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Association of vitamin D receptor TaqI and ApaI genetic polymorphisms with nephrolithiasis and end stage renal disease: a meta-analysis

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Abstract

Background: The deficiency of vitamin D receptor (VDR) or its ligand, vitamin D₃, is linked to the development of renal diseases. The TaqI (rs731236) and ApaI (rs7975232) polymorphisms of VDR gene are widely studied for their association with renal disease risk. However, studies have largely been ambiguous.

Methods: Meta-analysis was carried out to clarify the association of TaqI (2777 cases and 3522 controls) and ApaI (2440 cases and 3279 controls) polymorphisms with nephrolithiasis (NL), diabetic nephropathy (DN) and end stage renal disease (ESRD).

Results: The VDR TaqI C-allele under allele contrast was significantly associated with ESRD in both fixed effect and random effect models, and ApaI C-allele with ESRD only under fixed effect model. Cochrane Q-test showed no evidence of heterogeneity for TaqI polymorphism and a significant heterogeneity for ApaI polymorphism. No publication bias was observed for both the polymorphisms.

Conclusions: The present meta-analysis identifies TaqI and ApaI polymorphisms of VDR gene as risk factors for renal diseases.

Keywords: Vitamin D receptor gene polymorphism, End stage renal disease, Nephrolithiasis, Diabetic nephropathy, Meta-analysis

Introduction

In human skin, solar rays facilitate the formation of vitamin D₃ from 7-dehydrocholesterol. The vitamin D₃ undergoes two-step hydroxylation to form 25-hydroxy vitamin D₃ (25-OHD₃) and biologically active 1,25-dihydroxyvitamin D₃ (1,25-(OH)₂D₃) [1]. Vitamin D receptor (VDR) is a ligand-activated transcriptional factor requiring 1,25(OH)₂D₃ for its activation [2]. The deficiency of 25OHD or VDR is reported to activate renin-angiotensin system resulting in high angiotensin II levels, which damage renal parenchyma leading to

increased risk for renal disease [3]. Considering the pivotal role of VDR in maintaining normal renal function, a number of studies have explored the possibility of association of VDR gene polymorphisms with renal disease risk. Among VDR polymorphisms reported to date, ApaI, and TaqI are widely studied for their association with ESRD, NL and DN [4–6]. The ApaI variant (rs7975232), which results in A to C transition, is located in the intron 8 of VDR gene, while TaqI variant (rs731236), which results in T to C transition is located in exon 9 [7].

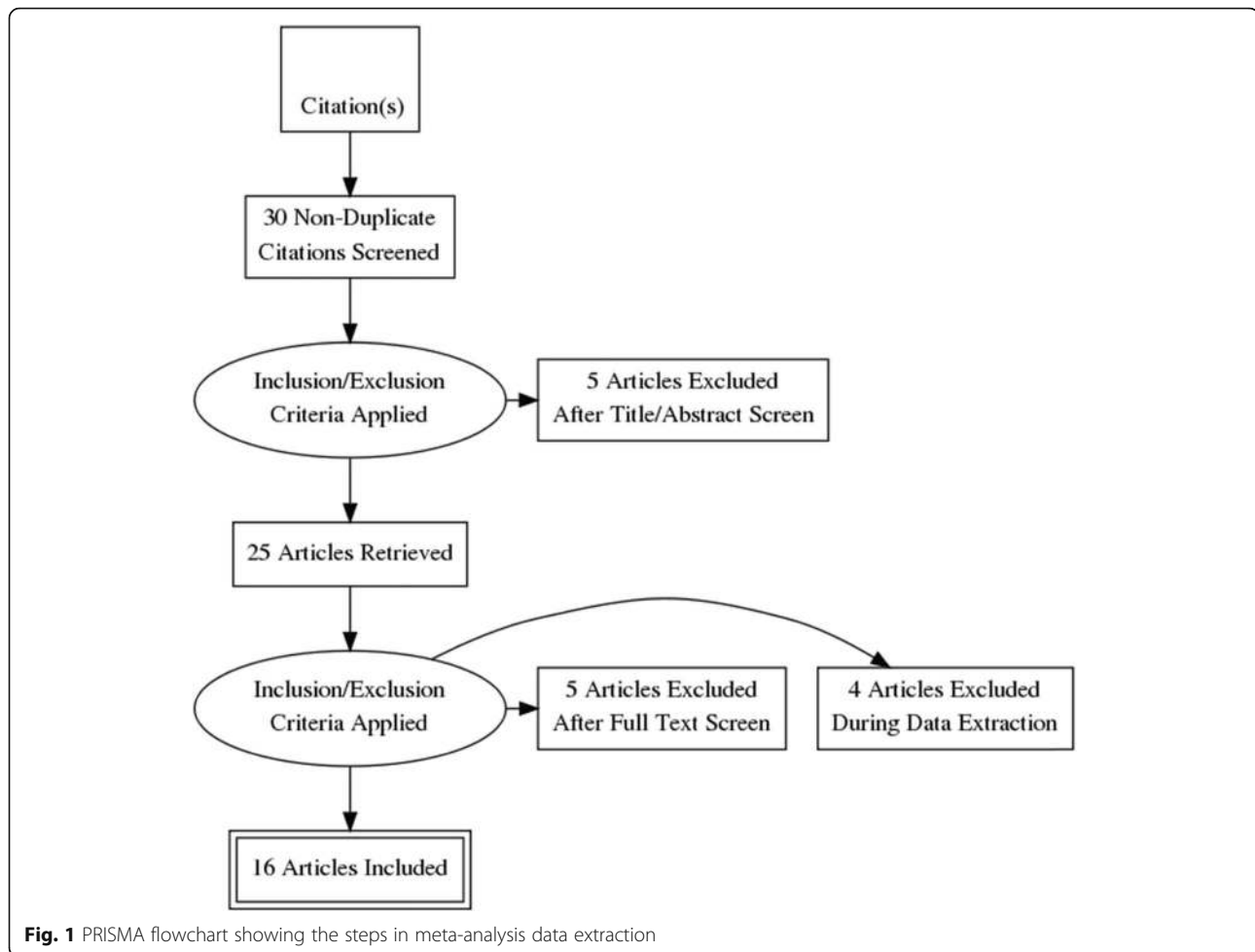
The rs7975232 (NG_008731.1:g.64978G > T) is an intronic variant predicted to influence splice site changes that might affect the translation of VDR. The frequency of this variant is high as evidenced by 734 and 16,751 homozygous mutants in 1000G and ExAC databases.

