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TSH- β gene polymorphism in Saudi patients with thyroid cancer: A case-control study

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ABSTRACT

Background: The role of thyroid-stimulating hormone in the pathogenesis of thyroid cancer is not yet fully explored. This study aimed to evaluate the role of the TSH- β polymorphism in thyroid cancer in a Saudi cohort.

Methods: A prospective case-control study was conducted on 507 patients with differentiated thyroid carcinoma and compared them with 560 controls of Saudi origin. The association of two variants, the rs201857310, and rs7530810, in the TSH- β gene with thyroid cancer risk as well as thyroxine dose, were evaluated.

Results: The rs201857310_A > G [OR: 0.50 (95 % CI: 0.35–0.71); $P < 0.0001$] was strongly associated with thyroid cancer. The multivariable analysis adjusted the effect of possible confounders (age, sex, body mass index, and smoking). Multivariable analysis elucidated that the rs201857310 maintained its significant association with the disease [OR: 0.47 (95 % CI: 0.32–0.68); $P < 0.0001$]. There was no significant association between the other rs7530810 variant and the disease. There was no association between any of the variants and the thyroxine dose requirement ($P = 0.79$ and 0.73).

Conclusions: Our findings indicate that the TSH- β gene could have a role in the pathogenesis of differentiated thyroid carcinoma in the Saudi population.

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1. Introduction

The thyroid-stimulating hormone (TSH) is composed of an alpha subunit (TSH- α), which is common to all glycoprotein hormones, and a unique beta subunit (TSH- β) (Carvalho and Dupuy, 2017). Consequently, the transcription of the TSH- β -subunit gene is essential for a functioning TSH hormone (Sasaki et al., 2018). The transcription process is regulated by the thyroid hormones T3 and T4, which inhibit the transcription of TSH encoding genes, whereas thyrotropin-releasing hormone (TRH) promotes gene expression (Sasaki et al., 2018). Mutations in TSH- β could lead to malfunctioning thyroid pathways and, consequently, thyroid cancer. Previous research on the TSH- β pathway evaluated the connections between TSH receptors and thyroid functions or clinical outcomes, and several causal single-base substitutions were dis-

covered (Muthukrishnan et al., 2010; Partsch et al., 2006; Vuissoz et al., 2001). A G85A TSH- β homozygous missense mutation was described in a child with hypothyroidism born of consanguineous parents (Muthukrishnan et al., 2010), homozygous deletion, delta-313T, has been linked to congenital central hypothyroidism (Partsch et al., 2006), and another variant, Q49X, has been linked to severe isolated TSH deficiency (Vuissoz et al., 2001). The mutations in the TSH- β subunit site required for dimerization with the α -subunit prevent TSH secretion (Vuissoz et al., 2001).

The effects of thyroid hormone gene polymorphisms on thyroid function were previously studied, with varying results. The variability of thyroid hormone levels was attributed to genetic heredity in up to 65 % of cases (Hansen et al., 2004; Samollow et al., 2004). These findings suggest that the TSH- β polymorphism can affect blood hormone levels and, as a result, hormonal treatment outcomes. Therefore, we investigated the TSH- β gene polymorphism, its potential role in developing differentiated thyroid carcinoma (DTC), and its association with thyroxine dose requirement in a Saudi cohort.

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2. Materials and methods

2.1. Design and patients

A prospective case-control study was conducted on 507 patients with DTC and compared them with 560 controls of Saudi origin. DTC included papillary thyroid cancer (PTC), follicular thyroid cancer (FTC), or the Hurthel cell subtype. Patients with DTC were maintained on L-thyroxine following thyroidectomy and radioiodine ablation to maintain TSH levels in the suppressed state (below 0.1 mU/L) or near suppressed state (between 0.1 and 0.5 mU/L) with normal T4 levels (12–22 pmol/L).

Among DTC patients, 403 were in TNM stage I, 71 in stage II, 19 in stage III, and 14 in stage IV. Four-hundred seventy-one patients had radioactive iodine ablation for remnant tumors (mean dose: 105 mCi and range: 30–164), and 46 patients had a second radioactive iodine dose (mean dose: 143 mCi and range: 96–211). Remission was defined as a negative whole-body (DxWBS) and neck ultrasound scan with a thyroglobulin level < 1 ng/dl. Remission was achieved in 396 patients, while 111 patients had biochemical or radiological evidence of persistent disease. Of the 111 patients with persistent disease, 13 had positive DxWBS, and 98 had high serum thyroglobulin but negative DxWBS. Family history of thyroid disease was positive in 30 % of patients with PTC.

