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META-ANALYSIS

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Association between vitamin D receptor gene polymorphisms and Graves' disease: a systematic review and meta-analysis

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Abstract

Purpose The pathogenesis of Graves' disease (GD) and orbitopathy (GO) is not completely elucidated. On the other hand, vitamin D receptor (VDR) gene polymorphisms have been associated with vulnerability to a plethora of chronic autoimmune diseases. The primary aim of this study was to synthesize evidence on the association between VDR gene polymorphisms and GD. Secondary aim was to investigate their association with GO.

Methods A comprehensive search was conducted in PubMed, CENTRAL and Scopus, up to December 8, 2018. Data were expressed as odds ratio (OR) with 95% confidence intervals (CI). Heterogeneity was quantified with I^2 index.

Results Ten studies were included in the qualitative and quantitative analysis. TT subtype of TaqI polymorphism was associated with an increased risk of GD compared with Tt and tt polymorphisms (OR: 1.42; 95% CI, 1.05–1.94, $p = 0.025$), whereas tt was associated with a lower risk of GD, compared with TT and Tt polymorphisms (OR: 0.79; 95% CI, 0.62-0.99, $p = 0.043$). No association was found for ApaI, BsmI, and FokI polymorphisms. The bb subtype of BsmI polymorphism was associated with a lower risk in Asian, but with a higher GD risk in Caucasian populations, compared with BB/Bb subtypes. No eligible study was found regarding the association between VDR gene polymorphisms and the risk of GO.

Conclusions The TT subtype of the TaqI polymorphism was associated with a higher susceptibility for GD compared with Tt and tt. Regarding BsmI, the bb subtype was associated with increased GD risk in Caucasians, whereas it is protective in Asians.

Keywords Vitamin D receptor · VDR · Gene · Polymorphisms · Graves' disease

Introduction

Graves' disease (GD) is an autoimmune thyroid disorder, constituting the most common cause of hyperthyroidism. It usually affects women between ages 30 and 50 [1, 2]. GD hyperthyroidism is caused by autoantibodies that bind to thyroid-stimulating hormone (TSH) receptor (TSHR) and lead to stimulation of the thyroid gland [3]. The pathogenesis of GD has not been completely clarified, but it is known that both genetic and environmental factors contribute to the susceptibility for developing GD [4]. With regard to predisposition to GD, several genes may be implicated, such as the immune regulatory genes: human leukocyte antigen-D related (*HLA-DR*), cluster of differentiation 40 (*CD40*), cytotoxic T-lymphocyte associated protein 4 (*CTLA-4*), protein tyrosine phosphatase non-receptor type 22 (*PTPN22*), interleukin-2 receptor alpha chain (*CD25*), as well as thyroid-specific genes, such as *TSHR* and thyroglobulin (*TG*) [5, 6]. The same mechanisms may potentially be implicated in the pathogenesis Graves's orbitopathy (GO), which affects about one-fourth of patients with GD, significantly impairing their quality of life [7].

Vitamin D seems to exert various extraskeletal actions, except for its well-documented role in bone metabolism. One of these effects is implicated in immune system

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functions [8]. More specifically, vitamin D receptor (VDR) is expressed in blood B- and T-lymphocytes, as well as in dendritic cells and macrophages [9]. Dendritic cells differentiated in vitro from monocytes remain in an immature state, in the presence of the active metabolite of vitamin D, the 1,25-dihydroxy-vitamin D3 [1,25$(OH)_2D_3$]. This immature state of dendritic cells is characterized by immunological tolerance [9]. As a result, the levels of pro-inflammatory factors, such as interleukin-12 (IL-12) and tumor-necrosis-factor alpha (TNF-α) decrease, in contrast to the increased concentrations of the anti-inflammatory cytokine, interleukin 10 (IL-10) [9]. Furthermore, similar effects of vitamin D have been observed in macrophages [9]. In addition, vitamin D interferes with B-cell differentiation and decreases antibody production [10]. VDR is expressed in various T-cell populations, including $CD4^+$ Th cells, $CD8^+$ cytotoxic T cells, and T-cell receptor-γδ (TCR-γδ) cells. The effects of 1,25$(OH)_2D_3$ on T cells include also the modulation of cytokine secretion and differentiation. This active form of vitamin D could suppress the production of inflammatory cytokines by several T-cell populations [9–11].

