Clinical and Experimental Immunology, 2022, **208**, 372–379
https://doi.org/10.1093/cei/uxac044
Advance access publication 3 May 2022
Research Article

Clinical & Experimental IMMUNOLOGY

OXFORD

Research Article

Genetic correlation between thyroid hormones and Parkinson's disease

Jiyi Xu[1,2,‡], Cheng Zhao[3,‡], Ye Liu[4], Congjie Xu[5,6], Bin Qin[7], Hui Liang[8,9,*]

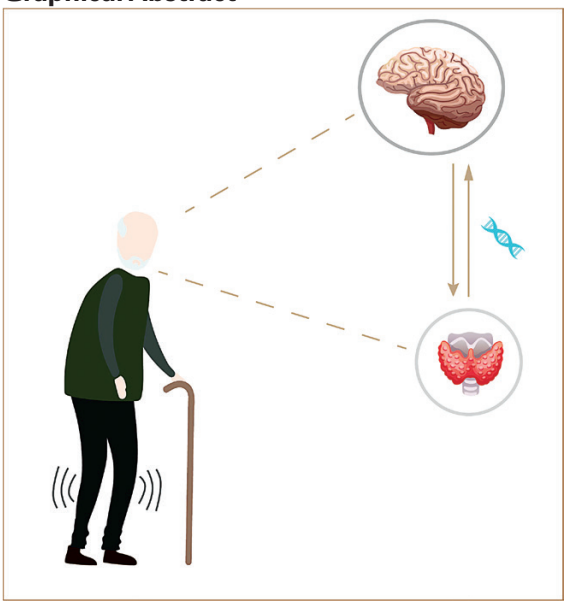
From the [1]The National Clinical Research Center for Mental Disorders & Beijing Key Laboratory of Mental Disorders, Beijing Anding Hospital, Capital Medical University, Beijing, P.R. China;
[2]Advanced Innovation Center for Human Brain Protection, Capital Medical University, Beijing, P.R. China
[3]Department of Neurology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong, P.R. China
[4]The Key Laboratory of Geriatrics, Beijing Institute of Geriatrics, Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, Beijing Hospital/National Center of Gerontology of National Health Commission, Beijing, P.R. China
[5]Hainan General Hospital, Hainan Affiliated Hospital of Hainan Medical University, Haikou, P.R. China
[6]Hainan Province Clinical Medical Center, Haikou, P.R. China
[7]Department of Neurology, Beijing Hospital, National Center of Gerontology; Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, Beijing, P.R. China
[8]Department of Neurology, Hainan General Hospital, Hainan Affiliated Hospital of Hainan Medical University, Haikou, P.R. China and
[9]Hainan Province Clinical Medical Center and Hainan Academician Innovation Platform, Haikou, P.R. China

*Correspondence: Hui Liang, Department of Neurology, Hainan General Hospital, Hainan Affiliated Hospital of Hainan Medical University, Haikou, P.R. China.
Email: 18689533923@163.com
‡Jiyi Xu and Cheng Zhao contributed equally as the first author to this work.

Abstract

Parkinson's disease (PD) was reported to be connected with thyroid diseases clinically, which might be a critical clew to immune pathogenesis of PD. However, there was no further research to study the pathogenesis correlation between PD and thyroid diseases. In this study, except for investigating the difference in thyroid hormone between PD and the control group, we explored genetic correlation between thyroid and PD. We tried to find their shared molecular pathway by analyzing the effect of PD risk genes on thyroid function. Interestingly, most of those 12 meaningful SNPs we found could affect PD and thyroid function through immune mechanism, which is consistent with our original conjecture and provides significant evidence for the immune pathogenesis of PD.

Graphical Abstract



Keywords: Parkinson's disease, thyroid hormones, immune pathogenesis, risk genes, SNPs

Received 15 March 2022; Accepted for publication 29 April 2022

Abbreviations: α-syn: α-synuclein; DA: dopamine; FT3: free 3,5,3′-triiodothyronine; FT4: free thyroxine; GD: Gaucher's disease; GWAS: genome-wide association study; MCT: monocarboxylate transporter; NPC: Niemann pick type C; PD: Parkinson's disease; ROS: toxic reactive oxygen species; rT3: r-triiodothyronine; SNP: single nucleotide polymorphisms; T3: 3,5,3′-triiodothyronine; T4: thyroxine; TGAb: antithyroglobulin antibody; TPOAb: anti-thyroid peroxidase antibody; TRH: thyroid-stimulating hormone-releasing hormone; TSH: thyroid-stimulating hormone; TT3: total 3,5,3′-triiodothyronine; TT4: total thyroxine.

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease, which is characterized by tremor, bradykinesia, myotonia, and non-motor symptoms clinically. And degeneration of dopaminergic neurons in the substantia nigra, α-synuclein (α-syn) deposition, and Louie microform are the characteristic pathological changes. With the aging of society, the incidence of PD is increasing, but the exact pathogenesis is still unknown. It is supposed that mitochondrial dysfunction, oxidative stress, and inflammation caused by heredity and environment have some connection with the pathogenesis of PD [1]. Dysfunction of the immune system is considered to be a critical cause of PD and has received increasing attention in the past decade. To the best of our knowledge, autoimmune diseases are relevant to an increased risk of PD [2]. A large epidemiological study, which was conducted in Sweden involving more than 300 000 subjects, showed that patients with autoimmune diseases, such as amyotrophic lateral sclerosis, Graves' disease/hyperthyroidism Hashimoto's thyroiditis/hypothyroidism, multiple sclerosis, and rheumatoid myalgia, had an additional 33% risk of PD [3]. Interestingly, PD shares molecular pathways with a variety of autoimmune diseases, and the association between PD and autoimmune diseases can be explained by genes [2]. For example, LRRK2, a well-known risk gene of PD, is highly expressed in immune cells like monocytes, has been reported to be associated with an increasing risk of Crohn's disease.