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The rs731236 (NG_008731.1:g.65058 T > C) variant is near the exon-intron boundary (GCTG/attg) and hence likely to influence splicing and thus might affect the translation of VDR. The frequency of this variant is lower than that of rs7975232 with 242 and 7505 homozygous mutants identified in 1000G and ExAC databases.

Importantly, genetic studies examining the role of TaqI and ApaI polymorphisms in the pathogenesis of NL, DN and ESRD remained ambiguous [4–6, 8–12]. Considering the significance of VDR signaling in the protection against renal diseases and the ambiguity in the studies relating VDR gene polymorphism with the disease etiology, present meta-analysis comprising 2669 renal disease cases and 3342 controls was carried out to clarify the association of VDR gene TaqI and ApaI polymorphisms with nephrolithiasis, ESRD and diabetic nephropathy.

Methods

Data extraction

The literature retrieval was carried out using keywords: vitamin D receptor or VDR, renal disease,

nephrolithiasis or urolithiasis, diabetic nephropathy, TaqI (rs731236) and ApaI (rs7975232) in PubMed, Medline and google scholar databases. All the free full texts were retrieved and wherever full text was not available, reprint request was sent to the corresponding author of the respective article. The criteria to include in the meta-analysis were: 1) availability of full text of the article, 2) inclusion of studies involving both cases and controls (either online or through reprint from the corresponding author), 3) availability of raw data on genotypes, and 4) restricting to studies published in only English language. The information related to each study such as first author, year of study, ethnic group or population studied, distribution of genotypes in cases and controls etc. was computed. The decision on the studies to be included in meta-analysis was taken by all the authors of this study.

Meta-analysis

The data computed in four columns wherein first two columns represent the number of variant alleles

