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ARTICLE

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Interleukin 1 alpha genetic polymorphisms as potential biomarkers for oral health-related quality of life in Para athletes

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Abstract

Aims: To assess the impact of dental caries on OHRQoL in Para athletes and to evaluate whether *interleukin 1 alpha* **(***IL1A)* (rs17561, rs1304037)*, interleukin 10 (IL10)* (rs1800871), and *interleukin 1 receptor antagonist (IL1RN)* (rs9005) genes are potential biomarkers for OHRQoL in Para athletes.

Materials and Methods: A cross-sectional study consisting of 264 Para athletes (athletics, 143; powerlifting, 61; and swimming, 60) aged between 14 and 79 years was conducted. The decayed-missing-filled teeth index was used for the clinical evaluation. The Brazilian version of the Oral Health Impact Profile (OHIP-14) was used to measure the OHRQoL. Genomic DNA was extracted from the saliva. Genetic polymorphisms were analyzed by real-time polymerase chain reaction. Descriptive and bivariate analyses were performed.

Results: The overall mean OHIP-14 score observed was 6.24 (standard deviation, 7.05) and 10.03 (standard deviation, 8.11) in Para athletes with no caries experience and with caries experience, respectively ($p = .002$). Para athletes with the A allele in the *IL1A* gene (rs17561), in a dominant model, had a significantly higher risk of poor psychological discomfort than those with the other allele ($p = .03$).

Conclusion: Dental caries affected the OHRQoL in Para athletes. *IL1A* genetic polymorphisms were the potential biomarkers for OHRQoL in Para athletes.

KEYWORDS
genetic polymorphisms, oral health, para athletes, quality of life

1 | INTRODUCTION

One billion people, or 15% of the world's population, live with some form of long-term disability, with 2%–4% experiencing significant difficulties in functioning.[1] Sports can be an efficient way for the promotion of health, disability rights, and social integration for individuals with disabilities.[2] Sports activity has also contributed to increased self-confidence, self-acceptance, and psychological balance promoting a healthy lifestyle, life satisfaction, and improving health-related quality of life (HRQoL).[3]

The Paralympic movement start started as a rehabilitation practice, and has become a high-performance expression.[4] The Paralympic Games is the most important competition for persons with impairment, and during the event the Local Organize Committee provide multidisciplinary support - physicians, nurses, physiotherapists, massage therapists, acupuncturists, orthotic technicians, and podiatrists and dentists.[5] During the 2010 Winter Paralympic games medical services recorded 204 dental treatments.[5]

A systematic review including 34 studies concluded that athletes participating across a wide range of sports had poor oral health. Dental caries affected the majority of the athletes included in these studies and the prevalence of periodontitis was high.[6] Moreover, several studies have reported that oral health affects the performance of athletes[6–8] and negatively affects oral health-related quality of life (OHRQoL).[9]

The Consortium for Genetics and Quality of Life Research (GeneQoL) developed a list of potential biological markers, such as candidate genes, involved in quality-of-life outcomes.[10] They suggested that some genes associated with HRQoL through symptoms, such as pain, fatigue, and negative (depressed mood) and positive (well-being/happiness) emotional and social functioning.[11] Some studies related to health sciences have recently explored the genetic basis of HRQoL.[12–16] Among the candidate genes reported by the GeneQoL consortium study, *interleukin 1 alpha (IL1A), interleukin 1 10 (IL10)*, and *interleukin 1 receptor antagonist (IL1RN)* were associated with HRQoL symptoms related to general health, such as pain, fatigue, and emotional and social functioning.[11]

To the best of our knowledge, there are no studies in the dentistry field assessing the impact of genetic polymorphisms on the OHRQoL of Para athletes with dental caries. Furthermore, it is necessary to explore genetic biomarkers for OHRQoL in Para athletes. Therefore, in this study, we first assessed the impact of dental caries on OHRQoL in Para athletes. Second, we evaluated whether genetic polymorphisms in *IL1A, IL10*, and *IL1RN* genes are potential biomarkers for OHRQoL in Para athletes. The null hypothesis tested was that dental caries does not affect OHRQoL, and genetic polymorphisms in *IL1A, IL10*, and *IL1RN* genes are not associated with an increased risk of poor OHRQoL.

