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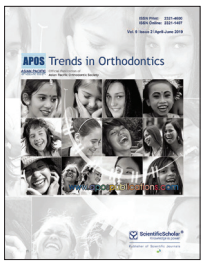

Systematic Review and Meta-analysis

Association of TGFB3 and FGFs gene polymorphisms with cleft lip with or without cleft palate a systematic review

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ABSTRACT

Objectives: The objective of this study was to conduct a systematic review of the possible association between transforming growth factor B3 (TGFB3) and fibroblast growth factors (FGFs) gene polymorphisms and non-syndromic cleft lip with or without cleft palate (NSCL/P).

Material and Methods: Two reviewers independently screened studies by examining all titles and abstracts. Studies were included if they met the following criteria: The outcome of interest was NSCL/P; the polymorphisms studied were TGFB3 and FGF; they presented sufficient data, that is, allele/genotype frequency between cases and controls; or their odds ratio with 95% confidence interval. Study quality was independently assessed by a risk of bias assessment for genetic association studies.

Results: Based on the inclusion criteria, we have selected a total of six articles (four for TGFB and two for FGF). Particularly for the TGFB gene, we have found significant results in exon 4 in the variant g.15812T>G, and in the single-nucleotide polymorphisms rs2300607 A/T, in the distribution between cases and controls. On the other hand, for the FGF gene, we observed a statistically significant in the genotype rs34010 CA.

Conclusion: None of the genetic variations that show the association is verified in different populations; therefore, there is not enough scientific validation regarding the association between TGFB and FGF polymorphism and NSCL/P. The findings of the different studies suggest the need for further investigations with samples composed of a larger number of individuals in different populations, which should be performed with all the standards for genetic studies, thus allowing an understanding of the molecular basis of the disease.

Keywords: Transforming growth factor B3 gene, Fibroblast growth factors genes, Polymorphism, Non-syndromic cleft lip with or without cleft palate

INTRODUCTION

Clefts of the lip and/or palate are among the most common congenital defects worldwide, characterized by their high genetic component and affect 1 in every 700 live births,[1] of which 70% of the cases are non-syndromic and 30% are syndromic.[2-4] Syndromic forms are usually caused by chromosomal aberrations or monogenic diseases, while non-syndromic forms derive from the interaction between genetic and environmental factors.[2,3]

The upper lip and palate are formed by the fusion of components of the frontonasal process and the maxillary processes; and failures in these events during development cause the appearance of the cleft lip with or without a cleft palate.[5,6] Thus, murine and knock-out mouse models have

allowed the identification of several genes and even different chromosomal loci as involved in cleft formation.[7,8]

For example, the Transforming Growth Factor-B3 Gene (transforming growth factor B3 [TGFB3], 14q24.3) is expressed in the epithelial cells of the medial border of the palatal processes and participates in events including: Membrane degradation, metalloproteinase-mediated remodeling of the extracellular matrix, and epithelial-mesenchymal transformation, which together generate the confluence of processes during palate formation.[9] Interestingly, studies in ethnically contrasting populations have verified positive findings between TGFB3 gene alterations and non-syndromic cleft lip with or without cleft palate (NSCL/P).[10,11] Most of these studies have been performed in white and Asian populations, thus reflecting the heterogeneity of the cleft phenotype as well as variability in environmental risk factors.[10-12]

Similarly, it has been verified that the fibroblast growth factors (FGFs) and its receptors play a crucial role through the regulation of cell proliferation, differentiation, and motility which are necessary for the development of the palate and upper lip.[13] Mutations in the genes coding these molecules have been shown to contribute significantly to the development of syndromic orofacial clefts, such as Apert syndrome.[14] In addition, case–control studies have shown evidence of the association of single-nucleotide polymorphisms (SNPs) in FGFs genes with susceptibility or decreased risk of NSCL/P, depending on the polymorphism and the gene analyzed.[15]

However, no single candidate gene has been consistently identified in all studies.[10-15] Therefore, the present study aims to perform a systematic review of the possible association between polymorphisms in TGFB3 and FGFs genes and NSCL/P.

