Polymorphisms in COL2A1 gene in Adolescents with Temporomandibular Disorders

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Objectives: *Temporomandibular disorder (TMD) is considered a functional disorder with multifactorial aspects. The goal of this study was to investigate if genetic polymorphisms in the COL2A1 gene could be associated with TMD in adolescents.* ***Study design:*** *The case group (TMD-affected) included individuals diagnosed with any of the following TMD subgroups according to the RDC/TMD criteria: myofascial pain, disc displacements and arthralgia. Genomic DNA for molecular analysis was extracted from buccal cells and genetic polymorphisms in COL2A1 were genotyped by real time polymerase chain reactions using the TaqMan assay. Data were analyzed using the Epi Info 3.5.7 and Stata software.* ***Results:*** *249 subjects were included in this study (148 subjects "affected" by TMD). There were no significant differences between the affected and unaffected individual (p>0.05), for TMD, arthralgia and myofascial pain however, rs2276454 was borderline in the genotype distribution (p=0.07) and was associated with disc displacement (p=0.03) in the allelic distribution. Recessive model showed significant differences between groups for with disc displacement (p=0.02).* ***Conclusions:*** *Genetic polymorphisms in COL2A1 are not associated with myofascial pain, arthralgia or TMD in adolescents but this study provides evidence that rs2276454 is involved in the disc displacement of the temporomandibular joint.*

Keywords: *Adolescents, Genetics, Temporomandibular disorder, Polymorphisms.*

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INTRODUCTION

Temporomandibular disorders (TMDs) are defined as the set of factors that affect bones, muscles, temporomandibular joints (TMJs) and associated structures in the craniofacial area primarily characterized by joint and / or muscular pain, noise in the TMJ.[1] These conditions were deemed to occur primarily in adults; however, many recent studies have reported a growing prevalence of signs and symptoms of TMDs in adolescents. [2,3]

Symptoms occurred early in individuals with TMD, [4] but it is still unclear whether the symptoms of TMD are deviations from normality that indicate preclinical symptoms of the disorder [5] or are caused by a deviation from normality due to craniofacial changes occurring in the individual who is in growth, [6] or a combination of all these etiological factors. TMD is classically divided into three groups: group I included muscle diagnosis (myofascial pain and myofascial pain with limited opening); group II included disc displacements, with and without reduction, and group III that included arthralgia, osteoarthrosis, and osteoarthritis.[7] In cases that present painful symptoms, management is more difficult since the mechanisms that react in the presence of myofascial pain and arthralgia are not completely understood. [8,9] In addition, people with TMD represents a large proportion of the costs in the health services.[10]

Because of the movement of the mandible that include a combination of rotation and translation movement beside the movement of the disc, this articulation is one of the most complex joints of the human body.[11] Joint hypermobility can be explained by fibrocartilage found in temporomandibular joint (TMJ) discs. This fibrocartilage differs from hyaline and articular cartilage in the ratio of type I collagen to type II collagen. In TMJ disc, for example, predominates type I collagen,[12] with trace amounts of collagen type II located in the intermediate zone.[13]

The gene encoding the production of type II collagen is Collagen Type II Alpha 1 (*COL2A1*). This gene is located on chromosome 12q13.11-13.2 and provides instructions for the production of collagen type II [14] and consists of 54 exons that encode 1487 amino acids of the protein. Genetic alterations in the *COL2A1* gene have been reported in several diseases, such as congenital dysplasia, knee osteoarthritis, collagen diseases [15,16,17] and TMD.[18] Most of the changes in the *COL2A1* gene are simple nucleotide substitutions, called polymorphisms. [19,20,21] Genetic mutations in this gene generate an autosomal dominant spectrum that is responsible for bone dysplasias [22] and have been responsible for at least 16 articular disorders.[17] This information reinforces the role played by the gene and demonstrates its importance in the structural maintenance of the joints.

As far as we know, the influence of *COL2A1* gene on TMD development is unknown, so our hypothesis is that genetic polymorphisms in this gene could be involved as mediating factors in TMD etiology. Thus, the aim of this study case-control study was to evaluate the influence of genetic polymorphisms in *COL2A1* on TMD in adolescents.

MATERIALS AND METHOD

This study was approved by the local ethics committee (Process no. 2.006.086) and followed the Declaration of Helsinki guidelines. For this case-control study, based on the prevalence of TMD caries in adolescents, the sample size was estimated in 800 adolescents, aged 10 to 14 years. All legal guardians and adolescents received written information about the study, and signed consent term.