2 | MATERIALS AND METHODS

2.1 | Ethical approval, type of study, and sampling

The study was approved by the local Committee of Human Participation in Research (#3.261.377), and appropriate written informed consent was obtained from all participants. The study followed the guidelines of the Strengthening the Reporting of Genetic Association study statement checklist.[17]

It was used a non-probabilistic convenience sampling composed of Para athletes, participating in the regional Brazilian competition, organized by the Brazilian Paralympic Committee, between April 12 and 14, 2019; in Curitiba, Paraná, Brazil. The event process involved athletes who participated in athletics, powerlifting, and swimming (Figure 1).

The exclusion criteria were as follows: Para athletes who did not sign an informed consent form, did not fill out the forms properly, or had an intellectual impairment that affected their ability to answer a questionnaire.

2.2 | Data collection

2.2.1 | Non-clinical data

Demographic data included questions regarding age, sex, education, and sport practiced.

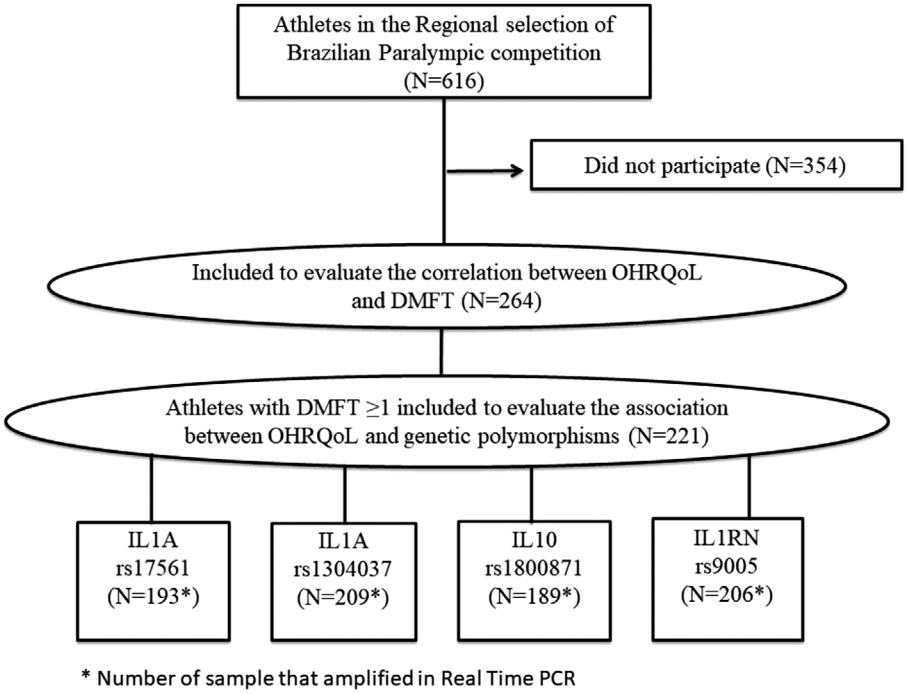

FIGURE 1 Study design flowchart

For the evaluation of OHRQoL, the Brazilian version of the Oral Health Impact Profile (OHIP), measured by the 14-question instrument (OHIP-14), was applied. A professional, previously trained, performed the interviews of the OHIP-14. The response categories of OHIP-14 were based on a five-point Likert scale (0 = never, 1 = rarely, 2 = sometimes, 3 = often, and 4 = always) and study participants could select one of the five options.[18,19] These scores were calculated by addition of the Para athletes' responses. The OHIP-14 value for each of its seven domains was also analyzed separately. This assessment method ranged from 0 to 56. High scores indicated poor OHRQoL.

