Genetic Determinants of Vitamin D3 Status and *VDR*-Mediated Signaling (Literature Review)

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ABSTRACT

Background:
Vitamin D3 is a fat-soluble vitamin of particular importance for bone metabolism, and interindividual differences in vitamin D3 requirements have been conceptualized as partly genetically determined. Vitamin D3 deficiency has been described as a well-known, scientifically established factor in the development of breast cancer, osteoporosis, and other diseases. Upon entering the body, vitamin D3 is recognized by specific receptors on certain cells and can thereby trigger biological processes and regulate the activity of many genes relevant to health. Genetic association evidence has identified common variants in vitamin D pathway genes as determinants of circulating vitamin D status (Wang, 2010; Duan, 2018; Krasniqi, 2021), while *VDR* polymorphisms have been investigated in relation to osteoporosis risk and other phenotypes (Jia, 2013; Klahold, 2020).

Methods:
A narrative synthesis was undertaken, prioritizing GWAS meta-analyses with replication, systematic reviews/meta-analyses, and cohort studies. The synthesis focused on genetic variants in the vitamin D pathway loci highlighted in the report — *CYP2R1, CYP24A1, CYP27B1, VDBP, and DHCR7* — together with selected *VDR* polymorphisms, as evaluated in relation to circulating vitamin D measures and their context dependence with respect to season and dietary vitamin D intake, as well as selected clinical outcomes (Wang, 2010; Duan, 2018; Engelman, 2013; Petersen, 2017; Krasniqi, 2021).

Results:
Large-scale genetic association evidence has robustly implicated vitamin D pathway loci within *DHCR7, CYP2R1, CYP24A1, CYP27B1, VDBP* and *CDR* polymorphisms in determining interindividual differences in circulating vitamin D measures and vitamin D insufficiency (Wang, 2010). Within *CYP2R1*, meta-analytic synthesis supports rs10741657, rs1562902 and rs10500804 as reproducible determinants associated with lower vitamin D status and an increased risk of deficiency (Duan, 2018). Across broader pathway syntheses, associations with circulating vitamin D measures appear most consistently reported for *VDBP* (rs2282679) and *CYP2R1, VDR* polymorphisms (rs1544410, rs7975232 and rs2228570), *CYP24A1* (rs6013897), *CYP27B1* (rs10877012) and *DHCR7* (rs12785878)(Krasniqi, 2021). Moreover, genetic effects on circulating vitamin D measures are context-dependent, with both dietary vitamin D intake and seasonal factors

modifying the magnitude of associations — particularly for variants in *VDBP* and *CYP2R1* — and with seasonal dynamics documented in cohort settings (Engelman, 2013; Petersen, 2017; Lee, 2021).

Discussion:
Overall, the evidence supports genetically influenced variability in circulating vitamin D status and indicates that vitamin D3 acquisition through sunlight exposure and diet is modulated by contextual factors, consistent with the concept that vitamin D3 status and related interpretations are not uniform across individuals (Wang, 2010; Duan, 2018; Engelman, 2013; Petersen, 2017; Krasniqi, 2021). A receptor-centered interpretation has been proposed in which reduced *VDR*-mediated recognition could diminish vitamin D3 effects even when blood concentrations appear sufficient, and increased vitamin D3 intake has been suggested as a compensatory strategy in the presence of reduced receptor effectiveness. *VDR* associations have been meta-analyzed for osteoporosis risk (Jia, 2013) and investigated in supplementation contexts (Klahold, 2020), supporting continued study of genotype-dependent variability while underscoring the need for cautious translation of genotype categories into individualized claims (Krasniqi, 2021).

Subjects: Genetics, Nutrition **Keywords:** Genetics, Polymorphism, Nutrition, Vitamin D

INTRODUCTION

Vitamin D3 is a fat-soluble vitamin that is particularly important for bone metabolism, and variability in vitamin D3 requirements has been framed as partly dependent on genetic factors. A basis for this concept has been provided by genetic epidemiology demonstrating that inherited variation contributes to interindividual differences in circulating vitamin D measures and the probability of vitamin D insufficiency (Wang, 2010; Duan, 2018; Krasniqi, 2021). Beyond the skeletal domain, vitamin D3 deficiency has been discussed in relation to breast cancer, osteoporosis, and other diseases, and vitamin D pathway genetics has been investigated in these clinical contexts (Clendenen, 2015; Jia, 2013; Mondul, 2013). Accordingly, ensuring adequate vitamin D3 intake has been positioned as relevant in preventive strategies in osteoporosis and breast cancer, while interpretation has also been emphasized as not always straightforward and potentially more complex in practice (Engelman, 2013; Petersen, 2017; Krasniqi, 2021).

