Effects of genetic variants on serum parathyroid hormone in hyperparathyroidism and end-stage renal disease patients

A systematic review and meta-analysis

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Abstract

Background: Parathyroid hormone (PTH) is one of the principal regulators of calcium homeostasis, crucial for normal functioning of the kidneys, bones, heart, and nervous system. Different pathologic conditions can affect serum PTH level resulting in hyperparathyroidism or hypoparathyroidism. Our study assessed the association of previously reported polymorphisms with the level of PTH (expressed in pg/mL) among individuals with different pathologic conditions affecting PTH level.

Methods: We searched Web of Science, MEDLINE, and Scopus to identify relevant articles published up to July 2017. The search yielded 6967 publications of which 44 fulfilled the inclusion criteria. We conducted meta-analyses for calcium-sensing receptor gene (CaSR) rs1801725 polymorphism in patients with primary hyperparathyroidism and vitamin D receptor gene (VDR) rs1544410 polymorphism in patients with end-stage renal disease (ESRD).

Results: None of the polymorphisms were significantly associated with PTH levels in the overall population. In subgroup analysis by ethnicity for VDR rs1544410 gene polymorphism, we found significant differences under dominant model (SMD: −0.18 [−0.32, −0.05], P < .01) and AA versus GG comparison (SMD: −0.29 [−0.52, −0.06], P < .01) in Asian patients with ESRD, while nominally significant results (P < .05) were observed for AG versus GG and AA versus GG comparisons in European individuals with ESRD.

Conclusion: Scientific evidence of genetic association of serum PTH level among individuals with different pathologic conditions remains deficient and published results provide weak evidence. Further well-conducted studies on larger sample sets designed according to evidence-based principles are warranted to assure clinically applicable findings.

Abbreviations: CaSR = calcium-sensing receptor, CSI score = Confounding-Selection-Information score, ESRD = end-stage renal disease, PTH = parathyroid hormone, SMD = standardized mean difference, VDR = vitamin D receptor.

Keywords: genetic analysis, meta-analysis, parathyroid hormone, single nucleotide polymorphism, systematic review

1. Introduction

Parathyroid hormone (PTH) is one of the principal regulators of calcium homeostasis. Synthesis and secretion of PTH are triggered by decreased calcium levels in the blood, while PTH inhibition occurs as a result of increased levels of calcium. PTH production represents the most important mechanism for rapid control of ionized calcium in the extracellular fluid (ECF).[1] Proper calcium balance is crucial for normal functioning of the kidneys, bones, heart, and nervous system.[2] Up to 60% of PTH variability is attributed to genetic factors.[3]

Different pathological conditions can influence PTH levels. Hyperparathyroidism is the most common pathological condition caused by excessive secretion of PTH and is usually subdivided into levels of clinical relevance as primary, secondary, and tertiary.[4] Primary hyperparathyroidism is the unregulated overproduction of PTH caused by a single adenoma, multiple adenomas or hyperplasia, and rarely, parathyroid carcinoma.[4] Secondary hyperparathyroidism occurs due to chronic kidney disease, vitamin D deficiency, or other causes of low blood calcium, while tertiary hyperparathyroidism is characterized by excessive secretion of PTH after extended secondary (renal) hyperparathyroidism.[4] The less common pathological condition of PTH deficiency is hypoparathyroidism. Two types of hypoparathyroidism are known: primary hypoparathyroidism, which is a state of inadequate PTH activity, and secondary hypoparathyroidism, a physiologic state in which PTH levels are high in response to a primary process that causes hypercalcemia.[5]

Vitamin D plays an essential role in the regulation of serum PTH levels and, consequently in calcium homeostasis. Vitamin D
deficiency manifests from an increase in PTH, while an overdose of vitamin D results in a decrease in PTH. Vitamin D acts through its metabolite, 1,25(OH)2D3, on the long-term regulation of parathyroid function. 1,25(OH)2D3 may act on the secretion of PTH and its gene regulation and the regulation of transcriptional activity of genes encoding the calcium-sensing receptor (CaSR) and the vitamin D receptor (VDR). CaSR polymorphisms are one of the genetic determinants of extracellular calcium, and a possible predictor of disorders that affect bone and mineral metabolism. The VDR-encoding gene is widely studied to predict differences in bone density and the risk of osteoporosis.

