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Congenital Hypothyroidism Patients With Thyroid Hormone Receptor Variants Are Not Rare: A Systematic Review

Dong-Zhu Da, MM[1,2,*], Ye Wang, MD, PhD[1,*], Min Wang, MD, PhD[1,*], Zhi Long, MM[3], Qian Wang, MD, PhD[3], and Jun Liu, MD, PhD[1]

Abstract

Background: Primary congenital hypothyroidism (CH) is a common endocrine and metabolic disease. Various genetic factors, including the thyroid hormone receptor (TSHR), play an important role in CH.

Aim: To explore the occurrence of pathogenic *TSHR* variants in CH.

Methods: We searched published articles in PubMed, Web of Science, and Cochrane Library databases, from the establishment of the database to September 26, 2021. Studies with sequencing partial or full exons of *TSHR* in CH patients were included. Gene polymorphism was excluded.

Results: A total of 66 articles (44 case-control studies and 22 case reports) were selected from the database. Though case-control studies, we found the incidence of pathogenic *TSHR* variants were not rare (range from 0% to 30.6%) and varied greatly in different countries and race. The pathogenic genotypes varied in different regions. All the variants were "loss-of-function" mutations, in which the p.(Arg450His) variant was the most common variant. In addition, we analyzed the case reports and found that CH patients with a family genetic background expressed homozygous genotypes. Homozygotes had more obvious symptoms of hypothyroidism and higher risk of comorbidities than heterozygotes.

Conclusion: Pathogenic *TSHR* variants are not uncommon cause of the CH, especially in the Arabs. The role of *TSHR* gene detection in the treatment of children with CH needs to be further studied.

Keywords

congenital hypothyroidism, receptors, thyroid hormone, mutation, sequence analysis, systematic review

Core Tip

Pathogenic *TSHR* variant is one of the factors of CH pathogenesis, and the pathogenic variant rate and high-frequency genotypes of people in different countries and races are different. *TSHR* may occur simultaneously with other gene pathogenic variants, which together lead to the occurrence of

[1]Department of Breast-Thyroid-Vascular Surgery, Shanghai General Hospital, Shanghai, China
[2]Department of Breast and Thyroid Surgery, The Affiliated Huaian No.1 People's Hospital of Nanjing Medical University, Huaian, Jiangsu, China
[3]Department of Pediatrics, Shanghai General Hospital, Shanghai, China

*Dong-Zhu Da, Ye Wang and Min Wang contributes equally to this work

Corresponding Author:
Jun Liu, MD, PhD, Department of Breast-Thyroid-Vascular Surgery, Shanghai General Hospital, 650 Xinsongjiang Rd, Songjiang District, Shanghai 201620, China.
Email: liujun95039@163.com

What do we already know about this topic?
The occurrence of CH may be involved in the pathogenic *TSHR* variant.

How does your research contribute to the field?
We investigated that pathogenic *TSHR* variant is one of the factors of CH pathogenesis, and the high-frequency genotype of people in different countries are different.

What are your research's implications toward theory, practice, or policy?
The sequencing of *TSHR* gene helps clinicians guide the treatment for patients with CH.

CH. The sequencing of *TSHR* gene helps clinicians guide treatment for patients with CH.

Introduction

Primary congenital hypothyroidism (CH) is one of the most common endocrine and metabolic diseases in infants, with an annual neonatal incidence of about 1/2000 to 1/4000.[1] CH is characterized by increased TSH levels caused by decreased thyroid hormone production during neonatal screening. In the absence of therapeutic intervention, CH children will have symptoms and signs of impaired metabolism accompanied by motor and cognitive dysfunction. Studies have found that CH is associated with more than 20 genes and about 800 variants, including thyroid hormone receptor (TSHR).[2,3]

TSHR promotes thyroid cells to synthesis and secret the thyroid hormone (T3, T4) when stimulating by TSH. Pathogenic *TSHR* variant can cause TSH-TSHR axis malfunction. The gain-of-function of pathogenic genotypes are related to hyperfunctioning thyroid adenoma and nonautoimmune hyperthyroidism, while *TSHR* "loss-of-function" pathogenic genotypes are common cause of CH in some populations. It can lead to thyroid dysplasia and TSH resistance,[4] which characterized by heterozygous, compound heterozygous or homozygous. To this day, there were several case and series reports about pathogenic *TSHR* variants in CH.