MATERIAL AND METHODS

Based on the guidelines for preferred reporting elements for systematic reviews in the RevMan manual,[16] the specific PICO question[17] "What is the association of polymorphisms in TGFB3 and FGFs genes with NSCL/P?," was developed being:

(P) Participants: Patients with cleft lip and palate.
(I) Interventions of interest: TGFB3 and FGFs genes.
(C) Controls: Groups of patients without cleft lip and palate.
(O) Outcome measures: Would be the association of polymorphism with cleft lip and palate.

The relevant studies for the present systematic review were identified in the digital databases of PubMed, Scielo, BVS, AJODO, and Google Scholar, and the last search in all databases was performed on January 31, 2022. The search terms used were the following: "Gene polymorphism and cleft lip," "gene polymorphism and cleft palate," "gene polymorphism and cleft lip and cleft palate," "genetic and cleft lip," and "genetic and cleft palate."

Two reviewers (Andrea Soledasd Quizhpi-Quito, Diego Mauricio Bravo-Calderon) independently selected studies by examining all titles and abstracts. Any association study in humans, and meeting the following criteria were included in the study: the outcome of interest was NSCL/P, the polymorphisms studied were TGFB3 and FGFs, presenting sufficient data, that is, allele/genotype frequency between cases and controls; or their odds ratio (OR) with 95% confidence interval (CI). Reference lists of selected articles were also reviewed to identify additional relevant publications. On the other hand, animal studies, family-based studies, case reports, and publications with insufficient information such as letters from the author were excluded and, specifically for the TGFB3 gene, studies before December 2013 were not considered because the most recent systematic review on the subject was published on the aforementioned date.[18] In sequence, the lists of articles were compared, validated and disagreements were resolved by consensus among the reviewers. [Figure 1] summarizes the literature search strategy according to PRISMA guidelines. The pattern of the present systematic review was customized to summarize mainly relevant data.

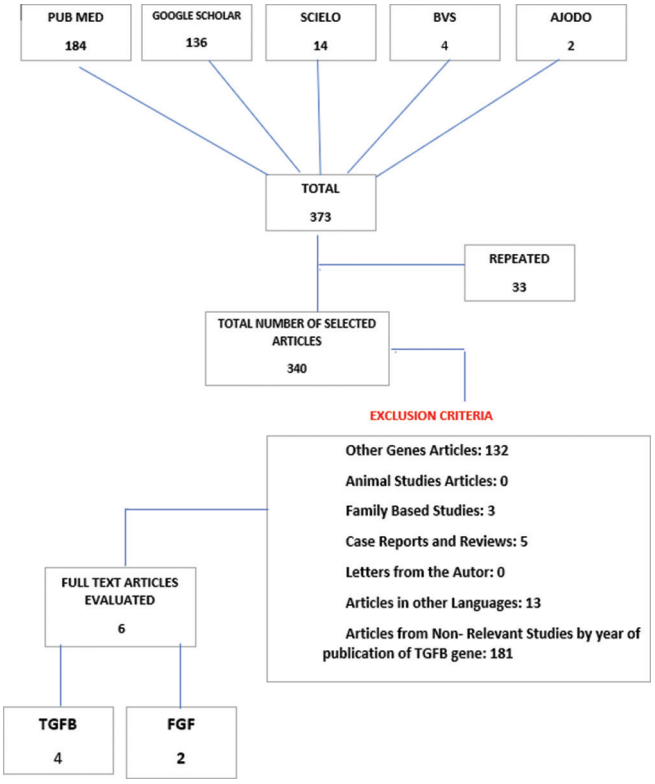

Figure 1: Flow chart for item selection.

Data extraction

A data extraction sheet was developed in Microsoft Excel, from the selected studies, the information was extracted from each study including: title, author, year of publication, database, type of gene, SNPs, type of study, and being genetic in nature, it was checked if they performed Hardy–Weinberg equilibrium (HWE).

