSTP1 SOD2 CAT eNOS PON1 CYBA	- genotype, allele and haplotype frequencies were not statistically different between chronic migraineurs and non-migraineurs.	- lack of association between oxidative stress-related genes SNPs and chronic migraine.
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 (rs3792603) Intergenic (rs217693) CALCA8 (r2956) CALCRL (rs858745) RAMP1 (rs302680) ADCYAPIRI (rs2267730, rs2299908)	- 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.
Oh, S. K., et al. (2015)[73]	Family study	Hearing loss and MO (12)	ATP1A2	- c 0.571 G4A [p.(Val191Met)] was linked with the ATP1A2 gene that showed co-segregation with the phenotype in the family.	- a variant in Na^+/K^+-ATPase can be involved in both migraine and hearing loss.
Zarrilli, F., et al. (2015)[74]	Case-control study	CH (54); & controls (200)	ADH4 NRXN3	- 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 *TRHDE* 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.
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.	- polygenic contribution to migraine risk in an isolated population; - specific SNPs (including rs171251) that regulate the expression of USMG5 are critical for mitochondrial function.
Wan, D., et al. (2015)[76]	Case-control study	MO (21); MA (5); & controls (25)	RAMP1	- 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.	- DNA methylation at RAMP1 promoter might play a role in migraine; - lower methylation level may be a risk of migraine in females.
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.
Zandifar, A., et al. (2015)[78]	Case-control study	Migraine (103); & controls (148)	PTX3 (rs3816527)	- genotype frequency of PTX3 was significantly different between the migraine patients and the control subjects; - CC variant homozygote genotype was	- association between the PTX3 rs3816527 gene with susceptibility to migraine only in men migraineurs.

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Table 3 (*continued*)

Publication data	Study Design	Diagnosis of samples (*n*)	Gene/Allele Under Study	Results	Conclusions
				statistically more frequent in the patients than in the controls; - C allele was not significantly more frequent in the patients.	
Jacobsen, K. K., et al. (2015)[79]	GWAS	Bipolar patients having migraine (460); & bipolar patients without migraine (914)	NBEA (rs1160720)	- one genome-wide significant association of rs1160720, an intronic SNP in the NBEA gene, although this was not replicate in a smaller sample of 289 migraine cases.	- no proof of association was found, suggesting that the association might be specific to migraine co-morbid with bipolar disorder.
Van der Auwera, S., et al. (2015)[80]	Polygenic scores study	Migraine and schizophrenia patients (3973)	SRR	- 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.	- a decreased versus increased activation of NMDA receptors may play a role in the etiology of schizophrenia, as well as in migraine.

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 I; ADH4: alcohol dehydrogenase 4; ASTN2: astrotactin 2; ATP1A2: ATPase Na+/K+ transporting subunit alpha 2; C7orf10: succinate-hydroxymethylglutarate 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: cathecol-O-methyltransferase; CTTH: Chronic Tension Type Headache; CYBA: cytochrome B-245 alpha chain; CYP: cytochrome P450; DAO: D-amino acid oxidase; DBH: dopamine beta-hydroxylase; DLG2: disks large MAGUK scaffold protein 2; eNOS: endothelial nitric oxide synthase; ESR1: estrogen receptor 1; FETTH: Frequent Episodic Tension-Type Headache; FHL5: four and a half LIM domains 5; FSHR: follicle stimulating hormone receptor; GABRA: gamma-aminobutyric acid type A receptor subunit alpha 1; GABRE: gamma-aminobutyric acid type A receptor subunit epsilon; GABRQ: gamma-aminobutyric acid type A receptor subunit theta; GABRR2: gamma-aminobutyric acid type A receptor subunit rho-2; GABRR3: gamma-aminobutyric acid type A receptor subunit rho-3; GFRA1: GDNF family receptor alpha 1; GRIA: glutamate ionotropic receptor AMPA type subunit 1; GST1: glutathione S-transferase 1; GSTM1: glutathione S-transferase M1; GSTP1: glutathione 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; MME: membrane metalloendopeptidase; MO: migraine without aura; mRNA: messenger RNA; MTDH: metadherin; MTHFR: methylenetetrahydrofolate reductase; NBEA: neurobeachin; NMNAT2: nicotinamide nucleotide adenylyltransferase 2; NNMT: nicotinamide N-methyltransferase; NOS1: nitric oxide synthase 1; NRIP1: 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; RETN: resistin; RLE: Recent Negative Life events; SCNNIA: 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 cation 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.

Table 4
Systematized information on genes and pathways associated with Temporomandibular Disorders.