The sociodemographic data and information regarding the oral health indicators were collected through interviews with Para athletes.

2.2.2 | Clinical data

A team composed of dentists (LSA, LAA, RVH) and note-takers (JAB, MFP), who were previously trained, performed the Para athlete's oral examination. The calibration process was coordinated by an experienced examiner in epidemiological surveys (gold standard), who guided the conduct of the theoretical and practical training steps. Inter-examiner and intra-examiner Kappa values after calibration was higher than 0.90 indicating a high degree of data reproducibility.

The oral examination was performed at the competition site with the Para athlete seated in a chair, using natural light, tongue depressors, and gauze. The decayed-missing-filled teeth (DMFT) index recommended by the World Health Organization for oral health surveys was used.[20] The number of teeth with dental caries (D), missing teeth (M), and teeth with fillings (F) were recorded, and the DMFT index was calculated.

The determination of the phenotypes was based on caries experience as follows: caries-free Para athletes (DMFT = 0; control group), and caries experience Para athletes (DMFT ≥1; case group).

2.2.3 | Deoxyribonucleic acid sample collection and genotyping

Genomic Deoxyribonucleic acid (DNA) for genotyping analysis was extracted from the buccal cells isolated from the saliva. Buccal cells were collected by rinsing the mouth for 60 s with 15 ml of saline and expectorating the rinse in a 50 ml propylene tube. The samples were stored at -20°C until the beginning of the DNA extraction step as previously described and established.[21]

Para athletes were asked to vigorously rinse their mouths with a 5-ml saline solution for 60 s.

The amount and purity of the DNA were determined using a spectrophotometer (Nanodrop 1000; Thermo Scientific, Wilmington, DE, USA). Candidate genes were

TABLE 1 Details on the genetic markers' studied

Gene (SNP)	SNP ID	Position	SNP type	Ref SNP alleles	MAF
IL1A (rs17561)	C___9546471_10	Chr.2:112779646	Missense Mutation	A/C	A = 0.269
IL1A (rs1304037)	C___1839915_10	Chr.2: 112774659	Transition Substitution, UTR 3, Intragenic	C/T	C = 0.311
IL10 (rs1800871)	C___1747362_10	Chr.1: 206773289	Intron	A/G	A = 0.312
IL1RN (rs9005)	C___3133528_10	Chr.2: 113133835	UTR 3, Transition Substitution, Intragenic	A/G	A = 0.274

Note: Obtained from databases: http://www.thermofisher.com, http://www.ncbi.nlm.nih.gov and http://genome.ucsc.edu.
Abbreviations: SNPsingle nucleotide polymorphisms.

selected according to the Consortium for Genetics and Quality of Life Research (GENEQoL).[22] We used the University of California Santa Cruz Genome Browser website to identify previously characterized single nucleotide polymorphisms (SNPs) for each candidate gene, according to their possible functional regulation and allele frequency. A total of four SNPs in *IL1A* (rs17561, rs1304037), *IL10* (rs1800871), and *IL1RN* genes (rs9005) were selected and investigated. The characteristics of the studied SNPs are presented in Table 1.

The primers were pre-designed by Applied Biosystems. Genotyping was performed using the TaqMan SNP Genotyping Assays (Life Technologies) in Stratagene Mx3005P (Agilent Technologies). The real-time polymerase chain reaction (PCR) reactions were performed in a total volume of 3 ml (4 ng DNA/reaction, 1.5 ml Taqman PCR master mix, and 0.075 SNP assay; Applied Biosystems). Thermal cycling was performed by starting with a hold cycle of 95°C for 10 min, followed by 45 amplification cycles of 92°C for 15 s and 60°C for 1 min. Applied Biosystems (Foster City, CA, USA) supplied assays and reagents. All examiners at the laboratory were blinded to the sample group assignment. The Hardy-Weinberg equilibrium was evaluated using the chi-square test within each SNP in each population and only those results that were in the Hardy-Weinberg equilibrium were further analyzed.