Here, we searched global literatures about *TSHR* sequencing in CH patients through systematic review and studied the occurrence characteristics of pathogenic *TSHR* variants in CH population, aiming to find the high-risk population of pathogenic *TSHR* variants in CH and the clinical characteristics of patients with these genotypes, so as to guide treatment and prognosis.

Materials and Methods

We reported this systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis 2009 guidelines.[5]

Search Strategy

PubMed, Web of Science, and Cochrane Library were retrieved to collect all the published studies on the pathogenic *TSHR* variant of CH patients. The key words searched were: "TSHR" or "thyroid hormone receptor," "mutation" or "pathogenic variant" or "deleterious nucleotide changes," "congenital hypothyroidism" or "neonatal hypothyroidism." The retrieval time was from the establishment of the database to September 26, 2021.

Selection of Articles

After all relevant articles are obtained through database retrieval, duplicate literatures in different databases are deleted. Preliminary screening was carried out through titles and abstracts to remove articles that did not meet the inclusion criteria. The full text of the remaining articles was read, and the studies that did not meet the inclusion criteria were deleted. Two researchers screened the literature independently, cross-checked the screening results, and discussed the differences. A third researcher was asked to weigh in on issues that were divisive and difficult to determine. The final article enters the stage of quality evaluation.

Inclusion Criteria

①Subjects were patients clinically diagnosed as CH; ②partial or all exons of *TSHR* gene were sequenced and described; ③case control studies, cross-sectional studies, cohort studies, or case reports.

Exclusion Criteria

①Object of study is animal model; ②in vitro cytology experiments; ③subjects were non-CH people; ④the research content was *TSHR* polymorphism or non-*TSHR* variant; ⑤secondary research literature, conference presentations, editorials, commentaries, or articles containing abstracts only; ⑥languages other than Chinese or English.

Quality Assessment

The quality of the included study was assessed independently by two investigators. The case-control study was evaluated using the Newcastle-Ottawa Scale. Eight items are evaluated from three aspects, namely (1) selection: ①Is the case definition adequate? ②Representativeness of the cases; ③Selection of Controls; ④Definition of Controls; (2) Comparability: ①Comparability of cases and controls on the basis of the design or analysis; (3) Exposure: ①Ascertainment of exposure; ②Same method of ascertainment for cases and controls;

③Non-Response rate. The full scale is 9 stars and studies that achieved five or more stars were considered high quality.

The evaluation of case report was adopted JBI Critical Appraisal Checklist for Case Reports, including: ①Were patient's demographic characteristics clearly described? ②Was the patient's history clearly described and presented as a timeline? ③Was the current clinical condition of the patient on presentation clearly described? ④Were diagnostic tests or assessment methods and the results clearly described? ⑤Was the intervention(s) or treatment procedure(s) clearly described? ⑥Was the post-intervention clinical condition clearly described? ⑦Were adverse events (harms) or unanticipated events identified and described? ⑧Does the case report provide takeaway lessons? For every 1 point that meets the criteria, the score of the essay is the sum of the total number of conditions met. We believe that 0–4, 5–6, and 7–8 marks are the high, medium and low risks of article quality, respectively.

