Vitamin D, discovered nearly a century ago, still receives intensive attention worldwide. In *The Lancet* today, Thomas Wang and colleagues, through a monumental effort by a large consortium of experts (the SUNLIGHT consortium), provide new data that help to explain the large variability of vitamin D status, as revealed by serum concentrations of 25-hydroxyvitamin D.

Vitamin D deficiency, even when defined conservatively as a concentration of 25-hydroxyvitamin D lower than 50 nmol/L, is common and probably affects more than one billion people worldwide. This deficiency causes rickets, which is still highly prevalent around the world, and accelerates age-related bone loss and morbidity from falls and fractures. Moreover, vitamin D insufficiency is associated with nearly all major diseases of the developed world, such as cancer, immune diseases, cardiovascular risks, and all factors of the metabolic syndrome. Vitamin D status is thought to depend mainly on endogenous conversion of 7-dehydrocholesterol (7-DHC) into (pre)vitamin D3 during exposure to ultraviolet B from sunlight and to only partly depend on nutritional vitamin D intake, because most common foods, apart from fatty fish, have very low vitamin D content. Moreover, most experts believe that the production of 25-hydroxyvitamin D is poorly regulated and largely depends on access to its substrate, vitamin D3. Serum 25-hydroxyvitamin D ceases to increase linearly with vitamin D intake only at much higher concentrations than the usual intake. Overall vitamin D status around the world lies at a mean concentration of about 50 nmol/L with little variation between countries (mean concentrations in different countries grossly fluctuate between 30 and 75 nmol/L) and much greater variation within countries (from lower than 20 to 200 nmol/L).

Data from today’s genome-wide association study, taken from about 30 000 white people drawn from initially five, and later 15, major epidemiological cohorts, show that at least three, and probably four, genes contribute to the variability of serum concentrations of 25-hydroxyvitamin D. Indeed, the relative differences in mean 25-hydroxyvitamin D concentration between minor and major homozygotes for the strongest genetic variants were close to those seen with usual vitamin D supplementation, and nearly as large as those seen with seasonal variation between winter and summer. However, this combined gene effect is much lower than the heritability predicted on the basis of twin studies. The genes involved encode three key enzymes: 7-DHC reductase (responsible for the availability of 7-DHC in the skin), the liver 25-hydroxylase CYP2R1 (involved in the conversion of vitamin D into 25-hydroxyvitamin D), and CYP24A1 (a key degradation enzyme). Additionally, polymorphisms in GC, the gene encoding vitamin D binding-protein, had the greatest effect on serum 25-hydroxyvitamin D concentration. Participants in the top quartile of genotype scores had about twofold elevated odds of vitamin D insufficiency. These results thus help to explain the variation in serum 25-hydroxyvitamin D status and show that, indeed, some gene polymorphisms might protect against, or accelerate, vitamin D deficiency.

Some of today’s results were unexpected. None of the identified genes proved to be linked with skin pigmentation, even though skin pigmentation is known to be a major factor in vitamin D status. Moreover, no genes that are linked with any of the major diseases associated with vitamin D deficiency were picked up. This finding suggests that vitamin D status, rather than gene polymorphisms, influences these health problems.

Today’s study also generates new questions. Do these genes also modify the 25-hydroxyvitamin D response to vitamin D supplementation, and should we take this into account when prescribing vitamin D, as suggested?
To what extent is the serum concentration of the active hormone 1,25-dihydroxyvitamin D, regulated by these or other gene polymorphisms? Is 25-hydroxyvitamin D concentration in non-white people regulated by the same genes as those in white people?

Finally, the GC polymorphism follows a strong latitude gradient: the GC2 haplotype is more frequent in populations living in northern climates and this genotype is strangely associated with lower concentrations of 25-hydroxyvitamin D and vitamin D binding protein. The evolutionary drive for this GC polymorphism thus remains unclear. Today’s results only partly explain the wide variability of vitamin D status, and whether these genetically based variations modify the health outcomes in vitamin D deficiency is not known. Therefore the battle against vitamin D deficiency will probably not be modified by these new findings. We need additional studies to explain the mechanisms underlying the pandemic of vitamin D deficiency and, above all, we need a strategy to correct this serious worldwide deficiency.10

Roger Bouillon
Clinic and Laboratory of Experimental Medicine and Endocrinology, Katholieke Universiteit Leuven (KUL), 3000 Leuven, Belgium
roger.bouillon@med.kuleuven.ac.be

I have been a consultant for Eli Lilly, Amgen, and MSD, and have received royalties from Hybrigenix for a vitamin D analogue.