The thyroid is the organ with the highest occurrence of autoimmune diseases. In recent years, the comorbidity of PD with autoimmune diseases such as thyroid diseases has been reported from time to time [4]. In our clinical practice, PD patients combined with thyroid dysfunction sometimes. In our opinion, the correlation between thyroid function and PD is worth exploring. To our knowledge, bioinformatics analyses have found some genetic connections between PD and thyroid function, but there are few real-world studies to verify these associations. In that case, we aim to answer the following questions: (1) whether there is a difference in thyroid hormone levels between PD and healthy controls and (2) whether PD-related genes affect thyroid hormone levels.

Materials and methods

Participants

The inclusion criteria for the patients were outpatients aged between 40 and 85 years and met Parkinson's Disease Society Brain Bank criteria for PD. All participants should have the ability to communicate and provide written informed consent. Those with serious medical problems, severe mental illness, or pregnancy would be excluded. Healthy controls should be free of any neurodegenerative disease, lifetime DSM-IV Axis I psychiatric disorder, and significant physiological disease (e.g. chronic inflammatory disorders, diabetes, cardiovascular disease, thyroid disease, or cancer) and current pregnancy. Each participant signed written informed consent. The study protocol was approved by the Human Research and Ethics Committee of Beijing Hospital in accordance with the Declaration of Helsinki.

Genetic testing

The RelaxGene Blood DNA System DNA isolation kit (Tiangen, Beijing, China) was used for preparing genomic DNA following the recommendations of the manufacturer. Screening SNPs were identified according to PD-related gene GWAS research. Genotyping was performed using the MassARRAY high-throughput DNA analysis system with matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (Sequenom, Inc., San Diego, CA, USA). The primers were designed using MassARRAY Assay Design software (version 3.1). SNPs were genotyped using iPLEX Gold technology (Sequenom) followed by automated data analysis with the TYPE RT software, version 4.0. Three samples were removed due to failed genotyping.

Statistical analysis

SPSS 25.0 software was used for statistical analysis. The measurement data in line with normal distribution were expressed in mean ± SD, and the comparison between the two means was conducted by independent sample *t*-test. The measurement data of non-normal distribution are expressed in the form of the median (interquartile range). Mann–Whitney *U* test was used for data comparison between the two groups while Kruskal–Wallis *H* rank-sum test is used for multi-group comparison. $P < 0.05$ showed that the difference was statistically significant.

Results

Differences in thyroid function indexes between the PD group and control group

Table 1 summarizes the characteristics and thyroid function indexes of participants. There was no significant difference in age and sex between the two groups, and the mean course of the PD group was 2.66 ± 2.43 years. Comparing the eight indexes of thyroid function in the two groups, it was found that the levels of TT3, FT3, FT4, and TSH in the PD group were significantly lower than those in the control group, while rT3 was significantly higher than that in the control group.

Effects of PD-related genes on thyroid hormone levels

We identified 48 SNPs associated with PD pathogenesis by retrieving PD-related genes in the GWAS study (Supplementary Table). According to the genotype of those SNPs, eight indexes of thyroid hormone (TT4, TT3, TSH, FT3, FT4, TPOAb, and TGAb, rT3) of each group were compared. The results showed significant differences in thyroid function indicators among genotypes of 12 SNPs ($P < 0.05$), which were rs1955337/STK39, rs199347/GPNMB, rs329648/MIR4697, rs3775442/SNCA, rs3775442/SNCA, rs4388272/Parkin, rs5756909/SLC16A8, rs67255253/KIF17, rs76904798/LRRK2, rs139796557/BCL2, rs11724635/BST1, and rs12456492/RIT2 (Table 2).

Table 1. Characteristics and thyroid function indexes of participants

	PD group ($N = 126$)	Control group ($N = 39$)	P
Age	67 ± 9.85	63.38 ± 10.08	0.056
Gender (F/M)	61/65	19/20	
Duration	2.66 ± 2.43		
TT4 (ug/dl)	8.28 (7.40, 9.40)	8.20 (7.50, 9.04)	0.8
TT3 (ng/ml)	1.06 (0.96, 1.22)	1.19 (1.08, 1.33)	0.003*
TSH (μlU/ml)	1.48 (0.96, 2.44)	2.21 (1.58, 2.54)	0.008*
FT3 (pg/ml)	3.04 (2.82, 3.27)	3.25 (3.02, 3.68)	<0.001*
FT4 (ng/dl)	1.24 (1.11, 1.36)	1.36 (1.19, 1.50)	0.008*
TPOAb (U/ml)	37 (28, 49)	41 (28, 60)	0.3
TGAb (U/ml)	24 (19, 60)	36 (15, 59)	0.1
rT3 (ng/dl)	58 (49, 66)	48 (41, 56)	<0.001*

*$P < 0.05$ means that PD group was significantly different from control group.

Discussion

PD and thyroid hormones

The thyroid mainly secretes two hormones: thyroxine (T4) and 3,5,3′ -triiodothyronine (T3), of which T4 accounts for 93%. About 80% of T3 is generated by the deiodization of T4 through the outer ring in the external thyroid tissue, which is the main pathway of T3 production. Generally, serum-free T4(FT4) and T3(FT3) exert the most biological activity of these hormones while most T3 and T4 outside the thyroid bind to binding proteins. Binding proteins act as storage and buffering by maintaining the concentration of free T4 and free T3 in serum within a narrow range and ensuring T4 and T3 access to tissues rapidly and continuously. The index of total thyroxine (TT4) and total triiodothyronine (TT3) can be used to estimate thyroid hormone reserve levels. Our study found that the level of TT3, FT3, and FT4 in the PD group was significantly lower than that in the control group. Parkinson's disease is associated with thyroid hormone. A recent large cohort study showed that the risk of PD in hypothyroidism was nearly two times higher [5], while the study of Umehara suggested that FT3 level was negatively correlated with the severity of motor symptoms [6]. Kincaid found that hypothyroidism reduced dopamine nerves in mice [7]; Lee et al. found that thyroid hormone could induce the differentiation of dopamine nerve and promote its recovery after injury, which also confirmed the protective effect of thyroid hormone on dopamine nerve from the side [8]. Reverse T3(rT3) is generated by the deiodization of T4 outside the thyroid gland. Different from T3, rT3 has no biological activity at all. T3 and rT3 were competitively synthesized. Clinically, the significant increase of rT3 is often accompanied by hypothyroidism. In this study, the significant increase of rT3 in the PD group is also evidence that hypothyroidism is closely related to the occurrence of PD.

