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The association of *PDE8B* (rs4704397) and *FOXE1* (rs1867277) gene polymorphisms with Congenital hypothyroidism.

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Background and aim: Congenital hypothyroidism is one of the most common endocrine diseases that occur as a result of the inactivity of the thyroid gland and, can lead to impaired mental and physical development. The thyroid hormone is essential for the normal development of the nervous system. The aim of this study was to investigate the relationship between *FOXE1* and *PDE8B* polymorphism in patients with congenital hypothyroidism.

Methods: *FOXE1* and *PDE8B* polymorphism were analyzed in 100 blood samples as control and case groups via polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) and AS-PCR. Blood samples were taken from healthy people and patients, which included 50 patients and 50 control samples.

Results: The results of genotype comparison in this study showed no statistical difference between case and control samples. The following studies confirm that according to calculation of OR (OR >1) and CI (the least CI 95% was less than one), there was no significant correlation between the two groups of healthy subjects and patients for rs4704397 polymorphism in *PDE8B* and rs1867277 polymorphism in *FOXE1* with the incidence of congenital hypothyroidism in the population.

Conclusion: This study shows that rs1867277 polymorphism of *FOXE1* and rs4704397 of *PDE8B* were not associated with congenital hypothyroidism and are not endorsed as a risk factor for the disease.

Introduction

Congenital hypothyroidism is the most common endocrine disease occurs as a result of inactivity of the thyroid gland and, if untreated, could lead to impaired mental and physical development (1). Incidence of congenital hypothyroidism varies due to the geographic area of approximately 1: 2000 to 1: 4000 births. The disease is asymptomatic at birth, which is due to the passage of thyroid hormone from the mother to the placenta. Early diagnosis and treatment may affect the result of the disease (2).

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Congenital hypothyroidism is a thyroid hormone deficiency in infants. Thyroid hormone deficiency in children is commonly caused by a problem in the thyroid gland or thyroid hormone biosynthesis. The result of this disorder is hypothyroidism which can occur primarily or secondarily due to TSH deficiency. Congenital TSH deficiency rarely occurs as a separate problem but is often associated with other conditions of the pituitary hormone that is part of congenital hypothyroidism.

Congenital hypothyroidism is classified into permanent and transient. Permanent congenital hypothyroidism is a constant thyroid hormone deficiency that requires long-term treatment. Transient congenital hypothyroidism is the temporary lack of thyroid hormone, which is present at birth, but natural thyroid hormone will be produced after recovery. Permanent congenital hypothyroidism can be classified into two groups: primary and secondary. In addition, some types of congenital hypothyroidism are related to other body systems that are classified as hypothyroidism syndrome (3).

In the initial evaluation, the most common symptoms include an umbilical hernia, a large tongue, and mottled or cold skin (4). The thyroid hormone is essential for bone formation and maturation (5). So, it can lead to a wide anterior fontanel of more than 5 mm. These symptoms, along with persistent jaundice and malnutrition, are the most common clinical features of this disease (6). Some neonates with congenital hypothyroidism may have a palpable goiter. In further assessment, these patients have reduced heart rates and bulged abdomen with a large umbilical hernia. Neurological findings include hypotonia with delayed reflexes (7).

FOX proteins are a family of transcription factors which involved in regulating the expression of genes involved in cell growth, proliferation, and differentiation. Many *FOX* proteins are important in embryonic development(8). *FOXE1* is a nuclear protein (9) that identifies DNA sequences of two genes, called thyroglobulin and Thyroperoxidase, and then binds to them (10). *FOXE1* can also activate or inhibit the transcription of these genes (11). *FOXE1* binds to the AAACA sequence of the Thyroperoxidase gene (12). This connection occurs with other transcription factors, including NF1/CTF, resulting in increased expression of Thyroperoxidase and response to external hormonal stimuli (13). However *FOXE1* binding to DNA sequences, other than thyroglobulin and Thyroperoxidase, remains almost unknown (14). Mutations in the human *FOXE1* cause Bamforth-Lazarus syndrome that is associated with congenital hypothyroidism, cleft palate, hair-outs, blockage of ducts, and hypertelorism (15). In addition, *FOXE1 mutations* can be associated with cancer including papillary thyroid cancer (16).

Rs1867277 polymorphism is located in the 5'UTR locus of the *FOXE1* and can therefore regulate the expression of *FOXE1* (16). Nucleotide substitution of G with A can be effective in the expression of *FOXE1*. Rs1867277 polymorphism in the presence of G alleles results in the signing of a series of transcription factors, called USF1/USF2, in the -283 area. But in the absence of the G allele, due to the absence of USF1/USF2 factors, expression of *FOXE1* will be affected. In fact, USF1/USF2 transcription factors affect the expression of these genes by binding to the promoter of the *FOXE1* (17).

