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Identification and analysis of 35 genes associated with vitamin D deficiency: A systematic review to identify genetic variants

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ABSTRACT

Vitamin D deficiency is a public health concern associated with, but not limited to, skeletal anomalies, chronic diseases, immune conditions, and cancer, among others. Hypovitaminosis D is mainly associated with environmental and lifestyle factors that affect sunlight exposure. However, genetic factors also influence 25-hydroxyvitamin D (25[OH]D) serum concentration. Although there is available information of genes with clear biological relevance or markers identified by Genome-Wide Association Studies, an overall view and screening tool to identify known genetic causes of altered serum levels of 25(OH)D is lacking. Moreover, there are no studies including the total genetic evidence associated with abnormal serum concentration of 25(OH)D. Therefore, we conducted a *de-novo* systematic literature review to propose a set of genes comprehensive of all genetic variants reported to be associated with deficiency of vitamin D. Abstracts retrieved from PubMed search were organized by gene and curated one-by-one using the PubTerm web tool. The genes identified were classified according to the type of genetic evidence associated with serum 25(OH)D levels and were also compared with the few commonly screened genes related to vitamin D status. This strategy allowed the identification of 35 genes associated with serum 25(OH)D concentrations, 27 (75%) of which are not commercially available and are not, therefore, analyzed in clinical practice for genetic counseling, nor are they sufficiently studied for research purposes. Functional analysis of the genes identified confirmed their role in vitamin D pathways and diseases. Thus, the list of genes is an important source to understand the genetic determinants of 25(OH)D levels. To further support our findings, we provide a map of the reported functional variants and SNPs not included in ClinVar, minor allelic frequencies, SNP effect sizes, associated diseases, and an integrated overview of the biological role of the genes. In conclusion, we identified a comprehensive candidate list of genes associated with serum 25(OH)D concentrations, most of which are not commercially available, but would prove of importance in clinical practice in screening for patients that should respond to supplementation because of alterations in absorption, patients that would have little benefit because alterations in the downstream metabolism of vitamin D, and to study non-responsiveness to supplementation with vitamin D.

1. Introduction

An optimal serum concentration of 25(OH)D is essential for human health. Hypovitaminosis D is currently a public health concern that affects approximately 13–50% of the world´s population. Higher prevalence of vitamin D deficiency have been found in the Middle East, Asia, and Northern Europe [1–3]. The most important source of vitamin D is sun exposure, thus, the factors determining hypovitaminosis D have been defined as the geographic latitude, weather seasons, skin color, the use of sunscreen, and the type of clothing. Fat mass content and dietary patterns have also been shown to be of influence [4,5]. However recent reports highlight the high prevalence of vitamin D deficiency even in sunny regions at adequate latitudes and with sufficient sun exposure, such as Mexico [5,6], exposing the possibility of the influence of genetic elements. Genetic factors are even more relevant considering that heritability of hypovitaminosis D has been estimated between 22% and 86%[7–9].

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Most of this fat-soluble vitamin is mainly synthesized in the skin (80%–90%) [1] as 7-dehydrocholesterol (previtamin D_3) [10] by the enzyme 7-dehydrocholesterol reductase (encoded by *DHCR7*) in a process dependent on ultraviolet B (UVB) radiation [11]. Previtamin D_3 is then transported to the liver by vitamin D binding protein (DBP; encoded by *GC*), where it is converted to 25(OH)D_3 by *CYP2R1* (although *CYP27A1* or *CYP3A4* can also achieve 25-hydroxylation). 25(OH)D_3, bounded to DBP by means of megalin and cubilin, encoded by the genes LRP2 and CUBN, respectively, is further hydroxylated in the kidney by *CYP27B1,* resulting in 125-dihydroxyvitamin D_3 (125[OH]$_2D_3$), known as calcitriol, the active form of vitamin D [12]. 125[OH]$_2D_3$, bounded to its receptor (*VDR*) in a heterodimer complex with *RXRA* (*VDR/RXRA* complex), modulates vitamin D biological activity in bone health [13], the immune system [14], gene expression [15], and cellular differentiation [16], among other functions. Hypovitaminosis D has been associated, but not limited to, with skeletal disturbances, immunological diseases, infectious diseases, cardiometabolic problems, and cancer [13,17–19]. Several common single nucleotide polymorphisms (SNP) in the genes *VDR*, *GC*, *CYP2R1*, *CYP24A1*, *DHCR7*, and *RXRA* have been associated with low serum 25(OH)D concentrations in different cohorts [12]. In addition, the genes *VDR*, *CYP2R1,* and *CYP27B1* have been recognized as causes of chronic vitamin D deficiency in the rare condition of autosomal recessive inherited rickets [20–22].

Novel gene polymorphisms, such as *DHCR7/NADSYN1*, *CYP2R1*, *CYP24A1*, *GC*, *SEC23A*, and *AMDHD1*, which represent risk factors for vitamin D deficiency, have also been identified using Genome-Wide Association Studies (GWAS), which recognize potential genes or loci involved in a particular trait [23] The implementation of Next Generation Sequencing (NGS) technology allows for rapid analysis of many genes from several samples. Although NGS analysis as a whole exome or even genome is increasing, sequencing of a specific set of genes is highly desired for research purposes and for clinical settings due to the lower cost, maximum coverage of target regions, and more accessible data interpretation [24]. Many diverse disease-specific panels have been designed and are clinically available for other clinical conditions. However, panels focused on all known genes involved in vitamin D deficiency are lacking.

A panel proposed for a few selected vitamin D associated genes [25] has been limited to those directly involved in the vitamin D pathway, but other genes reported by GWAS have not been included. Likewise, recent reviews have focused on genes involved in the vitamin D pathway [12] or have described genes identified in GWAS studies [26]. Nevertheless, to date, there are no studies including all the available genetic evidence associated with the metabolism and deficiency of vitamin D.

Given the lack of comprehensive genetic screening tools for vitamin D, we conducted a *de-novo* systematic literature review to propose a set of genes, including all reported genetic variants associated with abnormal serum concentration of 25(OH)D. Approximately 1800 abstracts were curated and full-text articles were selected to identify and classify each gene associated with vitamin D deficiency. In addition, genes which have not been included in any commercial panel or in previous reviews, as well as polymorphisms that have not been recognized in databases, such as ClinVar, were considered. Finally, a pathway and disease-centered functional analysis of the genes identified, a map of the reported functional variants and SNPs, an integrated overview of the role of the genes, and ultimately, the annotations of the curation process are provided.

