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Research article

Pulp stones and kidney stones-related gene: An investigation of single nucleotide polymorphisms in the gene encoding parathyroid hormone

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ABSTRACT

Introduction: Pulp stones (PS), whose origins remain unclear, present a challenge for clinical practice in Endodontics. Similar to other calcifications, a relationship with parathyroid hormone is hypothesized.
Purpose: The aim of this study was to investigate the association between the presence of PS and kidney stones (KS) and single nucleotide polymorphisms (SNPs) in the parathyroid hormone (*PTH*) gene, which is related to KS.
Methods: This cross-sectional study included adults of both sexes, divided into groups: with PS and without PS. PS diagnosis was based on radiographic evaluation. Saliva samples were collected from all participants, and prior history of KS was recorded. The samples were processed, and genomic DNA was used to genotype the rs694, rs6256, and rs307247 SNPs. The Hardy-Weinberg equilibrium was assessed using the Chi-square test. Genotypic and allelic profiles under additive, dominant, and recessive models were evaluated using a univariate logistic regression model and the Wald test, with analyses conducted in SPSS® version 23.0. Additionally, Fisher's exact test was used to compare the haplotype frequencies. Statistical significance was set at 5 %.
Results: The study included 63 patients with PS and 54 without PS, with a mean age of 32.5 years. No statistically significant association was observed between the groups regarding the presence of KS. Allelic and genotypic analyses revealed no significant association ($P > 0.05$) between the presence of PS and SNPs analyzed in the groups studied.
Conclusion: None of the SNPs studied in the gene encoding PTH were associated with PS or KS.

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1. Introduction

Pulp stones (PS) are mineralized structures found in the pulp chamber [1], occurring frequently in the population, particularly among females, older individuals, and in posterior teeth [2]. Crystallographic analysis of PS reveals densely mineralized masses containing calcium and phosphorus ions [3], very similar to the composition of dentin hydroxyapatite [4]. The histological similarity between PS and dentin tissue suggests the hypothesis that their formation may be regulated by the same genes controlling ameloblast and odontoblast expression [5], indicating a potential genetic influence.

Parathyroid Hormone (PTH) is a hormone composed of 84 amino acids, synthesized and secreted by the parathyroid glands [6], plays an important role in the mineral metabolism of dental and bone structures, contributing to their formation and maintenance [7, 8]. During dental development, alterations in the levels of this hormone can lead to abnormalities in enamel, dentin, cementum and pulp, including the occurrence of pulp calcifications [9,10].

The *PTH* gene, located on chromosome 11, position 11p15, encodes a family of peptides that regulates blood calcium and phosphate levels [11]. Excess production of these peptides can lead to hypercalcemia and the formation of kidney stones (KS) [12].

PS is a multifactorial condition [2] associated with various alterations, including KS, as reported in both a systematic review [13] and a recent study involving a Brazilian population [14]. PS and KS share a similar chemical composition, and, notably, KS has been linked to single nucleotide polymorphisms (SNPs) in *PTH* [15].

Based on the literature, genes involved in mineral metabolism homeostasis are plausible candidates for influencing PS development. It is also possible that PS and KS share a similar genetic background. Therefore, the main goal of this study was to investigate whether SNPs in the *PTH* gene (a gene associated with KS) are linked to PS and explore whether *PTH* could serve as a common factor for both PS and KS. The null hypothesis is that SNPs in *PTH* are not associated with either condition.

2. Materials and methods

2.1. Sample

This study was approved by the local Ethics and Research Committee (CAAE 94846918.5.0000.0093, opinion 2.805.133) and elaborated according to the Strengthening the Reporting of Genetic Association Studies (STREGA) guidelines [16]. All participants provided written informed consent for participation and for the publication of their data.

This cross-sectional study is part of a previous investigation [14]. Fig. 1 describes the research stages and criteria used. Initially, digital panoramic radiographs of adults aged 18–65 years from a dental radiology service at a private university in Curitiba, PR, Brazil, were assessed. All images taken from 2018 to 2019 (N = 1047) were allocated into two groups: with PS and without PS. Radiographs in the PS group displayed images suggesting the presence of calcifications in posterior teeth (molars and/or premolars), while those in the without PS group showed no evidence of this alteration in any permanent teeth.

Following the application of inclusion and exclusion criteria, saliva collection was conducted from June 2019 to February 2020, resulting in samples from 117 patients. During anamnesis, information on age, gender, and self-reported history of KS was obtained.