On a clinical basis, vitamin D deficiency has been associated with various chronic autoimmune diseases, such as rheumatoid arthritis, multiple sclerosis and type I diabetes mellitus [12]. Numerous studies have also demonstrated an association between vitamin D deficiency and GD [13–15]. Interestingly, several polymorphisms of the VDR gene, such asBsmI (rs1544410), ApaI (rs7975232), TaqI (rs731236), and FokI (rs10735810), may be associated with the development of GD, with a variable degree of susceptibility in different ethnic populations [6, 16, 17]. However, some studies found no association at all [4, 17].

The primary question was as follows: is there any association between VDR polymorphisms and the risk of GD? Secondary question was as follows: is there any association between VDR polymorphisms and the risk of GO?

Subjects and methods

Guidelines followed

This systematic review followed the MOOSE (Meta-analyses Of Observational Studies in Epidemiology) guidelines [18]. A flow diagram is shown in Fig. 1. A completed MOOSE checklist has been submitted as Supplementary Table 1.

Search strategy

The following PICO (Population, Intervention or exposure, Comparison, Outcome) elements were applied as inclusion criteria for the systematic review: (i) Population: general population; (ii) Intervention: specific VDR gene polymorphisms (ApaI, BsmI, TaqI, FoqI) positive; (iii) Comparison group: specific VDR polymorphisms (ApaI, BsmI, TaqI, FoqI) negative; (iv) Outcome: GD or GO. A systematic literature search for English publications through PubMed (Medline), Scopus and Cochrane databases was performed, up to December 8, 2018. The following search-string was used for PubMed, with specific modifications for the databases as required: (“receptors, calcitriol”[mh] OR ((“Vitamin D”[tiab] OR calcitriol[tiab] OR cholecalciferol [tiab]) AND (receptor[tiab])) OR (VDR[tiab])) AND (polymorphism[tiab] OR polymorphisms[tiab] OR pleomorphism[tiab] OR gene[tiab] OR genes[tiab])) AND ((“Graves disease”[mh] OR Hyperthyroidism[mh] OR thyrotoxicosis[mh]) OR (Graves[tiab] OR Hyperthyroidism [tiab] OR thyrotoxicosis[tiab] OR “thyroid eye” [tiab])) NOT (Animal[mesh] NOT Human[mesh])”.

All studies that met the inclusion criteria were retrieved. Review articles and case reports were excluded. Furthermore, the references in all selected studies were manually searched to identify additional eligible trials. The main search was completed independently by two investigators (SV and AMA), who checked all the available articles. Any

