SIN-CHN
SCIENTIFIC PRESS PTE.LTD.

Molecular & Cellular Biomechanics 2025, 22(1), 751.
https://doi.org/10.62617/mcb751

Article

Association analysis of clinical phenotype and exon gene mutation locus in children with hyperthyroidism

Xiaojian Mao[1], Hongman He[2], Hongyi Li[1], Heyong Wang[2,*], Wen Zhang[1], Li Liu[1], Abdalbari Headar[2]

[1] Department of Genetics and Endocrinology, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou 510623, China
[2] Center of Big Data and Business Intelligent, South China University of Technology, Guangzhou 510006, China
*** Corresponding author:** Heyong Wang, wanghey@scut.edu.cn

CITATION

Mao X, He H, Li H, et al. Association analysis of clinical phenotype and exon gene mutation locus in children with hyperthyroidism. Molecular & Cellular Biomechanics. 2025; 22(1): 751.
https://doi.org/10.62617/mcb751

ARTICLE INFO

Received: 8 November 2024
Accepted: 21 November 2024
Available online: 10 January 2025

Abstract: Background: To explore the association between the clinical phenotype of hyperthyroidism in children and the exon gene mutation locus of hyperthyroidism in children. **Methods:** This study collected data from 39 children with hyperthyroidism at Guangzhou Women and Children's Medical Center in 2023. Apriori association rules are used to analyze the clinical phenotype of 39 children with hyperthyroidism and the association between exon gene mutation locus. **Results:** It is discovered that girls with hyperthyroidism are associated with mutations in TG, LHCGR, TSHR and other genes. Hyperthyroidism often occurs in children of school age, and the age of patients is related to the mutations of TG, TSHR and other genes. When there is no family history of hyperthyroidism, children are mostly associated with GNAS and CTLA4 gene mutations. It is also found that there is a no correlation between the gene mutation and the abnormal liver functions in children with hyperthyroidism. Mutations in DBH, LHCGR and TSHR genes are strongly associated with 2-degree goiter of the thyroid gland. The mutated genes associated with exophthalmos are GPR 1, TSHR, FSHR and LHCGR. Further findings show that the gene mutation loci (LHCGR, chr2,48688732, A > G) is strongly related to abnormal value of TPOAb, TGAb, TG and TRAb. **Conclusions:** These findings emphasize the significant impact of gene mutations on the development of hyperthyroidism, highlighting potential biomarkers for genetic counseling and personalized treatment methods. This study deepens our understanding of the genetic basis of hyperthyroidism in children and lays the foundation for future personalized research and genetic diagnosis based on these preliminary findings.

Keywords: children with hyperthyroidism; gene mutation locus; clinical phenotype; apriori association rules; biochemical indicators

1. Introduction

Hyperthyroidism is a common endocrine disease in clinical medicine. The latest epidemiological data show that the incidence rate of hyperthyroidism in China is between 1.3% to 2%. The data further show that the incidence rate in women is 2%, and the incidence rate in men is 1.3%. Due to the low attention given to Chinese residents concerning thyroid diseases, hyperthyroidism crisis caused by long-term untreated hyperthyroidism occurs frequently. Hyperthyroidism often occurs in children of school age, and serious hyperthyroidism has caused major obstacles to children's growth and development. At present, there are only three treatments for hyperthyroidism, including drug treatment, iodine-131 treatment and surgical treatment. Therefore, while seeking treatment methods, it is still necessary to actively strengthen the clinical prevention and treatment of hyperthyroidism in

children of school-age to help medical practitioners further understand and clarify the pathogenesis, promote the treatment of hyperthyroidism, and assist doctors in identification and diagnosis.

Although research has begun to focus on the genetic factors of hyperthyroidism, most studies have focused on mutations in the TSHR gene, while research on other related genes is relatively insufficient. Foreign researchers Abu Hassan et al. [1] studied the relationship between MTHFR gene polymorphism and thyroid dysfunction using polymerase chain reaction restriction fragment length polymorphism technology, and found that the g.1298A > C polymorphism of MTHFR gene may regulate the risk of thyroid disease. Chinese researchers pay more attention to the effect of TSHR gene mutations on the pathogenesis of hyperthyroidism, while relatively few studies focus on non-TSHR genes. However, there is still a gap in the existing literature regarding the association between gene mutations and clinical phenotypes in children with hyperthyroidism. Especially, there is a lack of comprehensive analysis on the relationship between patients' medical history, clinical manifestations, biochemical indicators, and multiple gene mutation sites.

By studying the primary clinical data of children with hyperthyroidism and the relationship between different locus of gene mutation in children with hyperthyroidism, we can study the corresponding disease from the level of gene mutation, and then understand the disease from the root and clarify the pathogenesis. The incidence of hyperthyroidism is related to the age and sex of children. Therefore, the premise of prevention of hyperthyroidism is to understand all kinds of information such as gender, age, and family history and the relationship between these information and hyperthyroidism related gene mutations. In this study, apriori association rules are used to study the association between the basic information about children with hyperthyroidism and gene mutations at different locus, providing a new perspective of the study of the association between different locus of gene mutations and clinical phenotype of children with hyperthyroidism.