2. Methods

Overall, the procedure followed in this systematic review is summarized in Fig. 1, adapted from a previous study in our group [27]. Briefly, the results of the PubMed search were retrieved for curation [28]. A list of categories of genes was defined based on the evidence of genetic alterations related to vitamin D deficiency and each gene was assigned to the corresponding category. Details of the process are described in the following sections.

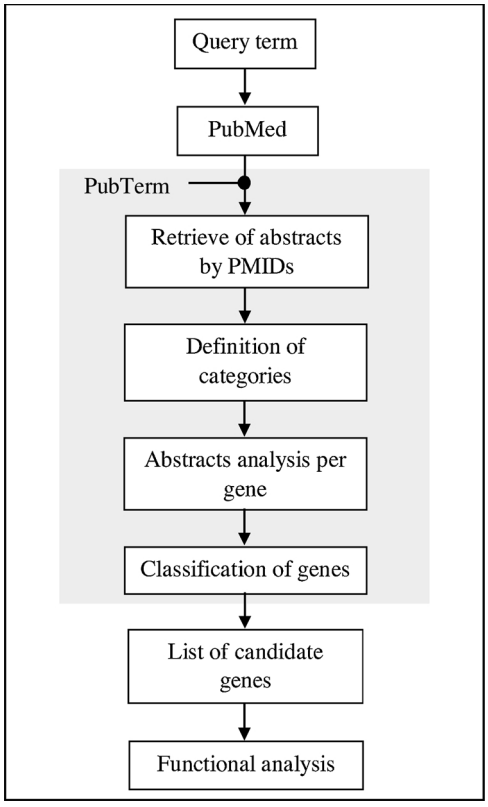

Fig. 1. Gene selection workflow. The review process started from a PubMed query and ended in a list of candidate genes.

2.1. Search strategy for candidate genes

A systematic review of the literature was achieved using the electronic database PubMed to identify evidence of genes affecting vitamin D metabolic pathways and serum 25(OH)D concentrations. The term search integrated synonyms and related terms for three elements: 1) vitamin D terminology; 2) specification of serum 25(OH)D concentration; and 3) types of genetic variants. Different query terms were tested to obtain enough data and to avoid unspecific information. The final fine-tuned query used was: ("vitamin D"[TIAB] OR "25-hydroxyvitamin D"[TIAB]) AND ("deficiency"[TIAB] OR "insufficiency"[TIAB] OR "inadequacy"[TIAB] OR "lack of"[TIAB] OR "absence"[TIAB] OR "levels"[TIAB] OR "concentration"[TIAB] OR "dysfunction"[TIAB] OR "abnormal"[TIAB]) AND ("mutations"[TIAB] OR "mutation"[TIAB] OR "variant"[TIAB] OR "variants"[TIAB] OR "polymorphism"[TIAB] OR "polymorphisms"[TIAB] OR "GWAS"[TIAB] OR "SNP"[TIAB]) NOT review[Publication Type]. Only original studies published in English were considered for this systematic review.

2.2. Study eligibility

The query terms used for this research were approved by all researchers. The data curations (PubTerm) was performed by one researcher (MSV) and reviewed by the other authors. The annotations were randomly reviewed by two researchers (LE and VT) at different times and in an independent way. All observations were reviewed and resolved in consensus (MSV, LE, and VT). All the researchers were able to consult the search sessions at any moment.

Table 1
Level of evidence for gene annotation.

CATEGORY	CRITERIA
Annotation error	The annotation is related to a different disease or biological activity (imprecise annotation of the gene/disease)
Unrelated	Precise annotation that is non-related to the gene/disease.
Negative association	Lack of association between the genetic variant and serum 25(OH)D levels.
Biologically related but without of functional variant	Experimental evidence derived only from non-human models (cell culture or animal model).
Genetic alterations in a related disease	The evidence of a genetic variant in 25(OH)D levels/metabolism is associated with another disease.
Other evidence of genetic alteration	Non-specific functional variant is provided: (i) GWAS (Genome-wide association studies) or (ii) rs (reference sequence), leading us to further sub-classification: GWAS/rs within the gene GWAS/rs in intergenic region, haplotypes, or interactions
Experimental evidence of functional variant	Experimental evidence of functional variant in humans is provided.

2.3. Web tool for abstracts curation

For data curation we created a session in PubTerm [28], a free web tool developed by our research group that allows to categorize, organize, and annotate the abstracts retrieved from the PubMed search (http://bioinformatica.mty.itesm.mx:8080/Biomatec/pubterm.html). One of the functions of PubTerm is the accurate annotation of the genes mentioned in the abstracts. The abstracts can then be organized for each annotation gene, facilitating the review process. In PubTerm, a list of the categories that define the levels of genetic evidence available regarding its possible association with vitamin D deficiency was created. The categories were adapted based on our previous analysis [27]. The final categories were: *Annotation error, unrelated, negative association, biologically related but no evidence of functional variant, genetic alteration in a related disease, other evidence of genetic alteration, and experimental evidence of functional variant* (a description of each category is shown in Table 1). A, in the "Term View" option in PubTerm, the abstracts were organized per gene and human genes were filtered using "Hs" (*Homo sapiens*) in the search section.

2.4. Assessment of scientific evidence per gene

Each abstract was manually reviewed and assigned to the corresponding category of each gene. If different abstracts provided information for more than one category of a specific gene, the category was assigned in order of importance (descendent), namely, if at least one study showed experimental evidence of functional variant, the gene was assigned to that category. When the relation of the gene with vitamin D was not evident in the abstract or the functional variant in the gene was not reported in ClinVar, the full text was reviewed. Details of the search and annotations may be consulted on the website of PubTerm (http://bioinformatica.mty.itesm.mx:8080/Biomatec/pubterm.html) using the fields e-mail: "m_sepulveda@tec.mx"; and project: Vitamin D genes_1800.

2.5. Schematic representation of genes

To provide further evidence for understudied genes, only those classified in the categories *experimental evidence of functional variant* not reported in ClinVar and *other evidence of genetic alteration within the gene* were considered for a schematic representation. The reference sequence (mRNA) for each gene was obtained from the NCBI. The genetic variants that were identified in this systematic review, but were not reported in ClinVar, were annotated manually with the information obtained from the original articles. This information is provided as supplementary material. For the genes categorized as *other evidence of genetic alteration*, the variants that occurred in a non-coding region (introns) were assigned to the locus of the SNP. The probable functional range of the SNP was represented with a bar on top of the gene. When the information was available, the associated key SNP was flanked by neighboring SNPs with strong linkage disequilibrium. In the absence of precise information, the range was established at an average distance of 5 kbps upstream and downstream of the SNP of interest (as an approximated average distance in GWAS arrays).

