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Novel missense mutation in *PTPN22* in a Chinese pedigree with Hashimoto's thyroiditis

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Abstract

Background: Hashimoto's thyroiditis is a complex autoimmune thyroid disease, the onset of which is associated with environmental exposures and specific susceptibility genes. Its incidence in females is higher than its incidence in males. Thus far, although some susceptibility loci have been elaborated, including *PTPN22*, *FOXP3*, and *CD25*, the aetiology and pathogenesis of Hashimoto's thyroiditis remains unclear.

Methods: Four affected members from a Chinese family with Hashimoto's thyroiditis were selected for whole-exome sequencing. Missense, nonsense, frameshift, or splicing-site variants shared by all affected members were identified after frequency filtering against public and internal exome databases. Segregation analysis was performed by Sanger sequencing among all members with available DNA.

Results: We identified a missense mutation in *PTPN22* (NM_015967.5; c. 77A > G; p.Asn26Ser) using whole-exome sequencing. *PTPN22* is a known susceptibility gene associated with increased risks of multiple autoimmune diseases. Cosegregation analysis confirmed that all patients in this family, all of whom were female, carried the mutation. All public and private databases showed that the missense mutation was extremely rare.

Conclusions: We found a missense mutation in *PTPN22* in a Chinese HT pedigree using whole-exome sequencing. Our study, for the first time, linked a rare variant of *PTPN22* to Hashimoto's thyroiditis, providing further evidence of the disease-causing or susceptibility role of *PTPN22* in autoimmune thyroid disease. Functional studies regarding the effects of this variant on thyroid autoimmunity and thyroid function are warranted.

Keywords: Hashimoto's thyroiditis, Whole-exome sequencing, *PTPN22*, Mutation

Background

Autoimmune thyroid disease (AITD) constitutes a complex class of diseases, including Graves' disease (GD) and Hashimoto's thyroiditis (HT); these are associated with interactions of specific susceptibility genes and environmental exposures [1, 2]. Both GD, manifested as hyperthyroidism, and HT, manifested as hypothyroidism, exhibit common characteristics of the production of thyroid autoantibodies and the invasion of thyroid lymphocytes. AITD is one of the most prevalent autoimmune diseases, affecting approximately 5% of the general population [1, 2]. The incidence of GD and HT demonstrates a significant genetic effect in populations with adequate iodine intake

in different geographical locations, because these populations encounter different environmental factors [3]. Approximately 37% of families with AITD exhibit either of these two disorders [4]. In the Whickham survey, the prevalence of spontaneous hypothyroidism was 1.5% in females—far higher than the 0.1% observed in males [5]. Thus far, the aetiology and pathogenesis of AITD remain unclear. Some scholars have speculated that separate genetic factors are related to the onset of GD and HT, while others support the concept of common genetic susceptibility factors [4].

Previous studies advancing the understanding of the genetic aetiology of AITD have expanded the field of thyroid autoimmunity. Although some susceptibility loci associated with AITD have been elaborated in past reports, the following correlations with AITD may prove more conclusive: *PTPN22*/1q13.2 (T lymphocyte signalling),

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TSHR/14q31.1 (thyrotropin receptor), *HLA*/6p21 (human leukocyte antigen) and *CTLA4*/2q33.2 (T-regulatory cell function) [6]. *TSHR* has been confirmed as a disease-specific locus by GWAS and other association studies [7]. The disease-predisposing genotype (TT) of SNP rs12101261 has been associated with reduced thymic expression of *TSHR* mRNA [7]. Reduction in thymic expression of *TSHR* may contribute to sustained escape of pathogenic T cells from the centre and an increased risk of *TSHR* autoimmunity. *FOXP3* and *CD25*, in connection with AITD, play a key role in the establishment of peripheral tolerance [8]. The *DXS573* microsatellite in *FOXP3* linkage disequilibrium (LD) is associated with AITD in Caucasian female AITD patients [9]. An A/C polymorphism at -3279 has been associated with the development of therapeutic resistance in patients with GD, whereas the CC genotype at -2383 has been associated with severe HT [10]. Taken together, these prior studies demonstrate that the *FOXP3* polymorphism is associated with AITD. Several other susceptible loci have also been associated with AITD, including *FCRL3* (Fc receptor-like 3), *RNA-SET2* (ribonuclease T2), *SCGB3A2* (secretoglobin, family 3A member 2) [6, 11–14].

