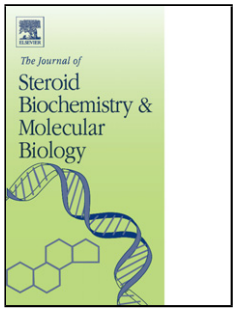


Title: Single nucleotide polymorphisms in the vitamin D pathway associating with circulating concentrations of vitamin D metabolites and non-skeletal health outcomes: review of genetic association studies.

Author: David A Jolliffe Robert T Walton Christopher J Griffiths Adrian R Martineau

PII: S0960-0760(15)30153-9
DOI: http://dx.doi.org/doi:10.1016/j.jsbmb.2015.12.007
Reference: SBMB 4587

To appear in: *Journal of Steroid Biochemistry & Molecular Biology*

Received date: 15-6-2015
Revised date: 3-11-2015
Accepted date: 9-12-2015

Please cite this article as: David A Jolliffe, Robert T Walton, Christopher J Griffiths, Adrian R Martineau, Single nucleotide polymorphisms in the vitamin D pathway associating with circulating concentrations of vitamin D metabolites and non-skeletal health outcomes: review of genetic association studies., Journal of Steroid Biochemistry and Molecular Biology http://dx.doi.org/10.1016/j.jsbmb.2015.12.007

Single nucleotide polymorphisms in the vitamin D pathway associating with circulating concentrations of vitamin D metabolites and non-skeletal health outcomes: review of genetic association studies.

David A Jolliffe[1*] d.a.jolliffe@qmul.ac.uk, Robert T Walton[1], Christopher J Griffiths[1], Adrian R Martineau[1*] a.martineau@qmul.ac.uk

[1]Centre for Primary Care and Public Health, Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London E1 2AB, UK

[*]Corresponding author at: Centre for Primary Care and Public Health, Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, 58 Turner St, London E1 2AB, UK. Tel: +44 207 882 2551, Fax: +44 207 882 2552.

Highlights

- We review a total of 120 genetic association studies on vitamin D pathway SNP
- Significant associations reported for a total of 55 SNP in 11 vit D pathway genes
- 44 studies report 114 findings of SNP which determine metabolite concentration
- 76 studies report 105 findings of SNP which affect non-skeletal health outcomes
- Infectious and auto-immune related disease were most frequent to associate with SNP
- Limited overlap of SNP predicting vit D status and SNP affecting disease outcomes

Abstract

Polymorphisms in genes encoding proteins involved in vitamin D metabolism and transport are recognised to influence vitamin D status. Syntheses of genetic association studies linking these variants to non-skeletal health outcomes are lacking. We therefore conducted a literature review to identify reports of statistically significant associations between single nucleotide polymorphisms (SNP) in 11 vitamin D pathway genes (*DHCR7, CYP2R1, CYP3A4, CYP27A1, DBP, LRP2, CUB, CYP27B1, CYP24A1, VDR* and *RXRA*)and non-bone health outcomes and circulating levels of 25-hydroxyvitamin D (25[OH]D and 1,25-dihydroxyvitamin D ($1,25[OH]_2D$). A total of 120 genetic association studies reported positive associations, of which 44 investigated determinants of circulating 25(OH)D and / or $1,25(OH)_2D$ concentrations, and 76 investigated determinants of non-skeletal health outcomes. Statistically significant associations were reported for a total of 55 SNP in the 11 genes investigated. There was limited overlap between genetic determinants of vitamin D status and those associated with non-skeletal health outcomes: polymorphisms in *DBP*, *CYP2R1* and *DHCR7* were the most frequent to be reported to associate with circulating concentrations of 25(OH)D, while polymorphisms in *VDR* were most commonly reported to associate with non-skeletal health outcomes, among which infectious and autoimmune diseases were the most represented.

Keywords: Vitamin D; Single Nucleotide Polymorphism; Vitamin D status; Non-skeletal diseases; Candidate Gene Association Studies; Genome-wide Association Studies

1. Introduction

Genetic variation in the vitamin D pathway was first reported to influence human health more than 20 years ago, when Morrison and colleagues found associations between allelic variants in the gene encoding the vitamin D receptor (VDR) and bone density (1, 2). Since then the scope of genetic association studies in the vitamin D field has widened to investigate the effects of variation in other genes in the vitamin D pathway on both skeletal and non-skeletal health outcomes. Several systematic reviews of the literature linking *VDR* polymorphisms to various disease outcomes have been performed to date (3-7). Reviews of studies investigating the influence of variation in other vitamin D pathway genes on bone health have also been performed (8). However, reviews of studies that have investigated associations with non-skeletal health and variants in vitamin D pathway genes other than VDR are lacking. This is a significant omission, because genome-wide association studies have reported that polymorphisms in the genes encoding enzymes responsible for both synthesis and catabolism of 25-hydroxyvitamin D influence vitamin D status (9, 10). Such variants might therefore be expected to influence non-skeletal health outcomes in their own right, or to modify the effects of vitamin D supplementation on risk of extra-skeletal disease – a hypothesis that we have addressed in clinical trials (11, 12).

We therefore conducted a literature review to identify genetic association studies reporting positive associations between risks of non-skeletal disease outcomes and single nucleotide polymorphisms (SNP) in the following genes encoding key players in the vitamin D pathway: *DHCR7, CYP2R1, CYP3A4, CYP27A1, DBP, LRP2, CUBN, CYP27B1, CYP24A1, VDR* and *RXRA*. The role for each of these genes in the vitamin D metabolic, transport and signalling pathways is illustrated in Figure 1.

2. Methods

2.1. Search Method

To identify eligible studies we searched the Pubmed database using the following terms: 'DHCR7'; 'CYP2R1'; 'CYP3A4'; 'CYP27A1'; 'DBP'; 'LRP2'; 'Megalin'; 'CUBN'; 'Cubilin'; 'CYP27B1'; 'CYP24A1'; 'VDR'; 'RXRA'. Our initial search was conducted in April of 2012 and captured manuscripts published from 2000-2012; we then conducted the same search in June of 2015 to capture manuscripts published

from 2012-2015. Abstracts and titles were reviewed to select studies on the basis of inclusion / exclusion criteria below. All articles were assessed for eligibility by one author (DAJ); those selected for inclusion were re-assessed by a second (ARM).

2.2. Inclusion/exclusion criteria

2.2.1 Inclusion criteria: Candidate and genome-wide association studies in which SNP in the genes above were reported to associated with:

- *Circulating concentrations of 25-hydroxyvitamin D*
- *Circulating concentrations of 1,25-dihydroxyvitamin D*
- *Susceptibility to, severity of, or prognosis of any non-skeletal health outcome.*

2.2.2. Exclusion criteria:

- *Studies in which SNP in the above genes were reported to be associated with skeletal health outcomes*
- *Studies which investigated associations between a given polymorphism and a given health outcome which had been previously reviewed in a meta-analysis. In which case, we reviewed the meta-analysis instead.*

3. Results

3.2. *Identification and selection of studies*

Fig. 2 depicts the study selection process. Our initial search identified 3,828 publications of which 120, containing a total of 55 individual SNP, met eligibility criteria.

3.3. Study characteristics

Of the 120 studies selected for inclusion, 44 studies reported a combined 114 findings of significant association between the concentration of 25-hydroxyvitamin D or 1,25-dihydroxyvitamin D and genotype of 35 vitamin D pathway SNP. Of these 35 SNP, 13 were in *DBP*; 7 in *CYP2R1*; 7 in *DHCR7*; 4 in *CYP27B1*; 2 in *CYP24A1* 1 in *RXRA*; and 1 in *VDR*. The remaining 76 studies reported a combined 105 reports of significant association between non-skeletal health outcomes (50 different diseases) and genotype of 29 vitamin D pathway SNP. Of these 29 SNP, 12 were in *VDR*; 4 in *DBP*; 3 in *CYP24A1*; 3 in *CYP27B1*; and 1 in each of: *CYP2R1, CYP3A4, CYP27A1, DHCR7, LRP2, CUBN* and *RXRA*. 11 SNP associated with both vitamin D metabolite concentration and susceptibility to non-skeletal disease.

3.4. Study findings

Table 1 presents results of 44 studies to have reported at least one association between a SNP in the vitamin D pathway and vitamin D metabolite concentrations: the majority of findings relate to variation in *DBP* gene, though a significant number were also identified for *CYP2R1* and *DHCR7* genes. Tables 2 & 3 present results from 76 studies to have reported at least one association between a SNP in the vitamin D pathway and susceptibility to non-skeletal health outcomes: variation in *VDR* represents the bulk of the findings. Of note, four of the most commonly investigated *VDR* polymorphisms (*FokI, ApaI, BsmI and TaqI)* account for 64% of the identified associations. Of the fifty different disease states identified as being associated with genetic variation in the vitamin D pathway, infectious and auto-immune diseases represent the most reported category (24/50), followed by cancers (12/50).

4. Discussion

To our knowledge, this is the first literature review to synthesise the literature reporting positive associations between genetic variation in the vitamin D pathway as a whole and biochemical and non-skeletal health outcomes. As might be expected, mutations in *DBP*, which encodes the binding protein that maintains serum concentration of 25(OH)D, is the most widely investigated source of variation in circulating concentrations of vitamin D metabolites. Mutations in *CYP2R1* and *DHCR7,* which encode the major enzymes 'upstream' of 25(OH)D, were also consistently shown to be determinants of vitamin D status. This review also highlights a considerable number of SNP within these and other vitamin D pathway genes that were not identified as determinants of vitamin D status by the major GWAS. In many cases they have been validated and remain significant in different ethnic groups: this highlights the value of candidate-gene approaches in identifying rarer SNP whose effects may not be detected in genome-wide studies. A large number of studies (76 - of which 19 were meta-analyses) reported associations between genetic variation in the vitamin D pathway and susceptibility, severity, or prognosis of extra-skeletal disease. The largest disease group for which such associations were reported are infectious and auto-immune related disorders (48%): this finding highlights the growing appreciation of the immunomodulatory effects of vitamin D and their importance for human health. The observation that there is limited overlap between genetic determinants of vitamin D status and those associated with non-skeletal health outcomes is striking. This may reflect the relative lack of

studies investigating influence of variation in genes other than VDR on health outcomes; alternatively it may have biological significance, suggesting that variation in VDR is a more important determinant of phenotype than circulating 25(OH)D concentrations.