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; - rs1042713in 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 (intronic SNP) and one significant allele association rs1815739 (R577X nonsense).	- ACTN3 genotypes can influence ENPP1 expression, as can changes in cartilage mechanical strain environments.
Slade et al. (2020)[83]	Randomized controlled trial	Non-Hispanic white individuals with myalgia, with or without arthralgia (143)	COMT (rs4680)	- Cumulative response curves proved higher efficacy for G:G homozygotes than for A:A homozygotes.	- Observed antagonistic effect of the A allele on propranolol's success, reinforcing the need for better knowledge of COMT's part in pain pathogenesis if the gene is to be used for precision medicine treatment of TMD.
Dalewski et al. (2020)[84]	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.	- 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)	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 the patients of Western Mexico was found.	- 1607 1G/2G SNP is associated with the development 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.
Pinto Fiamengui, L. M. S., et al. (2020)[86]	Case-control study	TMD patients including myofascial pain, arthralgia and mixed diagnosis encompassing these ones and disc displacement (131); & controls (137)	IL6–174 COMT Val158Met TNFA-308	- SNP IL6–174 envisioned higher pain sensitivity in the TMJ and in anterior temporalis muscle; - SNP Val158Met influenced increase pain sensibility in the masseter muscle.	- TNFA-308 was associated with TMD and SNP IL6–174 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)	- rs1256049 in ESR2 was associated with disc displacement and arthralgia in adults.	- 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 (rs7932320) FGF10 (rs900379) FGF13 (rs5931572) FGF13 (rs5974804)	- rs7932320 in FGF3 and rs900379 in FGF10 were associated with the presence of muscle disorder; - rs1893047 in FGF3, rs900379 in FGF10, and rs5974804 and rs5931572 in FGF13, were linked with the presence of disk displacement; - rs1893047 and rs7932320 in FGF3, rs900379 in FGF10, and rs900379 in FGF10 were associated with other TMD conditions.	- SNPs in FGF3, FGF10, and FGF13 genes were associated with temporomandibular disorders in a population with dentofacial deformities.

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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 (rs3813034 & rs1042173) COMT (rs4818 & rs6269)	- 5HTT rs1042173 was associated with painful TMD (arthralgia and myofascial pain); - rs4818 in COMT 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 (rs9332377) ADRB2 (rs1042713)	- rs9332377 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, rs13078961, rs10092633, rs34612513, rs28865059)	- rs13078961 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+252 in TMD patients compared to healthy controls. TNF-β+252A/G genotype distribution was associated with chewing problems.	- 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 (rs2273206) ESRRB (rs1676303) ENPP1 (rs858339) ESR1 (rs164321, rs3020318)	- rs2273206 in ESR1 gene was strongly associated with the risk of developing muscle TMDs and TMJ pain; - rs1676303 in ESRRB gene was associated with the presence of articular TMDs related with other chronic arthralgia.	- ESR1 and ESRRB genes influence the presence of TMDs associated with chronic joint pain.
Tumer 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.

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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.	- 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, rs504762, 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)	- ESR1 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; - AT genotype was identified as a risk factor of TMD with respect to the rest of our population.	- ESR1 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.