2.6. Functional analysis

The genes classified as *experimental evidence of functional variant* and *other evidence of genetic alteration* were considered for functional annotation analysis using the bioinformatic tools DAVID [29] and EnrichR [30]. The biological terms that involved more than three genes from the list described were analyzed using a raw p-value < 0.05 and an adjusted p-value for multiple tests < 0.1. Terms with similar gene content were grouped and classified by biological function/activity. To improve biological interpretation the results were labeled as: metabolic pathways, gene ontology (GO) or related diseases. The Human Gene Mutation Database [31] (HGMD) was consulted to identify other genetic diseases associated with the genes assigned to the categories experimental evidence of functional variant and other evidence of genetic alteration. The minor allelic frequency (MAF) was obtained from the 1000 Genomes project [32] at the ENSEMBL web site (http://www.ensembl.org). The effect size estimations, reported as beta coefficient for GWAS results or Z-score for meta-analysis results, [33,34] were obtained from the GWAS Catalog [35] or from the specific articles.

3. Results

The results of the systematic review for the level of evidence assigned to each gene are summarized in Fig. 2 and described in the following sections. The functional analysis is presented as well.

3.1. Levels of evidence of genetic alteration

During October 2018, our search retrieved 1801 abstracts that referred to 889 different genes. After the "Hs" filter was applied 209 non-human genes from the analysis were discarded. Afterwards, curation and categorization of the 680 human genes were performed according to the evidence reported in the abstracts and the full texts. Similarly to another study [27], the genes recognized in 100 or more abstracts were considered highly probable to be well known in association with Vitamin D metabolism, such as *DHCR7*, *VDR*, *GC*, *CYP24A1*, *CYP2R1*, and *CYP27B1*. These genes were confirmed during the curation process.

A total of 507 genes were labeled as *absent of genetic alterations*. This classification included 320 unrelated genes, 143 genes biologically related to vitamin D metabolism/deficiency without evidence of functional variants, and 44 genes registered as *annotation errors*. The most common reasons to assign a gene to the category *unrelated* were either that the gene codified for enzymes used to recognize a specific polymorphism (e.g., *CXD2*, an enzyme frequently used to recognize polymorphic sites in the *VDR* gene, mentioned in 40 abstracts) or that the gene was a biomarker for a condition not associated with vitamin D. The most common genes biologically related to serum concentration of 25(OH)D without evidence of a functional variant were *BGLAP* and

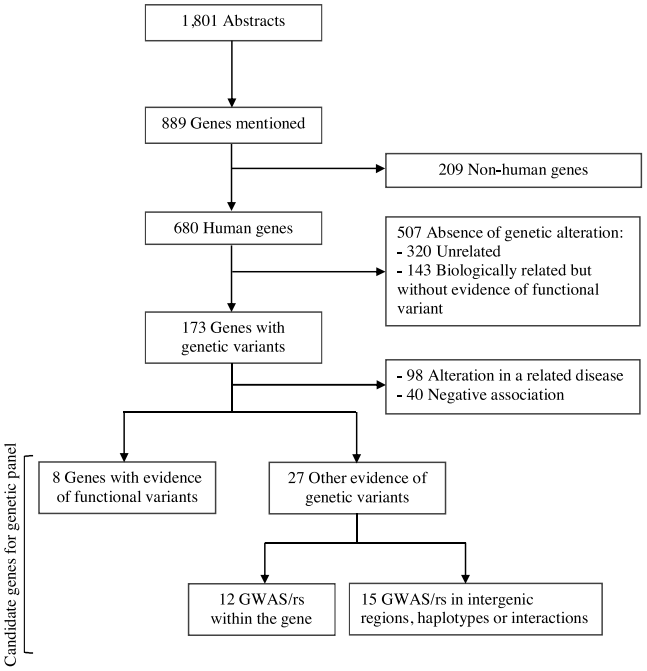

Fig. 2. Results of the systematic review for the level of evidence assigned to each gene.

FGF23 (mentioned in 67 and 38 abstracts respectively). The genes were categorized as *annotation error* when either an imprecise annotation of the genes was found (e.g., DBP:D-box binding PAR bZIP transcription factor, not "vitamin D binding protein" encoded by the gene *GC*) or when an abbreviation was mistakenly recognized as a gene symbol (e.g., ALP was found as an abbreviation for alkaline phosphatase). The remaining 173 genes were identified as genes with some evidence of genetic variant. From these, 98 variants were found to belong to the category *alteration in a related disease* (e.g., variants in the gene *CASR* were associated with alterations in calcium metabolism and those in the gene *PHEX* with hypophosphatemia), while 40 genes were found to fit in the category *negative association* with serum concentration of 25(OH)D (e.g., the genetic variant in *CRP* or *CTNNB1* genes did not affect serum 25(OH)D levels).

Eight genes with clear evidence of a *functional variant* affecting 25(OH)D concentration (*VDR*, *CYP2R1*, *CYP24A1*, *GC*, *CYP27B1*, *CYP3A4*, *FLG*, and *CUBN*) were identified. The first six of these genes have been previously recognized as indispensable in the canonical vitamin D pathway [12]. Most of these were mentioned in more than 100 abstracts or reported in ClinVar for conditions related to Vitamin D (Table 2). For the remaining 27 genes classified as *other evidence of genetic alteration*, the genetic variation corresponded to SNPs identified by GWAS. Therefore, for an accurate sub-classification, the reference sequence (rs ID) in the genome was mapped using the SNP database [36]. This analysis allowed to identify 12 genes with markers placed within the gene: *HLA-B*44*, *DHCR7/NADSYN1*, *CYP27A1*, *PDE3B*, *SULT2A1*, *NEBL*, *DAB1*, *BLOC1S5*, *CYP3A43*, *AMDHD1*, and *SEC23A*, which highly suggests their involvement in the metabolic pathway of vitamin D. Thirteen out of the remaining 15 variants were mapped to the intergenic regions and originally assigned to the nearest gene: *PTH*, *RXRA*, *EDN1*, *TYRP1*, *SSTR4/FOXA2*, *ANO6/ARID2*, *KIF4B*, *HTR2A*, *IVL*, *PRKACG*, and *MLPH*. However, since the SNP marker was found to be placed at an intergenic position, the gene to which a particular variant was allocated to, might not necessarily be the nearest one, thus the gene identified remains putative. Considering that the distance of the SNP marker to the commencement of the gene might be a good indicator of the likelihood to be the target gene, the distance to the gene was also annotated in these circumstances to further assist biological interpretations (Table 2). *PTH*, well-known to reduce *VDR* expression, affects vitamin D metabolism [37] possibly via polymorphisms in its promoter region [38]. We noted for instance, that the SNP near the gene *PTH* was positioned at a short distance, approximately 5 Kbps, to its transcription starting site. Similar distances should likely be associated to the marked gene. On the other hand, the SNP rs2207173, located around a poorly studied region containing lncRNAs, pseudogenes, and other understudied transcripts, was found to be usually related with the gene *FOXA2*. The SNPs for the two remaining genes, *LRP2* and *MXD1*, were positioned close to their corresponding gene. The SNP situated close to the gene *LRP2* was found to have a genetic effect over serum 25(OH)D concentration, but this was only observed in haplotypes [39]. Finally, for the SNP identified close to gene *MXD1,* the association with serum 25(OH)D levels was only observed when consumption of n-3 polyunsaturated fatty acids was described [40]. The category, the PubMed ID (PMID) used to define each category, and other annotation details for all genes are provided as supplementary material.