References

1. Morrison NA, Yeoman R, Kelly PJ, Eisman JA. Contribution of trans-acting factor alleles to normal physiological variability: vitamin D receptor gene polymorphism and circulating osteocalcin. Proc Natl Acad Sci U S A. 1992;89(15):6665-9.
2. Morrison NA, Qi JC, Tokita A, Kelly PJ, Crofts L, Nguyen TV, et al. Prediction of bone density from vitamin D receptor alleles. Nature. 1994;367(6460):284-7.
3. Tizaoui K, Berraies A, Hamdi B, Kaabachi W, Hamzaoui K, Hamzaoui A. Association of vitamin D receptor gene polymorphisms with asthma risk: systematic review and updated meta-analysis of case-control studies. Lung. 2014;192(6):955-65.
4. Ahn J, Albanes D, Berndt SI, Peters U, Chatterjee N, Freedman ND, et al. Vitamin D-related genes, serum vitamin D concentrations and prostate cancer risk. Carcinogenesis. 2009;30(5):769-76.
5. Gao L, Tao Y, Zhang L, Jin Q. Vitamin D receptor genetic polymorphisms and tuberculosis: updated systematic review and meta-analysis. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2010;14(1):15-23.
6. Tizaoui K, Kaabachi W, Hamzaoui A, Hamzaoui K. Association between vitamin D receptor polymorphisms and multiple sclerosis: systematic review and meta-analysis of case-control studies. Cell Mol Immunol. 2015;12(2):243-52.
7. Mohammadi Z, Fayyazbakhsh F, Ebrahimi M, Amoli MM, Khashayar P, Dini M, et al. Association between vitamin D receptor gene polymorphisms (Fok1 and Bsm1) and osteoporosis: a systematic review. J Diabetes Metab Disord. 2014;13(1):98.
8. Bhan I. Vitamin d binding protein and bone health. International journal of endocrinology. 2014;2014:561214.
9. Wang TJ, Zhang F, Richards JB, Kestenbaum B, van Meurs JB, Berry D, et al. Common genetic determinants of vitamin D insufficiency: a genome-wide association study. Lancet. 2010;376(9736):180-8.
10. Ahn J, Yu K, Stolzenberg-Solomon R, Simon KC, McCullough ML, Gallicchio L, et al. Genome-wide association study of circulating vitamin D levels. Human molecular genetics. 2010;19(13):2739-45.
11. Martineau AR, Timms PM, Bothamley GH, Hanifa Y, Islam K, Claxton AP, et al. High-dose vitamin D(3) during intensive-phase antimicrobial treatment of pulmonary tuberculosis: a double-blind randomised controlled trial. Lancet. 2011;377(9761):242-50.
12. Martineau AR, MacLaughlin BD, Hooper RL, Barnes NC, Jolliffe DA, Greiller CL, et al. Double-blind randomised placebo-controlled trial of bolus-dose vitamin D3 supplementation in adults with asthma (ViDiAs). Thorax. 2015;70(5):451-7.
13. Engelman CD, Fingerlin TE, Langefeld CD, Hicks PJ, Rich SS, Wagenknecht LE, et al. Genetic and environmental determinants of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels in Hispanic and African Americans. The Journal of clinical endocrinology and metabolism. 2008;93(9):3381-8.
14. Lee HJ, Muindi JR, Tan W, Hu Q, Wang D, Liu S, et al. Low 25(OH) vitamin D3 levels are associated with adverse outcome in newly diagnosed, intensively treated adult acute myeloid leukemia. Cancer. 2014;120(4):521-9.
15. Lauridsen AL, Vestergaard P, Hermann AP, Brot C, Heickendorff L, Mosekilde L, et al. Plasma concentrations of 25-hydroxy-vitamin D and 1,25-dihydroxy-vitamin D are related to the phenotype of Gc (vitamin D-binding protein): a cross-sectional study on 595 early postmenopausal women. Calcified tissue international. 2005;77(1):15-22.
16. Kurylowicz A, Ramos-Lopez E, Bednarczuk T, Badenhoop K. Vitamin D-binding protein (DBP) gene polymorphism is associated with Graves' disease and the vitamin D status in a Polish population study. Experimental and clinical endocrinology & diabetes : official journal, German Society of Endocrinology [and] German Diabetes Association. 2006;114(6):329-35.

17. Wjst M AJ, Braig C, Bahnweg M, Andre E. A genome-wide linkage scan for 25-OH-D(3) and 1,25-(OH)2-D3 serum levels in asthma families. The Journal of steroid biochemistry and molecular biology. 2007(103):799–802.
18. Abbas S, Linseisen J, Slanger T, Kropp S, Mutschelknauss EJ, Flesch-Janys D, et al. The Gc2 allele of the vitamin D binding protein is associated with a decreased postmenopausal breast cancer risk, independent of the vitamin D status. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2008;17(6):1339-43.
19. Fu L, Yun F, Oczak M, Wong BY, Vieth R, Cole DE. Common genetic variants of the vitamin D binding protein (DBP) predict differences in response of serum 25-hydroxyvitamin D [25(OH)D] to vitamin D supplementation. Clinical biochemistry. 2009;42(10-11):1174-7.
20. Sinotte M, Diorio C, Berube S, Pollak M, Brisson J. Genetic polymorphisms of the vitamin D binding protein and plasma concentrations of 25-hydroxyvitamin D in premenopausal women. The American journal of clinical nutrition. 2009;89(2):634-40.
21. Fang Y, van Meurs JB, Arp P, van Leeuwen JP, Hofman A, Pols HA, et al. Vitamin D binding protein genotype and osteoporosis. Calcified tissue international. 2009;85(2):85-93.
22. Janssens W, Bouillon R, Claes B, Carremans C, Lehouck A, Buysschaert I, et al. Vitamin D deficiency is highly prevalent in COPD and correlates with variants in the vitamin D-binding gene. Thorax. 2010;65(3):215-20.
23. Robien K, Butler LM, Wang R, Beckman KB, Walek D, Koh WP, et al. Genetic and environmental predictors of serum 25-hydroxyvitamin D concentrations among middle-aged and elderly Chinese in Singapore. The British journal of nutrition. 2013;109(3):493-502.
24. Hibler EA, Hu C, Jurutka PW, Martinez ME, Jacobs ET. Polymorphic variation in the GC and CASR genes and associations with vitamin D metabolite concentration and metachronous colorectal neoplasia. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2012;21(2):368-75.
25. Lu L, Sheng H, Li H, Gan W, Liu C, Zhu J, et al. Associations between common variants in GC and DHCR7/NADSYN1 and vitamin D concentration in Chinese Hans. Human genetics. 2012;131(3):505-12.
26. Zhang Z, He J-W, Fu W-Z, Zhang C-Q, Zhang Z-L. An analysis of the association between the vitamin D pathway and serum 25-hydroxyvitamin D levels in a healthy Chinese population. J Bone Miner Res. 2013;28(8):1784-92.
27. Perna L, Felix JF, Breitling LP, Haug U, Raum E, Burwinkel B, et al. Genetic variations in the vitamin D binding protein and season-specific levels of vitamin D among older adults. Epidemiology. 2013;24(1):104-9.
28. Suaini NH, Koplin JJ, Ellis JA, Peters RL, Ponsonby AL, Dharmage SC, et al. Environmental and genetic determinants of vitamin D insufficiency in 12-month-old infants. The Journal of steroid biochemistry and molecular biology. 2014;144 Pt B:445-54.
29. Elkum N, Alkayal F, Noronha F, Ali MM, Melhem M, Al-Arouj M, et al. Vitamin D insufficiency in Arabs and South Asians positively associates with polymorphisms in GC and CYP2R1 genes. PLoS One. 2014;9(11):e113102.
30. Anderson D, Holt BJ, Pennell CE, Holt PG, Hart PH, Blackwell JM. Genome-wide association study of vitamin D levels in children: replication in the Western Australian Pregnancy Cohort (Raine) study. Genes and immunity. 2014;15(8):578-83.
31. Nissen J, Rasmussen LB, Ravn-Haren G, Andersen EW, Hansen B, Andersen R, et al. Common variants in CYP2R1 and GC genes predict vitamin D concentrations in healthy Danish children and adults. PLoS One. 2014;9(2):e89907.
32. Wood AM, Bassford C, Webster D, Newby P, Rajesh P, Stockley RA, et al. Vitamin D-binding protein contributes to COPD by activation of alveolar macrophages. Thorax. 2011;66(3):205-10.
33. Signorello LB, Shi J, Cai Q, Zheng W, Williams SM, Long J, et al. Common variation in vitamin D pathway genes predicts circulating 25-hydroxyvitamin D Levels among African Americans. PLoS One. 2011;6(12):e28623.

34. Xu W, Sun J, Wang W, Wang X, Jiang Y, Huang W, et al. Association of genetic variants of vit D binding protein (DBP/GC) and of the enzyme catalyzing its 25-hydroxylation (DCYP2R1) and serum vit D in postmenopausal women. Hormones. 2014;13(3):345-52.
35. Barry EL, Rees JR, Peacock JL, Mott LA, Amos CI, Bostick RM, et al. Genetic variants in CYP2R1, CYP24A1, and VDR modify the efficacy of vitamin D3 supplementation for increasing serum 25-hydroxyvitamin D levels in a randomized controlled trial. The Journal of clinical endocrinology and metabolism. 2014;99(10):E2133-7.
36. Cheung C-L, Lau K-S, Sham P-C, Tan KCB, Kung AWC. Genetic variant in vitamin D binding protein is associated with serum 25-hydroxyvitamin D and vitamin D insufficiency in southern Chinese. J Hum Genet. 2013;58(11):749-51.
37. Ramos-Lopez E, Bruck P, Jansen T, Herwig J, Badenhoop K. CYP2R1 (vitamin D 25-hydroxylase) gene is associated with susceptibility to type 1 diabetes and vitamin D levels in Germans. Diabetes/metabolism research and reviews. 2007;23(8):631-6.
38. Hassanein SI, Abu El Maaty MA, Sleem HM, Gad MZ. Triangular relationship between single nucleotide polymorphisms in the CYP2R1 gene (rs10741657 and rs12794714), 25-hydroxyvitamin d levels, and coronary artery disease incidence. Biomarkers. 2014;19(6):488-92.
39. Batai K, Murphy AB, Shah E, Ruden M, Newsome J, Agate S, et al. Common vitamin D pathway gene variants reveal contrasting effects on serum vitamin D levels in African Americans and European Americans. Human genetics. 2014;133(11):1395-405.
40. Ye Z, Sharp SJ, Burgess S, Scott RA, Imamura F, InterAct C, et al. Association between circulating 25-hydroxyvitamin D and incident type 2 diabetes: a mendelian randomisation study. Lancet Diabetes Endocrinol. 2015;3(1):35-42.
41. Azad AK, Bairati I, Qiu X, Huang H, Cheng D, Liu G, et al. Genetic sequence variants in vitamin D metabolism pathway genes, serum vitamin D level and outcome in head and neck cancer patients. Int J Cancer. 2013;132(11):2520-7.
42. Cooper JD, Smyth DJ, Walker NM, Stevens H, Burren OS, Wallace C, et al. Inherited variation in vitamin D genes is associated with predisposition to autoimmune disease type 1 diabetes. Diabetes. 2011;60(5):1624-31.
43. Pillai DK, Iqbal SF, Benton AS, Lerner J, Wiles A, Foerster M, et al. Associations between genetic variants in vitamin D metabolism and asthma characteristics in young African Americans: a pilot study. J Investig Med. 2011;59(6):938-46.
44. Hypponen E, Berry DJ, Wjst M, Power C. Serum 25-hydroxyvitamin D and IgE - a significant but nonlinear relationship. Allergy. 2009;64(4):613-20.
45. Lange CM, Bojunga J, Ramos-Lopez E, von Wagner M, Hassler A, Vermehren J, et al. Vitamin D deficiency and a CYP27B1-1260 promoter polymorphism are associated with chronic hepatitis C and poor response to interferon-alfa based therapy. Journal of hepatology. 2011;54(5):887-93.
46. Ramagopalan SV, Dyment DA, Cader MZ, Morrison KM, Disanto G, Morahan JM, et al. Rare variants in the CYP27B1 gene are associated with multiple sclerosis. Annals of neurology. 2011;70(6):881-6.
47. Orton SM, Morris AP, Herrera BM, Ramagopalan SV, Lincoln MR, Chao MJ, et al. Evidence for genetic regulation of vitamin D status in twins with multiple sclerosis. The American journal of clinical nutrition. 2008;88(2):441-7.
48. Zhang Y, Wang X, Liu Y, Qu H, Qu S, Wang W, et al. The GC, CYP2R1 and DHCR7 genes are associated with vitamin D levels in northeastern Han Chinese children. Swiss medical weekly. 2012;142:w13636.
49. Strawbridge RJ, Deleskog A, McLeod O, Folkersen L, Kavousi M, Gertow K, et al. A serum 25-hydroxyvitamin D concentration-associated genetic variant in DHCR7 interacts with type 2 diabetes status to influence subclinical atherosclerosis (measured by carotid intima-media thickness). Diabetologia. 2014;57(6):1159-72.