Genetic polymorphisms in CaSR and VDR have been associated with the serum PTH levels in different pathological conditions that are, among other biochemical traits, characterized by an altered PTH level. The functional consequences of these polymorphisms are yet to be discovered. The normal physiological range of PTH is 12 to 65 pg/mL. For primary hyperparathyroidism, the range of PTH level varies from normal in some patients to >65 pg/mL in most patients, whereas for secondary hyperparathyroidism, the range of PTH levels is dependent on the primary process that causes hypercalcemia, but is above 65 pg/mL. The highest values of PTH are associated with end-stage renal disease (ESRD), with levels from 2 to 9 times above the upper physiological range. An understanding of the genetic regulation of serum PTH levels could be of valuable clinical importance.

The goal of this study was to perform a systematic review together with meta-analyses of reported genetic loci associated with serum PTH levels in pathological conditions. We provided meta-analyses among individuals suffering from different pathological conditions that influence PTH levels based on previously published candidate gene studies. Such a comprehensive overview has not been provided so far.

2. Materials and methods

2.1. Publication search

A systematic literature search was undertaken to identify all published studies investigating the association of genetic variants with the level of PTH in patients with different pathological conditions affecting PTH levels. This systematic review was conducted following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. We systematically searched 3 bibliographic databases: Web of Science, MEDLINE, and Scopus to identify relevant articles.

Two authors conducted the search and study selection. Discrepancies concerning study selection were resolved through discussion with the last author of this manuscript. The search was performed on July 4, 2017, using a combination of genetic and phenotype words and Medical Subject Headings terms (see SI Table for the detailed search strategy, http://links.lww.com/MD/C248).

The search yielded a total of 13,924 publications (5657 identified using Ovid Medline, 5600 using Web of Science, and 2667 using Scopus). After removal of duplicates, 6967 publications were assessed. First, 2 authors independently screened all titles and abstracts of articles identified through the search process, which resulted in the identification of 110 potentially relevant articles. Potentially relevant articles were read in full, and 33 of them fulfilled all inclusion criteria. Then, we supplemented the search by scanning the reference list of the relevant articles and previously published related systematic reviews applying the same standardized process, generating an additional set of 20 articles of which 11 were eligible for inclusion. In total, 44 studies fulfilled all inclusion criteria.

2.2. Study selection

Studies were included if they were original studies of human individuals, regardless of sample size. To provide a comprehensive insight into the field, studies on individuals with different pathologic conditions related to the disturbance of PTH levels were included but analyzed separately.

All animal and in vitro studies were excluded, as well as case reports, editorials, comments, and review articles. Studies testing for biallelic single-nucleotide polymorphisms or biallelic insertion-deletion marker type were included; otherwise, they were excluded. Further, studies were included if they reported the number of individuals and appropriate descriptive values for PTH levels for every analyzed genotype. Lastly, we limited the review to studies that were written in the English language.

2.3. Data collection and data items

Data were extracted by 2 authors independently using the same standardized form, with any disagreements being resolved by consensus. The following data were extracted from each study included in the systematic review: first author’s last name, year of publication, country where the study was performed, ethnicity of participants, type of subjects, sample size (number of cases and controls), sample size by genotype (number of cases and controls for every analyzed genotype), mean values and standard deviation for the PTH levels by genotype (for cases and controls), measurement method, and genotype technology. Whenever a report provided standard errors or mean confidence intervals (CIs), but did not provide standard deviations, they were calculated using standard procedures. The units of measurement of PTH levels in the studies included in the meta-analysis were all converted into pg/mL.

2.4. Summary measures and synthesis of results

Studies on individuals with different pathologic conditions were analyzed separately due to methodological restraints. The meta-analysis on patients with the same disease was performed for genetic variants that had at least four data sources.

The analysis was performed by multiple pairwise comparisons (e.g., AA vs Aa, AA vs aa, Aa vs aa) and by assuming dominant (AA + Aa vs aa) or recessive (aa + Aa vs AA) genetic models, in order to compare results. Exceptionally, for CaSR rs1801725 polymorphism in individuals with primary hyperparathyroidism, only the recessive genetic model was used because the majority of the included studies grouped carriers of the minor allele (GT+TT) and compared them with the major allele homozygous genotypes (GG).