Cyclic nucleotide cAMP plays an important role regulating the metabolism, for instance, triglyceride hydrolysis depends on intracellular cAMP. CAMP signaling pathways are also important in regulating gluconeogenesis, glycogenolysis, and insulin secretion (18). The phosphodiesterase enzymes (PDEs) catalyze the cAMP and cGMP hydrolysis and thus regulate the intracellular concentration and their physiological actions. These enzymes are composed of at least 11 families (PDE1-PDE11). Phosphodiesterase enzymes are negative regulators of the transmission message waterfalls of the cyclic nucleotide and are essential for the intracellular transmission message networks (19). These enzymes are the main extracellular signaling factors and are also important in the light transmission of cone and columnar cells of the retina and in other cells such as the taste buds (20).

A wide genome study reported a strong correlation between 6 polymorphisms in the *PDE8B* promoter, called rs461497, rs6453293, rs13158164, rs4704397, rs6885099, and rs2046045, with TSH levels (21). Despite the extensive analysis of 5q14.1 surrounding area, no potential sequences associated with TSH were observed (22) but TSH regulates thyroid function through the CAMP pathway and its serum levels regulate thyroid function, even in normal conditions. Although the

level of TSH indicates specific inheritance, the specific genetic mechanisms that influence TSH levels are unclear (23). Arnaud-Lopez and colleagues identified a single nucleotide polymorphism, called rs4704397, in the *PDE8B* that was associated with TSH levels. This variant is located in intron number 1 of the *PDE8B* that has a strong association with the TSH level. Studying Seq View of the NCBI website indicates the rs4704397 polymorphism (24).

Materials and methods

In this study, blood samples were taken from two groups of healthy subjects and patients, including 50 patients with congenital hypothyroidism and 50 healthy volunteers (control group) who visited the laboratory of 17 Shahrivar. The age range of the patients and control individuals was between 1-10 years. After obtaining consent, 200 microliters of blood were taken from them that was transferred to the laboratory in tubes containing ED TA for DNA extraction. The clinical trial code (by iranian registry of clinical trials) of this research is IRCT=52793 , and when this research was conducted, the confirmation of national ethics committee for biological researches was not mandatory.

Extraction of DNA

DNA was extracted from blood leukocytes using a genomic DNA extraction kit (Gpp solution, Gene Pajoohan, Iran) according to the manufacturer's guidelines. To evaluate the accuracy of the extracted DNA, horizontal electrophoresis with agarose gel 1% was used and was photographed by the Gel Documentation system (BIO-RAD). The purity and concentration of DNA were determined by measuring spectrophotometry absorbance at wavelengths of 260 and 280 nm. The obtained DNA was stored at -20 and used as a template for polymerase chain reaction (PCR).

Polymerase chain reaction

To assess rs1867277 polymorphism, first, a 479 bp fragment of DNA of the *FOXE1* was amplified by the polymerase chain reaction by Thermal Cycler (Bio-Rad). For this purpose, a pair of specific primers were designed by primer analysis software Oligo (Version 7.54, Molecular Biology Insights, USA). The sequence of primers used in gene FOX contained forward: TCCTAAACTAGCGGGCACCACA and reverse: CGCGCTCTTCCTTCACGGTA. Each reaction mixture was used with a final volume of 25 µL containing 30 ng DNA template, 1x Taq DNA polymerase Buffer, 1.5 mM magnesium chloride, 0.2 mM dNTP, 1.5 U Forward and reverse primers, and Taq DNA polymerase with a concentration of 5 U/µl (Bioflux, Japan). PCR conditions were initial denaturation at 94ºC for 3 minutes and then 35 cycles at 94ºC for 40 seconds, 57ºC for 40 seconds and 72ºC for 45 seconds, and final extension at 72ºC for 5 minutes. After amplification, to assess and observe PCR products, horizontal electrophoresis on agarose gel 2% was performed and stained with ethidium bromide 0.5 µg/mL.

To assess rs4704397 polymorphism of the *PDE8B* in PCR, two pairs of specific primers, suitable for amplification of the gene area containing polymorphism, were used that forward and reverse primers of the G allele included ATGATTTCTCCTTGCACGGTA and CACAAACAATGGAAGCTCCC and A allele include AGTCCCTGTAAACCCGCTA And is CACAAACAATGGAAGCTCCT, respectively. To identify the exact binding location of these primers to the *PDE8B*, the gene sequence was determined in the NCBI site and then sequencing primers were ordered using the Oligo 7 software.