Thyroid hormone level is mainly regulated by the feedback mechanism of hypothalamic–pituitary–thyroid axis. Thyroid-stimulating hormone-releasing hormone (TRH), produced by the hypothalamus, directly acts on the pituitary gland to secrete TSH, affecting the synthesis and secretion of thyroid T3 and T4. Besides, T3 and T4 can also negatively regulate TSH levels. Mohammadi believed that the hypothalamic-pituitary-thyroid axis was closely related to the dopamine system, and dopamine(DA) can up-regulate TRH and down-regulate TSH and thyroid hormone at the same time [4]. Some studies have suggested that DA can directly bind to thyroid-stimulating hormone cells and control TSH secretion by activating cytochrome P-450 enzyme complex or regulating the TSHβ subunit gene. It is worth noting that the inhibition of DA on TSH secretion overcomes the stimulation of DA on TRH, and its net effect is the inhibition of DA on TSH [4]. In this study, the TSH level of the PD group was significantly lower than that of the control group. Umehara found no difference in TSH between the two groups, while Munhoz's conclusion was consistent with our study. In this study, the low level of TSH in the PD group may be related to treatment since all PD patients in this group have received therapy of levodopa. Studies have shown that the basal TSH levels of PD patients who taking levodopa for a long time are lower, and TSH response to TRH is reduced. In addition, dopamine stimulation such as bromocriptine can also weaken the stimulating effect of TRH on TSH secretion and reduce the TSH level [4].

Thyroglobulin (TG) is the main site for the synthesis and storage of T3 and T4 in the thyroid. T4 and T3 from the thyroid are formed by iodization and coupling of tyrosine residues in TG, which require the catalysis of thyroid peroxidase (TPO). TGAb and TPOAb are antibodies to TG and TPO. The increase of TGAb and TPOAb often indicates Hashimoto thyroiditis, the continuous progress of which can eventually lead to hypothyroidism. Previous studies have generally suggested that Hashimoto's thyroiditis could increase the incidence rate of PD. However, in this study, there was no significant difference in the incidence of Hashimoto's thyroiditis between the PD group and the control group. And no significant difference in TGAb and TPOAb expression was found between the two groups. This may be related to the sample size, but also to the larger clinical value of TGAb and TPOAb.

PD-related genes and thyroid function

LRRK2 gene mutation is a common mutation in PD. It can not only cause familial early-onset PD but is also an important risk factor for sporadic PD [9]. To our knowledge, LRRK2 can lead to PD via a variety of pathological mechanisms, including oxidative stress, mitochondrial dysfunction, and α-Synuclein accumulation [10]. It has been reported that the LRRK2 gene has a strong correlation with thyroid cancer. The chromosome amplification of LRRK2 is a necessary condition for the occurrence of met tyrosine kinase in thyroid papillary carcinoma [11]. However, the effect of LRRK2 on human thyroid cancer cells is not clear. Jiang found that LRRK2 could affect the TC cell cycle and apoptosis by participating in the JNK signaling pathway [12]. The JNK signaling pathway is a highly conserved signaling pathway, which is involved in cell proliferation, differentiation, and apoptosis, and is related to many diseases, including cancer, nerve, and immune/inflammation [13]. It has been reported that the activation of the JNK signaling pathway causes thyroid dysfunction [14], and LRRK2 can inhibit the PD mitogen-activated protein kinase 4-JNK-c-Jun pathway [15]. Therefore, the JNK signaling pathway could be one of the overlapping pathways of LRRK2 affecting PD and thyroid function. In addition, Jiang showed that the LRRK2 gene and the gene encoding thyroglobulin (TG) can affect the occurrence of thyroid cancer, and the two