Table 1 Distribution of VDR1 TaqI polymorphism in different case-control studies

| Author | Year | Country | Renal disease type | Genotypes | | | | | | C-allele frequency | |
|-----------------|------|---------|--------------------|-----------|-----|-----|---------|-----|----|--------------------|---------|
| | | | | Cases | | | Control | | | Cases | Control |
| | | | | TT | TC | CC | TT | TC | CC | | |
| Wang [23] | 2016 | China | ESRD | 215 | 197 | 40 | 474 | 358 | 72 | 0.31 | 0.28 |
| Cakir [20] | 2016 | Turkey | NL | 35 | 44 | 19 | 31 | 29 | 10 | 0.42 | 0.35 |
| Guha [13] | 2015 | India | NL | 58 | 82 | 60 | 65 | 58 | 77 | 0.51 | 0.53 |
| Martin [24] | 2010 | Ireland | DN | 225 | 327 | 103 | 249 | 327 | 98 | 0.41 | 0.39 |
| Ozkaya [16] | 2003 | Turkey | NL | 33 | 27 | 4 | 50 | 30 | 10 | 0.27 | 0.28 |
| Mossetti [25] | 2003 | Italy | NL | 80 | 104 | 36 | 35 | 66 | 13 | 0.40 | 0.40 |
| Bucan [27] | 2009 | Croatia | DN | 5 | 6 | 3 | 13 | 14 | 6 | 0.43 | 0.39 |
| Nosratabadi [7] | 2010 | Iran | DN | 9 | 55 | 36 | 4 | 63 | 33 | 0.64 | 0.65 |
| Goknar [15] | 2016 | Turkey | NL | 25 | 41 | 12 | 14 | 43 | 3 | 0.42 | 0.41 |
| Tripathi [21] | 2010 | India | ESRD | 105 | 115 | 38 | 267 | 228 | 74 | 0.37 | 0.33 |
| Mittal [22] | 2010 | India | NL | 56 | 61 | 8 | 84 | 50 | 16 | 0.31 | 0.27 |
| Moyano [26] | 2007 | Spain | NL | 15 | 23 | 13 | 9 | 11 | 1 | 0.48 | 0.31 |
| Gunes [17] | 2006 | Turkey | NL | 37 | 63 | 10 | 61 | 73 | 16 | 0.38 | 0.35 |
| Seyhan [18] | 2007 | Turkey | NL | 27 | 35 | 18 | 13 | 25 | 2 | 0.44 | 0.36 |
| Aykan [19] | 2015 | Turkey | NL | 67 | 61 | 36 | 66 | 86 | 15 | 0.41 | 0.35 |
| Han [14] | 2015 | China | NL | 102 | 6 | 0 | 160 | 16 | 4 | 0.03 | 0.07 |

The following studies were shown to have deviation from HWE: Guha et al. ($p < 0.0001$), Nosratabadi et al. ($p = 0.0008$), Goknar et al. ($p = 0.0008$) and Han et al. ($p = 0.0008$)

ESRD end stage renal disease, NL nephrolithiasis, DN diabetic nephropathy

in cases and controls and last two columns represent the number of ancestral alleles in cases and controls. Log (odds ratio) or effect size and standard error (SE) are calculated based on these four column data. Based on these two parameters, variance (SE^2), weight and 95% confidence interval of effect size were calculated. Cochran Q test and I^2 statistics were performed to test the heterogeneity in the association. The plot of $1/SE$ and Z-statistics was also used as an index to test heterogeneity. The publication bias was based on the rank correlation of SE and v. The fixed effect and random effect models were generated based on Mantel Haenszel and DerSimonian Lair's methods, respectively. If no evidence of heterogeneity was found, fixed effect model was considered. If test heterogeneity was significant, random effect model was considered.

Results

Figure 1 depicts the data extraction process for the meta-analysis. Of the 16 case-control studies retrieved on the association of TaqI polymorphism with renal disease (Table 1), four studies showed deviation from Hardy-Weinberg equilibrium [7, 13–15]. Among the different population groups included in this meta-analysis, the largest being that of Turkish representing

five case-control studies [16–20], two studies from India [21, 22] and one each from China [23], Ireland [24], Italy [25], Spain [26] and Croatia [27]. In total, the final meta-analysis was based on the data of 2777 cases and 3522 controls representing 16 case-control studies.

Cochran Q-test ($Q: 13.72, p = 0.54$) and I^2 (0.00) statistics showed no evidence of heterogeneity in association. Egger's test revealed no evidence of publication bias ($p = 0.14$). The VDR TaqI C-allele, under allele contrast fixed effect model, was associated with renal diseases calculated collectively for DN, ESRD and NL (OR: 1.11, 95% CI: 1.03–1.20, $p = 0.008$). (Figure 2) As shown Table 2, subtype analysis revealed TaqI C-allele to be associated with ESRD (OR: 1.17, 95% CI: 1.02–1.34, $p = 0.03$) (Fig. 2). Among the different ethnic groups, Turkish population showed strong association between VDR TaqI polymorphism and renal disease in allele contrast model (C vs. T, OR: 1.19, 95% CI: 1.01–1.42, $p = 0.04$). Sensitivity analysis revealed that omitting either of the studies had no effect on overall outcome of disease risk.