2.2.4 | Statistical analysis

The data were analyzed using the Statistical Package for Social Science software (IBM, USA, version 23.0). The level of significance was set at 5% ($p < .05$). First, frequencies (%), the mean, and standard deviation (SD) were calculated for each of the sociodemographic and oral health variables. The variables were tested for normal distribution using the Kolmogorov-Smirnov test. The OHIP-14 scores were calculated by addition of the numeric responses for each item. The Mann-Whitney U test was used to compare OHRQoL domains between the caries-free (DMFT = 0) and the caries experience (DMFT ≥1) groups. Mann-Whitney U test and Kruskal-Wallis test were used to compare OHRQoL total scale and the variables age, gender and type of sport. In the group of Para athletes with DMFT ≥1, medians were obtained for overall items and subscale scores according to the genotype distributions. The Mann-Whitney U test was also used to compare genotype distributions between OHRQoL domains in a dominant model. The standard chi-square test was used to test for deviation from the Hardy-Weinberg equilibrium.

3 | RESULTS

A total of 264 Para athletes (143 athletics, 61 powerlifting, and 60 swimming) were included in this study, and the mean age was 31.25 (SD, 11.70). The sample characteristics, DMFT index, and the OHIP-14 scores of Para athletes among the three sports are presented in Table 2.

The overall mean OHIP-14 score recorded was 6.24 (SD, 7.05) and 10.03 (SD, 8.11), while the median scores were 4 (0.5–8) and 8 (4–15) ($p < .002$), in the control group and the case group, respectively. Regarding the subscale domain, caries experience Para athletes presented poor OHRQoL on the total scale ($p = .002$); functional limitation ($p = .020$), physical pain ($p = .024$), psychological discomfort ($p = .027$), physical disability ($p = .045$), psychological disability ($p = .005$), and handicap ($p = .017$) were statistically significant (Table 3).

Table 4 present the analyses of the variables age, gender and type of sport in relation to total scale of OHIP-14 in Para athletes with caries experience. A statistically significant difference was found in relation to the gender and total scale of OHIP-14. Female presented poor OHRQoL in relation to male on the total scale of OHIP-14 ($p = .008$).

The genotypic distribution of each genotype was consistent with the Hardy-Weinberg equilibrium proportions. The associations between genotypes and domains of quality of life (QoL) in Para athletes with DMFT ≥1 ($n = 221$) is summarized in Table 5. Para athletes with the A allele of the *IL1A* gene (rs17561), in a dominant model, had a significantly higher risk of poor psychological discomfort than those with the other allele ($p = .03$). There was no significant difference between the genetic polymorphisms

TABLE 2 Basic characteristics and oral health variables divided among the three sports of Para athletes

Variable	Para athletes (n = 264)	Athletics (N = 143)	Powerlifting (N = 61)	Swimming (N = 60)
Age in years (SD)				
	31.25 (11.70)	32.83 (12.71)	30.54 (10.01)	28.18 (10.15)
Gender (%)				
Male	169 (65.8)	95 (67.4)	37 (66.1)	37 (61.7)
Female	88 (34.2)	46 (32.6)	19 (33.9)	23 (38.3)
School education (%)				
<9 years study	55 (22.1)	24 (18.3)	9 (15)	22 (37.9)
≥9 years study	194 (77.9)	107 (81.7)	51 (85)	36 (62.1)
DMFT (%)				
DMFT = 0	58 (22)	20 (14.0)	15 (24.6)	23 (38.3)
DMFT≥1	206 (78)	123 (86)	46 (75.4)	37 (61.7)
Mean (SD)	6.41 (5.45)	7.64 (5.82)	5.67 (5.03)	4.25 (4.07)
OHIP-14 (SD)				
Total scale	9.44 (8.06)	9.96 (8.39)	9.41 (8.04)	8.20 (7.21)
Functional limitation	1.10 (1.50)	1.19 (1.56)	0.79 (1.07)	1.22 (1.72)
Physical pain	1.70 (1.80)	1.75 (1.91)	1.97 (1.74)	1.29 (1.49)
Psychological discomfort	2.32 (2.37)	2.24 (2.32)	2.56 (2.57)	2.27 (2.29)
Physical disability	0.94 (1.52)	1.00 (1.62)	1.05 (1.51)	0.69 (1.29)
Psychological disability	1.59 (1.92)	1.81 (2.04)	1.34 (1.73)	1.34 (1.76)
Social disability	1.30 (1.74)	1.40 (1.87)	1.31 (1.78)	1.05 (1.31)
Handicap	0.61 (1.26)	0.70 (1.38)	0.54 (1.10)	0.44 (1.09)