Study controls were healthy adults with no thyroid disease, negative family history of thyroid disease, and no previous exposure to radiation. Patients who had changed their thyroxine brand three months before enrollment or taking several medications were excluded from the study. Patients on antithyroid medications or any medicines affecting the pituitary-thyroid axis were excluded. Additionally, we excluded patients with mental illness, renal impairment, chronic liver disease, other types of cancer, and pregnant ladies. Study controls were recruited from participants of other genetic studies after confirming their eligibility to be included. We collected data related to participants' medical history, medications, smoking, TSH, and Free T4 levels. The study was approved by the Ethical Committee (Reference number: 2100025-KFSHRC), and written informed consent was obtained from all participants before enrollment. Study controls previously gave their consent to use their data in other genetic studies.

2.2. DNA extraction

A peripheral blood sample was collected and mixed with K2EDTA at room temperature in 6-ml tubes (1 Becton Drive, Franklin Lakes, NJ, USA). A whole blood sample (3 ml) was treated for 5 min in a red blood cell lysis buffer (Gentra Pure Gene, Qiagen Sciences, Maryland, USA), then the leucocyte pellet was isolated by centrifugation and re-suspended in cell lysis buffer solution. The protein lysates were then extracted by rotation for 20 s in 1 ml protein precipitation buffer and centrifuging for 5 min at 2000 g.

The genomic DNA was then precipitated by gently mixing the supernatant with isopropanol. After centrifuging and discarding the supernatant, a 75 % ethanol solution was used to wash the DNA pellet twice. After drying the DNA pellet in air, it was dissolved for 1 h in a hydration solution at 65 °C. The Nanodrop ND-1000 spectrophotometer (Wilmington, DE, USA) was used to quantify the genomic DNA.

2.3. Association studies

Two TSH- β gene variants, rs201857310 and rs7530810, were selected for the association studies. (Fig. 1) The studied variants were selected based on their location in the gene. The

rs201857310_A > G is coding SNP (resides in exon 2) that needs further study their relevance for disease manifestation. The rs7530810_G > A located in the promoter region is also considered important. It has become increasingly evident that the untranslated regions harbor important sequences for gene regulation and mRNA maturation processes. Real-time polymerase chain reaction (PCR) was used for genotyping the TSH- β gene. PCR was performed using the ABI Prism 7900HT Sequence Detection System (Applied Biosystems Inc., CA, USA), as previously described (Al-Rasheed et al., 2015; Alrasheed, n.d., 2019).

2.4. Statistical analysis

The Chi-Square test was used for categorical variables, and the Student's test or Man-Whitney test was appropriately used to compare continuous data. Multivariable logistic regression analysis for factors predicting DTC was performed, and odds ratios (OR) and their 95 % confidence intervals (95 % CI) were reported. The univariable model included age, gender, body mass index, and smoking. Factors with a *P*-value of <0.05 in the univariable analysis were included in the multivariable analysis. All statistical analyses were performed using the SPSS software version 24 (SPSS Inc., Armonk, NY, USA). Continuous data were expressed as mean and standard deviation or median and interquartile range and categorical data as numbers and frequencies when appropriate. A *P*-value of <0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics

The baseline characteristics of the patients and controls were compared with no significant differences in age, while males and smokers were significantly more among the controls. (Table 1).

3.2. Thyroid cancer

The association between two SNPs, the rs7530810_G > A in the promoter region and rs201857310_A > G in exon 2 of the TSH- β gene and thyroid cancer were studied. Following the establishment of the genotype frequencies and estimation of the Hardy-Weinberg equilibrium for the two SNPs (Table 2), a univariable analysis was performed to evaluate the relationship between the discovered individual variants and the disease. Only the rs201857310_A > G [OR: 0.50 (95 % CI: 0.35–0.71); *P* < 0.0001] was strongly associated with the disease. The effect of possible confounders (age, sex, body mass index, and smoking) was adjusted by the multivariable analysis. This analysis revealed that the rs201857310 retained its significant association with the disease [OR: 0.47 (95 % CI: 0.32–0.68); *P* < 0.0001]. There was no significant association between the other variant rs7530810 and the disease. (Tables 3 and 4).

3.3. Thyroxine dose

The association between the two SNPs was evaluated in relation to the thyroxine dose. Four hundred and fifty-three patients were included in this part of the analysis. (Table 5) Fifty-four patients were excluded because they did not meet the target therapeutic range of TSH or T4, suggesting non-compliance or inappropriate dose. There was no association between any of the variants and the thyroxine dose requirement. (Table 6).

