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Genotype association of *IP6K3* gene with Hashimoto's thyroiditis in Algerian population (Aures region)

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Abstract

Background: Hashimoto's thyroiditis (HT) is a chronic autoimmune disease of the thyroid gland and is also the main cause of hypothyroidism. A recent genome-wide association study (GWAS) suggested an association of three novel genetic variants with HT in a population of Caucasian origin (Croatian). A case-control study was performed to investigate the association of these three newly suggested genetic variants with HT in a non-Caucasian ethnic group, an Arab-Berber from Algeria.

Three variants (rs12944194 located 206 kb from *SDK2*, rs791903 inside *IP6K3*, and rs75201096 inside *GNA14*) were genotyped using real-time PCR.

Results: There were no significant differences in allele frequencies of the three genetic variants between HT cases and controls. However, the present study showed nominal significance in the genotype distribution of rs791903 (*IP6K3* gene) between HT patients and the control group ($P = 0.024$); we observed a decrease in the frequency of rs791903 recessive homozygotes (CC) in HT cases versus controls (OR = 0.476, $P = 0.025$).

Conclusion: This is the first study that showed the genotypic association of *IP6K3* intronic variant with decreased risk for HT in non-Caucasian, Algerian, population, whereas we did not confirm the association of *SDK2* and *GNA14* genetic variants with HT. The *IP6K3* gene (inositol hexaphosphate kinase 3), located near major histocompatibility complex (MHC), has previously been associated with other common autoimmune diseases beside HT, such as Graves's disease and rheumatoid arthritis, which is providing more evidence of a good candidacy for the genetic contribution to the development of HT and autoimmunity.

Keywords: Hashimoto's thyroiditis, *IP6K3* gene, rs791903 variant, Real-time PCR, Genetic association study, Algerian population

Background

Hashimoto's thyroiditis (HT), also known as chronic lymphocytic thyroiditis, is the most common form of autoimmune thyroid disease. HT is characterized by chronic inflammation of the thyroid gland and synthesis

of thyroid peroxidase antibodies (TPO Ab) and/or thyroglobulin antibodies (TG Ab) [1]. The pathogenesis of this autoimmune disease is complex, and it is generally accepted that the infiltration of T lymphocytes and plasma cells leads to the destruction of thyroid tissue [2, 3].

HT is the most common cause of hypothyroidism in areas with excess iodine intake [4, 5]. On the worldwide scale, it is reported that the incidence of HT is higher in women than men (0.28 per 1000 population/year for women and 0.03 per 1000 population/year for men) [6].

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In addition, according to Chabchoub et al. [7], the prevalence of HT is estimated to be 22.8% in Africa.

HT is multifactorial autoimmune diseases where interaction between genetic and environmental factors plays an important role [8–10]. Many recent studies also pointed the role of epigenetic modifications in HT pathogenesis [11]. However, family and twin studies suggested that genetic factors are the main drivers of HT. It is estimated that genetic predisposition contributes to about 80% to HT development [7, 12].

Several genetic studies suggested the contribution of two types of genes to HT susceptibility: immune regulatory genes (*HLA-DR*, *CTLA-4*, *PTPN22*) [13] and thyroid-specific ones (*TG* and *TPO*) [14]. Recently, several other genes (*IL15*, *IL27*, *FOXP3*, and *SEPS1*) have also been suggested to be associated with HT [15–18].

A first genome-wide association analysis (GWAS) on patients with autoimmune thyroid disease (AITD) used ImmunoChip and identified the association of four loci with HT: 2p25.1, 3q27.3/3q28, 6q15, and 11q21 [19]. Additionally, another GWAS by Inoue et al. [20] reported the association of *ZFAT* gene with HT severity but not with its development. Another GWAS by Oryoji et al. [21] directly compared HT and GD cases and indicated the association of rs7537605 in the *VAV3* locus with HT. Finally, a GWAS by Eriksson et al. [22] has shown the association of rs6679677 near *PTPN22*, rs3184504 in *SH2B3*, and rs2517532 in the *HLA* class I region with a large spectrum of autoimmune diseases.

Importantly, there was only one GWAS that focused exclusively on HT to date. That study was performed in the Croatian population and included 405 cases and 433 controls, followed up by replication in 303 cases and 302 controls from two replication cohorts [23]. That study suggested an association of three novel HT variants: rs12944194 located 206 kb from *SDK2*, rs791903 inside *IP6K3*, and rs75201096 inside *GNA14* [23]. These three genetic variants are located in genomic regions with good biological candidacy to HT/autoimmunity and with the regulation of thyroid function.