Genotyping

First, the amplified fragment of the *FOXE1* (479 bp) was digested at 37ºC by endonuclease enzyme (Thermo scientific, Fermentase Inc, Hanover, MD, USA). Then genotyped with electrophoresis on agarose gel 2% and stained with ethidium bromide. In the absence of Nrul polymorphic sites in the *FOXE1*, after digesting, a 479 bp fragment (A allele), and in the presence of Nrul, 349 and 130 bp (G allele) were produced.

Statistical analysis

For risk assessment of Congenital hypothyroidism among different genotypes, odd ratio (OR) and CI 95% were calculated. P values were estimated using the chi-square test. All statistical analysis was performed with MedCalc software (Version12,1, Mariakerke, Belgium). P level ≥0.05 was not considered statistically significant.

Results

According to the analysis of the allele frequency, P = 0.8864. Given the amount of P, no significant differences were observed in *PDE8B* allele frequencies between cases and controls.

Assessment of rs4704397 genotypes in the *PDE8B* in three genotypes in patients and controls showed polymorphism that included AA, AG, and GG. Homozygous genotype AA belonged to people with the A allele on both chromosomes (Wild type allele). Homozygous genotype GG belonged to people with G allele on both chromosomes (Mutant allele) and heterozygous AG was owned by people who had both A and G alleles. In the control group, among 50 healthy volunteers, 14 patients had genotype AA, 15 AG, and 21 GG. Of the 50 patients, 12 patients had genotype AA, 19 AG, and 19 GG. According to these results, no statistically significant difference was found in the allele results between the two groups (Table 1, Table 2, and Figure 1).

The frequency of the *FOXE1* allele showed that among 50 patients, there were 40 G and 60 A alleles, and in 50 healthy subjects, 55 G and 45 A alleles. The statistical analysis of the frequency the of *FOXE1* allele indicated $x^2 = 0.095$ with a P value of 0.776. Due to the P value, no significant differences in *FOXE1* allele frequencies were observed between the two groups of patients and controls. (P>0.05). Regarding the genotype frequency of the *FOXE1*, of 50 patients, 10 had genotype GG, 20 AG, and 20 AA. Among 50 healthy subjects, 20 patients had genotype GG, 15 AG, and 15 AA. To assess the significance of the results, the Chi-Square test was used which resulted in $X^2 = 4.762$ with a P value of 0.0925 (Table 3, Table,4, and Figure 2).

Discussion

The results showed that the genotype distribution of the single nucleotide rs1867277 polymorphism of the *FOXE1* and single nucleotide rs4704397 polymorphism of the *PDE8B* did not differ between the two groups of control and patients. Therefore, this polymorphism is not associated with the incidence of congenital hypothyroidism in the above population.

Congenital hypothyroidism is caused by thyroid gland hypo-activity in children. This gland is located in the neck and produces a hormone, called thyroxine, which is essential for the growth and development of the whole body, especially the nervous system. Several brain development stages continue during the postnatal period, so as thyroxin hormone levels are below normal in congenital hypothyroidism, normal brain growth, and development of children do not take place (25). Symptoms of the disease often appear late and symptoms become gradually visible with the increase in age (26).

The incidence of congenital hypothyroidism is increasing in East Asia. The incidence of this disease in the United States of America was 24.4 cases per 100,000 live births in 1987 which reached 42.2 cases per 100,000 live births in 2002 (27). In other words, the incidence of congenital hypothyroidism is rising by 3% per year in the United States (28). The incidence of congenital hypothyroidism is higher in the countries of East Asia, including Japan and China than in Western countries (29). The higher incidence in East Asian countries may be due to regional differences in screening programs for neonates. However, more genetics and family studies can also be an important factor in the higher incidence of diseases in East Asian countries (30). Due to the growing prevalence of the disease in East Asia and the importance of the disease, understanding the factors involved in the creation and development of congenital hypothyroidism is much more important. Genetic research, such as identifying candidate genes, linkage maps, and in particular genomic studies (GWAS), has increased our understanding of the importance of genetic predisposition in congenital hypothyroidism (18).