50. Voipio AJ, Pahkala KA, Viikari JS, Mikkila V, Magnussen CG, Hutri-Kahonen N, et al. Determinants of serum 25(OH)D concentration in young and middle-aged adults. The Cardiovascular Risk in Young Finns Study. Annals of medicine. 2015;47(3):253-62.
51. Davies JR, Chang YM, Snowden H, Chan M, Leake S, Karpavicius B, et al. The determinants of serum vitamin D levels in participants in a melanoma case-control study living in a temperate climate. Cancer causes & control : CCC. 2011;22(10):1471-82.
52. Hibler EA, Jurutka PW, Egan JB, Hu C, LeRoy EC, Martinez ME, et al. Association between polymorphic variation in VDR and RXRA and circulating levels of vitamin D metabolites. The Journal of steroid biochemistry and molecular biology. 2010;121(1-2):438-41.
53. Kresfelder TL, Janssen R, Bont L, Pretorius M, Venter M. Confirmation of an association between single nucleotide polymorphisms in the VDR gene with respiratory syncytial virus related disease in South African children. J Med Virol. 2011;83(10):1834-40.
54. Wilkinson RJ, Llewelyn M, Toossi Z, Patel P, Pasvol G, Lalvani A, et al. Influence of vitamin D deficiency and vitamin D receptor polymorphisms on tuberculosis among Gujarati Asians in west London: a case-control study. Lancet. 2000;355(9204):618-21.
55. Zhang H-Q, Deng A, Guo C-F, Wang Y-X, Chen L-Q, Wang Y-F, et al. Association between FokI polymorphism in vitamin D receptor gene and susceptibility to spinal tuberculosis in Chinese Han population. Arch Med Res. 2010;41(1):46-9.
56. Sharma PR, Singh S, Jena M, Mishra G, Prakash R, Das PK, et al. Coding and non-coding polymorphisms in VDR gene and susceptibility to pulmonary tuberculosis in tribes, castes and Muslims of Central India. Infection, genetics and evolution : journal of molecular epidemiology and evolutionary genetics in infectious diseases. 2011;11(6):1456-61.
57. Lee YH, Choi SJ, Ji JD, Song GG. Vitamin D receptor ApaI, TaqI, BsmI, and FokI polymorphisms and psoriasis susceptibility: a meta-analysis. Molecular biology reports. 2012;39(6):6471-8.
58. Li JH, Li HQ, Li Z, Liu Y, Gao JR, Zeng XJ, et al. [Association of Taq I T/C and Fok I C/T polymorphisms of vitamin D receptor gene with outcome of hepatitis B virus infection]. Zhonghua yi xue za zhi. 2006;86(28):1952-6.
59. Roth DE, Jones AB, Prosser C, Robinson JL, Vohra S. Vitamin D receptor polymorphisms and the risk of acute lower respiratory tract infection in early childhood. The Journal of infectious diseases. 2008;197(5):676-80.
60. Aslan S, Akil I, Aslan G, Onay H, Ozyurt BC, Ozkinay F. Vitamin D receptor gene polymorphism in children with urinary tract infection. Pediatric nephrology. 2012;27(3):417-21.
61. Samir Nabih E BKT. Association between vitamin D receptor gene FokI polymorphism and atopic childhood bronchial asthma Egyptian Journal of Chest Diseases and Tuberculosis. 2014;63(3):547-52.
62. Swapna N, Vamsi UM, Usha G, Padma T. Risk conferred by FokI polymorphism of vitamin D receptor (VDR) gene for essential hypertension. Indian J Hum Genet. 2011;17(3):201-6.
63. Luo XY, Wu LJ, Yang MH, Liu NT, Liao T, Tang Z, et al. [Relationship of vitamin D receptor gene Fok I polymorphism with systemic lupus erythematosus]. Xi bao yu fen zi mian yi xue za zhi = Chinese journal of cellular and molecular immunology. 2011;27(8):901-5.
64. Arjumand W, Ahmad ST, Seth A, Saini AK, Sultana S. Vitamin D receptor FokI and BsmI gene polymorphism and its association with grade and stage of renal cell carcinoma in North Indian population. Tumour biology : the journal of the International Society for Oncodevelopmental Biology and Medicine. 2012;33(1):23-31.
65. Lee YH, Bae S-C, Choi SJ, Ji JD, Song GG. Associations between vitamin D receptor polymorphisms and susceptibility to rheumatoid arthritis and systemic lupus erythematosus: a meta-analysis. Molecular biology reports. 2011;38(6):3643-51.
66. Mun MJ, Kim TH, Hwang JY, Jang WC. Vitamin D receptor gene polymorphisms and the risk for female reproductive cancers: A meta-analysis. Maturitas. 2015;81(2):256-65.

67. Penna-Martinez M, Ramos-Lopez E, Stern J, Hinsch N, Hansmann ML, Selkinski I, et al. Vitamin D receptor polymorphisms in differentiated thyroid carcinoma. Thyroid : official journal of the American Thyroid Association. 2009;19(6):623-8.
68. Panierakis C, Goulielmos G, Mamoulakis D, Petraki E, Papavasiliou E, Galanakis E. Vitamin D receptor gene polymorphisms and susceptibility to type 1 diabetes in Crete, Greece. Clinical immunology. 2009;133(2):276-81.
69. Gao Z, Fu HJ, Xue JJ, Wu ZX, Zhao LB. Genetic polymorphisms in VDR, ESR1 and ESR2 genes may contribute to susceptibility to Parkinson's disease: a meta-analysis. Molecular biology reports. 2014;41(7):4463-74.
70. Messaritakis I, Samonis G, Dimopoulou D, Maraki S, Papadakis JA, Daraki V, et al. Staphylococcus aureus nasal carriage might be associated with vitamin D receptor polymorphisms in type 2 diabetes. Clin Microbiol Infect. 2014;20(9):920-5.
71. Zhong X, Du Y, Lei Y, Liu N, Guo Y, Pan T. Effects of vitamin D receptor gene polymorphism and clinical characteristics on risk of diabetic retinopathy in Han Chinese type 2 diabetes patients. Gene. 2015;566(2):212-6.
72. Moodley A, Qin M, Singh KK, Spector SA. Vitamin D-related host genetic variants alter HIV disease progression in children. The Pediatric infectious disease journal. 2013;32(11):1230-6.
73. Torres C, Sanchez de la Torre M, Garcia-Moruja C, Carrero AJ, Trujillo MdM, Fibla J, et al. Immunophenotype of vitamin D receptor polymorphism associated to risk of HIV-1 infection and rate of disease progression. Curr HIV Res. 2010;8(6):487-92.
74. Feng M, Li H, Chen S-F, Li W-F, Zhang F-B. Polymorphisms in the vitamin D receptor gene and risk of autoimmune thyroid diseases: a meta-analysis. Endocrine. 2013;43(2):318-26.
75. Testa A, Mallamaci F, Benedetto FA, Pisano A, Tripepi G, Malatino L, et al. Vitamin D receptor (VDR) gene polymorphism is associated with left ventricular (LV) mass and predicts left ventricular hypertrophy (LVH) progression in end-stage renal disease (ESRD) patients. J Bone Miner Res. 2010;25(2):313-9.
76. Jia F, Sun RF, Li QH, Wang DX, Zhao F, Li JM, et al. Vitamin D receptor BsmI polymorphism and osteoporosis risk: a meta-analysis from 26 studies. Genetic testing and molecular biomarkers. 2013;17(1):30-4.
77. Jenab M, McKay J, Bueno-de-Mesquita HB, van Duijnhoven FJB, Ferrari P, Slimani N, et al. Vitamin D receptor and calcium sensing receptor polymorphisms and the risk of colorectal cancer in European populations. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2009;18(9):2485-91.
78. Orlow I, Roy P, Reiner AS, Yoo S, Patel H, Paine S, et al. Vitamin D receptor polymorphisms in patients with cutaneous melanoma. Int J Cancer. 2012;130(2):405-18.
79. Deng H, Liu F, Pan Y, Jin X, Wang H, Cao J. BsmI, TaqI, ApaI, and FokI polymorphisms in the vitamin D receptor gene and periodontitis: a meta-analysis of 15 studies including 1338 cases and 1302 controls. J Clin Periodontol. 2011;38(3):199-207.
80. Li L, Wu Y, Li L, Cai YF, Geng L, Gao XH, et al. Association of ApaI and BsmI polymorphisms with vitiligo risk: a meta-analysis. Clinical and experimental dermatology. 2015.
81. Ou C, Zhao HL, Zhu B, Huang LS, Li PZ, Lao M. Association of vitamin D receptor gene polymorphism with the risk of renal cell carcinoma: a meta-analysis. Journal of receptor and signal transduction research. 2014;34(6):463-8.
82. Liu SG, Li YY, Sun RX, Wang JL, Li XD, Han L, et al. Polymorphisms in the vitamin D receptor and risk of gout in Chinese Han male population. Rheumatology international. 2015;35(6):963-71.
83. Saito M, Eiraku N, Usuku K, Nobuhara Y, Matsumoto W, Kodama D, et al. ApaI polymorphism of vitamin D receptor gene is associated with susceptibility to HTLV-1-associated myelopathy/tropical spastic paraparesis in HTLV-1 infected individuals. J Neurol Sci. 2005;232(1-2):29-35.

84. Mahmoudi T, Mohebbi SR, Pourhoseingholi MA, Fatemi SR, Zali MR. Vitamin D receptor gene ApaI polymorphism is associated with susceptibility to colorectal cancer. Dig Dis Sci. 2010;55(7):2008-13.
85. SS AEG. Vitamin D receptor gene polymorphism and its association with 1,25-dihydroxyvitamin D_3 in patients with Graves disease in an Egyptian population: a pilot study. Endocr Pract. 2012;18(2):132-9.
86. Saadi A, Gao G, Li H, Wei C, Gong Y, Liu Q. Association study between vitamin D receptor gene polymorphisms and asthma in the Chinese Han population: a case-control study. BMC medical genetics. 2009;10:71.
87. Onen IH, Ekmekci A, Eroglu M, Konac E, Yesil S, Biri H. Association of genetic polymorphisms in vitamin D receptor gene and susceptibility to sporadic prostate cancer. Experimental biology and medicine. 2008;233(12):1608-14.
88. Jingwi EY, Abbas M, Ricks-Santi L, Winchester D, Beyene D, Day A, et al. Vitamin D receptor genetic polymorphisms are associated with PSA level, Gleason score and prostate cancer risk in African-American men. Anticancer research. 2015;35(3):1549-58.
89. Baur K, Mertens JC, Schmitt J, Iwata R, Stieger B, Eloranta JJ, et al. Combined effect of 25-OH vitamin D plasma levels and genetic vitamin D receptor (NR 1I1) variants on fibrosis progression rate in HCV patients. Liver international : official journal of the International Association for the Study of the Liver. 2012;32(4):635-43.
90. Heine G, Hoefer N, Franke A, Nothling U, Schumann RR, Hamann L, et al. Association of vitamin D receptor gene polymorphisms with severe atopic dermatitis in adults. The British journal of dermatology. 2013;168(4):855-8.
91. Dalessandri KM, Miike R, Wiencke JK, Farren G, Pugh TW, Manjeshwar S, et al. Vitamin D receptor polymorphisms and breast cancer risk in a high-incidence population: a pilot study. Journal of the American College of Surgeons. 2012;215(5):652-7.
92. Hung CH, Chiu YC, Hu TH, Chen CH, Lu SN, Huang CM, et al. Significance of vitamin d receptor gene polymorphisms for risk of hepatocellular carcinoma in chronic hepatitis C. Translational oncology. 2014;7(4):503-7.
93. Neela VS, Suryadevara NC, Shinde VG, Pydi SS, Jain S, Jonnalagada S, et al. Association of Taq I, Fok I and Apa I polymorphisms in Vitamin D Receptor (VDR) gene with leprosy. Human immunology. 2015.
94. Alagarasu K, Honap T, Mulay AP, Bachal RV, Shah PS, Cecilia D. Association of vitamin D receptor gene polymorphisms with clinical outcomes of dengue virus infection. Human immunology. 2012;73(11):1194-9.
95. Bektas-Kayhan K, Unur M, Yaylim-Eraltan I, Ergen HA, Toptas B, Hafiz G, et al. Association of vitamin D receptor Taq I polymorphism and susceptibility to oral squamous cell carcinoma. In vivo. 2010;24(5):755-9.
96. C C. Association between vitamin D receptor (VDR) gene polymorphisms and systemic lupus erythematosus in Portuguese patients. Lupus. 2015;[Epub ahead of print].
97. Li YJ, Tang YW, Shi YQ, Han S, Wang JB, Zhou XM, et al. Polymorphisms in the vitamin D receptor gene and risk of primary biliary cirrhosis: a meta-analysis. Journal of gastroenterology and hepatology. 2014;29(4):706-15.
98. Perna L, Butterbach K, Haug U, Schottker B, Muller H, Arndt V, et al. Vitamin D receptor genotype rs731236 (Taq1) and breast cancer prognosis. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2013;22(3):437-42.
99. Vasilopoulos Y, Sarafidou T, Kotsa K, Papadimitriou M, Goutzelas Y, Stamatis C, et al. VDR TaqI is associated with obesity in the Greek population. Gene. 2013;512(2):237-9.
100. Tanaka K, Miyake Y, Hanioka T, Arakawa M. VDR gene polymorphisms, interaction with smoking and risk of periodontal disease in Japanese women: the Kyushu Okinawa maternal and child health study. Scandinavian journal of immunology. 2013;78(4):371-7.