Of the 13 case-control studies (2440 cases and 3279 controls) retrieved on the association of ApaI polymorphism with renal disease (Table 3), five studies deviated from Hardy-Weinberg equilibrium [7, 15, 19, 21, 28]. Among the studies in accordance with HWE

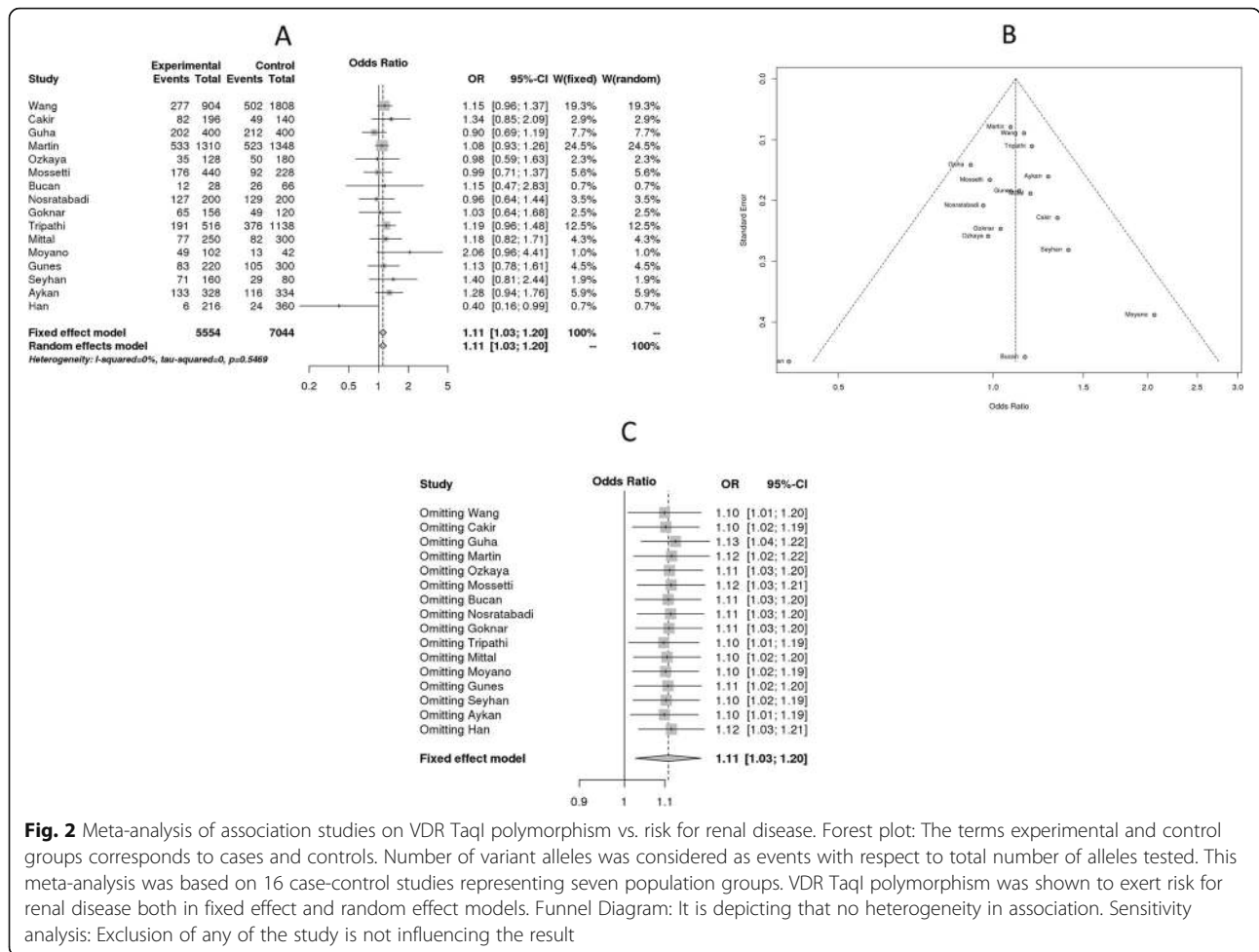


Fig. 2 Meta-analysis of association studies on VDR TaqI polymorphism vs. risk for renal disease. Forest plot: The terms experimental and control groups corresponds to cases and controls. Number of variant alleles was considered as events with respect to total number of alleles tested. This meta-analysis was based on 16 case-control studies representing seven population groups. VDR TaqI polymorphism was shown to exert risk for renal disease both in fixed effect and random effect models. Funnel Diagram: It is depicting that no heterogeneity in association. Sensitivity analysis: Exclusion of any of the study is not influencing the result