Huebner and colleagues reported the replacement of tryptophan amino acid with arginine at 97 loci (W97R) as homozygous in two non-identical twins with cleft palate, and curly hair (31). In a study in Czech, a genetic study of 170 patients with congenital hypothyroidism, due to thyroid gland dyschezia and non-goiter hypothyroidism, reported no cases of *TTF2* mutations and concluded that non-classical gene mutations or other unknown genes play a role in the incidence of congenital hypothyroidism (32). Andrey Bychkov et al showed in their study that rs1867277 polymorphism was associated with papillary thyroid cancer (PTC) (33). Another study was conducted by Anelia Horvath and colleagues on H305P mutation. The results of this study showed that the occurrence of this mutation in the *PDE8B* increased the level of TSH in patients (34). Lisette Arnaud-Lopez et al showed in their study that rs4704397 polymorphism is associated with increased levels of TSH. As a result, increased levels of TSH cause thyroid dysfunction in patients

(35). In a study by Michaela Granfors and colleagues, there was a relationship between the polymorphisms rs4704397 T_4 and TSH levels that will cause repeated abortion (36).

Conclusion

There is currently no clear explanations for the differences between the results. Possible reasons for the difference in findings of the present study with other studies may partly be racial and ethnic differences, disease status, sample size, and the complexity of gene expression or regulation at different levels. In general, the results of this study in patients with congenital hypothyroidism in the city of Rasht, Gilan province, showed that polymorphisms of rs1867277 and rs4704397 in *FOXE1* and *PDE8B* are not associated with congenital hypothyroidism and these are not endorsed as a risk factor for this disease. Given that congenital hypothyroidism is a multifactorial disease,

Table 1: Allele frequency of case and control groups (PDE8B).

Gene	Allele	Controls	Patients	2χ	p-value
PDE8B	A	43(43)	43(43)	0.0204	0.8864
	G	57(57)	57(57)		

Table 2: Number and percentage of different genotypes in case and control groups (PDE8B).

Gene	Genotypes	Patients n(%)	Controles n(%)	Odds-Ratio (95% CI)	P-value
PDE8B	AA	12(24)	14(28)	1.00 (reference)	
	AG	19(38)	15(30)	1.4778 (0.5297-4.1231)	0.45
	GG	19(38)	21(42)	1.0555 (0.3923-2.8401)	0.91

Table 3: Allele frequency of case and control groups (FOXE1).

Gene	Alleles	Cases	Controls	P	χ2
FOXE1	G	40(0.4)	55(0.55)	0.095	2.789
	A	60(0.6)	45(0.45)		

4:Number and percentage of different genotypes in case and control groups (FOXE1).

Gene	Genotypes	Patients n(%)	Controls n(%)	Odds-Ratio (95% CI)	P-value
FOXE1	GG	10(20)	20(40)	1.00 (reference)	
	AG	20(40)	15(30)	2.6667 (0.9692-7.3373)	0.0575
	AA	20(40)	15(30)	2.6667 (0.9692-7.3373)	0.0575

Illustrations

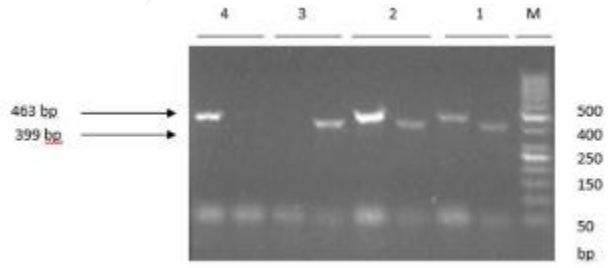

Figure 1: Detection of PDE8B gene variation in patients and controls. Lane M: 50bp DNA marker, Lane 1 and 2: Heterozygous (A/G) individuals, Lane 3: Homozygous (A/A) 399bp individuals and lane 4: Homozygous (G/G) 463 bp individuals.

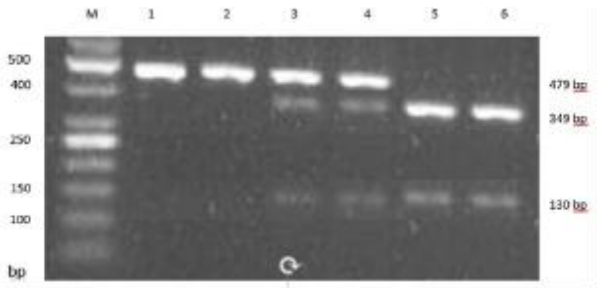

Figure 2: Detection of FOXE1 gene variation in patients and controls. Lane M: 50bp DNA marker, Lane 1 and 2: Homozygous (A/A) 479bp individuals, Lane 3 and 4: Heterozygous (A/G) individuals and Lane 5 and 6: Homozygous (G/G) 130 bp individuals.

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