101. Agliardi C, Guerini FR, Saresella M, Caputo D, Leone MA, Zanzottera M, et al. Vitamin D receptor (VDR) gene SNPs influence VDR expression and modulate protection from multiple sclerosis in HLA-DRB1*15-positive individuals. Brain, behavior, and immunity. 2011;25(7):1460-7.
102. Ovsyannikova IG, Dhiman N, Haralambieva IH, Vierkant RA, O'Byrne MM, Jacobson RM, et al. Rubella vaccine-induced cellular immunity: evidence of associations with polymorphisms in the Toll-like, vitamin A and D receptors, and innate immune response genes. Human genetics. 2010;127(2):207-21.
103. Wang L, Hara K, Van Baaren JM, Price JC, Beecham GW, Gallins PJ, et al. Vitamin D receptor and Alzheimer's disease: a genetic and functional study. Neurobiology of aging. 2012;33(8):1844 e1-9.
104. Dickinson JL, Perera DI, van der Mei AF, Ponsonby AL, Polanowski AM, Thomson RJ, et al. Past environmental sun exposure and risk of multiple sclerosis: a role for the Cdx-2 Vitamin D receptor variant in this interaction. Multiple sclerosis. 2009;15(5):563-70.
105. de la Torre MS, Torres C, Nieto G, Vergara S, Carrero AJ, Macias J, et al. Vitamin D receptor gene haplotypes and susceptibility to HIV-1 infection in injection drug users. The Journal of infectious diseases. 2008;197(3):405-10.
106. Kelly JL, Drake MT, Fredericksen ZS, Asmann YW, Liebow M, Shanafelt TD, et al. Early life sun exposure, vitamin D-related gene variants, and risk of non-Hodgkin lymphoma. Cancer causes & control : CCC. 2012;23(7):1017-29.
107. Kosiniak-Kamysz A, Marczakiewicz-Lustig A, Marcinska M, Skowron M, Wojas-Pelc A, Pospiech E, et al. Increased risk of developing cutaneous malignant melanoma is associated with variation in pigmentation genes and VDR, and may involve epistatic effects. Melanoma research. 2014;24(4):388-96.
108. Mutti DO, Cooper ME, Dragan E, Jones-Jordan LA, Bailey MD, Marazita ML, et al. Vitamin D receptor (VDR) and group-specific component (GC, vitamin D-binding protein) polymorphisms in myopia. Invest Ophthalmol Vis Sci. 2011;52(6):3818-24.
109. Butler MW, Burt A, Edwards TL, Zuchner S, Scott WK, Martin ER, et al. Vitamin D receptor gene as a candidate gene for Parkinson disease. Ann Hum Genet. 2011;75(2):201-10.
110. Jacobs ET, Martinez ME, Campbell PT, Conti DV, Duggan D, Figueiredo JC, et al. Genetic variation in the retinoid X receptor and calcium-sensing receptor and risk of colorectal cancer in the Colon Cancer Family Registry. Carcinogenesis. 2010;31(8):1412-6.
111. Anderson LN, Cotterchio M, Cole DE, Knight JA. Vitamin D-related genetic variants, interactions with vitamin D exposure, and breast cancer risk among Caucasian women in Ontario. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2011;20(8):1708-17.
112. Jorde R, Schirmer H, Wilsgaard T, Bogeberg Mathiesen E, Njolstad I, Lochen ML, et al. The DBP Phenotype Gc-1f/Gc-1f Is Associated with Reduced Risk of Cancer. The Tromso Study. PLoS One. 2015;10(5):e0126359.
113. Janssens W, Bouillon R, Claes B, Carremans C, Lehouck A, Buysschaert I, et al. Vitamin D deficiency is highly prevalent in COPD and correlates with variants in the vitamin D-binding gene. Thorax. 2010;65(3):215-20.
114. Peng Q, Yang S, Lao X, Li R, Chen Z, Wang J, et al. Association of single nucleotide polymorphisms in VDR and DBP genes with HBV-related hepatocellular carcinoma risk in a Chinese population. PLoS One. 2014;9(12):e116026.
115. Kong J, Xu F, Qu J, Wang Y, Gao M, Yu H, et al. Genetic polymorphisms in the vitamin D pathway in relation to lung cancer risk and survival. Oncotarget. 2015;6(4):2573-82.
116. Martineau AR, Leandro ACCS, Anderson ST, Newton SM, Wilkinson KA, Nicol MP, et al. Association between Gc genotype and susceptibility to TB is dependent on vitamin D status. The European respiratory journal. 2010;35(5):1106-12.
117. Bakke PS, Zhu G, Gulsvik A, Kong X, Agusti AG, Calverley PM, et al. Candidate genes for COPD in two large data sets. The European respiratory journal. 2011;37(2):255-63.

118. Tayeb MT, Clark C, Haites NE, Sharp L, Murray GI, McLeod HL. CYP3A4 and VDR gene polymorphisms and the risk of prostate cancer in men with benign prostate hyperplasia. British journal of cancer. 2003;88(6):928-32.
119. Fernandez P, Zeigler-Johnson CM, Spangler E, van der Merwe A, Jalloh M, Gueye SM, et al. Androgen Metabolism Gene Polymorphisms, Associations with Prostate Cancer Risk and Pathological Characteristics: A Comparative Analysis between South African and Senegalese Men. Prostate Cancer. 2012;2012:798634.
120. Leung TF, Wang SS, Tang MF, Kong AP, Sy HY, Hon KL, et al. Childhood asthma and spirometric indices are associated with polymorphic markers of two vitamin D 25-hydroxylase genes. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology. 2015;26(4):375-82.
121. Morrison MA, Silveira AC, Huynh N, Jun G, Smith SE, Zacharaki F, et al. Systems biology-based analysis implicates a novel role for vitamin D metabolism in the pathogenesis of age-related macular degeneration. Hum Genomics. 2011;5(6):538-68.
122. Fuhrman BJ, Freedman DM, Bhatti P, Doody MM, Fu Y-P, Chang S-C, et al. Sunlight, polymorphisms of vitamin D-related genes and risk of breast cancer. Anticancer research. 2013;33(2):543-51.
123. Shen H, Bielak LF, Ferguson JF, Streeten EA, Yerges-Armstrong LM, Liu J, et al. Association of the vitamin D metabolism gene CYP24A1 with coronary artery calcification. Arterioscler Thromb Vasc Biol. 2010;30(12):2648-54.
124. Fichna M, Zurawek M, Januszkiewicz-Lewandowska D, Gryczynska M, Fichna P, Sowinski J, et al. Association of the CYP27B1 C(-1260)A polymorphism with autoimmune Addison's disease. Experimental and clinical endocrinology & diabetes : official journal, German Society of Endocrinology [and] German Diabetes Association. 2010;118(8):544-9.
125. Bailey R, Cooper JD, Zeitels L, Smyth DJ, Yang JHM, Walker NM, et al. Association of the vitamin D metabolism gene CYP27B1 with type 1 diabetes. Diabetes. 2007;56(10):2616-21.
126. Wilke RA, Simpson RU, Mukesh BN, Bhupathi SV, Dart RA, Ghebranious NR, et al. Genetic variation in CYP27B1 is associated with congestive heart failure in patients with hypertension. Pharmacogenomics. 2009;10(11):1789-97.
127. Alloza I, Otaegui D, de Lapuente AL, Antiguedad A, Varade J, Nunez C, et al. ANKRD55 and DHCR7 are novel multiple sclerosis risk loci. Genes and immunity. 2012;13(3):253-7.
128. Wang LL, Pan XL, Wang Y, Tang HD, Deng YL, Ren RJ, et al. A single nucleotide polymorphism in LRP2 is associated with susceptibility to Alzheimer's disease in the Chinese population. Clinica chimica acta; international journal of clinical chemistry. 2011;412(3-4):268-70.
129. Vargas T, Bullido MJ, Martinez-Garcia A, Antequera D, Clarimon J, Rosich-Estrago M, et al. A megalin polymorphism associated with promoter activity and Alzheimer's disease risk. American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics. 2010;153B(4):895-902.
130. Ramos-Lopez E, Lange B, Penna-Martinez M, Bruck P, Swiech K, Mauf S, et al. The role of cubilin gene polymorphisms and their influence on 25(OH)D3 and 1,25(OH)2D3 plasma levels in type 1 diabetes patients. The Journal of steroid biochemistry and molecular biology. 2010;121(1-2):442-4.