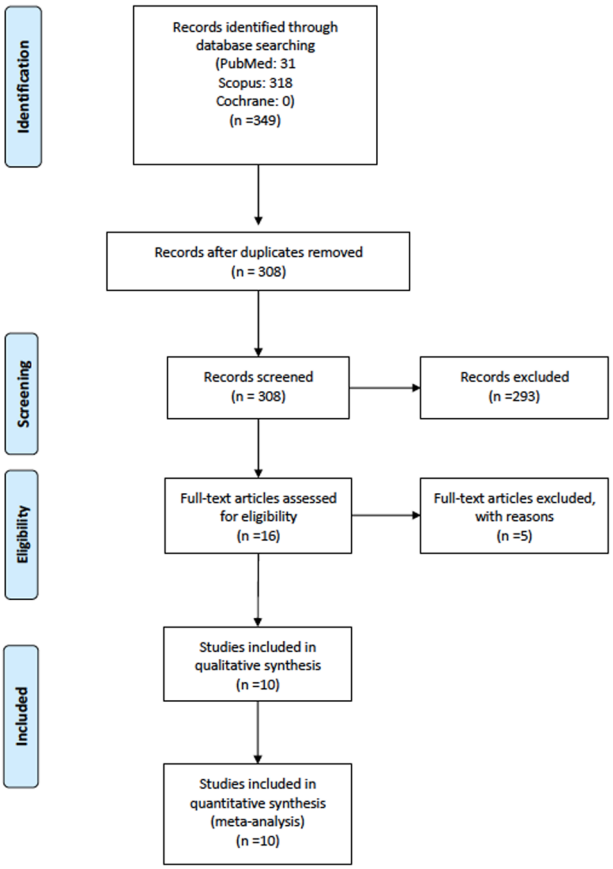

Fig. 1 Flowchart diagram

Table 1 Demographic characteristics of studies included in the analysis

ID	First author/year of publication	Country	Study design	Graves'	Controls	Race	Mean age Graves'	Mean age controls	Genotyping method	Polymorphisms
1	Meng/2015	China	Case-control	417	301	Asian	34.4 ± 13.9	33.60 ± 12.64	MALDI-TOF-MS	ApaI, BsmI, FokI, TaqI
2	Inoue/2014	Japan	Case-control	139	76	Asian	N/A	28.9 ± 11.0	PCR-RFLP	ApaI, BsmI, FokI, TaqI
3	Gawad/2012	Egypt	Case-control	90	55	African	38.0 ± 5.0	26-54	PCR-RFLP	ApaI, BsmI, TaqI
4	Horst- Sikorska/2008	Poland	Case-control	75	163	Caucasian	37.0 ± 3.8	65.0 ± 7.0	PCR-RFLP	ApaI, BsmI, FokI, TaqI
5	Chen/2007	Taiwan	Case-control	88	90	Asian	35.5 ± 10.6	N/A	PCR-RFLP	FokI
6	Ramos-Lopez/2005	Germany-Poland-Serbia	Case-control	789	823	Caucasian	N/A	N/A	PCR-RFLP	ApaI, BsmI, FokI, TaqI
7	Stefanić/2005	Croatia	Case-control	110	99	Caucasian	39.9 ± 12.7	36.0 ± 16.5	PCR-RFLP	ApaI, BsmI, TaqI
8	Collins/2004	UK	Case-control	768	864	Caucasian	N/A	N/A	PCR-RFLP	ApaI, BsmI, FokI, TaqI
9	Ban/2000	Japan	Case-control	180	195	Asian	N/A	N/A	PCR-RFLP	ApaI, BsmI, FokI
10	Ban/2000	Japan	Case-control	131	150	Asian	25-78	27-65	PCR-RFLP	FokI

N/A non-available, *PCR-RFLP* polymerase chain reaction–restriction fragment length polymorphism, *MALDI-TOF-MS* matrix assisted laser desorption ionization-time of flight mass spectrometer

discrepancy was resolved by consultation of a third investigator, not involved in the initial procedure (PA). We used the *EndNote V8* as our search software.

Trial selection

Inclusion criteria were as follows: (i) Case-control studies including patients with GD and apparently healthy individual controls; (ii) Studies providing extractable data on genotypic frequencies of ApaI, BsmI, FokI, and TaqI VDR polymorphisms in patients with GD and controls; (iii) Proper criteria for GD and GO diagnosis.

Data extraction

The following data from eligible studies were extracted by two independent researchers (SV, AMA) and recorded: (i) first author; (ii) year of publication; (iii) country in which the study was conducted; (iv) Study design (case-control or cohort); (v) Race of participants; (vi) Total number of participants; (vii) Number of cases with AA, Aa, and aa polymorphism of the *ApaI* gene; (viii) Number of controls with AA, Aa, and aa polymorphism of the *ApaI* gene; (ix) Number of patients with BB, Bb, and bb polymorphisms of the *BsmI* gene; (x) Number of controls with BB, Bb, and bb polymorphisms of the *BsmI* gene; (xi) Number of cases with FF, Ff, and ff polymorphisms of the *FoqI* gene; (xii) Number of controls with FF, Ff, and ff polymorphisms of the *FoqI* gene; (xiii) Number of patients with TT, Tt, and tt polymorphisms of *TaqI* gene; (xiv) Number of controls with TT, Tt, and tt polymorphisms of *TaqI* gene; (xv) Number of cases with GD; (xvi) Number of cases with GO; (xvii) Number of controls.