equilibrium, 3 studies were from Turkey [16, 17, 20], two from China [14, 23], and one each from Ireland [24] and Iran [29]. Cochrane Q-test (Q: 17.01, $p = 0.03$) and I^2 (48.3) statistics showed high-degree of heterogeneity in association. Egger’s test revealed no evidence of publication bias ($p = 0.54$). The fixed effect model showed positive association of VDR ApaI polymorphism with all the renal disease cases (C vs. A, OR: 1.10, 95% CI: 1.01–1.19), whereas, random effect model showed null association (OR: 1.05, 95% CI: 0.93–1.19) (Fig. 3). Sensitivity analysis for ApaI polymorphism revealed that the sources of heterogeneity are two studies i.e. Wang et al. and Tripathi et al. However, overall trend suggests ApaI variant as a risk factor for renal disease. As shown in Table 4, subgroup analysis revealed association of VDR ApaI polymorphism with ESRD (C vs. A, OR: 1.31, 95% CI: 1.15–1.50, $p = 0.0001$) and no association with NL and DN.

Discussion

Deficiency of vitamin D or defective activation of VDR by its ligand, 1,25-dihydroxy vitamin D results in secondary hyperparathyroidism, angiotensin II-mediated

renal damage and renal disease pathogenesis [3]. On the other hand, VDR activation suppressed inflammatory cell infiltration and inhibited nuclear factor- κ B activation [30]. Likewise, active vitamin D3 and lentivirus-mediated transforming growth factor- β (TGF- β) interference effectively reduced renal fibrosis in rat models [31]. These observations highlight the importance of VDR signaling in maintaining normal renal function. Accordingly, a number of studies have investigated the effects of polymorphisms in VDR gene on renal disease etiology. Among these, TaqI, and ApaI polymorphisms are widely studied [4–6]. However, there is a considerable ambiguity among these genetic studies, possibly stemming from sample size, ethnicity or gene-environmental interactions [4–6, 8–12]. To clarify whether TaqI and apaI polymorphisms have a role in renal disease pathogenesis, this meta-analysis comprising 2777 renal disease cases including DN, NL and ESRD and 3522 healthy controls was carried out. The present meta-analysis revealed an increased disease risk for subjects harboring TaqI C-allele under fixed and random effect models. Subgroup analysis based on type

Table 2 Subgroup analysis showing disease-specific risk with VDR TaqI polymorphism

| Model | Type of disease | N | OR | 95% CI | P value |
|--------------------------------|-----------------|----|------|------------------|---------|
| Allele contrast (A vs. a) | Overall | 16 | 1.11 | [1.0262; 1.1967] | 0.009 |
| | ESRD | 2 | 1.17 | [1.0171; 1.3357] | 0.028 |
| | NL | 11 | 1.09 | [0.9673; 1.2356] | 0.153 |
| | DN | 3 | 1.07 | [0.9250; 1.2322] | 0.371 |
| Recessive model (AA vs. Aa+aa) | Overall | 16 | 1.19 | [0.9266; 1.5392] | 0.170 |
| | ESRD | 2 | 1.14 | [0.8497; 1.5235] | 0.386 |
| | NL | 11 | 1.32 | [0.8084; 2.1503] | 0.268 |
| | DN | 3 | 1.11 | [0.8527; 1.4432] | 0.439 |
| Dominant model (AA+Aa vs. aa) | Overall | 16 | 1.14 | [1.0234; 1.2709] | 0.017 |
| | ESRD | 2 | 1.24 | [1.0367; 1.4863] | 0.019 |
| | NL | 11 | 1.09 | [0.9148; 1.2930] | 0.342 |
| | DN | 3 | 1.09 | [0.8737; 1.3505] | 0.456 |
| Overdominant (Aa vs. AA + aa) | Overall | 16 | 0.99 | [0.8106; 1.2040] | 0.904 |
| | ESRD | 2 | 1.19 | [0.9904; 1.4233] | 0.063 |
| | NL | 11 | 0.92 | [0.6575; 1.2975] | 0.647 |
| | DN | 3 | 1.01 | [0.8261; 1.2289] | 0.940 |
| pairw1 (AA vs. aa) | Overall | 16 | 1.20 | [1.0117; 1.4232] | 0.036 |
| | ESRD | 2 | 1.26 | [0.9280; 1.7151] | 0.138 |
| | NL | 11 | 1.23 | [0.9346; 1.6077] | 0.141 |
| | DN | 3 | 1.11 | [0.8081; 1.5149] | 0.528 |
| pairw2 (AA vs. Aa) | Overall | 16 | 1.16 | [0.8525; 1.5857] | 0.341 |
| | ESRD | 2 | 1.01 | [0.7443; 1.3803] | 0.932 |
| | NL | 11 | 1.30 | [0.7200; 2.3483] | 0.384 |
| | DN | 3 | 1.09 | [0.8304; 1.4407] | 0.524 |
| pairw3 (Aa vs. aa) | Overall | 16 | 1.09 | [0.9167; 1.2888] | 0.337 |
| | ESRD | 2 | 1.24 | [1.0233; 1.4966] | 0.028 |
| | NL | 11 | 1.04 | [0.7873; 1.3666] | 0.795 |
| | DN | 3 | 1.07 | [0.8487; 1.3425] | 0.577 |