Date Extraction

Data collation and analysis were carried out for the included studies after quality evaluation, and data were extracted independently by two researchers. In case of disagreement, they were discussed or solved with the assistance of the third

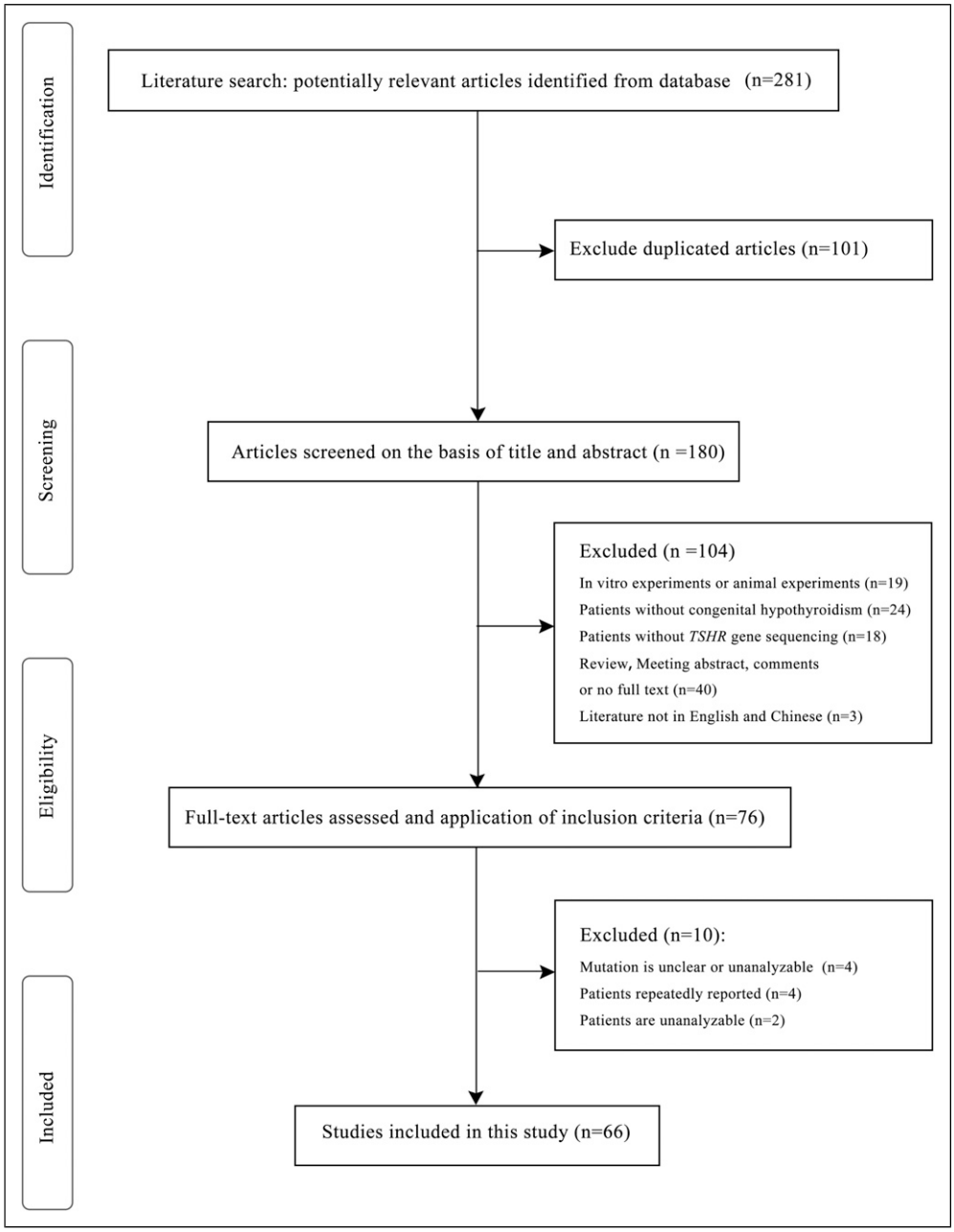

Figure 1. Flow diagram summarizing study selection process.

Table 1. Population study of pathogenic *TSHR* variants in CH patients.

