Latent autoimmune thyroid disease

Yhojan Rodríguez [a,b], Manuel Rojas [a,c], Diana M. Monsalve [a], Yeny Acosta-Ampudia [a], Yovana Pacheco [a], Mónica Rodríguez-Jiménez [a], Carolina Ramírez-Santana [a], Juan-Manuel Anaya [a,*]

[a] Center for Autoimmune Diseases Research (CREA), School of Medicine and Health Sciences, Universidad Del Rosario, Bogota, Colombia
[b] Clinica Del Occidente, Bogota, Colombia
[c] Doctoral Program in Biomedical and Biological Sciences, Universidad Del Rosario, Bogota, Colombia

ABSTRACT

Objective: To determine the prevalence of thyroid autoantibodies and the associated factors in euthyroid subjects.
Methods: 300 euthyroid subjects, chosen by stratified sampling from an inception cohort of 1335 individuals, were included. Thyroid function was evaluated by measuring the serum levels of TSH (0.3–4.5 μIU/mL) and FT4 (5.2–12.7μg/dL). Anti-peroxidase (TPOAbs), anti-thyroglobulin (TgAbs), and anti-TSH receptor (TrAbs) antibodies were evaluated with 23 additional autoantibodies as well as vitamin D (VitD) levels. The analysis included sociodemographic, clinical, and environmental characteristics. Data were analyzed by bivariate and multivariate tests.
Results: Thyroid autoimmunity was observed in 15.3% of the subjects (TPOAbs 11.3% and TgAbs 2.0%). In six individuals, both autoantibodies were positive. TrAbs were not detected in any individual. Familial thyroid disease (β = 3.4, 95% CI: 1.2–9.5, P = 0.021), the presence of other autoimmune diseases (β = 10.8, 95% CI: 1.6–72.9, P = 0.014) VitD insufficiency (P = 0.030), never smoke (β = 6.9, 95% CI: 1.6–30.4, P = 0.010), drinking more than 4 cups of coffee (β = 3.8, 95% CI: 1.1–13.1, P = 0.036), and a higher number of years exposed to wood smoke (P = 0.04) were associated with thyroid autoimmunity. In the case of TPOAbs, familial thyroid disease (β = 4.9, 95% CI: 1.7–14.0, P = 0.003), never smoke (β = 5.7, 95% CI: 1.4–21.0, P = 0.002), and drinking more than 4 cups of coffee (β = 3.6, 95% CI: 1.1–13.1, P = 0.047) were associated with their positivity. In addition, the presence of anti-SS–A/Ro52 (β = 36.7, 95% CI: 2.5–549.9, P = 0.009) and anti-Ku antibodies (β = 10.2, 95% CI: 1.1–100.7, P = 0.046) was also associated with TPOAbs. The presence of African ancestry (β = 10.5, 95% CI: 1.7–63.2, P = 0.01), anti-SS–A/Ro52 (β = 15.8, 95% CI: 1.2–198.6, P = 0.03), and anti-CENP-B antibodies (β = 31.2, 95% CI: 1.8–565.9 P = 0.02) were associated with TgAbs.
Conclusion: Latent thyroid autoimmunity is not rare. Environmental, genetic, and immunological factors as well as ancestry are associated risk factors. These results would facilitate the implementation of screening strategies in order to provide timely diagnosis and treatment.

1. Introduction

Hypothyroidism is an endocrine disease characterized by the presence of elevated serum levels of Thyroid-Stimulating Hormone (TSH) and low levels of free thyroxine (FT4). This disorder is described in up to 10% of the population and its etiology originates mainly from autoimmunity, particularly Hashimoto Thyroiditis (HT) [1]. One of the main clinical challenges relies on the absence of specific symptoms, therefore many individuals are affected for this disease without knowing it. This high prevalence of undiagnosed hypothyroidism leads to a high rate of associated comorbidities, including cardiovascular disease, hypercholesterolemia, atrial fibrillation, and depression [2–4].

Hyperthyroidism, in turn, is the opposite of hypothyroidism. In this case, the levels of TSH secreted by adenohypophysis are suppressed due to the high secretion of FT4 by the thyroid gland [5]. Its prevalence varies between 0.8% in Europe [6], to 1.3% in the United states [7]. Unlike hypothyroidism, the prevalence of asymptomatic patients is low. Therefore, the symptoms are clearly defined at the beginning of the disease. Excess of thyroid hormone produces a wide variety of symptoms such as fatigue, sweating, tremor, anxiety, disturbed sleep, palpitations,

weight loss, and heat intolerance [5]. The main nosology of hyperthyroidism is autoimmunity being Graves' disease (GD) the most important cause [5].

The prevalence of autoimmune thyroid disease (AITD) is around 5% [8], and the prevalence of thyroid autoantibodies in healthy subjects may be even higher [9]. This data is relevant, since the presence of thyroid autoantibodies could be a predictive tool of thyroid failure in genetically predisposed subjects, and in those individuals exposed to some environmental agents. In view of the high prevalence of AITD, many studies have sought to determine the prevalence of thyroid autoimmunity before the thyroid disease becomes overt by documenting the presence of thyroid autoantibodies in euthyroid individuals [7,10–15]. The reports from these studies ranged from the NHANES III study with a prevalence of 11.3% and 10.4% for anti-peroxidase antibodies (TPOAbs) and anti-thyroglobulin antibodies (TgAbs) respectively, to a prevalence of 13.1% in the Danish population. This is significant considering the importance of the thyroid autoantibodies as predictors of AITD [16,17]. The Whickham study reported a 2.1 risk per year in euthyroid subjects with TPOAbs of developing AITD [16].

Detection of risk factors for hypo- or hyperthyroidism allows the introduction of new approaches for primary prevention strategies. However, the risk factors influencing the appearance of thyroid autoimmunity are not fully understood. Therefore, given the high prevalence of AITD in areas with iodine sufficiency and the risk of comorbidity including polyautoimmunity (PolyA), the identification of thyroid autoimmunity in the general population becomes of high interest [2–4, 18–21]. Several studies have shown female:male ratios between 2:1 to 3:1 [7,11] and an age-associated increase in thyroid autoantibodies [22]. Genetic factors play also a role. A first approach to investigate their presence could be evaluated by analyzing the family history of AITD and other autoimmune diseases (ADs) [21]. Concerning environmental factors (i.e., autoimmune ecology), iodine, infections, vitamin D (vitD) deficiency, stress, drugs, and tobacco have been widely described in AITD [23]. In the current study we aimed to investigate the prevalence of thyroid autoantibodies in euthyroid individuals and the factors associated with latent thyroid autoimmunity in such individuals.