From these data (vii–xvii), odds ratios (OR) for the presence of each polymorphism and GD susceptibility were calculated. Parameters, such as mean age of the participants, gender distribution and ethnicity, were also recorded, where available. The following comparisons were made: (i) subjects with AA genotype were compared with those with Aa or aa genotype; (ii) subjects with BB genotype were compared with those with Bb or bb genotype; (iii) subjects with FF genotype were compared with those with Ff or ff genotype; and (iv) subjects with TT genotype were compared with those with Tt or tt genotype with respect to GD or GO diagnosis.

Risk of bias and study quality assessment

Each eligible study was assessed by Newcastle Ottawa scale (NOS). NOS is an instrument which is used in evaluating the quality and reliability of non-randomized studies included in a systematic review [19]. NOS evaluates studies based on three criteria: (i) participant selection;

(ii) comparability of study groups; and (iii) assessment of outcome or exposure. Every study can be awarded with maximum of four stars for selection category, maximum of two stars for comparability and maximum of three stars for outcome/exposure category. Finally, each study is characterized as good, fair or poor according to the number of obtained stars [19]. Data on bias assessment by NOS are presented in Supplementary Table 2.

Statistical methods

Random effects model was used for data synthesis (Mantel/Haenszel model) since significant heterogeneity was present among studies. Associations were reported as OR with 95% confidence intervals (CI). A p-value < 0.05 was considered as statistically significant. Heterogeneity was tested with the Cochrane chi-square test and the degree of heterogeneity was quantified by the I^2 statistics. Moderate heterogeneity was defined as moderate, if I^2 was 30–60%, whereas high degree of heterogeneity was considered for I^2 values > 60%. Publication bias was formally tested with the Begg-Mazumdar test and the Egger's test (with p-values > 0.1 indicating the absence of publication bias). To further explain the heterogeneity among studies, sensitivity analysis, subgroup analysis and meta-regression were performed. Sensitivity analysis (by the use of random effects model) was used to locate outliers, defined as studies that had large residuals ($|z| > 2$). Subgroup (stratified) analysis (by the use of random effects model) was performed for ethnicity, as a categorical variable, since it was anticipated that it could have a significant effect on the main outcome. Numerical (age) and categorical (gender) parameters were planned to be used as predictors of GD incidence (meta-regression by the use of random effects model). All analyses were done with the software *Comprehensive MetaAnalysis V2*.

Results

Systematic review

Our initial search yielded 349 results. After removal of duplicates, 308 studies were reviewed by title and abstract. Of those, 16 full-text articles were assessed for eligibility. Five of them were excluded for various reasons: (i) not answering research question ($n = 1$); (ii) improper study design (family-based study) ($n = 2$); (iii) no data available for statistical analysis ($n = 1$); and (iv) no specific data only on GD ($n = 1$). The excluded studies and the reason for this are presented in Supplementary Table 3. Eventually, ten studies were included in the qualitative and quantitative analysis (Fig. 1).

The characteristics of the studies and their participants are presented in Table 1. The included studies were published between 2000 and 2015. One study was conducted in China, three in Japan, one in Egypt, one in Poland, one in Taiwan, one in Croatia, one in UK, and one study was conducted in three countries (Germany, Poland, and Serbia). The number of participants in each study ranged from 145 to 1632. A total number of 5466 participants were included (2752 cases and 2714 controls). The mean age of the participants was 39.3 ± 16.3 years (data from three studies). With regard to gender, most studies did not provide adequate data for meta-analysis. Data regarding smoking status and levels of thyroid-stimulating immunoglobulin (TSI) antibodies were not available.

Primary aim: comparison between subjects according to the risk of GD

Comparison according to TaqI polymorphisms

Seven studies provided data on TaqI polymorphism. A total of 2380 cases and 2235 controls included in quantitative analysis. TT subtype of TaqI polymorphism was associated with an increased risk of GD (OR for the comparison of TT with Tt and tt subtypes: 1.42; 95% CI, 1.05–1.94, $p = 0.025$) (Fig. 2). On the other hand, the tt polymorphism was associated with a lower risk of GD, compared with TT and Tt subtypes (OR: 0.79; 95% CI, 0.62–0.99, $p = 0.043$) (Fig. 3).