Previous studies have shown that *PTPN22* is associated with a variety of immune diseases [15]. Jacobson et al. [16] reported that the R620W SNP was related to the occurrence of HT. However, some reports have indicated a negative correlation between R620W and AITD [17, 18], while other reports have indicated a positive correlation [19–21]; this dispute remains unresolved.

Notably, unrelated individuals have been the primary focus in past research studies; there are few pedigree studies, and it is difficult to establish whether HT is an inherited disease. Here, we report a Chinese HT pedigree with

six affected members who exhibit an autosomal-dominant inheritance pattern. Whole-exome sequencing (WES) revealed that a rare heterozygous missense variant in *PTPN22* co-segregated with this disorder. This mutation was identified for the first time in patients with HT.

Methods

Participants

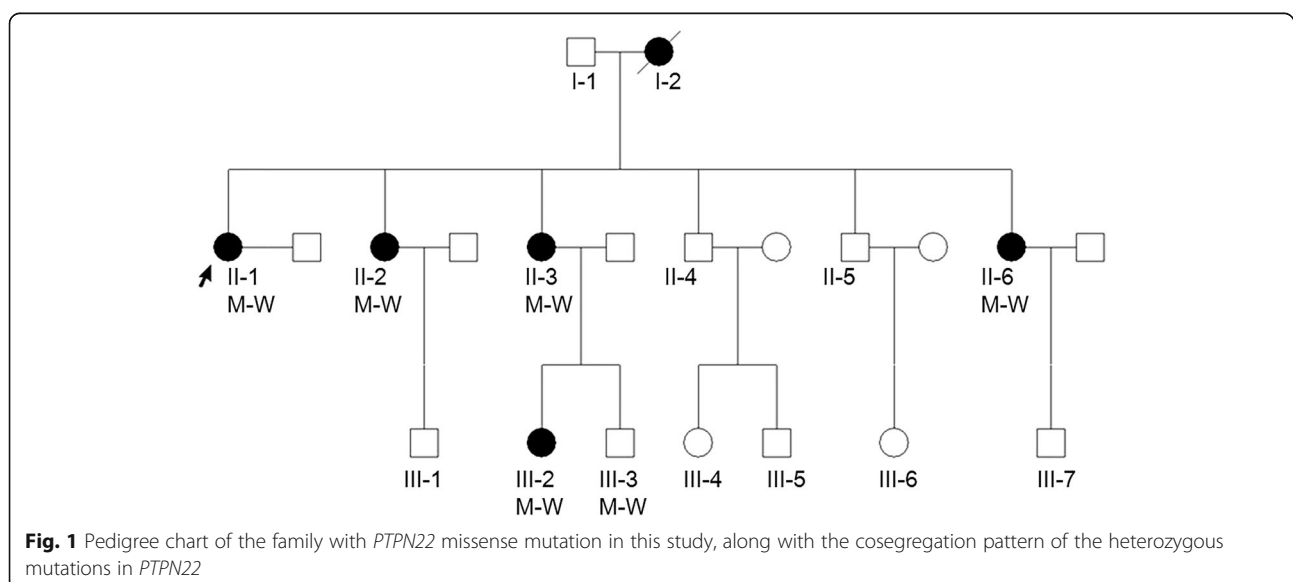
We examined a Chinese family in which six individuals across three generations exhibit hypothyroidism; all patients are females (Fig. 1). We collected peripheral blood samples from one unaffected and five affected individuals in this family, as well as results of thyroid function tests, thyroid antibody tests, rheumatoid factor and thyroid colour Doppler ultrasonography. This research was approved by the ethical committees of the China Japan Union Hospital of Jilin University. Written informed consent was obtained from all study participants.