The main aim of our study was to analyze the association of these three newly suggested genetic variants with HT in a different ethnic group than originally reported, the non-Caucasian, Arab-Berber population from Algeria.

Methods

Subjects

We performed a case-control study that included one hundred patients with HT and one hundred and twenty-six healthy subjects from the Aures region of Algeria that belong to an Arab-Berber ethnic group. Cases and controls were recruited in the period of 2 years (from January 2016 to February 2018).

HT patients (96% of women), with a median age of 39.5 years and median body mass index (BMI) of 27.26 kg/m², were recruited from three clinics: El Balsem el Chafy (Khenchela), Endocrinology & Metabolism Clinics of Dr. Malle and Endocrinology & Metabolism Clinics of Dr. Heddar (Batna). HT was diagnosed by specialists in nuclear medicine based on several criteria that included clinical symptoms, ultrasound findings, biochemical measurements of thyroid-stimulating hormone (TSH), and thyroid antibody (TPO Ab), according to European Thyroid Association (ETA) guidelines (Management of Subclinical Hypothyroidism) [24]. All HT patients had high levels of TSH and TPO-Ab and were treated with levothyroxine sodium (Merck KGaA, Frankfurter Str. 250, Darmstadt, Germany). We excluded patients with a personal history of any other autoimmune disease.

A control group (64.3% of women), with a median age of 33 years and a median BMI of 24.73 kg/m², were recruited from the University Hospital of Batna. All control participants were selected according to the following criteria: TPO Ab negative (5–34 UI/mL), TSH levels between 0.27 and 4.7 μ IU/mL, and FT4 levels between 12 and 22 pmol/L. None of the control subjects had a personal history of HT or any other autoimmune disease.

Clinical and demographic characteristics of HT patients and the control group are presented in Table 1.

The study was approved by the scientific-ethical committee of the University Hospital of Batna, under the number 524. Informed consent was obtained from all participants and the study was conducted according to the Declaration of Helsinki.

Blood samples and DNA extraction

Venous blood was collected in EDTA tubes (4 mL) from all study participants and stored at – 80° until extraction. Genomic DNA was extracted by the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. DNA concentration was measured using Nanodrop ND-1000 Spectrophotometer (ND-1000, Thermo Fisher Scientific, Waltham, MA, USA).

Genotyping

We selected single nucleotide polymorphisms (SNPs) (rs12944194, rs791903, and rs75201096) from the recently published GWAS of HT in Caucasian population [23]. SNP genotyping was performed by real-time PCR using ABI PRISM 7500 Sequence Detection System (Applied Biosystems, Foster City, USA) and pre-developed TaqMan SNP genotyping assays.

Association analysis

All statistical tests were performed by Plink software version 1.07 [25]. Prior association analysis, we checked if genotypes of the three investigated SNPs were

Table 1 Clinical and demographic characteristics of HT patients and control group

Characteristics	HT (N = 100)	Control (N = 126)
Gender, n (%)		
Men	4 (4%)	45 (35.7%)
Women	96 (96%)	81 (64.3%)
Age (years)	39.5 (32.5–47.75)	33 (28–40)
BMI (kg/m ²)	27.26 (24–30.19)	24.73 (23.04–26.68)
TPO Ab level (UI/mL)	411.5 (245.60–600)	11.1 (7.87–15.00) ^a
Log ₁₀ of TPO Ab level (mean ± SD)	2.57 ± 0.26 ^b	–

Data are presented by percentages for qualitative data and by a median with interquartile range (25–75th percentile) for quantitative data

^aReference values for TPO Ab levels: 5–34 UI/mL

^bTPO Ab level of HT patients is presented by mean ± SD after a logarithmic transformation

according to Hardy–Weinberg equilibrium (HWE) using an exact test [26]. Association of the three SNPs with HT was tested using a logistic regression model adjusted for age and BMI. Differences in the distribution of genotype frequencies of three SNPs were tested by Fisher's exact test. In addition, we checked the association of these three SNPs with TPO Ab levels in the group of HT cases only, using a linear regression model adjusted for age and BMI. A logarithmic transformation of TPO Ab levels in HT cases was performed prior analysis to ensure normal distribution.

Odds ratio (OR) and confidence intervals (95% CI) were calculated using IBM SPSS Statistics for Windows, Version 20.0. (Armonk, NY: IBM Corp). We used Bonferroni corrected *P* value of 0.017 (0.05 corrected for 3 SNPs) for declaring significant associations.

Results

Genotype distribution of all SNPs in HT patients and the control group was according to HWE (Table 2).

