Association between Polymorphisms in Vitamin D Pathway-Related Genes, Vitamin D Status, Muscle Mass and Function: A Systematic Review

Ermira Krasniqi [1,2,3], Arben Boshnjaku [2,4], Karl-Heinz Wagner [1,3] and Barbara Wessner [1,2,*]

1 Research Platform Active Ageing, University of Vienna, Althanstraße 14, 1090 Vienna, Austria; ph.ermirakrasniqi@gmail.com (E.K.); karl-heinz.wagner@univie.ac.at (K.-H.W.)
2 Centre for Sport Science and University Sports, University of Vienna, Auf der Schmelz 6, 1150 Vienna, Austria; arbenboshnjaku@gmail.com
3 Department of Nutritional Sciences, University of Vienna, Althanstraße 14, 1090 Vienna, Austria
4 Faculty of Medicine, University "Fehmi Agani" in Gjakova, Ismail Qemali n.n., 50000 Gjakovë, Kosovo
* Correspondence: barbara.wessner@univie.ac.at; Tel.: +43-1-4277-48875

Abstract: An association between vitamin D level and muscle-related traits has been frequently reported. Vitamin D level is dependent on various factors such as sunlight exposure and nutrition. But also on genetic factors. We, therefore, hypothesize that single nucleotide polymorphisms (SNPs) within the vitamin D pathway-related genes could contribute to muscle mass and function via an impact on vitamin D level. However, the integration of studies investigating these issues is still missing. Therefore, this review aimed to systematically identify and summarize the available evidence on the association between SNPs within vitamin D pathway-related genes and vitamin D status as well as various muscle traits in healthy adults. The review has been registered on PROSPERO and was conducted following PRISMA guidelines. In total, 77 studies investigating 497 SNPs in 13 different genes were included, with significant associations being reported for 59 different SNPs. Variations in GC, CYP2R1, VDR, and CYP24A1 genes were reported most frequently, whereby especially SNPs in the GC (rs2282679, rs4588, rs1155563, rs7041) and CYP2R1 genes (rs10741657, rs10766197, rs2060793) were confirmed to be associated with vitamin D level in more than 50% of the respective studies. Various muscle traits have been investigated only in relation to four different vitamin D receptor (VDR) polymorphisms (rs7975232, rs2228570, rs1544410, and rs731236). Interestingly, all of them showed only very low confirmation rates (6–17% of the studies). In conclusion, this systematic review presents one of the most comprehensive updates of the association of SNPs in vitamin D pathway-related genes with vitamin D status and muscle traits in healthy adults. It might be used for selecting candidate SNPs for further studies, but also for personalized strategies in identifying individuals at risk for vitamin D deficiency and eventually for determining a potential response to vitamin D supplementation.

Keywords: vitamin D; genetic variations; SNPs; GC; CYP2R1; VDR; CYP24A1; muscle-related traits

1. Introduction

In recent years, the association between "optimal" serum levels of vitamin D with different healthcare conditions has been given important attention in medical research. Studies have shown that various factors such as season, latitude (ultraviolet B (UVB) availability), air pollution, clothing style, sunshine exposure, skin pigmentation, sunscreen cream, age, diet, and nutritional supplementation directly or indirectly affect vitamin D status [1–3].

In the body, vitamin D occurs in different forms with several enzymes being involved in their metabolism. Briefly, vitamin D2 (ergocalciferol) built from the provitamin ergosterol and vitamin D3 (cholecalciferol) originating from 7-dehydrocholesterol

(7-DHC) are converted into the circulating 25-hydroxyvitamin D (including 25(OH)D2 and 25(OH)D3) and the biologically active 1,25-hydroxy-cholecalciferol (including 1,25(OH)2D2 and 1,25(OH)2D3) [4]. Subsequently, the active form exerts its action on various cell types through a specific vitamin D receptor (VDR) [5,6]. The processes including metabolism, transportation and signaling of vitamin D are regulated by a number of proteins encoded by specific genes (i.e., 7-dehydrocholesterol reductase (DHCR7/), cytochrome P450-2R1 (CYP2R1), cytochrome P450-27B1 (CYP27B1), vitamin binding protein (GC/DBP), VDR, and retinoid-X receptor A (RXRA) [7].

Low levels of vitamin D have been reported across various geographical regions [8–10]. Interestingly, vitamin D deficiency is commonly detected among older adults and is strongly associated with a decline in physical performance in this age group particularly [11]. Additionally, vitamin D deficiency has been described to be among the factors that lead to sarcopenia [5,12], a progressive, generalized, and age-related skeletal muscle disorder [13]. Furthermore, the supplementation of vitamin D seems to ameliorate mobility and muscle strength [14,15], especially when combined with resistance training [16], but also enhance muscle performance [17,18], suggesting a direct connection between vitamin D and muscle function. One compelling review from Garcia and colleagues described most appropriately the need to assess vitamin D level as one way to minimize physiological and functional changes in skeletal muscle [5].

Besides environmental factors influencing vitamin D levels, a genetic impact has also been questioned in various studies [19,20], and some of them investigated whether single nucleotide polymorphisms (SNPs) in vitamin D-associated genes such as the VDR contribute to muscular strength and mass [21]. However, investigation and integration of studies that explored the association of vitamin D pathway-related genes with muscle traits other than VDR are still missing to date.

In an attempt to broaden this hypothesis, we further assume that genetic variants in several vitamin D pathway-related genes would affect vitamin D levels and, as a consequence, various parameters of physical performance. Therefore, the aim of this systematic review was to comprehensively identify published SNPs in genes known to be associated with the vitamin D pathway and then to systematically analyze their influence on vitamin D levels and/or muscle function in adults, including older adults.

2. Materials and Methods

Details of the protocol for this systematic review were registered on PROSPERO [22]. The report followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [23].

2.1. Search Strategy

In order to identify potential candidate genes, PathCards (https://pathcards.genecards.org/, accessed on 27 November 2018) was used to identify genes that are related to the vitamin D pathway (*n* = 10). PathCards is a constituent network of metabolic pathways with mapping genes, which provides researchers with a rich, searchable systems analysis resource [24]. Additionally, we searched for similar genetic association studies to identify other candidate genes encoding key player proteins (LRP2, CUBN, CYP3A4, and CASR (calcium-sensing receptor)) [19,20]. Information on the finally identified 14 genes is summarized in Figure 1. In order to find publications related to genetic variations in each of the genes, the respective NCBI entry in the gene database was linked first to the SNP database of each gene and then to the PubMed entries. Consequently, these results were connected to a conservative search strategy on PubMed using the respective gene name or their aliases connected with the MeSH term "genetic variation".
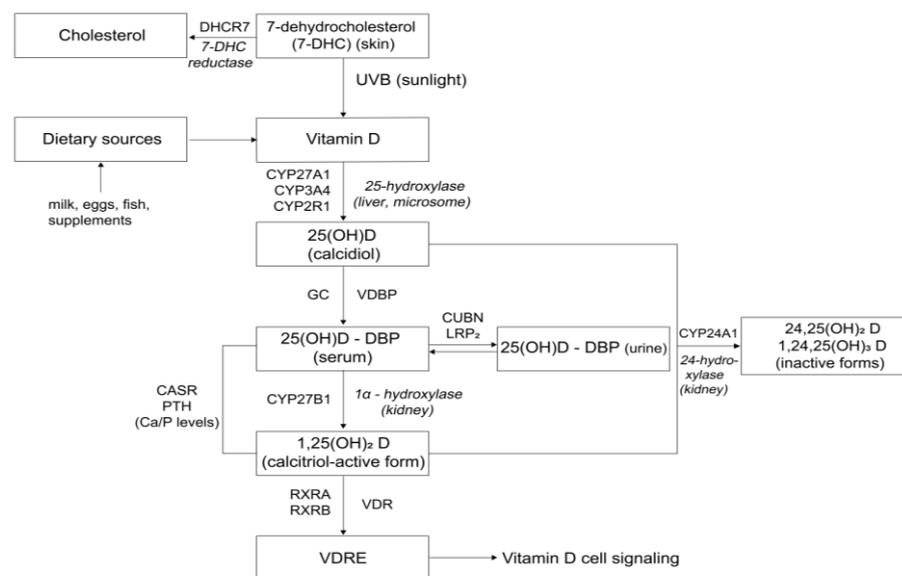
Figure 1. Vitamin D pathway, candidate genes (in bold), and associated enzymes. DHCR7 (7-dehydrocholesterol) gene encodes 7-DHC (7-dehydrocholesterol) reductase enzyme, which converts 7-DHC to cholesterol; CYP2R1 (cytochrome P450 family 2 subfamily R member 1), CYP3A4 (cytochrome P450 family 3 subfamily A member 4), and CYP27A1 (cytochrome P450 family 27 subfamily A member 1) genes encode 25-hydroxylation cytochrome P450 enzymes responsible for converting provitamin D that is absorbed from the diet or synthesized from the action of sunlight on the skin to the circulating form 25(OH)D (25-hydroxyvitamin D); vitamin D is transported bound to vitamin D binding protein (DBP) (encoded by GC gene); LRP2 and CUBN genes encode plasma membrane receptors megalin and cubilin, respectively (involved in re-absorption of 25(OH)D via receptor mediated endocytosis); CYP27B1 encodes the cytochrome p450 enzyme which coverts 1-alpha-hydroxylates 25(OH)D to the active form 1,25(OH)$_2$D (1,25-Dihydroxycholecalciferol, Calcitriol); CASR (calcium sensing receptor) binds calcium in extracellular matrix, impacting calcium homeostasis; Ca homeostasis impacts the synthesis of parathyroid hormone (PTH gene-a protein coding gene) which stimulates the synthesis of 1,25(OH)$_2$D from 25(OH)D by upregulating renal 1-α-hydroxylase; CYP24A1 encodes a 24-hydroxylase enzyme which catalyzes the degradation of 25(OH)D and 1,25(OH)$_2$D in inactive metabolites; VDR encodes the vitamin D receptor, a nuclear receptor which binds 1,25(OH)$_2$D and forms a heterodimer with the gene product of RXR—the retinoid X receptor—to mediate the biological actions of vitamin D.

The final search for PubMed was conducted on 27 November 2018 and followed a protocol developed a priori. The search strategy aimed to identify all articles where the specific genetic variants (i) were aligned with search terms for either vitamin D status (ii), muscle traits (iii), or both (ii AND iii):

(i)   each of the 14 vitamin D-pathway-related genes (including their aliases variation (MeSH terms])

(ii)   vitamin D status (vitamin D[MeSH] OR 25(OH)D OR 25(OH)D2 OR 25(OH) D3 OR Vitamin D Deficiency[MeSH] OR "vitamin D status" OR "vitamin D level" OR "vitamin D inadequacy" OR "hypovitaminosis D" OR "avitaminosis D") NOT Review[Publication Type], Filters: Humans; English; German

(iii) muscle strength and function (Muscle, Skeletal[MeSH] OR Muscle Strength[MeSH] OR Physical Fitness[MeSH] OR Walking Speed[MeSH] OR "muscle mass" OR "lean body mass" OR "muscle quality" OR "physical performance" OR SPPB OR "short physical performance battery" OR "handgrip strength" OR "chair stand" OR "arm curl") NOT Review[Publication Type], Filters: Humans; English; German

After conducting the initial structured search as outlined above, additional studies were added based on the reference lists of the finally selected studies (hand search).

2.2. Inclusion and Exclusion Criteria

Articles were included if studies:

(i) were conducted among humans aged >18 years from both sexes;
(ii) comprised candidate or genome-wide association studies being cross-sectional, cohort, case control, or intervention studies;
(iii) investigated healthy subjects or contained at least a separate control group with normal health status;
(iv) measured at least one genotype in a vitamin D pathway-related gene;
(v) reported vitamin D status (circulating plasma/serum levels, 25(OH)D, 25(OH)D2, or 25(OH)D3 metabolites) and/or reported results for muscle mass or function, muscle strength parameters or scores for the Short Physical Performance Battery (SPPB);
(vi) were published in English or German.

Articles were excluded if they:

(i) reported only vitamin D intake or vitamin D metabolites from urine;
(ii) investigated children (<18 years old);
(iii) investigated participants with severe chronic or acute illnesses with a known impact on either vitamin D status and/or muscle mass and strength (myopathies, hypocalciuric hypercalcemia), or pregnant or lactating women;
(iv) were published as case reports, systematic reviews, or meta-analyses.

2.3. Study Selection and Data Extraction

Study selection and data extraction was performed by two independent reviewers (EK, BW) in accordance with the above-mentioned inclusion and exclusion criteria. A third reviewer (KHW) was included in case of disagreements.

Data extraction from eligible studies included information as follows: (i) gene, (ii) SNP, (iii) bibliographic information, (iv) study design, (v) participants (age, gender, and ethnicity), (vi) sample size, (vii) main findings and outcomes, (viii) location, sampling season and analysis method of vitamin D level if available.

A narrative synthesis of the findings from the selected studies was performed using two frameworks in accordance with the following specific research questions: (i) association of vitamin D-related genetic polymorphisms and vitamin D status, and (ii) association of vitamin D-related genetic polymorphisms and muscle mass or strength. Results were described qualitatively rather than performing a quantitative meta-analysis as study designs and reported outcomes differed widely in order to quantitatively analyze them.

2.4. Risk of Bias (Quality) Assessment

In order to assess the quality of included studies, the STREGA recommendations (STrengthening the REporting of Genetic Association studies guidelines) were applied independently by two reviewers (three if there was any disagreement even after discussion) [25]. The quality of the studies was considered as "high" when the score was 18–22, "moderate-high" when the score was 13–17, and "low" with a score below 12. Results were reported, but no restrictions were made with respect to the inclusion or exclusion of the relevant studies.

