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Case Report

Could Primary Hyperparathyroidism be a Risk Factor for Sjogren's Syndrome?

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Abstract

Patients with Sjögren's Syndrome (SS) have been reported to develop Primary Hyperparathyroidism (PHPT), and there has been a reported case of primary SS with secondary hyperparathyroidism. However, it is unclear whether PHPT is a risk factor for SS. In this study, we report a case of PHPT with SS indicating that PHPT may have a causative role in SS. We also construct pathways to understand the pathological characteristics of the reported patient and identify the potential pathway through which PHPT exerts influence on SS. Furthermore, we conducted a meta-analysis using nine RNA expression datasets of SS patients to examine changes in the expression of molecules stimulated by PHPT. Our findings suggest that PHPT may be a potential risk factor for SS by activating five promoters, including IL6, LEP, PRL, TNF, and BCL2. However, meta-analysis results indicate that the 46 PHPT-driven molecules, including these five molecules, may not show significant expression changes in SS patients, suggesting that further investigation is needed to explore their impact on the pathological development of SS. Our study sheds light on the underlying mechanism of PHPT in SS and highlights the need for further investigation into the causal relationship between PHPT and SS.

Keywords: Sjögren's syndrome; Primary hyperparathyroidism; Pathway

Introduction

Primary Hyperparathyroidism (PHPT) is a condition characterized by the overproduction of Parathyroid Hormone (PTH) by one or more of the parathyroid glands. This leads to hypercalcemia, which can cause various symptoms such as digestive issues, psychiatric abnormalities, kidney stones, and bone disease [1]. Benign tumor or growth on the parathyroid glands is the primary cause of PHPT, but other factors can also contribute to its development [2]. The prevalence of PHPT is estimated to be up to 3% in the general population, with a higher incidence in individuals aged over 50 years [3-5]. Furthermore, women are four times more likely to develop PHPT than men [6].

Sjögren's Syndrome (SS) is an autoimmune disease that is chronic in nature and is characterized by dryness of the eyes and mouth. Additionally, it can cause other symptoms like vaginal dryness, numbness in the limbs, chronic cough, fatigue, muscle and joint pain, and thyroid problems [7]. Apart from these, SS can also seriously affect other organ systems like the nervous system, kidneys, and lungs [8]. The risk of lymphoma also increases by 15% in individuals with SS [9]. The estimated prevalence of SS in the general population is between 0.1% and 4%, with a higher incidence among middle-aged women with a female-to-male ratio of 9:1 [4,10].

Although there is currently no known direct genetic pathway connecting PHPT and SS, both conditions have been linked with several genetic and environmental factors that may increase their risk of development. For example, patients with SS have been found to have increased levels of serum gastrin [11], which has been demonstrated to play a role in PHPT pathogenesis [12]. Conversely, PHPT causes an increase in circulating interleukin-6 (IL-6) levels [13], which has been implicated in the pathogenesis of SS [14]. In some instances, SS patients have been reported to develop PHPT, which may be due to complications associated with SS, such as the formation of calcium deposits in the glands [15]. Additionally, a case published in 1990 described a 43-year-old woman with primary SS history who also had secondary hyperparathyroidism [16]. However, it is currently unclear whether PHPT is a risk factor for SS.

Here, we first reported and estimated a case of PHPT that exhibited SS, implying that PHPT might have a causative impact on SS. Subsequently, we established operational pathways to grasp the pathological characteristics of the patients mentioned and recognize the probable influence of PHPT on SS. Later on, we carried out a meta-analysis using RNA expression data to examine the changes in the expression of molecules stimulated by PHPT in SS patients. Our findings indicate that PHPT might act as a potential hazard for SS and plays a role in the onset of multiple linked health complications.

Case Presentation

Case 1

A 70-year-old woman, married and a farmer from Yongkang, Zhejiang, was admitted to the rheumatology department on October 30, 2022. She had been experiencing dry mouth for 3 years, accompanied by dry eyes, kidney stones, chronic renal insufficiency (predominantly renal tubular damage), severe osteoporosis, high IgG bias, positive RF, ANA at a titer of 1:1000, anti-SSA antibody +++,

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anti-SSA/Ro52 antibody +++, anti-SSB antibody +++, blood calcium level of 2.90 mmol/L (normal range is 2.1 mmol/L to 2.6 mmol/L), and high parathyroid hormone levels. Labial gland biopsy revealed multiple lymphocytic foci. In June 2019, she was diagnosed with kidney stones, hypercalcemia, and renal insufficiency. Dry mouth symptoms appeared in October 2019, but she did not seek medical attention. In October 2022, the patient was diagnosed simultaneously with SS, PHPT, parathyroid adenoma, and osteoporosis.