A pooled standardized mean difference (SMD) and its 95% CI were calculated in a random or fixed effects model, depending on the presence of heterogeneity among studies. If heterogeneity was detected, the random effects model was used. Otherwise, the fixed effects model was applied.

The Cochran Q test was used to assess the heterogeneity, and it was considered significant at P < 0.05. Heterogeneity was quantified with the I² metric, which includes values between 0% and 100%, with higher values denoting a greater degree of
heterogeneity. \( F \) values of 25%, 50%, and 75% were assigned as low, moderate, and high estimates, respectively.

As we tested the genetic association using 5 genetic models, Bonferroni correction was applied. A \( P \) value of less than .01 (0.05/5) was considered statistically significant.

All analyses were conducted using R, version 3.3.0. The Hardy–Weinberg equilibrium was tested with the HardyWeinberg package, using HWExact and HWChisq functions. Meta-analysis was performed with the meta package, using meta cont, forest, and funnel functions.

We reported our systematic review according to PRISMA guidelines.[15] This study was exempt from review by an ethics committee because it is a meta-analysis of previously published studies.

### 2.5. Risk of bias across studies and quality assessment of primary studies

The Venice criteria for assessing the strength of cumulative evidence in genetic association studies were used.[16] Briefly, credibility for each meta-analysis was graded on 3 levels: the amount of evidence, consistency of replication, and protection from bias categorized as “strong,” “moderate,” or “weak” (grades A, B, C, respectively). Meta-analysis was rated as 1) strong if it received three A grades, 2) moderate if no C grade received, and 3) weak if it received any C grade in any of the 3 criteria. As nonsignificant meta-analyses always received a C for the consistency of replication criterion and all of our results were nonsignificant for overall populations, the replication consistency score was fixed as C. Consequently, all the meta-analyses were rated as weak, and we did not investigate for the amount of evidence and protection from bias domains. Further, possible publication bias was evaluated graphically with the use of funnel plots and statistically by the Egger test for association with \( P < .05 \).

We created the Confounding-Selection-Information bias score (CSI score) for quality assessment of primary studies (S2 Table, http://links.lww.com/MD/C248) based on the Venice criteria for assessing cumulative epidemiologic evidence in genetic associations, Newcastle–Ottawa case-control, and quality scores in genetic epidemiology.[16–19] The credibility for each study was graded on 3 levels: confounding risk, selection bias risk, and reproducibility, categorized as “strong,” “moderate,” or “weak” (grades A, B, C, respectively).

### 2.6. Additional analysis

A sensitivity analysis was performed by examining the effects of excluding individual studies. We used this analysis to assess the contribution of each study to the final weighted effect in the analysis. When applicable, subgroup analysis based on ethnicity was performed to assess the potential impact of the source of heterogeneity.

### 3. Results

The detailed steps of our literature search are shown in Fig. 1. Forty-four studies performed on individuals with different pathological conditions were included. Included studies provided data regarding 40 distinct polymorphisms in or near 15 different genes. The most widely studied genes were the VDR (19 studies) and CaSR (10 studies). The majority of the studies were conducted in patients with primary hyperparathyroidism (21%), secondary hyperparathyroidism (18%), or ESRD (14%).

A meta-analysis was possible for VDR rs1544410 gene polymorphism in patients with ESRD and CaSR rs1801725 gene polymorphism in patients with primary hyperparathyroidism. We did not conduct a meta-analysis for other polymorphisms because fewer than 4 data sources were available for patients with the same disease.

Eight studies[20–27] were included in the meta-analysis for the relationship between VDR rs1544410 polymorphism and the PTH level among patients with ESRD. The pooled population comprised 1560 individuals. Three studies were conducted in Europe, 4 in Asia, and 1 in Africa. Table 1 summarizes the characteristics of the included studies. There was no significant result observed for any of the genetic models (Table 2, S1 Figure, http://links.lww.com/MD/C248). No publication bias was detected (\( P = .41, .31, .24, .36, \) and .50 for dominant, recessive, BB vs bb, BB vs Bb, and Bb vs bb models, respectively; S2 Figure, http://links.lww.com/MD/C248).