We did not detect significant allelic association of the three investigated SNPs with HT at the Bonferroni-corrected significance threshold (Table 3). However, we observed nominal significance in the distribution of rs791903 genotype (*P* = 0.024) between HT and the control group. Recessive homozygotes (CC) were less frequent in HT cases than in controls (*P* = 0.025) (Table 4).

Table 2 SNP characteristics in HT patients and control group

SNP	Chr	Position	MAF HT patients ^a	MAF control group ^b	<i>P</i> (HWE) HT patients ^c	<i>P</i> (HWE) control group ^d
rs12944194	17	71846563	0.365	0.361	0.280	0.564
rs791903	6	33702645	0.455	0.496	0.072	0.076
rs75201096	9	80098900	0.025	0.0119	1.0	1.0

Chr chromosome

^aMAF minor allele frequency of HT patients

^bMAF minor allele frequency of control group

^c*P* value for Hardy–Weinberg equilibrium test in HT patients

^d*P* value for Hardy–Weinberg equilibrium test in the control group

No associations were detected with TPO Ab levels in the group of HT patients (Table 5).

Discussion

The goal of our study was to explore the association of three newly suggested HT-associated genetic variants with the risk of developing HT in 100 HT patients and 126 controls of Arab-Berber ethnicity. To our knowledge, this is the first genetic study that focused on the evaluation of the association of these genetic variants (rs12944194, rs791903, and rs75201096) with susceptibility to HT in non-Caucasian population from Algeria. Our main result is the observation of a nominally significant decrease in the frequency of rs791903 recessive genotype in HT cases versus controls.

The original GWAS study, performed by Brčić et al. [23], showed an association of rs12944194, rs791903, and rs75201096 genetic variants with HT in Croatian population. The present study did not confirm the allelic association of these three SNPs and HT in our population. However, we observed that the rs791903 recessive homozygotes (CC) were significantly less frequent in HT patients than in controls (*P* = 0.025, OR = 0.476) (Table 4).

Genetic variant rs791903 is located in the intronic region of inositol hexaphosphate kinase 3 (*IP6K3*) gene on chromosome 6 (6p21). This locus has already been strongly associated with several inflammatory and autoimmune diseases [27–29].

A recent study observed association of rs791903 with rheumatoid arthritis (RA) [30], which is an autoimmune disease that is also present in 4.25% of patients with HT [31]. It is suggested that HT and RA share genetic background and our study adds more evidence to genetic contribution of rs791903 in, both, RA and HT. Furthermore, it has been reported that *IP6K3* gene is expressed in the thyroid tissue [32], but until now, its exact role remains unclear.

Several HT-related autoimmune diseases, such as systemic lupus erythematosus (SLE), GD, and RA, were already associated with genetic variants in *ITPR3* gene that belongs to thyroid hormone synthesis pathway [33]. *ITPR3* gene is located very near to our SNP rs791903 (38 kb away). According to Oishi et al. [33], the rs3748079, located in the promoter region of *ITPR3* gene

Table 3 Results of Association analysis for rs12944194, rs791903, and rs75201096 in HT case-control analysis

SNP	Gene/nearest gene	MA	OA	OR (95% CI)	P value
rs12944194	<i>SDK2</i> (206 kb away)	T	C	1.016 (0.623–1.654)	0.934
rs791903	<i>IP6K3</i>	C	G	0.849 (0.520–1.384)	0.387
rs75201096	<i>GNA14</i>	C	T	2.158 (0.318–14.63)	0.300

MA minor allele, OA other allele, OR odds ratio, CI confidence interval

and 114 kb from rs791903 ($D' = 0.671$, $r^2 = 0.1557$), was strongly associated with SLE in Japanese population. Also, two other markers of the same gene, rs9394159 and rs4713693, were associated with GD [34]. Genetic studies of AITD showed the existence of a common genetic background between HT and GD [35–37]. Almost 74% of SNPs related to GD have the same effect on HT [23]; therefore, the genetic overlap between HT and GD, as supported by our study, gives additional evidence of the role of this SNP in AITD.