Table 2. Effects of PD-related genes on thyroid hormone levels

SNP	rs1955337	Thyroid hormone	Genotypes			*P*
Gene	STK39		GT	GG	TT	
		TT4 (ug/dl)	7.90 (7.4, 9.03)	8.6 (7.38, 9.84)	9.38 (8.82,10.60)	0.007*
		TT3 (ng/ml)	1.06 (0.92, 1.21)	1.07 (0.96, 1.22)	1.09 (0.98, 1.30)	0.795
		TSH (μlU/ml)	1.34 (0.89, 1.88)	1.50 (1.12, 2.54)	2.31 (1.01, 3.24)	0.163
		FT3 (pg/ml)	3.07 (2.76, 3.32)	3.01 (2.83, 3.21)	3.04 (2.79, 3.10)	0.697
		FT4 (ng/dl)	1.25 (1.11, 1.36)	1.22 (1.11, 1.37)	1.30 (1.20, 1.44)	0.292
		TPOAb (U/ml)	34.00(28.00, 50.60)	37.50 (28.54, 47.65)	42.40 (28.30, 51.85)	0.75
		TGAb (U/ml)	19.40 (15.00,31.20)	19.50 (15.00, 26.15)	19.2 (15.40, 204.2)	0.737
		rT3 (ng/dl)	56.67 (50.05,63.70)	54.45 (46.87, 64.62)	63.28 (58.36, 67.51)	0.07
SNP	rs199347	Thyroid hormone		Genotypes		*P*
Gene	GPNMB		AA	GA	GG	
		TT4 (ug/dl)	8.27 (7.39,9.60)	8.50 (7.46, 9.28)	7.58 (4.34,9.60)	0.712
		TT3 (ng/ml)	1.06 (0.98,1.23)	1.07 (0.92, 1.25)	0.97 (0.64, 1.17)	0.492
		TSH (μlU/ml)	1.41 (0.89,2.27)	1.48 (1.16, 2.71)	2.13 (1.01, 5.45)	0.465
		FT3 (pg/ml)	3.06 (2.81,3.29)	3.03 (2.86, 3.23)	2.63 (2.55, 2.79)	0.043*
		FT4 (ng/dl)	1.25 (1.11,1.36)	1.24 (1.10, 1.38)	1.13 (0.84, 1.21)	0.253
		TPOAb (U/ml)	36.70 (28.00, 51.77)	32.98 (28.00, 47.80)	48.10 (37.62, 77.95)	0.292
		TGAb (U/ml)	19.35 (15.00, 30.09)	19.35 (15.00, 30.47)	15.60 (15.00, 33.81)	0.73
		rT3 (ng/dl)	55.80 (50.05, 65.66)	58.83 (47.99, 64.36)	62.02 (49.05, 67.40)	0.912
SNP	rs329648	Thyroid hormone		Genotypes		*P*
Gene	MIR4697		TC	CC	TT	
		TT4(ug/dL)	8.36 (7.40, 9.50)	8.53 (7.40, 9.30)	7.52 (7.38, 9.20)	0.585
		TT3 (ng/ml)	1.06 (0.93, 1.24)	1.07 (0.96, 1.25)	1.05 (0.91, 1.11)	0.649
		TSH (μlU/ml)	1.36 (0.85, 2.05)	1.63 (0.99, 2.78)	1.53 (1.29,2.46)	0.249
		FT3 (pg/ml)	3.08 (2.86, 3.32)	3.01 (2.69,3.22)	2.93 (2.67,3.27)	0.192
		FT4 (ng/dl)	1.25 (1.11, 1.38)	1.24 (1.10, 1.34)	1.28 (1.13,1.43)	0.689
		TPOAb (U/ml)	31.2 (28.00,47.8)	37.60 (30.09, 49.72)	55.6(28.55,364.85)	0.076
		TGAb (U/ml)	16.4 (15.00, 24.82)	20.10 (15.00, 37.30)	25.6 (15.35,176.49)	0.091
		rT3 (ng/dl)	60.64 (51.51, 67.42)	53.92 (47.62, 62.96)	52.00(46.13,59.49)	0.027*
SNP	rs3775442	Thyroid hormone		Genotypes		*P*
Gene	SNCA		CC	TC	TT	
		TT4 (ug/dl)	8.27 (7.26,9.55)	8.36 (7.40,9.40)	7.79 (7.55,9.01)	0.822
		TT3 (ng/ml)	1.03 (0.92,1.17)	1.18 (1.03,1.30)	0.92 (0.88,1.07)	0.001*
		TSH (μlU/ml)	1.57 (0.98,2.21)	1.42 (0.96,2.64)	1.25 (0.86, 2.30)	0.747
		FT3 (pg/ml)	3.09 (2.83,3.26)	3.06 (2.76,3.31)	2.98 (2.86, 3.03)	0.549
		FT4 (ng/dl)	1.24 (1.13,1.37)	1.23 (1.10,1.36)	1.30 (1.16, 1.45)	0.545
		TPOAb (U/ml)	37.00 (28.33,47.65)	28.00 (28.00,39.25)	31.40 (28.00, 41.50)	0.749
		TGAb (U/ml)	17.20 (15.00,25.55)	15.00 (15.00, 19.90)	16.20 (15.00, 25.60)	0.179
		rT3 (ng/dl)	56.32 (48.00,63.47)	57.15 (49.69, 64.59)	60.74 (51.65, 70.40)	0.342
SNP	rs3857059	Thyroid hormone		Genotypes		*P*
Gene	SNCA		AG	GG	AA	
		TT4 (ug/dl)	8.55 (7.47, 9.55)	8.07 (7.32, 9.00)	8.59 (7.32, 9.78)	0.264
		TT3 (ng/ml)	1.08 (1.02, 1.26)	1.08 (0.90, 1.25)	0.99 (0.91, 1.11)	0.047*
		TSH (μlU/ml)	1.54 (0.92, 2.71)	1.36 (1.08, 2.54)	1.47(0.83,2.20)	0.902
		FT3 (pg/ml)	3.06 (2.77, 3.24)	3.03 (2.82, 3.29)	3.07(2.86,3.33)	0.841
		FT4 (ng/dl)	1.25 (1.12, 1.42)	1.24 (1.12, 1.34)	1.22(1.10,1.33)	0.615
		TPOAb (U/ml)	37.4 (28.00, 54.90)	32.64 (28.00, 49.05)	33.80(28.72,48.70)	0.859
		TGAb (U/ml)	19.85 (15.00, 38.70)	16.60 (15.00, 26.30)	18.10(15.00,25.80)	0.582
		rT3 (ng/dl)	59.70 (48.02, 66.22)	56.70 (49.09, 63.04)	55.80 (49.65,64.06)	0.762
SNP	rs4388272	Thyroid hormone		Genotypes		*P*
Gene	Parkin		TC	TT	CC	
		TT4 (ug/dl)	8.80 (7.54,9.40)	8.19 (6.75, 9.11)	8.19 (7.12, 9.75)	0.578
		TT3 (ng/ml)	1.05 (0.96,1.21)	1.05 (0.91,1.20)	1.18 (0.98, 1.25)	0.494
		TSH (μlU/ml)	1.51 (1.07,2.46)	1.35 (0.93,2.54)	1.50 (0.89,2.39)	0.997
		FT3 (pg/ml)	3.08 (2.92,3.27)	3.04 (2.70,3.30)	2.92 (2.71,3.21)	0.226