Functional pathway for clinical features of the reported patient

To comprehend the clinical characteristics of the patient mentioned in the report, we created pathways based on literature that link PHPT, SS, and other pathological alterations in the patients. The relational data present in the pathways were obtained from the Elsevier Knowledge graph database (www.pathwaystudio.com). For quality assurance, a manual review of the referenced sources was carried out.

PHPT-driven molecules influencing SS

To investigate the potential impact of PHPT on SS, we performed a literature search to discover molecules stimulated by PHPT that also acted as upstream regulators of SS. Initially, we identified the downstream targets of PHPT with polarity, followed by identifying the upstream regulators of SS with polarity. Finally, the overlapping entities were utilized to create a molecular pathway linking PHPT to SS.

SS RNA expression data acquisition

To examine the quantitative alterations of PHPT-driven proteins in the context of SS, we obtained SS RNA array-expression datasets from GEO (https://www.ncbi.nlm.nih.gov/geo/) by using the keyword "Sjogren's syndrome" in our search, which yielded 80 series datasets. We then utilized the following criteria to select datasets for our study: 1) The data type was RNA expression by array; 2) The organism under investigation was Homo sapiens; 3) The dataset had an SS *vs.* healthy control study design; 4) The sample size was ≥ 10. We identified nine datasets that met the selection criteria and were available for expression analysis, as demonstrated in Table 1.

Mega-analysis models

A meta-analysis was performed to evaluate the impact of SS on downstream target genes of PHPT, where the gene expression LOG2 Fold-Change (LFC) was estimated from nine different SS expression datasets listed in Table 1 [17]. The meta-analysis utilized LFC data extracted from each dataset and compared the results of the random-effects model and fixed-effect model [17]. To assess the heterogeneity of the datasets, the between- and within-study variances were calculated and compared. The fixed-effect model was chosen over the random-effects model when the total variance Q was less than the expected value of the between-study variances (df) and set the ISq (percentage of the within-study variance over total variance) to zero. Matlab (R2017a version) was used to perform all analyses. Genes were deemed significant if they had an absolute LFC value of at least 1 and a p-value less than 0.05.

Analysis of influential factors

We utilized a Multiple Linear Regression (MLR) analysis to examine the potential impact of various factors such as study date, country of origin, and sample size on gene expression in SS patients and reported the corresponding P-values for each of these factors. The input for the MLR analysis comprised the expression LFC and the respective values of the potential influencing factors. To assess the effect of study date, we used the data publication age (current year minus year of data publication). The index number of each country was employed as input to test the effect of country of origin. The sample size was calculated as the total number of samples (#of cases+#of controls).

Results

Clinical features of reported PHPT patient

The patient was diagnosed with SS, PHPT, parathyroid adenoma, and osteoporosis simultaneously in October 2022. However, PHPT-related symptoms, such as kidney stones, hypercalcemia, and renal insufficiency, were diagnosed in June 2019, while the other two factors related to PHPT, PTH and osteoporosis, were not assessed at that time (Figure 1). Dry mouth symptoms occurred after that in October 2019. Therefore, it can be inferred that PHPT preceded SS, resulting in renal injury, kidney stones, and hypercalcemia. Following the onset of SS, new health issues such as osteoporosis, High IgG, positive RF, anti-SSA antibody +++, anti-SSA/Ro52 antibody +++, and anti-SSB antibody +++ emerged. Most of these symptoms were SS-related, except for increased PTH and osteoporosis, which were not initially evaluated. We thus postulate that PHPT may be a risk factor for SS, which we further explore in the subsequent section.

PHPT-driven molecular pathways influence SS

We constructed a molecular pathway based on literature to investigate the potential impact of PHPT on the pathological progression of SS, as depicted in Figure 2. According to our analysis, PHPT activates five SS promoters (IL6, LEP, PRL, TNF, and BCL2) but does not activate any SS inhibitors. Each of the connections shown in Figure 2 is supported by one or more scientific studies/references. The pathways depicted in Figure 2 indicate that PHPT has a predominantly adverse effect on SS and may thus be a risk factor for its development.

Expression of PHPT-driven molecules in SS patients

A total of 46 out of 49 molecules influenced by PHPT had available expression data in the 9 SS case/control expression datasets. We performed a meta-analysis to estimate the average expression

Table 1: The 9 Sjogren's syndrome RNA expression datasets from GEO.