Abbreviations: OHIP, Oral Health Impact Profile; DMFT, decayed-missing-filled teeth.

TABLE 3 The mean and standard deviations / median of OHIP-14 scores between caries-free and caries experience Para athletes

	DMFT = 0 (*n* = 41)		DMFT ≥1 (*n* = 221)		
	Mean (SD)	Median (Q1-Q3)	Mean (SD)	Median (Q1-Q3)	*p* value
Total scale	6.24 (7.05)	4 (0.5–8)	10.03 (8.11)	8 (4–15)	**.002**
Functional limitation	0.63 (1.11)	0 (0–1.5)	1.19 (1.55)	0.5 (0–2)	**.020**
Physical pain	1.20 (1.63)	0 (0–2)	1.79 (1.81)	2 (0–3)	**.024**
Psychological discomfort	1.61 (2.15)	0 (0–3)	2.45 (2.39)	2 (0–4)	**.027**
Physical disability	0.61 (1.38)	0 (0–0)	1.00 (1.55)	0 (0–2)	**.045**
Psychological disability	0.83 (1.28)	0 (0–2)	1.74 (1.98)	1 (0–3)	**.005**
Social disability	1.20 (1.72)	0 (0–2)	1.32 (1.75)	0 (0–2)	.683
Handicap	0.27 (0.92)	0 (0–0)	0.67 (1.30)	0 (0–1)	**.017**

Note: Q1 = percentile 25, Q3 = percentile 75; Mann-Whitney U test, with significance level of 0.05; Bold indicates statistical significance.
Abbreviations: OHIP, Oral Health Impact Profile, DMFT, decayed-missing-filled teeth.

in *IL1A* (rs1304037), *IL10* (rs1800871), *IL1RN* (rs9005) genes and OHRQoL (Table 5).

4 | DISCUSSION

The contemporary definitions of health comprise a new concept that takes a multidimensional holistic view of the individual, such as social well-being. In fact, treating the disease alone does not allow the individuals to enjoy their health fully. This evaluation should be especially considered for Para athletes. Although the importance of good oral health and quality of life in Para athletes is well known, there are no studies reporting the association of clinical characteristics, genetic markers, and OHRQoL in this population. Therefore, the data analyses in this study revealed that dental caries status consistently affects OHRQoL, and genetic polymorphisms in *IL1A* gene are associated with an increased risk of poor psychological discomfort.

TABLE 4 The mean and standard deviations / median of total scale OHIP-14 between variables age, gender and sport

	Total scale OHIP-14 DMFT ≥1 (n = 221)		
	Mean (SD)	Median (Q1–Q3)	p value
Age[a]			
≤ 20 years	9.38 (7.86)	7 (3–14)	.178
≥ 21 years and ≤ 40 years	9.61 (8.29)	7.50 (3.25–15)	
≥ 41 years	11.50 (7.71)	12.5 (5–16)	
Gender[b]			
Male	8.98 (7.64)	7 (2-14)	**.008**
Female	12.11 (8.65)	12.5 (5.75–17)	
Type of sport[a]			
Swimming	9.60 (7.86)	8 (2–16)	.785
Powerlifting	9.48 (7.83)	8 (2.75–13.25)	
Athletics	10.38 (8.33)	8 (4–16)	

Note: Q1 = percentile 25, Q3 = percentile 75.