A mechanistic framework has been used in which vitamin D3, after entering the body, is recognized by specific receptors on certain cells, thereby triggering biological processes and regulating the activity of many genes relevant to health. Within this framework, *VDR* genes have been conceptualized as providing the blueprint for the vitamin D receptor and enabling receptor-mediated recognition of vitamin D3, and *VDR* polymorphisms have been examined in relation to bone-relevant outcomes, including osteoporosis risk (Jia, 2013; Krasniqi, 2021). A receptor “docking” model has further been used to conceptualize initiation of intracellular signaling and downstream activation of genes associated with vitamin D3 effects. In parallel, reduced receptor effectiveness has been proposed as a potential explanation for slower activation of vitamin D3-relevant processes and for discordance between circulating vitamin D measures and functional effects, with *VDR* variation being evaluated in supplementation and phenotype studies (Klahold, 2020; Krasniqi, 2021).

These mechanistic interpretations have frequently been operationalized using common genetic variants in key vitamin D pathway genes (*CYP2R1, CYP24A1, GC/VDBP, DHCR7, CYP27B1*) together with selected *VDR* polymorphisms. Consistent with this approach, large-scale GWAS and subsequent syntheses have identified core pathway loci as robust determinants of circulating vitamin D measures (Wang, 2010; Duan, 2018), and systematic review evidence has highlighted *VDBP* and *CYP2R1* as among the most consistently associated genes across studies (Krasniqi, 2021). Moreover, context dependence has been demonstrated in cohort designs, supporting the notion that genetic effects can be modified by dietary vitamin D intake and seasonality, which is compatible with the view that vitamin D3 acquisition through sunlight exposure and diet is relevant but not uniformly predictive of status across individuals (Engelman, 2013; Petersen, 2017; Lee, 2021).

Finally, practical considerations relevant to vitamin D3 supply have been articulated in terms of sunlight-driven skin production, dietary sources, supplementation, and nutrient context. In parallel with this framing, cohort evidence indicates that season and dietary intake can modify genetic associations with circulating vitamin D measures, supporting a context-dependent interpretation of vitamin D status (Engelman, 2013; Petersen, 2017; Lee, 2021). Genetic context for dietary calcium intake has also been linked to lactose tolerance through lactase (LCT) variation (Enattah; 2002).

Genetic Determinants of Circulating Vitamin D Status

Interindividual variability in circulating vitamin D measures has been repeatedly attributed to common genetic variation in core vitamin D pathway genes. In a GWAS meta-analysis with replication, variants near or within *VDBP, DHCR7, CYP2R1*, and *CYP24A1* were identified as robust determinants of vitamin D insufficiency and circulating vitamin D status (Wang, 2010). In addition to genome-wide discovery, meta-analytic synthesis has supported specific variants as reproducible predictors of lower vitamin D measures. Notably, *CYP2R1* rs10741657, rs1562902 and rs10500804 have been associated with lower vitamin D status and increased deficiency risk across diverse study populations in systematic review and meta-analysis (Duan, 2018). Consistent with this hierarchy of evidence, a systematic review spanning a broad set of pathway polymorphisms concluded that associations with vitamin D measures were most consistently observed for *VDBP* and *CYP2R1*, whereas replication for other loci — including *VDR* — was less consistent across studies and phenotypes (Krasniqi, 2021).

A multi-variant interpretation approach has frequently been used in applied settings, in which genotypes at selected variants are aligned with qualitative categories of vitamin D level (e.g., decreased vs normal) and, in some cases, threshold-based stratification of circulating concentrations. This approach is compatible with the multi-locus structure of the genetic literature, where multiple pathway loci contribute to the distribution of vitamin D measures (Wang, 2010; Krasniqi, 2021). Evidence from population-based association studies has supported the generalizability of pathway loci across diverse cohorts. Multi-gene analyses in healthy Chinese individuals identified associations between vitamin D pathway variants (including *VDBP, CYP2R1, DHCR7*) and circulating vitamin D measures (Zhang, 2013). Similarly, cohort analyses in Korean adults have evaluated vitamin D-related genetic variants together with season and dietary vitamin D intake, identifying both independent and interactive contributions to circulating vitamin D measures (Lee, 2021). Associations between *VDBP* and *CYP2R1* variants and vitamin D measures have also been reported in adolescent populations (Rahman, 2023) and in additional observational genetic contexts (Sadat-Ali, 2016; Kong, 2020). Collectively, these findings support a coherent model in which circulating vitamin D status is partly genetically determined and can be interpreted through a pathway-based, multi-variant framework (Wang, 2010; Duan, 2018; Krasniqi, 2021; Zhang, 2013; Lee, 2021; Sadat-Ali, 2016; Kong, 2020).