Screening questionnaire was used to screen the adolescents and TMD affected and TMD unaffected individuals and clinical examinations for diagnosis of TMD were performed. Adolescents were divided in groups according to the TMD classification. Case group included TMD-affected diagnosed with any of the following TMD subgroups according to the RDC/TMD criteria: myofascial pain (with or without limited opening), arthralgia and disc displacements (with and without reduction). The control group included individuals without any symptoms or signs of TMD.

Genomic DNA for molecular analysis was extracted from buccal cells. Genetic polymorphisms in *COL2A1* were genotyped by real time polymerase chain reactions using the TaqMan assay (stepOnePlus Real-Time PCR System/Applied Biosystems, Foster City, USA). The polymorphisms *COL2A1* gene (rs10422173 and rs3813034) were selected through the consultation of the International HapMap Project (www.hapmap.org) page, which is a union of several countries for the development of a map with patterns of variations of the DNA sequence. Gene and polymorphism characteristics are described in Table 1.

Clinical examination and DNA collection took place during 2016 and 934 individuals were listed. Data obtained from these examinations were previously published, [3,23] however for this study, DNA of a subset of these adolescents (N=249) was selected using a random number generator website (www.randomizer.org).

Adolescents who presented pain of odontogenic origin, whose heads and / or students did not agree to participate in the study, patients with orthodontic appliances, miorrelaxative plaques or prostheses, severe facial anomalies, dental anomalies, caries with extensive coronary destruction, severe periodontal problems, systemic disorders with cognitive or behavioral impairment, speech disorders, use of medications such as antidepressants, muscle relaxants, nonsteroidal anti-inflammatory drugs and severe psychiatric disorders were excluded.

Data were analyzed using the Epi Info 3.5.7 and Stata software (StataCorp, College Station, TX, USA, version 11). The study-dependent variables were: myofascial pain, arthralgia, disc displacement and TMD. The comparison group in all analysis were adolescents unaffected by any sing of TMD. The associations between affected and unaffected groups were analyzed by chi-square test or Fisher's exact test in dominant and recessive models. A level of significance of 0.05 was used.

Table 1–Genes and studied polymorphisms.

Gene	Position	Polymorphisms	MAF	Change Base
COL2A1	12q13.11	rs1793953	0,449	C/T
	12q13.11	rs2276454	0,429	C/T

Note: MAF mean minor allele frequency.

Obtained from database: ncbi.nlm.nih.gov

RESULTS

Table 2 summarizes the genotypes and alleles distributions among unaffected and affected groups for each variable (myofascial pain, arthralgia, disc displacement and TMD). There were no significant association between the affected and unaffected groups ($p>0.05$) and genotypes, however rs2276454 was borderline in the genotype distribution and significant in the allelic distribution ($p=0.03$).

Since the genotypic and allelic models showed no association between studied polymorphisms and TMD, the possible association with alleles in the recessive and dominant models was showed at the table 3. For disc displacement, the genetic polymorphism rs2276454, was associated with disc displacement in a recessive model ($p=0.02$) and the C allele was more present in the group of unaffected individuals suggesting that this allele is a protection factor for TMD (OR: 1.89; 1.07-3.31).

Table 2 . Genotype and allele distributions between different phenotype of TMD subgroups.

Phenotype	rs#	Groups	Genotype n (%)			p-value	Allele		p-value
			CC	CT	TT		C	T	
	rs1793953	Unffected	91(41.0)	96(43.2)	35(15.8)	0,96	278(62.6)	166(37.4)	0.93
		Affected	12(41.2)	12(41.2)	5(17,6)		36(62.1)	22(37.9)	
Myofascial Pain			CC	CT	TT		C	T	
	rs2276454	Unffected	31(13.9)	101(45.3)	91(86.8)	0,81	163(36.5)	283(63.5)	0.62
		Affected	4(13.3)	12(40.0)	14(46.7)		20(33.3)	40(66.7)	
			CC	CT	TT		C	T	
	rs1793953	Unffected	71(42.5)	72(43.1)	24(14.4)	0.89	214(64.1)	120(35.9)	0.68
		Affected	2(33.3)	3(50.0)	1(16.7)		7(58.3)	5(41.7)	
Arthralgia			CC	CT	TT		C	T	
	rs2276454	Unffected	25(14.8)	75(44.3)	69(40.9)	0.98	125(36.9)	213(63.1)	0.92
		Affected	1(14.2)	3(42.9)	3(42.9)		5(35.7)	9(64.3)	
			CC	CT	TT		C	T	
	rs1793953	Unffected	77(41.4)	78(41.9)	31(16.7)	0.67	232(62.3)	140(37.7)	0.88
		Affected	26(40.0)	30(46.1)	9(13.9)		82(63.1)	48(36.9)	
Disc Displacement			CC	CT	TT		C	T	
	rs2276454	Unffected	28(15.1)	88(47.5)	69(37.4)	**0.07**	144(38.9)	226(61.1)	**0.03**
		Affected	7(10.2)	25(36.9)	36(52.9)		39(28.6)	97(71.4)	
			CC	CT	TT		C	T	
	rs1793953	Unffected	42(40.7)	40(40.7)	19(18.6)	0.53	126(61.1)	80(38.9)	0.59
		Affected	61(41.2)	66(44.5)	21(14.3)		188(63.5)	108(36.5)	
TMD			CC	CT	TT		C	T	
	rs2276454	Unffected	14(13.7)	49(48.0)	39(38.3)	0.60	77(37.7)	127(62.3)	0.54
		Affected	21(13.9)	64(42.3)	66(43.8)		106(35.1)	196(64.9)	

