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

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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

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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. 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). TSHR promotes thyroid cells to synthesize and secrete the thyroid hormone (T3, T4) when stimulated 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, 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.

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

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

Exclusion Criteria

1. Object of study is animal model; 2. in vitro cytology experiments; 3. subjects were non-CH people; 4. the research content was TSHR polymorphism or non-TSHR variant; 5. secondary research literature, conference presentations, editorials, commentaries, or articles containing abstracts only; 6. languages 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: ① Is the case definition adequate? ② Representativeness of the cases; ③ Selection of Controls; ④ Definition of Controls; (2) Comparability: ① Comparability of cases and controls on the basis of the design or analysis; (3) Exposure: ① Ascertained of exposure; ② Same method of ascertainment for cases and controls;
Non-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: ① Were patient’s demographic characteristics clearly described? ② Was the patient’s history clearly described and presented as a timeline? ③ Was the current clinical condition of the patient on presentation clearly described? ④ Were diagnostic tests or assessment methods and the results clearly described? ⑤ Was the intervention(s) or treatment procedure(s) clearly described? ⑥ Was the post-intervention clinical condition clearly described? ⑦ Were adverse events (harms) or unanticipated events identified and described? ⑧ Does 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.

**Data 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
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      | NA               | 15           | 8/7          | 1                                         | 1/0          | 6.67                          | NA                                                        |
|               | Wang 2020       | Coding exons and the 20 flanking base pairs surrounding the exons | 43 | 18/25 | 3 | 3/0 | 6.98 | NA |
|              | Fang 2019       | Exons and exon–intron boundaries | 220 | 110/110 | 13 | 10/3 | 5.91 | NA |
|              | Long 2018       | Entire coding regions and exon–intron boundaries | 106 | NA | 14 | NA | 13.21 | NA |
|              | Wang 2017       | Entire coding regions and exon–intron boundaries | 100 | 35/65 | NA | NA | NA | NA |
|               | Fan 2017        | Exons and exon–intron boundaries | 66 | NA | 1 | NA | 1.52 | 0/0/1 |
|               | Li 2016         | Exon 10          | 89           | 27/62 | 1 | 1/0 | 1.12 | 0/1/0 |
|               | Qiu 2016        | Exons and flanking intronic regions | 20 | 8/12 | 1 | 1/0 | 5 | 0/0/1 |
|               | Fu 2016         | Coding regions and flanking intronic regions | 384 | 190/194 | 10 | 4/6 | 2.6 | NA |
|               | Chang 2012      | TSHR p.(Arg450His) | 149 | 57/92 | 5 | 4/1 | 3.36 | 1/4/0 |
|               | Ma 2010         | Exons            | 18           | 11/7 | 1 | 1/0 | 5.56 | 1/0/0 |
| Korea         | Yuan 2008       | Exons            | 79           | NA | 2 | 2/0 | 2.53 | 0/1/1 |
|               | Shin 2011       | Exons            | 20           | 10/10 | 5 | 4/1 | 25 | 0/4/1 |
|               | Park 2016       | 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        | All coding exons and intronic flanking sequences | 43 | 30/13 | 5 | 4/1 | 11.63 | 1/4/0 |
|               | Lee 2011        | All exons and of flanking sequences | 79 | NA | 13 | 4/9 | 16.5 | 3/8/2 |
| Japan         | Watanabe 2021   | Exons or splicing regions | 25 | 12/13 | 3 | 1/2 | 10.33 | 0/1/2 |
|               | Tanaka 2020     | Coding regions   | 136          | 60/76 | 12 | NA | 8.82 | 4/7/1 |
|               | Abe 2018        | Coding exons and flanking introns | 395 | 192/203 | 35 | 15/11 | 8.86 | NA |
|               | Narumi 2011     | All coding exons and flanking introns | 24 | 11/13 | 2 | 0/2 | 8 | 0/0/2 |
|               | Narumi 2009     | All coding exons and flanking introns | 102 | 47/55 | 6 | 4/2 | 5.88 | 1/3/2 |
|               | Turkish and Pakistani | Cangul 2012 | All coding exons and intronic flanking sequences | 244 | 117/127 | 8 | NA | 3.28 | 6/2/0 |
| Arabia        | Zou 2018        | All exons        | 55           | NA | 6 | 3/3 | 10.9 | 6/0/0 |
|               | Deeb 2016       | All exons        | 10           | NA | 1 | NA | 10 | 0/1/0 |
| Israel        | Tenenbaum-        | All coding regions | 94 | 54/40 | 27 | 14/13 | 29 | 12/12/3 |
|               | rakover 2015    | All coding regions | 144 | 117/127 | 8 | NA | 3.28 | 6/2/0 |
| Italy         | Vigone 2017     | All exons        | 111          | NA | 34 | 17/17 | 30.6 | 0/29/5 |
|               | Vincenzi 2014   | All exons        | 26           | NA | 0 | 0/0 | 0 | 0/0/0 |
|               | Camilot 2007    | exon1-9          | 16           | NA | 3 | NA | 18.8 | 0/3/0 |
|               | Camilot 2005    | All exons        | 14           | 12/2 | 3 | NA | 21.4 | 1/2/0 |
|               | Calaciura 2002  | All 10 exons and intronic flanking regions | 8 | NA | 0 | 0/0 | 0 | 0/0/0 |