Figure Captions

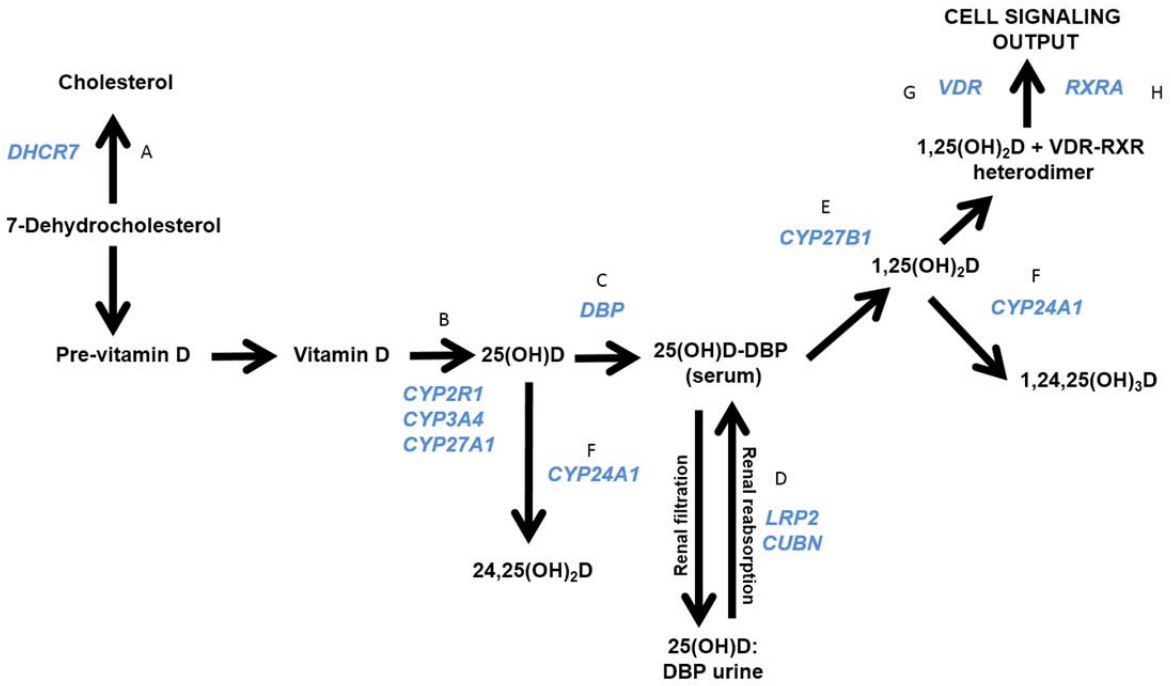
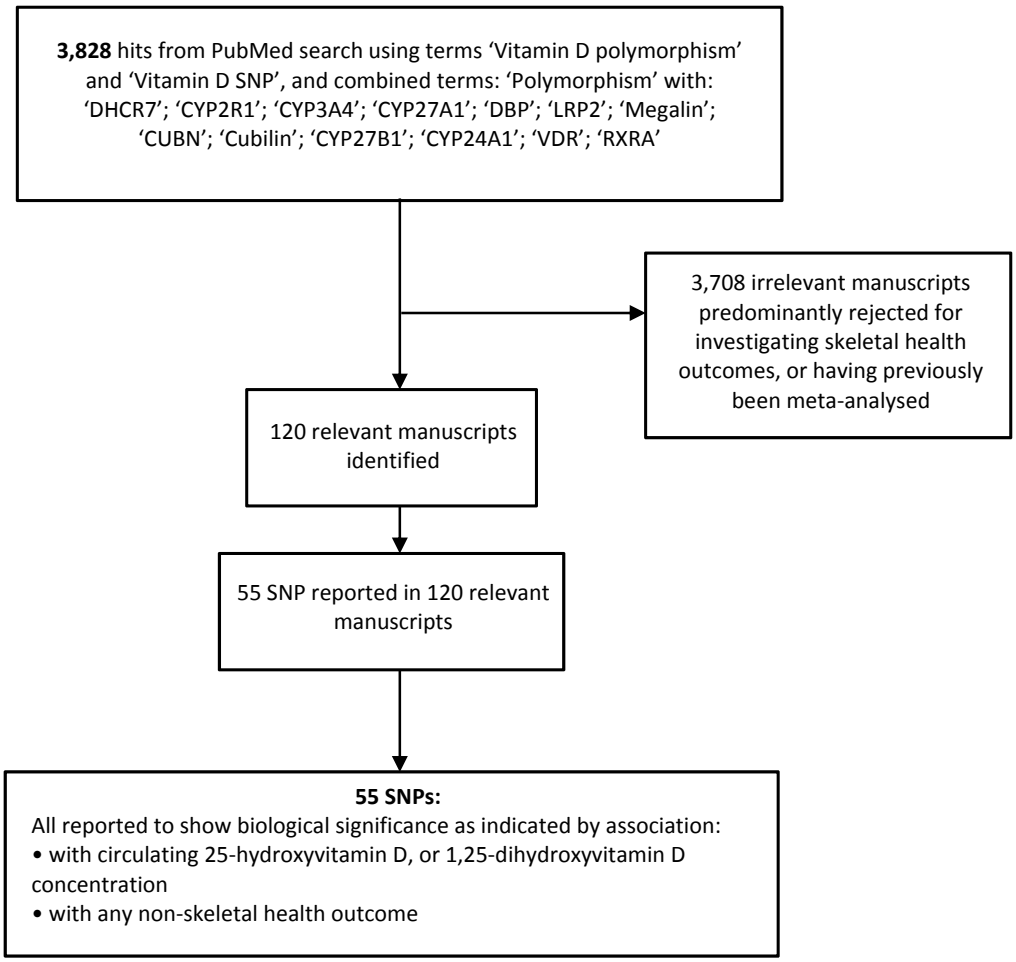


Figure.1: A diagram depicting vitamin D metabolic and signalling pathways and genes encoding key players (in blue): *DHCR7* (A) encodes the 7-dehydrocholesterol reductase enzyme, which catalyses the conversion of 7-dehydrocholesterol to cholesterol; *CYP2R1*, *CYP3A4*, and *CYP27A1* (B) encode 25-hydroxylating cytochrome P450 enzymes; the vitamin D binding protein gene (*DBP*, [C]) encodes the principle vitamin D transport protein; *LRP2* & *CUBN* (D) encode the proteins megalin and cubilin, respectively, involved in renal re-absorption of 25(OH)D via receptor-mediated endocytosis; *CYP27B1* (E) encodes the cytochrome P450 enzyme which 1-alpha-hydroxylates 25(OH)D to form $1,25(OH)_2D$; *CYP24A1* (F) encodes the cytochrome P450 enzyme responsible for 24-hydroxylating vitamin D metabolites including 25(OH)D and $1,25(OH)_2D$; *VDR* (G) encodes the vitamin D receptor, which binds $1,25(OH)_2D$ and forms a heterodimer with the gene product of *RXRA* (H) – the retinoid X receptor – to mediate the biological actions of vitamin D.

Figure.2: Flow diagram depicting the literature search and SNP selection process.



Tables

Table 1. Single nucleotide polymorphisms in vitamin D metabolic, transport and signalling pathways reported to associate with 25-hydroxyvitamin D (25D) and/or 1,25-dihydroxyvitamin D (1,25D) concentrations.

Gene (Location)	SNP	SNP Location/ description	Reference	Findings/Comments
VDR (chr12q13.11)	**rs10783219**	Intron 0, A>T.	**1.**Engelman, 2008 (13); **2.**Lee, 2014 (14)	**1.** Associates with 25D levels in San Antonio Hispanics (P=0.004); not San Luis Valley Hispanics, or Los Angeles African Americans. **2.** Associates with 25D levels in largely white cohort: TA more frequent in deficient group (63%); AA more frequent in replete group (70%), P=0.013.
DBP (chr4q13.3)	**rs4588**	Exon 11, C>A. Defines Gc phenotype with rs7041.	**1.**Lauridsen, 2005 (15); **2.** Kurylowicz, 2006 (16); **3.**Wjst, 2007 (17); **4.**Engelman, 2008 (13), **5.**Abbas, 2008 (18); **6.**Fu, 2009 (19); **7.**Sinotte, 2009 (20); **8.**Fang, 2009 (21); **9.**Janssens, 2010 (22); **10.**Ahn, 2010 (10); **11.**Robien, 2013 (23)	**1-11.** Minor allele (A) consistently associates with lower 25D/1,25D levels. rs4588-rs7041 haplotype: Gc1s-1s (CC rs4588; GG rs7041) associates with higher 25D status; Gc2-2 (AA rs4588; TT rs7041) associates with lower 25D status; Gc1s-1s (CC rs4588; GG rs7041) associates with higher 1,25D concentration; Gc2-2 (AA rs4588; TT rs7041) associates with lower 1,25D concentration.
	rs7041	Exon 11, T>G. Defines Gc phenotype with rs4588.	**1.**Lauridsen, 2005 (15); **2.**Engelman, 2008 (13); **3.**Abbas, 2008 (18); **4.**Sinotte, 2009 (20); **5.**Fang, 2009 (21); **6.**Janssens, 2010 (22); **7.**Ahn, 2009 (10); **8.**Wang, 2010 (9); **9.**Robien, 2013 (23);	**1-9.** Minor allele (G) consistently associates with higher 25D/1,25D levels. rs4588-rs7041 haplotype: Gc1s-1s (CC rs4588; GG rs7041) associates with higher 25D status; Gc2-2 (AA rs4588; TT rs7041) associates with lower 25D status; Gc1s-1s (CC rs4588; GG rs7041) associates with higher 1,25D concentration; Gc2-2 (AA rs4588; TT rs7041) associates with lower 1,25D concentration.
	rs1155563	Intron 1, T>C.	**1.**Ahn, 2009 (10); **2.**Hibler, 2012 (24); **3.**Lu, 2011 (25); **4.**Zhang, 2013 (26); **5.**Perna, 2013 (27); **6.**Suaini, 2014 (28); **7.**Elkum, 2014 (29); **8.**Anderson, 2014 (30)	**1&2.** GWAS HIT: associates with 25D levels in predominantly white participants. In high LD with rs2282679 and rs7041. **3&4.** Haplotypes including rs1155563 associates with 25D levels in Chinese cohorts. **5.** Season-specific association with 25D levels in German older adults. **6.** Minor allele associates with greater odds of vitamin D insufficiency (≤50 nmol/L) in 12 mo Caucasian infants. **7.** Associates with 25D levels in Arab (P=0.03), but not South Asian or Southeast Asian participants. **8.** GWAS in children: associates with 25D levels in those aged 14 yrs old.
	rs17467825	3'UTR, A>G.	**1.**Wang, 2010 (9); **2.**Suaini, 2014 (28); **3.**Elkum, 2014 (29); **4.**Anderson, 2014 (30); **5.**Nissen, 2014 (31)	**1.** GWAS HIT associates with 25D levels; replicated. Overall P=6.75×10^{-74}. **2.** Minor allele associates with greater odds of vitamin D insufficiency (≤50 nmol/L) in 12 mo Caucasian infants. **3.** Associates with 25D levels in Arab (P=0.02) and South Asian participants (P=0.001), but not Southeast Asians. **4.** GWAS in children: associates with 25D levels in 6 yr olds. **5.** Associates with 25D levels in Danish children and adults (P<0.0001): GG (Minor hom) -13.7 nmol/L *vs.* AA.
	rs2070741	A>C.	Wood et al., 2010 (32)	Minor allele (C) allele mildly associates with decreased 25D levels in Caucasians (p=0.05)
	rs2298849	Intron 1, T>C.	**1.**Signorello, 2011 (33); **2.**Robien, 2013 (23); **3.**Xu, 2014 (34)	**1.** Associates with 25D levels in African Americans (P=0.01): AA (Minor hom) -8.2 nmol/L *vs.* GG. No association in Caucasian participants. **2.** Associates with 25D levels in Chinese adults (P=0.001): CC (Min hom) +8.3 nmol/L *vs.* TT. **3.** Associates with 25D levels in post-menopausal Chinese Hans (P<0.001).
	rs16846876	A>T.	**1.**Hibler, 2012 (24); **2.**Nissen, 2014 (31)	**1.** Associates with 25D levels. Mean change under additive model: -2.95 (units not reported) (95% CI -4.27 to -1.63, P<0.001). **2.** Associates with 25D levels in Danish children and adults (P<0.001): TT (Minor hom) -11.2 nmol/L *vs.* AA.
	rs842999	G>C.	**1.**Hibler, 2012 (15); **2.**Nissen, 2014 (31)	**1.** Associates with 25D levels. Mean change under additive model: -1.92 (units not reported) (95% CI -3.10 to -0.73, P=0.002). **2.** Associates with 25D levels in Danish children and adults (P<0.001): CC (Minor hom) -11.1 nmol/L *vs.* GG.
	rs222035	Intron 8, A>C.	Hibler, 2012 (24)	Associates with 25D levels. Mean change under additive model: -2.21 (units not reported) (95% CI -3.46 to -0.95, P=0.001).
	rs3755967	G>A.	**1.**Wang, 2010 (9); **2.**Suaini, 2014 (28); **3.**Elkum, 2014 (29)	**1.** GWAS HIT: associates with 25D levels; replicated. Overall P=2.42×10^{-75}. **2.** Minor allele associates with greater odds of vitamin D insufficiency (≤50 nmol/L) in 12 mo Caucasian infants. **3.** Associates with 25D levels in Arab (P=0.04) and South Asian participants (P=0.0007), but not Southeast Asians.
	rs2298850	G>C.	**1.**Wang, 2010 (9); **2.**Elkum, 2014 (29)	**1.** GWAS HIT: associates with Vit D levels; replicated. Overall P=2.03×10^{-71}. **2.** Associates with 25D levels in Arab (P=0.04) and South Asian participants (P=0.01), but not Southeast Asians.In high LD (r^2>0.8) with rs4588.
	rs12512631	3'UTR, T>C.	**1.**Ahn, 2009 (4); **2.**Perna, 2013 (27); **3.**Nissen, 2014 (31); **4.**Barry, 2014 (35)	**1.** Associates with 25D levels (P=0.0004): CC (Minor hom) +8.2 nmol/L *vs.* TT. **2.** Season-specific association with 25D levels in German older adults. **3.** Associates with 25D levels in Danish children and adults. **4.** Associates with 25D levels in White adults, US (P<0.0001).