2. Literature review

2.1. Foreign studies on gene mutation of children with hyperthyroidism

A number of foreign case studies have found that the gene mutations associated with hyperthyroidism in children are closely related to family inheritance.

Abu Hassan et al. [1] studied the MTHFR gene polymorphism of hypothyroidism and hyperthyroidism in Jordanian women by using polymerase chain reaction restriction fragment length polymorphism technology to determine the genotype. The results showed that the g.1298a > C gene polymorphism of MTHFR may regulate the risk of thyroid disease. The authors noted that CC, TA and TC haplotypes influence the risk of hypothyroidism. Agretti et al. [2] found a case of sporadic congenital non autoimmune hyperthyroidism caused by the mutation of the thyrotropin receptor gene p639s through genetic testing. Bellarbi et al. [3] found a new heterozygous mutation in exon 10 of the THRβ gene ((c.1366T > G)) in a patient through genetic testing, and found family features after screening her children. Rita et al. [4] through years of follow-up treatment and genetic testing of a case,

sequencing of exon 10 of TSHR gene showed a new heterozygous germline I630L mutation. The results showed that the I630L mutation of TSHR gene not only occurred at the somatic level of toxic thyroid nodules, but also its presence in the germline is related to non autoimmune primary hyperthyroidism. Heike et al. [5] studied the molecular details and overall genetic defects and faults of TSHR gene in a child patient. Mikiko et al. [6] studied the correlation between hyperthyroidism and THRB gene mutation through the clinical, laboratory and imaging manifestations of children with hyperthyroidism.

2.2. Study on gene mutation of children with hyperthyroidism in China

Graves' disease is the most common cause of hyperthyroidism. The genetic research on Graves' disease mainly focuses on the mutation of TSHR gene, and the research on other related genes is insufficient. Many domestic scholars [7–11] have studied the influence of TSHR gene mutation on the pathogenesis of hyperthyroidism, which indicates that the mutation of TSHR gene is the research hotspot of hyperthyroidism.

Relevant studies on non TSHR genes are as follows. Gu et al. [12] used restriction fragments length polymorphism polymerase chain reaction (PCR-RFLP) to study the association between leukopenia and HLA-DQA1 gene polymorphism in Graves' disease patients of Han nationality in Tianjin. It was found that HLA-DQA1I0301 allele may be a susceptibility gene for GD hyperthyroidism in Han people in Tianjin, but not a susceptibility gene for leukopenia in GD hyperthyroidism. Luo et al. [13] used the same method to study the association between leukopenia and HLA-DQA1 gene polymorphism in Graves' disease patients of Han nationality in Tianjin. The study suggested that CD40 gene may be a susceptibility gene for GD hyperthyroidism, but not a susceptibility gene for GD hyperthyroidism liver damages. Jin et al. [14] studied the correlation between SHB gene and Graves' disease with PCR sequencing method. The study suggested that the single nucleotide polymorphism of SHB gene may be related to the pathogenesis of Graves' disease.

In addition, there are more studies related to the diagnosis [15,16] and treatment [6,17] of thyroid dysfunction, but both domestic and foreign studies are based on the relationship between a gene mutation [18,19] and children with hyperthyroidism, without considering the relationship between the patient's medical history [20], clinical phenotype [21], biochemical indicators and multiple gene mutations. The scope of these studies is typically limited to examining a single gene mutation or a single case, rather than a comprehensive analysis that considers multiple factors. Therefore, this study uses Apriori association rules to study the relationship between the clinical phenotype of children with hyperthyroidism and the different locus of multiple gene mutations.

3. Materials and methods

3.1. Establishment of case database

The research project involved in this article is approved by the Ethics Committee with approval number [2022] 228A01. The cases in this study came from Guangzhou women and children medical center. With the approval of the central ethics committee and the informed consent of the child's guardian, the peripheral blood of 39 children with hyperthyroidism is collected, DNA is extracted, and whole exome sequencing is performed to obtain the whole exome gene mutation database. At the same time, medical records of 39 children with hyperthyroidism are collected, including basic characteristics, clinical manifestations and biochemical indicators, such as gender, age of disease and family history; complications (whether the liver function is abnormal), degree of goiter and exophthalmos; TPOAb, TGAb, TG and TRAb. In addition, the data of gene mutation loci of children with hyperthyroidism are obtained by whole exome analysis, so as to analyze the correlation between the basic characteristics of children with hyperthyroidism and gene mutation loci, clinical manifestations and gene mutation loci, and biochemical indicators and gene mutation loci.

3.2. Data processing

In order to facilitate the study, the clinical performance data of children are processed as follows.

Age of illness: the age of all children is not more than 18 years old. Infancy: 0 < age ≤ 1 year; Toddlers: 1 year＜ age ≤ 3 years; Preschool age child: 3 years < age ≤ 6 years; School age child: 6 years＜ age ≤14 years; Adolescence: 14 years < age ≤ 18 years.

Degree of goiter: according to clinical manifestations, it is divided into 1-degree goiter, 2-degree goiter and 3-degree goiter.