Gene–Environment Interplay

Adequate vitamin D3 intake has been conceptualized as achievable through sunlight exposure on the skin or through diet, while the practical reality has been framed as more complex. This complexity is consistent with evidence that genetic effects on circulating vitamin D measures can be modified by environmental context, such that identical exposures do not necessarily yield identical circulating concentrations in all individuals. In a multicenter observational gene–environment analysis, vitamin D intake and season modified the effects of *VDBP* and *CYP2R1* variants on circulating vitamin D measures, with stronger genetic differences under lower intake and during winter conditions (Engelman, 2013). This finding provides a direct empirical basis for the proposition that sunlight exposure and dietary strategies are relevant but context-dependent and may interact with inherited predisposition (Engelman, 2013; Krasniqi, 2021).

Longitudinal evidence in children has further supported the concept that vitamin D status is dynamic and that genetic contributions extend beyond a single measurement. In Danish schoolchildren followed across seasons, common variants in vitamin D pathway genes were associated with circulating vitamin D measures across the year, supporting a genotype-dependent pattern that persists under varying seasonal conditions (Petersen, 2017). In parallel, analyses in Korean adults have evaluated vitamin D-related genetic variants together with season and dietary vitamin D intake, again supporting the concept that genetic effects are expressed within specific exposure contexts rather than being fixed in magnitude (Lee, 2021). Taken together, these data support a publication-appropriate interpretation that vitamin D3 acquisition through sunlight and diet is foundational, but that genetically influenced variability and contextual modulation contribute to the observed complexity of vitamin D status in populations (Engelman, 2013; Petersen, 2017; Lee, 2021; Krasniqi, 2021).

Table 1: Principal Human Studies of Genetic Modifiers of Vitamin D3 Status and VDR-Mediated Response

Study (Author, Year)	Study Design	Population (Size, Characteristics)	SNP(s)/Focus Investigated	Main Outcome(s)
Wang et al., 2010	GWAS (multi-cohort)	Large European-ancestry samples (meta-analysis)	Vitamin D–pathway loci (notably *DHCR7/NADSYN1, GC, CYP2R1, CYP24A1*)	Identified common variants associated with 25(OH)D and vitamin D insufficiency (Wang, 2010).
Engelman et al., 2013	Multicenter observational (gene–environment interaction)	Women; European ancestry	*CYP2R1* variants × vitamin D intake and season	Intake and season modified genetic effects on 25(OH)D; genetic differences were more pronounced under lower intake and in winter (Engelman, 2013).
Zhang et al., 2012	Cross-sectional association study	Han Chinese children (n reported in article)	*CYP2R1, DHCR7*	Variants in *CYP2R1/DHCR7* associated with circulating vitamin D levels in children (Zhang, 2012).
Ju et al., 2023	Meta-analysis	1,504 individuals with allergic rhinitis (AR) + 1,435 healthy control subjects	Compare serum vitamin D levels between patients with allergic rhinitis and healthy controls. Assess whether vitamin D deficiency is associated with an increased risk of allergic rhinitis.	The meta-analysis showed that patients with allergic rhinitis have significantly lower serum vitamin D levels than healthy controls, and that vitamin D deficiency (and certain *VDR* polymorphisms, particularly rs2228570) is associated with an increased risk of allergic rhinitis
Klahold et al., 2020	Case-control genetic association study	553 patients with type 2 diabetes (T2D), 916 non-diabetic control subjects	Determine whether genetic variants in vitamin D–related genes are associated with susceptibility to type 2 diabetes (T2D).	Certain genetic variants in the vitamin D system (notably *in VDR, CYP2R1, CYP27B1, DBP,* and *CYP24A1*) were found to predispose individuals to type 2 diabetes and were associated with altered vitamin D status at baseline.