DISCUSSION

In this case-control study with adolescents from Brazil, our hypothesis was that genetic polymorphisms in *COL2A1* gene could be associated with clinical signs and symptoms of TMD. We founded association between polymorphism rs2276454 and disc displacement raised the hypothesis that this gene might be involved in TMD etiology in adolescents.

Adolescence is a time of great hormonal changes, physical, emotional, and behavioral, which are fundamental for the individual's development into adulthood. Stage in which the anxiety can be frequent.[23] It has been observed that this period of life can also detect the first signs of TMD. High prevalence of TMD has been found in populations during adolescence.[3] Besides the emotional and behavioral changes in adolescence, biological changes may also be present, and therefore contribute to the increase in signs and symptoms of TMD.[24]

In fact, TMD is a multifactorial condition, and the contribution of each factor to development of TMD *still* remains *unclear. According RDC/TMD criteria, TMD could be classified in three different groups: muscle disorders, including myofascial pain, disc displacement and arthralgia. However myofascial pain and arthralgia characterize painful TMD,* the presence of any of the three conditions characterizes TMD.[8,25] and can be evidenced in this phase of life where physical and hormonal changes are quite common.[24]

We evaluated this three conditions in our study population. Regarding *Myofascial Pain, i*n the present study, a total of 30 (11.80%) adolescents were diagnosed positively despite that the perception of pain is particular for each individual, *the diagnosis of the myofascial pain is a challenge, particularly in this stage of life.* The prevalence reported here is lower than those reported in other studies.[7,24] Further study founded genotype association between myofascial pain and TMD but with *COMT* gene [26] but as far as we know, there is no association between this condition and genetic polymorphisms in the collagenase gene. We looked for this association but our results did not support the contribution of *COL2A1* gene towards myofascial pain because, both studied polymorphisms, showed not be associated with this condition.

Another variable analyzed in this study is arthralgia. Arthralgia, by definition, is the pain perceived unexpectedly by nociceptors located in the soft tissues adjacent to the joint during movement of the joint.[27] A study by Rukavina *et al* [28] showed a statistically significant main effect association polymorphisms in *COL2A1* and osteoarthritis. Although osteoarthritis is a different condition, it also involves structural proteins of the cartilage, so genes that codes for type II, like *COL2A1* could be candidate for studied. In our study, a few individuals reported arthralgia and there was no association between studied polymorphisms.

Disc displacement is the most common temporomandibular joint internal derangement and is characterized by an abnormal

Table 3. Analysis of polymorphisms in the dominant and recessive models.