(continued)
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.

| 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        | All exons and exon-intron boundaries   | 38           | 15/23        | 1                                           | 0/1          | 2.63                          | 0/1/0                                                     |
| Poland           | Kumorowicz-czoch 2015 | Selected fragments                      | 45           | 13/32        | 1                                           | 0/1          | 2.22                          | NA                                                       |
|                  | Jeziorowska 2006 | All exons                              | 24           | NA           | 1                                           | 0/1          | 4.17                          | 1/0/0                                                     |
| Hungary          | Labadi 2015     | Coding exons                           | 85           | NA           | 4                                           | NA           | 4.71                          | 0/1/3                                                     |
|                  | Cerqueira 2015  | All exons                              | 118          | 47/71        | 1                                           | 0/1          | .85                           | 0/1/0                                                     |
|                  | Krude 1996      | All exons                              | 100          | NA           | 1                                           | NA           | 1                             | 0/0/1                                                     |
| Russia           | Makretskaya 2018| NA                                     | 243          | 94/149       | 6                                           | NA           | 2.47                          | 2/3/1                                                     |
| Mexico           | Alcántara-ortigoza 2021 | Exons and their exon-intron boundaries | 128          | 29/99        | 1                                           | 0/1          | .78                           | 0/0/1                                                     |
| Brazil           | Cortinhasalves 2016 | All exons                              | 106          | 28/78        | 0                                           | 0/0          | 0                             | 0/0/0                                                     |
|                  | Brust 2012      | Coding regions and exon-intron boundaries | 14          | 7/7          | 0                                           | 0/0          | 0                             | 0/0/0                                                     |
|                  | Alves 2010      | Exon 10                                | 90           | 24/66        | 0                                           | 0/0          | 0                             | 0/0/0                                                     |
|                  | Kollati 2020    | Exons and their exon-intron boundaries | 45           | NA           | 10                                          | NA           | 22.22                         | /                                                         |
| Macedonia        | Zdraveska 2020  | 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 | All exons                              | 49           | 31/18        | 1                                           | 1/0          | 2.04                          | 0/1/0                                                     |

NA: not available.
The most common type among Caucasians and Hungarians 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 systematically 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 the-larce or pulmonary stenosis (valvular) and atrial septal defect; the p.(Pro556Arg) variant merger unilateral undescended testis; the p.(Tnp546*) variant combined recurrent infectious illnesses or benign bone tumor in forearm; the exon 2 deletion merger the p.(Trp546*) variant combined recurrent infectious illnesses or benign bone tumor in forearm; the exon 2 deletion merger the p.(Trp546*) variant combined recurrent infectious illnesses or benign bone tumor in forearm.

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. 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.

TSHR gene was first cloned by Parmentier et al in 1989 and initially found in Thrhrythyr mice about the influence on thyroid differentiation. 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. 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 Gas and Gas, activating the cyclic adenosine monophosphate (cAMP) cascade and phospholipase C (PLC) cascade, respectively. 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

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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         |