3. Results

3.1. Study Selection and Characteristics

In total, 1292 studies were identified from the initial searches in PubMed (*n* = 1282) and through other sources (*n* = 10, Figure 2). As the searches were conducted separately for each of the 14 vitamin D pathway-related genes and then combined, 161 articles had to be excluded as duplicates. During title/abstract screening, a further 936 articles were excluded based on the predefined inclusion and exclusion criteria. The remaining 195 articles were assessed for eligibility based on the full texts. Among these, a further 106 studies were not suitable with respect to the research question. Consequently, 89 studies were included in

the systematic review, with 77 of them reporting the association of genetic polymorphisms of vitamin D-related genes and vitamin D status, and only 12 studies dealing with genetic variants of vitamin D-related genes and muscle mass and/or function. Study designs included 57 cross-sectional studies, 20 case-control studies, and 12 intervention studies.
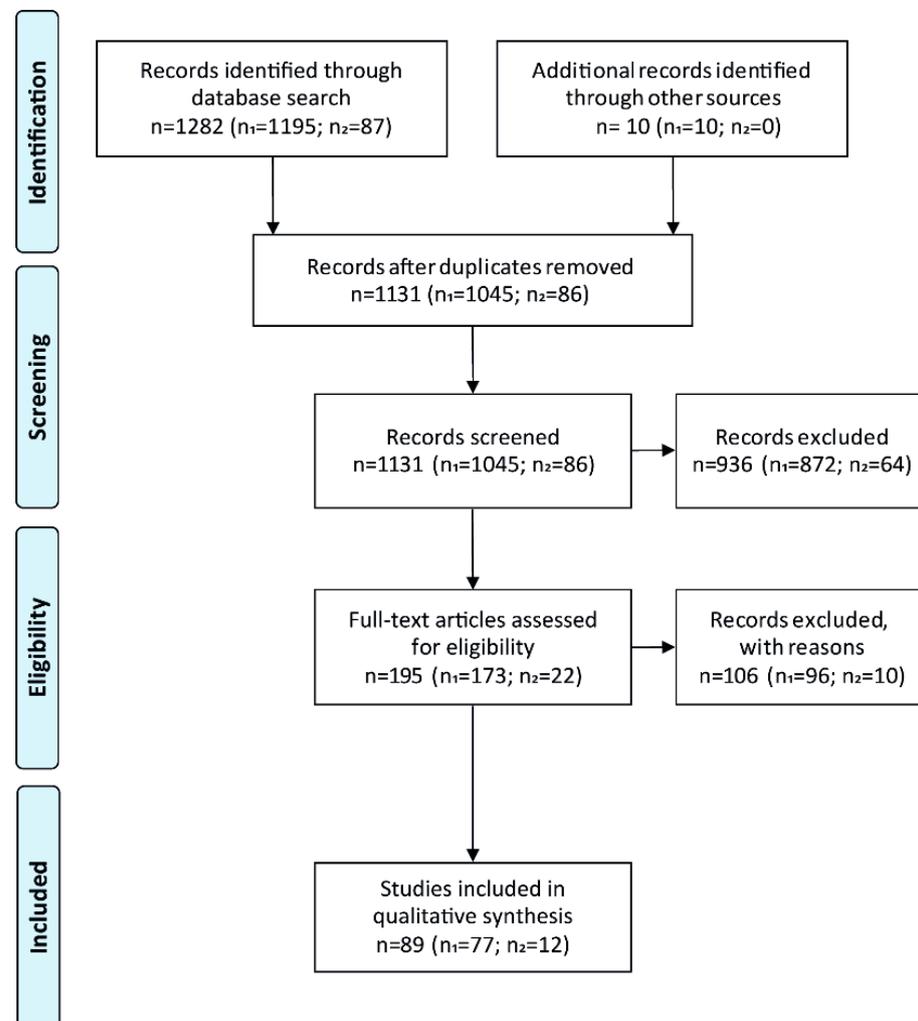

Figure 2. PRISMA-Flow diagram showing the selection of studies included in the systematic review. The number of studies reporting genetic variants and vitamin D status as well as the number of studies reporting genetic variants together with muscle mass and function, are given in parenthesis (n_1 and n_2).

3.2. Polymorphisms in Vitamin D Pathway-Related Genes and Vitamin D Status

As summarized in Table 1, 77 publications that have investigated a potential association between a certain genetic association and vitamin D levels were included in the report. Most of these publications were cross-sectional studies ($n = 46$); a further 19 studies were conducted as case-control studies and 12 studies as interventions. Altogether, these studies investigated 497 SNPs in 13 different genes (GC, CYP2R1, VDR, CYP24A1, DHCR7, CYP27B1, CYP27A1, CASR, PTH, CYP3A4, RXRA, CUBN, and RXRB). No suitable records were found for the gene lipoprotein receptor-related protein 2 (megalin, LRP2).

Table 1. SNPs in vitamin D pathway-related genes and vitamin D status.

Name Gene/ID	Description	Aliases	Studies	SNPs Investigated in Association with Circulating Vitamin D Levels	
				Significant Associations	Non-Significant
GC ID:2638	GC, vitamin D binding protein	DBP, DBP-maf, DBP/GC, GRD3, Gc-MAF, GcMAF, HEL-S-51, VDB, VDBG, VDBP	68 different SNPs reported by 56 studies [26–81]	rs115316390, rs1155563 *, rs11939173, rs12512631 *, rs16846876 *, rs16847015, rs17467825 *, rs222020 *, rs222040, rs222054, rs2282679 *, rs2298849 *, rs2298850 *, rs3755967 *, rs4588 *, rs7041 *, rs705119, rs705120, rs842999, rs9016	rs10011000, rs10488854, rs12640179, rs12644050, rs13117483, rs1352841, rs1352843, rs1352844, rs1352845, rs1491709, rs1491710, rs1491711, rs1491718, rs1491719, rs1565572, rs16846912, rs16846943, rs16847019, rs16847024, rs16847028, rs16847039, rs16847050, rs17383291, rs17830803, rs1873590, rs188812, rs2070741, rs222003, rs222010, rs222014, rs222016, rs222017, rs222023, rs222029, rs222035, rs222043, rs222049, rs2276461, rs3733359, rs3737549, rs3775152, rs4694105, rs4752, rs6817912, rs6835052, rs705117, rs705124, rs843006
CYP2R1 ID:120227	cytochrome P450 family 2 subfamily R member 1	-	29 different SNPs reported by 41 studies [27–36,38,39,42,44,46–48,50–52,55–57,60,62,63,65,67–69,72–74,76–83]	rs10500804 *, rs10741657 *, rs10766197 *, rs10832306, rs11023374 *, rs11023380 * rs12794714 *, rs1562902 *, rs1993116 *, rs2060793 *, rs7116978, rs7935792	rs1037379, rs10832312, rs10832313, rs11023371, rs114050796, rs11819875, rs12418214, rs12419657, rs1496167, rs16930609, rs16930625, rs206793, rs7117967, rs7125348, rs7129781, rs7936142, rs952301
VDR ID:7421	vitamin D receptor	NR1I1, PPP1R163	111 different SNPs reported by 41 studies [27–30,33,37,41,42,46,47,50,52,55–57,60–63,65,67,71,74,75,77,78,84–98]	rs10783219 *, rs11568820, rs1544410 *, rs2228570 * (merged rs10735810), rs2239186 *, rs2408876, rs4516035, rs7139166, rs731236 *, rs7968585, rs7975232 *	rs10083198, rs10747524, rs10783215, rs10783218, rs10875693, rs10875694, rs10875695, rs10875702, rs10875712, rs11168264, rs11168266, rs11168268, rs11168275, rs11168277, rs11168287, rs11168288, rs11168292, rs11168302, rs11168314, rs11540149, rs11574024, rs11574026, rs11574027, rs11574038, rs11574042, rs11574044, rs11574065, rs11574077, rs11574110, rs11574113, rs11574138, rs11574141, rs11574143, rs11608702, rs11834903, rs12308082, rs12314197, rs12370156, rs12717991, rs12721364, rs12721365, rs12721370, rs1540339, rs17882106, rs1859281, rs1989969, rs2071358, rs2107301, rs2189480, rs2238135, rs2238136, rs2238138, rs2239179, rs2239180, rs2239181, rs2239182, rs2239184, rs2239185, rs2248098, rs2254210, rs2283342, rs2525044, rs2525045, rs2544027, rs2544038, rs2853559, rs2853560, rs2853564, rs3782905, rs3819545, rs3847987, rs4077869, rs4328262, rs4334089, rs4442605, rs4760648, rs4760655, rs4760658, rs4760674, rs6580642, rs7136534, rs7299460, rs7302038, rs7302235, rs7305032, rs7310552, rs7311030, rs739837, rs757343, rs7962898, rs7963776, rs7965281, rs7967152, rs7971418, rs7975128, rs7976091, rs881383, rs886441, rs9729, rs987849

Table 1. *Cont.*

Name Gene/ID	Description	Aliases	Studies	SNPs Investigated in Association with Circulating Vitamin D Levels	
				Significant Associations	**Non-Significant**
CYP24A1 ID:1591	cytochrome P450 family 24 subfamily A member 1	CP24, CYP24, HCAI, HCINF1, P450-CC24	65 different SNPs reported by 31 studies [26–33,35,38,42,46,52,55–57,60–62,65,68,69,71–75,78,80,81,97]	rs17216707, rs2209314 *, rs2762939 *, rs2762941, rs6013897 *, rs73913757	rs11907350, rs13038432, rs1555439, rs1570669, rs1570670, rs17219315, rs1870969, rs2021940, rs2181874, rs2244719, rs2245153, rs2248137, rs2248359, rs2248461, rs2274130, rs2296239, rs2296241, rs2426496, rs2426498, rs2585413, rs2585422, rs2585423, rs2585428, rs2585439, rs2762926, rs2762929, rs2762932, rs35051736, rs3787555, rs3787557, rs3886163, rs4809957, rs4809958, rs4809959, rs4809960, rs6013905, rs6022990, rs6022999, rs6023005, rs6023009, rs6023012, rs6068810, rs6068812, rs6068816, rs6068824, rs6097797, rs6097801, rs6097805, rs6097809, rs6127112, rs6127119, rs73913755, rs751090, rs765058, rs765059, rs8124792, rs912505, rs927650, rs927651
DHCR7 ID:1717	7-dehydrocholesterol reductase	SLOS	25 different SNPs reported by 28 studies [27–29,31–33,35,36,38,39,42,44,46,51, 52,55–57,60,67,69,72–74,77,78,81,99]	rs11603330, rs12785878 *, rs1790349 *	rs11233570, rs11234027, rs11606033, rs12419279, rs12800438, rs1540129, rs1540130, rs1790325, rs1790329, rs1790334, rs1790373, rs1792272, rs1792284, rs3794060, rs3829251, rs4316537, rs4944957, rs4945008, rs7122671, rs7944926, rs7950649, rs949178
CYP27B1 ID:1594	cytochrome P450 family 27 subfamily B member 1	CP2B, CYP1, CYP1alpha, CYP27B, P450c1, PDDR, VDD1, VDDR, VDDRI, VDR	15 different SNPs reported by 22 studies [26–28,30,33,37,41,42,46, 52,55,56,60,62,65,74,75,77, 80,81,97,100]	rs10877012 *	rs1021469, rs1048691, rs10877011, rs10877013, rs12368653, rs2269720, rs3782130, rs4646536, rs4646537, rs4760169, rs703842, rs8176344, rs8176345, −1077
CYP27A1 ID:1593	cytochrome P450 family 27 subfamily A member 1	CP27, CTX, CYP27	27 different SNPs reported by 7 studies [26,28,30,33,74,80,81]	–	rs116071925, rs11677711, rs12623740, rs12694443, rs12987009, rs12990447, rs13013510, rs13382651, rs17470271, rs4646535, rs4674338, rs4674344, rs4674345, rs6436084, rs6436094, rs645163, rs647952, rs6709815, rs6716642, rs6723334, rs6740004, rs6751527, rs7566656, rs7568196, rs7594289, rs7603709, rs933994

Table 1. *Cont.*

Name Gene/ID	Description	Aliases	Studies	SNPs Investigated in Association with Circulating Vitamin D Levels	
				Significant Associations	Non-Significant
CASR ID:846	calcium-sensing receptor	CAR, EIG8, FHH, FIH, GPRC2A, HHC, HHC1, HYPOC1, NSHPT, PCAR1, hCasR	71 different SNPs reported by 6 studies [27,60,71,74,80,101]	rs17251221, rs1801725,	rs10222633, rs1042636, rs10934578, rs11715859, rs11716910, rs12485716, rs13093602, rs13324814, rs13327652, rs1354162, rs1393198, rs1501892, rs1501898, rs1501900, rs16832787, rs17203502, rs17203516, rs17282008, rs1801726, rs1814740, rs1847029, rs1973490, rs1979869, rs2036399, rs2134223, rs2134224, rs2173961, rs2202127, rs2221266, rs2270916, rs2279802, rs3749203, rs3749207, rs3792288, rs3792291, rs3804592, rs3804593, rs3804595, rs3845918, rs4677900, rs4678013, rs4678029, rs4678031, rs4678035, rs4678173, rs4678174, rs6438705, rs6438706, rs6438712, rs6764205, rs6764544, rs6768109, rs6776158, rs6799828, rs7614486, rs7617603, rs7628990, rs7635128, rs7639847, rs7644981, rs7647405, rs7648041, rs937626, rs9740, rs9820206, rs9826770, rs9866419, rs9875101, rs9875636
PTH ID: 5741	parathyroid hormone [Homo sapiens (human)]	PTH1	12 different SNPs reported by 6 studies [30,74,80,81,96,102]	rs10500783, rs1459015,	rs2593570, rs6254, rs6256, rs6264, rs694, rs10500784, rs177706, rs192802, rs3099597, rs751610
CYP3A4 ID:1576	cytochrome P450 family 3 subfamily A member 4	CP33, CP34, CYP3A, CYP3A3, CYPIIIA3, CYPIIIA4, HLP, NF-25, P450C3, P450PCN1	9 different SNPs reported by 5 studies [28,30,62,80,81]	rs2242480	rs12333983, rs2246709, rs2687116, rs2740574, rs35599367, rs3735451, rs4646437, rs6956344
RXRA ID: 6256	retinoid X receptor alpha	NR2B1	48 different SNPs reported by 3 studies [52,71,80]	rs11185644 *	rs1045570, rs10785870, rs10881577, rs10881578, rs10881580, rs10881582, rs10881583, rs11102986, rs11103473, rs11103482, rs11185647, rs11185659, rs12004589, rs12004786, rs1536475, rs1805348, rs1805352, rs12339187, rs3118523, rs3118526, rs3118536, rs3118570, rs3118571, rs3132294, rs3132296, rs3132299, rs3132300, rs34677682, rs35603635, rs3818738, rs3818739, rs3818740, rs4240705, rs4917347, rs4917352, rs4917353, rs4917354, rs6537944, rs7039190, rs7861779, rs7864987, rs7871655, rs842196, rs872298, rs877954, rs881657, rs914853