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Publication data	Study Design	Diagnosis of samples (*n*)	Gene/Allele Under Study	Results	Conclusions
Bonato et al. (2016)[102]	Case-control study	Patients with: RCD and TMD-free (16); RCD-free and TMD (13); RCD and TMD (49); & controls (30)	ESRRB (rs6574293)	- TMD individuals were seven times more susceptible to RCD than controls; - TMD/RCD subjects showed associations with rs4903399, rs10132091 and 2 haplotypes and lower muscle activity; - rs1676303 and rs6574293 were associated with RCD and TMD, respectively.	- ESRRB haplotypes and low muscle activity are common biomechanical characteristics in subjects with both diseases.
Luo, S., et al. (2015)[103]	Case-control study	Patients with: unilateral anterior disc displacement with reduction (141); unilateral anterior disc displacement without reduction (321); & controls (185)	MMP-1	- The susceptibility of 2G2G genotype carriers to ADDWOR with or without TMJOA was considerably higher than that of other genotypes carriers; - The susceptibility of 1G2G genotype carriers to ADDWOR with or without TMJOA was also considerably higher than that of other genotype carriers.	- 1607 1G/2G SNP of MMP-1 promoter may be related to the susceptibility to ADDWOR with or without TMJOA.
Milosevic, N., et al. (2015)[104]	Case-control study	TMD patients (100); & controls (182)	MMP-9 GSTM1 GSTT1 MTHFR	- MMP-9 SNP genotype and allele showed differences between the TMD group and controls; Null GSTT1 genotype as well as the combined non-null GSTM1/ null GSTT1 were associated with lower risk of TMD; - GSTM1 alone and MTHFR SNPs did not show an association with TMD.	- C-1562T SNP in the promoter region of the MMP-9 gene, the GSTT1 null, as well as the combined GSTM1 non-null and GSTT1 null genotypes are modulators of TMD risk in a Serbian population.
Xiao, J. L., et al. (2015)[105]	Case-control study with 114 patients having TMD	Patients with TMJOA	GDF5 SMAD3 RUNX2	- Association between the SNP in GDF5 or SMAD3 and TMJOA; - Weak association was observed in RUNX2; - The risk of TMJOA grew 5,09 times in the patients with five or six risk alleles in the triple combinational analysis.	- SNPs of genes related to TGFb family might contribute to the risk of TMJOA.
Jiang S et al. (2015)[106]	Case-control study	Patients with: anterior disc displacement with reduction (18); anterior disc displacement without reduction (20); osteoarthritis (12); & controls (7)	DKK-1 VEGF HIF-1α	- Increased expression levels of DKK-1 were concordant with increased expression levels of VEGF in the synovial fluid from patients with TMD; - Increased DKK-1 levels of VEGF and promoted HIF-1α nuclear localization in the synovial fibroblasts of TMD patients; - DKK-1 induced HUVEC cell migration, and HIF-1α siRNA inhibited DKK-1-induced cell migration.	- DKK-1 is associated with angiogenesis in the synovial fluid of TMD patients; - HIF-1α may be associated with DKK-1-induced HUVEC activation.
Huang et al. (2015)[107]	Case-control study	TMJ clicking patients (21); controls (20)	ANKH (ANKH-OR allele 1 and ANKH-TR allele 7)	- Occurrence of TMJ clicking was not related to age, gender and genotypes of ANKH-OR as well as ANKH-TR SNPs.	Similar distribution of ANKH genotypes in TMJ clicking and asymptomatic individuals.

Abbreviations: 5HTT: sodium-dependent serotonin transporter; ACTN3: actinin alpha-3; ADRB2: beta-2 adrenergic receptor; ANKH: ANKH inorganic pyrophosphate transport regulator; ANKK1: ankyrin repeat and kinase domain containing 1; COMT: catechol-O-methyltransferase; DKK-1: Dickkopf WNT signaling pathway inhibitor 1; DMD: Duchenne muscular dystrophin; DRD2: dopamine receptor D2; ENPP1: ectonucleotide pyrophosphatase/phosphodiesterase 1; ESR: estrogen receptor; 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-1α: hypoxia inducible factor 1 subunit alpha; IL: interleukin; MMP: matrix metalloproteinase; MRAS: muscle RAS oncogene homolog; MTHFR: methylenetetrahydrofolate reductase; NR3C1: nuclear receptor subfamily 3 group C member 1;: osteoprotegerin; RANK: receptor activator of nuclear factor kappa-B; RANKL: receptor activator of nuclear factor kappa-B ligand; RCD: rotator Cuiff disease; RXP2: relaxin family peptide receptor 2; SMAD3: SMAD family member 3; RUNX2: runt-related transcription factor 2; SGCA: sarcoglycan alpha; SNP: single nucleotide polymorphism; TMJOA: temporomandibular joint osteoarthritis; TMD: temporomandibular disorder; TMJ: temporomandibular joint; TNF: tumor necrosis factor; VEGF: vascular endothelial growth factor; VNTR: variable number tandem repeat.