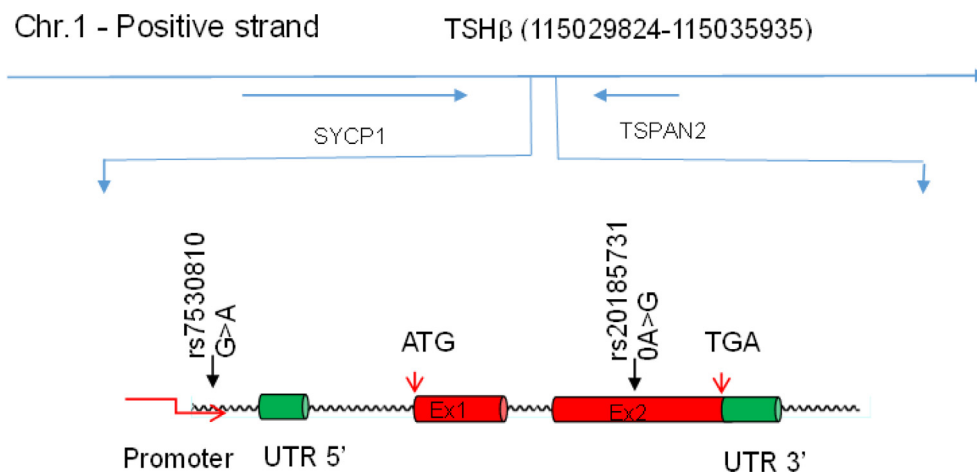


Fig. 1. The structure of the TSH-β gene showing the relative positions of the variants selected for the association study in the general population.

Table 1
Comparison of the baseline data between patients with differentiated thyroid cancer and healthy controls.

| | Patients (n = 507) | Controls (n = 560) | P-value |
|--|--------------------|--------------------|---------|
| Age (years); median (IQR) | 45 (34–56) | 44 (34–54) | 0.52 |
| Females; n (%) | 415 (81.85 %) | 401 (71.61 %) | <0.001 |
| BMI (Kg/m ²); median (IQR) | 28.9 (24.8–33.4) | 29.9 (26.4–33.9) | 0.02 |
| Smoking; n (%) | 36 (7.1 %) | 84 (15 %) | <0.001 |

BMI: body mass index.

Table 2
Estimation of the Hardy-Weinberg equilibrium (HWE) for the two studied TSH-β SNPs in the study population.

| SNP ID | Genotype | F (%) | HWE P-value |
|-------------|----------|-------------|-------------|
| rs7530810 | GG | 422 (41.33) | <0.001 |
| | GA | 335 (32.81) | |
| | AA | 264 (25.86) | |
| rs201857310 | AA | 875 (86.72) | <0.001 |
| | AG | 114 (11.30) | |
| | GG | 20 (1.98) | |

SNP ID: The single nucleotide polymorphism identification number.

F (%): The frequencies of the genotypes of alleles.

A: adenine; C: cytosine, G: guanine, and T: thymine.

4. Discussion

The role of the TSH-β polymorphism in thyroid cancer is not clear. The study investigated the potential association of TSH-β gene polymorphism and both differentiated thyroid carcinoma as well as thyroxine dose. Two linked SNPs were elected to be investigated in the Saudi population. Our results confirmed the association for one of the variants with the disease, unequivocally linking the gene with thyroid cancer. Currently, there is hardly any litera-

ture about the role of TSH-β gene polymorphism in thyroid cancer. Hence, our findings are novel and need to be verified further in larger studies. While no conclusions can be drawn solely based on these data, it is possible that this finding could be related to genetic mechanisms governing the function of the linked genic regions, a hypothesis that has to be examined further.

The associations of gene polymorphisms with other types of cancer, such as breast cancer (Campos-Verdes et al., 2018; Ling et al., 2015; Liu et al., 2021; Qiu et al., 2008), lung (Ahmed, 2021; Liu et al., 2019), gastric (Chen et al., 2010; Zeyaulah et al., 2021), leukemic (Drokow et al., 2020; Li et al., 2020), and lymphoma (Cao et al., 2014; Zhao et al., 2019), were described. However, data about the TSH-β genetic changes are still scarce. TSH is an indicator of thyroid function, and changes in TSH levels lead to thyroid disorders affecting approximately 10 % of the population (Choi et al., 2015). This association suggests that genetic changes in the TSH synthesis pathways could significantly lead to thyroid diseases, including cancers. TSH-R gene mutation was previously described in patients with functional thyroid disorders, such as toxic goiter and functioning adenoma (Bayram et al., 2013; Ferraz and Paschke, 2017). Moreover, there was an association between Leu512Arg and papillary carcinoma as well as hyperfunctioning thyroid disorders (Barbaro et al., 2006). TSH-R somatic gain-of-function mutations were associated with functional thyroid disorders such as functioning adenomas and toxic goiters. Still, its association with non-functioning thyroid disease (Bianco and Kim, 2006), TSH resistance, and congenital hypothyroidism (Sunthornthepvarakul et al., 1995) could not be elucidated.