Risk of bias assessment

Study quality was independently assessed using a risk of bias assessment for genetic association studies.[19,20] Briefly, the following domains were analyzed: Selection bias, information bias, and HWE assessment, whereby, each item was scored as 2; 1 or 0; corresponding to low risk of bias, high risk of bias, or unclear/insufficient information, respectively. Total scores ranged from 0 (worst) to 13 (best).

RESULTS

The search in the databases PubMed, Scielo, BVS, AJODO, and Google Scholar allowed us to locate a total of 373 studies, being that, after the exclusion of 33 duplicate records, 340 remained for further review. Of these 340 articles, 334 studies were discarded because after reading the abstracts, these articles clearly did not meet the inclusion criteria [Figure 1].

The reasons for ineligibility were mainly due to non-relevant genes or populations and studies published in years before the range established in the present review. Thus, there were finally six publications that were included in the systematic review, four for the TGFB3 gene, and two for the FGFs genes. The PRISMA flow chart provides an overview of the selection process of the polymorphisms studied and the number of studies selected [Figure 1].

[Table 1] describes the general characteristics of the selected studies. Among the selected articles, five had a case–control design, and one was of cross-sectional type. Regarding ethnicity, two studies were conducted in Asian, two in European, and two in Latino populations. Particularly for the TGFB3 gene, genetic variations located in exons 1–7[10-21] and the SNPs: rs2300607, rs2268625,[11] rs369477964, rs375973742, and rs117462711,[22] were studied.

In the study conducted by Ghazali *et al*. 2014,[10] exons 1–7 were analyzed, finding significant results for exon 4, indicating that individuals harbored the g.15812T.G variant with an OR of 0.313 and 95% CI: 0.082–1.191, $P = 0.089$; while, for the g.15966A.G variant with an OR of 0.356 and 95% CI: 0.092–1.382. $P = 0.315$ [Table 1].

On the other hand, the study by Oner and Tastan, in 2017, revealed two polymorphisms in exon 1: Pro10Leu and Arg25Pro, analyzing a total of 80 cases and 125 control patients. The differences in frequencies of CT and TT genotypes in the case group were not statistically significant compared to controls, OR = 2.18; 95% CI = 0.94–5.6; $P = 0.06$ and OR = 1.46; 95% CI = 0.67–3.19; $P = 0.315$, respectively. For the Arg25Pro polymorphism, there were 74 subjects out of the group of 80 cases. The frequency of the GC genotype was higher compared to the control group OR = 1.31 95% CI: 0.48–3.64, $P = 0.79$, but was not statistically significant. The frequency of C alleles was higher in cases than in controls OR = 0.29, 95% CI: 0.48–3.52, $P = 0.8$, but the differences were not significant [Table 1].

SNP rs2300607 A/T, from the study by Aljabeiti *et al*. 2017,[11] had a total of 237 cases and 168 controls, the χ^2 test revealed a statistically significant difference in the distribution of genotypes between cases and controls with the following $P = 0.0206$; $\chi^2 = 0.7626$ [Table 1]. Likewise for SNP rs2268625 C/T, 237 cases and 98 controls were analyzed, indicating that the distribution of rs2268625 C/T SNP genotypes differed significantly between cases and controls with $P = 0.041$ [Table 1].

In the study by Kumari *et al*. 2018,[22] the SNP rs3917219 was genotyped in 162 cases and 108 controls but revealed no association with FLAPNS. The SNP rs369477964 and rs375973742 were present in two cases and two controls, of the 162 cases and 108 controls analyzed, and finally, the SNP rs117462711 registered only two cases, obtaining $P < 0.001$ [Table 1].

While, for FGFs, the following SNPs were studied: rs6790664, rs11717284, rs1464942, rs12106855, rs1875735,[23] rs34010, and rs13317.[15] Regarding the FGF SNPs, of the genotypic frequencies observed in the study conducted by De Aquino, with 300 cases and 365 controls, none showed an association with NSCL/P, likewise the controls did not show significant differences. In the SNPs studied by Rafiqdoost *et al*.,[15] a statistically significant difference was observed between cases and controls in the rs34010 CA genotype with the following OR values = 0.29, 95% CI = 0.16–0.55, $P = 0.001$. With respect to the FGF rs13317 AG variant, no statistically significant values were found between the genotypic frequencies of patients and controls in the models analyzed [Table 2].