TPOAb(thyroid peroxidase antibody), TGAb(thyroglobulin antibody), TG(thyroglobulin) and TRAb(thyrotropin receptor antibody) are determined to be normal within the normal value range, and abnormal beyond the normal value range. TPOAb < 60 u/mL is normal, and TPOAb ≥ 60 u/mL is abnormal; TGAb < 60 u/mL is normal, and TGAb ≥ 60 u/mL is abnormal; 3.5 ng/mL ≤ TG ≤ 77 ng/ mL is normal, TG < 3.5 ng/mL and TG > 77 ng/mL IS abnormal; TRAb < 1.75 iu/L is normal, and TRAb ≥ 1.75 iu/L is abnormal.

Each gene mutation is expressed in the form of (Gene, chr, Position, Ref > Obs). "Gene" is the gene name and "chr" is the chromosome name; "Position" is the position of the gene; "Ref" is the reference base and "Obs" is the base after mutation.

There are 14 target genes in this study, which are: GRD1, TSHR, THRB, CTLA4, GNAS, MTTL1, UCP1, FSHR, LMOD1, DBH, LHCGR, TG, MTTK, GPR1.

3.3. Apriori algorithm

Association rule mining is to discover the closeness or relationship between data items. For a given item and transaction set, the correlation between items in the item set is obtained by analyzing the transaction set and described by association rules [22].

Apriori algorithm is a classical algorithm of association rule mining. The first step of the algorithm is to find all the frequent item sets, and the support of these frequent item sets cannot be lower than the predefined minimum support. The second step is to generate strong association rules satisfying the minimum reliability from the frequent item set [23]. Support (support, %) represents the frequency of occurrence of a given data set in all data sets; the confidence (confidence, %) represents the frequency of occurrence of one dataset in a transaction containing another dataset [24]. The minimum support threshold set in this study is 50%, and the minimum confidence threshold is 80%.

4. Results

4.1. Statistical analysis

As shown in **Table 1**, among the 39 children with hyperthyroidism, girls accounted for 74.36%, far higher than boys. At the age of onset, 69.23% of the children are found to be infected with hyperthyroidism in school age, and relatively few in toddler, preschool age and adolescence. Among them, 35.9% of the children had a family history of hyperthyroidism, and 23% of the children had abnormal liver function, which is one of the complications of hyperthyroidism. Among the clinical symptoms of hyperthyroidism, 1-degree goiter accounted for 5.13%, 2-degree goiter accounted for 76.92%, and 3-degree goiter accounted for 15.38%; 53.85% of the children had exophthalmos, and 43.59% of the children did not have exophthalmos. Among the biochemical indexes, the proportion of children whose TPOAb, TGAb, TG and TRAb are not in the normal value is 89.74%, 79.49%, 84.62% and 97.44% respectively.

Table 1. Statistical analysis.

Gender	**Count**	**Proportion**
Female	29	74.36%
male	10	25.64%
Age of onset	**Count**	**Proportion**
Adolescence	5	12.82%
Preschool age child	4	10.26%
School age child	27	69.23%
Toddlers	3	7.69%
Family history	**Count**	**Proportion**
Yes	14	35.90%
No	24	61.54%
Abnormal liver function	**Count**	**Proportion**
Yes	9	23.08%
No	30	76.92%
Goiter	**Count**	**Proportion**
1 degree	2	5.13%
2 degree	30	76.92%
3 degree	6	15.38%

Table 1. (*Continued*).

Exophthalmos	**Count**	**Proportion**
Yes	21	53.85%
No	17	43.59%
TPOAb	**Count**	**Proportion**
normal	4	10.26%
abnormal	35	89.74%
TGAb	**Count**	**Proportion**
normal	8	20.51%
abnormal	31	79.49%
TG	**Count**	**Proportion**
normal	6	15.38%
abnormal	33	84.62%
TRAb	**Count**	**Proportion**
normal	1	2.56%
abnormal	38	97.44%

4.2. Relationship between essential characteristics and gene mutation loci

4.2.1. Relationship between sex and gene mutation loci

From the association rules for female patients, the gene mutation locus with high correlation are (TSHR, chr14,81144239, G > C), (LHCGR, chr2,48688732, A > G), (GNAS, chr2,5893752, C > T) and (GPR1, chr2,26176329, T > C). As shown in the network diagram of **Figure 1**, most of the gene mutations in children with hyperthyroidism are related to girls, and their triggers are mostly TSHR, GPR1, LHCGR, FSHR and other gene mutations. The support of association rules of gene mutations are relatively low in boys. Although the support is low, it is all about the association rules between TG and TSHR genes. From the association rules for male patients, the hyperthyroidism-related genes in boys include TSHR, TG, GNAS and other genes.

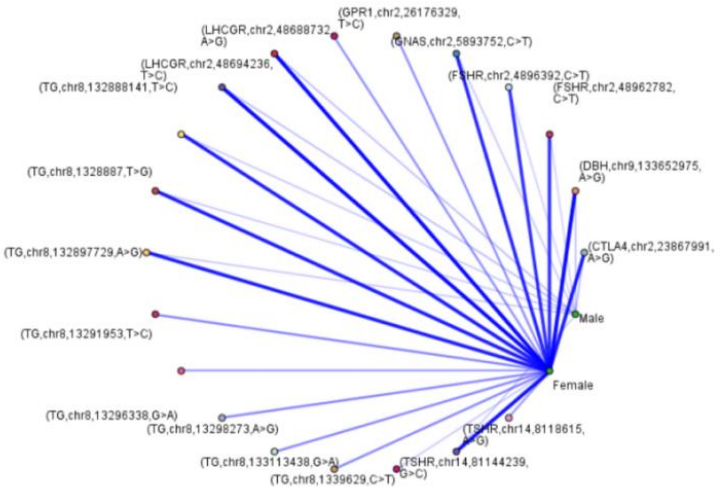

Figure 1. Network diagram of the relationship between sex and gene mutation loci.