Table 1. *Cont.*

Name Gene/ID	Description	Aliases	Studies	SNPs Investigated in Association with Circulating Vitamin D Levels	
				Significant Associations	**Non-Significant**
CUBN ID:8029	cubilin [Homo sapiens (human)]	IFCR, MGA1, gp280	14 different SNPs reported by 1 study [81]	–	rs10904881, rs11254370, rs1687705, rs1801222, rs1801223, rs1801224, rs1801225, rs1801231, rs1801232, rs1801234, rs1801241, rs2271462, rs3740165, rs703064
RXRB ID:6257	retinoid X receptor beta [Homo sapiens (human)]	DAUDI6, H-2RIIBP, NR2B2, RCoR-1	4 different SNPs reported by 1 study [81]	–	rs6531, rs2076310, rs3117040, rs9277935

SNPs-Single Nucleotide Polymorphisms, * significant associations with circulating vitamin D levels reported in more than one study.

The publication date of the included papers ranged from 2002 to 2018. In total, 81,896 healthy participants were investigated, whereby the number of study participants ranged from 31 (case-control) [89] to 8417 (cross-sectional studies) [57]. Participants with certain diseases such as type 1 [33] and type 2 [83] diabetes mellitus, osteomalacia [89], COPD [45], coronary artery disease [64], hemodialysis [87], Crohn's disease [86], pulmonary tuberculosis [100], melanoma [34], prostate [26,42], breast [32,61,73,97], colorectal [69] and non-small cell lung cancer [75] comprised the cases in the included case-control studies. However, the results of these participants were not included in the analyses of this systematic review.

The most frequently studied gene comprised the vitamin D binding protein (GC) which was investigated in 56 studies, followed by CYP2R1, coding for a vitamin D 25-hydroxylase, which was mentioned in 41 studies, and the vitamin D receptor (VDR) having been subject to 41 studies. In total, 59 SNPs located within 10 different genes showed a significant association with vitamin D levels in at least one study. Most importantly, 23 of these SNPs were confirmed to be related to vitamin D status in at least two other studies (Table 1). For genetic variants in the CYP27A1 gene (vitamin D 25-hydroxylase), CUBN gene (cubilin), and RXRB gene (retinoid-X receptor B), none of the studies reported a significant association with vitamin D level [26,27,30,33,71,101].

SNPs that were studied in at least 15 different studies showed significant associations in 8–77% of the respective studies. The highest confirmation rates were found for SNPs in the GC gene [rs2282679 (association to vitamin D status confirmed in 23 out of 30 studies (77%)); rs4588 (confirmed in 27 out of 37 studies (73%)); rs1155563 (confirmed in 12 out of 17 studies (71%)); rs7041 (confirmed in 27 out of 39 studies (69%))] and in the CYP2R1 gene [rs10741657 (confirmed in 21 out of 32 studies (66%)); rs10766197 (confirmed in 9 out of 15 studies (60%)); rs2060793 (confirmed in 8 out of 15 studies (53%))]. Further frequently studied SNPs located in the DHCR7 gene [rs12785878, confirmed in 6 out of 19 studies (32%)], the CYP24A1 gene [rs6013897, confirmed in 3 out of 18 studies (17%)], and the CYP2R1 gene [rs10877012, confirmed in 2 out of 15 studies (13%)]. Interestingly, SNPs in the VDR gene were frequently investigated, but their confirmation rate was very low [rs7975232 (alias ApaI, confirmed in 3 out of 18 studies (17%)); rs2228570 (confirmed in 4 out of 25 studies (16%)); rs1544410 (confirmed in 4 out of 28 studies (14%)); and rs731236 (confirmed in 2 out of 24 studies (8%)); rs11568820 (confirmed in 1 out of 16 studies (6%))]. A complete list can be found in Supplementary Table S1).

Most of the studies were performed in Europe (21 studies from Belgium, Czech Republic, Denmark, Finland, France, Germany, Hungary, Netherlands, Norway, Estonia, UK, France, Italy, Greece, Spain, Scotland, Sweden, United Kingdom), followed by the US (14 studies) and China (11 studies).

Measurement methods for vitamin D levels were very diverse and included radioimmunoassay, enzyme-linked immunosorbent assay (ELISA), chemiluminescent immunoassays, high performance liquid chromatography (HPLC), and liquid chromatography–tandem mass spectrometry. Mostly, total 25(OH)D (summing up 25(OH)D2 and 25(OH)D3) was measured, although some studies [20,26,34,37,39,41,42,49,52,54,56,70,76,83,92,94,95,100] discriminated between different vitamin D metabolites (Supplementary Table S1).

3.3. Polymorphisms in Vitamin D Pathway-Related Genes and Muscle Mass and Function

As reported in Table 2, 12 publications were included in the qualitative synthesis, whereby 11 studies were conducted as cross-sectional studies and one study as a case-control study [103]. All the selected studies were focusing on potential associations between VDR gene polymorphisms and muscle traits, investigating only four different SNPs in this gene [rs7975232 (alias ApaI), rs1544410 (alias BsmI), rs2228570 (alias FokI, including the merged SNP rs10735810), and rs731236 (alias TaqI)].

Table 2. SNPs in the VDR genes and their association with various muscle traits.

SNP/Traditional Name	Region, Reference	Participants (Number, Gender, Age)	Outcomes for Muscle Mass and Function	Main Findings
rs7975232/ ApaI	Tianjin, China [104]	n = 109 f (AA: 19.57 ± 0.53 y, Aa: 20.00 ± 1.20 y, aa: 19.89 ± 1.05 y)	Concentric and eccentric peak torque of knee extensors and flexors at 30°/s, 60°/s, and 180°/s; concentric peak torque of elbow extensors and flexors at 30°/s and 120°/s	aa + aA genotypes→higher knee extension peak torque at 120°s, higher elbow flexion at 120°/s and 30°/s than AA
	Fuki Prefecture, Japan [105]	n = 180 f; 60.1 ± 6.6 y	Handgrip strength; isokinetic concentric peak torque of knee extensors and flexors; isometric and isokinetic concentric and eccentric peak torque of trunk flexors and extensors	No significant differences in any muscle strength parameter between ApaI genotype groups (AA, Aa, aa) (data not shown in article)
	Northern Italy [106]	Centenarians (n = 102, 102.3 ± 0.3 y) versus septuagenarians (n = 163; 73.0 ± 0.6 y)	Handgrip strength	FF→significantly higher handgrip strength than Ff + ff
rs1544410/ BsmI	Sirente area, Italy [107]	n = 259 (87 m + 172 f); 85.0 ± 4.5 y	Handgrip strength, short physical performance battery (SPPB)	No significant differences between genotypes (BB, Bb, bb) in handgrip strength and SPPB score
	Baltimore, USA [108]	n = 864 (489 m + 375 f); 22–90 y;	Total and appendicular fat-free mass (DXA); handgrip strength; concentric peak torque of knee extensors at 30°/s and 180°/s; isometric peak torque at 120° and 140° knee ankle	No significant differences in fat-free mass Only modest differences in strength measurements: knee extensor isokinetic peak torque at 30°/s in females (bb > bB > BB)
	Northern Italy [106]	Centenarians (n = 102, 102.3 ± 0.3 y) versus septuagenarians (n = 163; 73.0 ± 0.6 y)	Handgrip strength	No significant differences in handgrip strength between genotypes
	Istanbul, Turkey [109]	n = 120 m; 69.0 ± 6.9 y	Fat-free mass (BIA); isokinetic peak torque of knee extensors, flexors at 60°/s	BB→higher knee extensor strength as compared to Bb + bb; No differences for flexors, muscle mass, and vitamin D level
	UK, Germany, France [110]	APUSS cohort (n = 3234 f; 54.3 ± 2.3 y); OPUS cohort (n = 1970 f; 66.9 ± 7.0 y)	Handgrip strength; chair rise test (difficulty and power with force plate); data only from OPUS cohort	BB + bB genotypes→higher max power, fewer difficulties to stand up from a chair No differences in handgrip strength
	London, UK [103]	COPD (n = 107; 75 m + 32 f; 63.5 ± 9.5 y); age-matched controls (n= 104; 48 m + 56 f; 61.8 ± 8.5 y)	Handgrip strength; quadriceps strength, calculated as quadriceps maximum voluntary contraction force; fat-free mass (BIA)	No significant differences between genotypes for fat-free mass and strength measures
	Leuven, Belgium [111]	493 (253 m (54.9 ± 10.2 y) + 240 f (41.5 ± 13.2 y))	Fat-free mass (estimated from skinfolds); handgrip strength; Isometric knee extension strength at 150°, 120°, and 90° knee ankle; Isometric knee flexion strength at 120°	No significant differences in any of the measured parameters [data not shown]
	Tianjin, China [104]	n = 109f (AA: 19.57 ± 0.53 y, Aa: 20.00 ± 1.20 y, aa: 19.89 ± 1.05 y)	Concentric and eccentric peak torque of knee extensors and flexors at 30°/s, 60°/s, and 180°/s; concentric peak torque of elbow extensors and flexors at 30°/s and 120°/s	BB + Bb genotypes→higher knee flexion peak torque at 180°/s than bb group No other differences

Table 2. *Cont.*

SNP/Tra-ditional Name	Region, Reference	Participants (Number, Gender, Age)	Outcomes for Muscle Mass and Function	Main Findings
	Uppsala, Sweden [112]	*n* = 175 f; 29.6 ± 5.9	Handgrip strength; Isokinetic knee-flexion and extension strength at 90°/s; lean body mass (DXA)	BB→higher hamstring strength as compared to bb No differences in lean mass
	Monongahela Valley, USA [113]	*n* = 302 m; 58−93 y	Peak and average isometric quadriceps strength at 125° knee ankle; appendicular and total fat-free mass (DXA)	No differences in any measured parameter
	n/A [114]	*n* = 501 f; >70 y (mean age: 75 y)	isometric muscle strength of the quadriceps; handgrip strength	bb + Bb→higher quadriceps strength than BB in non-obese females, but not in obese females
rs2228570/ FokI (rs10735810)	Sirente area, Italy [107]	*n* = 259 (87 m + 172f); 85.0 ± 4.5 y	Handgrip strength, short physical performance battery (SPPB)	No significant differences between genotypes (FF, Ff, ff) in handgrip strength and SPPB score
	Baltimore, USA [108]	*n* = 864 (489 m+ 375 f); 22–90 y;	Total and appendicular fat-free mass (DXA); handgrip strength; concentric peak torque of knee extensors at 30°/s and 180°/s; isometric peak torque at 120° and 140° knee ankle	No significant differences in fat-free mass; Males: no significant differences for any strength variable measured; Females: ff→higher isometric quadriceps strength (120°) in comparison to Ff and FF
	Northern Italy [106]	Centenarians (*n* = 102, 102.3 ± 0.3 y) versus septuagenarians (*n* = 163; 73.0 ± 0.6 y)	Handgrip strength	FF→significantly higher handgrip strength than Ff + ff
	Istanbul, Turkey [109]	*n* = 120 m; 69.0 ± 6.9 y	Fat-free mass (BIA); isokinetic peak torque of knee extensors, flexors at 60°/s	No significant differences between genotypes (FF, Ff, ff)
	UK, Germany, France [110]	APUSS cohort (*n* = 3234 f; 54.3 ± 2.3 y); OPUS cohort (*n* = 1970 f; 66.9 ± 7.0 y)	Handgrip strength; chair rise test (difficulty and power with force plate); data only from OPUS cohort	No significant differences between genotypes (FF, Ff, ff)
	London, UK [103]	cases with stable COPD (*n* = 107; 63.5 ± 9.5 y) and healthy age-matched controls (*n*= 104; 61.8 ± 8.5 y)	Handgrip strength; quadriceps strength, calculated as quadriceps maximum voluntary contraction force; fat-free mass (BIA)	FF→significantly lower quadriceps strength than Ff + ff
	Leuven, Belgium [111]	493(253 m (54.9 ± 10.2 y) + 240 f (41.5 ± 13.2 y))	Fat-free mass (estimated from skinfolds); handgrip strength; Maximal isometric knee extension strength at 150°, 120°, and 90° knee ankle; Maximal isometric knee flexion strength at 120° knee ankle;	Females: Ff→lower isometric knee extension strength at 120° and 90° than both FF and ff Males: no significant differences for any of the strength measurements
	Monongahela Valley, USA [113]	*n* = 302 m; 58–93 y	Peak and average isometric quadriceps strength at 125° knee ankle; appendicular and total fat-free mass (DXA)	FF→significantly lower appendicular and total fat-free mass than Ff and ff; FF→significantly lower peak and average isometric quadriceps strength than ff