Country	Author and year	Sequencing Range	Number of CH	Gender (M/F)	Number of Patients with Pathogenic Variants	Gender (M/F)	Pathogenic Variant Rate (%)	Genotype (Homozygous/ Heterozygous/ Compound Heterozygote)
China	Huang 2021[6]	NA	15	8/7	1	1/0	6.67	NA
	Wang 2020[7]	Coding exons and the 20 flanking base pairs surrounding the exons	43	18/25	3	3/0	6.98	NA
	Fang 2019[2]	Exons and exon–intron boundaries	220	110/110	13	10/3	5.91	NA
	Long 2018[8]	Entire coding regions and exon–intron boundaries	106	NA	14	NA	13.21	
	Wang 2017[9]	Entire coding regions and exon-intron boundaries	100	35/65	NA	NA	NA	NA
	Fan 2017[10]	Exons and exon–intron boundaries	66	NA	1	NA	1.52	0/0/1
	Li 2016[11]	Exon 10	89	27/62	1	1/0	1.12	0/1/0
	Qiu 2016[12]	Enons and flanking intronic	20	8/12	1	1/0	5	0/0/1
	Fu 2016[13]	Coding regions and flanking intronic regions	384	190/194	10	4/6	2.6	NA
	Chang 2012[14]	*TSHR* p.(Arg450His)	149	57/92	5	4/1	3.36	1/4/0
	Ma 2010[15]	Exons	18	11/7	1	1/0	5.56	1/0/0
	Yuan 2008[16]	Exons	79	NA	2	2/0	2.53	0/1/1
Korea	Shin 2021[17]	Exons	20	10/10	5	4/1	25	0/4/1
	Park 2016[18]	All coding exons, intron sequences, and untranslated regions (UTR) of 20-bp flanking each exon	170	NA	9	NA	5.29	1/6/2
	Jin 2014[19]	All coding exons and intronic flanking sequences	43	30/13	5	4/1	11.63	1/4/0
	Lee 2011[20]	All exons and of flanking sequences	79	NA	13	4/9	16.5	3/8/2
Japan	Watanabe 2021[21]	Exons or splicing regions	25	12/13	3	1/2	10.33	0/1/2
	Tanaka 2020[22]	Coding regions	136	60/76	12	NA	8.82	4/7/1
	Abe 2018[23]	Coding exons and flanking introns	395	192/203	35	15/11	8.86	NA
	Narumi 2011[24]	All coding exons and flanking introns	24	11/13	2	0/2	8	0/0/2
	Narumi 2009[25]	All coding exons and flanking introns	102	47/55	6	4/2	5.88	1/3/2
Turkish and Pakistani	Cangul 2012[26]	All coding exons and intronic flanking sequences	244	117/127	8	NA	3.28	6/2/0
Arabia	Zou 2018[27]	All exons	55	NA	6	3/3	10.9	6/0/0
	Deeb 2016[28]	All exons	10	NA	1	NA	10	0/1/0
Israel	Tenenbaum-rakover 2015[29]	All coding regions	94	54/40	27	14/13	29	12/12/3
Italy	Vigone 2017[30]	All exons	111	NA	34	17/17	30.6	0/29/5
	Vincenzi 2014[31]	All exons	26	NA	0	0/0	0	0/0/0
	Camilot 2007[32]	exon1-9	16	NA	3	NA	18.8	0/3/0
	Camilot 2005[33]	All exons	14	12/2	3	NA	21.4	1/2/0
	Calaciura 2002[34]	All 10 exons and intronic flanking regions	8	NA	0	0/0	0	0/0/0

(continued)

Table 1. (continued)