Table 2. Continued

SNP	rs1955337	Thyroid hormone	Genotypes			*P*
Gene	STK39		GT	GG	TT	
		FT4 (ng/dl)	1.24 (1.13,1.38)	1.23 (1.12,1.42)	1.27 (1.06,1.33)	0.748
		TPOAb (U/ml)	33.32 (28.00,48.55)	37.60 (28.90,54.87)	32.98 (28.00,50.00)	0.554
		TGAb (U/ml)	20.80 (15.00,32.90)	15.00 (15.00,25.57)	19.90 (15.00,31.10)	0.025*
		rT3 (ng/dl)	57.12 (47.66,66.96)	57.75 (52.67,62.95)	57.55 (49.19, 63.59)	0.95
SNP	rs12456492	Thyroid hormone		Genotypes		*P*
Gene	RIT2		GA	AA	GG	
		TT4 (ug/dl)	8.27 (7.13,9.22)	7.92 (7.40,10.08)	8.81 (7.44,9.34)	0.706
		TT3 (ng/ml)	1.07 (0.90, 1.21)	1.07 (1.00,1.28)	1.02 (0.92,1.23)	0.77
		TSH (μlU/ml)	1.63 (1.07, 2.55)	1.22 (0.83,2.02)	1.49 (1.16,2.75)	0.158
		FT3 (pg/ml)	2.96 (2.67, 3.23)	3.10 (2.98,3.43)	3.07 (2.88,3.31)	0.033*
		FT4 (ng/dl)	1.24 (1.10, 1.34)	1.28 (1.11,1.47)	1.22 (1.14,1.32)	0.377
		TPOAb (U/ml)	37.40 (28.00, 52.30)	34.90 (28.00,49.35)	32.98 (29.10,46.90)	0.949
		TGAb (U/ml)	16.2 (15.00, 25.20)	19.95 (15.00,30.72)	25.00 (15.00,41.36)	0.074
		rT3 (ng/dl)	57.72 (49.69, 67.12)	53.08 (47.19,62.76)	59.30 (56.20,66.82)	0.138
SNP	rs76904798	Thyroid hormone	Genotypes			*P*
Gene	LRRK2		NI	CC		
		TT4 (ug/dl)	8.28 (7.49, 9.40)	8.27 (7.05, 9.39)		0.349
		TT3 (ng/ml)	1.10 (0.97, 1.25)	1.04 (0.92, 1.19)		0.178
		TSH (μlU/ml)	1.46 (0.89, 2.42)	1.49 (1.07, 2.46)		0.748
		FT3 (pg/ml)	3.03 (2.76, 3.23)	3.08 (2.84, 3.32)		0.383
		FT4 (ng/dl)	1.25 (1.09, 1.35)	1.24 (1.14, 1.39)		0.52
		TPOAb (U/ml)	35.58 (28.00,50.50)	37.65 (28.05, 47.80)		0.785
		TGAb (U/ml)	15.00 (15.00, 16.30)	22.50 (15.00, 37.90)		0.037*
		rT3 (ng/dl)	48.96 (48.96, 56.67)	57.70 (49.82, 64.36)		0.979
SNP	rs139796557	Thyroid hormone	Genotypes			*P*
Gene	BCL2		GT	GG		
		TT4 (ug/dl)	9.14 (5.88, 9.79)	8.17 (7.40, 9.30)		0.703
		TT3 (ng/ml)	1.08 (1.04, 1.21)	1.06 (0.92, 1.25)		0.646
		TSH (μlU/ml)	1.42 (0.89,2.65)	1.49 (0.99,2.46)		0.984
		FT3 (pg/ml)	3.44 (2.92,3.57)	3.03 (2.78, 3.22)		0.049*
		FT4 (ng/dl)	1.27 (1.13, 1.46)	1.24 (1.11, 1.35)		0.661
		TPOAb (U/ml)	51.95 (28.00, 62.86)	35.24 (28.00,48.25)		0.455
		TGAb (U/ml)	20.50 (15.12, 26.25)	17.60 (15.00,25.70)		0.61
		rT3 (ng/dl)	53.50 (47.40, 64.08)	57.75 (50.16,65.64)		0.475
SNP	rs11724635	Thyroid hormone	Genotypes			*P*
Gene	BST1		CC	AA		
		TT4 (ug/dl)	8.19 (7.40,9.39)	8.41 (7.40, 9.40)		0.972
		TT3 (ng/ml)	1.05 (0.99, 1.20)	1.07 (0.92, 1.25)		0.895
		TSH (μlU/ml)	1.51 (1.07, 2.50)	1.42 (0.89, 2.42)		0.863
		FT3 (pg/ml)	3.06 (2.80, 3.31)	3.04 (2.82, 3.22)		0.377
		FT4 (ng/dl)	1.25 (1.11, 1.40)	1.24 (1.12, 1.35)		0.81
		TPOAb (U/ml)	39.11 (28.42, 54.55)	34.17 (28.00,46.90)		0.225
		TGAb (U/ml)	19.30 (15.00, 29.60)	19.20 (15.00,31.60)		0.728
		rT3 (ng/dl)	53.83 (46.81,62.06)	59.30 (51.45,66.63)		0.04*
SNP	rs5756909	Thyroid hormone	Genotypes			*P*
Gene	SLC16A8		GC	CC	GG	
		TT4 (ug/dl)	(8.91,9.5)	(8.44,9.39)	(7.745,8.9)	0.032*
		TT3 (ng/ml)	(1.05,1.21)	(1.055,1.1875)	(1.07,1.2625)	0.15
		TSH (μlU/ml)	(1.29,1.84)	(1.96,2.95)	(1.27,1.9675)	0.02*
		FT3 (pg/ml)	(3.04,3.24)	(3.07,3.205)	(3.075,3.4225)	0.695
		FT4 (ng/dl)	(1.28,1.36)	(1.23,1.315)	(1.25,1.445)	0.572
		TPOAb (U/ml)	(33.32,55.15)	(37.65,47.5)	(37.6,54.9)	0.118
		TGAb (U/ml)	(22.6,35.25)	(16.9,25.5)	(18.1,32.9)	0.357
		rT3 (ng/dl)	(59.19,65.235)	(57.725,65.92)	(52.7,61.27)	0.248