Table 2. *Cont.*

SNP/Traditional Name	Region, Reference	Participants (Number, Gender, Age)	Outcomes for Muscle Mass and Function	Main Findings
rs731236/TaqI	Tianjin, China [104]	*n* = 109f (AA: 19.57 ± 0.53 y, Aa: 20.00 ± 1.20 y, aa: 19.89 ± 1.05 y)	Concentric and eccentric peak torque of knee extensors and flexors at 30°/s, 60°/s, and 180°/s; concentric peak torque of elbow extensors and flexors at 30°/s and 120°/s	No significant differences between genotypes (TT, Tt, tt)
	Fuki Prefecture, Japan [105]	*n* = 180 f; 60.1 ± 6.6 y	Handgrip strength; isokinetic concentric peak torque of knee extensors and flexors; isometric and isokinetic concentric and eccentric peak torque of trunk flexors and extensors	No significant differences between genotypes (TT, Tt, tt)
	Baltimore, USA [108]	*n* = 864 (489 m + 375 f); 22–90 y;	Total and appendicular fat-free mass (DXA); handgrip strength; concentric peak torque of knee extensors at 30°/s and 180°/s; isometric peak torque at 120° and 140° knee ankle	No significant differences in fat-free mass; Males: no significant differences for any strength variable measured; Females: ff→higher isometric quadriceps strength (120°) in comparison to Ff and FF
	Northern Italy [106]	Centenarians (*n* = 102, 102.3 ± 0.3 y) versus septuagenarians (*n* = 163; 73.0 ± 0.6 y)	Handgrip strength	FF→significantly higher handgrip strength than Ff + ff
	Istanbul, Turkey [109]	*n* = 120 m; 69.0 ± 6.9 y	Fat-free mass (BIA); isokinetic peak torque of knee extensors, flexors at 60°/s	No significant differences between genotypes (TT, Tt, tt)

n-number, y-years, f-females, m-males.

In total, 5342 healthy subjects were included, with the number of participants ranging from 104 (case-control study) [103] to 1970 (cross-sectional study) [110]. The most frequently studied SNP was rs1544410 (BsmI), investigated by 11 studies, whereby five studies were reporting significant associations between its genotypes (BB, Bb, bb) and muscle traits such as knee flexion peak torque [104], knee extensor strength [109], maximal power [110], hamstring strength [112] and quadriceps strength [114]. Four studies included only female subjects [104,110,112,114].

The rs2228570 (FokI, rs10735810) SNP was mentioned in eight studies, five of which showing a significant association between its genotypes (FF, Ff, ff) and muscle traits: quadriceps strength [103,108,113], handgrip strength [106], and knee extension strength [111].

Rs7975232 (ApaI) was investigated by three studies [104–106], one of them showing significance between aa + aA genotypes and muscle strength [104]. For the genotypes of the SNP rs731236 (TaqI), none out of five studies reported any significant association [104–106,108,109].

3.4. Quality of Included Studies

The STREGA quality score for the studies relating the respective SNPs to vitamin D status was 18.8 ± 2.3 showing low to high quality with a range between 11 and 22. While for studies relating SNPs to muscle traits, the mean STREGA score was 16.8 ± 1.8 with a range between 13 and 19, indicating moderate to high quality.

4. Discussion

We have systematically evaluated the available scientific data showing the association of certain genotypes to vitamin D deficiency, and hence, poor muscle status. Variations in GC, CYP2R1, VDR, and CYP24A1 genes were reported most frequently, whereby especially SNPs in the GC (rs2282679, rs4588, rs1155563, rs7041) and CYP2R1 genes (rs10741657, rs10766197, rs2060793) were confirmed to be associated with vitamin D plasma level in more than 50% of the respective studies. Various muscle traits have been investigated only in relation to four different VDR polymorphisms (rs7975232, rs2228570, rs1544410, and rs731236). Interestingly, all of them showed only very low confirmation rates (6–17% of the studies).

Synthesized or consumed with the diet, in the liver, vitamin D is converted in its circulating form 25-hydroxyvitamin D (calcidiol), a process mediated by enzyme 25-hydroxylase, which is encoded by the CYP2R1 gene. Polymorphisms in this gene may impact vitamin D metabolism, while it shows catabolic effects toward Vitamin D2 and D3 by modulating 25-hydroxylase's activity and expression [115]. Accordingly, a significant impact of 9 polymorphisms on this gene (Table 1) with vitamin D status has been found to be replicated in more than two studies. Rs10741657, located in non-coding region 5′-UTR, was the most frequently studied SNP of this gene, with a significant association confirmed in 66% of the conducted studies with the beneficiary allele being the minor one. This data is in line with a recent meta-analysis on the effects of CYP2R1 gene variants on vitamin D levels [116]. Being located in 2-kb CYP2R1 mRNA transcript, it is believed that this SNP is able to change enzyme activities and affect vitamin D metabolism [117]. At the same time, two other SNPs, rs12794714 and rs10766197, located in the coding region of introns with the possibility of altering transcription rate [117] are confirmed in 79 and 60%, respectively, with the minor allele being the risk allele in the two aforementioned SNPs (Supplementary Table S1).

The transport of 25(OH)D toward target tissues for utilization and processes is enabled by vitamin D binding protein (DPB). This protein binds 85 to 90% of vitamin D circulating form, having the role of both carrier and reservoir. The remaining 10–15% of the circulating vitamin D is bound to albumin, or unbound, representing the available fraction based on the free hormone hypothesis [97]. This multifunctional and polymorphic protein is encoded by the GC gene (located on chromosome 4q12-q13), whose DNA sequence may impact the binding ability to vitamin D since its isoforms have different binding affinities,

possibly impacting the half-life of circulating 25(OH)D [28]. From at least 120 identified isoforms, the most common ones Gc1f and Gc1s (rs7041 locus), as well as Gc2 (rs4588 locus), refer to the two functional SNPs in exon 11 with rs7041 causing an Asp→Glu amino acid change and rs4588 causing a Thr→Lys exchange in the vitamin D binding protein [118]. Interestingly, those two SNPs were found to be significantly associated with the vitamin D level in 69 and 73% of the respective studies included in this review. In the aforementioned SNPs, the major allele was the beneficiary one in the majority of the studies (70 and 93%, respectively). In addition, this gene's polymorphisms are believed to influence the circulating concentration of DBP, which may alter the bioavailable circulating vitamin D [119]. This association might also be linked to the possible impact of these SNPs in the affinity of DPB to actin while modifying its actin-binding region and affecting 25(OH)D uptake and retention into skeletal muscle cells. Furthermore, it has been shown that C2 myotubes and primary rat muscle fibers express megalin and cubilin receptors, which enable endocytosis of DBP [120]. Studies on megalin and cubilin published after the search closing date of this systematic review did not reveal new findings [121,122]. In addition to the previously mentioned functional polymorphisms in the GC gene, there are also intron-located SNPs, which were found to be associated with vitamin D status, whereas the underlying mechanism remains unclear. One such, rs2282679, an intron variant (in linkage disequilibrium with rs4588) [123], was found to be significantly associated with vitamin D in 77% of the identified studies, all confirming the major allele as the beneficiary one. Finally, rs1155563 (an intron variant) was confirmed in 71% of the studies (of which 71% confirmed the major allele as the beneficiary one).

Furthermore, another important part of the vitamin D pathway chain is the vitamin D receptor, a high-affinity nuclear receptor encoded by the VDR gene. Vitamin D exerts its biological roles when its active metabolite 1alpha,25-dihydroxyvitamin D3 [1alpha,25(OH)2D3] binds to VDR, causing a transactivation function of VDR [124]. The resulting complex 1,25D-VDR-RXR then binds to vitamin D response elements in the DNA [125]. Consequently, VDR is involved in the regulation of many cellular functions such as phospholipid metabolism, apoptosis, cell differentiation, and oxidative stress. It also affects the expression of the vitamin D metabolism-related genes CYP27B1 and CYP24A1 [126,127]. Several studies aimed to prove the association between VDR gene polymorphism and vitamin D status. Among one of the most studied SNPs, Fok1 is a polymorphism located at the start codon of the coding part, whose polymorphic form produces a protein shorter by amino acids [128], altering the length of the VDR [106]. However, an association with vitamin D level has been confirmed in only 16% of the studies included in this systematic review. The exact role of other frequently studied polymorphisms in VDR is not fully elucidated. Three SNPs located in the 3′ end of the VDR gene rs1544410 (Bsm1), rs731236 (Taq1), and rs7975232 (Apa1), considered to be in high linkage disequilibrium with 3′ UTR polymorphisms [129]. An effective role of these genetic variants on vitamin D level is very unlikely as they have been associated with the vitamin D level in only 14, 8, and 17% of the studies, although investigated in 28, 24, and 18 studies, respectively. Although the regions around these SNPs are not translated to the VDR protein, they might have a role in mRNA stability because of their neighborhood to the poly-A tail [130].

Taken together, there seems to be limited evidence that genetic variations in the VDR gene will exert a meaningful association with vitamin D level, given the small number of studies showing significant associations in relation to the high number of studies investigating a potential association. This is further supported by the notation that even in those studies showing a significant association, there was no clear direction with respect to the identification of a beneficiary allele (Supporting File S1).

In addition, two SNPs on the DHCR7 genes have been highly investigated. This gene encodes the enzyme 7-dehydrocholesterol reductase, a key metabolite enzyme that catalyzes the conversion of 7-dehydrocholesterol to cholesterol [28]. Rs12785878 and rs1790349 were found to be significantly associated with the vitamin D level in 32 and 50% of the included studies, while the major allele could be identified to be the beneficiary

one in 83 and 80% of the studies. Therefore, no clear conclusion can be drawn on the involvement of these SNPs in affecting vitamin D level, which is confirmed in recent studies on adolescents with rs12785878 genotype showing no association to hypovitaminosis D [131], but an interaction between 25(OH)D levels and rs12785878 genotype in DHCR7 on overall survival of patients with metastatic colorectal cancer [132].

While vitamin D deficiency is an important public health topic, at least some vitamin D-related gene polymorphisms seem to play an important role in vitamin D status. However, an in-depth analysis of the study characteristics revealed (see Supplementary Table S1) that the included studies were characterized by heterogeneous methodology, including varying sample sizes, age groups, and, most importantly, different vitamin D measurement techniques. After concerns were raised about the accuracy of different vitamin D assays and the possibilities of misleading assessment of vitamin D levels [133], EFSA recommended liquid chromatography-tandem mass spectroscopy (LC-MS/MS) as the reference method in regard to 25(OH)D concentrations [4]. Notwithstanding, LC-MS/MS was found to be used in only 17 out of 77 studies (22.1%) included in this qualitative analysis, while the radioimmunoassay method (RIA) was the most used one (in 22 of 77 studies, 28.6%). It also must be noted that the search for genotypes differed as well—as most of the studies used a candidate genotype approach, although some SNPs were identified via SNP arrays [26–28,30,37,38,52,60,62,65,74,80,81,97].

As vitamin D level has been shown to be low in a significant proportion of adults worldwide [134], vitamin D supplementation remains an important method to achieve optimal levels. Its ability to enhance muscle strength [135], physical performance [17,18], including the lowering of the risk of falling in older adults with low serum 25(OH)D [17,136], has already been demonstrated. Notwithstanding, genetics might also affect the metabolic response toward vitamin D supplementation [80]. Accordingly, existing data implicate that polymorphisms in CYP2R1 (rs10766197, rs10741657), GC (rs4588, rs7041, rs2282679,) and VDR gene (rs2228570,) are associated with vitamin D dose-response, in view of the fact that these were individually replicated in at least two different intervention studies [27,35,40,41,54,56,60,74,78,80]. Although this was not the primary aim of this systematic review, it might comprise important information towards the necessity of personalized vitamin D treatment due to a possible intra-individual variability. It should be noted that we have not encountered studies investigating the direct link between vitamin D pathway-related gene polymorphisms and the effect of vitamin D supplementation on muscle traits. Although, data supporting the impact of these genes' polymorphisms in vitamin D status implicates their potential effect of vitamin D status in health outcomes such as muscle performance, particularly in vitamin D supplementation improvement in older adults with 25(OH)D levels <37–45 nmol/L [17,18].

While some outcomes of vitamin D deficiency, such as osteomalacia and osteoporosis are well known, the implications of vitamin D in muscle strength and function are still being investigated. Studies on vitamin D pathway-related genotypes and muscle traits were exclusively focused on the VDR gene. Genomic and non-genomic pathways might explain the effects of vitamin D on muscles. While the genomic effect is mediated through the already mentioned 1,25D-VDR-RXR complex, the non-genomic effect involves intracellular calcium and phosphate homeostasis resulting from transcriptional regulation of specific proteins in organs such as intestines, bone, and parathyroid gland [125]. In this respect, it has been shown that muscle fibers of VDR-null mice were smaller, more variable in size, and accompanied by abnormal expression of myoregulatory transcription factors (myf5, myogenin, and E2A). Hence, it is believed that VDR may be involved in transcriptional down-regulation of these factors during muscle differentiation [137]. Whereas these implications and underlying biology are still being studied [138], this review shows rs2228570 and rs1544410 within the VDR gene to be the most frequently investigated polymorphisms also with respect to their impact on skeletal muscle traits. Interestingly, the identified studies showed non-conclusive results as, i.e., upper body strength (major allele-the beneficiary one) [106] was controversially affected by the FokI (rs2228570) genotype

than the lower body strength (minor allele-the beneficiary one) [103,108,111,113]. Nevertheless, this demands further mechanistic investigations. For BsmI (rs1544410) genotype, the positive impact of major alleles in lower body muscles was confirmed in four studies [104,109,110,112]. A recent study, not being included in the systematic review focusing on further SNPs in the VDR gene (rs9729, rs17882106, rs7136534, rs11568820, rs10735810, rs4516035, and 11574024) did not reveal new findings, as neither muscle strength nor physical performance were associated to these genotypes [139]. To date, studies investigating the direct impact of vitamin D pathway-related genes (other than VDR gene) and muscle traits are still lacking.