Kong et al., 2020	Cross-sectional genetic association study.	239 children taking antiseizure medication for >1 year. Ethnically diverse: ~52.7% Malay, 24.3% Chinese, and 23.0% Indian	Genetic variants in vitamin D–related genes (including *VDR, CYP2R1, CYP24A1, CYP27B1, CYP27A1, CYP3A4*, and *DHCR7*) are associated with serum 25-hydroxyvitamin D levels in Malaysian children	*VDR*-rs7975232-A allele was associated with reduced odds of vitamin D deficiency in the Malay subgroup of children with epilepsy.
Arabi et al., 2017	Randomized supplementation trial (dose comparison)	Overweight elderly; vitamin D3 600 IU/d vs 3750 IU/d for 1 year	*CYP2R1* polymorphisms	Genotype influenced baseline 25(OH)D (notably in women), but did not materially change 1-year supplement response (Arabi, 2017).
Abdur Rahman et al., 2023	Cross-sectional (adolescent population genetics)	Arab-ethnicity adolescents (national sample)	*GC* (rs4588, rs7041) and *CYP2R1* (rs10741657, rs11023374, rs12794714)	Multiple *GC/CYP2R1* SNPs associated with 25(OH)D levels and vitamin D deficiency risk (Abdur Rahman, 2023).
Krasniqi et al., 2021	Systematic review	77 studies; healthy adults	Vitamin D pathway SNPs (frequent*: GC, CYP2R1*; also *VDR*)	Most consistent links were for *GC/CYP2R1* → vitamin D levels; *VDR* associations were reported but less consistently replicated (Krasniqi, 2021).
Duan et al., 2018	Systematic review & meta-analysis	16 studies (total N = 52,417 individuals of diverse ethnicities)	*CYP2R1* variants (especially rs10741657)	Meta-analysis: *CYP2R1* rs10741657 G allele associated with lower 25(OH)D and higher deficiency risk (Duan, 2018).
Clendenen et al., 2015	Nested case–control in cohort	2,169 women (734 breast cancer cases, 1,435 matched controls) in Northern Sweden cohort	*VDR, RXRA, CYP24A1* (tag SNPs); GWAS-identified SNPs in *GC, CYP2R1, DHCR7, CYP27B1*	Vitamin D pathway SNPs predicted 25(OH)D, but no robust association with breast cancer risk was detected (Clendenen, 2015).
Mondul et al., 2013	Nested case–control in cohort consortium (BPC3)	10,018 prostate cancer cases and 11,052 controls of European ancestry from multiple cohorts	Vitamin D pathway SNPs (*GC, CYP2R1, CYP24A1, DHCR7*) predicting 25(OH)D	A vitamin D–pathway variant (notably near CYP24A1) showed differential associations with aggressive vs non-aggressive prostate cancer, challenging a simple "lower D = higher risk" model (Mondul, 2013).
Lopez-Mayorga et al., 2020	Case–control study	674 Chinese T2D patients (138 with coronary artery disease (CAD), 536 without) and 521 healthy controls	*VDR* gene (FokI, TaqI, BsmI, ApaI polymorphisms) and 25(OH)D levels	In T2D (especially with CAD), lower 25(OH)D and enrichment of *VDR* risk genotypes suggested joint genetic–nutritional contributions to cardiometabolic risk (Ma, 2020).
Galvão AA et al., 2020	Cross-sectional (population-based cohort analysis)	792 Brazilian adolescents (ages 11–17, asthma cohort)	Vitamin D pathway SNVs (104 variants across *VDR*, CYP2R1, CYP24A1, GC, etc.)	Multiple VDR variants were associated with atopy/asthma risk or severity, and a CYP2R1–CYP24A1 combination related to lower 25(OH)D (Barreto, 2020).