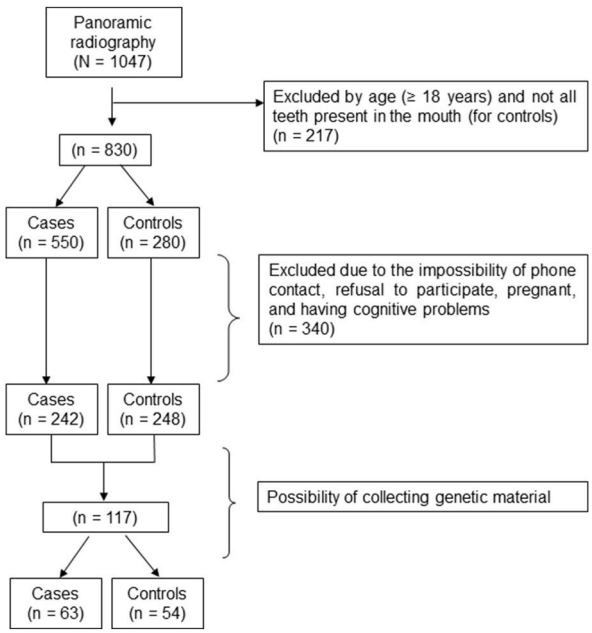

Fig. 1. Sample flowchart.

Patients initially classified as having PS underwent periapical radiographic examination for confirmation and final allocation to the PS group.

All steps were performed by three trained researchers. For PS diagnosis, inter-examiner agreement was assessed for calibration (Cohen's Kappa = 0.88, indicating excellent agreement). For genetic material collection (mucosal scraping), the same researchers were trained by an experienced professor.

2.2. DNA collection and genotyping

The processing of the samples was carried out by only one of the researchers. Genomic DNA for genotyping analysis was extracted from buccal cells isolated from saliva [17]. DNA quantity and purity were determined by a spectrophotometer (Nanodrop 1000; ThermoFisher Scientific, Wilmington, NC, USA). SNP candidates in *PTH* were chosen based on their previous association with KS and/or by consulting the UCSC Genome Browser website (https://genome.ucsc.edu/) to identify those already characterized for the candidate gene, according to their possible function regulation and minor allele frequency. Allelic discrimination was carried out in 2022 by a single investigator in a blinded manner. Thus, three SNPs in the PTH gene (rs694, rs6256, and rs307247) were selected and investigated. The characteristics of the SNPs are shown in Table 1.

Genotyping was performed using TaqMan SNP Genotyping Assays (Life Technologies; ThermoFisher Scientific, Wilmington, NC, USA) on Stratagene Mx3005P (Agilent Technologies, Santa Clara, CA, USA). The final reaction volume for Real-time PCR was 3 μL, which contained 1 μL of 4 ng/μL genomic DNA, 1.5 μL TaqMan Universal PCR master mix, 0.075 μL SNP assay, and 0.425 μL of deionized water for each reaction. Applied Biosystems reagents (Foster City, CA, USA) were used. Thermal cycling was performed with a maintenance cycle at 95 °C for 10 min, followed by 45 amplification cycles at 92 °C for 15 s and 60 °C for 1 min.

2.3. Statistical analysis

The Chi-square test was used to estimate the Hardy-Weinberg equilibrium (https://wpcalc.com/en/equilibrium-hardy-weinberg/).

Groups with and without PS were established as the dependent variable. Genotypic and allelic distributions in additive, dominant, and recessive models were adjusted for age and KS using a multivariate logistic regression model with the Wald test. Results were presented as odds ratios (OR) with a 95 % confidence interval (95%CI). Pearson's Chi-Square test was also applied to investigate association between PS and KS. Data analysis was conducted in SPSS® version 23.0 (IBM® SPSS® Statistics v. 23.0, SPSS Inc, Chicago, IL, USA), with a significance level set at 5 %. Additionally, Fisher's exact test was used to compare haplotype frequencies, conducted using PLINK version 1.06 (https://zzz.bwh.harvard.edu/plink/ld.shtml).

3. Results

A total of 117 individuals were included in the study, comprising 63 (53.8 %) with PS and 54 (46.2 %) without PS. The mean age of the overall sample was 32.5 (±11.3) years. The mean age for the group without PS was 27 (±8.9) years, while the group with PS had a mean age of 37 (±11.2). Women represented 70.9 % (n = 83) of the sample, with 42 in the group without PS and 41 in the group with PS; no statistically significant difference was observed (P = 0.271).