Heterogeneity among studies was detected (Table 2); therefore, to ascertain an effect due to ethnic differences, we performed a subgroup analysis based on ethnicity with 3 studies on Europeans and 4 studies on Asians. Marginally significant differences (\( P < .05 \)) among European individuals were observed for AG versus GG (SMD: \( -0.30 \) \([-0.03, -0.57\]) and AA versus AG comparisons (SMD: \( -0.28 \) \([-0.55, -0.01\]). \( P < .04 \)). Heterogeneity was no longer significant for any of the genetic models. Results for the Asian population showed significant differences under a dominant model (SMD: \( -0.18 \) \([-0.32, -0.05\], \( P < .01 \) and AA versus GG comparisons (SMD: \( -0.29 \) \([-0.52, -0.06\], \( P < .01 \) (Fig. 1). High heterogeneity was observed only for the AG versus GG comparison (S2 Figure, http://links.lww.com/MD/C248).

Four studies[28–31] providing 5 data points were included in the meta-analysis for CaSR rs1801725 gene polymorphism in patients with primary hyperparathyroidism. The pooled population comprised 308 individuals and all studies were conducted in Europe. Characteristics of the included studies are presented in Table 3.

No significant result was observed for the recessive model (SMD: \( -0.03 \) \([-0.44, -0.39\], \( P = .91 \)) (S3 Figure, http://links.lww.com/MD/C248), but a moderate degree of heterogeneity among studies was revealed (\( I^2 = 64.2\% \) [5.9%, 86.4%]; \( Q = 11.18, P = .03 \)). After excluding the study by Diaz-Soto et al[31] from the analysis, the heterogeneity was no longer significant (\( I^2 = 0.0\% \) [0.0%, 69.5%]; \( Q = 0.68, P = .71 \)) while the association remained not significant (SMD: \( -0.04 \) \([-0.22, 0.29\], \( P = .79 \) ). A small sample size could be the reason for the influential role of this study in the heterogeneity among studies. No publication preference was identified (\( P = .85 \), S4 Figure, http://links.lww.com/MD/C248).

The sensitivity analysis for all meta-analyses revealed that our results were statistically stable, as none of the studies contributed to a lack of a difference in the significance between the estimates.

### 4. Discussion

Our systematic review and meta-analysis is the first comprehensive study to date of published literature regarding polymorphic variants and the level of PTH in a population with pathological conditions affecting PTH serum levels. We found no significant association between reported polymorphisms and PTH levels in patients with primary hyperparathyroidism. The association between VDR rs1544410 polymorphisms and PTH levels in patients with ESRD was significant only in minor allele
homozygous Asians who had higher PTH levels than patients with the major allele homozygous genotype.

The most frequently investigated polymorphisms in previous candidate studies were those involving the VDR and CaSR genes. The VDR binds the active form of vitamin D, thus modulating many biological activities of the endocrine, immune, and nervous systems.\textsuperscript{[32,33]} VDR polymorphisms were widely studied in association with primary hyperparathyroidism,\textsuperscript{[34,35]} secondary hyperparathyroidism in hemodialysis patients,\textsuperscript{[22,24,25,27]} nephrolithiasis,\textsuperscript{[36]} renal failure,\textsuperscript{[37]} sarcoidosis,\textsuperscript{[38]} multiple sclerosis,\textsuperscript{[39,40]} diabetes mellitus type 1,\textsuperscript{[41,42]} diabetes mellitus type 2,\textsuperscript{[43,44]} and osteoporosis.\textsuperscript{[45,46]} The most commonly studied polymorphisms were rs2228570 (FokI), rs1544410 (BsmI), rs731236 (TaqI), and rs7975232 (ApaI) and, although heavily

Figure 1. Forest plots for associations between VDR rs1544410 gene polymorphism and PTH level among end-stage renal disease of Asian patients under (A) dominant; (B) recessive; (C) AA versus GG; (D) AA versus AG; and (E) AG versus GG genetic models.
studied, only a few studies showed associations with genetic loci in different pathological conditions. Lower VDR and higher PTH mRNA levels were associated with primary hyperparathyroidism for minor allele homozygotes of rs1544410 and rs7975232, and major allele homozygotes of rs731236 polymorphism. The level of PTH has been associated with renal failure for rs2282570 major allele homozygotes.