Table 3 Distribution of VDR1 Apal polymorphism across different case-controls studies

| Author | Year | Country | Renal disease type | Genotypes | | | | | | C-allele frequency | |
|---------------------|------|---------|--------------------|-----------|-----|-----|---------|-----|-----|--------------------|----------|
| | | | | Cases | | | Control | | | Cases | Controls |
| | | | | AA | AC | CC | AA | AC | CC | | |
| Wang [23] | 2016 | China | ESRD | 206 | 207 | 39 | 502 | 350 | 52 | 0.32 | 0.25 |
| Cakir [20] | 2016 | Turkey | NL | 43 | 40 | 15 | 26 | 34 | 10 | 0.36 | 0.39 |
| Ghorbanihaghjo [29] | 2014 | Iran | CH | 10 | 23 | 13 | 16 | 16 | 11 | 0.53 | 0.44 |
| Martin [24] | 2010 | Ireland | DN | 185 | 323 | 147 | 200 | 322 | 152 | 0.47 | 0.46 |
| Ozkaya [16] | 2003 | Turkey | NL | 13 | 30 | 21 | 4 | 50 | 36 | 0.56 | 0.68 |
| Zhang [28] | 2012 | China | DN | 19 | 89 | 74 | 11 | 65 | 46 | 0.65 | 0.64 |
| Han [14] | 2015 | China | DN | 2 | 50 | 56 | 18 | 80 | 82 | 0.75 | 0.68 |
| Nosratabadi [7] | 2010 | Iran | DN | 9 | 64 | 27 | 9 | 63 | 28 | 0.59 | 0.60 |
| Goknar [15] | 2016 | Turkey | NL | 24 | 42 | 12 | 11 | 40 | 9 | 0.42 | 0.48 |
| Tripathi [21] | 2010 | India | ESRD | 80 | 116 | 62 | 171 | 324 | 74 | 0.47 | 0.41 |
| Mittal [22] | 2010 | India | NL | 43 | 70 | 12 | 57 | 71 | 22 | 0.38 | 0.38 |
| Gunes [17] | 2006 | Turkey | NL | 40 | 58 | 12 | 59 | 72 | 19 | 0.37 | 0.37 |
| Aykan [19] | 2015 | Turkey | NL | 14 | 5 | 145 | 12 | 0 | 155 | 0.90 | 0.93 |

The following studies were shown to have deviation from HWE: Ozkaya et al. ($p = 0.03$), Nosratabadi et al. ($p = 0.009$), Goknar et al. ($p = 0.03$), Tripathi et al. ($p < 0.0001$) and Aykan et al. ($p < 0.0001$)

ESRD end stage renal disease, NL nephrolithiasis, CH chronic hemodialysis, DN diabetic nephropathy