4.2.2. Relationship between age and gene mutation loci

As shown in **Figure 2**, from the association rules with the "school age child", it is found that the frequency of TG and TSHR genes appear the most. The gene mutation locus with high correlation are (TG, chr8,13291953, T > C) and (TSHR, chr14,81144239, G > C). The support and confidence of the association rules for "school-age children" are higher than those for "adolescent" patients. Most of the mutated genes related to "adolescent" patients are TG, TSHR and FSHR, similar to the mutated genes of children in school age, but the mutated genes are less than those of children in school age.

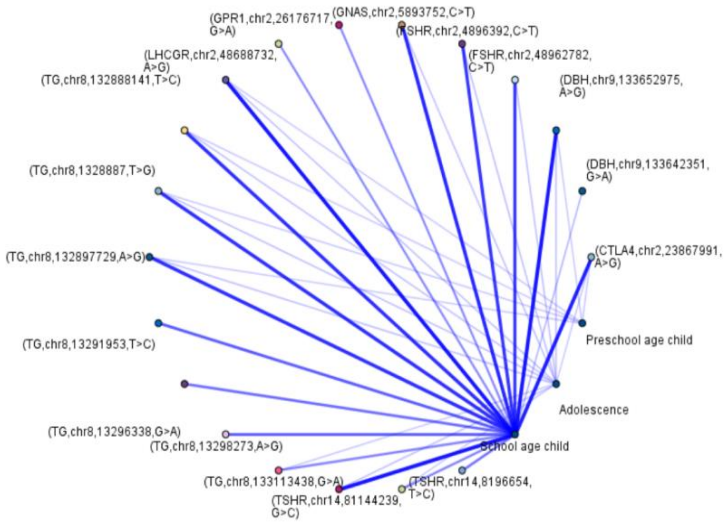

Figure 2. Network diagram of the relationship between the age of children and gene mutation loci.

4.2.3. Relationship between family history and gene mutation loci

As shown in **Figure 3**, the association rules shows that when there is no family history of hyperthyroidism, children are mostly associated with TG, GNAS and CTLA4 gene mutations, specifically with chr8 chromosome mutation of TG. The association rules shows that children with hyperthyroidism who have a family history of hyperthyroidism have high correlation among GPR1, TSHR and TG gene mutations. Regardless of family history, the TG gene will undergo mutations. This indicates that patients with a family history are highly related to GPR1 and TSHR gene mutations, while patients without a family history are highly related to GNAS and CTLA4 gene mutations. Among children with hyperthyroidism, children with no family history have more mutated genes than those with family history, and the mutated genes are similar.

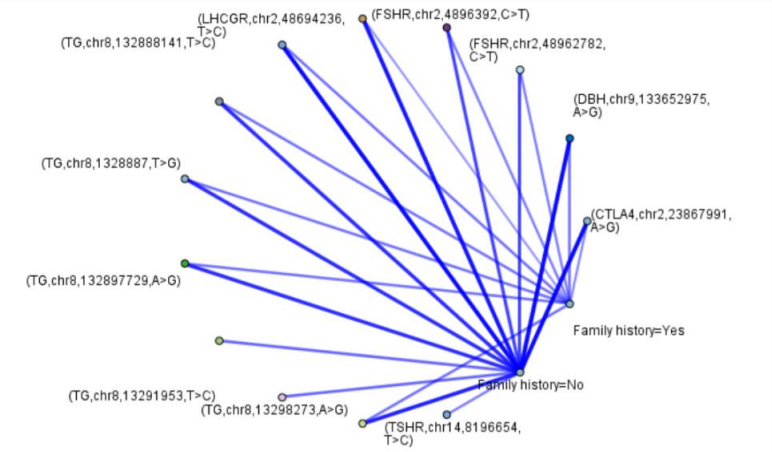

Figure 3. Network diagram of the relationship between family history and gene mutation loci.

4.3. Relationship between clinical manifestations and gene mutation loci

4.3.1. Relationship between abnormal liver function and gene mutation loci

As shown in **Table 2**, the sequence of gene mutation is highly related to the complications without abnormal liver function in children with hyperthyroidism. It can be seen from the association rules (TG, chr8,1328887, T > G) and (TG, chr8,132897729, A > G) and (LHCGR, chr2,48694236, T > C)→Abnormal liver function = No (90% support, 80.56% confidence) that the node position mutation in chr8 chromosome in TG gene is highly related to normal liver function. Therefore the abnormal liver function is not related to the mutation of each gene studied in this paper.

Table 2. Association rules between abnormal liver function and gene mutation loci.