Finally, this systematic review highlighted that there are promising candidate SNPs in vitamin D pathway-related genes that might impact vitamin D level and eventually muscle traits. However, it should be noted that heterogeneity among the selected studies represents a potential limitation, which also caused the decision to refrain from conducting a meta-analysis. Despite this limitation, the strength lies in the extensive information on individual SNPs in most of the relevant vitamin D pathway-related genes. To extract this detailed information from all included studies caused the rather long duration from the underlying systematic search to reporting the results. However, no conflicting results were found when comparing the outcomes of our study to recently published data [121,122,140–149]. The focus of recently published data remains in the same gene's polymorphisms: GC, CYP2R1, VDR, CYP24A1, and CYP27B1. Except for these genes, Fediriko et al., 2019 and Jorde et al., 2019 identified potentially novel SNPs in vitamin D-related candidate genes (LRP2 and CUBN), but none of those were statistically significant [121,122].

5. Conclusions

To the best of our knowledge, this systematic review presents a very comprehensive update of the association of polymorphisms in vitamin D pathway-related genes with vitamin D status in healthy adults. While especially SNPs in the GC (rs2282679, rs4588, rs1155563, rs7041) and CYP2R1 genes (rs10741657, rs10766197, rs2060793) were confirmed to be associated with vitamin D levels in more than 50% of the respective studies, various muscle traits have been investigated only in relation to four different VDR polymorphisms (rs7975232, rs2228570, rs1544410, and rs731236) and outcomes remain inconclusive. Taken together, these data could be used in various ways: (1) to use the identified SNPs as candidate genes to be validated in further studies, (2) to identify individuals at potential risk, and (3) to optimize potential interventions with all these suggestions being important for precision nutrition.

References

1. Lips, P.; van Schoor, N.M. The effect of vitamin D on bone and osteoporosis. *Best Pract. Res. Clin. Endocrinol. Metab.* **2011**, *25*, 585–591. [CrossRef]
2. O'Neill, C.M.; Kazantzidis, A.; Ryan, M.J.; Barber, N.; Sempos, C.T.; Durazo-Arvizu, R.A.; Jorde, R.; Grimnes, G.; Eiriksdottir, G.; Gudnason, V.; et al. Seasonal Changes in Vitamin D-Effective UVB Availability in Europe and Associations with Population Serum 25-Hydroxyvitamin D. *Nutrients* **2016**, *8*, 533. [CrossRef] [PubMed]
3. Wacker, M.; Holick, M.F. Sunlight and Vitamin D: A global perspective for health. *Dermatoendocrinology* **2013**, *5*, 51–108. [CrossRef]
4. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). Dietary reference values for vitamin D. *EFSA J.* **2016**, *15*, e04780. [CrossRef]
5. Garcia, M.; Seelaender, M.; Sotiropoulos, A.; Coletti, D.; Lancha, A.H., Jr. Vitamin D, muscle recovery, sarcopenia, cachexia, and muscle atrophy. *Nutrition* **2019**, *60*, 66–69. [CrossRef] [PubMed]
6. Wang, Y.; Zhu, J.; DeLuca, H.F. Where is the vitamin D receptor? *Arch. Biochem. Biophys.* **2012**, *523*, 123–133. [CrossRef]
7. Holick, M.F. Vitamin D status: Measurement, interpretation, and clinical application. *Ann. Epidemiol.* **2009**, *19*, 73–78. [CrossRef]
8. Cashman, K.D.; Dowling, K.G.; Skrabakova, Z.; Gonzalez-Gross, M.; Valtuena, J.; De Henauw, S.; Moreno, L.; Damsgaard, C.T.; Michaelsen, K.F.; Molgaard, C.; et al. Vitamin D deficiency in Europe: Pandemic? *Am. J. Clin. Nutr.* **2016**, *103*, 1033–1044. [CrossRef]
9. Liu, X.; Baylin, A.; Levy, P.D. Vitamin D deficiency and insufficiency among US adults: Prevalence, predictors and clinical implications. *Br. J. Nutr.* **2018**, *119*, 928–936. [CrossRef]
10. van Schoor, N.; Lips, P. Global Overview of Vitamin D Status. *Endocrinol. Metab. Clin. N. Am.* **2017**, *46*, 845–870. [CrossRef]
11. Wicherts, I.S.; van Schoor, N.M.; Boeke, A.J.; Visser, M.; Deeg, D.J.; Smit, J.; Knol, D.L.; Lips, P. Vitamin D status predicts physical performance and its decline in older persons. *J. Clin. Endocrinol. Metab.* **2007**, *92*, 2058–2065. [CrossRef]
12. Remelli, F.; Vitali, A.; Zurlo, A.; Volpato, S. Vitamin D Deficiency and Sarcopenia in Older Persons. *Nutrients* **2019**, *11*, 2861. [CrossRef] [PubMed]
13. Cruz-Jentoft, A.J.; Bahat, G.; Bauer, J.; Boirie, Y.; Bruyere, O.; Cederholm, T.; Cooper, C.; Landi, F.; Rolland, Y.; Sayer, A.A.; et al. Sarcopenia: Revised European consensus on definition and diagnosis. *Age Ageing* **2019**, *48*, 16–31. [CrossRef] [PubMed]
14. Rosendahl-Riise, H.; Spielau, U.; Ranhoff, A.H.; Gudbrandsen, O.A.; Dierkes, J. Vitamin D supplementation and its influence on muscle strength and mobility in community-dwelling older persons: A systematic review and meta-analysis. *J. Hum. Nutr. Diet.* **2017**, *30*, 3–15. [CrossRef] [PubMed]
15. Zhang, L.; Quan, M.; Cao, Z.B. Effect of vitamin D supplementation on upper and lower limb muscle strength and muscle power in athletes: A meta-analysis. *PLoS ONE* **2019**, *14*, e0215826. [CrossRef] [PubMed]
16. Antoniak, A.E.; Greig, C.A. The effect of combined resistance exercise training and vitamin D3 supplementation on musculoskeletal health and function in older adults: A systematic review and meta-analysis. *BMJ Open* **2017**, *7*, e014619. [CrossRef] [PubMed]
17. Dawson-Hughes, B. Vitamin D and muscle function. *J. Steroid Biochem. Mol. Biol.* **2017**, *173*, 313–316. [CrossRef]
18. Ceglia, L. Vitamin D and its role in skeletal muscle. *Curr. Opin. Clin. Nutr. Metab. Care* **2009**, *12*, 628–633. [CrossRef]
19. Arem, H.; Yu, K.; Xiong, X.; Moy, K.; Freedman, N.D.; Mayne, S.T.; Albanes, D.; Arslan, A.A.; Austin, M.; Bamlet, W.R.; et al. Vitamin D metabolic pathway genes and pancreatic cancer risk. *PLoS ONE* **2015**, *10*, e0117574. [CrossRef]
20. Jolliffe, D.A.; Walton, R.T.; Griffiths, C.J.; Martineau, A.R. 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. *J. Steroid Biochem. Mol. Biol.* **2016**, *164*, 18–29. [CrossRef]
21. Puthucheary, Z.; Skipworth, J.R.; Rawal, J.; Loosemore, M.; Van Someren, K.; Montgomery, H.E. Genetic influences in sport and physical performance. *Sports Med.* **2011**, *41*, 845–859. [CrossRef] [PubMed]
22. Wessner, B.; Krasniqi, E.; Boshnjaku, A.; Wagner, K.-H. *Association between Polymorphisms in Vitamin D Pathway-Related Genes, Vitamin D Status, Muscle Mass and Function: A Systematic Review*; PROSPERO: York, UK, 2018; CRD42018117989.
23. Moher, D.; Liberati, A.; Tetzlaff, J.; Altman, D.G.; Group, P. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *Int. J. Surg.* **2010**, *8*, 336–341. [CrossRef]
24. Belinky, F.; Nativ, N.; Stelzer, G.; Zimmerman, S.; Iny Stein, T.; Safran, M.; Lancet, D. PathCards: Multi-source consolidation of human biological pathways. *Database* **2015**, *2015*. [CrossRef]
25. Little, J.; Higgins, J.P.; Ioannidis, J.P.; Moher, D.; Gagnon, F.; von Elm, E.; Khoury, M.J.; Cohen, B.; Davey-Smith, G.; Grimshaw, J.; et al. STrengthening the REporting of Genetic Association Studies (STREGA): An extension of the STROBE statement. *PLoS Med.* **2009**, *6*, e22. [CrossRef]
26. Ahn, J.; Albanes, D.; Berndt, S.I.; Peters, U.; Chatterjee, N.; Freedman, N.D.; Abnet, C.C.; Huang, W.Y.; Kibel, A.S.; Crawford, E.D.; et al. Vitamin D-related genes, serum vitamin D concentrations and prostate cancer risk. *Carcinogenesis* **2009**, *30*, 769–776. [CrossRef]
27. Barry, E.L.; Rees, J.R.; Peacock, J.L.; Mott, L.A.; Amos, C.I.; Bostick, R.M.; Figueiredo, J.C.; Ahnen, D.J.; Bresalier, R.S.; Burke, C.A.; 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. *J. Clin. Endocrinol. Metab.* **2014**, *99*, E2133–E2137. [CrossRef] [PubMed]

28. Batai, K.; Murphy, A.B.; Shah, E.; Ruden, M.; Newsome, J.; Agate, S.; Dixon, M.A.; Chen, H.Y.; Deane, L.A.; Hollowell, C.M.; et al. Common vitamin D pathway gene variants reveal contrasting effects on serum vitamin D levels in African Americans and European Americans. *Hum. Genet.* **2014**, *133*, 1395–1405. [CrossRef]

29. Brouwer-Brolsma, E.M.; Vaes, A.M.M.; van der Zwaluw, N.L.; van Wijngaarden, J.P.; Swart, K.M.A.; Ham, A.C.; van Dijk, S.C.; Enneman, A.W.; Sohl, E.; van Schoor, N.M.; et al. Relative importance of summer sun exposure, vitamin D intake, and genes to vitamin D status in Dutch older adults: The B-PROOF study. *J. Steroid Biochem. Mol. Biol.* **2016**, *164*, 168–176. [CrossRef]

30. Bu, F.X.; Armas, L.; Lappe, J.; Zhou, Y.; Gao, G.; Wang, H.W.; Recker, R.; Zhao, L.J. Comprehensive association analysis of nine candidate genes with serum 25-hydroxy vitamin D levels among healthy Caucasian subjects. *Hum. Genet.* **2010**, *128*, 549–556. [CrossRef]

31. Cheung, C.L.; Lau, K.S.; Sham, P.C.; Tan, K.C.; Kung, A.W. 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*, 749–751. [CrossRef]

32. Clendenen, T.V.; Ge, W.; Koenig, K.L.; Axelsson, T.; Liu, M.; Afanasyeva, Y.; Andersson, A.; Arslan, A.A.; Chen, Y.; Hallmans, G.; et al. Genetic Polymorphisms in Vitamin D Metabolism and Signaling Genes and Risk of Breast Cancer: A Nested Case-Control Study. *PLoS ONE* **2015**, *10*, e0140478. [CrossRef]

33. Cooper, J.D.; Smyth, D.J.; Walker, N.M.; Stevens, H.; Burren, O.S.; Wallace, C.; Greissl, C.; Ramos-Lopez, E.; Hypponen, E.; Dunger, D.B.; et al. Inherited variation in vitamin D genes is associated with predisposition to autoimmune disease type 1 diabetes. *Diabetes* **2011**, *60*, 1624–1631. [CrossRef] [PubMed]

34. Davies, J.R.; Chang, Y.M.; Snowden, H.; Chan, M.; Leake, S.; Karpavicius, B.; Haynes, S.; Kukalizch, K.; Randerson-Moor, J.; Elliott, F.; 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.* **2011**, *22*, 1471–1482. [CrossRef] [PubMed]

35. Didriksen, A.; Grimnes, G.; Hutchinson, M.S.; Kjaergaard, M.; Svartberg, J.; Joakimsen, R.M.; Jorde, R. The serum 25-hydroxyvitamin D response to vitamin D supplementation is related to genetic factors, BMI, and baseline levels. *Eur. J. Endocrinol.* **2013**, *169*, 559–567. [CrossRef] [PubMed]

36. Elkum, N.; Alkayal, F.; Noronha, F.; Ali, M.M.; Melhem, M.; Al-Arouj, M.; Bennakhi, A.; Behbehani, K.; Alsmadi, O.; Abubaker, J. Vitamin D insufficiency in Arabs and South Asians positively associates with polymorphisms in GC and CYP2R1 genes. *PLoS ONE* **2014**, *9*, e113102. [CrossRef]

37. Engelman, C.D.; Fingerlin, T.E.; Langefeld, C.D.; Hicks, P.J.; Rich, S.S.; Wagenknecht, L.E.; Bowden, D.W.; Norris, J.M. Genetic and environmental determinants of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels in Hispanic and African Americans. *J. Clin. Endocrinol. Metab.* **2008**, *93*, 3381–3388. [CrossRef] [PubMed]

