Association of Vitamin D Receptor TaqI and ApaI Genetic Polymorphisms with Nephrolithiasis and End Stage Renal Disease: A Meta-Analysis and an Investigation into Latitudinal Effect on Disease Penetrance

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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. **Objectives**: Here, a meta-analysis comprising 2669 renal disease cases and 3342 controls was carried out to clarify the association of TaqI and ApaI polymorphisms with nephrolithiasis (NL), diabetic nephropathy (DN) and end stage renal disease (ESRD). **Methods and Results**: The VDR TaqI C-allele under allele contrast and fixed effect models was significantly associated with NL and ESRD, and ApaI T-allele with ESRD only under fixed effect model. Cochrane Q-test showed no evidence of heterogeneity for TaqI polymorphism and a significant heterogeneity for Apa I polymorphism. No publication bias was observed for both the polymorphisms. Interestingly, increased disease penetrance with an increase in latitude from south to north across the globe was found only in the case of TaqI polymorphism but not with ApaI. **Conclusions and Implications**: The present meta-analysis identifies TaqI and ApaI polymorphisms of VDR gene as significant risk factors for renal diseases. Besides, increased disease penetrance with TaqI polymorphism from south to north may corroborate with combined effect of defective VDR expression and decreased vitamin D synthesis due shorter durations of sun exposure with increasing latitude. On the other hand, possibility of ApaI polymorphism in linkage disequilibrium with an adjacent functional polymorphism and lack of their co-segregation may have resulted in reduced disease penetrance. Present findings may have implications in understanding the role of gene-environmental interaction in renal disease risk.

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-$(OH)_2$D3)[1]. Vitamin D receptor VDR is a ligand-activated transcriptional factor requiring 1,25(OH)2D 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].

Importantly, genetic studies examining the role of TakI and ApaI polymorphisms in the pathogeneses 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. Further, the effect of geographical location (latitude) on renal disease penetrance with

respect to presence of TaqI or ApaI polymorphisms was investigated, considering latitude dependent-variations in sun exposure durations and their corresponding effect on vitamin D synthesis.

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: i) availability of full text of the article, ii) inclusion of studies involving both cases and controls, iii) availability of raw data on genotypes, iv) accordance with Hardy-Weinberg equilibrium and v) 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.

Meta-analysis

The data computed in four columns wherein first two columns represent the number of variant alleles in cases and controls and last two columns represent the number of wild 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. Cochrane 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

Of the 16 case-control studies retrieved on the association of TaqI polymorphism with renal disease (Table 1), four were excluded due to their 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 2291 cases and 2982 controls representing 12 case-control studies.

Cochrane Q-test (Q: 5.62, p = 0.90) 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 and fixed effect models, was significantly associated with renal diseases calculated collectively for DN, ESRD and NL (OR: 1.15, 95% CI: 1.05—1.25). Similalrly, TaqI T- allele correlated with the renal disease protection when all the 3 renal disease types analyzed together (OR: 0.87, 95% CI: 0.80—0.95). Subtype analysis revealed TaqI C- allele to be associated with NL (OR: 0.84, 95% CI: 0.73—0.97, p = 0.02) and ESRD (OR: 0.86, 95% CI: 0.75—0.98, p = 0.03), and TaqI T- allele to be protective against these disease subtypes (OR: 0.87, 95% CI: 0.80—0.950 (Figure 1). These associations correspond to two studies of end stage renal disease and 8 studies of NL (Egger's p = 0.13). Contrastingly, diabetic nephropathy showed no association with VDR TaqI polymorphism (OR: 0.92, 95% CI: 0.79—1.08). Among the different ethnic groups, Turkish population showed strong association between VDR TaqI polymorphism and renal disease in allele contrast model (T vs. C, OR: 0.82, 95% CI: 0.68—0.99, p = 0.04). Indian population showed similar association in recessive model (TT vs. TC+CC, OR: 0.73, 95% CI: 0.57—0.95, p = 0.02). Sensitivity analysis revealed that omitting either of the studies had no effect on overall outcome of disease risk. In the present meta-analysis, increased renal disease penetrance with an increase in latitude from south to north across the globe was noticed in the case of TaqI C-allele (number of 'C'-alleles in cases/total number of 'C'-alleles both in cases and controls) (Table 2).

Of the 13 case-control studies retrieved on the association of ApaI polymorphism with renal disease (Table 3), five were excluded as they deviated from Hardy-Weinberg equilibrium [7, 15, 19, 21, 28]. The remaining eight studies representing 1658 cases and 2261 controls were included in the meta-analysis. Among these, 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 = 0.02) and I^2 (58.85) 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 (A vs. C, OR: 0.90, 95% CI: 0.82—0.99), whereas, random effect model showed null association (OR: 0.93, 95% CI: 0.78—1.10) (Figure 2). Subgroup analysis revealed association of VDR ApaI polymorphism with ESRD (A vs. C, OR: 0.73, 95% CI: 0.61—0.87, p = 0.0004) and no association with NL (A vs. C, OR: 1.12, 0.92—1.37, p = 0.26) and DN (A vs. C, OR: 0.93 (0.81—1.07, p = 0.32). Interestingly, no latitudinal effect was found on renal disease risk in the case of Apal polymorphism.