Consequent	Antecedent	Support %	Confidence %
Abnormal liver function = No	(TG, chr8,132888141, T > C)	90.00	80.56
Abnormal liver function = No	(TG, chr8,1328887, T > G) and (TG, chr8,132897729, A > G)	90.00	80.56
Abnormal liver function = No	(TG, chr8,1328887, T > G) and (TG, chr8,132897729, A > G) and (LHCGR, chr2,48688732, A > G)	90.00	80.56
Abnormal liver function = No	(TG, chr8,1328887, T > G) and (TG, chr8,132897729, A > G) and (LHCGR, chr2,48694236, T > C)	90.00	80.56

4.3.2. Relationship between goiter and gene mutation loci

As shown in **Table 3**, the association analysis between the degree of goiter and gene mutation loci shows that 2-degree goiter has a high correlation with gene mutation loci, degree 1-degree and 3-degree goiter have a low correlation with gene mutation loci. Most children with hyperthyroidism show 2-degree goiter. From the analysis of specific association rules (LHCGR, chr2,48688732, A > G) → Goiter = Goiter 2 degree (80% support, 81.25% confidence), (TSHR, chr14,81144239, G > C) → Goiter = Goiter 2 degree (75% support, 83.33% confidence), under the association rules with high support and confidence, the mutations of DBH, LHCGR and TSHR genes are strongly related to the presence of 2-degree goiter. There is a high correlation between 2-degree goiter and gene mutation locus, including (DBH,

chr9,133652975, A > G), (LHCGR, chr2,48688732, A > G) and (LHCGR, chr2,48694236, T > C).

Table 3. Association rules between goiter and gene mutation loci.

Consequent	Antecedent	Support %	Confidence %
Goiter = Goiter 2 degree	(DBH, chr9,133652975, A > G)	80.00	81.25
Goiter = Goiter 2 degree	(LHCGR, chr2,48694236, T > C)	80.00	81.25
Goiter = Goiter 2 degree	(LHCGR, chr2,48688732, A > G)	80.00	81.25
Goiter = Goiter 2 degree	(GRD1,0,0,0) and (LHCGR, chr2,48694236, T > C) and (LHCGR, chr2,48688732, A > G)	80.00	81.25
Goiter = Goiter 2 degree	(DBH, chr9,133652975, A > G) and (LHCGR, chr2,48694236, T > C) and (LHCGR, chr2,48688732, A > G)	80.00	81.25
Goiter = Goiter 2 degree	(TSHR, chr14,81144239, G > C)	75.00	83.33

4.3.3. Relationship between exophthalmos and gene mutation loci

Compared with the degree of association between goiter and genes, the support and confidence of association rules between exophthalmos and genes are lower. As shown in **Figure 4**, according to the association rules, the mutated genes associated with exophthalmos are GPR 1, TSHR, FSHR and LHCGR. The association rules show that when the clinical manifestation of exophthalmos occurs in children with hyperthyroidism, the most common gene mutation locus are (GPR1, chr2,206176717, G > A), (TSHR, chr14,81096654, T > C), (FSHR, chr2,48962782, C > T) and (LHCGR, chr2,48688732, A > G).

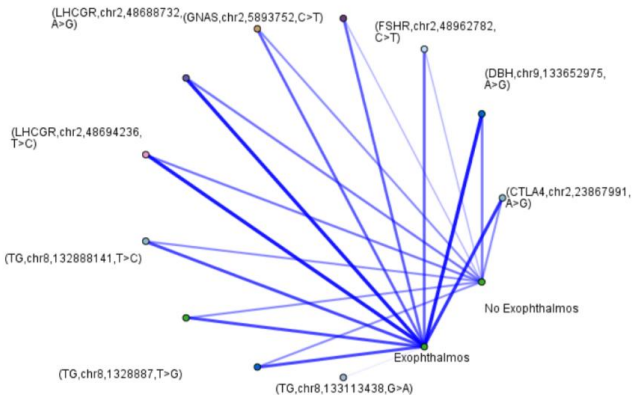

Figure 4. Network diagram of the relationship between exophthalmos and gene mutation loci.

4.4. Relationship between biochemical indexes and gene mutation loci

4.4.1. Relationship between TPOAb and gene mutation loci

As shown in **Table 4**, the support and confidence of association rules formed by abnormal values of TPOAb and gene mutation loci are high, indicating that hyperthyroidism patients with gene mutation have a higher probability of abnormal value of TPOAb. From the association rules with high support, mutations in LHCGR, DBH, CTLA4 and TSHR genes have a strong correlation with the value of TPOAb abnormality. The mutations at the locus of “48694236” and “48688732” of chr2

chromosome of LHCGR gene have the strongest correlation with the value of TPOAb abnormality. Besides, the abnormal value of TPOAb is related to the gene mutation locus, including (DBH, chr9,133652975, A > G), (CTLA4, chr2,23867991, A > G) and (TSHR, chr4,81144239, G > C).

Table 4. Association rules between TPOAb and gene mutation loci.