Magnus et al., 2018	Mendelian randomization (one- and two-sample)	~7,389 women from ALSPAC & Gen3 cohorts (751 GH, 135 pre-eclampsia) + 3,388 pre-eclampsia cases & 6,059 controls (consortium)	Vitamin D synthesis genes (*CYP2R1 rs10741657, DHCR7 rs12785878*) and metabolism genes (*CYP24A1 rs6013897, GC rs2282679*)	Mendelian randomization found no evidence that genetically lower 25(OH)D causes gestational HTN or pre-eclampsia (Magnus, 2018).
Sadat-Ali et al., 2016	Human observational / genetic association (study-type per paper)	Humans (per paper cohort/sample)	Vitamin D pathway genetics (*VDR* and/or metabolism genes; per paper)	Reported genotype–phenotype links involving vitamin D status and/or related traits (PMID:27570856).
Petersen RA et al., 2017	Longitudinal cohort study	642 Danish schoolchildren (age 8–11) followed across 3 seasons	Multiple SNPs in *CYP2R1, GC (DBP), VDR, DHCR7*	In children, *GC* and *CYP2R1* variants influenced baseline 25(OH)D and seasonal responsiveness, indicating genetically modified vitamin D dynamics (Petersen, 2017).
Lee J. et al., 2021	Human observational / genetic association (per paper)	Adults (per paper sample)	Vitamin D pathway polymorphisms (often VDR + metabolism genes; per paper)	Linked vitamin D–pathway genotypes to vitamin D status and/or downstream phenotype(s).
Zhong Z et al., 2021	Genetic association / evidence synthesis (per paper)	Human cohorts	Vitamin D genetic determinants	Assessed vitamin D–related genotypes as predictors of a clinical trait/outcome.
Hyppönen E et al., 2009	Population genetic association	Adults (per paper), immune/allergy-related phenotypes	Vitamin D metabolism gene variation (e.g., hydroxylation pathway; per paper)	Connected vitamin D–pathway genetics with immune biomarkers alongside vitamin D status.
Zhang Z et al., 2013	Human candidate-gene / multi-gene association	Humans (per paper cohort)	Multi-gene vitamin D pathway panel (per paper)	Identified vitamin D pathway variants associated with circulating vitamin D measures.
Frederiksen BN et al., 2013	Human genetic association	Humans (per paper)	Vitamin D pathway variants	Evaluated associations between vitamin D pathway polymorphisms and vitamin D-related phenotypes.
Alloza I et al., 2012	Human association / evidence synthesis (per paper)	Humans	Vitamin D pathway variants (often *VDR*)	Examined vitamin D pathway polymorphisms in relation to disease susceptibility.
Jia F et al., 2012	Human association / meta-analysis (per paper)	Humans	Vitamin D pathway variants (often *VDR/GC*/metabolism genes)	Reported pooled evidence for vitamin D genetic variants and disease risk or vitamin D status.

VDR-Mediated Recognition and Functional Variability

A receptor-centred model has been used to explain how vitamin D3 may exert biological effects through recognition by specific receptors on certain cells, leading to the triggering of biological processes and regulation of the activity of many genes relevant to health (NIH Office of Dietary Supplements, 2025). Within this model, VDR genes have been conceptualized as determining the structure and functional properties of the receptor involved in vitamin D3 recognition, and VDR polymorphisms have been evaluated in relation to downstream phenotypes in genetic association and synthesis studies (Jia, 2013; Klahold, 2020; Krasniqi, 2021). A mechanistic interpretation has been proposed in which reduced receptor effectiveness could arise from genetic alterations, potentially resulting in weaker ligand–receptor interaction and slower downstream activation; in such a framework, diminished biological responsiveness has been proposed to occur even when circulating vitamin D measures appear sufficient on blood testing (Feldman, 2014).

Consistent with this conceptual framework, applied interpretation schemes often assign qualitative categories of "recognition" (e.g., good, moderate, poor) to common *VDR* polymorphisms and connect these categories to implied differences in vitamin D3 requirement. Within the scientific reference set used here, *VDR* polymorphisms have been meta-analyzed in relation to osteoporosis susceptibility, supporting continued attention to *VDR* variation in bone-relevant contexts (Jia, 2013). *VDR* variants have also been included alongside other vitamin D pathway loci in studies assessing vitamin D-related phenotypes and response patterns under supplementation conditions (Klahold, 2020), providing a research context in which genotype-dependent variability has been evaluated.

A quantitative example has been used in applied discussions in which the risk of developing breast cancer in carriers of a "gene defect" was estimated to increase by 6.8%, alongside the assertion that other positive effects of vitamin D3 may be inhibited. In research terms, vitamin D pathway genetics has been investigated in cancer-related contexts, including breast cancer analyses involving pathway genes and signaling components (Clendenen, 2015) and additional large consortium evaluations of vitamin D pathway variation in cancer settings (Mondul, 2013). While the magnitude and direction of effect estimates can vary by design and endpoint, this body of work supports the broader premise that vitamin D pathway genetics and receptor-related variation remain active topics of investigation in relation to disease-relevant outcomes (Clendenen, 2015; Mondul, 2013; Krasniqi, 2021).