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-B activation [30]. Likewise, active vitamin D3 and lentivirus-mediated transforming growth factor- (TGF-) 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 2669 renal disease cases including DN, NL and ESRD and 3342 healthy controls was carried out. The present meta-analysis revealed a protection from renal disease for subjects carrying VDR TaqI T-allele and increased disease risk for subjects harboring TaqI C-allele under fixed and random effect models. Subgroup analysis based on type of renal disease showed that VDR TaqI polymorphism is associated with ESRD and NL in allele contrast model, whereas no significant association was found between TaqI polymorphism and DN. In the case of ApaI polymorphism, ApaI C-allele was found to be linked to DN but not to ESRD or NL under fixed effect model.

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]. Since duration of sun exposure depends on the latitude of the geographical location of the region and given the solar rays dependent vitamin D synthesis and its significance in VDR signaling, it is of imperative to examine the effect of latitude on renal disease incidence. In the present study, a clear correlation between increasing latitude from south to north and increasing renal disease penetrance was detected. This suggests that decreasing duration of solar exposure with an increase in latitude and corresponding decrease in vitamin D levels may have contributed to increased disease penetrance. Interestingly, in the present study, increased disease penetrance was found to be associated with only TaqI polymorphism but not with ApaI despite the subjects with TaqI and ApaI polymorphisms representing similar latitude. This discrepancy could be due to the possibility of TaqI polymorphism per se or any other adjacent polymorphism in linkage disequilibrium with Taq1 polymorphism being the functional polymorphism contributing to abnormal VDR expression and increased disease penetrance. On the other hand, ApaI polymorphism might merely be a marker to an adjacent functional polymorphism and depending on the segregation of ApaI with or without this functional polymorphism might determine the association of ApaI polymorphism with renal disease outcome. This possibly explains the lack of disease penetrance associated with ApaI polymorphism.

Conclusions

this meta-analysis revealed VDR TaqI polymorphism as a risk factor for NL and ESRD and ApaI polymorphism a risk factor for ESRD alone. Besides, the meta-analysis observed the effect of latitude on renal disease penetrance due to differences in solar exposure duration and its effect on vitamin D levels in interaction with TaqI polymorphism but not with ApaI. 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.

List Of Abbreviations

VDR-vitamin D receptor; NL- nephrolithiasis; DN- diabetic nephropathy; ESRD- end stage renal disease; 25-OHD3- 25-hydroxy vitamin D3; 1,25 $(OH)_2$D3- 1,25-dihydroxyvitamin D3

Declarations

Ethics approval and consent to participate: Not applicable

Consent for publication: Not applicable

Availability of data and materials: All data generated or analyzed during this study are included in this manuscript.

Competing interests: The authors declare that they have no competing interests

Authors' contributions: 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.

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Tables

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

Author	Year	Ethnicity	Renal disease type	Genotypes						C-allele frequency	
				Cases			Control				
				TT	TC	CC	TT	TC	CC	Cases	Control
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

ESRD-end stage renal disease; NL-nephrolithiasis; DN-diabetic nephropathy

Table 2. Latitude and renal disease penetrance from south to north across the globe

Country	Latitude	Penetrance
India	20.5937	0.48
Turkey	38.9637	0.54
Spain	40.4637	0.79
Italy	41.8719	0.66