2. Methods

2.1. Population

Three hundred euthyroid Colombian individuals belonging to different socioeconomic strata as well as level of education and occupation participated in this study. The sample size was obtained by randomized stratified sampling of a population of 1335 individuals paired by age and gender using Epidat®, version 4.1. A confidence level of 95%, a power of 80%, and an estimated 11% prevalence of autoantibodies in euthyroid patients was obtained with a minimum sample size of 300 subjects (Fig. 1) [7]. None of the participants was on levothyroxine treatment, were under 18, presented undefined thyroid disease, history of hypothyroidism/hyperthyroidism, previous thyroid disease during pregnancy, had thyroid surgery nor history of thyroid cancer.
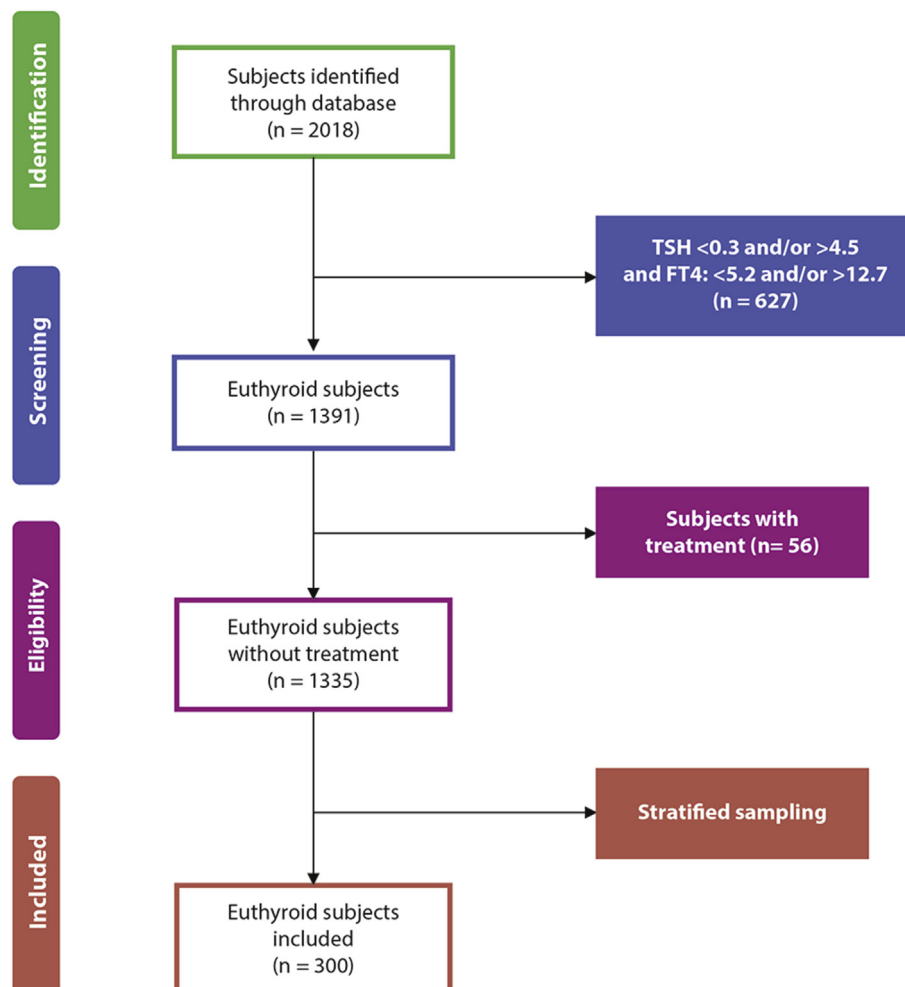

Fig. 1. Flow Diagram of Patient Recruitment.

2.2. Sociodemographic and clinical factors

Sociodemographic information such as age, gender, ethnicity, socio-economic stratum, and place of birth was obtained as previously described [20,24]. Additionally, subjects were asked about clinical antecedents such as contraceptive methods, comorbidities, obstetric, surgical, and pharmacological antecedents. Furthermore, habits such as consumption of coffee and tobacco, occupational and home exposures to toxic agents were also recorded [20,24] as were symptoms related to thyroid dysfunction and the presence of hypo or hyperthyroidism [1,5]. The clinical evaluation and data collection were done at the CREA between July and November of 2017. The clinical evaluation included the assessment of weight, height, abdominal perimeter, blood pressure, and reflex assessment.

2.3. Laboratory measurements

The thyroid function was evaluated by measuring TSH and FT4 serum levels. In addition, vitD levels, TPOAbs, TgAbs, and anti-TSH receptor antibodies (TrAbs) were detected as markers for thyroid autoimmunity. Furthermore, a panel of 23 autoantibodies were evaluated. TSH, FT4, and vitD levels were measured by electroquimioluminiscence using the following thresholds: TSH (0.3–4.5 μIU/mL), FT4 (5.2–12.7 UI/dL), and vitD, a level above 30 ng/mL was considered to be sufficiency; below 30 ng/mL, insufficiency; and below 20 ng/mL, deficiency [25].

TPOAbs, TgAbs, rheumatoid factor (RF) IgM, the anti-citrullinated protein antibodies (ACPA) IgG, the anti-cardiolipin antibodies (ACA) IgM and IgG, the Beta 2-glycoprotein (β2GP1) antibodies IgM and IgG were measured using indirect ELISA (Inova Diagnostics, Inc. San Diego, CA, USA), while TrAbs were measured with competitive ELISA (Eagle Biosciences, Nashua, NH, USA). The remaining 17 autoantibodies were evaluated by immunoblot assay (double-stranded DNA [dsDNA], nucleosomes, histones, SmD1, proliferating cell nuclear antigen [PCNA], P0, Anti-Sjögren's syndrome type A [SS-A/Ro60], SS-A/Ro52, Anti-Sjögren's syndrome type B [SS-B/La], centromere autoantigen B [CENP-B], Scl70, U1-snRNP, Anti-mitochondrial M2 antibody [AMA M2], Jo-1, PM-Scl, Mi-2, Ku) using IMTEC ANA-LIA Maxx from Human diagnostics, Magdeburg Germany. Latent autoimmunity was defined as presence of autoantibodies without fulfillment of international classification criteria [26].

