Journal of Steroid Biochemistry & Molecular Biology 164 (2016) 18–29

Contents lists available at ScienceDirect

Journal of Steroid Biochemistry & Molecular Biology

journal homepage: www.elsevier.com/locate/jsbmb

Review

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*, Robert T. Walton, Christopher J. Griffiths, Adrian R. Martineau*

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

ARTICLE INFO

Article history:
Received 15 June 2015
Received in revised form 3 November 2015
Accepted 9 December 2015
Available online 11 December 2015

Keywords:
Vitamin D
Single nucleotide polymorphism
Vitamin D status
Non-skeletal diseases
Candidate gene association studies
Genome-wide association studies

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.

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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].

* Corresponding authors 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. Fax: + 44 207 882 2552.
E-mail addresses: d.a.jolliffe@qmul.ac.uk (D.A. Jolliffe), a.martineau@qmul.ac.uk (A.R. Martineau).

http://dx.doi.org/10.1016/j.jsbmb.2015.12.007
0960-0760/

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 signaling pathways is illustrated in Fig. 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 to 2012; we then conducted the same search in June of 2015 to capture manuscripts published from 2012 to 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.

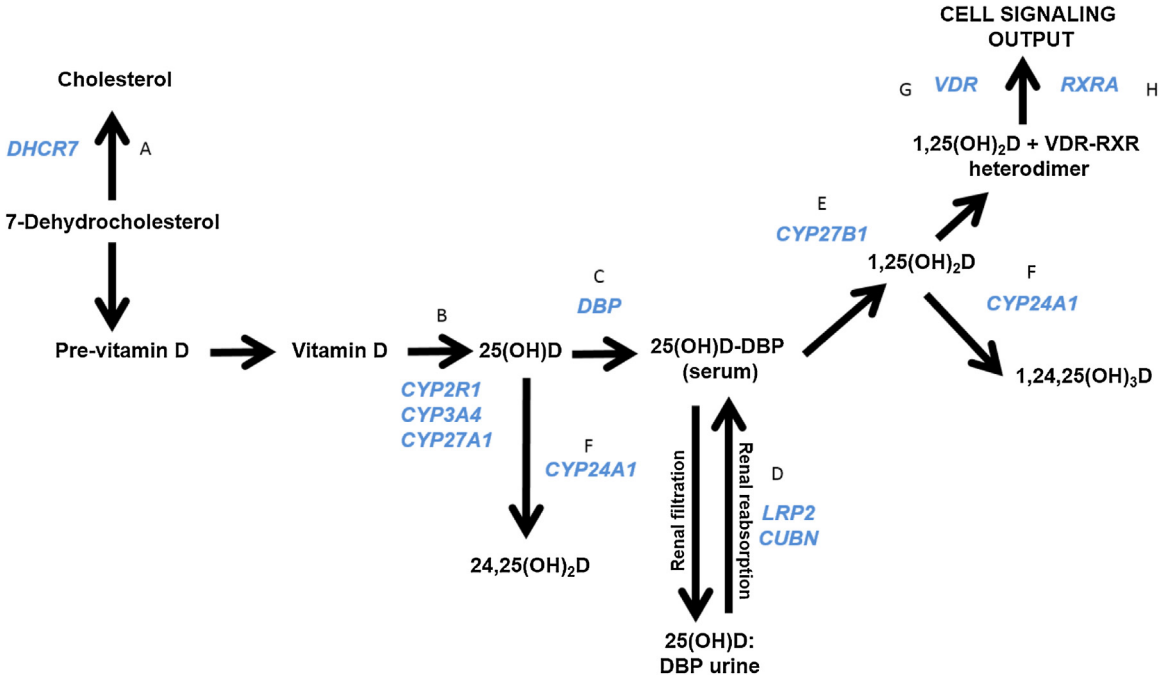

Fig. 1. A diagram depicting vitamin D metabolic and signalling pathways and genes encoding key players (in blue): *DHCR7* (A) encodes the 7-dehydrocholesterol reductase enzyme, which catalyses the conversion of 7-dehydrocholesterol to cholesterol; *CYP2R1*, *CYP3A4*, and *CYP27A1* (B) encode 25-hydroxylating cytochrome P450 enzymes; the vitamin D binding protein gene (*DBP*, [C]) encodes the principle vitamin D transport protein; *LRP2* and *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. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)