3.2. Support and mapping of genetic variants

Fig. 3 shows the genetic locations of functional variants and SNPs consistent with the genes of interest identified from the literature as part of this review. Genes displayed in Fig. 3 correspond to those with genetic variants that were not reported in ClinVar. The gene *CYP3A4* belongs to the category of *experimental evidence of functional variant,* while the remaining 12 genes belong to the category of *other evidence of genetic alteration within the gene*. For the last set of genes, the probable functional range of the SNP was represented with a bar on top of the gene. For genes categorized as *other evidence of genetic alteration in intergenic regions, haplotypes or interactions* in which the association of the gene may not be clear, the distance of the reported SNP closest to the end of the gene was annotated (Table 2). We also annotated the MAF obtained from the 1000 Genomes project (Table 2) and the specific ethnic MAF (Supplementary Table 3) together with corresponding effect sizes when the information was available.

Probable functional ranges of the SNPs are represented as bars on top of the markings, corresponding to the reference sequences. The range was based on the information provided in the original publication of the genes (green line in *DAB1*, *NADSYN1*, *PDE3B*, and *SEC23A*). For the remaining genes, the range was established at ~5 kbps upstream and downstream of the SNP of interest (red dotted line).

3.3. Functional analysis of the genes

Functional analysis of the genes was defined as genes associated with abnormal serum concentration of 25(OH)D. To validate the former and to explore other possible associations we performed a systematic functional analysis in public databases, including metabolic pathways, GO terms, and diseases. The genes categorized as *experimental evidence of functional variant* or *other evidence of genetic alteration* were analyzed using the bioinformatic tools David [29] and Erichr [30] selecting only significant terms (Fig. 4). Genes involved in essential roles in vitamin D and lipid metabolism were validated. Other interesting related terms, such as *Melanogenesis*, *Signaling by GPRC* and *Adaptative Immune System* were also included.

Fig. 4 summarizes the role of this set of genes in biological and molecular processes based on GO terms. Overall, we identified the relevant activity of the genes *CYP* in most of the biological and metabolic pathways, the involvement of the gene *VDR,* not only in metabolic pathways, but also in cellular signaling and differentiation, as well as the participation of the gene *HLA-B**44 in autoimmune processes. We also found that the genes *AMDHD1*, *BLOC1S5*, *IVL*, *MLPH*, and *MXD1* have reduced or limited metabolic activity, therefore, their relationship with serum 25(OH)D levels will be described in the next sections. We confirmed the contribution of the genes in diseases associated with

Table 2
Genetic panels reviewed.

Level of evidence	Symbol	Name	Abstracts	ClinVar	Genetic panels	Previous reviews	GWAS Marker	MAF	Distance Kbps
Experimental evidence of functional variant	*CUBN*	Cubilin	8	Yes*	1	–	–	–	–
	CYP24A1	Cytochrome P450 family 24 subfamily A member 1	140	Yes	2	Yes [12,25,26]	–	–	–
	CYP27B1	Cytochrome P450 family 27 subfamily B member 1	115	Yes	3	Yes [12,25]	–	–	–
	CYP2R1	Cytochrome P450 family 2 subfamily R member 1	139	Yes	3	Yes [12,25,26]	–	–	–
	CYP3A4	Cytochrome P450 family 3 subfamily A member 4	11	–	–	–	–	–	–
	FLG	Filaggrin	5	Yes*	–		–	–	–
	GC	GC, vitamin D binding protein	141	Yes	4	Yes [12,25,26]	–	–	–
	VDR	Vitamin D receptor	885	Yes	3	Yes [12,25]	–	–	–
GWAS/rs within the gen	*AMDHD1*	Amidohydrolase domain containing 1	2	–	–	Yes [26]	rs10745742	0.50	–
	BLOC1S5	Biogenesis of lysosomal organelles complex 1 subunit 5	1	–	–	–	rs9328451	0.17	–
	CYP27A1	Cytochrome P450 family 27 subfamily A member 1	27	–	–	–	rs17470271	0.25	–
	CYP3A43	Cytochrome P450 family 3 subfamily A member 43	1	–	–	–	rs680055	0.12	–
	DAB1	DAB1, reelin adaptor protein	1	–	–	–	rs6680429	0.42	–
	DHCR7	7-dehydrocholesterol reductase	79	–	1	Yes [12]	rs11603330	0.35	–
	HLA-B	Major histocompatibility complex, class I, B	2	–	–	–	*44	–	–
	NADSYN1	NAD synthetase 1	35	–	2	Yes [25,26]	rs3829251	0.27	–
	NEBL	Nebulette	1	–	–	–	rs10828183	0.40	–
	PDE3B	Phosphodiesterase 3B	2	–	–	–	rs11023332	0.35	–
	SEC23A	Sec 23 homolog A, coat complex II component	2	–	–	Yes [26]	rs8018720	0.22	–
	SULT2A1	Sulfotransferase family 2A member 1	2	–	–	–	rs296361	0.06	–
GWAS/rs in intergenic regions, haplotypes or interactions	*ANO6*	Anoctamin 6	1	–	–	–	rs719700	0.02	195
	ARID2	AT-rich interaction domain 2	1	–	–	–	rs719700		94
	EDN1	Endothelin 1	3	–	–	–	rs7356986	0.11	4
	FOXA2	Forkhead box A2	1	–	–	–	rs2207173	0.30	238
	HTR2A	5-hydroxytryptamine receptor 2A	1	–	–	–	rs1410656	0.03	71
	IVL	Involucrin	1	–	–	–	rs11586313	0.48	6
	KIF4B	Kinesin family member 4B	1	–	–	–	rs79666294	0.02	29
	LRP2	LDL receptor related protein 2	11	–	–	–	Haplotype	–	–
	MLPH	Melanophilin	1	–	–	–	rs7565264	0.21	73
	MXD1	MAX dimerization protein 1	1	–	–	–	Interaction	–	–
	PRKACG	Protein kinase cAMP-activated catalytic subunit gamma	1	–	–	–	rs12001326	0.40	20
	PTH	Parathyroid hormone	166	–	–	–	rs1459015	0.15	5
	RXRA	Retinoid X receptor alpha	36	–	–	Yes [12]	rs9409929	0.27	8
	SSTR4	Somatostatin receptor 4	2	–	–	–	rs2207173	0.30	210
	TYRP1	Tyrosinase related protein 1	3	–	–	–	rs2150097	0.44	293