Table 2. Continued

SNP	rs1955337	Thyroid hormone	Genotypes			*P*
Gene	STK39		GT	GG	TT	
SNP	rs67255253	Thyroid hormone	Genotypes			*p*
Gene	KIF17		GG	GA	AA	
		TT4 (ug/dl)	(7.89,9.115)	(8.315,9.62)	(8.315,9.62)	0.104
		TT3 (ng/ml)	(1.05,1.21)	(1.085,1.27)	(1.085,1.27)	0.28
		TSH (μlU/ml)	(1.56,2.6025)	(1.38,2.2725)	(1.38,2.2725)	0.38
		FT3 (pg/ml)	(3.09,3.3725)	(3.035,3.2475)	(3.035,3.2475)	0.205
		FT4 (ng/dl)	(1.22,1.36)	(1.25,1.405)	(1.25,1.405)	0.423
		TPOAb (U/ml)	(35.58,51.95)	(36.705,48)	(36.705,48)	0.698
		TGAb (U/ml)	(23.85,33.125)	(16.25,20.7)	(16.25,20.7)	0.083
		rT3 (ng/dl)	(56.67,63.22)	(55.35,65.7075)	(55.35,65.7075)	0.031*

*$P < 0.05$ means that thyroid function was significantly different among different genotype.

genes are strongly correlated in protein association analysis [12]. In this study, differences in TGAb levels were found between LRRK2 genotypes, which was consistent with Jiang's study. LRRK2 is abundantly expressed in monocytes and other immune cells [16]. Although how it regulates immune cell function and participates in the pathogenesis of PD is still unclear, previous studies have suggested that Rab protein and GTPase may be an important intermediate link in establishing the relationship between them [2]. In addition, two-thirds of lrrk2-PD patients in the study of Gatto et al. developed autoimmune diseases such as hypothyroidism and Hashimoto thyroiditis, suggesting that the gene may affect PD and thyroid diseases through immune mechanisms [17].

Parkin gene mutations can lead to autosomal-recessive PD [18]. E3 ubiquitin ligase Parkin, a protein of the gene, plays an important role in the mitochondrial quality control pathway. Activated Parkin produces ubiquitin chains on mitochondrial outer membrane proteins, leading to impaired mitochondrial autophagy [19]. Damaged mitochondria are thought to be the source of toxic reactive oxygen species (ROS), which can lead to neuronal cell death and PD [19]. Lee found Parkin v380l point mutation in thyroid Hurthle cell carcinoma [20]. They believe that parkin gene mutation could be a potential factor for the excessive accumulation of abnormal mitochondria in Hurthle cell carcinoma cells. Our study found that there were differences in TGAb levels among parkin genotypes. The changes in TG levels were often reported in Hurthle cell carcinoma, which was also the main index of clinical follow-up of Hurthle cell carcinoma [21]. In addition, the Parkin gene may also be associated with the thyroid through the immune pathway apart from the mitochondrial oxidative stress pathway [19]. The expression of parkin and another PD-related gene PINK1 can inhibit the antigen presentation of MHC molecules in immune cells. Mutations in these genes can block these inhibitory effects and increase immune responses mediated by inflammatory bodies or CD8+ cytotoxic T cells, which in turn may affect thyroid function.

It is reported that GPNMB is a risk gene for PD and Murthy verified that the brain expression of GPNMB protein is related to PD [22]. In addition, GPNMB is also associated with Gaucher's disease (GD) and Niemann Pick type C (NPC), two lysosomal storage diseases, and GD has a close correlation with PD. Lin has shown that the expression of GPNMB protein in blood is significantly correlated with the levels of FT3, FT4, and TSH. They believe that excessive thyroid hormone may result in increased GPNMB secretion in the liver [23]. Our study found that there were significant differences in the expression concentration of FT3 among different GPNMB genotypes. Lin also found that the concentration of GPNMB in blood was significantly correlated with the level of thyroid antibodies including TRAb and TPOAb [23]. Previous studies showed that GPNMB can regulate autoimmune response through bone marrow-derived suppressor cells or antigen-presenting cells, and GPNMB is possibly involved in the autoimmune process of thyroid diseases [23]. In addition, GPNMB is highly expressed in glial cells involved in neuroimmune response and less expressed in neurons [23, 24]. Therefore, the immune mechanism may be the main mechanism of the GPNMB gene involved in thyroid disease and PD.

BCL-2 protein is involved in apoptosis and autophagy. BCL-2 protein is an anti-apoptotic factor, and its high expression can promote cell survival. The abnormal expression of BCL-2 could affect the pathogenesis of PD. The level of BCL-2 in PD patients decreased significantly and was negatively correlated with the course of disease and severity [25]. BCL-2 gene is also associated with autoimmune thyroid disease. Inoue believed that there were significant differences in the frequency of BCL2-938AA genotype and BCL2 + 127G/A allele between patients with autoimmune thyroid disease and the control group [26]. In this study, there were significant differences in FT3 expression among different genotypes of BCL-2/RS139796557. Although the BCL-2 locus in this study was different from Inoue, the two studies both suggested that BCL-2 might be involved in autoimmune thyroid diseases and affect thyroid function. Apoptosis was a necessary way to maintain self-tolerance by clearing surrounding autoreactive immune cells. Pathway abnormal could bring about the induction and aggravation of autoimmune diseases [26]. Therefore, BCL-2 may participate in autoimmunity through the apoptosis mechanism, and then affect PD and autoimmune thyroid diseases at the same time.

RIT2 is a risk gene for PD. Although the function of the protein, encoded by RIT2, is still unclear, many studies have shown that RIT2 plays a crucial role in neuronal differentiation and function [27]. Moreover, the expression of RIT2 in substantia nigra of PD patients was reduced in an autopsy, suggesting that RIT2 may play a role in the death

of dopaminergic neurons [28]. Our study found significant differences in FT3 expression among RIT2 genotypes. There is no direct evidence of their connection. Microtubule-associated protein (MAPT) gene expresses a microtubule-associated protein involved in axon transport and integrity in the central nervous system. MAPT gene mutation can lead to the accumulation of tau protein in dopaminergic cells and the formation of intracellular nerve fiber tangles, which can induce PD. Interestingly, pathway analysis showed that RIT2 and MAPT belong to the same disease pathway [4]. And some research have shown that calmodulin 1 could bind to not only MAPT but also to RIT2 protein. It has been found that the maturation of MAPT mRNA is regulated by the T3 level [4]. Although the mechanism is undiscovered, we speculate that the correlation between RIT2 and FT3 may be similar to MAPT.