Comparison according to ApaI polymorphisms

Eight studies provided data on ApaI polymorphism. A total of 2533 cases and 2474 controls were included in the quantitative analysis. No significant association was observed between ApaI polymorphism and GD occurrence. In detail, the ORs for the comparison of AA with Aa plus aa, Aa with AA plus aa, and aa with AA plus Aa subtypes were 0.82 (95% CI, 0.57–1.19, $p = 0.302$), 0.97 (95% CI, 0.86–1.08, $p = 0.544$) and 1.19 (95% CI, 0.9–1.58, $p = 0.213$), respectively.

Comparison according to BsmI polymorphisms

Eight studies provided data on BsmI polymorphism. A total of 2536 cases and 2576 controls were included in the quantitative analysis. No association between BsmI polymorphism and GD was found. In particular, the OR for the comparison of BB with bb and Bb subtypes was 0.75 (95% CI, 0.5–1.11, $p = 0.148$), whereas for the comparison between Bb and BB plus bb subtypes was 1.01 (95% CI, 0.84–1.23, $p = 0.888$). When bb was compared with BB plus Bb, the OR was 1.12 (95% CI, 0.83–1.51, $p = 0.473$).

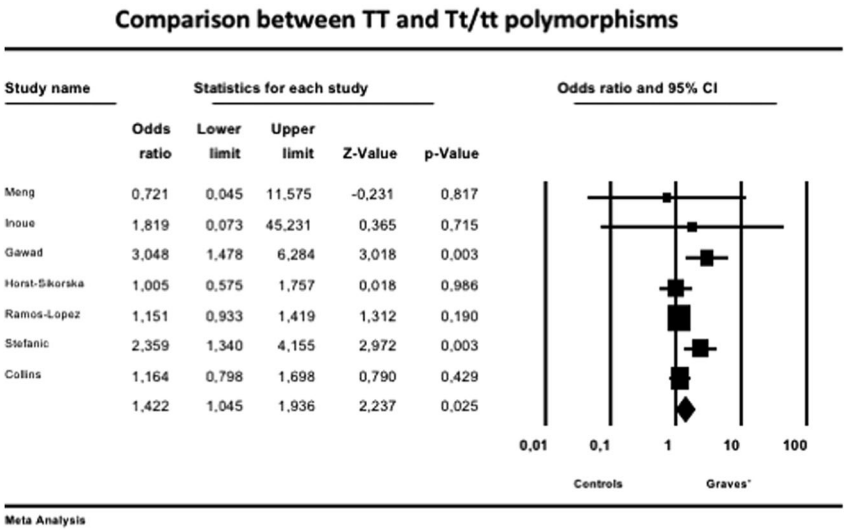

Fig. 2 Forest plot for the comparison of TT with Tt/tt polymorphisms

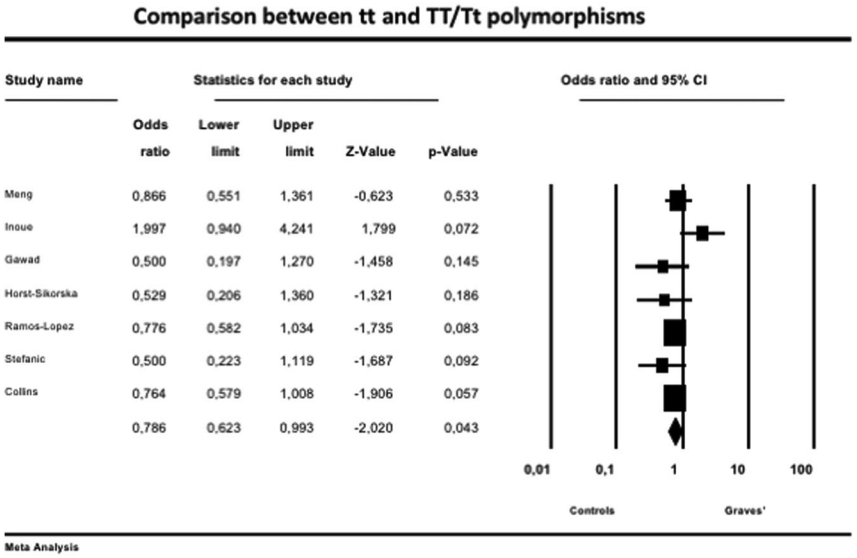

Fig. 3 Forest plot for the comparison of tt with TT/Tt polymorphisms

Comparison according to FoqI polymorphisms

Eight studies provided data on FoqI polymorphism. A total of 2587 cases and 2603 controls were included in the quantitative analysis. No association was found between FoqI polymorphism and GD prevalence. The ORs for the comparison of FF with Ff/ff subtypes were 1.16 (95% CI, 0.93–1.44, $p = 0.189$), 0.9 (95% CI, 0.76–1.08, $p = 0.260$) for the comparison of Ff with FF plus ff and 0.95 (95% CI, 0.71–1.26, $p = 0.697$) when ff was compared with FF plus Ff subtypes.

Subgroup analysis

When subgroup analysis was conducted according to ethnicity, a significant association was found for BsmI polymorphism and GD in both Asian (OR for the comparison of bb with the combination of BB plus Bb: 0.67; 95% CI, 0.49–0.92, $p = 0.013$) and Caucasian populations (OR for bb compared with BB plus Bb: 1.31, 95% CI, 1.04–1.65, $p = 0.022$). Association was also found for TaqI polymorphism only in Caucasian population (OR for the comparison of tt with TT plus Tt: 0.74, 95% CI, 0.61–0.90, $p = 0.002$).

Secondary aim: Comparison between subjects according to the risk of GO

No eligible study was found with regard to the association between VDR gene polymorphisms and the risk of GO development.