As shown in [Table 3], the quality analysis verified a score that varied between 6 and 10 points for the studies on the TGFB3 gene, and as for HWE, only 50% performed it.

On the other hand, the value ranged between 9 and 10 points for the investigations on FGFs genes, and all FGFs polymorphisms measured HWE [Table 4].

DISCUSSION

The findings found in each study analyzed are detailed below. Once the articles have been selected, it should be noted that, for the TGFB gene, two papers, despite not

Table 1: General characteristics of the included studies about TGFB genes.

Title	Author	Country	Ethnia	Study design	Number of cases	Number of controls	Snp/Exon	Locus	Variant/ Allele	OR	95% IC	*P*-value
Screening of transforming growth factor beta 3 and jagged2 genes in the Malay population with non-syndromic cleft lip with or without cleft palate	Ghazali *et al.* 2014[10]	Malasia	European	Cross – sectional	96	96	EXON 1–7	TGFB3	g. 15812T.G g. 15966A.G	0.313 0.356	(0.082–1.191) (0.92–1.382)	*P*=0.089 *P*=0.315
Association between the transforming growth factor beta 1 gene polymorphisms and Turkish patients with non-syndromic cleft lip with/without cleft palate	Oner and **Tastan** 2016[21]	Turqui	European	Case control	80	125	EXON 1	TGFB3	Pro10Leu Arg25Pro	CT 2.18 TT 1.46 GC 1.31 CC 0.29	CT (0.94–5.06) TT (6.67–3.19) GC (0.48–3.64) C (0.48–3.52)	CT *P*=0.06 TT *P*=0.66 GC *P*=0.79 C *P*=0.80
Association of TGFβ3 variants with non-syndromic cleft lip and palate in guatemalan population	Aljabeiti *et al.* 2017[11]	Guatemala	American	Case control	237	266	rs2300607 rs2268625	TGFB3	rs2300607 A/T rs2268625 C/T			*P*=0.020 *P*=0.041
TGFB3, MSX1, and MMP3 as candidates for NSCL+P in an Indian population	Kumari *et at.* 2018[22]	India	Asia	Case control	162	108	rs3917219 rs369477964 rs375973742 rs117462711	TGFB3	rs3917219 rs369477964 rs375973742 rs117462711			*P*=0.008 *P*<0.001

TGFB: Transforming growth factor beta, MSX: Muscle segment homeobox, MMP: Metalloproteinases, NSCL/P: Non-syndromic cleft lip with or without cleft palate

Table 2: General characteristics of the included studies about FGFs genes.

Title	Author	Country	Ethnia	Study design	Number of cases	Number of controls	Snp/Exon	Locus	Variant/ Allele	OR	95% IC	*P*-value
Polymorphisms in FGF12, VCL, CX43 and VAX1 in Brazilian patients with non-syndromic cleft lip with or without cleft palate	Aquino *et al.* 2013[23]	Brasil	American	Case control	300	385	rs6790664	FGF	rs6790664 C/A	1.11	(0.87–1.41)	*P*=0.56
							rs11717284		rs11717284	0.74	(0.58–0.95)	*P*=0.91
							rs1464942		rs1464942	0.94	(0.72–1.24)	*P*=0.5
							rs12106855		rs12106855	1.12	(0.87–1.43)	*P*=0.53
							rs1875735		rs1875735	0.93	(0.72–1.18)	*P*=0.76
Investigation of FGF1 and FGFR gene polymorphisms in a group of Iranian patients with non-syndromic cleft lip with or without cleft palate	Rafiqdoost *et al.* 2014[15]	Irani	Asia	Case control	100	100	rs34010	FGF1	rs34010 C/A	0.29	(0.16–0.55)	*P*=0.001
							rs13317		rs13317 A/G	0.84	(0.46–1.56)	*P*=0.588