We conducted a meta-analysis for rs1544410 VDR polymorphism in 1560 patients with ESRD. Recently, a meta-analysis on the association of VDR rs1544410 (BsmI) gene polymorphism and serum PTH level was conducted among the 596 patients with ESRD. Results of that meta-analysis revealed that the PTH level in patients carrying the AG genotype was higher than in patients carrying the GG genotype, both in the overall population as well as in Caucasians. Only 1 study on an Asian population was included in the previously mentioned meta-analysis; therefore, the results of the meta-analysis on Asians were not robust.

### Table 1

| Author          | Year | Country | Sample size | AA  | AG  | GG  | AA’ | AG’ | GG’ |
|-----------------|------|---------|-------------|-----|-----|-----|-----|-----|-----|
| Akiba et al.    | 1997 | Japan   | 97          | 2   | 18  | 77  | 127 | 256 | 215 |
| Karczewska et al. | 1998 | Poland  | 88          | 24  | 43  | 21  | 234 | 299 | 156 |
| Nagaba et al.   | 1998 | Japan   | 877         | 54  | 152 | 671 | 86  | 102 | 131 |
| Tomegroya et al. | 2000 | Spain   | 94          | 35  | 43  | 16  | 178 | 210 | 105 |
| Marco et al.    | 2001 | Spain   | 143         | 28  | 64  | 51  | 148 | 277 | 236 |
| Erturk et al.   | 2002 | Turkey  | 91          | 20  | 35  | 36  | 222 | 149 | 297 |
| El-Shehaby et al. | 2013 | Egypt   | 80          | 14  | 39  | 27  | 767 | 562 | 541 |
| Pourfarzam et al. | 2014 | Iran    | 90          | 20  | 54  | 16  | 546 | 445 | 661 |

| Author          | Year | Country | Sample size | GG  | GT+TT | GG’ | GT+TT’ |
|-----------------|------|---------|-------------|-----|-------|-----|--------|
| Diaz-Soto et al. | 2016 | Spain   | 41          | 24  | 17    | 92  | 110    |
| Diaz-Soto et al. | 2016 | Spain   | 20          | 14  | 6     | 170 | 104    |

### Table 2

| Model          | SMD (95% CI) | P  | I² (95% CI) | Q (F) |
|----------------|-------------|----|-------------|-------|
| Pairwise comparisons |             |    |             |       |
| AA vs GG       | 0.00 (–0.30 to 0.30) | 0.98 | 55.8% (25.8–80.0) | 15.84 (0.03) |
| AA vs AG       | 0.02 (–0.28 to 0.32) | 0.90 | 62.7% (19.6–82.7) | 18.74 (0.01) |
| AG vs GG       | 0.00 (–0.25 to 0.24) | 0.98 | 62.7% (19.6–82.7) | 18.78 (0.01) |
| Dominant       | –0.01 (–0.24 to 0.21) | 0.92 | 61.1% (15.8–82.1) | 18.02 (0.01) |
| Recessive      | –0.03 (–0.26 to 0.21) | 0.83 | 50.5% (0.0–77.8) | 14.10 (0.05) |

*The units of PTH level in the studies included in the meta-analysis were all converted into pg/mL. Data are expressed as mean (SD)."
fewer studies, misleading inferences about publication bias could
publication bias are underpowered for meta-analyses of 10 or
languages. Also, we were unable to adjust our analysis for
restricted to papers published in English, so there is a possibility
comprehensive literature search, it is possible that some relevant
results must be cautiously considered. The existence of
unpublished data and the inability to obtain the raw data from
some authors may be a possible source of bias.
Furthermore, although we performed a very extensive and
comprehensive literature search, it is possible that some relevant
manuscripts have been missed. Our literature search was
restricted to papers published in English, so there is a possibility
for the systematic exclusion of studies published in other
languages. Also, we were unable to adjust our analysis for
covariates, such as age and sex. As tests for the assessment of
publication bias are underpowered for meta-analyses of 10 or
fewer studies, misleading inferences about publication bias could
be generated. Another limitation of the study is the use of the
invalidated CSI score for quality assessment of primary studies. In
addition, almost all studies had at least one C grade for the
quality assessment (S3 Table, http://links.lww.com/MD/C248),
pointing out drawbacks in study designs, which produces weak
evidence. Despite the aforementioned limitations, we intended to
provide an original, comprehensive summary of the literature and
make conclusions that could be useful in clinical practice.