Discussion

This study shows that TaqI polymorphism of the VDR gene is associated with the risk of developing GD. In particular, the TT subtype is associated with increased risk compared with either Tt or tt. Race seems also to modify the relationship between VDR and GD, since the bb subtype of BsmI polymorphism is associated with higher susceptibility to GD compared with Bb and BB polymorphisms in Caucasian populations, whereas it seems to play a protective role in Asians. Furthermore, the tt subtype of TaqI polymorphism appears to protect Caucasians from GD compared with TT and Tt subtypes.

The clinical implications of this study are that, in cases where VDR genotyping is feasible, the presence of the t allele (either as tt or Tt) seems to protect against the risk of GD, especially in Caucasians. This is also the case for the B allele. These data may contribute in developing predictive models of GD and further facilitate in elucidating the pathogenesis of the disease. Thus, if patient is characterized by the TT subtype (or the bb one, if he/she is of Caucasian origin), he/she may warrant a close clinical and hormonal monitoring for GD, especially in the presence of other risk factors, such as female gender, smoking, goiter or positive family history of AITD.

Three meta-analyses have been conducted so far on this topic. The first was published in 2009, including seven studies. The authors concluded that ApaI, BsmI, and FokI polymorphisms were associated with increased risk of GD in Asian but not in Caucasian populations [respective ORs: 1.31 (95% CI, 1.04–1.66, $p = 0.02$), 1.58 (95% CI, 1.13–2.22, $p = 0.007$) and 1.68 (95% CI, 1.28–2.20, $p = 0.0002$)]. It must be underlined that subgroup analysis was provided only according to ethnicity. Moreover, the sample size of this meta-analysis was relatively small and, thus, the conclusions are precarious [20]. The second meta-analysis was conducted in 2013 and studied the association of VDR polymorphisms with autoimmune thyroid disease (AITD), in general. Eight studies met the inclusion criteria. According to the results, significant association was found between BsmI [OR: 0.801 (95% CI, 0.705–0.910) for B versus b, OR: 0.526 (95% CI, 0.393–0.703) for BB versus bb) or TaqI [OR: 0.854 (95% CI, 0.757–0.963) for t versus T] polymorphism and increased AITD risk. No association was found for ApaI or FokI polymorphism [21].