2.4. Statistical analysis

Categorical variables were analyzed by frequencies, and quantitative continuous variables were expressed as mean and standard deviations (SD) and in the median and interquartile ranges (IQR) [27]. To assess associations between outcomes of interest and other variables, the $\chi2$, Kruskal-Wallis and Mann–Whitney U test were used. Binary Logistic regression analysis was done. Shortly, TPOAbs and TgAbs were included as dependent variables, while those variables with biological plausibility were selected as independent variables. Obtained models were tested for goodness of fit by Hosmer–Lemeshow test, and their discrimination capacity were considered relevant if c-statistic was higher than 0.7. The significance level of the study was set to 0.05. Statistical analyses were done in SPSS statistics version 2.4.

3. Results

The sociodemographic, clinical, and thyroid variables are shown in Tables 1 and 2. The group of subjects mainly consists of women and young people. Thyroid autoimmunity was observed in 15.3% of the cases, TPOAbs in 11.3%, and TgAbs in 2%. Both autoantibodies were described in six individuals. TrAbs were not detected in any individual.

Table 3 shows habits and environmental factors. Unlike tobacco consumption, which was low, coffee consumption was very important in this population. Organic solvents were the main toxin they have been

Table 1
Sociodemographic and clinical characteristics.

Characteristics	n = 300 (%)
Gender	
Women	287 (95.7)
Age	
Median (IQR)	34 (27–40)
Ethnicity	
Amerindian origin	275/292 (94.2)
African origin	13/292 (4.5)
Native	4/292 (1.4)
SES	
1,2,3	294/298 (98.7)
4,5,6	4/298 (1.3)
Comorbidities	
Arterial hypertension	6 (2.0)
Diabetes mellitus 2	4 (1.3)
Dyslipidemia	6 (2.0)
Cancer	3/299 (1.0)
Abortion	61/285 (21.4)
Polycystic ovary syndrome	10/282 (3.5)
VitD status	
VitD level (IQR)	15.9 (11.0–23.6)
VitD sufficiency	25/238 (10.5)
VitD insufficiency	70/238 (29.4)
VitD deficiency	143/238 (60.1)

SES: Socioeconomic status, VitD: Vitamin D.

Table 2
Thyroid data.

Characteristics	n = 300 (%)
Thyroid autoimmunity	
TPOAbs	34 (11.3)
TgAbs	6 (2.0)
TgAbs and TPOAbs	6 (2.0)
Biological data	
TSH (IQR)	2.3 (1.7–3.3)
FT4 (IQR)	8.4 (7.6–9.1)
Clinical data	
Familial thyroid disease*	38 (12.7)
Fatigue	98/297 (33.0)
Anxiety	80/297 (26.9)
Weight gain	75/295 (25.4)
Weight loss	31/298 (10.4)
Cold intolerance	30/299 (10.0)
Heat intolerance	24/299 (8.0)
Menstrual disorders	105/278 (37.8)
Dry Skin	79/298 (26.5)
Diaphoresis	34 (11.3)
Alopecia	81 (27.0)
Constipation	83 (27.7)
Voice Alteration	14 (4.7)
Fullness of throat	37 (12.3)
Bradilalia, Bradipsiquia	34 (11.3)
Hyporeflexia	13/297 (4.4)
Tremor	30 (10.0)
Palpitations	50 (10.7)
Diplopia	18 (6.0)
Infertility	9 (3.0)
Low libido	37 (12.3)

TPOAbs: Anti-peroxidase antibodies, TgAbs: Anti-thyroglobulin antibodies, TSH: Thyroid-Stimulating Hormone, FT4: Free thyroxine. First degree relatives*.

exposed throughout life, followed by using of hair dyes and exposure to wood smoke. With respect to exposure at work or home, the main working or housing areas in which these individuals were exposed to toxins were farms followed by airports and laundries. Immunological data are described in Table 4. RF, ACA IgM, and β2GP1 IgM were the most prevalent autoantibodies in these subjects. In addition, an interesting percentage of familial autoimmunity and the presence of other ADs was found.

Table 3

Environmental characteristics.

Characteristics	n = 300 (%)
Habits	
Never smoke	232 (77.3)
Former smoker	44 (14.7)
Active smoker	24 (8.0)
1–5 pack-year	20 (6.7)
6–15 pack-year	2 (0.7)
More than 15 pack-year	2 (0.7)
Never coffee	22 (7.3)
Former coffee drinker	9 (3.0)
Coffee drinker	266/297 (89.6)
Less than a cup/day	85/299 (28.4)
One cup/day	53/298 (17.8)
2–4 cups/day	110/298 (36.9)
More than 4 cups/day	19/298 (6.4)
Environmental exposures	
Organic solvents	255 (85.0)
Hair dyes	184/299 (61.3)
Wood smoke	94 (31.3)
Psychoactive substances	7 (2.3)
Pesticides	8 (2.7)
Asbestos	18 (6.0)
Ever live/work	
Farms	41 (13.7)
Airports	32 (10.7)
Laundry	27 (9.0)
Factories	13 (4.3)
Garbage deposits	10 (3.3)

Table 4

Immunological data.

Characteristics	n = 300 (%)
Familial autoimmunity	21 (7.0)
Other autoimmune diseases	9 (3.0)
Autoantibodies	
RF	116 (38.7)
ACA IgM	15 (5.0)
β2GP1 IgM	13 (4.3)
SS-B/La	12 (4.0)
SmD1	9 (3.0)
SS-A/Ro60	7 (2.3)
PM-Scl	7 (2.3)
PCNA	7 (2.3)
β2GP1 IgG	5 (1.7)
ACPA	3 (1.0)
Ku	4 (1.3)
SS-A/Ro52	3 (1.0)
CENP-B	3 (1.0)
U1-snRNP	2 (0.7)
Mi-2	2 (0.7)
dsDNA	1 (0.3)
Nucleosomes	1 (0.3)

RF: Rheumatoid factor, ACA: Anti-cardiolipin antibodies, β2GP1: Beta 2-glycoprotein 1 antibodies, SS-B/La: Anti-Sjögren's syndrome type B antibodies, SS-A/Ro: Anti-Sjögren's syndrome type A antibodies, ACPA: Anti-citrullinated protein antibodies, dsDNA: Anti-double stranded DNA antibodies, PCNA: Anti-proliferating cell nuclear antigen antibodies, Sm: Anti-Smith antibodies, RNP: Anti-ribonucleoprotein antibodies, CENP-B: Anti-centromere antibody subunit B.