38. Engelman, C.D.; Meyers, K.J.; Iyengar, S.K.; Liu, Z.; Karki, C.K.; Igo, R.P., Jr.; Truitt, B.; Robinson, J.; Sarto, G.E.; Wallace, R.; et al. Vitamin D intake and season modify the effects of the GC and CYP2R1 genes on 25-hydroxyvitamin D concentrations. *J. Nutr.* **2013**, *143*, 17–26. [CrossRef]

39. Fohner, A.E.; Wang, Z.; Yracheta, J.; O'Brien, D.M.; Hopkins, S.E.; Black, J.; Philip, J.; Wiener, H.W.; Tiwari, H.K.; Stapleton, P.L.; et al. Genetics, Diet, and Season Are Associated with Serum 25-Hydroxycholecalciferol Concentration in a Yup'ik Study Population from Southwestern Alaska. *J. Nutr.* **2016**, *146*, 318–325. [CrossRef]

40. Fu, L.; Yun, F.; Oczak, M.; Wong, B.Y.; Vieth, R.; Cole, D.E. 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. *Clin. Biochem.* **2009**, *42*, 1174–1177. [CrossRef]

41. Gaffney-Stomberg, E.; Lutz, L.J.; Shcherbina, A.; Ricke, D.O.; Petrovick, M.; Cropper, T.L.; Cable, S.J.; McClung, J.P. Association Between Single Gene Polymorphisms and Bone Biomarkers and Response to Calcium and Vitamin D Supplementation in Young Adults Undergoing Military Training. *J. Bone Miner. Res.* **2017**, *32*, 498–507. [CrossRef]

42. Gilbert, R.; Bonilla, C.; Metcalfe, C.; Lewis, S.; Evans, D.M.; Fraser, W.D.; Kemp, J.P.; Donovan, J.L.; Hamdy, F.C.; Neal, D.E.; et al. Associations of vitamin D pathway genes with circulating 25-hydroxyvitamin-D, 1,25-dihydroxyvitamin-D, and prostate cancer: A nested case-control study. *Cancer Causes Control.* **2015**, *26*, 205–218. [CrossRef] [PubMed]

43. Gozdzik, A.; Zhu, J.; Wong, B.Y.; Fu, L.; Cole, D.E.; Parra, E.J. Association of vitamin D binding protein (VDBP) polymorphisms and serum 25(OH)D concentrations in a sample of young Canadian adults of different ancestry. *J. Steroid Biochem. Mol. Biol.* **2011**, *127*, 405–412. [CrossRef]

44. Hansen, J.G.; Gao, W.; Dupuis, J.; O'Connor, G.T.; Tang, W.; Kowgier, M.; Sood, A.; Gharib, S.A.; Palmer, L.J.; Fornage, M.; et al. Association of 25-Hydroxyvitamin D status and genetic variation in the vitamin D metabolic pathway with FEV1 in the Framingham Heart Study. *Respir. Res.* **2015**, *16*, 81. [CrossRef] [PubMed]

45. Janssens, W.; Bouillon, R.; Claes, B.; Carremans, C.; Lehouck, A.; Buysschaert, I.; Coolen, J.; Mathieu, C.; Decramer, M.; Lambrechts, D. Vitamin D deficiency is highly prevalent in COPD and correlates with variants in the vitamin D-binding gene. *Thorax* **2010**, *65*, 215–220. [CrossRef]

46. Jolliffe, D.A.; Hanifa, Y.; Witt, K.D.; Venton, T.R.; Rowe, M.; Timms, P.M.; Hypponen, E.; Walton, R.T.; Griffiths, C.J.; Martineau, A.R. Environmental and genetic determinants of vitamin D status among older adults in London, UK. *J. Steroid Biochem. Mol. Biol.* **2016**, *164*, 30–35. [CrossRef]

47. Junaid, K.; Rehman, A.; Jolliffe, D.A.; Wood, K.; Martineau, A.R. High prevalence of vitamin D deficiency among women of child-bearing age in Lahore Pakistan, associating with lack of sun exposure and illiteracy. *BMC Womens Health* **2015**, *15*, 83. [CrossRef]

48. Lafi, Z.M.; Irshaid, Y.M.; El-Khateeb, M.; Ajlouni, K.M.; Hyassat, D. Association of rs7041 and rs4588 Polymorphisms of the Vitamin D Binding Protein and the rs10741657 Polymorphism of CYP2R1 with Vitamin D Status Among Jordanian Patients. *Genet. Test. Mol. Biomark.* **2015**, *19*, 629–636. [CrossRef]

49. Larcombe, L.; Mookherjee, N.; Slater, J.; Slivinski, C.; Singer, M.; Whaley, C.; Denechezhe, L.; Matyas, S.; Turner-Brannen, E.; Nickerson, P.; et al. Vitamin D in a northern Canadian first nation population: Dietary intake, serum concentrations and functional gene polymorphisms. *PLoS ONE* **2012**, *7*, e49872. [CrossRef]

50. Li, L.H.; Yin, X.Y.; Wu, X.H.; Zhang, L.; Pan, S.Y.; Zheng, Z.J.; Wang, J.G. Serum 25(OH)D and vitamin D status in relation to VDR, GC and CYP2R1 variants in Chinese. *Endocr. J.* **2014**, *61*, 133–141. [CrossRef]

51. Lu, L.; Sheng, H.; Li, H.; Gan, W.; Liu, C.; Zhu, J.; Loos, R.J.; Lin, X. Associations between common variants in GC and DHCR7/NADSYN1 and vitamin D concentration in Chinese Hans. *Hum. Genet.* **2012**, *131*, 505–512. [CrossRef]

52. McKay, G.J.; Young, I.S.; McGinty, A.; Bentham, G.C.; Chakravarthy, U.; Rahu, M.; Seland, J.; Soubrane, G.; Tomazzoli, L.; Topouzis, F.; et al. Associations between Serum Vitamin D and Genetic Variants in Vitamin D Pathways and Age-Related Macular Degeneration in the European Eye Study. *Ophthalmology* **2017**, *124*, 90–96. [CrossRef]

53. Medlej-Hashim, M.; Jounblat, R.; Hamade, A.; Ibrahim, J.N.; Rizk, F.; Azzi, G.; Abdallah, M.; Nakib, L.; Lahoud, M.; Nabout, R. Hypovitaminosis D in a Young Lebanese Population: Effect of GC Gene Polymorphisms on Vitamin D and Vitamin D Binding Protein Levels. *Ann. Hum. Genet.* **2015**, *79*, 394–401. [CrossRef]

54. Nimitphong, H.; Saetung, S.; Chanprasertyotin, S.; Chailurkit, L.O.; Ongphiphadhanakul, B. Changes in circulating 25-hydroxyvitamin D according to vitamin D binding protein genotypes after vitamin D(3) or D(2)supplementation. *Nutr. J.* **2013**, *12*, 39. [CrossRef]

55. Nissen, J.; Rasmussen, L.B.; Ravn-Haren, G.; Andersen, E.W.; Hansen, B.; Andersen, R.; Mejborn, H.; Madsen, K.H.; Vogel, U. Common variants in CYP2R1 and GC genes predict vitamin D concentrations in healthy Danish children and adults. *PLoS ONE* **2014**, *9*, e89907. [CrossRef]

56. Nissen, J.; Vogel, U.; Ravn-Haren, G.; Andersen, E.W.; Madsen, K.H.; Nexo, B.A.; Andersen, R.; Mejborn, H.; Bjerrum, P.J.; Rasmussen, L.B.; et al. Common variants in CYP2R1 and GC genes are both determinants of serum 25-hydroxyvitamin D concentrations after UVB irradiation and after consumption of vitamin D(3)-fortified bread and milk during winter in Denmark. *Am. J. Clin. Nutr.* **2015**, *101*, 218–227. [CrossRef]

57. Ordonez-Mena, J.M.; Maalmi, H.; Schottker, B.; Saum, K.U.; Holleczek, B.; Wang, T.J.; Burwinkel, B.; Brenner, H. Genetic Variants in the Vitamin D Pathway, 25(OH)D Levels, and Mortality in a Large Population-Based Cohort Study. *J. Clin. Endocrinol. Metab.* **2017**, *102*, 470–477. [CrossRef]

58. Perna, L.; Felix, J.F.; Breitling, L.P.; Haug, U.; Raum, E.; Burwinkel, B.; Schottker, B.; Brenner, H. Genetic variations in the vitamin D binding protein and season-specific levels of vitamin D among older adults. *Epidemiology* **2013**, *24*, 104–109. [CrossRef]

59. Powe, C.E.; Evans, M.K.; Wenger, J.; Zonderman, A.B.; Berg, A.H.; Nalls, M.; Tamez, H.; Zhang, D.; Bhan, I.; Karumanchi, S.A.; et al. Vitamin D-binding protein and vitamin D status of black Americans and white Americans. *N. Engl. J. Med.* **2013**, *369*, 1991–2000. [CrossRef]

60. Rees, J.R.; Mott, L.A.; Barry, E.L.; Baron, J.A.; Bostick, R.M.; Figueiredo, J.C.; Bresalier, R.S.; Robertson, D.J.; Peacock, J.L. Lifestyle and Other Factors Explain One-Half of the Variability in the Serum 25-Hydroxyvitamin D Response to Cholecalciferol Supplementation in Healthy Adults. *J. Nutr.* **2016**, *146*, 2312–2324. [CrossRef]

61. Reimers, L.L.; Crew, K.D.; Bradshaw, P.T.; Santella, R.M.; Steck, S.E.; Sirosh, I.; Terry, M.B.; Hershman, D.L.; Shane, E.; Cremers, S.; et al. Vitamin D-related gene polymorphisms, plasma 25-hydroxyvitamin D, and breast cancer risk. *Cancer Causes Control.* **2015**, *26*, 187–203. [CrossRef]

62. Robien, K.; Butler, L.M.; Wang, R.; Beckman, K.B.; Walek, D.; Koh, W.P.; Yuan, J.M. Genetic and environmental predictors of serum 25-hydroxyvitamin D concentrations among middle-aged and elderly Chinese in Singapore. *Br. J. Nutr.* **2013**, *109*, 493–502. [CrossRef]

63. Sadat-Ali, M.; Al-Turki, H.A.; Azam, M.Q.; Al-Elq, A.H. Genetic influence on circulating vitamin D among Saudi Arabians. *Saudi Med. J.* **2016**, *37*, 996–1001. [CrossRef]

64. Sedky, N.K.; Hassanein, S.I.; Gad, M.Z. Independent assortment of GC gene polymorphism (rs2282679) and 25-hydroxyvitamin D levels in coronary artery disease. *Can. J. Physiol. Pharm.* **2018**, *96*, 345–351. [CrossRef]

65. Signorello, L.B.; Shi, J.; Cai, Q.; Zheng, W.; Williams, S.M.; Long, J.; Cohen, S.S.; Li, G.; Hollis, B.W.; Smith, J.R.; et al. Common variation in vitamin D pathway genes predicts circulating 25-hydroxyvitamin D Levels among African Americans. *PLoS ONE* **2011**, *6*, e28623. [CrossRef]

66. 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. *Am. J. Clin. Nutr.* **2009**, *89*, 634–640. [CrossRef]

67. Slater, N.A.; Rager, M.L.; Havrda, D.E.; Harralson, A.F. Genetic Variation in CYP2R1 and GC Genes Associated With Vitamin D Deficiency Status. *J. Pharm. Pract.* **2017**, *30*, 31–36. [CrossRef]

68. Szili, B.; Szabo, B.; Horvath, P.; Bakos, B.; Kirschner, G.; Kosa, J.P.; Toldy, E.; Putz, Z.; Lakatos, P.; Tabak, A.; et al. Impact of genetic influence on serum total- and free 25-hydroxyvitamin-D in humans. *J. Steroid Biochem. Mol. Biol.* **2018**, *183*, 62–67. [CrossRef]

69. Theodoratou, E.; Palmer, T.; Zgaga, L.; Farrington, S.M.; McKeigue, P.; Din, F.V.; Tenesa, A.; Davey-Smith, G.; Dunlop, M.G.; Campbell, H. Instrumental variable estimation of the causal effect of plasma 25-hydroxy-vitamin D on colorectal cancer risk: A mendelian randomization analysis. *PLoS ONE* **2012**, *7*, e37662. [CrossRef]

70. Thongthai, P.; Chailurkit, L.O.; Chanprasertyothin, S.; Nimitphong, H.; Sritara, P.; Aekplakorn, W.; Ongphiphadhanakul, B. Vitamin D binding protein gene polymorphism as a risk factor for vitamin D deficiency in Thais. *Endocr. Pract.* **2015**, *21*, 221–225. [CrossRef]

71. Touvier, M.; Deschasaux, M.; Montourcy, M.; Sutton, A.; Charnaux, N.; Kesse-Guyot, E.; Assmann, K.E.; Fezeu, L.; Latino-Martel, P.; Druesne-Pecollo, N.; et al. Determinants of vitamin D status in Caucasian adults: Influence of sun exposure, dietary intake, sociodemographic, lifestyle, anthropometric, and genetic factors. *J. Investig. Dermatol.* **2015**, *135*, 378–388. [CrossRef]

72. Voipio, A.J.; Pahkala, K.A.; Viikari, J.S.; Mikkila, V.; Magnussen, C.G.; Hutri-Kahonen, N.; Kahonen, M.; Lehtimaki, T.; Mannisto, S.; Loo, B.M.; et al. Determinants of serum 25(OH)D concentration in young and middle-aged adults. The Cardiovascular Risk in Young Finns Study. *Ann. Med.* **2015**, *47*, 253–262. [CrossRef]

73. Wang, W.; Ingles, S.A.; Torres-Mejia, G.; Stern, M.C.; Stanczyk, F.Z.; Schwartz, G.G.; Nelson, D.O.; Fejerman, L.; Wolff, R.K.; Slattery, M.L.; et al. Genetic variants and non-genetic factors predict circulating vitamin D levels in Hispanic and non-Hispanic White women: The Breast Cancer Health Disparities Study. *Int. J. Mol. Epidemiol. Genet.* **2014**, *5*, 31–46.