Country	Author and year	Sequencing Range	Number of CH	Gender (M/F)	Number of Patients with Pathogenic Variants	Gender (M/F)	Pathogenic Variant Rate (%)	Genotype (Homozygous/ Heterozygous/ Compound Heterozygote)
Finland	Lof 2016[35]	All exons and exon-intron boundaries	38	15/23	1	0/1	2.63	0/1/0
Poland	Kumorowicz-czoch 2015[36]	Selected fragments	45	13/32	1	0/1	2.22	NA
	Jeziorowska 2006[37]	All exons	24	NA	1	0/1	4.17	1/0/0
Hungary	Labadi 2015[38]	Coding exons	85	NA	4	NA	4.71	0/1/3
French	Cerqueira 2015[39]	All exons	118	47/71	1	0/1	.85	0/1/0
Germany	Krude 1996[40]	All exons	100	NA	1	NA	1	0/0/1
Russia	Makretskaya 2018[41]	NA	243	94/149	6	NA	2.47	2/3/1
Mexico	Alcántara-ortigoza 2021[42]	Exons and their exon–intron boundaries	128	29/99	1	0/1	.78	0/0/1
Brazil	Cortinhasalves 2016[43]	All exons	106	28/78	0	0/0	0	0/0/0
	Brust 2012[44]	Coding regions and exon–intron boundaries	14	7/7	0	0/0	0	0/0/0
	Alves 2010[45]	Exon 10	90	24/66	0	0/0	0	0/0/0
Indian	Kollati 2020[46]	Exons and their exon–intron boundaries	45	NA	10	NA	22.22	/
Macedonia	Zdraveska 2020[47]	All coding exons and exon/intron boundaries	29	NA	4	NA	13.79	0/4/0
UK, Oman, Saudi Arabia, UAE and Turkey	Nicholas 2016[48]	All exons	49	31/18	1	1/0	2.04	0/1/0

NA: not available.

researcher. The extracted data include: article type, author name, title, journal, year of publication; (2) the country of the research object; number of CH patients and ratio of male to female patients; The number of variants, the number of male and female patients with pathogenic variants, frequency, genotypes and amino acid changes; thyroid ultrasound, complications and other gene variant of patients with pathogenic *TSHR* variants.

Results

Search Results

A total of 281 literatures published online were retrieved. According to the inclusion and exclusion criteria, 44 case-control studies and 22 case reports were selected. After quality evaluation and discussion, all literatures were included in the study. The flow chart and results of the included literature are shown in Figure 1. Due to the different emphasis of case-control studies and case reports, we conducted separate systematic reviews of the two types of research articles.

Pathogenic TSHR Variants in CH Patients in Case-Control Studies

A total of 44 case-control studies were included in this study (Table 1). The mean incidence of pathogenic *TSHR* variant in these CH was 7.83%. The incidence of pathogenic *TSHR* variant in male (68/957, 7.11%) was somewhat similar to female (46/1250, 3.68%). We found that the incidence of pathogenic variant in children with CH varies greatly in different races. The pathogenic variant rate in CH patients was relatively high among Arabs. An Israel study found that up to 29% (26/88) of Arab patients had variants. Asia's average pathogenic variant rate followed behind, and Europe's was slightly lower than in Asia. There were no reports of pathogenic *TSHR* variants in the three studies of Brazilian CH patients. In addition, the pathogenic variant rate of the Italian population fluctuated greatly in different studies (range from 0% to 30.6%). Pathogenic *TSHR* variants had different amino acid changes in different races (Table 2). The p.(Arg450His) variant was most common type in Asians.

Table 2. Pathogenic *TSHR* variants in different races.

Race	Number of Patients with Pathogenic Variant	Pathogenic Variant	Frequency
Asian	142	p.(Arg450His)	71
		p.(Gly132Arg)	14
		p.(Ala204Val)	7
		p.(Gly245Ser)	7
Caucasian	62	p.(Pro162Ala)	10
		p.(Cys41Ser)	8
		p.(Pro68Ser)	3
		p.(Pro162Ser)	3
		p.(Arg450His)	3
Arab	33	p.(Leu653Val)	15
		p.(Pro68Ser)	6
Hungarian	4	p.(Pro162Ala)	3

The most common type among Caucasians and Hungarian was the p.(Pro162Ala) variant, while Arabs were p.(Leu653Val) variant.

Pathogenic TSHR Variants in CH Patients in Case Reports

A total of 22 case reports with 41 CH patients were systematic reviewed (Table 3). 65.85% (27/41) patients showed homozygous for pathogenic *TSHR* variant, only 14.63% (6/41) were heterozygous, and the remaining 8 patients were compound heterozygote. *TSHR* gene sequencing was also performed on family members of 38 patients, and the heterozygous genotype of the same pathogenic variant was found in at least one of the patients' father and mother. The heterozygous *TSHR* parent presented as a normal individual or only mildly abnormal thyroid function, rather than a CH.