Clinical examinations

Diagnosis of HT was made on the following basis: clinical and biochemical evidence of hypothyroidism requiring thyroxine replacement therapy, as well as increased expression of autoantibodies to thyroid peroxidase (TPO) and antithyroglobulin, as measured by specific radioimmunoassay. Each participant was interviewed and signed a letter of consent before inclusion in the study.

WES and validation

DNA was extracted from peripheral venous blood by using the QIAamp DNA Blood Mini Kit (QIAGEN, Hilden, Germany). Exons of DNA samples were captured with the SureSelect Human All Exon V5 (Agilent, Santa Clara, CA, USA) and then sequenced on the Illumina



Hiseq4000 sequencer (Illumina, Saint Diego, CA, USA). By using BWA – 0.7.10 (the Burrows-Wheeler Alignment Tool), the reads were mapped to the human reference genome (hg19). Variants including single nucleotide variants (SNVs) and indels were called by using GATK 3.v4 (Genome Analysis Toolkit) and annotated with SnpEff_v4.1.

Segregation analysis

Sanger sequencing was used to perform co-segregation analysis of c. 77A > G of *PTPN22* among pedigree members with available DNA. The primers were as follows: forward, 5'- GTTCATTTGGGACATAAGG-3'; reverse, 5'- CCAGGAGTTCAAGGCTAC-3'.

Results

Clinical features

This family exhibited HT with unique clinical characteristics. Over three generations, six family members were affected, and all affected individuals were female. The proband (II-1) was a 58-year-old woman who was admitted to the hospital for review of thyroid disease. She had exhibited thyroiditis for 3 years and had been tested for thyroid nodule and diffuse thyroid changes. Thyroid function tests showed that she had an elevated thyroid peroxidase autoantibody (TPOAb) level (244 IU/ml, normal range: 0–34.0 IU/ml) and an elevated thyroid stimulating hormone (TSH) level (5.37 mIU/L, normal range: 0.372–4.94 mIU/L). Therefore, she was diagnosed with HT. Her two sisters and a niece also exhibit thyroid nodules and diffuse thyroid changes; all affected members' results of thyroid function tests were similar to those of the proband, with abnormally high values of TPOAb. Additionally, II-6 also had rheumatoid arthritis with a high serum level of rheumatoid factor (74.7 IU/ml, normal range: 0–20 IU/ml). All patients received different doses of thyroxine replacement therapy after diagnosis. We performed colour Doppler echocardiography, blood routine examination, and biochemical examination for all patients; no secondary systemic diseases caused by hypothyroidism were found. Other family members did not exhibit significant thyroid abnormalities. Clinical examination results are shown in Table 1.

WES sequencing

We selected the proband and her three affected family members (II-2, II-6, III-2) for WES. We focused on missense, nonsense, splice-site, and frameshift mutations that were shared by all sequenced members. Variants with a frequency > 1% in public databases (1000Genomes, ESP6500si, and ExAC Asian population) and an internal database (400 exomes) were discarded. After this filtering had been performed, 18 genes remained, among which we found a rare missense heterozygous variant (NM_015967.5:c.A77G; p.N26S) in *PTPN22*, a

Table 1 Characteristics of inspection results

Patients	TPOAb(IU/ml)	TSH(mIU/L)	TgAb	TN	DTC	TRT
II-1	244.0	5.37	N	+	+	Y
II-2	397.8	8.12	N	+	+	Y
II-3	235.5	9.86	N	N	N	Y
II-6	267.8	3.16	N	+	+	Y
III-2	230.3	19.84	N	+	+	Y

When we first contacted the family, all patients had begun thyroxine replacement therapy. The measured values of thyroxine in all patients were in the normal range. TPOAb Thyroid peroxidase autoantibody, TSH Thyroid-stimulating hormone, TgAb Antithyroglobulin autoantibody, TN Thyroid nodule, + Existence of this change, N Refused the examination, DTC Diffuse thyroid changes (caused by thyroiditis), TRT Thyroxine replacement therapy, Y Receiving treatment

known susceptibility gene for HT. In this variant, an A to G substitution occurred at the 77th base, leading to an amino acid change from asparagine to serine at the 22nd residue. This variant was rare in several public databases (0.02% in 1000Genomes, 0.05% in ESP6500, none in ExAC Asian population) and absent from our internal exome database. Therefore, we considered the variant to have a high likelihood of association with familial HT.