	rs2282679	Intron 12, A>C.	**1.**Ahn, 2009 (4); **2.**Wang, 2010 (9); **3.**Signorello, 2011 (33); **4.**Perna, 2013 (27); **5.**Cheung, 2013 (36); **6.**Suaini, 2014 (28); **7.**Elkum, 2014 (29); **8.**Nissen, 2014 (31)	**1.** Associates with 25D levels (P=0.00004): CC (Minor hom) -6.6 nmol/L *vs.* AA. **2.** GWAS hit: strong association with 25D levels ($P=1.9\times10^{-109}$); is in LD with rs7041 and rs1155563. **3.** Associates with 25D levels in African Americans (P=0.03): GG (Minor hom) -8.3 nmol/L *vs.* TT. No association in Caucasian participants. **4.** Season-specific association with 25D levels in German older adults. **5.** Minor allele associated with greater odds of vitamin D insufficiency (≤50 nmol/L) in adult Chinese females: OR 1.51 (95% CI 1.19 - 1.93, $P=8.6\times10^{-4}$). **6.** Minor allele associates with greater odds of vitamin D insufficiency in 12 mo Caucasian infants. **7.** Associates with 25D levels in Arab and South Asian participants. **8.** Associates with 25D levels in Danish children and adults.
CYP2R1 (chr11p15.2)	**rs10741657**	G>A.	**1.**Ramos-Lopez, 2007 (37); **2.**Wang, 2010 (9); **3.**Robien, 2013 (23); **4.**Hassanein, 2014 (38); **5.**Barry, 2014 (35); **6.**Batai, 2014 (39); **7.**Nissen, 2014 (31); **8.**Ye, 2015 (40)	**1.** Associates with 25D levels (P=0.003). **2.** GWAS Hit: associates with 25D levels; replicated ($OverallP=3.3\times10^{-20}$). **3.** Associates with 25D levels in Chinese adults (P=0.2): AA (Min hom) +5.1 nmol/L *vs.* GG. **4.** Associates with 25D levels in males. **5.** Associates with 25D levels in White adults, US (P<0.0001). **6.** Minor allele (A) associates with increased 25D levels in African Americans (P=0.01) and European Americans (0.003). **7.** Associates with 25D levels in Danish children and adults (P<0.0001): AA (Min hom) +9.4 nmol/L *vs.* GG. **8.** Associates with 25D levels in large combined dataset of participants of European descent: -3.22 nmol/L per risk allele (95% CI 1.79 - 4·66, P<0.05).
	rs2060793	5'UTR, G>A.	**1.**Ahn, 2010 (10); **2.**Zhang, 2012 (26)	**1.** GWAS Meta-analysis: associates with 25D levels (Overall $P=1.4x10^{-5}$). **2.** Associated with 25D levels in Chinese Hans (9.4×10^{-14}). In perfect LD ($r^2=1.0$) with rs10741657.
	rs1993116	Intron 1, C>T.	**1.**Wang, 2010 (9); **2.**Ahn, 2010 (10); **3.**Robien, 2013 (23); **4.**Batai, 2014 (39)	**1&2.** GWAS HIT: associates with 25D levels (Overall $P=6.25\times10^{-11}$ in Wang, 2010). **3.** Associates with 25D levels in Chinese adults (P=0.4): TT (Min hom) +3.9 nmol/L *vs.* CC. **4.** Minor allele (T) associates with increased 25D levels in African Americans (P=0.02) and European Americans (0.0006).
	rs7116978	C>T.	**1.**Wang, 2010 (9); **2.**Nissen, 2014 (31)	**1.** GWAS HIT: associates with 25D levels (Overall $P=4.99\times10^{-9}$). **2.** Associates with 25D levels in Danish children and adults (P<0.0001): TT (Min hom) +10.7 nmol/L *vs.* CC.
	rs12794714	Exon 1,G>A.	**1.**Wang, 2010 (9); **2.**Robien, 2013 (23); **3.**Barry, 2014 (35); **4.**Batai, 2014 (39)	**1.** GWAS HIT: associates with 25D levels (Overall $P=1.84\times10^{-9}$). **2.** Associates with 25D levels in Chinese adults (P<0.001): AA (Min hom) -10.6 nmol/L *vs.* GG. **3.** Associates with 25D levels in White adults, US (P<0.0001). **4.** Minor allele (A) associates with decreased 25D levels in African Americans (P=0.01) and European Americans (P=0.005).
	rs10500804	A>C.	**1.**Wang, 2010 (9); **2.**Azad, 2012 (41); **3.**Elkum, 2014 (29)	**1.** GWAS HIT: associates with 25D levels (Overall $P=2.67\times10^{-9}$). **2.** CC (Min hom) associates with lower 25D levels *vs.* AA in Canadians (P=0.001). **3.** Associates with 25D levels in Arab (P=0.04), but not South Asian, or South East Asian participants.
	rs10766197	G>A.	**1.**Zhang, 2012 (26); **2.**Barry, 2014 (35); **3.**Nissen, 2014 (31)	**1.** Associates with 25D levels in Chinese Hans (P=0.004). **2.** Associates with 25D levels (P=0.0002) and differential response to vitamin D supplementation (P=0.02) in White adults, US. **3.** Associates with 25D levels in Danish children and adults (P<0.0001): AA (Min hom) -7.4 nmol/L *vs.* GG.
CYP24A1 (chr20q13.2)	**rs6013897**	G>A.	**1.**Wang, 2010 (9); **2.**Cooper, 2011 (42); **3.**Barry, 2014 (35)	**1.** GWAS HIT: associates with 25D levels (Overall $P=6.0\times10^{-10}$). **2.** Associates with 25D levels in UKBS-CC cohort (P=0.02). **3.** Associates with differential response to vitamin D supplementation in White adults, US (P=0.04).
	rs2248137	C>G.	Pillai, 2011 (43)	Minor allele associates with decreased 25D levels (P=0.006).
CYP27B1 (chr12q14.1)	**rs10877012**	Promoter region, C>A.	**1.**Hyppönen, 2009 (44); **2.**Signorello, 2011 (33); **3.**Lange, 2011 (45)	**1.** Associates with 25D levels: 1.9% difference for A vs. C allele (P = 0.01). **2.** Minor allele associates with higher 25D levels in African Americans; no association in Caucasians. **3.** Associates with 1,25D levels: 72, 61, and 60 pmol/ml for AA, AC, and CC, respectively (P=0.04).
	rs118204009	C>T.	Ramagopalan, 2011 (46)	Associates with 1,25D levels. Causes complete loss of CYP27B1 function
	rs703842	5' UTR, T>C.	Orton, 2008 (47)	Associates with 25D levels in Canadian twins (P<0.001): TT genotype +27 nmol/L *vs.* CC genotype
	rs4646536	Intron 6, T>C.	Orton, 2008 (47)	Associates with 25D levels in Canadian twins (P<0.001): TT genotype +24 nmol/L *vs.* CC genotype
DHCR7 (chr11q13.4)	**rs12785878**	Intron 2, G>T.	**1.**Wang, 2010 (9); **2.**Zhang, 2012(2) (48); **3.**Cheung, 2013 (36); **4.**Strawbridge, 2014 (49); **5.**Voipio, 2015 (50)	**1.** GWAS Hit: associates with 25D levels; replicated ($OverallP=2.12\times10^{-27}$). **2.** Associated with 25D levels in Chinese Han children (P=0.01). **3.** Associated with vitamin D insufficiency (<50 nmol/L) in Southern Chinese women (P=0.04). **4.** G allele associates with decreased 25D levels (P=0.0006). **5.** G allele associates with increased odds of vitamin D insufficiency (<50 nmol/L) in Finnish adults: OR 1.31 (95% CI 1.00 - 1.70, P<0.05)*vs.* T allele.
	rs3829251	G>A.	**1.**Ahn, 2010 (10); **2.**Lu, 2011 (25); **3.**Zhang, 2012(2) (48); **4.**Strawbridge, 2014 (49)	**1.** GWAS Meta-analysis: associates with 25D levels (Overall $P=8.8\times10^{-7}$). **2.** Risk alleles (AG) for rs3829251 and rs1790349 associate with decreased 25D levels in Chinese Han adults. **3.** Associated with 25D levels in Chinese Han children (P=0.001). **4.** Minor allele (A) associates with decreased 25D levels (P=0.0004).
	rs7944926	Intron 1, G>A.	**1.**Wang, 2010 (9); **2.**Davies, 2011 (51)	**1.** GWAS Hit: associates with 25D levels; replicated ($OverallP=8.96\times10^{-16}$). **2.** Associates with 25D levels in UK participants: AA genotype-6.0 nmol/L *vs.* GG (P=0.03).
	rs12800438	G>A.	**1.**Wang, 2010 (9); **2.**Batai, 2014 (39)	**1.** GWAS Hit: associates with 25D levels; replicated ($OverallP=2.54\times10^{-15}$). **2.** Risk genotype associated with increased odds of vitamin D insufficiency (<50 nmol/L) in African Americans: OR 0.76 (95% CI 0.58 – 0.99, P=0.04). In perfect LD with rs12785878 ($r^2=1.0$).

	rs3794060	C>T.	Wang, 2010 (9)	GWAS Hit: associates with 25D levels; replicated (OverallP=3.38×10^{-15}). In perfect LD with rs12785878 (r^2=1.0).
	rs4945008	G>A.	Wang, 2010 (9)	GWAS Hit: associates with 25D levels; replicated (OverallP=4.55×10^{-15}). In high LD with rs12785878 (r^2=0.95).
	rs4944957	G>A.	Wang, 2010 (9)	GWAS Hit: associates with 25D levels; replicated (OverallP=8.70×10^{-15}). In perfect LD with rs12785878 (r^2=1.0).
RXRA (chr9q34.3)	**rs9409929**	G>A.	Hibler, 2010 (52)	Associates with 1,25D levels: increasing concentration with increasing no. copies of the *A* allele (p-trend=0.003).

Abbreviations: CI: confidence interval, Min hom: minor homozygous, VDR: vitamin D receptor, DBP: vitamin D binding protein, Gc: group-specific component; GWAS: genome-wide association study, LD: linkage disequilibrium, 3'UTR: 3-prime untranslated region, CYP2R1: cytochrome P450-2R1, 5'UTR: 5-prime untranslated region, UKBS-CC: U.K. Blood Services Common Controls, CYP24A1: cytochrome P450-24A1, CYP27B1: cytochrome P450-27B1, DHCR7: 7-dehydrocholesterol reductase, RXRA: retinoid-X receptor A.