The bivariate analysis showed an association between thyroid autoantibodies and familial thyroid disease (OR: 2.2, 95% CI: 1.1–5.0, $P = 0.04$), and low libido (OR: 2.3 95% CI: 1.1–5.2, $P = 0.04$). Furthermore, regarding environmental and biological factors, never smoke (OR: 2.7 95% CI: 1.1–7.1, $P = 0.04$), vitD insufficiency ($P = 0.03$), and a greater number of years of exposure to wood smoke ($P = 0.04$) were associated with the presence of thyroid autoimmunity.

In a further analysis, TPOAbs and TgAbs were studied separately. Familial thyroid disease (OR: 2.8 95% CI: 1.2–6.2, $P = 0.01$), never smoke (OR: 2.9 95% CI: 1.1–8.6, $P = 0.04$), and low libido (OR: 2.9 95% CI: 1.3–6.5, $P = 0.009$) were associated with anti-TPO positivity. Moreover, an association between TSH levels and TPOAbs was observed (Fig. 2). An association of TgAbs with the presence of menstrual irregularity (OR: 0.3 95% CI: 0.08–0.9, $P = 0.022$) and SS-A/Ro52 (OR: 13 95% CI: 1.1–154, $P = 0.009$) was observed. No association between TSH levels and TgAbs was seen despite a suggestive trend (Fig. 3).

The multivariate analysis included a logistic regression with the presence of thyroid autoantibodies as dependent variable. In this analysis, the history of familial thyroid disease, the presence of other ADs, never smoke, drinking more than 4 cups of coffee per day, and low libido were significantly associated with the presence of thyroid autoimmunity (Table 5).

Multivariate analysis using TPOAbs as the dependent variable shows that the presence of familial thyroid disease, never smoke, drinking more than 4 cups of coffee per day, and low libido were associated with anti-TPO positivity. In addition, the presence of anti–SS–A/Ro52 and anti- Ku antibodies was associated with the presence of TPOAbs (Table 6). The multivariate analysis using the TgAbs as a dependent variable showed that african ethicity, anti–SS–A/Ro52, and anti-CENP-B antibodies were associated with TgAbs positivty (Table 7).

4. Discussion

Environmental factors (i.e., autoimmune ecology) that impair the immune response and give rise to the recognition of thyroid self-antigens in susceptible individuals is pivotal to the development of AITD. This causes an autoimmune response which eventually culminates in overt disease. All these steps are immersed in the natural history of the disease as it goes through a series of states from the pre-pathogenic phase, which
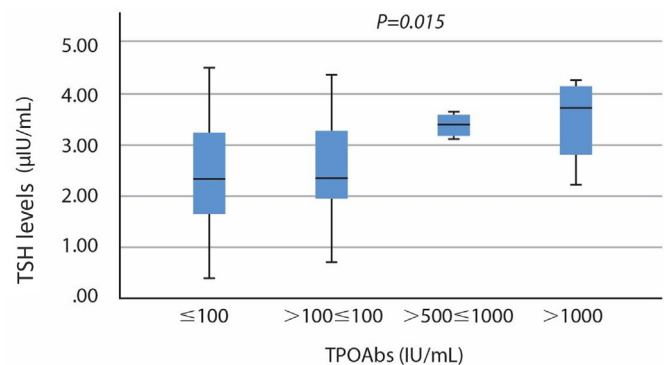
Fig. 2. There was a significant association between TSH levels and TPOAbs levels. An increase in TSH levels in same proportion to TPOAbs levels was observed.
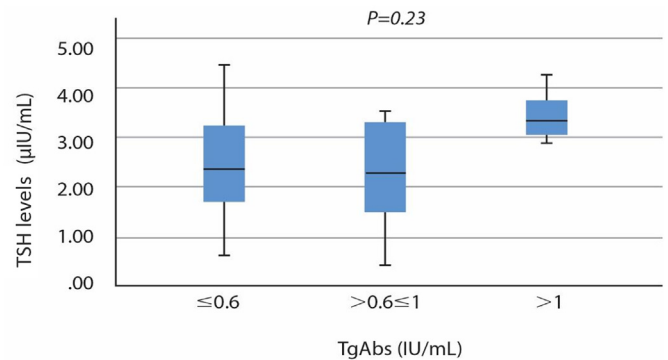
Fig. 3. Although there was not statistically significant association between the TSH levels and levels of TgAbs, a trend in the influences of these autoantibodies on TSH levels was observed.

Table 5
Factors associated with thyroid autoantibodies.

Characteristic	β	95% CI		P
Familial thyroid disease	3.384	1.200	9.542	0.021
Other autoimmune diseases	10.811	1.603	72.901	0.014
Never smoke	6.942	1.586	30.378	0.010
Drinking more than 4 cups of coffee	3.776	1.090	13.075	0.036
Low libido	3.753	1.324	10.633	0.013

Table 6
Factors associated with TPOAbs.

Characteristic	β	95% CI		P
Familial thyroid disease	4.894	1.705	14.049	0.003
Never smoke	5.428	1.397	21.090	0.015
Drinking more than 4 cups of coffee	3.641	1.015	13.055	0.047
Low libido	5.680	2.013	16.028	0.001
SS-A/Ro52	36.729	2.453	549.874	0.009
Ku	10.235	1.040	100.734	0.046

TPOAbs: Anti-peroxidase antibodies, SS-A/Ro: Anti-Sjögren's syndrome type A antibodies.

Table 7
Factors associated with TgAbs.

Characteristic	β	95% CI		P
African ancestry	10.500	1.745	63.196	0.010
β2GP1 IgG	7.875	0.761	81.522	0.084
SS-A/Ro52	15.750	1.249	198.573	0.033
CENP-B	31.500	1.753	565.945	0.019

TgAbs: Anti-thyroglobulin antibodies, β2GP1: Beta 2-glycoprotein 1 antibodies, SS-A/Ro: Anti-Sjögren's syndrome type A antibodies, CENP-B: Centromere autoantigen B antibodies.

is asymptomatic, to the pathogenic period, characterized by the presence of symptoms [28]. Considering the current evidence, this study sought to confirm the role of some factors which had previously been studied in relation to the presence of thyroid autoantibodies as well as to find new ones that might contribute to the understanding of latent AITD.