Co-segregation analysis

Co-segregation analysis showed that all affected members carried the variant (Fig. 2). In addition, we found that III-3, a male member with normal health thus far, also carried the variant.

Discussion

PTPN22 is located at chromosome 1p13.2 and encodes a tyrosine phosphatase that is expressed by haematopoietic cells and acts as a key regulator of immune homeostasis through inhibition of T-cell receptor signalling and promotion of type I interferon responses [22]. *PTPN22* has been identified as the main susceptible gene for multiple autoimmune diseases, including rheumatoid arthritis [23], juvenile idiopathic arthritis [24], psoriatic arthritis [25], systemic lupus erythematosus [26], systemic sclerosis [27] and some forms of vasculitis [28]. This gene is considered the second-most important predisposing gene for human autoimmune diseases, after *HLA*. Therefore, abnormalities of *PTPN22* can lead to the occurrence of autoimmune diseases.

The *PTPN22* gene encodes lytic tyrosine phosphatase (LYP), which comprises 807 amino acid residues [29]. LYP acts as an inhibitor of T cell activation by binding to variety of signal transduction molecules, such as Csk kinase, which is active in T cell activation. Arginine substitution for tryptophan at codon 620 of the LYP protein (R620W) has been associated with increased risks of rheumatoid arthritis [23, 30] and systemic lupus erythematosus (SLE) [15]. Further studies showed an association between this SNP and AITD, including GD [31]

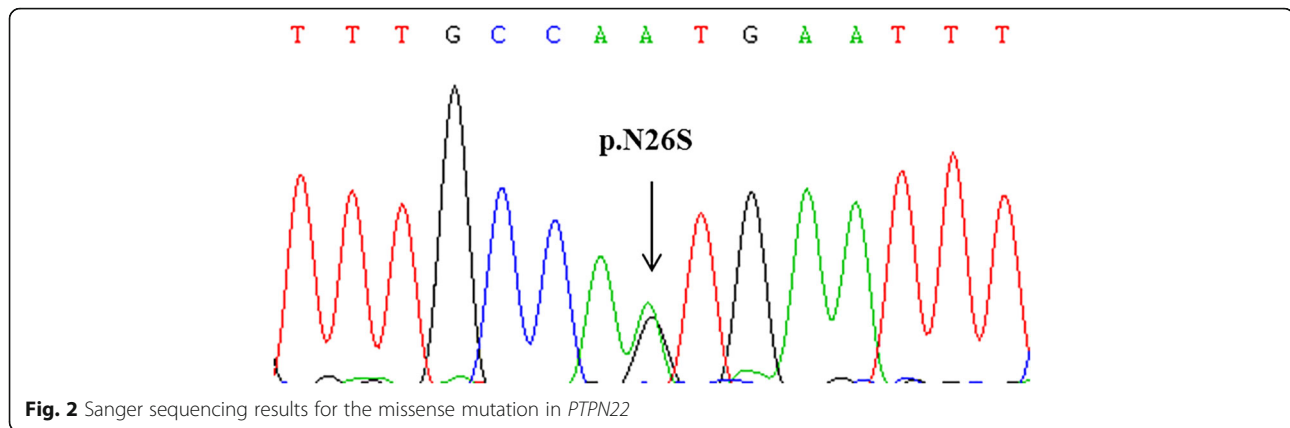


Fig. 2 Sanger sequencing results for the missense mutation in *PTPN22*

and HT [32]. The *PTPN22* R620W SNP elicits a functional change in LYP, such that the tryptophan-bearing LYP allele cannot bind the C-terminal src kinase (Csk) [33]; this causes proliferation of T cells. Concomitantly, the levels of several Ig isotypes are increased [32]. Among these antibodies, levels of IgG and IgG4 were positively correlated with the titre of anti-thyroperoxidase antibody (anti-TPO) [34]. Changes in level of anti-TPO correlated positively with the development of hypothyroidism and an increased inflammatory reaction [34]. As shown in Table 1, the patients in this study have higher TPO levels than normal, a phenomenon that supports this mechanism. We hypothesized that the mechanism of the missense mutation in *PTPN22* (N26S) is similar to that of R620W SNP.