Phenotype	rs#		Groups	Genotype n (%)		p-value	Odds ratio
		C		**CC + CT**	**TT**		
Myofascial Pain	rs1793953	Dominant	Unaffected	187(84.2%)	35(15.8%)	**0,83**	**1.11(0.39-3.11**
			Affected	24(82.7%)	5(17,6%)		
		T		**CT+TT**	**CC**		
		Recessive	Unaffected	131(59.1%)	91(40.9%)	0.98	1.01 (0.46-2.22)
			Affected	17(58.6%)	12(41.4)		
	rs2276454	T		CT + TT	CC		
		Dominant	Unaffected	192(86.1%)	31(13.9%)	0.93	0.95(0.31-2.91)
			Affected	26(86.6%)	4(13.4%		
		C		**CC + CT**	**TT**		
		Recessive	Unaffected	132(59.1%)	91(40.9%)	0.54	1.26(0.59-2.72)
			Affected	16(53.3%)	14(46.7%)		
Arthralgia	rs1793953	C		**CC + CT**	**TT**		
		Dominant	Unaffected	143(85.6%)	24(14.4%)	0,87	1.19(0.13-10.6)
			Affected	5(83.3%)	1(16,7%)		
		T		**CT+TT**	**CC**		
		Recessive	Unaffected	96(57.41%)	71(42.6%)	0.65	0.67 (0.12-3.79)
			Affected	4(66.6%)	2(33.4%)		
	rs2276454	T		**CT + TT**	**CC**		
		Dominant	Unaffected	144(85.2%)	25(14.8%)	0.97	0.96(0.11-8.31)
			Affected	6(85.7%)	1(14.3%		
		C		**CC+CT**	**TT**		
		Recessive	Unaffected	100(59.1%)	69(40.9%)	0.91	1.08(0.23-5.01)
			Affected	4(57.1%)	3(42.9%)		
Disc displacement	rs1793953	C		**CC + CT**	**TT**		
		Dominant	Unaffected	155(83.3%)	31(16.7%)	0,59	0.80(0.36-1.19)
			Affected	56(86.1%)	9(13,9%)		
		T		**CT+TT**	**CC**		
		Recessive	Unaffected	109(58.6%)	41(41.8%)	0.95	1.01 (0.57-1.79)
			Affected	39(40.4%)	28(59.6%)		
	rs2276454	T		**CT + TT**	**CC**		
		Dominant	Unaffected	157(84.8%)	28(15.2%)	0.64	0.64(0.26-1.55)
			Affected	61(89.7%)	7(10.3%		
		C		**CC+CT**	**TT**		
		Recessive	Unaffected	116(62.7%)	69(37.3%)	0.02	1.89(1.07-3.31)
			Affected	32(47.1%)	36(52.9%)		
TMD	rs1793953	C		**CC + CT**	**TT**		
		Dominant	Unaffected	84(81.5%)	19(18.5%)	0,36	0.73(0.37-1.44
			Affected	127(85.8%)	21(14,2%)		
		T		**CT+TT**	**CC**		
		Recessive	Unaffected	61(59.2%)	42(40.8%)	0.94	1.01 (0.61-1.69)
			Affected	87(58.7%)	61(41.3)		
	rs2276454	T		**CT + TT**	**CC**		
		Dominant	Unaffected	88(86.2%)	14(13.8%)	0.96	1.01(0.49-2.10)
			Affected	130(86.1%)	21(13.9%)		
		C		**CC+CT**	**TT**		
		Recessive	Unaffected	63(61.7%)	39(38.3%)	0.38	1.25(0.75-2.09)
			Affected	85(56.2%)	66(43.8%)		

relationship of the disc to the mandibular condyle, articular eminence and glenoid fossa.[29] For diagnosis of disc displacement, comprehensive assessments both from somatic and psychological aspects for each TMD patient are necessary, especially for the patients with chronic pain.[30] Disc displacement can be classified in with reduction and without reduction, in the first case the disc returns the initial position during the closing of the mouth while in the second the reduction does not occur.[31] Prevalence of this condition increases with age and it seems that biomechanical factors contribute decisively to its occurrence. In addition the mean peak occurs during the years of adolescence.[32] In our study we included both cases, with and without reduction, and the prevalence of this condition was around 10%.

A previous study investigate and found association between the polymorphism of MMP-1 with the susceptibility to anterior disc displacement in TMD individuals [33] point to genetic factor that contribute for this condition. In the present study, the investigation of the *COL2A1* gene related to some evidence that this gene could contribute to disc displacement and TMD etiology. To the best of our knowledge, this is the first research that investigates if genetic polymorphism in *COL2A1* gene is associated with TMD. Indeed, there is a wide spectrum of evidence and clinical situations associated with genetic alterations in *COL2A1* gene with collagenopathies, like achondrogenesis type II and skeletal dysplasia but there is no association with TMD. In our study we found evidence that associated dislocation with polymorphism rs2276454 suggesting that this polymorphism may contribute to disc displacement.

CONCLUSION

In the present study, despite its limitations, the investigation of these two polymorphism was related to some evidence that *COL2A1* could contribute to TMD etiology. In fact, to the best of our knowledge, this is the first research that investigates if genetic polymorphisms in *COL2A1 is* associated with TMD.

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