Genetic and Racial Differences in the Vitamin D Endocrine System

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KEYWORDS

• Vitamin D • Vitamin D binding protein • CYP2R1 • CYP24A1
• Delta-7-steroid-reductase • 25-Hydroxyvitamin D • Gene polymorphism • Race

KEY POINTS

- The vitamin D status is best assessed by serum 25-hydroxyvitamin D (25OHD).
- Serum 25OHD is highly variable around the world and depends on environmental and genetic factors.
- Twin studies suggest that serum 25OHD is highly genetically driven (explaining overall more than 50% of the variation).
- Genome-wide association study and candidate gene studies conclude that 4 gene polymorphisms (delta-7-steroid-reductase, CYP2R1, CYP24A1, and above all, DBP/GC) explain about 5% of the variations in serum 25OHD.
- Racial differences in DBP/GC only contribute minimally to the wide variations in total or free serum 25OHD concentrations.

Vitamin D is essential for calcium and bone homeostasis and may have many other nonskeletal effects.[1–4] The "nutritional status" of vitamin D is usually assessed by measurements of serum 25-hydroxyvitamin D (25OHD), because this reflects the access to either exogenous (food) or endogenous (skin) synthesis of the parent vitamin D. Indeed, most of the supply of vitamin D is rapidly cleared from serum and is metabolized into 25OHD, with an estimated conversion efficacy of about 25% to 33%, as based on comparison between vitamin D status after oral intake of the parent vitamin D or 25OHD.[5,6] The hormonal status of vitamin D is reflected in serum concentrations of $1,25(OH)_2D$ as the renal conversion of 25OHD into $1,25(OH)_2D$ is tightly feedback-controlled by several hormones.[1–4] The paracrine/autocrine status of vitamin D, being the local conversion of 25OHD into $1,25(OH)_2D$ in several tissues by locally expressed CYP27B1, so far cannot be easily assessed. From several twin studies, one can

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conclude that the vitamin D status as reflected by serum 25OHD is genetically highly regulated. Indeed, depending on the type of study (Table 1), between 25% and even 80% of the variation would be under genetic control. The influence of genes as based on the results of twin studies on serum 1,25$(OH)_2$D is, however, much lower when compared with serum 25OHD (see Table 1). Therefore, the obvious question is which genes are involved in the metabolism and action of vitamin D? Indeed, gene polymorphisms may be part of the genetic and racial differences in vitamin D status or action. The potentially large genetic influence on serum 25OHD is rather unexpected because 25OHD is thought to be an excellent indicator of combined (nutritional intake and endogenous synthesis) access to vitamin D. Both types of access to vitamin D are highly dependent on the environmental and lifestyle factors rather than genetic background. Although twin studies are considered the best strategy to overcome environmental and other confounding factors (by comparing nonidentical from identical twins, living in similar situations), possible remaining confounding resulting in overestimation of genetic factors is always a possible concern. In this article, the author summarizes existing data concerning the ethnic, racial, and genetic influences on the vitamin D endocrine system.

ETHNIC AND RACIAL DIFFERENCE IN VITAMIN D STATUS LARGELY DUE TO ENVIRONMENTAL FACTORS

The nutritional intake of vitamin D is dependent on the intake of a few food items with high vitamin D content, such as oily fish. Overall, the intake of vitamin D in most countries around the world is rather low and only contributes to (far) less than 50% (and usually even <20%) of the overall supply. Exceptions are of course populations with high habitual intake of oily fish (or fish oil). Most European populations have a daily oral intake of less than 5 μg[7] and thus well below the minimal requirements of (at least) 10 μg/d for humans of all ages.[8] In populations with a high intake of vitamin D (eg, Iceland), the seasonal variation in serum 25OHD is therefore much lower than the seasonal variation in other countries or regions with a much lower vitamin D intake. There are, indeed, some ethnic differences in choice or access to vitamin D–rich food, but these situations are due to environmental, economic, or cultural factors and not really genetically or racially driven. Differences in food intake are thus unlikely factors involved in the genetic control of serum vitamin D metabolites. Endogenous production of vitamin D, however, may be more sensitive to ethnic, racial, or genetic factors. Access to UV-B irradiation from sunlight is of course dependent on many

Table 1
Genetic determinants of serum 25-hydroxyvitamin D and 1,25$(OH)_2$D

Authors	25OHD, %	1,25$(OH)_2$D, %	Comments
Hunter et al,[76] 2001	43		UK twins
Wjst et al,[77] 2007	80	30	Germany asthma patients
Orton & Ebers,[78] 2011	77		Canadian twins
Engelman et al,[79] 2008	23–41	16–48	US Hispanics and African Americans
Snellman et al,[80] 2009	50		Sweden (summertime)
Shea et al,[81] 2009	25		US Framingham
Karohl et al,[82] 2010	70		Vietnam twin
Mills et al,[83] 2015	86		Australia
Arguelles et al,[84] 2009	36		Chinese adolescents