LYP is an approximately 105-kDa Class I protein tyrosine phosphatase (PTP) [35, 36], which includes a C-terminal PEST-enriched domain and a classical N-terminal protein tyrosine phosphatase catalytic domain; these are separated by an approximately 300-amino acid interdomain [30]. The enzyme includes four putative polyproline motifs (P1-P4) [30]. The missense mutation *PTPN22* (N26S) is located on the classical catalytic domain of the N-terminal protein tyrosine phosphatase; however, little is known regarding its specific function.

The inter domain of LYP harbours protein-protein interaction motifs and putative phosphorylation sites. Liu et al. [30] showed that through a direct intramolecular interaction and inhibition of the catalytic domain, the interdomain plays an important role in regulating catalytic activity of the protein. For example, on the basis of a constitutive interaction between the N-terminal SH2 domain and the catalytic domain, SHP-1 is inhibited; it is released following recruitment of the domain to phosphorylated targets [37]. Changes in the interactions between domains can indirectly mediate the functional effects of protein interactions and/or post-translational modifications located in other parts of the protein. We hypothesize that the R620W SNP affects interactions among domains in LYP, leading to the occurrence of

HT. Identification of the specific molecular mechanism requires further research.

In this study, we found that the patients with HT were all females in this family, consistent with the previously reported finding that the incidence of thyroid disease in females is much higher than in males [38]. Prior reports had showed that the preponderance of thyroid autoimmunity in females is most likely due to the influence of sex steroids. Furthermore, the presence of TPO autoantibodies is the strongest risk factor for both hyper- and hypothyroidism; smoking is negatively correlated with the presence of TPO antibodies. Overall, the incidence of HT in females was significantly higher than the incidence of HT in males [39].

In the present study, we found that III-3 carried the missense mutation of *PTPN22* (A77G), but did not exhibit any thyroid disorder. Men are less susceptible to autoimmune disease than women, which may be why III-3 was unaffected. Additionally, the young age of III-3 (24 years of age) may be a contributing factor, because autoimmune diseases occur most frequently between the ages of 45 and 65 [34]. Finally, we hypothesize that *PTPN22* N26S may be similar to the R620W SNP as a risk locus, which can increase the risk of thyroid disease; however, it may not show disease in carriers.

Conclusions

In summary, we identified a missense mutation in *PTPN22* in a Chinese HT pedigree by using WES. This finding supports follow-up studies regarding HT, potentially facilitating more comprehensive genetic research in HT. Follow-up experiments are needed.

Abbreviations

AITD: Autoimmune thyroid disease; GD: Graves' disease; HT: Hashimoto's thyroiditis; SNVs: Single-nucleotide variants; TPO: Thyroid peroxidase; WES: Whole-exome sequencing; TPOAb: Thyroid peroxidase autoantibody; TSH: Thyroid-stimulating hormone; LYP: Lytic tyrosine phosphatase; SLE: Systemic lupus erythematosus; Csk: C-terminal src kinase; PTP: Protein tyrosine phosphatase

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Availability of data and materials

The datasets used and analysed during the current study available from the corresponding author on reasonable request.

Authors' contributions

GLC and LBH processed the data analysis and participated in writing of the manuscript, WJ was responsible for writing the manuscript, PH processed the data analysis, QAH and ZSY assisted in the experiments, WJY revised the manuscript, and YP participated the work on both the design of experiment and the data analysis. WBB guided the experimental design and conducted the study. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The research was approved by the ethical committees of China Japan Union Hospital of Jilin University. Written informed consent was obtained from all participants.

Consent for publication

Written informed consent was obtained from all study participants.

Competing interests

The authors declare that they have no competing interests.

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