We also studied the complications of CH patients and found 8 patients with comorbidities. 7 of them (87.5%) were homozygous, including the p.(Arg609*) *TSHR* variant merger thelarche or pulmonary stenosis (valvular) and atrial septal defect; the p.(Pro556Arg) variant merger unilateral undescended testis; the p.(Trp546*) variant combined recurrent infectious illnesses or benign bone tumor in forearm; the exon 2 deletion merger epileptiform or cognitive impairment and strabism in the eye. Only one patient with heterozygous *TSHR* p.(Glu34Lys) showed Albright's hereditary osteodystrophy, combining with pathogenic GNAS gene variant. The mother and sister of this patient with wild-type *TSHR* gene and *GNAS* gene variants both suffered from Albright's hereditary osteodystrophy. Multiple pathogenic variants in different thyroid genes always coexisted in the same CH patient, and pathogenic *TSHR* variants were often coexisted with *DUOX2* or *TPO* variant.

Discussion

In most cases (80–85%), CH is due to thyroid dysgenesis (TD), including athyreosis, thyroid dysplasia, or ectopic thyroid. In other cases (15–20%), CH is due to errors in thyroid hormone biosynthesis, secretion, or recycling.[1] CH is associated with multiple pathogenic variants, including genes associated with thyroid dysfunction *DUOX2*, *TG*, *SLC26A4*, *SLC5A5*, and *TPO*.[3,71] The *GNAS* gene is associated with thyrotropin resistance. Gene-related pathogenic variants associated with thyroid dysgenesis include *TTF1*, *TTF2*, *PAX8*, *NKX2-5*, *DUOX2*, and *TSHR* genes.[3,71]

TSHR gene was first cloned by Parmentier[72] et al in 1989 and initially found in $Tshr^{hyt/hyt}$ mice about the influence on thyroid differentiation.[73] It is located on chromosome 14q and contains 10 exons. The protein encoded by *TSHR* gene has 764 amino acids, of which the molecular weight is 87 kDa. It is a member of the G protein coupled receptors (GPCR) family, which is located on the basement membrane of thyroid follicular membrane.[74] The main function is to bind TSH, regulate thyroid cell growth and proliferation, and participate in the synthesis of thyroid hormones. TSHR consists of α and β subunits connected by disulfide linkage. The long amino terminal segment of the extracellular α subunit has high affinity for TSH and can bind TSH. The β subunit of short transmembrane and intracellular domains contains seven transmembrane (TM) domains connected by extracellular loops (ECL) and intracellular loops (ICL), which can be linked to G protein to initiate intracellular signaling. The study found that the G protein subtypes that mediate TSHR signaling are mainly Gαs and Gαq,[75] activating the cyclic adenosine monophosphate (cAMP) cascade and phospholipase C (PLC) cascade, respectively.[76] Many inactive variants that lead to a "loss of function" phenotype are characterized by impaired basal signaling, leading to the resistance to TSH or hyperthyroxinemia. Information about all pathogenic *TSHR* genotypes can be accessed https://www.tsh-receptor-mutation-database.org/map.html

The loss of function of pathogenic *TSHR* variant is one of the risk factors for CH. We studied the pathogenic *TSHR* variants in patients diagnosed with CH in the literatures in the database. The incidence of the variant is not low, ranging from 0% to 30.6%, which is related to countries and race among the studies we included. *TSHR* has a relatively high

Table 3. Case report of pathogenic *TSHR* variants in CH patients.