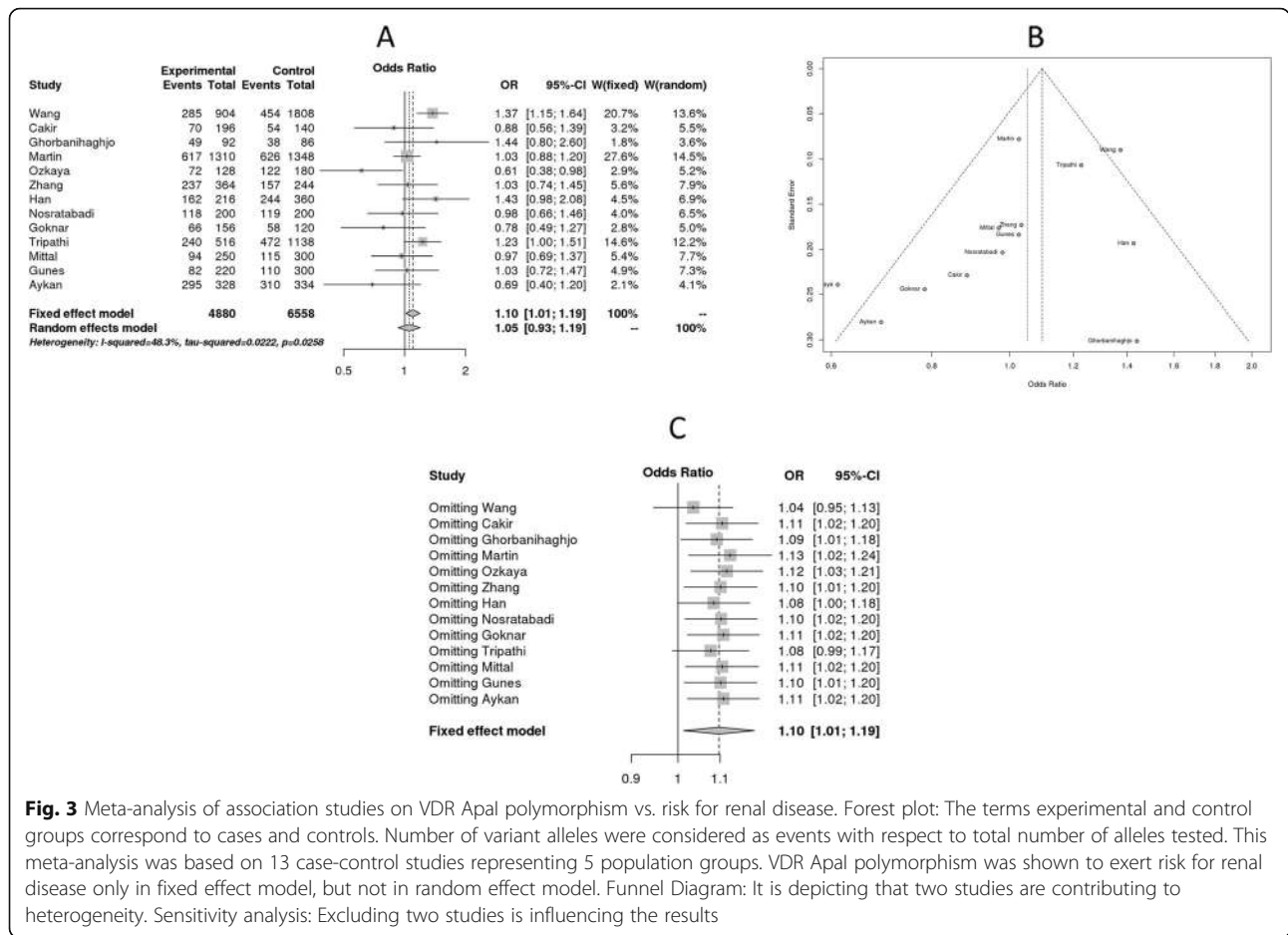


Fig. 3 Meta-analysis of association studies on VDR Apal polymorphism vs. risk for renal disease. Forest plot: The terms experimental and control groups correspond to cases and controls. Number of variant alleles were considered as events with respect to total number of alleles tested. This meta-analysis was based on 13 case-control studies representing 5 population groups. VDR Apal polymorphism was shown to exert risk for renal disease only in fixed effect model, but not in random effect model. Funnel Diagram: It is depicting that two studies are contributing to heterogeneity. Sensitivity analysis: Excluding two studies is influencing the results

of renal disease showed that VDR TaqI polymorphism is associated with ESRD in allele contrast model, whereas no significant association was found between TaqI polymorphism and DN and NL. In the case of Apal polymorphism, Apal C-allele was found to be linked to ESRD, but not with DM or NL under fixed effect model. Earlier, Yang et al. performed a meta-analysis on 1510 cases and 1812 controls and found no association of BsmI, FokI, TaqI, and Apal polymorphisms of VDR with end-stage renal disease. Inclusion of more studies benefited the current meta-analysis.

The direct role of solar rays in the synthesis of vitamin D is well known. In human skin, solar rays facilitate the formation of vitamin D3 from 7-dehydrocholesterol, which is evident from the presence of higher mean serum vitamin D levels in summer than in winter [32]. Likewise, higher vitamin D levels were found in populations living in regions known to have longer durations of sun exposure [33].

Conclusions

This meta-analysis revealed the association of VDR TaqI and Apal polymorphisms with ESRD risk. This

is the first meta-analysis study to simultaneously evaluate the association of DN, NL and ESRD with renal disease risk. Ethnicity, sample size, gene-environmental interactions appear to be responsible for inconsistencies observed in the association studies examining VDR polymorphisms and renal diseases. The limitations of this meta-analysis include; exclusion of studies where raw data or full text were not accessible and one-to-one correlation between vitamin D3 profile and risk could not be established as no parallel studies were conducted.