Table 2. Single nucleotide polymorphisms in the vitamin D signalling pathway, reported to associate with non-skeletal health outcomes

Gene	SNP (description)	Disease association	Reference	Findings/Comments
VDR (chr12q13.11)	**rs10735810** (Exon 2, C[F]>T[f], *FokI* restriction endonuclease. Previously rs2228570)	Severe RSV infection	Kresfelder, 2011 (53)	f allele associates with increased risk in South African children: OR 1.820 (95% CI 1.183 - 2.801, p=0.006) *vs.* F allele.
		Tuberculosis	**1.**Wilkinson, 2000(54) **2.**Zhang, 2010 (55) **3.**Sharma, 2011 (56)	**1.** ff genotype or undetectable serum 25D levels associate with increased risk in Gujarati Asians living in West London: OR 5.1 (95% CI 1.4– 18.4, P=0.008) *vs.* FF. **2.** ff genotype associates with increased spinal TB susceptibility in Chinese Hans: OR 2.18 (95% CI 1.24 - 3.83, P<0.05) *vs.* FF. **3.** ff genotype associates with increased risk of MDR smear +ve TB in North Central Indian castes: OR 3.4 (P=0.01) *vs.* FF.
		Psoriasis	Lee, 2012 (57)	Meta-analysis: ff genotype associates with increased risk in Turkish cohorts: OR 3.58 (95% CI 1.60 – 8.01, P=0.002) *vs.* FF.
		Hepatitis B	Li, 2006 (58)	fF/ff genotypes associate with increased risk: OR 1.70 (P=0.02) *vs.* FF.
		Acute Lower Respiratory Infection	Roth, 2012 (59)	ff genotype associates with increased risk in early childhood: OR 7.38 (95% CI 1.17 - 46.55, P=0.03) *vs.* FF.
		Urinary Tract Infection	Aslan, 2012 (60)	ff genotype associates with increased risk in children: OR 3.94 (95% CI 1.71 - 9.09, P<0.01) *vs.* FF.
		Asthma	**1.**Pillai, 2011 (43) **2.**Samir, 2014 (61)	**1.** Associates with IgE concentration (P=0.002); pre-bronchodilator and change in FEV_1/FVC (P=0.02), in young African Americans. **2.** ff genotype associates with increased IgE and Th2 cytokine concentrations in Egyptian children (P=0.007).
		Hypertension	Swapna, 2011 (62)	FF genotype associates with increased risk: OR 1.20 (95% CI 1.23 - 3.93, P<0.01) *vs.* ff.
		Systemic Lupus Erythematosus	Luo, 2011 (63)	F allele associates with increased risk: RR 1.630 (95% CI 1.21 - 2.20, P=0.001) *vs.* f allele
		Renal Cell Carcinoma	Arjumand, 2011 (64)	ff genotype combined with bb genotype for *BsmI* associates with increased risk in North Indians: OR 1.88 (95% CI 1.05 - 3.63, P=0.04) *vs.* FF+BB genotypes.
		Rheumatoid arthritis	Lee, 2010 (65)	Meta-analysis: F allele associates with increased risk in Europeans: OR 1.50 (95% CI 1.16 -1.95, P=0.002) *vs.* f allele.
		Breast cancer	Mun, 2015 (66)	Meta-analysis: ff genotype associates with increased risk (P<0.05) *vs.* FF.
		Thyroid cancer	Penna-Martinez, 2009 (67)	ff genotype associates with increased risk in Germans (P=0.04) *vs.* FF.
		Diabetes (type 1)	Panierakis, 2009 (68)	F allele associates with decreased risk in Cretan Greeks: OR 0.52 (95% CI 0.32 - 0.85, P=0.008) *vs.* f allele.
		Ovarian cancer	Mun, 2015 (66)	Meta-analysis: ff genotype associates with increased risk (P<0.05) *vs.* FF.
		RSV-related disease	Kresfelder, 2011 (53)	Associates with risk in South African children (P=0.008).
		Parkinson's Disease	Gao, 2014 (69)	Meta-analysis: f allele associates with increased risk: OR 1.41 (95% CI 1.14–1.75, P=0.001) *vs.* F allele.
		S.aureus carriage	Messaritakis, 2014 (70)	ff genotype associates with increased risk in Cretan Greeks with Type 2 Diabetes (P<0.001) *vs.* FF.
		Diabetic Retinopathy	Zhong, 2015 (71)	f allele associates with increased risk in Chinese Hans with Type 2 Diabetes: OR 1.47 (P<0.01) *vs.* F allele.
	rs1544410 (Intron 8, A[B]>G[b], *BsmI* restriction endonuclease. In high LD [r^2=0.9] with rs731236)	HIV	**1.**Moodley, 2013 (72) **2.**Torres, 2010 (73)	**1.** BB genotype associates with more rapid disease progression in Hispanic children: HR 6.60(P=0.03) *vs.* bb. **2.** bb genotype associates with delayed progression to AIDS and increased resistance to HIV-1.
		Psoriasis	Lee et al., 2012 (57)	Meta-analysis: B allele associates with decreased risk in Asians: OR 0.64 (95% CI 0.41 - 0.98, P=0.04) *vs.* b allele.
		Autoimmune thyroid diseases	Feng, 2013 (74)	Meta-analysis: B allele associates with decreased risk of autoimmune thyroid diseases (Graves' disease & Hashimoto's thyroiditis): OR 0.80 (95% CI 0.71 – 0.91, P=0.001) *vs.* b allele.
		Tuberculosis	Sharma, 2011 (56)	bb genotype associates with risk of smear +ve & MDR TB in three Central India populations: Tribes (OR 3.7, P=0.002); South Eastern-Castes (OR 2.1, P=0.0004); and Muslims (OR 6.7 P=0.01) *vs.* BB.
		SLE & Lupus Nephritis	Lee, 2011 (65)	Meta-analysis: B allele associates with increased risk of SLE (OR 3.58, 95% CI 1.41 - 9.13, P=0.007) and LN (OR 3.65, 95% CI 1.35 - 9.90, P=0.011) in Asians, *vs.* b allele.
		End-stage renal disease	Testa, 2010 (75)	Associates with risk of ESRD, as measured by left-ventricular mass index (P=0.006).
		Diabetes (type 1)	Panierakis, 2009 (68)	B allele associates with decreased risk in Cretan Greeks: OR 0.65 (95% CI 0.44 - 0.97, P=0.04) *vs.* b allele.
		Osteoporosis	Jia, 2013 (76)	Meta-analysis: bb genotype associates with decreased risk across 26 studies: OR 0.61 (95% CI 0.40 - 0.92, P<0.05) *vs.* BB.
		Colorectal cancer	Jenab, 2009 (77)	BB genotype associates with decreased risk in Europeans: RR, 0.76 (95% CI 0.59 - 0.98, P<0.05) *vs.* bb.
		Melanoma	Orlow, 2012 (78)	bb genotype associates with increased risk in multi-centre study; predominantly Caucasians: OR 1.30 (95% CI 1.04 - 1.63, P<0.05) *vs.* BB.
		Periodontitis	Deng, 2011 (79)	Meta-analysis: bb genotype associates with decreased risk in Asians: OR 0.63 (95% CI 0.42 - 0.94, p=0.02) *vs.* BB.
		Vitiligo	Li, 2015 (80)	Meta-analysis: bb genotype associates with increased risk in East Asians: OR 1.32 (95% CI 1.09 – 1.59, P<0.01) *vs.* BB.
		Renal Cell Carcinoma	Ou, 2014 (81)	Meta-analysis: BB genotype associates with risk in Asians (P<0.05) *vs.* bb.

	Gout	Liu, 2015 (82)	b allele associates with increased risk in male Chinese Hans: OR 1.57 (95% CI 1.14 - 2.18, P=0.006) *vs.* B allele.
rs7975232 (Intron 8, A[A]>C[a], *ApaI* restriction endonuclease)	HAM/TSP	Saito, 2005 (83)	AA genotype associates with reduced risk of HAM/TSP: OR 0.28 (95% CI 0.13 - 0.63, P=0.001) *vs.* aa.
	Colorectal Cancer	Mahmoudi, 2010 (84)	aa genotype associates with increased risk of CRC in Iranians: OR 2.32 (95% CI 1.19 - 4.54, P=0.014) *vs.* AA.
	Graves' Disease	Abd El Gawad, 2011 (85)	aa genotype associates with increased risk of GD: OR 2.79 (95% CI 1.12 - 6.93, P<0.05) *vs.* AA.
	Psoriasis	Lee, 2012 (57)	Meta-analysis: A allele associates with decreased risk of psoriasis in Turkish populations: OR 0.68 (95% CI 0.48 - 0.99, P=0.04) *vs.* a allele.
	Asthma	Saadi, 2009 (86)	AA genotype associates with increased risk of asthma in Chinese Han population: OR 1.33 (95% CI 1.10 - 1.60, P=0.002) *vs.* aa.
	Thyroid cancer	Penna-Martinez, 2009 (67)	aa genotype associates with increased risk in Germans (P=0.04) *vs.* AA.
	Diabetes (type 1)	Panierakis, 2009 (68)	A allele associates with increased risk in Cretan Greeks: OR 1.61 (95% CI 1.07 - 2.41, P=0.02) *vs.* a allele.
	Prostate cancer	**1.**Onen, 2008 (87) **2.**Jingwi, 2015 (88)	**1.** Associates with risk of sporadic PCa (P=0.009). **2.** Associates with PCa risk in African Americans (P<0.05).
	Periodontitis	Deng, 2011 (79)	Meta-analysis: AA genotype associates with increased risk in Asians:OR 2.20 (95% CI 1.39 - 3.48, P<0.001) *vs.* aa.
	Hepatitis C	Baur, 2012 (89)	aa genotype associates with rapid fibrosis progression: OR 2.32 (95%CI 1.05 – 5.10, P=0.04); increased risk of cirrhosis: OR 2.67 (95% CI 1.29 – 5.51, P=0.009) *vs.* AA, in >90% Caucasian Swiss patients.
	Atopic Dermatitis	Heine, 2013 (90)	a allele associates with increased risk: OR 1.57 (95% CI 1.10 – 1.96, P=0.006) *vs.* A allele.
	Breast cancer	Dalessandri, 2011 (91)	aa genotype associates with increased risk (P=0.0003) *vs.* AA genotype.
	Hepatocellular carcinoma	Hung, 2014 (92)	aa genotype associates with increased development: OR 3.02 (95% CI 1.65 – 5.51, P<0.05) *vs.* AA.
	Leprosy	Neela, 2015 (93)	A allele associates with increased risk in Indians (P=0.001) *vs.* a allele.
	Vitiligo	Li, 2015 (80)	Meta-analysis: aa/aA genotypes associate with increased risk in East Asians: OR 1.40 (95% CI 1.01 – 1.96, P<0.05) *vs.* AA.
	Renal Cell Carcinoma	Ou, 2014 (81)	Meta-analysis: AA genotype associates with risk in Asians (P<0.05) *vs.* aa.
	Dengue fever	Alagarasu, 2012 (94)	a allele associates with decreased risk: OR 0.54 (95% CI 0.36 – 0.82, P=0.01) *vs.* A allele.
rs731236 (Exon 9,T[T]>C[t], *TaqI* restriction endonuclease)	Oral Squamous Cell Carcinoma	Bektas-Kayhan, 2010 (95)	Associates with risk (P<0.05).
	Graves' Disease	Abd El Gawad, 2011 (85)	TT genotype associates with increased risk: OR 3.05 (95% CI 1.48 - 6.28, P<0.05) *vs.* tt.
	Diabetes (type 1)	Panierakis, 2009 (68)	T allele associates with increased risk in Cretan Greeks: OR 2.24 (95% CI 1.49 - 3.36, P=0.0001) *vs.* t allele.
	Autoimmune Thyroid Diseases	Feng, 2013 (74)	Meta-analysis: t allele associates with decreased risk: OR 0.85 (95% CI 0.76 – 0.96, P=0.01) *vs.* T allele.
	Systemic Lupus Erythematous	Carvalho, 2014(96)	TT genotype associates with increased disease severity in North Portugese (P=0.046) *vs.* tt.
	Primary Biliary Cirrhosis	Li, 2014 (97)	T allele associates with decreased risk in Europeans and Asians: OR 0.75 (95% CI 0.63 – 0.89, P=0.001) *vs.* t allele.
	Breast cancer	Perna, 2013 (98)	tt genotype associates with increased risk of breast cancer mortality: HR 2.80 (95% CI 1.10 – 7.20, P<0.05) *vs.* TT.
	Obesity	Vasilopoulos, 2013 (99)	T allele associates with increased risk in Greeks: OR 2.07 (95% CI 1.12 - 3.82, P=0.02) *vs.* t allele.
	Periodontitis	Tanaka, 2013 (100)	tt genotype associates with increased risk in Japanese women: OR 3.68 (95% CI 1.06 – 12.78, P<0.05) *vs.* TT.
	Tuberculosis	Martineau, 2011 (11)	tt genotype associates with increased effect of vitamin D supplementation on sputum culture conversion time: 8.09 (95% CI 1.36 – 48.01, P=0.02) *vs.* TT.
	Multiple Sclerosis	Agliardi, 2011 (101)	TT genotype associates with decreased risk in HLA-DRB1*15-positive MS patients: OR: 0.53 (95% CI 0.33 - 0.83, P=0.004) *vs.* tt.
rs11568820 (Promoter, G>A, cdx2)	Rubella	Ovsyannikova, 2010 (102)	Minor allele (A) associates with decreased TNF-α concentration post rubella vaccination (P=0.02) *vs.* G allele.
	Alzheimer's Disease	Wang, 2012 (103)	Minor allele (A) associates with increased risk of late-onset AD: OR 1.69 ($P=9.1\times10^{-6}$) *vs.* G allele
	Gout	Liu, 2015 (82)	Minor allele (A) associates with increased risk in male Chinese Hans: OR 1.25 (95% CI 1.05 - 1.49, P=0.01) *vs.* G allele.
rs7976091 (Promoter, C>T)	Alzheimer's Disease	Wang, 2012 (103)	Minor allele (T) associates with increased risk of late-onset AD: OR 1.55 ($P=8.9\times10^{-5}$) *vs.* C allele. In perfect LD ($r^2=1.0$) with rs11568820.
rs11574010	Multiple sclerosis	Dickinson, 2009 (104)	G allele associates with increased risk of MS in those with low sun exposure during childhood (P=0.01).
rs4516035 (EcoRV, A>G)	HIV	Torre, 2008 (105)	In a 5 SNP haplotype which associates with risk of HIV-1 infection: OR 0.4 (95% CI 0.22 - 0.72, P=0.003).
	Non-Hodgkin Lymphoma	Kelly, 2012 (106)	Associates with modified effect of early life sun exposure on risk of non-Hodgkin lymphoma (P for interaction=0.006).
	Melanoma	Orlow, 2012 (78)	GG genotype (min hom) associates with increased risk in predominantly Caucasian cohort: OR 1.25 (95% CI 1.01 - 1.55, P=0.05) *vs.* AA.
rs7970314	Rubella	Ovsyannikova, 2010 (102)	Minor allele (G) associates with decreased TNF-α concentration post rubella vaccination (P=0.03) *vs.* A allele. In high LD ($r^2=0.92$) with rs11568820.