GWAS study showed that SLC16A8 is a risk gene for PD. SLC16 gene family has 14 members, mainly encoding monocarboxylate transporter (MCT). Structurally, although these MTCs are highly conserved and homologous, their differential expression, regulation, and variable amino acid residues allow each subtype to have dynamic ligand specificity and unique physiological effects [29]. MCT3 encoded by SLC16A8 is involved in the regulation of neurotransmitter and lactate transport, while MCT8 encoded by SLC16A2 mainly affects the transport of thyroid hormone. SLC16A2 gene mutation can cause Allen Herndon Dudley syndrome (AHDS). This mutation can lead to reduced cell uptake of T3 and high serum T3. In this study, there are significant differences in TT4 and TSH among different genotypes of SLC16A8. Although there are not enough studies to prove that MCT3 is involved in thyroid metabolism, due to the homology of MCT3 and MCT8 structures, the results of this study may have suggestive significance for the follow-up study of MCTs function.

BST1, also known as CD157, is associated with an increased risk of sporadic PD [30]. CD157 is generally expressed in cells of the granulomonocyte lineage, especially in monocytes, neutrophils, and immature myeloid stages, and plays a role in the immune response. In this study, it was found that the level of rT3 was different in different BST1 genotypes. STK39 gene is abundant in the brain and pancreas. Aside from PD, it is related to inflammation and autism, hypertension, and various types of cancer [31]. This study found differences in the expression of TT4 among STK39 genotypes. At present, no study on the association between bst1 and STK39 and thyroid diseases has been found through a literature search. We speculate that BST1 and STK39 may affect thyroid metabolism through the immune mechanisms. SNCA gene is located on human chromosome 4 and encodes a-syn, which is strongly correlated with familial PD and sporadic PD. In this study, significant differences in TT3 were found at two SNCA loci (rs3775442 and rs3775442). However, by searching the literature, there is no study on the relationship between SNCA and thyroid function.

Conclusion

Many studies have shown that there is a correlation between thyroid function and PD, but the mechanism is not completely clear. Except from investigating the difference in thyroid hormone between PD and the control group, we explored the genetic correlation between thyroid and PD. By analyzing the effect of PD-related genes on thyroid function, we tried to find their shared molecular pathway. Interestingly, most of those 12 meaningful SNPs we found could affect PD and thyroid function through the immune mechanisms, which is consistent with our original conjecture and provides significant evidence for the immune pathogenesis of PD.

Supplementary data

Supplementary data is available at *Clinical and Experimental Immunology* online.

Funding

This study was supported in part by grants from Shandong Natural Funds for Young Scientists, ZR202102240027. This study was supported in part by grants from Hainan General Hospital Qingnian Fund, QN202002.

Conflicts of interest

The authors declare that they have no competing interests.

Author contributions

Bin Qin and Hui Liang contributed to the conception of the study; Jiyi Xu and Cheng Zhao performed the experiment; Congjie Xu and Ye Liu contributed significantly to the analysis and manuscript preparation; Jiyi Xu and Cheng Zhao performed the data analyses and wrote the manuscript; Bin Qin and Hui Liang helped perform the analysis with constructive discussions. All authors reviewed the manuscript.

Ethical approval

The experimental protocol was established, according to the ethical guidelines of the Helsinki Declaration and was approved by the Human Ethics Committee of Beijing Hospital.

Patient consent

Written informed consent was obtained from individual or guardian participants.

Data availability

All data generated or analyzed during this study are included in this published article.

References

1. De Virgilio A, Greco A, Fabbrini G, et al. Parkinson's disease: autoimmunity and neuroinflammation. *Autoimmun Rev* 2016, 15, 1005–11. doi:10.1016/j.autrev.2016.07.022.
2. Tan EK, Chao YX, West A, et al. Parkinson disease and the immune system—associations, mechanisms and therapeutics. *Nat Rev Neurol* 2020, 16, 303–18. doi:10.1038/s41582-020-0344-4.
3. Li X, Sundquist J, Sundquist K. Subsequent risks of Parkinson disease in patients with autoimmune and related disorders: a nationwide epidemiological study from Sweden. *Neurodegener Dis* 2012, 10, 277–84. doi:10.1159/000333222.
4. Mohammadi S, Dolatshahi M, Rahmani F. Shedding light on thyroid hormone disorders and Parkinson disease pathology: mechanisms and risk factors. *J Endocrinol Invest* 2021, 44, 1–13. doi:10.1007/s40618-020-01314-5.