Abbreviations: OHIP, Oral Health Impact Profile; DMFT, decayed-missing-filled teeth.

[a]Kruskal-Wallis test; with significance level of 0.05; Bold indicates statistical significance.

[b]Mann-Whitney U test.

Oral health problems are far from being solved, and international data on the impact of oral health on the OHRQoL of athletes are scarce. In this study, we assessed dental caries status using the DMFT index that is widely utilized in epidemiological surveys of oral health for measuring and comparing the experience of dental caries in different populations.[6,20,22] In our study sample of Para athletes, DMFT index affected all domains of the OHIP-14, except for social disability. This could be explained by the fact that dental caries and subsequent tooth loss frequently cause impaired chewing, decreased appetite, sleep problems, and performance problems during sports training and competition. Although they are occasional problems, both can affect the OHRQoL. Therefore, measures of improving OHRQoL, combined with clinical and behavioral indicators, can contribute to the evaluation and development of policies and procedures, and joint actions for health promotion and disease prevention programs involving the Para athletes.

In this study, we also hypothesized that OHRQoL could be influenced by the individual genetic background. Several studies have provided evidence of associations between genetic polymorphisms and QoL outcomes,[12–16] suggesting that variations in DNA could be biomarkers for QoL. However, there is a lack of studies on OHRQoL and genetic polymorphisms. To the best of our knowledge, this is the first study to evaluate cytokine genes as potential biomarkers for OHRQoL in a group of Para athletes. Polymorphisms in regulatory, promoter, and coding regions in cytokine encoding genes may affect the production and function of cytokines and are closely related to overall immune functioning.[23] The interleukin-1 family consists of several pro- and anti-inflammatory proteins. IL-1α is responsible for the control of pro-inflammatory responses and is one of the first cytokines produced by stress, while IL-1RN, a naturally occurring receptor antagonist, acts as an inhibitor of IL-1 receptor signaling.[24] IL-10 is a Th2-type cytokine with anti-inflammatory properties that suppresses the immune response in multiple ways.[25]

Several studies have shown that polymorphisms in genes involved in the pro- and anti-inflammatory cytokines are associated with psychobehavioural symptoms (fatigue, depression, and cognitive impairment) and can affect QoL before, during, and after treatment.[11,12,16] In case of the *interleukin 1 beta (IL1B)* gene (rs1143623), patients who were heterozygous or homozygous and carried at least one C allele had an increased risk for lower social well-being domain of QoL in women with breast cancer.[16] Another study showed that polymorphisms in a number of cytokine genes were associated with changes in physical functioning (i.e., interleukin [IL] 1B, IL10, and IL1RN), mental health (IL1RN), emotional role functioning (IL6), and social functioning (IL6, IL1RN, and tumor necrosis factor super family) in a study consisting of lung cancer survivors.[12] In this study, we found an association between the polymorphism in the *IL-1α* gene (rs17561) and OHRQoL perception in the domain of psychological discomfort. In the general score and the psychological disability domain, the values were borderline, reinforcing the existence of this association. Overall, our findings are consistent with studies examining polymorphisms in pro- and anti-inflammatory cytokine genes and psychobehavioral symptoms to support an inflammatory basis to modulate the impact on OHRQoL. Strategies to identify individuals at higher risk and to inhibit the effects of such cytokines could therefore have a profound impact on QoL.