Kbps: kilobases pairs from the tagged gene; MAF: Minor allele frequency. *Reported for other medical conditions/diseases.

abnormal serum concentration of 25(OH)D, such as skeletal disturbances [13], different types of cancer, and autoimmune and chronic diseases, like type 2 Diabetes Mellitus. We also revised HGMD to provide a comprehensive list of the diseases associated with the genes. The results shown in Supplementary Table 2 confirm the overall results and provide details of other rare diseases.

3.4. Other genetic panels and new candidate genes

We explored whether the genes identified are commonly screened by available genetic panels related to vitamin D status. To date, we found five genetic panels that evaluate a maximum of eight genes (three panels that focus on serum 25(OH)D levels, while the other two panels include genes related to vitamin D as part of a genetic screening for vitamins and minerals). Additionally, a panel of genes involved in the metabolism of vitamin D was suggested in one study [25]. Including all panels, the gene *GC* was found to be assessed in four out of five panels, followed by the genes *CYP27B1*, *CYP2R1,* and *VDR* that were shown to be present in three panels. The gene *CYP24A1* and *NADSYN1* were found to evaluated in two panels and finally the genes *CUBN* and *DHCR7* that appeared to be present in only one panel. Most of these genes belong to the category *evidence of functional variant*. Noteworthy, more than 75% of the 35 genes we identified to be associated with 25(OH)D levels have not been analyzed, therefore they are not available for the clinical setting, nor have they been sufficiently studied for research purposes. Details of these 35 genes are shown in Table 2.

4. Discussion

In this systematic review we identified 35 genes associated with abnormal serum concentration of 25(OH)D. An insight into the possible mechanisms that link these genes to the canonical vitamin D pathway is shown in Fig. 5. Twelve of the genes encode proteins that are known to be directly involved in vitamin D metabolism [12] (*DHCR7/NADSYN1*, *GC*, *CYP2R1*, *CYP3A4*, *CYP27A1*, *CYP24A1*, *LRP2*, *CUBN*, *CYP27B1*, *PTH*, *VDR,* and *RXRA)*. Seven of these genes correspond to the category *evidence of functional variant* and appear to be critical genes in vitamin D pathways leading to diseases. For example, a functional variant in

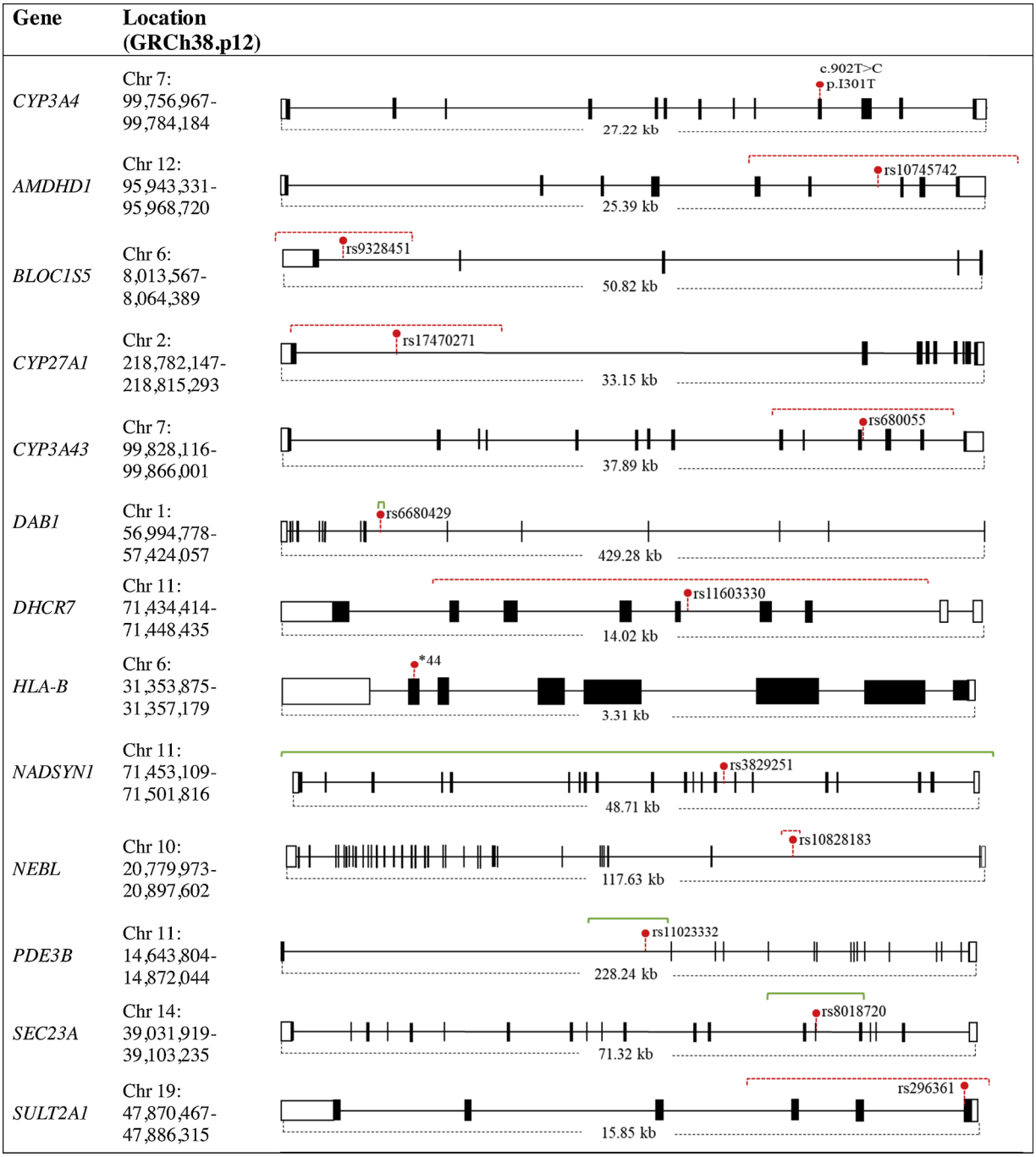

Fig. 3. Schematic representation of functional variants and SNPs in selected genes.