5. Chen SF, Yang YC, Hsu CY, Shen YC. Risk of Parkinson's disease in patients with hypothyroidism: a nationwide population-based cohort study. *Parkinsonism Relat Disord* 2020, 74, 28–32. doi:10.1016/j.parkreldis.2020.04.001.
6. Umehara T, Matsuno H, Toyoda C, Oka H. Thyroid hormone level is associated with motor symptoms in de novo Parkinson's disease. *J Neurol* 2015, 262, 1762–8. doi:10.1007/s00415-015-7780-x.
7. Kincaid AE. Spontaneous circling behavior and dopamine neuron loss in a genetically hypothyroid mouse. *Neuroscience* 2001, 105, 891–8. doi:10.1016/s0306-4522(01)00229-9.
8. Lee EH, Kim SM, Kim CH, et al. Dopamine neuron induction and the neuroprotective effects of thyroid hormone derivatives. *Sci Rep* 2019, 9, 13659. doi:10.1038/s41598-019-49876-6. PMID: 31541140; PMCID: PMC6754465.
9. Kluss JH, Mamais A, Cookson MR. LRRK2 links genetic and sporadic Parkinson's disease. *Biochem Soc Trans* 2019, 47, 651–61. doi:10.1042/BST20180462.
10. Li JQ, Tan L, Yu JT. The role of the LRRK2 gene in Parkinsonism. *Mol Neurodegener* 2014, 9, 47. doi:10.1186/1750-1326-9-47.
11. Looyenga BD, et al. Chromosomal amplification of leucine-rich repeat kinase-2 (LRRK2) is required for oncogenic MET signaling in papillary renal and thyroid carcinomas. *Proc Natl Acad Sci USA* 2011, 108, 1439–44. doi:10.1073/pnas.1012500108.
12. Jiang Z-C, Chen X-J, Zhou Q, et al. Downregulated LRRK2 gene expression inhibits proliferation and migration while promoting the apoptosis of thyroid cancer cells by inhibiting activation of the JNK signaling pathway. *Int J Oncol* 2019, 55, 21–34. doi:10.3892/ijo.2019.4816.
13. Lan-Lan W, Huang H, Chang-Rong Z, et al. Cloning and functional characterization of c-Jun NH2-terminal kinase from the Mediterranean species of the Whitefly Bemisia tabaci complex. *Int J Mol Sci* 2013, 14, 13433–46. doi:10.3390/ijms140713433.
14. Xu B, Yang H, Sun M, et al. 2,3′,4,4′,5-pentachlorobiphenyl induces inflammatory responses in the thyroid through JNK and aryl hydrocarbon receptor-mediated pathway. *Toxicol Sci* 2016, 149, 300–11. doi:10.1093/toxsci/kfv235.
15. Chen CY, Weng YH, Chien KY, et al. (G2019S) LRRK2 activates MKK4-JNK pathway and causes degeneration of SN dopaminergic neurons in a transgenic mouse model of PD. *Cell Death Differ* 2012, 19, 1623–33. doi:10.1038/cdd.2012.42.
16. Schapansky JD, et al. The complex relationships between microglia, alpha-synuclein, and LRRK2 in Parkinson's disease. *Neuroscience* 2015, 302, 74–88. doi:10.1016/j.neuroscience.2014.09.049.
17. Gatto EM, Parisi V, Converso DP, et al. The LRRK2 G2019S mutation in a series of Argentinean patients with Parkinson's disease: clinical and demographic characteristics. *Neurosci Lett* 2013, 537, 1–5. doi:10.1016/j.neulet.2013.01.011.
18. Seirafi M, Kozlov G, Gehring K. Parkin structure and function. *FEBS J* 2015, 282, 2076–88. doi:10.1111/febs.13249.
19. Matheoud D, Sugiura, A, Bellemare-Pelletier A, et al. Parkinson's disease-related proteins PINK1 and Parkin repress mitochondrial antigen presentation. *Cell* 2016, 166, 314–27. doi:10.1016/j.cell.2016.05.039.
20. Junguee L, Sujin H, Hee LM, et al. Dysregulation of Parkin-mediated mitophagy in thyroid Hürthle cell tumors. *Carcinogenesis* 2015, 36, 1407–18. doi:10.1093/carcin/bgv122.
21. Kure S, Ohashi R. Thyroid Hürthle cell carcinoma: clinical, pathological, and molecular features. *Cancers (Basel)* 2020, 13, 26. doi:10.3390/cancers13010026.
22. Nalls MA, Pankratz N, Lill CM, et al. Large-scale meta-analysis of genome-wide association data identifies six new risk loci for Parkinson's disease. *Nat Genet* 2014, 46, 989–93. doi:10.1038/ng.3043.
23. Lin J, Zhang P, Huang Y. et al. Elevated circulating Gpnmb levels are associated with hyperthyroidism. *Endocr Connect* 2020, 9, 783–92. doi:10.1530/EC-20-0240.
24. Zhang Y, Chen K, Sloan SA, et al. An RNA-sequencing transcriptome and splicing database of glia, neurons, and vascular cells of the cerebral cortex. *J Neurosci* 2014, 34, 11929–47. doi:10.1523/JNEUROSCI.1860-14.2014.
25. Liu J, Liu W, Yang H. Balancing apoptosis and autophagy for Parkinson's disease therapy: targeting BCL-2. *ACS Chem Neurosci* 2019, 10, 792–802. doi:10.1021/acschemneuro.8b00356.
26. Inoue N, Watanabe M, Ishido N, et al. Involvement of genes encoding apoptosis regulatory factors (FAS, FASL, TRAIL, BCL2, TNFR1 and TNFR2) in the pathogenesis of autoimmune thyroid diseases. *Hum Immunol* 2016, 77, 944–51. doi:10.1016/j.humimm.2016.07.232.
27. Shi GX, Han J, Andres DA. Rin GTPase couples nerve growth factor signaling to p38 and b-Raf/ERK pathways to promote neuronal differentiation. *J Biol Chem* 2005, 280, 37599–609. doi:10.1074/jbc.M507364200.
28. Bossers K, Meerhoff G, Balesar R, et al. Analysis of gene expression in Parkinson's disease: possible involvement of neurotrophic support and axon guidance in dopaminergic cell death. *Brain Pathol* 2009, 19, 91–107. doi:10.1111/j.1750-3639.2008.00171.x.
29. Felmlee MA, Jones RS, Rodriguezcruz V, et al. Monocarboxylate transporters (SLC16): function, regulation, and role in health and disease. *Pharmacol Rev* 2020, 72, 466–85. doi:10.1124/pr.119.018762.
30. Shen YT, Wang JW, Wang M, et al. BST1 rs4698412 allelic variant increases the risk of gait or balance deficits in patients with Parkinson's disease. *CNS Neurosci Ther* 2019, 25, 422–9. doi:10.1111/cns.13099.
31. Huang T, Zhou Y, Cao Y, et al. STK39, overexpressed in osteosarcoma, regulates osteosarcoma cell invasion and proliferation. *Oncol Lett* 2017, 14, 4599–604. doi:10.3892/ol.2017.6728.