FGF: Fibroblast growth factors, VCL: Vinculin, VAX: Ventral anterior homeobox, FGFR: Fibroblast growth factor receptor

performing the HWE balance, we consider that they have a high score in the quality analysis; this is because they meet other methodological parameters but emphasize the need to perform the HWE analysis in genetic studies.[24]

Although NSCL/P is among the most common congenital defects, the exact genetic and environmental events associated with its pathogenesis are still unknown.[11-23] Identification of the genetic alterations causing NSCL/P could lead to a better understanding of the molecular basis of the disease, and of craniofacial development.[22-23]

The present systematic review focuses on two genes, TGFB3 and FGF, which are involved in facial development, and some of their variants have been shown to be risk factors for NSCL/P, although to different degrees.[10-22]

Particularly for the TGFB3 gene, Ghazali *et al.*, in 2014, considered the g.15812T>G variant as a polymorphism because it was present in more than 1% of the study population, and also indicates that the side most affected by clefting was the left side, which was affected 2.8 times more frequently than the right, possibly because blood is more abundant on the right side than on the left.[10]

On the other hand, Oner and Tastan, in 2016, indicates that no statistically significant differences were found in the Pro10Leu and Arg25Pro variants in exon 1.[21] However, it is demonstrated that genetic evidence of TGFB is functionally required for secondary palate formation.[10-21]

Likewise, in the study conducted by Aljabeiti *et al.* 2017,[11] in the population of Guatemala, the results showed, for the first time, the association between TGFB3 rs2268625 C/T polymorphism and NSCL/P, which coincide with the results found in the study Ichikawa *et al.*, in a Japanese population in the rs2300607 A/T polymorphism.[25] In this study, comparisons of allele frequencies for both mutations were made, finding a higher proportion of mutated alleles in cases compared to controls.[11] Therefore, it is suggested that both mutations of the TGFB3 gene are involved in the etiology of NSCL/P.[11]

In relation to FGFs genes, in the study conducted by De Aquino *et al.* 2013, in a Brazilian population, no significant association of FGF12 with NSCL/P was found, the author indicates that this is due to the sample size used in the study; therefore, it is possible that associations of polymorphisms and cleft risk were overlooked, indicating that their study was based on samples from European studies,[23] and also performed additional analyses on the dominant and recessive genetic models which also revealed no differences in the distribution between groups.[23]

In the SNPs studied by Rafiqdoost *et al.*, in 2014, a statistically significant difference was observed between NSCL/P patients and the control group in SNP rs34010.[15] The FGF1 rs34010

Table 3: Bias risk analysis of included studies about TGFB genes.

Parameters	Articles on TGFB gene polymorphisms											
	Ghazali *et al.* 2014[10]			Oner and Tastan 2016[21]			Aljabeiti *et al.* 2017[11]			Kumari *et al.* 2018[22]		
	2	1	0	2	1	0	2	1	0	2	1	0
Representativeness of the cases												
Consecutives/randomly selected from the population of cases with a clearly defined sampling frame												
Consecutive/randomly selected from the case population without a clearly defined sampling frame or broad inclusion/exclusion criteria		x			x			x			x	
No selection method is described												
Representativeness of the controls												
Controls were drawn consecutively/randomly from the same sampling frame (neighborhood/community) as cases												
Controls were drawn consecutively/randomly from a different sampling frame as cases		x			x			x			x	
Not described												
Determination of flaps												
Clearly described objective criteria for the diagnosis of NSCL/P	x			x			x			x		
Diagnosis of NSCL/P by patient self-report or patient history												
Not described												
Verification of controls												
Controls were tested to rule out NSCL/P	x			x						x		
Controls were subjects who did not report NSCL/P; no objective tests								x				
Not described												
Evaluation of the partnership												
Evaluate the association between genotypes and NSCL/P with appropriate statistics and adjustment for confounding factors	x									x		
To evaluate the association between genotypes and NSCL/P with appropriate statistics without adjustment for confounding factors					x			x				
Inappropriate statistics used												
Genotyping test*												
Genotyping performed under the "blind" condition without knowledge of the sample group												
Not blinded or not mentioned			x			x			x			x
Hardy–Weinberg equilibrium												
Hardy–Weinberg equilibrium in the control group					x					x		
Hardy–Weinberg disequilibrium in the control group												
Without testing Hardy–Weinberg equilibrium			x						x			
Total, risk of bias		8			9			6			10	