CYP2R1 causes impaired 25-hydroxylase activity with the subsequent reduction in the synthesis of 25-hydroxyvitamin D, resulting in vitamin D-dependent rickets type 1B [20]. Similarly, variants in *CYP27B1* give rise to vitamin D-dependent rickets type 1A [21], variants in *VDR* originate vitamin D-dependent rickets type II [22], and those in *CYP3A4* lead to vitamin D-dependent rickets type 3 [41]. Regarding the gene GC, the *T436K* substitution affects DBP serum concentration and a lower affinity for both, 25(OH)D_3 and 125(OH)$_2$$D_3$, [42,43] which results in low serum 25(OH)D concentrations. The variant *FM2* in the gene *CUBN* induces a truncated cubilin receptor associated with loss of 25(OH)D in the urine, [44] a condition that can also be affected by a genetic variant in the gene *GC*.

However, not all the genes identified with evidence of functional variant have been shown to induce a decrease in serum 25(OH)D concentrations. The variant in gene *CYP24A1* has been known to affect vitamin D catabolic activity, which results in accumulation of vitamin D metabolites, leading to idiopathic infantile hypercalcemia [45]. The genetic variant in the gene *FLG* has also been described to possibly increase serum 25(OH)D concentrations [46]. Although this gene has not been directly involved in vitamin D pathways, a decrease in the function of *FLG* might reduce the epidermal protection against UVB and increase the production of 7-dehydrocholesterol with a subsequent rise in the synthesis of 25(OH)D_3 [46].

It has been well-known that common SNPs represent a risk factor for a particular trait in which the causal variant commonly occurs at any given genomic locus around the tagged SNP [47,48]. Therefore, we classified the genes into two sub-groups, those genes carrying a tagged SNP *within the gene* and those occurring in *intergenic regions*, in order to

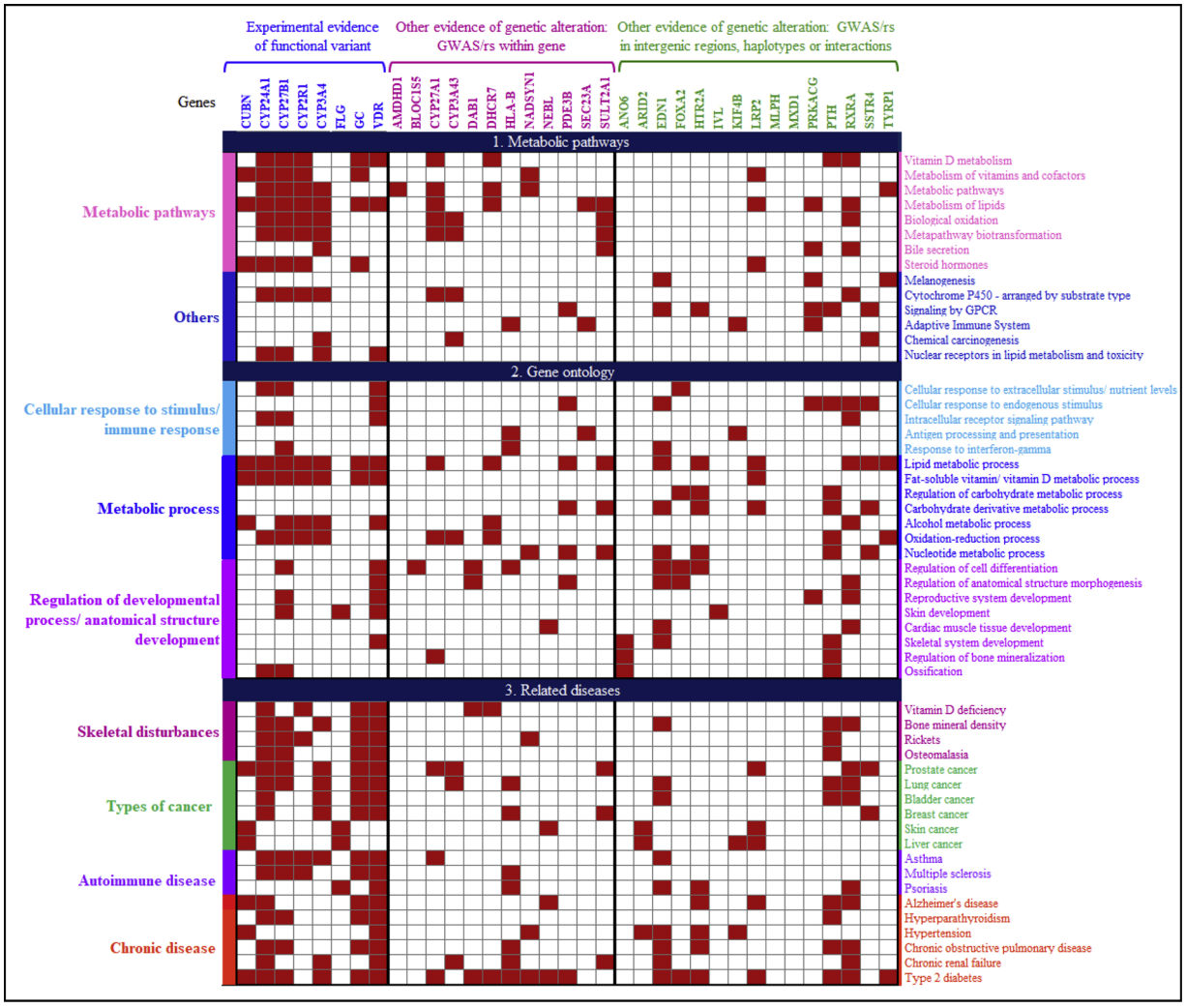

Fig. 4. Functional analysis of vitamin D related genes. For biological interpretation, results are presented in three sections: (1) gene involvement in vitamin D metabolic pathways, (2) gene ontology, and (3) related diseases. The upper part of the figure shows the genes grouped by categories. The left side of the figure displays the biological function/activity or disease associated with each gene, while the right side indicates the biological processes or related diseases with similarity, labeled and grouped by color code. Filled squares illustrate the association of the gene with the related genetically altered metabolic pathways or related diseases.

arrange the analysis of the gene based on its association with abnormal concentrations of 25(OH)D. In this analysis we identified that the genes *CYP3A4*, *FLG*, *AMDHD1*, *BLOC1S5*, *CYP27A1*, *CYP3A43*, *DAB1*, *HLA-B*44*, *NEBL*, *PDE3B*, *SEC23A*, *SULT2A1, ANO6/ARID2, EDN1, HTR2A, IVL, KIF4B, MLPH, MXD1, PRKACG, SSTR4/FOXA2, TYRP1, LRP2, PTH,* and *RXRA* have not been considered in any genetic panel.