GEOID	#Control/control	Country	Study Age	Platform	Sample Source	Sample Organism
GSE7451	10-Oct	USA	17	GPL570	whole saliva	Homo sapiens
GSE23117	4-Nov	USA	13	GPL570	salivary gland	Homo sapiens
GSE40611	18/17	USA	12	GPL570	parotid tissue	Homo sapiens
GSE51092	32/190	USA	11	GPL6884	whole peripheral blood	Homo sapiens
GSE66795	29/36	United Kingdom	9	GPL10558	whole blood	Homo sapiens
GSE84844	30/30	Japan	7	GPL570	Whole blood	Homo sapiens
GSE93683	24/24	Japan	7	GPL570	memory CD8 T-cells	Homo sapiens
GSE94510	18/18	Japan	7	GPL570	central memory CD4 T-cells	Homo sapiens
GSE97614	9-Mar	Greece	7	GPL6244	salivary gland	Homo sapiens

Table 2: The 9 Sjogren's syndrome RNA expression datasets from GEO.

Gene Name	Meta-analysis results				MLR analysis results		
	Random Effects Model	#Study	Effect size	p-value	Country	Sample size	Study Age
TNF	NO	9	0.13	0.19	0.0068	0.98	0.13
IL6	NO	9	0.047	0.3	0.0088	0.94	0.88
PRL	NO	8	-0.01	0.46	0.7	0.19	0.14
LEP	NO	9	-0.05	0.33	0.078	0.73	0.9
BCL2	NO	9	-0.07	0.17	0.046	0.75	0.91

levels of each of these 46 molecules in SS cases compared to healthy controls. Our findings revealed that none of these molecules exhibited significant changes in expression (abs (LFC) ≥ 1 & p<0.05) among SS patients, as displayed in Figure 3. Thus, these results indicate that the 46 molecules influenced by PHPT were not downstream targets of SS.

Table 2 shows that the five molecules identified in the PHPT-driven pathway (Figure 2) exhibited minor changes in SS patients compared to healthy controls. TNF and IL6 showed only minor increases in expression, while the remaining three were slightly down-regulated. Although these molecules were not found to be downstream targets of SS, this does not contradict previous reports that suggest their role as upstream regulators of SS. By activating these SS regulators, PHPT may impact the development of SS (Table 2).

It should be noted that sample region appears to have a notable impact on the expression of the majority of the five molecules listed in Table 2, while sample size and study age do not. Nonetheless, given the lack of significant expression changes observed, the results from the multiple linear regression analysis may not be relevant to this study.

Discussion

PHPT and SS are both severe diseases that affect a large population, with up to 1% and 4% prevalence rates, respectively, and contribute to the development of several associated health problems [3,4,10]. SS is particularly associated with autoimmune or rheumatic disorders, such as fibromyalgia, SLE (lupus), autoimmune thyroiditis, multiple sclerosis, and spondyloarthropathy [18], celiac disease [19,20], and several malignancies, particularly non-Hodgkin lymphoma [18,21]. Additionally, SS has been shown to increase the risk of secondary hyperparathyroidism [16], and there has been a case report of a PHPT patient with a medical history of SS [15]. However, to date, no study has suggested PHPT as a risk factor for SS. This study is one of the first to explore the possible influence of PHPT on SS.

In this study, we present a case of a patient with PHPT and SS and explore the possible clinical characteristics related to the two conditions. The patient was initially diagnosed with PHPT-related symptoms such as kidney stones, hypercalcemia, and renal insufficiency, which preceded the onset of SS symptoms (dry mouth) by four months [15]. Based on this observation, we hypothesize that PHPT could be a risk factor for SS. The functional pathway illustrated in Figure 1 shows the relationship between PHPT, SS, and other associated medical conditions reported in the patient. While some of these conditions, such as osteoporosis, renal injury, and malignancies, are associated with both PHPT and SS, earlier diagnosed symptoms such as kidney stones and osteoporosis, and high blood calcium levels, are specifically linked to PHPT and not SS. These findings support our hypothesis that PHPT precedes the development of SS [15].

The molecular pathway constructed in Figure 2 provides molecular-level support for the influence of PHPT on SS. The pathway was created using large-scale literature data mining assisted by Pathway Studio (www.pathwaystudio.com). Interestingly, it only supports the negative role of PHPT on SS, as it activates five promoters of SS: IL6, LEP, PRL, TNF, and BCL2. BCL2 expression is significantly up regulated in PHPT [22] and is involved in primary SS gland injury [23], which creates a PHPT→BCL2→SS pathway. It has also been suggested that interleukin-6 (IL-6), IL-10, and Transforming Growth Factor-Beta (TNF) are important in the induction and/or maintenance of SS [24]. The circulating levels of IL-6 and TNF-alpha are elevated in PHPT patients [25], creating another promoting pathway: PHPT→(IL6, TNF)→SS. Patients with PHPT have higher serum leptin (LEP) levels than healthy subjects [26], which have been shown to be associated with several stages of SS [27]. PHPT patients also Present Elevated Prolactin (PRL) levels [28], which have been suggested to play a role in the pathogenesis of SS [29,30]. These studies propose two additional promoting pathways of PHPT to SS: PHPT→(LEP, PRL)→SS.