The evaluation of these autoantibodies is relevant because they represent the highest risk of developing AITD [7,16]. An annual risk of 2.1% per year of developing hypothyroidism in the presence of thyroid autoantibodies has been documented [7]. Spite of diverse heritability, our study showed a prevalence of TPOAbs and TgAbs similar to other studies [15] (Table 8) [7,10–14,29].

One relevant finding was the relationship between autoantibodies and ethnicity. Although African ethnicity was only observed in 4.5%, it could act as a risk factor for developing thyroid autoimmunity, particularly, TgAbs. These results are different from other studies, where AITD was lower in African people [7,30]. In fact, a study done on military personnel in the United States, where the prevalence of AITD by ethnicity was assessed, showed that the incidence of HT was highest in whites as compared to blacks unlike GD, where the incidence was higher in the latter population [31]. Thus, given the link between the thyroglobulin locus and GD reported in some studies [32,33], it is tempting to speculate

that the association found in our black population may be caused by genetic susceptibility and the presence of thyroid autoantibodies [34]. However, the studies that report this association come from non-black population groups; thus, further studies are warranted to define the influence of this locus on AITD in black population.

The environmental factors to which this population is exposed could be crucial for the development of thyroid autoimmunity [23]. Smoking has a significant effect on thyroid function [35]. Some authors have observed the presence of thyroid autoantibodies with the cessation of smoking [36]. This means that tobacco could be protective for AITD in current-smokers [37]. The first epidemiological descriptions of the effect of tobacco and the presence of thyroid autoantibodies and hypothyroidism were addressed in the NHANES III survey which showed that active smokers have lower TSH levels compared to non-smokers [37]. In addition, other studies have provided new evidence regarding the role of tobacco in AITD showing that up to 85% of ex-smokers had higher rates of hypothyroidism attributable to cessation of smoking [36]. This information opens a debate on a parodoxical effect of tobacco on thyroid autoimmunity. Several experimental studies have shown that some components of tobacco such as the alkaloids – nicotine and anatabine – exhibit an immunomodulatory effect. Nicotine is widely known for its anti-inflammatory effects [38]. This mechanism is mediated by the link between nicotine and its receptor. The link is expressed not only centrally and peripherally in pre-ganglionic fibers and neuromuscular synapses, but also in immune cells such as macrophages, dendritic cells, and CD4+ T-cells. The expression of the nicotinic receptor in these immune cells has been studied as a therapeutic target in order to enhance its anti-inflammatory effect [39].

Another component of tobacco which has been object of recent studies is anatabine. This alkaloid, like nicotine, has anti-inflammatory properties that could influence the control of an immune response against the thyroid. However, it is not associated with the toxicity and addiction rates shown with nicotine. Also, it has a longer plasma half-life [40,41]. The first studies of anatabine were done on murine models and showed that the mice exposed to this alkaloid had a lower incidence and severity of thyroiditis (RR 0.59, $P = 0.0174$) [42]. This study showed a reduction in the immune response mediated by thyroid autoantibodies (i.e., TgAbs) and a control of the macrophage production of inducible nitric oxide synthase and cyclooxygenase 2 [42]. The previous results were confirmed in clinical trial in which anatabine decreased thyroid autoimmunity [43].

In addition, the presence of cyanide in cigarette smoke and metabolized to thiocyanate could be associated with a mild immunomodulatory response given the interference of thiocyanate in the transportation and uptake of iodine [37,44]. Therefore, the preparation of screening strategies for the population is necessary in order to evaluate the presence of thyroid autoantibodies in patients at risk of developing AITD, and who have recently abandoned tobacco.

The relationship between vitD levels and autoimmunity is widely known since low levels are associated with the risk of developing ADs, and once the AD is overt, the low levels of vitD have been associated with disease activity [45]. The results of our study confirm the association between low levels of VitD and thyroid autoimmunity [46,47]. However,

Table 8
Prevalence of thyroid autoantibodies.

Publication date	Geographic location	Number of cases		Female prevalence n (%)	Male prevalence n (%)	Ref
		Female	Male			
1990	United Kingdom	698	–	124 (17.8)	–	[13]
1993	Japan	1134	2896	133 (11.7)	167 (5.7)	[12]
1995	United Kingdom	942	762	248 (26.4)	67 (8.8)	[11]
2000	Norway	582	360	81 (13.9)	10 (2.8)	[14]
2002	United States	8619	7914	1258 (14.6)	633 (8.0)	[7]
2003	Germany	455	840	117 (25.8)	120 (14.4)	[10]
2010	Netherlands	1216	1178	144 (11.9)	56 (4.8)	[30]

the prevalence of individuals with vitD insufficiency should be considered a public health problem and not exclusively a matter of ADs [48].

Despite the extensive study of environmental factors associated with AITD, the effect of coffee has been poorly studied. The results of this study showed an association between the presence of thyroid autoimmunity and coffee consumption, especially for those consuming more than 4 cups per day. With respect to these results, it could be presumed that the consumption of this amount of coffee may encourage the release of thyroglobulin as previously described [49] thus triggering an autoimmune response against this antigen. However, this is controversial since in other reports the effect of caffeine was protective [50]. This study documented a strong association between the presence of familial autoimmune disease and PolyA and the presence of thyroid autoantibodies. These are validated by different studies that have reported a heritability between 0.54 and 0.66 for the presence of thyroid autoantibodies [51].

5. Conclusions

The prevalence and associated factors of latent thyroid autoimmunity were determined in a sample of Colombian population. The results from the present study will facilitate the implementation of screening strategies in order to provide timely diagnosis and treatment. For now, there is still a lack of genetic studies that proffer in the genetic cause of AITD. The study of exposures evaluated in this study was carried out through a questionnaire. In that sense, it is necessary to study this type of exposition through the analysis of exposome.

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Conflict of interest

None.

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References

[1] L. Chaker, A.C. Bianco, J. Jonklaas, R.P. Peeters, Hypothyroidism, Lancet 390 (2017) 1550–1562, https://doi.org/10.1016/S0140-6736(17)30703-1.

[2] L.H. Duntas, Thyroid disease and lipids, Thyroid 12 (2002) 287–293, https://doi.org/10.1089/10507250252949405.

[3] A.R. Cappola, P.W. Ladenson, Hypothyroidism and atherosclerosis, J. Clin. Endocrinol. Metab. 88 (2003) 2438–2444, https://doi.org/10.1210/jc.2003-030398.