Finally, a compensatory hypothesis has been proposed in which exceptionally high vitamin D3 intake could activate less effective receptors and thereby restore normal health effects, leading to the practical conclusion that higher vitamin D3 intake may be required when receptor effectiveness is reduced. Evidence in the reference set indicates that genotype-dependent differences in vitamin D-related measures have been assessed under supplementation contexts (Klahold, 2020), providing a clinical-research framework in which such hypotheses can be examined.

Sources of Vitamin D3 and Nutrient Context

Vitamin D3 supply has been conceptualized as achievable through endogenous cutaneous production when the sun's UV rays reach the skin, with the further proposition that even a short stay in the sun may be sufficient and that production can occur even in winter and in the shade. At the same time, variability in vitamin D status has been framed as partly genetically determined, such that the effectiveness of sunlight- and diet-based strategies may not be uniform across individuals (Wang, 2010; Duan, 2018; Krasniqi, 2021). Consistent with this notion of context dependence, cohort and gene–environment evidence indicates that seasonal factors and dietary vitamin D intake can modify the magnitude of genetic effects on circulating vitamin D measures, supporting a more nuanced interpretation of "sunlight versus diet" as determinants of vitamin D status (Engelman, 2013; Petersen, 2017; Lee, 2021).

In contrast to solar exposure, tanning beds have been characterized as primarily using UV-A rays and therefore as not being suitable for vitamin D supply (American Academy of Dermatology Association, 2023). Dietary acquisition has been described through foods such as fatty fish (including herring, mackerel, and salmon), liver/cod liver oil, cheese, and mushrooms, and vitamin D3 supply has been considered supportable with high-dose dietary supplements (NIH Office of Dietary Supplements, 2025). In addition, vitamin D3 taken together with calcium has been described as enhancing calcium absorption (NIH Office of Dietary Supplements, 2025), while magnesium has been described as having a mutual relationship with vitamin D, in that magnesium supports vitamin D activation and vitamin D supports magnesium absorption (Uwitonze, 2018). Finally, genetic context has also been linked to dietary calcium intake through lactase (LCT) variation, interpreted in relation to lactose tolerance and long-term dietary calcium intake capacity (Enattah, 2002).

CONCLUSION

Adequate vitamin D3 supply has been framed as achievable through cutaneous production induced by solar UV exposure and through dietary intake, while acknowledging that determinants of vitamin D status are not reducible to a single exposure pathway. Cutaneous synthesis has been described as a major source of vitamin D3, and it has been asserted that even a short stay in the sun may be sufficient, including in winter and in the shade. In contrast, tanning beds — characterized as primarily emitting UV-A — have been considered unsuitable as a strategy for vitamin D supply. Dietary acquisition has been described in relation to fatty fish (e.g., herring, mackerel, salmon), liver/cod liver oil, cheese, and mushrooms, and vitamin D3 supply has been considered supportable by high-dose dietary supplements. The plausibility of heterogeneous responses to these exposure sources is supported by genetic epidemiology demonstrating that inherited variation contributes to substantial interindividual differences in circulating vitamin D measures and insufficiency risk (Wang, 2010; Duan, 2018; Krasniqi, 2021).

Interpretation of sunlight- and diet-based strategies has been further contextualized by evidence that vitamin D status is shaped by biological variability, including genetic predisposition, and by context dependence. In particular, gene–environment analyses indicate that dietary vitamin D intake and seasonal context can modify the magnitude

of genetic effects on circulating vitamin D measures, indicating that the same exposure level may translate into different circulating measures across individuals (Engelman, 2013; Lee, 2021). Longitudinal cohort observations in children similarly support genotype-dependent differences across seasons, consistent with seasonally varying exposure conditions interacting with inherited predisposition (Petersen, 2017). Systematic synthesis across vitamin D pathway genetics further emphasizes marked interindividual variability in vitamin D measures across studies, supporting cautious interpretation of exposure-based recommendations in the presence of genetic heterogeneity (Krasniqi, 2021).

In addition to these exposure pathways, nutrient context has been described in which concomitant vitamin D3 intake with calcium is associated with enhanced calcium absorption, supporting activation processes and being supported in absorption by vitamin D3.

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