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

| Author and year | Number of Patients with Variants | Gender (M/F) | Family Inheritance | Thyroid Ultrasound | Comorbidities | Pathogenic Variants Site | Frequency | Other Gene Variant |
|-----------------|----------------------------------|--------------|--------------------|-------------------|---------------|--------------------------|-----------|-------------------|
| Larrivée-Vanier 2020 | 3 | 2/1 | Y | 3/0/0 | NA | N | p.(Phe244Leu) | 3 | NA |
| Watanabe 2020 | 2 | 1/1 | Y | 0/2/0 | N | N | p.(Val473Ile) | 2 | NA |
| Sasivari 2019 | 1 | 1/0 | NA | 0/1/0 | N | N | p.(Cys41Ser) | 1 | DUOX2 (p.Q202Tfs) |
| Sugisawa 2018 | 1 | 1/0 | Y | 0/0/1 | Slightly small gland | N | p.(Arg109Gln)+p.(Arg450His) | 1 | WT |
| Park 2018 | 1 | 1/0 | Y | 1/0/0 | NA | NA | p.(Arg450His) | 1 | DIO2 T92 A |
| Satoh 2015 | 1 | 1/0 | Y | 0/1/0 | NA | N | p.(Arg450His) | 1 | DUOX2 p.A1323 T+ p.L1343 F) |
| Cangul 2014 | 1 | 1/0 | Y | 1/0/0 | Athyreosis Pulmonary stenosis (valvular) and atrial septal defect | p.(Arg609*) | 1 | NA |
| Cangul 2014 | 2 | 1/1 | Y | 2/0/0 | Athyreosis Hypoplastic gland | N | c.(317 + 1G>a) | 2 | NA |
| Cangul 2014 | 2 | 0/2 | Y | 2/0/0 | | | Exon 2 deletion | 2 | NA |
| Bas 2012 | 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 |
| Biebermann 2012 | 1 | 1/0 | NA | 1/0/0 | N | N | p.(Pro162Ala) | 1 | NA |
| | 1 | NA | Y | 0/0/1 | a hypoplastic gland | NA | p.(Trp546*)+p.(Pro639Leu) | 1 | NA |
| Sriphrapradang 2012 | 1 | 1/0 | Y | 0/0/1 | N | NA | p.(Trp546*)+p.(Pro639Leu) | 1 | NA |
| | 2 | 2/0 | Y | 0/0/2 | N | N | p.(Gln90Pro)+p.(Leu653Val)+p.(Leu89=) | 2 | NA |

(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 | Site Frequency | Other Gene Variant |
|-----------------|---------------------------------|--------------|--------------------|----------------------------------------------------------|-------------------|--------------|--------------------------|---------------|----------------------|
| Sriphrapradang 2011 | 1 | 1/0 | Y | 1/0/0 | NA | NA | p.(Pro264Ser)+p.(Gln90Pro)+p.(Leu89=) | 1 | TPO G493S |
| Lado-abeal 2011 | 1 | 0/1 | Y | 0/1/0 | NA | Albright's hereditary osteodystrophy | p.(Glu34Lys) | 1 | GNAS c.750_751insA |
| Ma 2005 | 1 | 1/0 | Y | 0/1/0 | N | NA | p.(Glu34Lys) | 1 | NA |
| Shibayama 2005 | 1 | 0/1 | Y | 1/0/0 | N | N | p.(Arg450His) | 1 | WT |
| Fricke-otto 2005 | 2 | 2/0 | Y | 2/0/0 | N | N | p.(Ala593Val) | 2 | NA |
| Richter-unruh 2004 | 4 | 3/0 | Y | 3/0/0 | Hypoplastic gland | N | p.(Arg609*) | 3 | NA |
| | | | | | Hypoplastic gland | Thelarche | p.(Arg609*) | 1 | NA |
| Park 2004 | 2 | 1/1 | Y | 0/0/2 | Adhyreosis | NA | p.(Trp546*)+p.(Ala553Thr) | 2 | NA |
| Jordan 2003 | 2 | 2/0 | Y | 2/0/0 | N | Recurrent infectious illnesses OR benign bone tumor in left forearm | p.(Trp546*) | 2 | NA |
| Tiosano 1999 | 5 | 2/3 | Y | 5/0/0 | N | N | p.(Arg609*) | 5 | NA |
| Biebermann 1997 | 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 et al found that homozygous related to whether the genotype is homozygous or heterozygous in thyroid function. This may be because patients with homozygous and are normal individuals or only show mild abnormalities.

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 TSHR 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
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding
The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The authors disclosed receipt of the following financial support for the research: This work was supported by the Shanghai Songjiang District Science and Technology Commission for funding the project [grant number 19SJKJGG117].

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