Moreover, a more recent meta-analysis investigated the impact of VDR polymorphisms on AITD risk ($n = 22$ studies) [22]. The authors concluded that only TaqI and FoqI polymorphisms were associated with AITD risk. Regarding TaqI, the tt subtype was associated with a reduced risk of AITD (in general) and Hashimoto's thyroiditis (HT) [OR for tt versus TT: 0.67 (95% CI, 0.48–0.93) and 0.58 (95% CI, 0.40–0.85), respectively]. Regarding FoqI, the ff/Ff subtype was associated with a lower risk for both AITD and HT (but not for GD) compared with the FF subtype [OR: 0.71 (95% CI, 0.54–0.93) and 0.69 (95% CI, 0.50–0.97), respectively]. Subgroup analysis according to ethnicity showed significance for TaqI in Asians and Africans (in contrast to our study), and for FoqI in Asians (not in the European populations). Overall, no association between AITD and ApaI or BsmI polymorphisms was observed. Compared with BB, the bb/Bb subtype was associated with a reduced risk of AITD in European and African and with an increased risk in Asian populations. Regarding ApaI, the dominant model was associated with increased AITD risk only in Africans [22]. It must be emphasized that our meta-analysis included fewer studies ($n = 10$) because it was confined to the association of VDR polymorphisms and GD and not AITD, in general. Additional studies included in the aforementioned meta-analysis were written in Chinese language or were referring to HT.

Accumulative evidence suggests that vitamin D deficiency is associated with a higher risk of GD [23]. The active form of vitamin D exerts its biological effects through the VDR, which is expressed in various tissues and also in several immune system cells [24]. VDR consists of two main domains, the DNA-binding and the ligand-binding domain (LDB). Vitamin D binding to LDB forms the vitamin D/VDR complex, which is transferred into the nucleus and forms a heterodimer with the retinoid X receptor [25]. This heterodimer recognizes and binds, along with the transcription factor IIB (TFIIB), to a vitamin D response element, which leads to the transcriptional suppression or activation of vitamin D response genes [25].

Impaired VDR function attributed to its polymorphisms may evolve to an abnormal interaction of vitamin D with immune cells. In particular, VDR is expressed in some immune cells, such as macrophages, dendritic cells, B-lymphocytes, and T-lymphocytes. Immune cells may also express vitamin D-activating enzymes such as 1α-hydroxylase, which is produced by CYP27B1 gene expression [25]. CYP27B1 expression by monocytes/macrophages is strongly upregulated by interferon-γ, the Toll-like receptor (TLR)4-ligand LPS (lipopolysaccharides) and ligands triggering the TLR2/1-complex, such as the 19 kDa lipoprotein of Mycobacterium tuberculosis and viral infections. This explains vitamin's D potential role as an immune modulator factor [25]. This also seems to be the case for VDR

polymorphisms and GD, as indicated by the present meta-analysis. However, more studies are needed to further elucidate the underlying pathogenetic mechanisms and, more specifically to explain the diversity according to ethnicity. In any case, genetic predisposition based on VDR polymorphism, may add to what is already known with regard to an individual's risk for developing GD.

The present meta-analysis has several limitations. First, the effect of some confounding factors, such as age and gender distribution for each polymorphism, that might have interfered with our results, could not be estimated, since respective data could not be extracted by most of the included studies. Second, the number of the included studies was relatively small to perform a subgroup analysis. Third, the gene–gene and gene–environment interaction could not be estimated by available data. Fourth, it must be underlined that VDR gene has more polymorphisms than those four studied in our meta-analysis, which may also confer a predisposition to GD or GO, but available data are currently lacking. Fifth, potential heterogeneity across studies with respect to GD diagnosis should also be considered.

Conclusions

The TT subtype of the TaqI polymorphism is associated with a higher risk of GD compared with Tt and tt subtypes. Race seems to affect this relationship, since the bb subtype of BsmI polymorphism is associated with a higher susceptibility to GD compared with Bb and BB polymorphisms in Caucasian populations, whereas it seems to play a protective role in Asians. In contrast, the tt subtype of the TaqI polymorphism appears to be protective only in Caucasians, compared with TT and Tt polymorphisms. These findings and their clinical implications need to be replicated in future well-designed studies.

Author contributions S.V. searched the literature, extracted and analyzed the data and wrote the first draft of the paper with P.A., who also designed the study and resolved discrepancies regarding the quality of the studies. A.-M.A. extracted and analyzed the data. F.A., K.B., and M.K. reviewed the manuscript and provided critical scientific input.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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