[4] J.V. Parle, P. Maisonneuve, M.C. Sheppard, P. Boyle, J.A. Franklyn, Prediction of all-cause and cardiovascular mortality in elderly people from one low serum thyrotropin result: a 10-year cohort study, Lancet 358 (2001) 861–865, https://doi.org/10.1016/S0140-6736(01)06067-6.

[5] S. De Leo, S.Y. Lee, L.E. Braverman, Hyperthyroidism, Lancet 388 (2016) 906–918, https://doi.org/10.1016/S0140-6736(16)00278-6.

[6] A. Garmendia Madariaga, S. Santos Palacios, F. Guillén-Grima, J.C. Galofré, The incidence and prevalence of thyroid dysfunction in Europe: a meta-analysis, J. Clin. Endocrinol. Metab. 99 (2014) 923–931, https://doi.org/10.1210/jc.2013-2409.

[7] J.G. Hollowell, N.W. Staehling, W.D. Flanders, W.H. Hannon, E.W. Gunter, C.A. Spencer, L.E. Braverman, Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): national health and nutrition examination survey (NHANES III), J. Clin. Endocrinol. Metab. 87 (2002) 489–499, https://doi.org/10.1210/jcem.87.2.8182.

[8] D.L. Jacobson, S.J. Gange, N.R. Rose, N.M.H. Graham, Epidemiology and estimated population burden of selected autoimmune diseases in the United States, Clin. Immunol. Immunopathol. 84 (1997) 223–243, https://doi.org/10.1006/clin.1997.4412.

[9] S.H.S. Pearce, N.J. Leech, Toward precise forecasting of autoimmune endocrinopathy, J. Clin. Endocrinol. Metab. 89 (2004) 544–547, https://doi.org/10.1210/jc.2003-032142.

[10] K. Zöphel, B. Saller, G. Wunderlich, T. Grüning, R. Koch, J. Wilde, K. Mann, W.-G. Franke, Autoantibodies to thyroperoxidase (TPOAb) in a large population of euthyroid subjects: implications for the definition of TPOAb reference intervals, Clin. Lab. 49 (2003) 591–600. http://www.ncbi.nlm.nih.gov/pubmed/14651330.

[11] M.P. Vanderpump, W.M. Tunbridge, J.M. French, D. Appleton, D. Bates, F. Clark, J. Grimley Evans, D.M. Hasan, H. Rodgers, F. Tunbridge, The incidence of thyroid disorders in the community: a twenty-year follow-up of the whickham survey, Clin. Endocrinol. (Oxf.) 43 (1995) 55–68, https://doi.org/10.1111/j.1365-2265.1995.tb01894.x.

[12] N. Konno, K. Yuri, H. Taguchi, K. Miura, S. Taguchi, K. Hagiwara, S. Murakami, Screening for thyroid diseases in an iodine sufficient area with sensitive thyrotrophin assays, and serum thyroid autoantibody and urinary iodide determinations, Clin. Endocrinol. (Oxf). 38 (1993) 273–281, https://doi.org/10.1111/j.1365-2265.1993.tb01006.x.

[13] L.M. Prentice, D.I. Phillips, D. Sarsero, K. Beever, S.M. McLachlan, B.R. Smith, Geographical distribution of subclinical autoimmune thyroid disease in Britain: a study using highly sensitive direct assays for autoantibodies to thyroglobulin and thyroid peroxidase, Acta Endocrinol. (Copenh). 123 (1990) 493–498, https://doi.org/10.1530/acta.0.1230493.

[14] T. Bjoro, J. Holmen, O. Krüger, K. Midthjell, K. Hunstad, T. Schreiner, L. Sandnes, H. Brochmann, Prevalence of thyroid disease, thyroid dysfunction and thyroid peroxidase antibodies in a large, unselected population. The Health Study of Nord-Trondelag (HUNT), Eur. J. Endocrinol. 143 (2000) 639–647, https://doi.org/10.1530/eje.0.1430639.

[15] I.B. Pedersen, N. Knudsen, T. Jørgensen, H. Perrild, L. Ovesen, P. Laurberg, Thyroid peroxidase and thyroglobulin autoantibodies in a large survey of populations with mild and moderate iodine deficiency, Clin. Endocrinol. (Oxf.) 58 (2003) 36–42, https://doi.org/10.1046/j.1365-2265.2003.01633.x.

[16] W.M. Tunbridge, D.C. Evered, R. Hall, D. Appleton, M. Brewis, F. Clark, J.G. Evans, E. Young, T. Bird, P.A. Smith, The spectrum of thyroid disease in a community: the Whickham survey, Clin. Endocrinol. (Oxf.) 7 (1977) 481–493, https://doi.org/10.1111/j.1365-2265.1977.tb01340.x.

[17] Y. Li, D. Teng, Z. Shan, X. Teng, H. Guan, X. Yu, C. Fan, W. Chong, F. Yang, H. Dai, X. Gu, Y. Yu, J. Mao, D. Zhao, J. Li, Y. Chen, R. Yang, C. Li, W. Teng, Antithyroperoxidase and antithyroglobulin antibodies in a five-year follow-up survey of populations with different iodine intakes, J. Clin. Endocrinol. Metab. 93 (2008) 1751–1757, https://doi.org/10.1210/jc.2007-2368.

[18] J.-J. Sheu, J.-H. Kang, H.-C. Lin, H.-C. Lin, Hyperthyroidism and risk of ischemic stroke in young adults: a 5-year follow-up study, Stroke 41 (2010) 961–966, https://doi.org/10.1161/STROKEAHA.109.577742.

[19] D.S. Ross, R.M. Neer, E.C. Ridgway, G.H. Daniels, Subclinical hyperthyroidism and reduced bone density as a possible result of prolonged suppression of the pituitary-thyroid axis with L-thyroxine, Am. J. Med. 82 (1987) 1167–1170, https://doi.org/10.1016/0002-9343(87)90219-1.

[20] J.-S. Franco, J. Amaya-Amaya, N. Molano-González, J. Caro-Moreno, M. Rodríguez-Jiménez, Y. Acosta-Ampudia, R.D. Mantilla, A. Rojas-Villarraga, J.-M. Anaya, Autoimmune thyroid disease in Colombian patients with systemic lupus erythematosus, Clin. Endocrinol. (Oxf.) 83 (2015) 943–950, https://doi.org/10.1111/cen.12662.