Consequent	Antecedent	Support %	Confidence %
TPOAb = abnormal	(DBH, chr9,133652975, A > G) and (LHCGR, chr2,48688732, A > G)	97.50	89.74
TPOAb = abnormal	(LHCGR, chr2,48694236, T > C) and (LHCGR, chr2,48688732, A > G)	97.50	89.74
TPOAb = abnormal	(CTLA4, chr2,23867991, A > G)	92.50	89.19
TPOAb = abnormal	(TSHR, chr14,81144239, G > C) and (DBH, chr9,133652975, A > G)	92.50	89.19
TPOAb = abnormal	(TG, chr8,132897729, A > G) and (DBH, chr9,133652975, A > G)	90.00	88.89
TPOAb = abnormal	(TG, chr8,132897729, A > G) and (LHCGR, chr2,48694236, T > C)	90.00	88.89

4.4.2. Relationship between TGAb and gene mutation loci

As shown in **Table 5**, the support and confidence of association rules formed by abnormal value of TGAb and gene mutation loci are high, indicating that hyperthyroidism patients with gene mutation have a higher probability of abnormal value of TGAb. From the association rules with high support, mutations in GNAS, LHCGR and DBH genes have strong correlation with the value of TGAb abnormality, and the mutation at the loci of "58903752" of GNAS gene has the strongest correlation with the value of TGAb abnormality. Besides, the abnormal value of TGAb is related to the gene mutation locus, including (DBH, chr9,133652975, A > G), (LHCGR, chr2,48688732, A > G), (LHCGR, chr2,48694236, T > C) and (TG, chr8,132888141, T > C).

Table 5. Association rules between TGAb and gene mutation loci.

Consequent	Antecedent	Support%	Confidence %
TGAb = abnormal	(GNAS, chr2,5893752, C > T) and (LHCGR, chr2,48688732, A > G)	87.50	82.86
TGAb = abnormal	(GNAS, chr2,5893752, C > T) and (LHCGR, chr2,48694236, T > C)	87.50	82.86
TGAb = abnormal	(GNAS, chr2,5893752, C > T) and (DBH, chr9,133652975, A > G)	87.50	82.86
TGAb = abnormal	(GNAS, chr2,5893752, C > T) and (TSHR, chr14,81144239, G > C) and (LHCGR, chr2,48694236, T > C) and (DBH, chr9,133652975, A > G)	82.50	81.82
TGAb = abnormal	(GNAS, chr2,5893752, C > T) and (TSHR, chr14,81144239, G > C) and (LHCGR, chr2,48694236, T > C)	82.50	81.82
TGAb = abnormal	(GNAS, chr2,5893752, C > T) and (TG, chr8,132888141, T > C)	80.00	81.25

4.4.3. Relationship between TG and gene mutation loci

As shown in **Table 6**, the support and confidence of association rules formed by abnormal value of TG and gene mutation loci are high, indicating that hyperthyroidism patients with gene mutation have a higher probability of abnormal value of TG. From the association rules with high support, the mutations of LHCGR, DBH, CTLA4 and TSHR genes have strong correlation with the value of TG abnormality, among which the mutations at the locus of "48694236" and "48688732" of chr2 chromosome of LHCGR gene have the strongest correlation with the value

of TG abnormality. Besides, the abnormal value of TG is related to gene mutation locus, including (LHCGR, chr2,48688732, A > G), (LHCGR, chr2,48694236, T > C), (DBH, chr9,133652975, A > G), (CTLA4, chr2,23867991, A > G) and (TSHR, chr14,81144239, G > C).

Table 6. Association rules between TG and gene mutation loci.

Consequent	Antecedent	Support %	Confidence %
TG = abnormal	(LHCGR, chr2,48688732, A > G) and (LHCGR, chr2,48694236, T > C) and (DBH, chr9,133652975, A > G)	97.50	84.62
TG = abnormal	(DBH, chr9,133652975, A > G)	97.50	84.62
TG = abnormal	(CTLA4, chr2,23867991, A > G) and (DBH, chr9,133652975, A > G)	92.50	83.78
TG = abnormal	(TSHR, chr14,81144239, G > C) and (LHCGR, chr2,48688732, A > G) and (LHCGR, chr2,48694236, T > C)	92.50	83.78

4.4.4. Relationship between TRAb and gene mutation loci

As shown in **Table 7**, the support and confidence of association rules formed by abnormal value of TRAb and gene mutation loci are high, indicating that hyperthyroidism patients with gene mutation have a higher probability of abnormal value of TRAb. From the association rules with high support, the mutations of LHCGR, DBH, CTLA4 and TG genes have strong correlation with the value of TRAb abnormality. The abnormal value of TRAb is related to gene mutation locus, including (LHCGR, chr2,48688732, A > G), (DBH, chr9,133652975, A > G) and (TG, chr8,132897729, A > G).

Table 7. Association rules between TRAb and gene mutation loci.

Consequent	Antecedent	Support %	Confidence %
TRAb = abnormal	(LHCGR, chr2,48688732, A > G) and (LHCGR, chr2,48694236, T > C) and (DBH, chr9,133652975, A > G)	97.50	97.44
TRAb = abnormal	(CTLA4, chr2,23867991, A > G) and (LHCGR, chr2,48694236, T > C) and (DBH, chr9,133652975, A > G)	92.50	97.30
TRAb = abnormal	(TG, chr8,132897729, A > G) and (TG, chr8,132888141, T > C) and (DBH, chr9,133652975, A > G)	90.00	97.22
TRAb = abnormal	(TG, chr8,132897729, A > G) and (TG, chr8,132888141, T > C)	90.00	97.22
TRAb = abnormal	(TG, chr8,132897729, A > G) and (TG, chr8,132888141, T > C) and (LHCGR, chr2,48694236, T > C) and (DBH, chr9,133652975, A > G)	90.00	97.22

5. Conclusion

In this study, the clinical phenotype of children with hyperthyroidism and exon gene mutation loci are analyzed. The results show that the basic characteristics, clinical manifestations, biochemical indicators and other clinical phenotype of children with hyperthyroidism are related to gene mutations at different locus of the whole exon. These findings emphasize the important role of gene mutations in the pathogenesis of hyperthyroidism in children and provide potential biomarkers for future genetic counseling, risk assessment, and personalized treatment.