Author and year	Number of Patients with Variants	Gender (M/F)	Family Inheritance	Genotype (Homozygous/ Heterozygous/ Compound Heterozygote)	Thyroid Ultrasound	Comorbidities	Pathogenic Variants Site	Frequency	Other Gene Variant
Larrivée-Vanier 2020[49]	3	2/1	Y	3/0/0	NA	N	p.(Phe244Leu)	3	NA
Watanabe 2020[50]	2	1/1	Y	0/2/0	N	N	p.(Val473Ile)	2	NA
Sasivari 2019[51]	1	1/0	NA	0/1/0	N	N	p.(Cys41Ser)	1	DUOX2 (p.Q202Tfs)
Sugisawa 2018[52]	1	1/0	Y	0/0/1	Slightly small gland	N	p.(Arg109Gln)+p.(Arg450His)	1	WT
Park 2018[53]	1	1/0	Y	1/0/0	NA	NA	p.(Arg450His)	1	DIO2 T92 A
Satoh 2015[54]	1	1/0	Y	0/1/0	NA	N	p.(Arg450His)	1	DUOX2 p.A1323 T+ p.L1343 F)
Cangul 2014[55]	1	1/0	Y	1/0/0	Athyreosis	Pulmonary stenosis (valvular) and atrial septal defect	p.(Arg609*)	1	NA
Cangul 2014[56]	2	1/1	Y	2/0/0	Athyreosis	N	c.(317 + 1G> a)	2	NA
Cangul 2014[57]	2	0/2	Y	2/0/0	Hypoplastic gland	Epileptiform OR cognitive impairment and strabism in the left eye	Exon 2 deletion	2	NA
Bas 2012[58]	1	1/0	NA	1/0/0	The left lobe was severely hypoplastic, the right lobe could not be detected	Unilateral undescended testis	p.(Pro556Arg)	1	NA
	1	1/0	NA	1/0/0	N	N	p.(Pro162Ala)	1	NA
Biebermann 2012[59]	1	NA	Y	0/0/1	a hypoplastic gland	NA	p.(Trp546*)+p.(Pro639Leu)	1	NA
	1	1/0	Y	0/0/1	N	NA	p.(Trp546*)+p.(Pro639Leu)	1	NA
Sriphrapradang 2012[60]	2	2/0	Y	0/0/2	N	N	p.(Gln90Pro)+p.(Leu653Val)+p.(Leu89=)	2	NA

(continued)

Table 3. (continued)

Author and year	Number of Patients with Variants	Gender (M/F)	Family Inheritance	Genotype (Homozygous/ Heterozygous/ Compound Heterozygote)	Thyroid Ultrasound	Comorbidities	Pathogenic Variants Site	Frequency	Other Gene Variant
Sriphrapradang 2011[61]	1	1/0	Y	1/0/0	NA	NA	p.(Pro264Ser)+p.(Gln90Pro)+p.(Leu89=)	1	TPO G493S
Lado-abeal 2011[62]	1	0/1	Y	0/1/0	NA	Albright's hereditary osteodystrophy	p.(Glu34Lys)	1	GNAS c.750_751insA
	1	1/0	Y	0/1/0	N	NA	p.(Glu34Lys)	1	NA
Ma 2005[63]	1	1/0	Y	1/0/0	Dysplasia	NA	p.(Arg450His)	1	NA
Shibayama 2005[64]	1	0/1	Y	1/0/0	N	N	p.(Arg450His)	1	WT
Fricke-otto 2005[65]	2	2/0	Y	2/0/0	N	N	p.(Ala593Val)	2	NA
Richter-unruh 2004[66]	4	3/0	Y	3/0/0	Hypoplastic gland	N	p.(Arg609*)	3	NA
		0/1	Y	1/0/0	Hypoplastic gland	Thelarche	p.(Arg609*)	1	NA
Park 2004[67]	2	1/1	Y	0/0/2	Athyreosis	NA	p.(Trp546*)+p.(Ala553Thr)	2	NA
Jordan 2003[68]	2	2/0	Y	2/0/0	N	Recurrent infectious illnesses OR benign bone tumor in left forearm	p.(Trp546*)	2	NA
Tiosano 1999[69]	5	2/3	Y	5/0/0	N	N	p.(Arg609*)	5	NA
Biebermann 1997[70]	1	0/1	Y	0/0/1	Reduced thyroid volume	N	p.(Cys390Trp)	1	NA