In the group with PS, 16 patients reported a history of KS, compared to seven in the group without PS, with no statistically significant difference found (P = 0.092; OR = 2.30; 95%CI: 0.86–6.06).

All assessed SNPs were in Hardy-Weinberg equilibrium. Table 2 shows the allele frequencies for the three SNPs studied in the groups with and without PS, revealing no statistically significant differences between the groups (P > 0.05).

The results of the logistic regression analysis, adjusted for age and KS as covariates, are presented in Table 3. Additive, dominant, and recessive models were used, with no significant differences observed between the groups with or without PS (P > 0.05). PS was not associated with the SNPs in the *PTH* gene in the multivariate analysis (P > 0.05).

Furthermore, the genotypic and allelic distributions between patients who reported KS and those who did not (regardless of PS status) showed no statistically significant association with the rs694, rs6256, and rs307247 SNPs (P > 0.05). To investigate SNP-SNP interactions, haplotype analysis was conducted, yielding 13 combinations across four different loci (Table 4). None of these combinations were associated with PS (P > 0.05).

Table 1
Gene and polymorphisms studied.

SNP	Base change	Functional consequence	Clinical significance	MAF
rs694	C > T	Intron variant	benign	T = 0.260
rs6256	G > T	Stop gained	benign	T = 0.125
rs307247	G > A	3′ untranslated region	benign	A = 0.395

Note: MAF - minor allele frequency.
Source: https://www.ncbi.nlm.nih.gov/snp/

Table 2
Analysis of the SNPs studied in the allelic model.

SNP	Allele	With PS n (%)	Without PS n (%)	P-value[a]	OR (95%CI)
rs694	T	36 (45.0)	72 (47.4)		
	C	44 (55.0)	80 (52.6)	0.837	1.10 (0.64–1.89)
rs6256	G	98 (52.7)	26 (56.5)		
	T	88 (47.3)	20 (43.5)	0.762	0.85 (0.45–1.64)
rs307247	A	37 (54.4)	89 (53.6)		
	G	31 (45.6)	77 (46.4)	0.911	1.03 (0.59–1.82)

[a] Logistic regression model; Wald test ($P < 0.05$).

Table 3
Genotypic distribution in additive, dominant and recessive models between the groups with PS and without PS, adjusted for age and KS as covariates (n = 117).

SNP	Model	Genotype	With PS (%)	Without PS n (%)	P-value[a]	OR (95%CI)
rs694	Additive	CC	12 (19.4)	11 (20.4)	0.449	0.99 (0.34–2.93)
		CT	20 (32.2)	14 (25.9)	0.158	1.18 (0.45–3.10)
		TT (ref.)	30 (48.4)	29 (53.7)	–	–
	Dominant T	CC	12 (19.4)	11 (20.4)	0.665	0.94 (0.33–2.63)
		CT/TT (ref.)	50 (80.6)	43 (79.6)	–	–
	Recessive C	CC/CT	32 (51.6)	25 (46.3)	0.701	1.10 (0.48–2.50)
		TT (ref.)	30 (48.4)	29 (53.7)	–	–
rs6256	Additive	GG	40 (64.5)	35 (64.8)	0.247	0.31 (0.02–3.99)
		GT	18 (29.0)	18 (33,0)	0.191	0.25 (0.02–3.48)
		TT (ref.)	4 (6.5)	1 (1.9)	–	–
	Dominant G	TT	4 (6.5)	1 (1.9)	0.255	3.48 (0.27–44.9)
		GT/GG (ref.)	58 (93.5)	53 (98.1)	–	
	Recessive T	GT/TT	22 (35.4)	19 (35.2)	0.973	0.93 (0.39–2.23)
		GG (ref.)	40 (64.6)	35 (64.8)	–	–
rs307247	Additive	AA	8 (12.7)	6 (11.1)	0.605	1.31 (0.36–4.77)
		AG	21 (33.3)	19 (35.2)	0.241	0.78 (0.32–1.92)
		GG (ref.)	34 (54.0)	29 (53.7)	–	–
	Dominant G	AA			0.553	1.44 (0.42–4.99)
		AG/GG (ref.)			–	–
	Recessive A	AA/AG	29 (46.0)	25 (46.3)	0.977	0.90 (0.40–2.04)
		GG (ref.)	34 (54.0)	29 (53.7)	–	–

[a] Multivariate logistic regression model; Wald test ($P < 0.05$). Note: ref. – reference category.