The role of the genes *CYP27A1*, *CYP3A43*, *LRP2, PTH*, and *RXRA* in vitamin D metabolism has been well documented [12,49,50], nevertheless for other genes, the association with vitamin D has been less described. In the liver, for example, the gene *SULT2A1* has been shown to mediate the conversion of 25(OH)D_3 to 25 (OH)D_3-3-*O*-sulfate, which appears to have a high affinity for DBP [51]. When bound to DBP, 25(OH)D_3-3-*O*-sulfate has been described to probably prevent 25(OH)D_3-3-*O*-sulfate renal excretion, mediated by megalin and cubilin, to maintain optimal serum 25(OH)D concentrations, as occurs with the 25(OH)D_3/DBP complex [12,51]. Furthermore, genes involved in the biogenesis of melanosomes and skin pigmentation, such as *BLOC1S5*, *MLPH* [52], *EDN1*, *PRKACG* [53], and *TYRP1* [53,54], as well as the gene *IVL* that provides structural support for the skin, [55] have also been shown to feasibly affect vitamin D synthesis.

For some genes a detailed search was needed to identify their role in vitamin D metabolic pathways (Fig. 5). For instance, 125$(OH)_2D_3$, through *VDR/RXRA*, has been shown to induce the expression of *MXD1* [56], which in turn acts as an antagonist of *MYC* to maintain normal epidermal differentiation. This mechanism might explain one of the anti-cancer properties of vitamin D [56]. Other genes have been shown to exert diverse mechanisms involving calcium regulation in several organs or tissues. Genes *NEBL* and *ANO6* have been implicated in calcium homeostasis, participating in the downstream action of vitamin D to promote calcium uptake by the intestine. Variants in the gene *NEBL* have appeared to affect calcium function in cardiomyocytes, leading to dilated cardiomyopathy, [57] while those of *ANO6* have been shown to be needed for optimal bone mineralization [58]. While evidence has shown that calcium inhibits lipolysis via *PDE3B* in adipocytes, [59] it has also been described that the real effect of the SNP in *PDE3B* might affect *CYP2R1* [60].

For other genes, the relationship with vitamin D metabolic pathways is uncertain. The association of the gene *FOXA2*, a hepatic nuclear factor, with vitamin D is still doubtful, given the distance of the gene to the tagged SNP (Table 2). A proposed mechanism has indicated that the gene *FOXA2* might indirectly regulate the expression of the gene *CYP3A4* via *PXR*, a transcriptional regulator of *CYP3A4*. Different SNPs in alleged *FOXA2* binding sites in *PXR* have been suggested to affect *PXR* expression, which in turn regulates the transcription of *CYP3A4* [61].