NSCL/P: Non-syndromic cleft lip with or without cleft palate, TGFB: Transforming growth factor beta

CA genotype had a markedly higher frequency in controls compared to NSCL/P; and in the CA + AA genotype, it was more frequent in the control group.[15] With respect to the FGF1 rs13317 AG variant, no statistically significant values were found between genotypic frequencies.[15] Highlighting the protective role of the FGF1 rs34010 C/A polymorphism, therefore, the FGFs signaling pathway has constant functions in lip and palate morphogenesis, and the perturbation of its expression patterns sometimes leads to cleft pathogenesis.[15]

On the other hand, in the study conducted by De Aquino *et al.* 2013, in a Brazilian population, no significant association of FGF12 with NSCL/P was found, the author indicates that this is due to the sample size used in the study; therefore, it is possible that associations of polymorphisms and cleft risk were overlooked, indicating that his study was based on samples from European studies.[23]

In summary, understanding the etiology of NSCL/P patients may help to predict and prevent its occurrence in the future. Specifically, the present review did not verify significant associations between gene polymorphisms TGFB3 and FGF with NSCL/P, and these results may be based on the limited number of studies exploring these relationships and the ethnic variability of the populations among the investigations analyzed.

Table 4: Bias risk analysis of included studies about FGFs genes.

Parameters	Articles on FGF gene polymorphisms					
	Aquino *et al.* 2013[23]			Rafiqdoost *et al.* 2014[15]		
	2	1	0	2	1	0
Representativeness of the cases						
Consecutives/randomly selected from the population of cases with a clearly defined sampling frame						
Consecutive/randomly selected from the case population without a clearly defined sampling frame or broad inclusion/exclusion criteria		x			x	
No selection method is described						
Representativeness of the controls						
Controls were drawn consecutively/randomly from the same sampling frame (neighborhood/community) as cases						
Controls were drawn consecutively/randomly from a different sampling frame as cases		x			x	
Not described						
Determination of flaps						
Clearly described objective criteria for the diagnosis of NSCL/P	x			x		
Diagnosis of NSCL/P by patient self-report or patient history						
Not described						
Verification of controls						
Controls were tested to rule out NSCL/P	x			x		
Controls were subjects who did not report NSCL/P; No objective tests						
Not described						
Evaluation of the partnership						
Evaluate the association between genotypes and NSCL/P with appropriate statistics and adjustment for confounding factors						
To evaluate the association between genotypes and NSCL/P with appropriate statistics without adjustment for confounding factors		x			x	
Inappropriate statistics used						
Genotyping test*						
Genotyping performed under the "blind" condition without knowledge of the sample group		x				
Not blinded or not mentioned						x
Hardy–Weinberg equilibrium						
Hardy–Weinberg equilibrium in the control group	x			x		
Hardy–Weinberg disequilibrium in the control group						
Without testing Hardy–Weinberg equilibrium						
Total, risk of bias		10			9	

*Parameter evaluated as 1=low risk and 0=high risk. NSCL/P: Non-syndromic cleft lip with or without cleft palate, FGF: Fibroblast growth factors

Moreover, facial development and its alterations, such as NSCL/P, are not only determined by genes, but also by their interaction with environmental factors such as habits, nutrition, and trauma.[26]

On the other hand, it should be noted that in this review age or gender was not considered as a determining factor because they are birth defects and measurements of genetic expressions are taken among affected individuals.

CONCLUSION

None of the genetic variations that show the association is verified in different populations; therefore, there is not enough scientific validation regarding the association between TGFB and FGF polymorphism and NSCL/P. Therefore, the findings of the different studies suggest the need for new research with samples composed of a larger number of individuals in different populations, which should be performed with all the standards for genetic studies, thus allowing to have certified information that would allow a better understanding of the molecular basis of the disease.

Ethical approval

The Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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Data availability

Data sets related to this article will be available upon request to the corresponding author.

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