The most important limitation of our study is the sample size. Future studies of the genetic background of HT in our ethnic group should include larger sample sizes to confirm the results from this study. It is important to note that there is a difference in gender distribution between our case and control group: our case group consists of 96% women (as is expected for this female prevalent disease) [38, 39] whereas the control group consists of 64.3% of women. The difference in the gender distribution between cases and controls should not affect our results as the latest scientific reports encourage using mixed-sex controls (those consisted of both males and females) in studies of sex-specific traits (such as HT, which is predominantly affecting women). This largest genetic study including 61,094 women and 53,769 men showed that there are no allele frequency

Table 5 Results of association analysis of three SNPs with TPO-Ab levels

SNP	Minor allele	TPO Ab	
		β (SE)	P value
rs12944194	T	-0.0159 (0.0337)	0.6365
rs791903	C	-0.0276 (0.0383)	0.4724
rs75201096	C	-0.0173 (0.1113)	0.8763

β linear regression slope coefficient, SE standard error

differences at common SNPs between men and women [40]. The advantages of our study include the stringent selection of HT patients, which are characterized by the presence of significantly higher levels of TPO Ab than controls (< 0.001). Our patients also had a higher BMI than controls, which is in line with the observations from most studies [41]. Another advantage is the careful selection of controls in clinical settings. We excluded individuals with any type of thyroid or any other autoimmune disorder from controls. Controls had TPO Ab levels in the reference ranges, thus minimizing potential bias (Table 1).

Finally, it is now a common practice to analyze genetic variants in different ethnic groups than originally reported, as we now know that differences in the strength and even the direction of genetic signals across different populations exist. We believe that results of our study add to the current scientific knowledge on genetic susceptibility to HT. However, in the present time, when genetic influence on HT is just starting to be deciphered, there is no translational benefit for study subjects. Therefore, it is important to continue these efforts and perform replication studies and additional functional studies using other high-throughput analytic methods, to understand the mechanisms by which *IP6K3* gene

Table 4 Genotype association of rs12944194, rs791903, and rs75201096 with HT

SNPs	HT, n (%)			Control group, n (%)			OR (95% CI)	P value
	TT	TC	CC	TT	TC	CC		
rs12944194	16(16%)	41(41%)	43(43%)	18(14.2%)	55(43.7%)	53(42.1%)	-	0.899
	TT + TC vs. CC (dominant model)						0.962 (0.566–1.637)	0.887
	TT vs. TC + CC (recessive model)						1.143 (0.550–2.375)	0.720
rs791903	CC	CG	GG	CC	CG	GG		
	16(16%)	59(59%)	25(25%)	36(28.6%)	53(42.1%)	37(29.3%)	-	0.024
	CC + CG vs. GG (dominant model)						1.247 (0.689–2.257)	0.465
CC vs. CG + GG (recessive model)						0.476 (0.246–0.921)	0.025	
rs75201096	CC	CT	TT	CC	CT	TT		
	0(00%)	5 (5%)	95(95%)	0 (00%)	3 (2.4%)	123 (97.6%)	-	0.471
	CC + CT vs. TT (dominant model)						2.158 (0.503–9.256)	0.471
CC vs. CT + TT (recessive model)						-	1.0	

OR odd ratio, CI confidence interval

exerts its roles in HT. The final aim in the future is to benefit patients by translating new knowledge on genetic factors (thus biological mechanisms) into clinical practice.

Conclusion

In conclusion, this is the first genetic study that was focused on understanding the genetic basis of HT in Algerian population. Our results suggest the lack of allelic association of rs12944194, rs791903, and rs75201096 with HT. However, we found differences in the genotype distribution of rs791903 between HT and the control group, where recessive homozygotes (CC) were significantly less frequent in HT patients.

Due to the increased prevalence of HT in the Arab-Berber ethnical group from Algeria, future large-scale case-control studies are necessary for replication of our results.

Abbreviations

HT: Hashimoto's thyroiditis; *IP6K3* gene: Inositol hexaphosphate kinase 3 gene; MHC: Major histocompatibility complex; TPO Ab: Thyroid peroxidase antibody; TG Ab: Thyroglobulin antibody; GWAS: Genome-wide association studies; AITD: Autoimmune thyroid disease; GD: Graves' disease; ETA: European Thyroid Association; BMI: Body mass index; SNP: Single nucleotide polymorphism; HWE: Hardy-Weinberg equilibrium; OR: Odds ratio; RA: Rheumatoid arthritis; SLE: Systemic lupus erythematosus

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Authors' contributions

MY, SB, LH, and VBP supervised and conceived study conception and design. WK participated in data collection and/or processing. WK, DK, VBP, and LB carried out the molecular genetic work, the statistical analysis, and interpretation. WK, VBP, and DK drafted the manuscript. All authors read and approved the final manuscript and accepted the publication.

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Availability of data and materials

The data used or analyzed during the study are available from the corresponding author.

Ethics approval and consent to participate

The study was approved by scientific committee of University Hospital of Batna, under the number 524. Informed written consent was obtained from all participants. Reference number: not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests

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