5.1. Relationship between basic characteristics and gene mutation loci

The study uncovers a pronounced link between the female gender and TSHR

gene mutations, especially among school-age children, indicating gender's potential role in hyperthyroidism susceptibility. Moreover, the incidence of hyperthyroidism in school-age children is tightly connected to mutations in genes like TG and TSHR, contrasting with a weaker correlation in preschool and adolescent children devoid of a familial hyperthyroidism background.

5.2. Relationship between clinical manifestations and gene mutation loci

In children lacking a familial history of hyperthyroidism, mutations in the GNAS and CTLA4 genes are predominantly associated. In contrast, a positive family history shows a high correlation with GPR1 and TSHR gene mutations, although this association is less supported.

5.3. Relationship between biochemical indexes and gene mutation loci

Notable correlations are identified between clinical presentations like goiter degree and gene mutations, with the most robust associations being for mutations in the DBH, LHCGR, and TSHR genes. Additionally, biochemical indices such as abnormal TPOAb, TGAb, TG, and TRAb values are significantly tied to specific gene mutations, especially those in the LHCGR gene located on chromosome 2.

6. Discussion

By illuminating the genetic factors linked to the diverse clinical features of hyperthyroidism, our study enhances the precision of diagnostic and therapeutic strategies for clinicians. Our findings underscore the critical influence of specific genetic mutations, thereby amplifying the genetic research landscape and emphasizing the urgency for further exploration into the genetic roots of hyperthyroidism. The emphasis on genetic determinants in this study has certain theoretical significance for promoting personalized medicine, and provide reference for practical clinical applications.

Firstly, by identifying gene mutations associated with specific gender and age groups, we can better predict the risk of hyperthyroidism and provide early screening and intervention for high-risk children. For example, we found TSHR gene mutations associated with school aged girls, suggesting that targeted physical screening may be beneficial in this specific population.

Secondly, our research findings emphasize the role of family history in the pathogenesis of hyperthyroidism. For children without a family history, the discovery of GNAS and CTLA4 gene mutations may help identify genetic risk children who may not have been captured by traditional family history assessments.

Finally, our research emphasizes the potential of genetic testing in the management of hyperthyroidism. By identifying specific genetic mutations, doctors can provide patients with more accurate diagnosis, prognosis assessment, and treatment options. This not only helps improve treatment effectiveness, but may also reduce unnecessary treatment and related side effects.

7. Future work

The 39 data used in this study are actual data from hospitals and all available

data that we can obtain. We consider 39 pieces of data as limited resources for preliminary exploratory research to gain a preliminary understanding of the medical phenomena we are studying. We have strictly controlled and verified the quality, accuracy, and reliability of the data. Although this small sample cannot represent a broad population, they provide useful insights about specific contexts and provide a foundation for further research.

In the future, we will increase the sample size through multi center collaboration. We plan to collaborate with other medical centers in China, expand the time dimension, share data and sample resources to collect a wider range of patient samples, in order to improve the reliability and universality of our research results.

We also plan to consider and control for some potential confounding factors that may affect the thyroid gland function in future research. We will design a detailed questionnaire survey to collect information on participants' environmental exposure history, lifestyle habits, and dietary habits.

Author contributions: Conceptualization, XM and HW; methodology, HW and HH; software, HH; validation, XM, HW, WZ and LL; formal analysis, WZ, LL and AH; investigation, XM, WZ and LL; resources, XM, WZ and LL; data curation, HH and AH; assist in completing the research, HL; writing—original draft preparation, HH; writing—review and editing, HW; visualization, HH; supervision, XM; project administration, HW; funding acquisition, HW. All authors have read and agreed to the published version of the manuscript.

Funding: This research was supported by Project of Guangzhou Science and technology plan project, Grant No. 202201020609.

Acknowledgments: This study was performed with the support of Department of Genetics and Endocrinology, Guangzhou Women and Children's Medical Center. The authors are indebted to the patients, physicians, and nurses who made this work possible.

Ethics approval: Although this study is a retrospective analysis of data collected from patient care routines, rather than experimental research. However, the study was conducted in accordance with the Declaration of Helsinki, the research project involved in this article is approved by the Ethics Committee with approval number [2022]228A01. The cases in this study are obtained from Guangzhou Women and Children's Medical Center, approved by the ethics committee of the guardian of hyperthyroidism and with written informed consent by the guardians of the children.

Availability of data and material: All data generated or analysed during this study are included in this published article.

Consent for publication: Not applicable.

Conflict of interest: The authors declare no conflict of interest.