74. Waterhouse, M.; Tran, B.; Armstrong, B.K.; Baxter, C.; Ebeling, P.R.; English, D.R.; Gebski, V.; Hill, C.; Kimlin, M.G.; Lucas, R.M.; et al. Environmental, personal, and genetic determinants of response to vitamin D supplementation in older adults. *J. Clin. Endocrinol. Metab.* **2014**, *99*, E1332–E1340. [CrossRef] [PubMed]

75. Wu, X.; Cheng, J.; Yang, K. Vitamin D-Related Gene Polymorphisms, Plasma 25-Hydroxy-Vitamin D, Cigarette Smoke and Non-Small Cell Lung Cancer (NSCLC) Risk. *Int. J. Mol. Sci.* **2016**, *17*, 1597. [CrossRef]

76. Xu, W.; Sun, J.; Wang, W.; Wang, X.; Jiang, Y.; Huang, W.; Zheng, X.; Wang, Q.; Ning, Z.; Pei, Y.; 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*, 345–352. [CrossRef]

77. Xu, X.; Mao, J.; Zhang, M.; Liu, H.; Li, H.; Lei, H.; Han, L.; Gao, M. Vitamin D Deficiency in Uygurs and Kazaks Is Associated with Polymorphisms in CYP2R1 and DHCR7/NADSYN1 Genes. *Med. Sci. Monit.* **2015**, *21*, 1960–1968. [CrossRef]

78. Yao, P.; Sun, L.; Lu, L.; Ding, H.; Chen, X.; Tang, L.; Xu, X.; Liu, G.; Hu, Y.; Ma, Y.; et al. Effects of Genetic and Nongenetic Factors on Total and Bioavailable 25(OH)D Responses to Vitamin D Supplementation. *J. Clin. Endocrinol. Metab.* **2017**, *102*, 100–110. [CrossRef]

79. Yao, S.; Hong, C.C.; Bandera, E.V.; Zhu, Q.; Liu, S.; Cheng, T.D.; Zirpoli, G.; Haddad, S.A.; Lunetta, K.L.; Ruiz-Narvaez, E.A.; et al. Demographic, lifestyle, and genetic determinants of circulating concentrations of 25-hydroxyvitamin D and vitamin D-binding protein in African American and European American women. *Am. J. Clin. Nutr.* **2017**, *105*, 1362–1371. [CrossRef] [PubMed]

80. Zhang, M.; Zhao, L.J.; Zhou, Y.; Badr, R.; Watson, P.; Ye, A.; Zhou, B.; Zhang, J.; Deng, H.W.; Recker, R.R.; et al. SNP rs11185644 of RXRA gene is identified for dose-response variability to vitamin D3 supplementation: A randomized clinical trial. *Sci. Rep.* **2017**, *7*, 40593. [CrossRef]

81. 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*, 1784–1792. [CrossRef]

82. Arabi, A.; Khoueiry-Zgheib, N.; Awada, Z.; Mahfouz, R.; Al-Shaar, L.; Hoteit, M.; Rahme, M.; Baddoura, R.; Halabi, G.; Singh, R.; et al. CYP2R1 polymorphisms are important modulators of circulating 25-hydroxyvitamin D levels in elderly females with vitamin insufficiency, but not of the response to vitamin D supplementation. *Osteoporos. Int.* **2017**, *28*, 279–290. [CrossRef] [PubMed]

83. Wang, Y.; Yu, F.; Yu, S.; Zhang, D.; Wang, J.; Han, H.; Sun, H.; Xue, Y.; Ba, Y.; Wang, C.; et al. Triangular relationship between CYP2R1 gene polymorphism, serum 25(OH)D3 levels and T2DM in a Chinese rural population. *Gene* **2018**, *678*, 172–176. [CrossRef] [PubMed]

84. Abbas, S.; Nieters, A.; Linseisen, J.; Slanger, T.; Kropp, S.; Mutschelknauss, E.J.; Flesch-Janys, D.; Chang-Claude, J. Vitamin D receptor gene polymorphisms and haplotypes and postmenopausal breast cancer risk. *Breast Cancer Res.* **2008**, *10*, R31. [CrossRef]

85. Arabi, A.; Mahfoud, Z.; Zahed, L.; El-Onsi, L.; El-Hajj Fuleihan, G. Effect of age, gender and calciotropic hormones on the relationship between vitamin D receptor gene polymorphisms and bone mineral density. *Eur. J. Clin. Nutr.* **2010**, *64*, 383–391. [CrossRef]

86. Carvalho, A.Y.; Bishop, K.S.; Han, D.Y.; Ellett, S.; Jesuthasan, A.; Lam, W.J.; Ferguson, L.R. The role of Vitamin D level and related single nucleotide polymorphisms in Crohn's disease. *Nutrients* **2013**, *5*, 3898–3909. [CrossRef] [PubMed]

87. Ghorbanihaghjo, A.; Argani, H.; Samadi, N.; Valizadeh, S.; Halajzadeh, J.; Yousefi, B.; Rashtchizadeh, N. Relationship between vitamin D receptor gene FokI and ApaI polymorphisms and serum levels of fetuin-A, vitamin D, and parathyroid hormone in patients on hemodialysis. *Iran. J. Kidney Dis.* **2014**, *8*, 394–400.

88. Issa, C.T.; Silva, A.S.; Toscano, L.T.; Medeiros, M.S.; Persuhn, D.C.; da Silva Diniz, A.; de Carvalho Costa, M.J.; Rodrigues Goncalves Mda, C. Relationship between cardiometabolic profile, vitamin D status and BsmI polymorphism of the VDR gene in non-institutionalized elderly subjects: Cardiometabolic profile, vitamin D status and BsmI polymorphism of the VDR gene in non-institutionalized elderly subjects. *Exp. Gerontol.* **2016**, *81*, 56–64. [CrossRef]

89. Kahraman, H.; Duman, B.S.; Alagol, F.; Tanakol, R.; Yilmazer, S. Lack of association between vitamin D receptor gene polymorphism (BsmI) and osteomalacia. *J. Bone Miner. Metab.* **2004**, *22*, 39–43. [CrossRef]

90. Laaksonen, M.; Karkkainen, M.; Outila, T.; Vanninen, T.; Ray, C.; Lamberg-Allardt, C. Vitamin D receptor gene BsmI-polymorphism in Finnish premenopausal and postmenopausal women: Its association with bone mineral density, markers of bone turnover, and intestinal calcium absorption, with adjustment for lifestyle factors. *J. Bone Miner. Metab.* **2002**, *20*, 383–390. [CrossRef]

91. Macdonald, H.M.; McGuigan, F.E.; Stewart, A.; Black, A.J.; Fraser, W.D.; Ralston, S.; Reid, D.M. Large-scale population-based study shows no evidence of association between common polymorphism of the VDR gene and BMD in British women. *J. Bone Miner. Res.* **2006**, *21*, 151–162. [CrossRef]

92. Mayer, O.; Seidlerova, J.; Cerna, V.; Kucerova, A.; Karnosova, P.; Hronova, M.; Wohlfahrt, P.; Fuchsova, R.; Filipovsky, J.; Cifkova, R.; et al. Serum Vitamin D Status, Vitamin D Receptor Polymorphism, and Glucose Homeostasis in Healthy Subjects. *Horm. Metab. Res.* **2018**, *50*, 56–64. [CrossRef]

93. Santos, B.R.; Lecke, S.B.; Spritzer, P.M. Apa-I polymorphism in VDR gene is related to metabolic syndrome in polycystic ovary syndrome: A cross-sectional study. *Reprod. Biol. Endocrinol.* **2018**, *16*, 38. [CrossRef] [PubMed]

94. Schuch, N.J.; Garcia, V.C.; Vivolo, S.R.; Martini, L.A. Relationship between Vitamin D Receptor gene polymorphisms and the components of metabolic syndrome. *Nutr. J.* **2013**, *12*, 96. [CrossRef] [PubMed]

95. Tanabe, R.; Kawamura, Y.; Tsugawa, N.; Haraikawa, M.; Sogabe, N.; Okano, T.; Hosoi, T.; Goseki-Sone, M. Effects of Fok-I polymorphism in vitamin D receptor gene on serum 25-hydroxyvitamin D, bone-specific alkaline phosphatase and calcaneal quantitative ultrasound parameters in young adults. *Asia Pac. J. Clin. Nutr.* **2015**, *24*, 329–335. [CrossRef] [PubMed]

96. Vupputuri, M.R.; Goswami, R.; Gupta, N.; Ray, D.; Tandon, N.; Kumar, N. Prevalence and functional significance of 25-hydroxyvitamin D deficiency and vitamin D receptor gene polymorphisms in Asian Indians. *Am. J. Clin. Nutr.* **2006**, *83*, 1411–1419. [CrossRef]

97. Yao, S.; Zirpoli, G.; Bovbjerg, D.H.; Jandorf, L.; Hong, C.C.; Zhao, H.; Sucheston, L.E.; Tang, L.; Roberts, M.; Ciupak, G.; et al. Variants in the vitamin D pathway, serum levels of vitamin D, and estrogen receptor negative breast cancer among African-American women: A case-control study. *Breast Cancer Res.* **2012**, *14*, R58. [CrossRef]

98. Zhou, J.C.; Zhu, Y.M.; Chen, Z.; Mo, J.L.; Xie, F.Z.; Wen, Y.H.; Guo, P.; Peng, J.; Xu, J.; Wang, J.; et al. Oral vitamin D supplementation has a lower bioavailability and reduces hypersecretion of parathyroid hormone and insulin resistance in obese Chinese males. *Public Health Nutr.* **2015**, *18*, 2211–2219. [CrossRef]

99. Abu El Maaty, M.A.; Hassanein, S.I.; Sleem, H.M.; Gad, M.Z. Effect of polymorphisms in the NADSYN1/DHCR7 locus (rs12785878 and rs1790349) on plasma 25-hydroxyvitamin D levels and coronary artery disease incidence. *J. Nutr. Nutr.* **2013**, *6*, 327–335. [CrossRef]

100. Selvaraj, P.; Prabhu Anand, S.; Harishankar, M.; Alagarasu, K. Plasma 1,25 dihydroxy vitamin D3 level and expression of vitamin d receptor and cathelicidin in pulmonary tuberculosis. *J. Clin. Immunol.* **2009**, *29*, 470–478. [CrossRef]

101. Majid, H.; Khan, A.H.; Moatter, T. R990G polymorphism of calcium sensing receptor gene is associated with high parathyroid hormone levels in subjects with vitamin D deficiency: A cross-sectional study. *Biomed. Res. Int.* **2015**, *2015*, 407159. [CrossRef]

102. Al-Daghri, N.M.; Al-Attas, O.S.; Krishnaswamy, S.; Yakout, S.M.; Mohammed, A.K.; Alenad, A.M.; Chrousos, G.P.; Alokail, M.S. Association between promoter region genetic variants of PTH SNPs and serum 25(OH)-vitamin D level. *Int. J. Clin. Exp. Pathol.* **2015**, *8*, 8463–8471.

103. Hopkinson, N.S.; Li, K.W.; Kehoe, A.; Humphries, S.E.; Roughton, M.; Moxham, J.; Montgomery, H.; Polkey, M.I. Vitamin D receptor genotypes influence quadriceps strength in chronic obstructive pulmonary disease. *Am. J. Clin. Nutr.* **2008**, *87*, 385–390. [CrossRef] [PubMed]

104. Wang, P.; Ma, L.H.; Wang, H.Y.; Zhang, W.; Tian, Q.; Cao, D.N.; Zheng, G.X.; Sun, Y.L. Association between polymorphisms of vitamin D receptor gene ApaI, BsmI and TaqI and muscular strength in young Chinese women. *Int. J. Sports Med.* **2006**, *27*, 182–186. [CrossRef] [PubMed]

105. Iki, M.; Saito, Y.; Dohi, Y.; Kajita, E.; Nishino, H.; Yonemasu, K.; Kusaka, Y. Greater trunk muscle torque reduces postmenopausal bone loss at the spine independently of age, body size, and vitamin D receptor genotype in Japanese women. *Calcif. Tissue Int.* **2002**, *71*, 300–307. [CrossRef]

106. Gussago, C.; Arosio, B.; Guerini, F.R.; Ferri, E.; Costa, A.S.; Casati, M.; Bollini, E.M.; Ronchetti, F.; Colombo, E.; Bernardelli, G.; et al. Impact of vitamin D receptor polymorphisms in centenarians. *Endocrine* **2016**, *53*, 558–564. [CrossRef] [PubMed]

107. Onder, G.; Capoluongo, E.; Danese, P.; Settanni, S.; Russo, A.; Concolino, P.; Bernabei, R.; Landi, F. Vitamin D receptor polymorphisms and falls among older adults living in the community: Results from the ilSIRENTE study. *J. Bone Miner. Res.* **2008**, *23*, 1031–1036. [CrossRef]

108. Walsh, S.; Ludlow, A.T.; Metter, E.J.; Ferrucci, L.; Roth, S.M. Replication study of the vitamin D receptor (VDR) genotype association with skeletal muscle traits and sarcopenia. *Aging Clin. Exp. Res.* **2016**, *28*, 435–442. [CrossRef]