Y: yes; N: normal; NA: not available; WT: wild type.

pathogenic variant rate among Arabs. The pathogenic *TSHR* variant rate in Asia and Europe is slightly lower. The current literature lacks more variants in other countries. In addition to the differences in pathogenic variant rates, the situation of pathogenic variant sites was also different in different races. The p.(Arg450His) variant is most common form in Asia, while the p.(Pro162Ala) variant was the majority in Caucasians and Hungarian, and p.(Leu653Val) in Arab. It may be related to the initial variant of the population, also known as the founder effect, but more evidence is still needed. This result may be biased due to too little literature. It can be speculated that if more pathogenic *TSHR* variant data for different ethnicities are added, a more accurate ethnic pathogenic variant rate may be obtained.

As is well known that the incidence of CH patients related to *TSHR* germline variants and the severity of the disease are related to whether the genotype is homozygous or heterozygous. Tenenbaum-rakover[29] et al found that homozygous CH patients showed a more severe phenotype than heterozygous (TSH 53.6 vs 9.24, P <.0001). During the follow-up period of up to 11 years, the mean serum free thyroxine (FT4) level of homozygous individuals at the last visit was significantly lower than that at the first visit (P = .05). Heterozygous subjects are euthyroid or only mildly hypothyroid. Through systematic reviews of case reports, we also found similar results that homozygotes will have more severe clinical or neurodevelopmental course than heterozygotes. We found that 87.5% of pathogenic-*TSHR*-variant-related individuals with comorbidities are homozygous. *TSHR* sequencing of family members found that homozygous patients usually have heterozygous parents with the same genotype and are normal individuals or only show mild abnormalities in thyroid function. This may be because patients with homozygous variants in *TSHR* gene exhibit more obvious resistance to TSH and appear to more severe manifestations, requiring earlier and longer thyroid hormone replacement therapy. As homozygous variants may lead to more severe hypothyroidism or a higher probability of comorbidities, patients diagnosed with CH after neonatal screening should undergo *TSHR* sequencing. We recommend that homozygous individuals require closer systemic follow-up and more frequent thyroid function reviews. Due to the difference in thyroid function detection methods and accuracy in different literatures, we cannot compare the difference in thyroid function levels between homozygous and heterozygous. Because the pathogenic *GNAS* variant associated with thyrotropin resistance appeared in the case report, the *THSR* heterozygous genotype may be part of the pathogenesis or accidental occurrence of CH.

Simultaneous detection of pathogenic-*TSHR*-variant-related patients and family members found that pathogenic *TSHR* variants have a genetic background by systematic review of literatures. We recommend that the couple of CH patients with pathogenic *TSHR* variants perform *TSHR* gene sequencing to detect and intervene in high-risk offspring as early as possible to reduce occurrences and adverse outcomes.

In conclusion, we retrospectively analyzed pathogenic *TSHR* variants in CH patients. According to case-control studies, we found that pathogenic *TSHR* variant is related to the occurrence of CH, and the pathogenic variant rate and high-frequency genotypes vary greatly in different countries. East Asians are most commonly seen with the p.(Arg450His) variant, while Italy and Turkey patients often occur at codon 162. According to case reports, we found that pathogenic *TSHR* variants with a family background often appear to be homozygous. We recommend that the role of *TSHR* gene detection in the treatment of children with CH needs to be further studied.

Author Contributions

Dong-Zhu Da and Jun Liu designed the research; Dong-Zhu Da and Jun Liu performed the research; Ye Wang, Zhi Long, and Qian Wang extracted the data; Dong-Zhu Da and Jun Liu wrote the paper; all authors read and approved the final manuscript.

Declaration of Conflicting Interests

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ORCID iDs

Dong-Zhu Da https://orcid.org/0000-0002-6133-3234
Min Wang https://orcid.org/0000-0003-0101-1855

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