5. Conclusion
This systematic review indicates that the deficiency of genetic
association studies on PTH levels among different pathological
conditions affected PTH level. Our findings point to the weakness
of results of candidate studies published so far and indicate that
future well-conducted genome-wide association studies of serum
PTH levels among different pathological conditions affecting
PTH levels are highly warranted. Studies using a larger sample set
and designed according to evidence-based principles would
assure clinically important findings that can be used in
personalized health care and the treatment of patients.

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critically assessed the search strategy; A.M. and M.P. performed
the search and extracted the data; A.M. performed the data
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References
[1] Mihail R, Farndon JR. Parathyroid disease and calcium metabolism. Br J
Anaes 2000;83:29–43.
[2] Michels TC, Kelly KM. Parathyroid disorders. Am Fam Phys
2013;88:249–57.
[3] Hunter D, De Lange M, Snieder H, et al. Genetic contribution to bone
metabolism, calcium excretion, and vitamin D and parathyroid hormone
regulation. J Bone Miner Res 2001;16:371–8.
[4] Fraser WD. Hyperparathyroidism. Lancet 2009;374:145–58.
[5] Abate EG, Clarke BL. Review of hypoparathyroidism. Front Endocrinol
2016;7:172.
[6] Khundmiri SJ, Murray RD, Lederer E. PTH and Vitamin D. Compr
Physiol 2016;6:561–601.
[7] Beckerman P, Silver J. Vitamin D and the parathyroid. Am J Med Sci
1999;317:363–9.
[8] Potts JT. Parathyroid hormone: past and present. J Endocrinol
2005;187:311–25.
[9] Ebeling PR. Vitamin D and bone health: epidemiologic studies. Bonekey
Rep 2014;3:511.
[10] Wu J, Shang D-P, Yang S, et al. Association between the vitamin D receptor
gene polymorphism and osteoporosis. Bonekey Rep 2016;5:233–6.
[11] McCarthy JT, Klee GG, Kao PC, et al. Serum bioactive parathyroid
hormone in hemodialysis patients*. J Clin Endocrinol Metab
1989;68:340–5.
[12] Silverberg SJ, Gao P, Brown I, et al. Clinical utility of an immunor-
adometric assay for parathyroid hormone (1–84) in primary hyperpara-
thyroidism. J Clin Endocrinol Metab 2003;88:4725–30.
[13] Uhlig K, Berns JS, Kestenbaum B, et al. KDOQI US commentary on the
2009 KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation,
and Treatment of CKD-Mineral and Bone Disorder (CKD-MBD). Am J
Kidney Dis 2010;55:773–99.
[14] Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for
reporting systematic reviews and meta-analyses of studies that evaluate
care interventions: explanation and elaboration. BMJ 2009;
339:b2070.
[15] Shamsaei L, Moher D, Clarke M, et al. Preferred reporting items for
systematic review and meta-analysis protocols (PRISMA-P) 2015:
 elaboration and explanation. BMJ 2015;353:g647.
[16] Ioannisidis JPA, Boffetta P, Little J, et al. Assessment of cumulative
evidence on genetic associations: interim guidelines. Int J Epidemiol
2008;37:120–32.
[17] Hartling L, Hann M, Milne A, et al. Validity and Inter-Rater Reliability
Testing of Quality Assessment Instruments Appendix E, Decision Rules
for Application of the Newcastle-Ottawa Scale 2012. Available at:
https://www.ncbi.nlm.nih.gov/books/NBK92291/. Accessed September
4, 2017.
[18] Anderson CA, Pettersson FH, Clarke GM, et al. Data quality control in
genetic case-control association studies. Nature Protocols 2010;5:1564–73.
[19] Patarică I, Gelemannoţi A, Kirin M, et al. The role of host genetic factors
in respiratory tract infectious diseases: systematic review, meta-analyses
and field synopsis. Sci Rep 2015;5:16119.
[20] Akiba T, Ando R, Kiri harsha S, et al. Is the bone mass of hemodialysis
patients genetically determined? Kidney Int Suppl 1997;6:2829–71.
[21] Karkoszka H, Chudek J, Strzelczyk P, et al. Does the vitamin D receptor
genotype predict bone mineral loss in haemodialysed patients? Nephrol
Dial Transplant 1998;13:2077–80.
[22] Nagaba Y, Heishi M, Tazawa H, et al. Vitamin D receptor gene
polymorphisms affect secondary hyperparathyroidism in hemodialysed
patients. Am J Kidney Dis 1998;32:464–9.
[23] Torregrosa J-V, Ybarra J, Moreno A, et al. Vitamin D receptor gene
polymorphisms and bone mineral density in patients on hemodialysis.
Nephron 2000;Nephron Karger, 381–2.
[24] Marco MP, Craver L, Betriu A, et al. Influence of vitamin D receptor gene polymorphisms on mortality risk in hemodialysis patients. Am J Kidney Dis 2001;38:965–74.