109. Bahat, G.; Saka, B.; Erten, N.; Ozbek, U.; Coskunpinar, E.; Yildiz, S.; Sahinkaya, T.; Karan, M.A. BsmI polymorphism in the vitamin D receptor gene is associated with leg extensor muscle strength in elderly men. *Aging Clin. Exp. Res.* **2010**, *22*, 198–205. [CrossRef]

110. Barr, R.; Macdonald, H.; Stewart, A.; McGuigan, F.; Rogers, A.; Eastell, R.; Felsenberg, D.; Gluer, C.; Roux, C.; Reid, D.M. Association between vitamin D receptor gene polymorphisms, falls, balance and muscle power: Results from two independent studies (APOSS and OPUS). *Osteoporos. Int.* **2010**, *21*, 457–466. [CrossRef]

111. Windelinckx, A.; De Mars, G.; Beunen, G.; Aerssens, J.; Delecluse, C.; Lefevre, J.; Thomis, M.A. Polymorphisms in the vitamin D receptor gene are associated with muscle strength in men and women. *Osteoporos. Int.* **2007**, *18*, 1235–1242. [CrossRef]

112. Grundberg, E.; Brandstrom, H.; Ribom, E.L.; Ljunggren, O.; Mallmin, H.; Kindmark, A. Genetic variation in the human vitamin D receptor is associated with muscle strength, fat mass and body weight in Swedish women. *Eur. J. Endocrinol.* **2004**, *150*, 323–328. [CrossRef] [PubMed]

113. Roth, S.M.; Zmuda, J.M.; Cauley, J.A.; Shea, P.R.; Ferrell, R.E. Vitamin D receptor genotype is associated with fat-free mass and sarcopenia in elderly men. *J. Gerontol. A Biol. Sci. Med. Sci.* **2004**, *59*, 10–15. [CrossRef] [PubMed]

114. Geusens, P.; Vandevyver, C.; Vanhoof, J.; Cassiman, J.J.; Boonen, S.; Raus, J. Quadriceps and grip strength are related to vitamin D receptor genotype in elderly nonobese women. *J. Bone Miner. Res.* **1997**, *12*, 2082–2088. [CrossRef]

115. Cheng, J.B.; Levine, M.A.; Bell, N.H.; Mangelsdorf, D.J.; Russell, D.W. Genetic evidence that the human CYP2R1 enzyme is a key vitamin D 25-hydroxylase. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 7711–7715. [CrossRef]

116. Duan, L.; Xue, Z.; Ji, H.; Zhang, D.; Wang, Y. Effects of CYP2R1 gene variants on vitamin D levels and status: A systematic review and meta-analysis. *Gene* **2018**, *678*, 361–369. [CrossRef]

117. 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 Metab. Res. Rev.* **2007**, *23*, 631–636. [CrossRef]

118. Bikle, D.D.; Schwartz, J. Vitamin D Binding Protein, Total and Free Vitamin D Levels in Different Physiological and Pathophysio-logical Conditions. *Front. Endocrinol.* **2019**, *10*, 317. [CrossRef]

119. Wang, T.J.; Zhang, F.; Richards, J.B.; Kestenbaum, B.; van Meurs, J.B.; Berry, D.; Kiel, D.P.; Streeten, E.A.; Ohlsson, C.; Koller, D.L.; et al. Common genetic determinants of vitamin D insufficiency: A genome-wide association study. *Lancet* **2010**, *376*, 180–188. [CrossRef]

120. Abboud, M.; Puglisi, D.A.; Davies, B.N.; Rybchyn, M.; Whitehead, N.P.; Brock, K.E.; Cole, L.; Gordon-Thomson, C.; Fraser, D.R.; Mason, R.S. Evidence for a specific uptake and retention mechanism for 25-hydroxyvitamin D (25OHD) in skeletal muscle cells. *Endocrinology* **2013**, *154*, 3022–3030. [CrossRef]

121. Fedirko, V.; Mandle, H.B.; Zhu, W.; Hughes, D.J.; Siddiq, A.; Ferrari, P.; Romieu, I.; Riboli, E.; Bueno-de-Mesquita, B.; van Duijnhoven, F.J.B.; et al. Vitamin D-Related Genes, Blood Vitamin D Levels and Colorectal Cancer Risk in Western European Populations. *Nutrients* **2019**, *11*, 1954. [CrossRef]

122. Jorde, R.; Wilsgaard, T.; Grimnes, G. Polymorphisms in the vitamin D system and mortality—The Tromso study. *J. Steroid Biochem. Mol. Biol.* **2019**, *195*, 105481. [CrossRef]

123. Malik, S.; Fu, L.; Juras, D.J.; Karmali, M.; Wong, B.Y.; Gozdzik, A.; Cole, D.E. Common variants of the vitamin D binding protein gene and adverse health outcomes. *Crit. Rev. Clin. Lab. Sci.* **2013**, *50*, 1–22. [CrossRef]

124. Kato, S.; Takeyama, K.; Kitanaka, S.; Murayama, A.; Sekine, K.; Yoshizawa, T. In vivo function of VDR in gene expression-VDR knock-out mice. *J. Steroid Biochem. Mol. Biol.* **1999**, *69*, 247–251. [CrossRef]

125. Girgis, C.M.; Clifton-Bligh, R.J.; Hamrick, M.W.; Holick, M.F.; Gunton, J.E. The roles of vitamin D in skeletal muscle: Form, function, and metabolism. *Endocr. Rev.* **2013**, *34*, 33–83. [CrossRef]

126. Bouillon, R.; Carmeliet, G.; Verlinden, L.; van Etten, E.; Verstuyf, A.; Luderer, H.F.; Lieben, L.; Mathieu, C.; Demay, M. Vitamin D and human health: Lessons from vitamin D receptor null mice. *Endocr. Rev.* **2008**, *29*, 726–776. [CrossRef]

127. Holick, M.F. Vitamin D deficiency. *N. Engl. J. Med.* **2007**, *357*, 266–281. [CrossRef] [PubMed]

128. Laczmanski, L.; Jakubik, M.; Bednarek-Tupikowska, G.; Rymaszewska, J.; Sloka, N.; Lwow, F. Vitamin D receptor gene polymor-phisms in Alzheimer's disease patients. *Exp. Gerontol.* **2015**, *69*, 142–147. [CrossRef]

129. Uitterlinden, A.G.; Fang, Y.; Van Meurs, J.B.; Pols, H.A.; Van Leeuwen, J.P. Genetics and biology of vitamin D receptor polymorphisms. *Gene* **2004**, *338*, 143–156. [CrossRef]

130. Vuolo, L.; Di Somma, C.; Faggiano, A.; Colao, A. Vitamin D and cancer. *Front. Endocrinol.* **2012**, *3*, 58. [CrossRef] [PubMed]

131. Kelishadi, R.; Heidari-Beni, M.; Akbarian, S.A.; Hasan Tajadini, M.; Haghjooy Javanmard, S. Genetic Variation in Cytochrome P450 2R1 and Vitamin D Binding Protein Genes are associated with Vitamin D Deficiency in Adolescents. *Int. J. Vitam. Nutr. Res.* **2020**, *90*, 339–345. [CrossRef]

132. Yuan, C.; Renfro, L.; Ambadwar, P.B.; Ou, F.S.; McLeod, H.L.; Innocenti, F.; Meyerhardt, J.A.; Wolpin, B.M.; Goldberg, R.M.; Grothey, A.; et al. Influence of genetic variation in the vitamin D pathway on plasma 25-hydroxyvitamin D3 levels and survival among patients with metastatic colorectal cancer. *Cancer Causes Control.* **2019**, *30*, 757–765. [CrossRef]

133. Carter, G.D. Accuracy of 25-hydroxyvitamin D assays: Confronting the issues. *Curr. Drug Targets* **2011**, *12*, 19–28. [CrossRef] [PubMed]

134. Giustina, A.; Bouillon, R.; Binkley, N.; Sempos, C.; Adler, R.A.; Bollerslev, J.; Dawson-Hughes, B.; Ebeling, P.R.; Feldman, D.; Heijboer, A.; et al. Controversies in Vitamin D: A Statement From the Third International Conference. *JBMR Plus* **2020**, *4*, e10417. [CrossRef]

135. Beaudart, C.; Buckinx, F.; Rabenda, V.; Gillain, S.; Cavalier, E.; Slomian, J.; Petermans, J.; Reginster, J.Y.; Bruyere, O. The effects of vitamin D on skeletal muscle strength, muscle mass, and muscle power: A systematic review and meta-analysis of randomized controlled trials. *J. Clin. Endocrinol. Metab.* **2014**, *99*, 4336–4345. [CrossRef]

136. Broe, K.E.; Chen, T.C.; Weinberg, J.; Bischoff-Ferrari, H.A.; Holick, M.F.; Kiel, D.P. A higher dose of vitamin d reduces the risk of falls in nursing home residents: A randomized, multiple-dose study. *J. Am. Geriatr. Soc.* **2007**, *55*, 234–239. [CrossRef]

137. Endo, I.; Inoue, D.; Mitsui, T.; Umaki, Y.; Akaike, M.; Yoshizawa, T.; Kato, S.; Matsumoto, T. Deletion of vitamin D receptor gene in mice results in abnormal skeletal muscle development with deregulated expression of myoregulatory transcription factors. *Endocrinology* **2003**, *144*, 5138–5144. [CrossRef]

138. McCarthy, E.K.; Kiely, M. Vitamin D and muscle strength throughout the life course: A review of epidemiological and intervention studies. *J. Hum. Nutr. Diet.* **2015**, *28*, 636–645. [CrossRef]

139. Bjork, A.; Ribom, E.; Johansson, G.; Scragg, R.; Mellstrom, D.; Grundberg, E.; Ohlsson, C.; Karlsson, M.; Ljunggren, O.; Kindmark, A. Variations in the vitamin D receptor gene are not associated with measures of muscle strength, physical performance, or falls in elderly men. Data from MrOS Sweden. *J. Steroid Biochem. Mol. Biol.* **2019**, *187*, 160–165. [CrossRef]

140. Wang, Y.; Han, H.; Wang, J.; Shen, F.; Yu, F.; Wang, L.; Yu, S.C.; Zhang, D.D.; Sun, H.L.; Xue, Y.; et al. Polymorphisms in CYP2R1 Gene Associated with Serum Vitamin D Levels and Status in a Chinese Rural Population. *Biomed. Environ. Sci.* **2019**, *32*, 550–553. [CrossRef]

141. Tuncel, G.; Temel, S.G.; Ergoren, M.C. Strong association between VDR FokI (rs2228570) gene variant and serum vitamin D levels in Turkish Cypriots. *Mol. Biol. Rep.* **2019**, *46*, 3349–3355. [CrossRef]

142. Ragia, G.; Archontogeorgis, K.; Simmaco, M.; Gentile, G.; Borro, M.; Zissimopoulos, A.; Froudarakis, M.; Manolopoulos, V.G.; Steiropoulos, P. Genetics of Obstructive Sleep Apnea: Vitamin D Receptor Gene Variation Affects Both Vitamin D Serum Concentration and Disease Susceptibility. *OMICS* **2019**, *23*, 45–53. [CrossRef]

143. Santos, B.R.; Costa, N.C.; Silva, T.R.; Oppermann, K.; Magalhaes, J.A.; Casanova, G.; Spritzer, P.M. Prevalence of vitamin D deficiency in women from southern Brazil and association with vitamin D-binding protein levels and GC-DBP gene polymorphisms. *PLoS ONE* **2019**, *14*, e0226215. [CrossRef]

144. Khan, A.H.; Jafri, L.; Siddiqui, A.; Naureen, G.; Morris, H.; Moatter, T. Polymorphisms in the GC Gene for Vitamin D Binding Protein and Their Association with Vitamin D and Bone Mass in Young Adults. *J. Coll. Physicians Surg. Pak.* **2019**, *29*, 715–719. [CrossRef]

145. Pooyan, S.; Rahimi, M.H.; Mollahosseini, M.; Khorrami-Nezhad, L.; Maghbooli, Z.; Mirzaei, K. The Association between Vitamin D Deficiency and variants of Vitamin D Binding protein gene among Healthy Iranian Adults. *Int. J. Vitam. Nutr. Res.* **2020**, *90*, 249–256. [CrossRef]

146. Yu, S.; Li, X.; Wang, Y.; Mao, Z.; Xie, Y.; Zhang, L.; Wang, C.; Li, W. Family-based Association between Allele T of rs4646536 in CYP27B1 and vitamin D deficiency. *J. Clin. Lab. Anal.* **2019**, *33*, e22898. [CrossRef]

147. Ye, X.; Jia, J.; Zhang, N.; Ding, H.; Zhan, Y. Associations of genetic polymorphisms of the vitamin D pathway with blood pressure in a Han Chinese population. *Clin. Exp. Hypertens.* **2019**, *41*, 460–465. [CrossRef]

148. Bjork, A.; Mellstrom, D.; Ohlsson, C.; Karlsson, M.; Mallmin, H.; Johansson, G.; Ljunggren, O.; Kindmark, A. Haplotypes in the CYP2R1 gene are associated with levels of 25(OH)D and bone mineral density, but not with other markers of bone metabolism (MrOS Sweden). *PLoS ONE* **2018**, *13*, e0209268. [CrossRef] [PubMed]

149. Manousaki, D.; Mitchell, R.; Dudding, T.; Haworth, S.; Harroud, A.; Forgetta, V.; Shah, R.L.; Luan, J.; Langenberg, C.; Timpson, N.J.; et al. Genome-wide Association Study for Vitamin D Levels Reveals 69 Independent Loci. *Am. J. Hum. Genet.* **2020**, *106*, 327–337. [CrossRef]