Previous studies reported an association between microsatellite markers and intronic SNPs, such as Asp727Glu located in the TSH-R gene, and low TSH levels with normal free T4 in healthy individuals (Hansen et al., 2007; Peeters et al., 2003). One study showed that this variant causes the receptor's cAMP response to TSH to be increased (Leonard et al., 2001), while another proposed a link between TSH-R mutations and iodine supply (Curcio-Morelli

Table 3
Comparison of the two TSH-β SNP genotypes between patients with thyroid cancer and controls.

| SNP ID | Alleles | Patients (n = 507) | Control (n = 560) | P-value |
|-------------------|---------|--------------------|-------------------|---------|
| rs201857310_A > G | A | 930 (94.7 %) | 934 (90.2 %) | <0.001 |
| | G | 52 (5.3 %) | 102 (9.2 %) | |
| rs7530810_A > G | A | 467 (47.2 %) | 510 (48.5 %) | 0.55 |
| | G | 523 (52.8 %) | 542 (51.5 %) | |

SNP ID: The single nucleotide polymorphism identification number.

A: adenine; C: cytosine, G: guanine, and T: thymine.

Table 4

The univariable and multivariable analysis for the association of the two TSH-β SNP with thyroid cancer.

| | Univariable | | Multivariable | |
|-----------------------------|---------------------------------------|---------|---------------------------------------|---------|
| | Odds ratio (95 % confidence interval) | P-value | Odds ratio (95 % confidence interval) | P-value |
| rs201857310_A > G | 0.50 (0.35–0.71) | <0.001 | 0.47 (0.32–0.68) | <0.001 |
| rs7530810_A > G | 0.94 (0.79–1.12) | 0.50 | 1.12 (0.93–1.36) | 0.22 |
| Age | 0.99 (0.99–1.00) | 0.40 | 0.99 (0.98–1.002) | 0.19 |
| Gender | 0.55 (0.44–0.67) | <0.001 | 0.62 (0.48–0.80) | <0.001 |
| Body mass index | 1.02 (1.00–1.03) | 0.01 | 1.01 (0.99–1.03) | 0.08 |
| Smoking | 0.46 (0.35–0.62) | <0.001 | 1.95 (0.99–3.85) | 0.05 |

Table 5

Demographics data of individuals involved in the thyroxine dose association study.

| | All (n = 453) | Male (n = 82) | Female (n = 371) | P-value |
|-------------------------------|---------------|---------------|------------------|---------|
| Age (years) | 45.57 ± 12.90 | 47.74 ± 14.57 | 45.09 ± 12.47 | 0.09 |
| BMI (Kg/m²) | 30.34 ± 6.57 | 28.11 ± 5.72 | 30.84 ± 6.65 | <0.001 |
| TSH (mU/l) | 0.16 ± 0.44 | 0.21 ± 0.46 | 0.15 ± 0.43 | 0.26 |
| FT4 (pmol/l) | 20.70 ± 1.70 | 20.69 ± 1.82 | 20.70 ± 1.67 | 0.96 |
| L-T4 dose (μg/kg) | 2.05 ± 0.45 | 2.09 ± 0.51 | 2.04 ± 0.44 | 0.37 |

BMI: body mass index; TSH: stimulating thyroid hormone; FT4: free thyroxine level.
Data are presented as mean and standard deviation.

Table 6

Influence of TSH-β variants on T4 dose requirement.

| SNP ID | Genotypes | N | T4 dose (μg) | P-value |
|--------------------|-----------|-----|----------------|---------|
| rs201857310 | A | 901 | 151.73 ± 32.96 | 0.79 |
| | G | 51 | 150.48 ± 34.02 | |
| rs7530810 | A | 455 | 151.22 ± 33.13 | 0.73 |
| | G | 505 | 151.96 ± 33.30 | |

SNP ID: The single nucleotide polymorphism identification number.

A: adenine; C: cytosine; G: guanine, and T: thymine.

Data are presented as mean and standard deviation.

et al., 2003). Furthermore, in non-diabetic older men, insulin resistance was related to the variations in thyroid hormone serum levels and the Asp727Glu (Peeters et al., 2007). However, another study did not confirm these results, suggesting that the polymorphism of Asp727Glu could be linked to other polymorphisms in a haplotype form (Dechairo et al., 2005). Data on the Pro52Thr variation of TSH-R's responsiveness to TSH stimulation in healthy individuals were inconclusive. Some research did not elucidate any relationship between it and the variation in thyroid hormone levels (TSH, T3, or T4). This finding can be explained by the mild effect of the variant or its low frequency (Peeters et al., 2003). As a result, a dominant transmission of partial TSH resistance could result from heterozygous loss-of-function mutation, presumably due to intracellular entrapment and decreased maturation of the wild-type TSH-R by inert mutants (Calebiro et al., 2005).

The study has several limitations, including the case-control design, single-center experience, and the inclusion of differentiated thyroid cancer only. The generalization of the results needs further studies.

In summary, our findings indicate that the TSH-β gene could have a role in thyroid cancer in the Saudi population, a notion that needs to be verified in bigger population studies.

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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