4. Discussion

This study aimed to investigate whether SNPs in the *PTH* gene, previously associated with mineral metabolism disorders [18–21], and with KS [15], might contribute to the etiology of PS. It was hypothesized that the SNPs examined could serve as a common factor elucidating the connection between PS and KS; however, the results indicated no association between the presence of PS and the rs694, rs6256, and rs30724 SNPs. Consequently, the null hypothesis was accepted.

The frequency of PS in the population can reach up to 36.5 % [2]. Notably, the presence of PS coincides with that of KS [13,14], suggesting a structural similarity between these conditions, characterized by the presence of calcium and phosphorus ions as primary

Table 4
Haplotype analysis.

Gene	SNPs	Locus	Haplotype	Frequency with PS	Frequency without PS	P-value[a]
PTH	rs694|rs6256|rs307247	H1	CGA	0.31	0.27	0.554
	rs694|rs6256|rs307247	H1	TTG	0.20	0.20	0.919
	rs694|rs6256|rs307247	H1	CGG	0.06	0.06	0.990
	rs694|rs6256|rs307247	H1	TGG	0.43	0.48	0.531
	rs694|rs6256	H2	TT	0.20	0.19	0.891
	rs694|rs6256	H2	CG	0.36	0.32	0.535
	rs694|rs6256	H2	TG	0.43	0.48	0.483
	rs694|rs307247	H3	CA	0.31	0.27	0.554
	rs694|rs307247	H3	CG	0.06	0.05	0.990
	rs694|rs307247	H3	TG	0.64	0.67	0.568
	rs6256|rs307247	H4	GA	0.31	0.28	0.632
	rs6256|rs307247	H4	TG	0.20	0.19	0.891
	rs6256|rs307247	H4	GG	0.49	0.53	0.586

[a] Fisher's exact test ($P < 0.05$).

components [4,15]. Therefore, it was hypothesized that both phenotypes may share a similar genetic background. Although the rs694, rs6256, and rs30724 SNPs in *PTH* were not found to be a common factor to both conditions, the authors believe that other genes may be involved in the relationship between PS and KS.

The inorganic components present in PS and KS are also found in bones and regulated/influenced by the action of PTH, which is recognized as an important mediator of mineral homeostasis in the human body [8]. Alterations in serum PTH levels can affect the transport of paracellular and transcellular calcium [15]. Among its various functions, PTH activates a metabolic cascade whereby activated osteoclasts release calcium, potentially leading to hypercalcemia [22]. Furthermore, PTH regulates phosphate metabolism, which, associated with calcium, forms insoluble salts that may contribute to the development of KS [15].

The gene encoding PTH and the rs694, rs6256, and rs307247 SNPs were selected for this research due to their established associations with KS [15] and previous publications linking them to calcifying diseases [15,23], bone conditions [20], and dental phenotypes [19]. The study by Mitra et al. [15] reported that the risk of KS formation was four times greater among individuals with AA genotype at rs307247, identifying this allele as a risk factor for the development of the condition and suggesting that this SNP could serve as a potential genetic marker for KS diagnosis. Although it was not find an association between KS and rs307247, the small sample of patients with self-reported KS may have contributed to a type II error. This limited size could also explain the lack of association between PS and KS.

The literature has identified the *PTH* gene as candidate for osteoporosis and bone mineral density [18,21] as well as altered bone growth [20]. In women diagnosed with postmenopausal osteoporosis, the regulation of bone remodeling during this phase was not found to be associated with rs307247 [18]. However, due to PTH's direct involvement in bone homeostasis, rs6256 has also been investigated in osteoporosis research. Lin et al. [21] reported an association between this SNP and decreased bone density.