[21] J.-M. Anaya, The autoimmune tautology. A summary of evidence, Jt. Bone Spine 84 (2017) 251–253, https://doi.org/10.1016/j.jbspin.2016.11.012.

[22] S. Mariotti, P. Sansoni, G. Barbesino, P. Caturegli, D. Monti, A. Cossarizza, T. Giacomelli, G. Passeri, U. Fagiolo, A. Pinchera, Thyroid and other organ-specific autoantibodies in healthy centenarians, Lancet (London, England) 339 (1992) 1506–1508, https://doi.org/10.1016/0140-6736(92)91265-a.

[23] G.A. Brent, Environmental exposures and autoimmune thyroid disease, Thyroid 20 (2010) 755–761, https://doi.org/10.1089/thy.2010.1636.

[24] J.-S. Franco, N. Molano-González, M. Rodríguez-Jiménez, Y. Acosta-Ampudia, R.D. Mantilla, J. Amaya-Amaya, A. Rojas-Villarraga, J.-M. Anaya, The coexistence of antiphospholipid syndrome and systemic lupus erythematosus in Colombians, PLoS One 9 (2014), e110242, https://doi.org/10.1371/journal.pone.0110242.

[25] D. Vásquez-Awad, C.A. Cano-Gutiérrez, A. Gómez-Ortiz, M. Ángel González, R. Guzmán-Moreno, J.I. Martínez-Reyes, O. Rosero-Olarte, C. Rueda-Beltz, J.L. Acosta-Reyes, Vitamina D. Consenso colombiano de expertos, Rev. Med. 39 (2017) 140–157.

[26] J.-M. Anaya, P. Restrepo-Jiménez, Y. Rodríguez, M. Rodríguez-Jiménez, Y. Acosta-Ampudia, D.M. Monsalve, Y. Pacheco, C. Ramírez-Santana, N. Molano-González, R.D. Mantilla, Sjögren's syndrome and autoimmune thyroid disease: two sides of the same coin, Clin. Rev. Allergy Immunol. 56 (2019) 362–374, https://doi.org/10.1007/s12016-018-8709-9.

[27] M. Rojas, Y. Rodriguez, Y. Pacheco, E. Zapata, D.M. Monsalve, R.D. Mantilla, M. Rodríguez-Jimenez, C. Ramírez-Santana, N. Molano-González, J.-M. Anaya, Resilience in women with autoimmune rheumatic diseases, Jt. Bone Spine 85 (2018) 715–720, https://doi.org/10.1016/j.jbspin.2017.12.012.

[28] W.M. Tunbridge, M. Brewis, J.M. French, D. Appleton, T. Bird, F. Clark, D.C. Evered, J.G. Evans, R. Hall, P. Smith, J. Stephenson, E. Young, Natural history of autoimmune thyroiditis, Br. Med. J. 282 (1981) 258–262.

[29] A. Roos, T.P. Links, L.T.W. de Jong-van den Berg, R.O.B. Gans, B.H.R. Wolffenbuttel, S.J.L. Bakker, Thyroid peroxidase antibodies, levels of thyroid stimulating hormone and development of hypothyroidism in euthyroid subjects, Eur. J. Intern. Med. 21 (2010) 555–559, https://doi.org/10.1016/j.ejim.2010.09.001.

[30] C.L. Burek, N.R. Rose, K.E. Guire, W.H. Hoffman, Thyroid autoantibodies in black and in white children and adolescents with type 1 diabetes mellitus and their first degree relatives, Autoimmunity 7 (1990) 157–167, https://doi.org/10.3109/08916939008993388.

[31] D.S.A. McLeod, P. Caturegli, D.S. Cooper, P.G. Matos, S. Hutfless, Variation in rates of autoimmune thyroid disease by race/ethnicity in US military personnel, J. Am. Med. Assoc. 311 (2014) 1563–1565, https://doi.org/10.1001/jama.2013.285606.

[32] Y. Tomer, Y. Ban, E. Concepcion, G. Barbesino, R. Villanueva, D.A. Greenberg, T.F. Davies, Common and unique susceptibility loci in Graves and Hashimoto diseases: results of whole-genome screening in a data set of 102 multiplex families, Am. J. Hum. Genet. 73 (2003) 736–747, https://doi.org/10.1086/378588.

[33] K. Sakai, S. Shirasawa, N. Ishikawa, K. Ito, H. Tamai, K. Kuma, T. Akamizu, M. Tanimura, K. Furugaki, K. Yamamoto, T. Sasazuki, Identification of susceptibility loci for autoimmune thyroid disease to 5q31-q33 and Hashimoto's thyroiditis to 8q23-q24 by multipoint affected sib-pair linkage analysis in Japanese, Hum. Mol. Genet. 10 (2001) 1379–1386, https://doi.org/10.1093/hmg/10.13.1379.

[34] Y. Tomer, D.A. Greenberg, E. Concepcion, Y. Ban, T.F. Davies, Thyroglobulin is a thyroid specific gene for the familial autoimmune thyroid diseases, J. Clin. Endocrinol. Metab. 87 (2002) 404–407, https://doi.org/10.1210/jcem.87.1.8291.

[35] P. Vestergaard, Smoking and thyroid disorders-a meta-analysis, Eur. J. Endocrinol. 146 (2002) 153–161, https://doi.org/10.1530/eje.0.1460153.

[36] A. Carlé, I. Bülow Pedersen, N. Knudsen, H. Perrild, L. Ovesen, L. Banke Rasmussen, T. Jørgensen, P. Laurberg, Smoking cessation is followed by a sharp but transient rise in the incidence of overt autoimmune hypothyroidism - a population-based, case-control study, Clin. Endocrinol. (Oxf.) 77 (2012) 764–772, https://doi.org/10.1111/j.1365-2265.2012.04455.x.

[37] R.M. Belin, B.C. Astor, N.R. Powe, P.W. Ladenson, Smoke exposure is associated with a lower prevalence of serum thyroid autoantibodies and thyrotropin concentration elevation and a higher prevalence of mild thyrotropin concentration suppression in the third National Health and Nutrition Examination Surve, J. Clin. Endocrinol. Metab. 89 (2004) 6077–6086, https://doi.org/10.1210/jc.2004-0431.