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

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

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

Figures

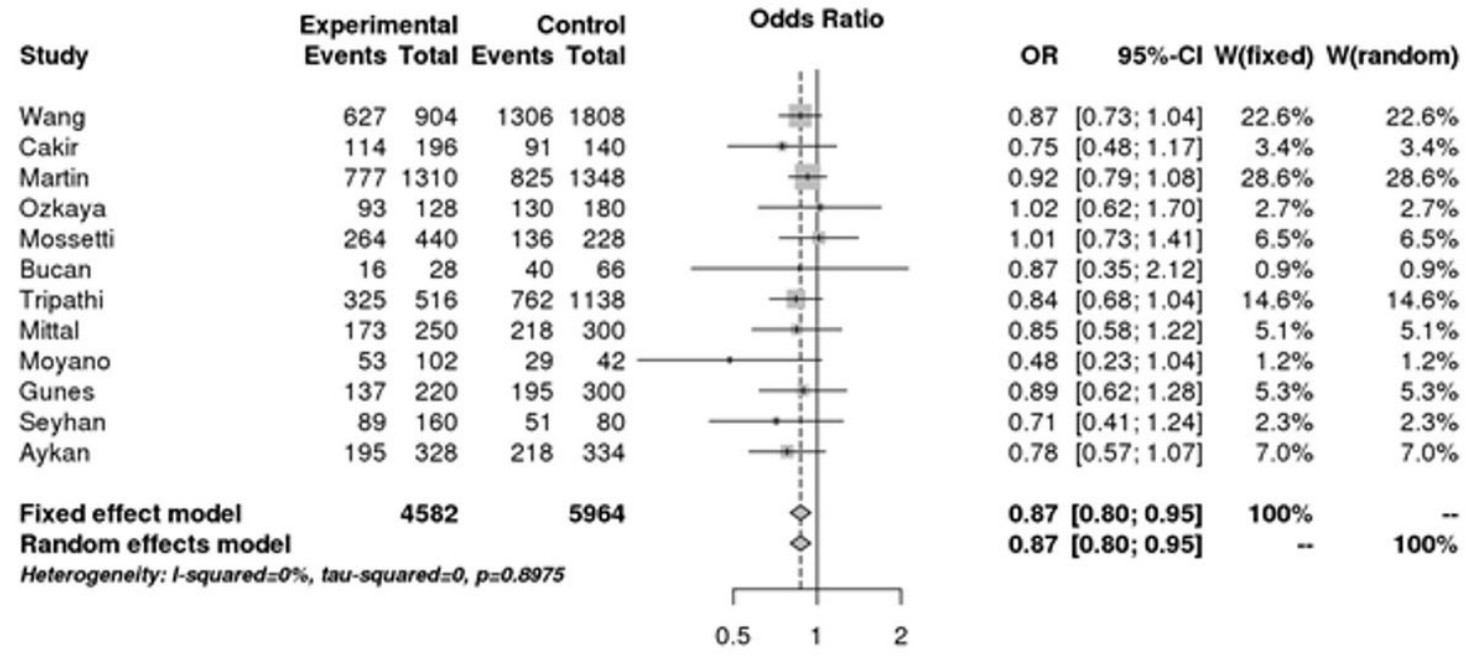

Figure 1

Meta-analysis of association studies on VDR TaqI polymorphism vs. risk for renal disease This meta-analysis was based on 12 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.

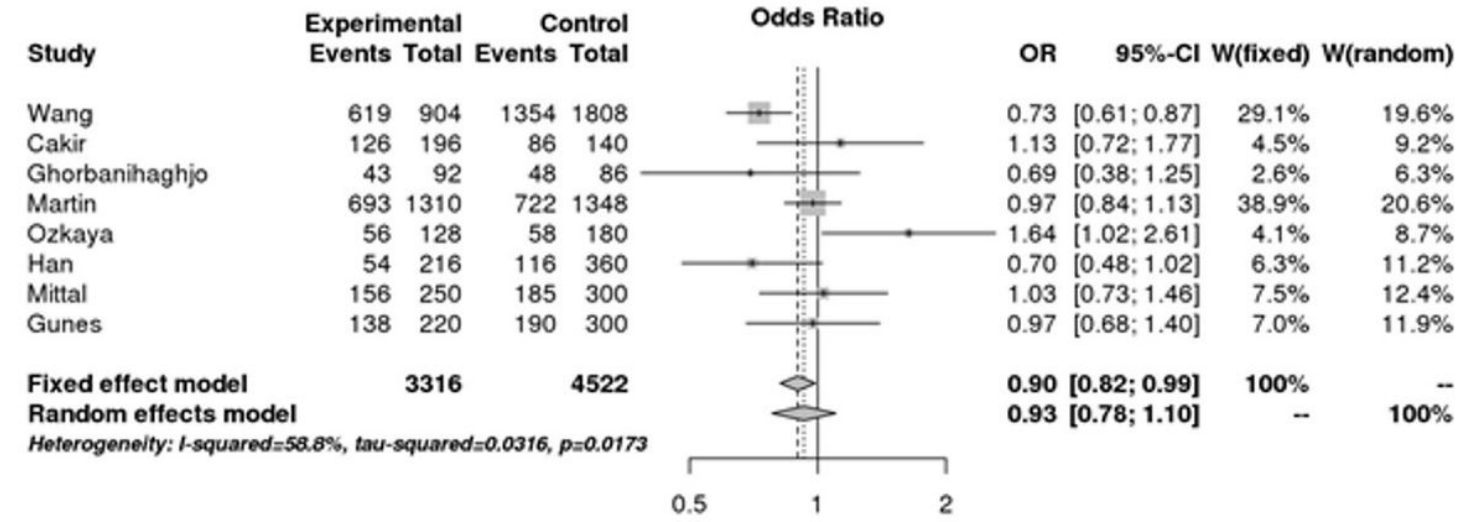

Figure 2

Meta-analysis of association studies on VDR ApaI polymorphism vs. risk for renal disease This meta-analysis was based on 8 case-control studies representing 5 population groups. VDR ApaI polymorphism was shown to exert risk for renal disease only in fixed effect model, but not in random effect model.

Supplementary Files

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