[25] Erturk S, Kutlay S, Karabulut HG, et al. The impact of vitamin D receptor genotype on the management of anemia in hemodialysis patients. Am J Kidney Dis 2002;40:816–23.

[26] El-Shehaby AM, El-Khatib MM, Marzouk S, et al. Relationship of BsmI polymorphism of vitamin D receptor gene with left ventricular hypertrophy and atherosclerosis in hemodialysis patients. Scand J Clin Lab Invest 2013;73:75–81.

[27] Pourfarram M, Nia KM, Atapour A, et al. The influence of BsmI and TaqI vitamin D receptor gene polymorphisms on the intensity of hyperparathyroidism in Iranian hemodialysis patients. Adv Biomed Res 2014;3:213.

[28] Medlich S, Lamesch P, Mueller A, et al. Frequency of the calcium-sensing receptor variant A986S in patients with primary hyperparathyroidism. Eur J Endocrinol 2001;145:421–7.

[29] Getani F, Borsani S, Vignali E, et al. Calcium-sensing receptor gene polymorphisms in primary hyperparathyroidism. J Endocrinol Invest 2002;25:614–9.

[30] Corbetta S, Eller-Vainicher C, Filopanti M, et al. R990G polymorphism of the calcium-sensing receptor and renal calcium excretion in patients with primary hyperparathyroidism. Eur J Endocrinol 2006;155:687–92.

[31] Diaz-Soto G, Romero E, Castrillon JLP, et al. Clinical expression of calcium-sensing receptor polymorphism (A986S) in normocalcemic and asymptomatic hyperparathyroidism. Horm Metab Res 2016;48:163–8.

[32] Carling T, Rudefelt P, Hellman P, et al. Vitamin D receptor polymorphisms correlate to parathyroid cell function in primary hyperparathyroidism. J Clin Endocrinol Metab 1997;82:1772–9.

[33] Poon AH, Gong L, Brasch-Andersen C, et al. Very important pharmacogene summary for VDR. Pharmacogenet Genomics 2012;22:575–83.

[34] Carling T, Rastad J, Akerstrom G, et al. Vitamin D receptor (VDR) and polymorphic VDR alleles in human parathyroid tumors. J Clin Endocrinol Metab 1998;83:2255–60.

[35] Pacheco D, Menarguez J, Cristobal E, et al. BsmI vitamin D receptor gene polymorphism and pathogenesis of parathyroid adenoma. Med Sci Monit 2000;6:658–60.

[36] Zhou TB, Jiang ZP, Li AH, et al. Association of vitamin D receptor BsmI (rs1544410), FokI (rs2228570), TaqI (rs731236) and Apal (rs7975232) gene polymorphism with the nephrolithiasis susceptibility. J Recept Signal Transduct Res 2015;35:107–14.

[37] Gago EV, Cadarso-Suarez C, Perez-Fernandez R, et al. Association between vitamin D receptor FokI polymorphism and serum parathyroid hormone level in patients with chronic renal failure. J Endocrinol Invest 2003;26:177–21.

[38] Niimi T, Tomita H, Sato S, et al. Vitamin D receptor gene polymorphisms in patients with sarcoidosis. Am J Respir Crit Care Med 1999;160:1107–9.

[39] Cierny D, Michalik J, Skerenova M, et al. Apal, BsmI and TaqI VDR gene polymorphisms in association with multiple sclerosis in Slovaks. Neurol Res 2016;38:678–84.

[40] Al-Temaimi RA, Al-Enezi A, Al-Serri A, et al. The association of Vitamin D receptor polymorphisms with multiple sclerosis in a case-control study from Kuwait. PLoS One 2015;10:e0142265.