	(Promoter,A>G)	Parkinson's Disease	Gao, 2014(69)	Meta-analysis: Minor allele (G) associates with increased risk: OR 1.32 (95% CI 1.17 – 1.50, P<0.001) *vs.* A allele.
	rs2238136 (Intron 2, G>A)	Colorectal cancer	Mahmoudi, 2010 (84)	AA genotype associates with increased risk of colorectal cancer: OR 2.09 (95% CI 1.15 - 3.78, P = 0.02) *vs.* GG.
		Melanoma	Kosiniak-Kamysz, 2014 (107)	GCCC haplotype for rs2238136-rs4516035-rs7139166-rs11568820 associates with increased risk: OR 5.65 (1.79 – 17.81, P=0.003).
	rs2853559 (T/C)	Myopia	Mutti, 2011 (108)	T allele associates with increased risk of myopia in Caucasians: OR = 1.99 (P= 0.003).
	rs4334089 (G/A)	Parkinson's Disease	Butler, 2010 (109)	Associates with age-at-onset (P=0.02).
RXRA (chr9q34.3)	**rs7861779** (G>A)	Colorectal Cancer	Jacobs, 2010 (110)	A allele associates with increased risk: OR 1.42 (95% CI 1.03 - 1.97, P=0.03) *vs.* G allele.

Abbreviations: VDR: vitamin D receptor, RSV: respiratory syncytial virus, OR: odds ratio, CI: confidence interval, TB: tuberculosis, MDR: multi-drug resistant, +ve: positive, IgE: Immunoglobulin E, Th2: T helper cell type-2, RR: risk ratio, PD: Parkinson's disease, *S.aureus: Staphylococcus aureus*, HIV: human immunodeficiency virus, LD: linkage disequilibrium, AIDS: acquired immune deficiency syndrome, AITD: autoimmune thyroid disease, SLE: systemic lupus erythematous, LN: lupus nephritis, HAM/TSP: HTLV-I(Human T-lymphotropic virus I)-associated myelopathy/tropical spastic paraparesis, PCa: prostate cancer, HR: hazard ratio, TNF-α: tumour necrosis factor-alpha, Cdx-2: caudal type homeobox-2, HIV-1: human immunodeficiency virus-1.

Table 3. Single nucleotide polymorphisms in pathways of vitamin D metabolism and transport, reported to associate with non-skeletal health outcomes

Gene	SNP (description)	Disease association	Reference	Findings/Comments
DBP (chr4q13.3)	**rs7041/rs4588** (Exon 11, T>G; C>A)	Breast cancer	Anderson, 2011 (111)	TT genotype associates with increased risk of breast cancer in female Caucasians in Ontario: OR 1.23 (95% CI 1.01 - 1.51, P<0.05) *vs.* GG.
		Cancer	Jorde, 2015 (112)	Gc-1f/1f genotype associates with decreased risk in Norwegians: HR 0.74 (95% CI 0.59 – 0.93, P = 0.008), *vs.* Gc-2/2
		COPD	Janssens, 2010 (113)	TT genotype associates with increased risk in Caucasians: OR 2.11 (95% CI 1.20 - 3.71, P=0.009) *vs.* GG.
		HCC	Peng, 2014 (114)	G allele associates with increased risk of HCC in Chinese Han patients with HCV: OR 1.50 (95% CI 1.06 - 2.14, P=0.034) *vs.* T allele.
		Lung cancer	Kong, 2015 (115)	GG genotype associates with decreased risk: OR 0.57 (95% CI 0.35 - 0.93, P<0.001) *vs.* TT.
		Tuberculosis	Martineau, 2010 (116)	Gc-2/2 associates with increased risk in Gujarati Asians, with 25D levels <20 nmol/L: OR 2.81 (95% CI 1.19 – 6.66, P=0.009) *vs.* Gc-1/1.
	rs1155563 (Intron 1, T>C)	COPD	Bakke, 2011 (117)	Associates with clinical marker of disease severity (FEV_1/FVC [P<0.05]).
	rs17467825 (3'UTR, A>G)	COPD	Bakke, 2011 (117)	Associates with clinical marker of disease severity (FEV_1 % predicted [P<0.05]). In high LD with rs1155563 (r^2=0.86).
	rs2070741 (A>C)	Bronchiectasis/COPD	Wood, 2010 (32)	C allele associates with increased risk of bronchiectasis: OR 1.80 (95% CI 1.02 - 3.19, P=0.03) and increased risk of airway bacterial colonisation: OR 3.84 (95% CI 1.78 - 6.92, P=0.04).
CYP2R1 (chr11p15.2)	**rs10766197** (G>A)	Asthma	Pillai, 2011 (43)	Associates with risk of asthma in young African Americans (P=0.04).
CYP3A4 (chr7q21.1)	**rs2740574** (promoter, A>G, *CYP3A4*1B*)	Prostate Cancer	**1.**Tayeb, 2003 (118) **2.**Fernandez, 2012 (119)	**1.** GG genotype associates with increased risk of prostate cancer: RR 2.7 (95% CI 0.77 - 7.66) *vs.* AA. **2.** AG/GG genotypes associate with increased risk of prostate cancer in White and mixed ancestry South Africans: OR 3.27 (95% CI 2.30 - 4.65, P<0.004) *vs.* AA.
CYP27A1 (chr2q35)	**rs17470271** (A>T)	Asthma	Leung, 2015 (120)	Associates with clinical marker of asthma severity (FEV_1 [P=0.03]).
CYP24A1 (chr20q13.2)	**rs6127118** (Intron 7, G>A)	AMD	Morrison, 2011 (121)	Associates with risk of AMD in family cohort study (P=0.03).
	rs2762934 (Exon 12, G>A)	AMD	Morrison, 2011 (121)	Associates with risk of AMD in family cohort study (P=0.01).
		Breast cancer	Fuhrman, 2013 (122)	Minor allele associates with increased risk: OR 1.35 (95% CI 1.09 - 1.67, P for trend=0.005), for each additional allele.
	rs2762939 (Intron 5, G>A)	Coronary Artery Calcification	Shen, 2010 (123)	Meta-analysis: C allele associates with decreased risk in 3 studies (Overall P=$2.9x10^{-6}$).
CYP27B1 (chr12q14.1)	**rs10877012** (promoter, C>A,)	Autoimmune Addison's Disease	Fichna, 2010 (124)	C allele associates with increased risk: OR 1.53 (95% CI 1.07 - 2.19, P=0.02) *vs.* A allele.
		Hepatitis C	Lange, 2011 (45)	C allele associates with reduced ability to achieve sustained virologic response (P=0.02) *vs.* A allele.
	rs4646536 (Intron 6, T>C,)	Diabetes(Type 1)	Bailey, 2007 (125)	TT genotype associates with increased risk: OR 1.20 (95% CI 1.07 - 1.36, P=0.01) *vs.* CC. In perfect (r^2=1.0) LD with rs10877012.
		Congestive Heart Failure	Wilke, 2009 (126)	CC genotype associates with increased risk in patients with hypertension, of predominantly European ancestry: OR 2.14 (95% CI 1.05 - 4.39, P<0.05), *vs.* TT.
	rs4646537 (Intron 8, A>C)	Hypertension	Wilke, 2009 (126)	AC genotype associates with decreased risk in predominantly European ancestry participants: OR 0.35 (95% CI 0.13 - 0.91, P<0.05) *vs.* AA.
DHCR7 (chr11q13.4)	**rs12785878** (G>T)	Multiple Sclerosis	Alloza et al., 2011 (127)	Associates with risk (P<0.01).
LRP2 (chr4q35.1)	**rs3755166** (promoter, G>A)	Alzheimer's Disease	**1.**Wang, 2010 (128) **2.**Vargas, 2010(129)	**1.** A allele associates with increased risk in Chinese Hans: OR 1.38 (95% CI 1.02 - 1.87, P=0.04) *vs.* G allele. **2.** AA genotype associates with increased risk in Europeans without ApoE4 mutation: OR 1.41 (95% CI 1.10 – 1.90, P=0.03) *vs.* GG.
CUBN (chr10p12.31)	**rs3740165** (G>A)	Diabetes (Type 1)	Ramos-Lopez, 2010 (130)	AA genotype associates with increased risk (P=4×10^{-7}) *vs.* GG.
RXRA	**rs7861779**	Colorectal Cancer	Jacobs, 2010 (110)	A allele associates with increased risk: OR 1.42 (95% CI 1.03 - 1.97, P=0.03) *vs.* G allele.

(chr9q34.3)	(G>A)

Abbreviations: DBP: vitamin D binding protein, CYP2R1: cytochrome P450-2R1, CYP3A4: cytochrome P450-3A4, CYP27A1: cytochrome P450-27A1, CYP24A1: cytochrome P450-24A1, CYP27B1: cytochrome P450-27B1, DHCR7: 7-dehydrocholesterol reductase, LRP2: lipoprotein receptor-related protein 2 (Megalin), CUBN: cubilin , OR: odds ratio, CI: confidence interval, COPD: chronic obstructive pulmonary disease, HCC: hepatocellular carcinoma, HCV: hepatitis C virus, LD: linkage disequilibrium, FEV_1: forced expiratory volume in 1 second, FVC: forced vital capacity, AMD: age-related macular degeneration.