On the other hand, the results of the meta-analysis, which utilized nine RNA expression datasets from SS patients, revealed that the five molecules (IL6, LEP, PRL, TNF, and BCL2) and 41 other molecules linked to PHPT did not exhibit any significant changes in expression

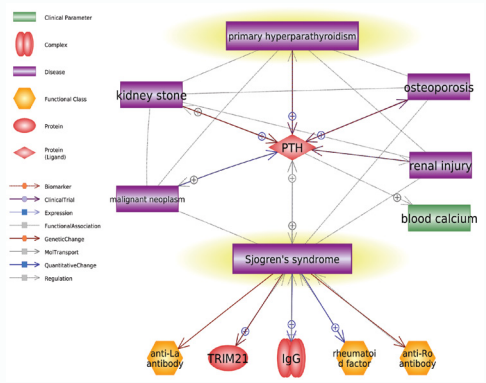

Figure 1: Functional pathways explaining the clinical features of the reported primary hyperparathyroidism patients.

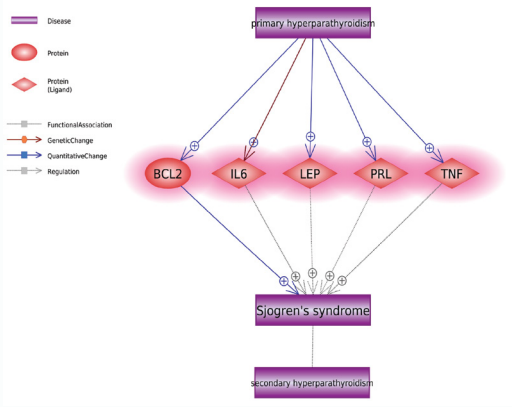

Figure 2: Primary hyperparathyroidism-driven molecular pathways influencing the development of Sjogren's syndrome.

levels in SS patients compared to healthy controls (Figure 3). The findings imply that these molecules were not downstream targets of SS in this study. Nonetheless, it is essential to investigate further the influence of quantitative changes of these molecules on the pathological development and maintenance of SS.

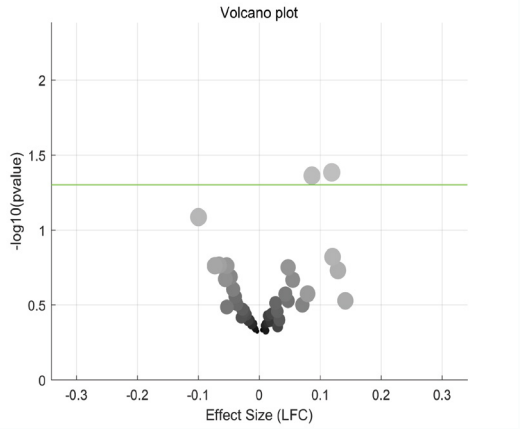

Figure 3: Volcano plot of the meta-analysis results for 46 primary hyperparathyroidism-driven molecular in Sjogren's syndrome patients.

Although the meta-analysis results did not show significant expression changes in the downstream targets of PHPT in SS patients compared with healthy controls, it is possible that the limited data used in the analysis and the genetic complexity of the causality of SS may have affected the results. Quantitative changes in these genes have been reported previously in the pathology of SS, such as elevated plasma levels of BCL2 [23], increased expression of TNF-α, IFN-γ, and IL-6 in labial salivary gland [31], and increased serum leptin [27] in SS patients.

On the other hand, the SS patients in the studies employed in our meta-analysis presented SS disease status without the involvement of the promoters mentioned above. Therefore, by activating these promoters, PHPT may exert a promoting effect on SS, constructing a casual relationship between PHPT and SS. Considering up to 3% epidemiology of PHPT and the significant malignant effect of SS on human health and the vast increase in mortality (46% increase), especially for elderly male patients with vasculitis, positive anti-La/SSB interstitial, lung disease, low complements, and cryoglobulinemia [32], the possible causality relationship between PHPT and SS is worthy of further exploration.

Moreover, the meta-analysis results also suggest that a patient can develop SS without the involvement of the promoters mentioned above. Therefore, it is possible that PHPT exerts a promoting effect on SS by activating these promoters, establishing a causal relationship between PHPT and SS. Considering the high prevalence of PHPT (up to 3%) and the significant negative impact of SS on human health, which can lead to increased mortality (up to 46%), particularly in elderly male patients with vasculitis, positive anti-La/SSB interstitial, lung disease, low complements, and cryoglobulinemia [32], further investigation into the potential causal relationship between PHPT and SS is warranted.

Conclusion

The case report suggests that PHPT may increase the risk of developing SS, which is supported by molecular pathway analysis. Our findings reveal PHPT as a potential risk factor for SS and shed light on its underlying mechanism, warranting further investigation into the causal relationship between PHPT and SS.

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