The findings of this study should be interpreted considering some limitations. First, analyses of Para athletes were not performed according to their International Paralympic Committee classification system or impairment. This classification is sport-specific to minimize the impact of impairment on sports performance. Even so, our findings contribute to providing a comprehensive and holistic approach for planning oral health actions for Para athletes and form the basis of future integrated studies. Second, for the screening process, the protocol focused on decayed, missing, and filled teeth due to caries in the permanent teeth, but the severity of the condition was not reported. The absence of pain or discomfort assessments, such as the use of PUFA index and periodontal examination was not possible given the dynamics imposed on para-athletes on

TABLE 5 Association between IL1A gene (rs17561, rs1304037); IL10 gene (rs1800871) and IL1RN gene (rs9005) and OHRQoL in the group with DMFT ≥1

		OHIP-14															
		All		Functional limitation		Physical pain		Psychological discomfort		Physical disability		Psychological disability		Social disability		Handicap	
	Gene	Median (Q1-Q3)	*p* value	Median (Q1-Q3)	*p* value	Median (Q1-Q3)	*p* value	Median (Q1-Q3)	*p* value	Median (Q1-Q3)	*p* value	Median (Q1-Q3)	*p* value	Median (Q1-Q3)	*p* value	Median (Q1-Q3)	*p* value
IL1A gene (rs17561)																	
DMFT ≥1	AA+AC (82)	11 (4-17)	.126	0 (0-2)	.838	2 (0-3)	.867	3 (0-4.25)	**.037**	0 (0-2)	.276	2 (0-3)	.187	0 (0-2.25)	.351	0 (0-1)	.849
	CC (111)	7 (4-14)		1 (0-2)		2 (0-2)		2 (0-4)		0 (0-2)		1 (0-2)		0 (0-2)		0 (0-1)	
IL1A gene (rs1304037)																	
DMFT ≥1	CC +CT (109)	9 (4-16)	.410	0 (0-2)	.926	2 (0-3)	.269	2 (0-4)	.154	0 (0-2)	.615	2 (0-3)	.639	0 (0-2.5)	.431	0 (0-1)	.500
	TT (100)	8 (3-14)		1 (0-2)		2 (1-3)		2 (0-4)		0 (0-2)		1 (0-2)		0 (0-2)		0 (0-1)	
IL10 gene (rs1800871)																	
DMFT ≥1	AA + AG (128)	8 (4-14)	.518	1 (0-2)	.660	2 (0-3)	.890	2 (0-4)	.229	0 (0-2)	.631	1 (0-2)	.093	0 (0-2)	.839	0 (0-1)	.409
	GG (61)	8 (4-15.5)		0 (0-2)		1 (0-3)		2 (0-5)		0 (0-2)		2 (0-3)		0 (0-2)		0 (0-1)	
IL1RN gene (rs9005)																	
DMFT ≥1	AA+AG (105)	8 (4-16)	.718	1 (0-2)	.406	2 (0-3)	.812	2 (0-4)	.541	0 (0-2)	.169	1 (0-3)	.983	0 (0-2)	.795	0 (0-1)	.183
	GG (101)	8 (4-15)		0 (0-2)		2 (0-3)		2 (0-4)		0 (0-2)		2 (0-2)		0 (0-2)		0 (0-2)	

Note: Q1 = percentile 25, Q3 = percentile 75; Mann-Whitney U test, with significance level of 0.05; Bold indicates statistical significance.

Abbreviations: IL1A, interleukin 1 alpha; DMFT, decayed-missing-filled teeth; OHIP-14, Oral Health Impact Profile.

the day of competitions. The use of other diagnostic tools, such as radiographs and probes, could increase the amount of data collected.

In summary, this study presents new evidence regarding the genetic polymorphisms that modulate the impact of caries experience. This study suggests that the anti-inflammatory cytokine gene may be a biomarker of OHRQoL in Para athletes and requires confirmation in future studies.

5 | CONCLUSION

Dental caries affected the OHRQoL in Para athletes. *IL1A* genetic polymorphisms were the potential biomarkers for the OHRQoL in Para athletes.

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CONFLICT OF INTEREST

No potential conflict of interest was reported by the authors.

ETHICS STATEMENT

This study was approved by the local Committee of Human Participation in Research (#3.261.377).

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