[41] Zemunik T, Skracic V, Boraska V, et al. FokI polymorphism, vitamin D receptor, and interleukin-1 receptor haplotypes are associated with type 1 diabetes in the Dalmatian population. J Mol Diagn 2005;7:600–4.

[42] Panierakis C, Goulalems G, Mamoulakis D, et al. Vitamin D receptor gene polymorphisms and susceptibility to type 1 diabetes in Crete, Greece. Clin Immunol 2009;133:276–81.

[43] Jia J, Ding H, Yang K, et al. Vitamin D receptor genetic polymorphism is significantly associated with risk of type 2 diabetes mellitus in Chinese Han population. Arch Med Res 2015;46:572–9.

[44] Bid HK, Konwar R, Aggarwal CG, et al. Vitamin D receptor (FokI, BsmI and TaqI) gene polymorphisms and type 2 diabetes mellitus: a North Indian study. Indian J Med Sci 2009;63:187–94.

[45] Horst-Sikorska W, Dryfeld J, Wawrzyznik A, et al. Vitamin D receptor gene polymorphisms, bone mineral density and fractures in postmenopausal women with osteoporosis. Mol Biol Rep 2013;40:383–90.

[46] Singh M, Singh P, Singh S, et al. Vitamin D receptor (VDR) gene polymorphism influences the risk of osteoporosis in postmenopausal women of Northwest India. Arch Osteoporos 2013;8:147.

[47] Zhang YF, Zhou TB, Jiang ZP, et al. Association of vitamin D receptor BsmI (rs1544410) gene polymorphism with the intact parathyroid hormone (iPTH) level among patients with end-stage renal disease. J Recept Signal Transduct Res 2015;35:133–6.

[48] Jorde LB, Wooding SP. Genetic variation, classification and ‘race’. Nat Genet 2004;36 suppl:S28–33.

[49] Riccardi D, Brown EM. Physiology and pathophysiology of the calcium-sensing receptor in the kidney. Am J Physiol Renal Physiol 2010;298:F485–99.

[50] Pollak MR, Brown EM, Chou YH, et al. Mutations in the human Cal2+/-sensing receptor gene cause familial hypocalciuric hypercalcaemia and neonatal severe hyperparathyroidism. Cell 1993;75:1297–303.

[51] Pearce SH, Trump D, Wooding C, et al. Calcium-sensing receptor mutations in familial benign hypercalcaemia and neonatal hyperparathyroidism. J Clin Invest 1995;96:2683–92.

[52] Yokoyama K, Shigematsu T, Tsukada T, et al. Calcium-sensing receptor gene polymorphism affects the parathyroid response to moderate hypercalciemic suppression in patients with end-stage renal disease. Clin Nephrol 2002;57:131–5.

[53] Eren PA, Turan K, Berber I, et al. The clinical significance of parathyroid tissue calcium sensing receptor gene polymorphisms and expression levels in end-stage renal disease patients. Clin Nephrol 2009;72:114–21.

[54] Speer G, Caesh K, Mucsi K, et al. Calcium-sensing receptor A986S polymorphism in human rectal cancer. Int J Colorectal Dis 2002;17:20–4.

[55] Basci K, Hitre E, Kosa JP, et al. Effects of the lactase 13910C/T and calcium-sensor receptor A986S G/T gene polymorphisms on the calcium-sensor receptor gene polymorphism in men. Indian J Med Sci 2009;63:187–94.

[56] Jenab M, McKay J, Bueno-de-Mesquita HB, et al. Vitamin D receptor gene polymorphisms and susceptibility to breast cancer in the EPIC-Potsdam cohort. Breast Cancer Res Treat 2009;116:77–83.

[57] Bacsi K, Hitre E, Kosa JP, et al. Effects of the lactase 13910C/T and calcium-sensor receptor A986S G/T gene polymorphisms on the calcium-sensor receptor gene polymorphism in men. Indian J Med Sci 2009;63:187–94.

[58] Speer G, Caesh K, Mucsi K, et al. Calcium-sensing receptor A986S polymorphism in human rectal cancer. Int J Colorectal Dis 2002;17:20–4.

[59] Basci K, Hitre E, Kosa JP, et al. Effects of the lactase 13910C/T and calcium-sensor receptor A986S G/T gene polymorphisms on the calcium-sensor receptor gene polymorphism in men. Indian J Med Sci 2009;63:187–94.