[38] K.J. Tracey, Physiology and immunology of the cholinergic antiinflammatory pathway, J. Clin. Investig. 117 (2007) 289–296, https://doi.org/10.1172/JCI30555.

[39] M. Bencherif, P.M. Lippiello, R. Lucas, M.B. Marrero, Alpha7 nicotinic receptors as novel therapeutic targets for inflammation-based diseases, Cell. Mol. Life Sci. 68 (2011) 931–949, https://doi.org/10.1007/s00018-010-0525-1.

[40] I.B. Karaconji, Facts about nicotine toxicity, Arh. Hig. Rada. Toksikol. 56 (2005) 363–371. http://www.ncbi.nlm.nih.gov/pubmed/16370520.

[41] N.L. Benowitz, Nicotine addiction, N. Engl. J. Med. 362 (2010) 2295–2303, https://doi.org/10.1056/NEJMra0809890.

[42] P. Caturegli, A. De Remigis, M. Ferlito, M.A. Landek-Salgado, S. Iwama, S.-C. Tzou, P.W. Ladenson, Anatabine ameliorates experimental autoimmune thyroiditis, Endocrinology 153 (2012) 4580–4587, https://doi.org/10.1210/en.2012-1452.

[43] L.R. Schmeltz, T.C. Blevins, S.L. Aronoff, K. Ozer, J.D. Leffert, M.A. Goldberg, B.S. Horowitz, R.H. Bertenshaw, P. Troya, A.E. Cohen, R.K. Lanier, C. Wright, Anatabine supplementation decreases thyroglobulin antibodies in patients with chronic lymphocytic autoimmune (Hashimoto's) thyroiditis: a randomized controlled clinical trial, J. Clin. Endocrinol. Metab. 99 (2014) E137–E142, https://doi.org/10.1210/jc.2013-2951.

[44] E.N. Pearce, L.E. Braverman, Environmental pollutants and the thyroid, Best Pract. Res. Clin. Endocrinol. Metabol. 23 (2009) 801–813, https://doi.org/10.1016/j.beem.2009.06.003.

[45] W. Dankers, E.M. Colin, J.P. van Hamburg, E. Lubberts, Vitamin D in autoimmunity: molecular mechanisms and therapeutic potential, Front. Immunol. 7 (2016) 697, https://doi.org/10.3389/fimmu.2016.00697.

[46] E.E. Mazokopakis, D.A. Kotsiris, Hashimoto's autoimmune thyroiditis and vitamin D deficiency. Current aspects, Hellenic J. Nucl. Med. 17 (2014) 37–40, https://doi.org/10.1967/s002449910120.

[47] A. Misharin, M. Hewison, C.-R. Chen, V. Lagishetty, H.A. Aliesky, Y. Mizutori, B. Rapoport, S.M. McLachlan, Vitamin D deficiency modulates Graves' hyperthyroidism induced in BALB/c mice by thyrotropin receptor immunization, Endocrinology 150 (2009) 1051–1060, https://doi.org/10.1210/en.2008-1191.

[48] P. Welsh, M.J.L. Peters, N. Sattar, Vitamin D insufficiency, N. Engl. J. Med. 364 (2011), https://doi.org/10.1056/NEJMc1101911, 1378–9; author reply 1380.

[49] M. Clozel, C.L. Branchaud, G.S. Tannenbaum, J.H. Dussault, J.V. Aranda, Effect of caffeine on thyroid and pituitary function in newborn rats, Pediatr. Res. 17 (1983) 592–595, https://doi.org/10.1203/00006450-198307000-00015.

[50] E. Spindel, M. Arnold, B. Cusack, R.J. Wurtman, Effects of caffeine on anterior pituitary and thyroid function in the rat, J. Pharmacol. Exp. Ther. 214 (1980) 58–62. http://www.ncbi.nlm.nih.gov/pubmed/6104718.

[51] M. Medici, E. Porcu, G. Pistis, A. Teumer, S.J. Brown, R.A. Jensen, R. Rawal, G.L. Roef, T.S. Plantinga, S.H. Vermeulen, J. Lahti, M.J. Simmonds, L.L.N. Husemoen, R.M. Freathy, B.M. Shields, D. Pietzner, R. Nagy, L. Broer, L. Chaker, T.I.M. Korevaar, M.G. Plia, C. Sala, U. Völker, J.B. Richards, F.C. Sweep, C. Gieger, T. Corre, E. Kajantie, B. Thuesen, Y.E. Taes, W.E. Visser, A.T. Hattersley, J. Kratzsch, A. Hamilton, W. Li, G. Homuth, M. Lobina, S. Mariotti, N. Soranzo, M. Cocca, M. Nauck, C. Spielhagen, A. Ross, A. Arnold, M. van de Bunt, S. Liyanarachchi, M. Heier, H.J. Grabe, C. Masciullo, T.E. Galesloot, E.M. Lim, E. Reischl, P.J. Leedman, S. Lai, A. Delitala, A.P. Bremner, D.I.W. Philips, J.P. Beilby, A. Mulas, M. Vocale, G. Abecasis, T. Forsen, A. James, E. Widen, J. Hui, H. Prokisch, E.E. Rietzschel, A. Palotie, P. Feddema, S.J. Fletcher, K. Schramm, J.I. Rotter, A. Kluttig, D. Radke, M. Traglia, G.L. Surdulescu, H. He, J.A. Franklyn, D. Tiller, B. Vaidya, T. de Meyer, T. Jørgensen, J.G. Eriksson, P.C. O'Leary, E. Wichmann, A.R. Hermus, B.M. Psaty, T. Ittermann, A. Hofman, E. Bosi, D. Schlessinger, H. Wallaschofski, N. Pirastu, Y.S. Aulchenko, A. de la Chapelle, R.T. Netea-Maier, S.C.L. Gough, H. Meyer Zu Schwabedissen, T.M. Frayling, J.-M. Kaufman, A. Linneberg, K. Räikkönen, J.W.A. Smit, L.A. Kiemeney, F. Rivadeneira, A.G. Uitterlinden, J.P. Walsh, C. Meisinger, M. den Heijer, T.J. Visser, T.D. Spector, S.G. Wilson, H. Völzke, A. Cappola, D. Toniolo, S. Sanna, S. Naitza, R.P. Peeters, Identification of novel genetic Loci associated with thyroid peroxidase antibodies and clinical thyroid disease, PLoS Genet. 10 (2014), e1004123, https://doi.org/10.1371/journal.pgen.1004123.