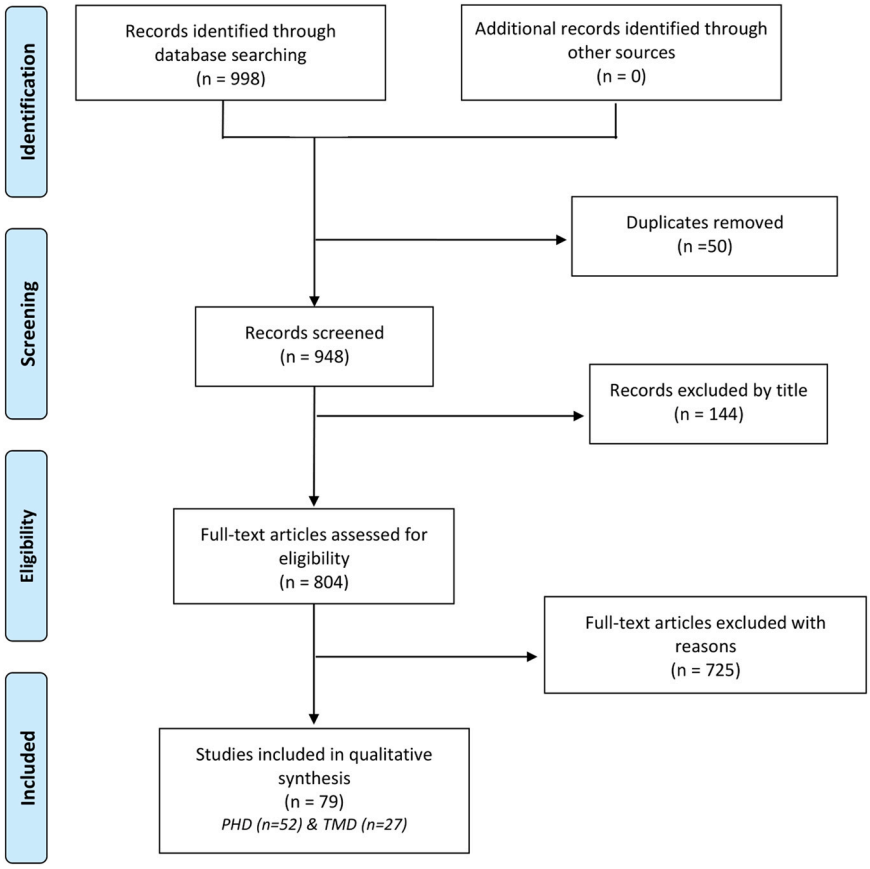

Fig. 1. Flowchart from PRISMA (Preferred reporting items for systematic reviews and meta-analyses) method depicting the articles' selection process. Adapted from [21].

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

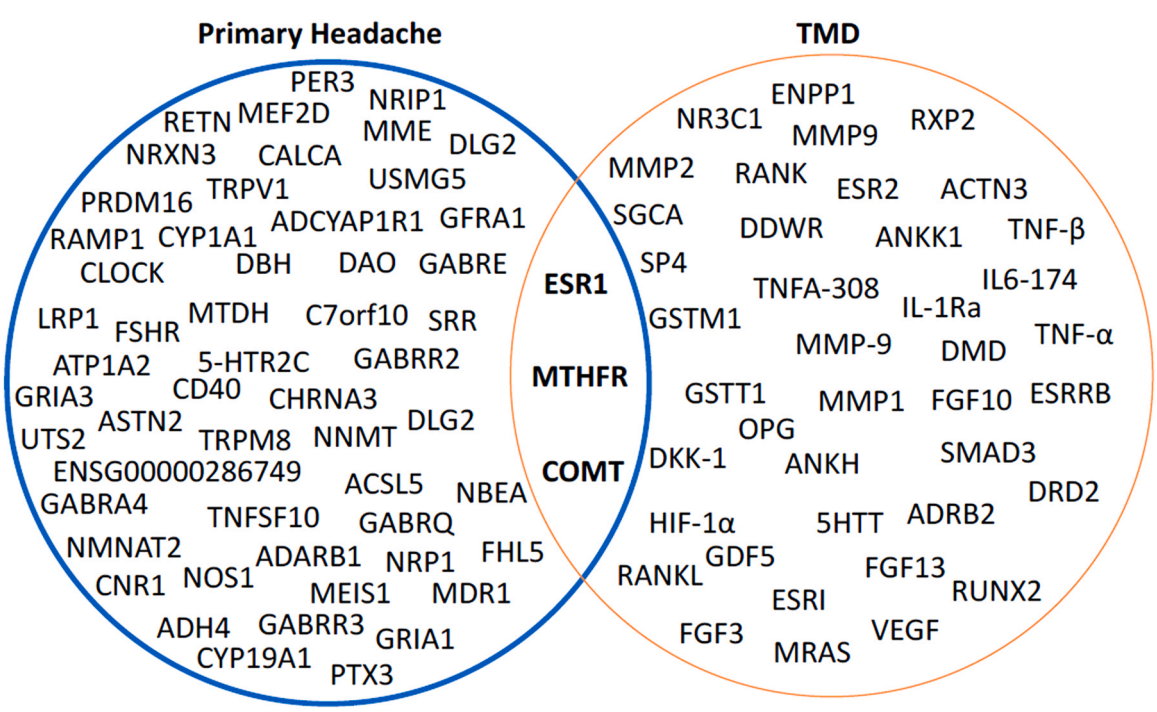

Fig. 2. Schematization of the collected data - Venn Diagram of the included genes of both Primary Headaches and Temporomandibular Disfunction.