Abbreviations

1,25 (OH)₂D₃: 1,25-dihydroxyvitamin D₃; 25-OHD₃: 25-hydroxy vitamin D₃; DN: diabetic nephropathy; ESRD: end stage renal disease; NL: nephrolithiasis; VDR: vitamin D receptor

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Author's contribution

TH conceived the study, participated in data analysis and manuscript writing, SMN participated in data analysis and manuscript writing, AA participated in data analysis, SA participated in data compilation and manuscript writing, AAM participated in data analysis and manuscript writing, MOA participated in data analysis. NANA participated in data compilation and manuscript writing. All authors have read and approved the manuscript.

Table 4 Subgroup analysis showing disease-specific risk with VDR Apal polymorphism

| Model | Type of disease | N | OR | 95% CI | p-val |
|--------------------------------|-----------------|----|------|------------------|--------|
| Allele contrast (A vs. a) | Overall | 13 | 1.05 | [0.9282; 1.1931] | 0.4259 |
| | ESRD | 2 | 1.31 | [1.1454; 1.4996] | 0.0001 |
| | NL | 6 | 0.86 | [0.7193; 1.0175] | 0.0777 |
| | CH | 1 | 1.44 | [0.7974; 2.5983] | 0.2268 |
| | DN | 4 | 1.06 | [0.9361; 1.1997] | 0.3589 |
| Recessive model (AA vs. Aa+aa) | Overall | 13 | 1.10 | [0.8891; 1.3548] | 0.3865 |
| | ESRD | 2 | 1.85 | [1.3925; 2.4544] | 0.0000 |
| | NL | 6 | 0.77 | [0.5591; 1.0553] | 0.1035 |
| | CH | 1 | 1.15 | [0.4482; 2.9300] | 0.7760 |
| | DN | 4 | 1.06 | [0.8695; 1.2818] | 0.5840 |
| Dominant model (AA+Aa vs. aa) | Overall | 13 | 1.03 | [0.8131; 1.3008] | 0.8153 |
| | ESRD | 2 | 1.21 | [0.7844; 1.8716] | 0.3868 |
| | NL | 6 | 0.76 | [0.5034; 1.1586] | 0.2049 |
| | CH | 1 | 2.13 | [0.8380; 5.4311] | 0.1120 |
| | DN | 4 | 1.09 | [0.8749; 1.3545] | 0.4466 |
| Overdominant (Aa vs. AA + aa) | Overall | 13 | 0.99 | [0.8143; 1.2066] | 0.9300 |
| | ESRD | 2 | 0.91 | [0.4290; 1.9490] | 0.8167 |
| | NL | 6 | 0.96 | [0.6559; 1.3933] | 0.8147 |
| | CH | 1 | 1.69 | [0.7239; 3.9340] | 0.2256 |
| | DN | 4 | 1.03 | [0.8660; 1.2221] | 0.7472 |
| pairw1 (AA vs. aa) | Overall | 13 | 1.09 | [0.8006; 1.4779] | 0.5907 |
| | ESRD | 2 | 1.81 | [1.3275; 2.4638] | 0.0002 |
| | NL | 6 | 0.70 | [0.4803; 1.0158] | 0.0604 |
| | CH | 1 | 1.89 | [0.6130; 5.8330] | 0.2677 |
| | DN | 4 | 1.09 | [0.8307; 1.4252] | 0.5399 |
| pairw2 (AA vs. Aa) | Overall | 13 | 1.10 | [0.8709; 1.3854] | 0.4280 |
| | ESRD | 2 | 1.74 | [0.9540; 3.1683] | 0.0709 |
| | NL | 6 | 0.86 | [0.5968; 1.2327] | 0.4068 |
| | CH | 1 | 0.82 | [0.2948; 2.2927] | 0.7082 |
| | DN | 4 | 1.02 | [0.8306; 1.2477] | 0.8635 |
| pairw3 (Aa vs. aa) | Overall | 13 | 1.03 | [0.7832; 1.3445] | 0.8515 |
| | ESRD | 2 | 1.06 | [0.5720; 1.9761] | 0.8464 |
| | NL | 6 | 0.79 | [0.4507; 1.3857] | 0.4113 |
| | CH | 1 | 2.30 | [0.8331; 6.3500] | 0.1080 |
| | DN | 4 | 1.10 | [0.8688; 1.3802] | 0.4417 |

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Availability of data and materials

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

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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