References

1. Abu-Hassan D W. MTHFR gene polymorphisms in hypothyroidism and hyperthyroidism among Jordanian females.

Archives of Endocrinology and Metabolism. 2019;63:280-287.
2. Agretti P, Marco G D, Biagioni M, et al. Sporadic congenital nonautoimmune hyperthyroidism caused by P639S mutation in thyrotropin receptor gene. European Journal of Pediatrics. 2012;171:1133-1137.
3. Bellarbi D, Chentli F, Azzoug S. RESISTANCE TO THYROID HORMONES: A NOVEL MUTATION OF THE THYROID HORMONE RECEPTOR β GENE IN AN ALGERIAN FAMILY. Acta Endocrinologica (Bucharest). 2017;13:502-505.
4. Bertalan R, Sallai, ágnes, Sólyom, János, et al. Hyperthyroidism Caused by a Germline Activating Mutation of the Thyrotropin Receptor Gene: Difficulties in Diagnosis and Therapy. Thyroid Official Journal of the American Thyroid Association. 2010;20:327-332.
5. Biebermann H, Winkler F, Kleinau G. Genetic defects, thyroid growth and malfunctions of the TSHR in pediatric patients. Frontiers in bioscience (Landmark edition). 2010;15:913-933.
6. Okazaki Hada Mikiko, Nishihara Eijun,Hisakado Mako, et al. Autoimmune thyroid disease and thyroid function test fluctuations in patients with resistance to thyroid hormone. European journal of endocrinology. 2021;73-82.
7. LI Jie, LIU Yun-feng. Research Progress on the mechanism of TSHR gene in hyperthyroidism. Chinese Journal of Integrative Medicine on Cardio-Cerebrovascular Disease. 2022;20:1435-1437.
8. FENG Ping. TSH receptor gene mutation and thyroid disease. International Journal of Endocrinology and Metabolism. 1996;02:63-64.
9. YU Jian. Research progress of TSH receptor gene mutation and thyroid diseases. Medical Recapitulate. 2002;03:164-166.
10. LI Zhen-ke, LIU Guo-liang. TSH receptor gene mutation and congenital non autoimmune hyperthyroidism. Journal of Practical Diabetology. 2021;17:3-5.
11. LIU Chao, WU Xiao-hong, JIANG Xu-qin. TSH receptor and thyroid diseases. International Journal of Endocrinology and Metabolism. 2001;02:62-65.
12. GU Yi, LI Mei, QIU Ming-cai, et al. The association between leukopenia in hyperthyroidism of Graves' disease and polymorphism in HLA-DQA1 alleles. Tianjin Medical Journal. 2006;01:10-12.
13. LUO Hui-xin, ZHANG Peng, GAO Zhi-hong, et al. Association between hepatic injury of Graves' disease and a C/T single-nucleotide polymorphism of the CD40 gene. Tianjin Medical Journal. 2006(08):525-526.
14. JIN Yan, WU Gang, WANG Xue-qin, et al. Association study of SUB gene with Graves disease. Suzhou University Journal of Medical Science. 2009;29:688-690.
15. Gurnell, M., Bashari, W., Senanayake, R., et al. Thyroid-stimulating hormone-producing pituitary tumours. DeGroot's Endocrinology. 2022;1, 145-154.
16. Moran, C., Schoenmakers, N., Halsall, D., et al. Approach to the Patient With Raised Thyroid Hormones and Nonsuppressed TSH. The Journal of Clinical Endocrinology Metabolism. 2024;109(4), 1094-1108.
17. Donnars, A., Leplat, A., Grosheny, C., et al. Clinically symptomatic resistance to thyroid hormone β syndrome because of THRB gene mosaicism. The Journal of Clinical Endocrinology Metabolism. 2022;107(9), e3548-e3552.
18. Moran, C., Schoenmakers, N., Visser, W. E., et al. Genetic disorders of thyroid development, hormone biosynthesis and signalling. Clinical endocrinology. 2022;97(4), 502-514.
19. Okosieme, O. E., Usman, D., Taylor, P. N., et al. Cardiovascular morbidity and mortality in patients in Wales, UK with resistance to thyroid hormone β (RTHβ): a linked-record cohort study. The Lancet Diabetes Endocrinology. 2023;11(9), 657-666.
20. Abdellaoui, Y., Magkou, D., Bakopoulou, S., et al. Coexistence of autoimmune hyper-and hypothyroidism in a kindred with reduced sensitivity to thyroid hormone. European Thyroid Journal. 2020;9(5), 263-268.
21. Lauffer, P., Bikker, H., Garrelfs, M. R., et al. Defective levothyroxine response in a patient with dyshormonogenic congenital hypothyroidism caused by a concurrent pathogenic variant in thyroid hormone receptor-β. Thyroid. 2021;31(11), 1757-1762.
22. QIAN Xue-zhong, KONG Fang. Research of Apriori algorithm in mining association rules. Computer Engineering and Applications. 2008;17:138-140.
23. LIU Hong-qiang. Analysis and improvement of Apriori association rule mining algorithm. Journal of Shengli College China University of Petroleum. 2009;23:17-19.
24. YAN Ai-li, LIU Man-dan. Users' frequent tracks mining based on dynamic multi-minimum support. Computer Engineering and Design. 2022;43:1657-1664.