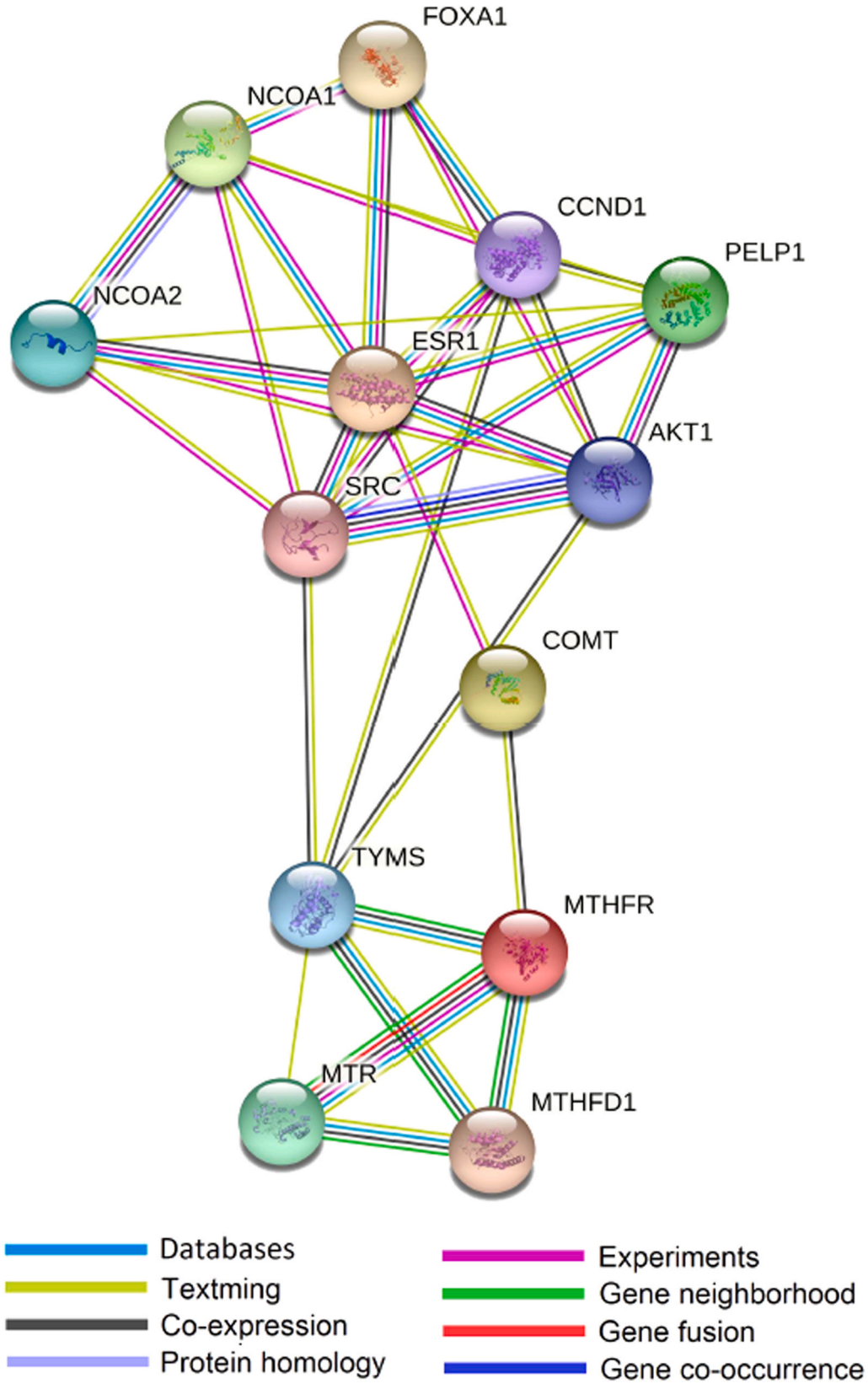

Fig. 3. Functional networks of genes and proteins interactions found to have an association between PHD and TMD within this systematic review. To build a functional network map the *MTHFR*, *ESR1* and *COMT* genes were analyzed using STRING software. The diverse clusters are colored differently.

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 (ICDH-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 dorsolateral prefrontal 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 therapeutical 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.

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Appendix A. Supporting information

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

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