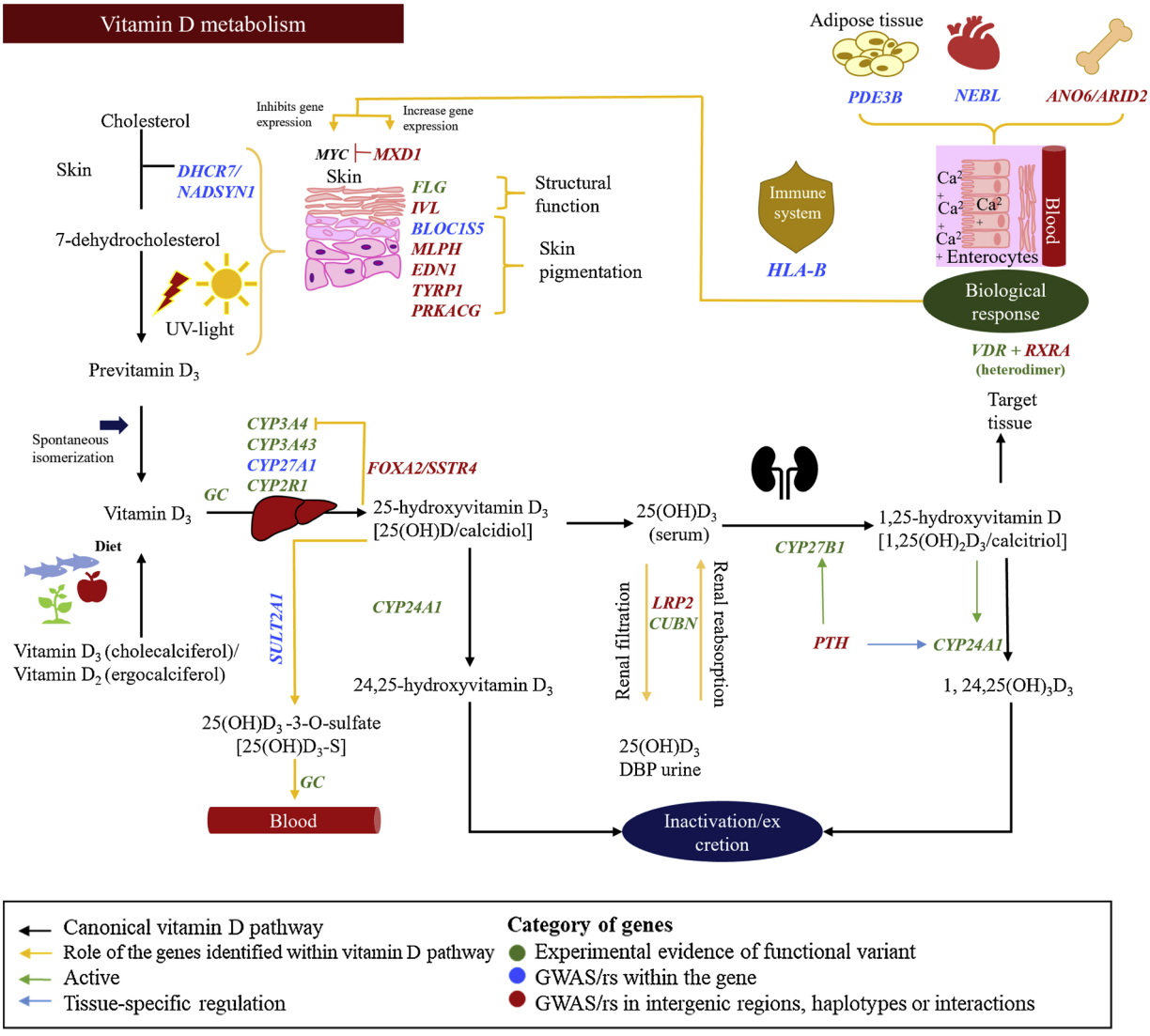

Fig. 5. Integrative overview of the canonical vitamin D pathway and of the genes identified in the present work. A brief description is provided only for newly integrated mechanisms. Genes *FLG* and *IVL* have a structural function in the skin, while genes *BLOC1S5*, *MLPH*, *EDN1*, *TYRP1*, and *PRKACG* are involved in skin pigmentation, possibly influencing the sensitivity to sunlight. Gene *ANO6/ARID2* is implicated in optimal bone mineralization, gene *NEBL* in heart function, and gene *PDE3B* in the regulation of lipolysis in adipose tissue. In the immune system, vitamin D regulates the expression of *HLA* genes. $125(OH)_2D_3$ increases the expression of the gene *MXD1*, leading to cell differentiation and tumor suppression. Simultaneously, *MXD1* inhibits *MYC* expression to control cell growth, proliferation, immortalization, and oncogenesis. In the liver, the sulfotransferase 2A1, encoded by the gene *SULT2A1*, metabolizes $25(OH)D_3$ into $25(OH)D_3$-3-O-sulfate, which partially binds DBP to avoid renal excretion. Genetic variants affecting the downstream vitamin D metabolism pathwasy may be implicated in chronic low serum 25(OH)D concentrations and thus, might be associated with non-responsiveness to vitamin D supplementation therapy. For more details see main text.

Following our *de-novo* strategy, we were able to further identify other genes related with vitamin D metabolic pathways that are not well-known or are less described in the literature, such as *ARID2*, *SSTR4, AMDHD1, DAB1, SEC23A, HTR2A,* and *KIF4B*. These genes have been associated with serum 25(OH)D concentrations, although their biological link is not yet clear. However, the possibility that the gene *ARID2* was annotated instead of the gene *ANO6* has to be considered; *ANO6* might be a better candidate, since it is a neighbor gene in chromosome 12 related to calcium homeostasis and bone mineralization [58]. Similarly, uncertainty exists for gene *SSTR4*, as its locus has been shown to be at a similar distance than that of *FOXA2* [61]. Consideration has to be given to the association of any SNP with its gene, bearing in mind that this relationship may not be exclusively dependent upon the distance to the nearest gen or to the tagged gene, but may include regulatory elements capable of acting distally to the target genes [47,48].

Our functional analysis was also able to define the associations of the genes identified with diseases related to vitamin D deficiency. The identification of these genes allowed for confirmation that optimal 25(OH)D serum concentration has not only been needed for bone health; [13] but it has also been associated with inhibition of cell proliferation, with induction of apoptosis in cancer [10], and with downregulation of proinflammatory pathways in immune-mediated diseases [62]. In addition, it has been demonstrated that suboptimal serum 25(OH)D concentrations, through calcium-dependent mechanisms, predispose to chronic diseases via abnormal glucose metabolism, impaired insulin response, chronic inflammation, and disturbed adipose activity [59,63]. Fig. 5 summarizes the genes involved in vitamin D metabolism.

In view of the important role in vitamin D metabolism of the genes identified, consideration should be given to develop a genetic panel that could be used in the clinical setting for those individuals or populations

particularly vulnerable to vitamin D deficiency. As well, the panel would be beneficial for these might include specially patients with proven vitamin D deficiency or insufficiency who do not respond to appropriate doses of vitamin D supplementation, subjets who are vitamin D deficient in spite of enough sunlight exposure or who live in countries at an adequate latitude, and those with sufficient ingestion of vitamin D rich foods. As well, the panel would be beneficial for patients with renal failure, hepatic insufficiency, immune diseases such as eczema, psoriasis, type 1 diabetes mellitus, multiple sclerosis, and rheumatoid arthritis, and patients with obesity or inflammatory bowel disease. Finally, the genetic panel would be valuable for children and older adults, for individuals living at low latitudes, for those rarely exposed to sunlight, and for subjects living in countries where clothing covers most of the skin surface.

5. Conclusions

To conclude, to the best of our knowledge, this is the first systematic review that encompasses all the available genetic evidence associated with abnormal serum concentration of 25(OH)D, given that previous work has been limited to describe a few genes involved in vitamin D pathways or the common genes identified by GWAS [12,25,26]. Altogether, we revised 1801 scientific publications. We identified 35 genes putatively associated with abnormal serum 25(OH)D concentrations. Only eight of these genes have been included in genetic panels related to vitamin D status (*GC*, *CYP27B1*, *CYP2R1*, *VDR*, *CYP24A1*, *NADSYN1*, *CUBN* and *DHCR7*). The remaining 27 genes not only have been understudied for research purposes, but have never been included in any genetic panel, even though our functional analysis confirmed that these 27 genes are indeed involved in the metabolism of vitamin D. The 27 genes are: *CYP3A4*, *FLG*, *AMDH1*, *BLOC1S5*, *CYP27A1*, *CYP3A43*, *DAB1*, *HLA-B*44*, *NEBL*, *PDE3B*, *SEC23A*, *SULT2A1*, *ANO6/ARID2*, *EDN1*, *HTR2A*, *IVL*, *KIF4B*, *MLPH*, *MXD1*, *PRKACG*, *SSTR4/FOXA2*, *TYRP1*, *LRP2*, *PTH*, and *RXRA*. We also provide an updated overview of how these genes seem to be implicated in regulating 25(OH)D serum levels in humans. Through our strategy for the systematic review, the list of genes we describe may be valuable to design a new genetic panel that focuses on 25(OH)D serum levels. This genetic panel could assist the clinicians in the clinical practice to screen and identify patients who would not benefit from supplementation with vitamin D because of genetic alterations in the downstream metabolism rather than in absorption. Our results might also aid in promoting awareness from the scientific community of researchers to identify the involved mechanisms. In addition, the methodology employed in this systematic review allows easy updates of the list of genes, starting from the PubTerm session when necessary.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jsbmb.2019.105516.

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