Küchler et al. [20] assessed mandibular bone growth in relation to SNPs in *PTH* gene. According to their findings, mandibular retrognathism was significantly influenced by changes in the *PTH* gene, for rs694 and rs307247, in the genotypic and allelic models. Specifically for rs694, differences were observed in CC/CT and C allele genotypes, while for rs307247, differences were noted only found in AA homozygotes. Their study also identified significant differences in the haplotype analysis for individuals TGG and CGA when exposed to the three aforementioned polymorphisms. Thus, the authors concluded that *PTH* SNPs influence the human mandibular morphology. In this study, the preliminary analysis based on allelic and genotypic distribution was unpromising, as no significant allelic or genotypic associations with PS were observed. Nevertheless, the authors proceeded with a haplotype analysis to determine whether these combined SNPs contributed to PS formation. Despite identifying 13 haplotype combinations, none revealed an association with PS, providing compelling evidence that these SNPs are not related to PS.

More recently, variations in the dimensions of the dental crown of permanent teeth have been associated with SNPs in the *PTH* gene. Gerber et al. [19] reported that differences were observed in relation to rs694, with individuals possessing the TT genotype exhibiting a smaller buccolingual dimension compared to those with the CC genotype. Regarding rs307247, individuals with AG and GG genotypes had a larger buccolingual dimension than those with the AA genotype. Therefore, the authors concluded that while the results do not elucidate the precise mechanism by which *PTH* influences the variability in dental crown size, there is evidence supporting future studies aimed at identifying candidate genes involved in this process.

This study has limitations. The analysis of panoramic radiographs was based on previous studies [24,25], as its examinations is commonly requested in clinical dental practice, making it accessible and non-invasive [26]. While the use of panoramic and periapical radiographs may introduce biases, more accurate assessments could be achieved through computed tomography or histological examinations to confirm the presence of PS [27,28]. However, these resources are not routinely indicated. Additionally, the responses regarding the presence or absence of KS were based on self-reports from the participants, which may introduce bias, as these claims were not validated through medical examinations. Another limitation is the lack of measurement of serum PTH levels, which could have provided more precise insights into signs of hyper- or hypoparathyroidism [29].

To date, this study is the first to explore genetic connection between PS and KS. Furthermore, rs694 and rs307247 are considered regulatory SNPs, which may modify gene expression by controlling nuclear mRNA, affecting translational efficiency, or altering the three-dimensional structure of the synthesized protein [30]. Conversely, rs6256, located within a coding region, directly impacts the protein. It is also noteworthy that the three selected SNPs encompass a substantial region of the *PTH* gene, yet no associations were found between them and PS.

Further studies should incorporate methodological tools that simultaneously assess the SNPs and the patients' medical records to elucidate the role of genes in the pathogenesis of PS and their connection with other systemic conditions. Also, employing alternative study designs, such as case-control studies, is recommended. Furthermore, it is essential to consider the potential interactions of polymorphisms in different genes as contributing factors to PS. Thus, the integration of a genetic model involving other genes, along with a diplotype analysis, is advisable.

5. Conclusion

The results indicated that the rs694, rs6256, and rs30724 SNPs in the gene encoding PTH were not associated with the presence of PS and KS. Thus, the hypothesis that these SNPs serve as a common factor for both conditions was not supported.

CRediT authorship contribution statement

Prescila Mota de Oliveira Kublitski: Writing – original draft, Visualization, Methodology, Investigation, Data curation, Conceptualization. **Bruna de Souza Romano:** Writing – original draft, Methodology, Investigation, Data curation. **Vania Gomes**

Moraes: Writing – original draft, Methodology, Investigation, Data curation. **Manoel Damião Sousa-Neto:** Writing – review & editing, Visualization, Data curation. **Lívia Azeredo Alves Antunes:** Writing – review & editing, Writing – original draft, Visualization, Investigation, Data curation. **Erika Calvano Küchler:** Writing – review & editing, Writing – original draft, Visualization, Resources, Investigation, Funding acquisition, Data curation. **Leonardo Santos Antunes:** Writing – review & editing, Writing – original draft, Visualization, Resources, Investigation, Data curation. **João Armando Brancher:** Writing – original draft, Visualization, Methodology, Investigation, Data curation, Conceptualization. **Edgard Michel-Crosato:** Writing – original draft, Visualization, Validation, Methodology, Data curation, Conceptualization, Supervision. **Marilisa Carneiro Leão Gabardo:** Writing – original draft, Supervision, Methodology, Investigation, Data curation, Conceptualization.

Ethics statement

This study was approved by the Ethics and Research Committee of Universidade Positivo with the approval number: CAAE 94846918.5.0000.0093, opinion 1.805.133), dated August 4, 2018.

Data availability statement

Data associated with the study has not been deposited into a publicly available repository. Data will be made available on reasonable request.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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