

Abstract

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Common genetic determinants of vitamin D insufficiency: a genome-wide association study.

Wang TJ, Zhang F, Richards JB, Kestenbaum B, van Meurs JB, Berry D, Kiel DP, Streeten EA, Ohlsson C, Koller DL, Peltonen L, Cooper JD, O'Reilly PF, Houston DK, Glazer NL, Vandepuut L, Peacock M, Shi J, Rivadeneira F, McCarthy MI, Anneli P, de Boer IH, Mangino M, Kato B, Smyth DJ, Booth SL, Jacques PF, Burke GL, Goodarzi M, Cheung CL, Wolf M, Rice K, Goltzman D, Hidiroglou N, Ladouceur M, Wareham NJ, Hocking LJ, Hart D, Arden NK, Cooper C, Malik S, Fraser WD, Hartikainen AL, Zhai G, Macdonald HM, Forouhi NG, Loos RJ, Reid DM, Hakim A, Dennison E, Liu Y, Power C, Stevens HE, Jaana L, Vasani RS, Soranzo N, Bojunga J, Psaty BM, Lorentzon M, Foroud T, Harris TB, Hofman A, Jansson JO, Cauley JA, Uitterlinden AG, Gibson Q, Jarvelin MR, Karasik D, Siscovick DS, Econs MJ, Kritchevsky SB, Florez JC, Todd JA, Dupuis J, Hyppönen E, Spector TD.

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BACKGROUND: Vitamin D is crucial for maintenance of musculoskeletal health, and might also have a role in extraskeletal tissues. Determinants of circulating 25-hydroxyvitamin D concentrations include sun exposure and diet, but high heritability suggests that genetic factors could also play a part. We aimed to identify common genetic variants affecting vitamin D concentrations and risk of insufficiency.

METHODS: We undertook a genome-wide association study of 25-hydroxyvitamin D concentrations in 33 996 individuals of European descent from 15 cohorts. Five epidemiological cohorts were designated as discovery cohorts (n=16 125), five as in-silico replication cohorts (n=9367), and five as de-novo replication cohorts (n=8504). 25-hydroxyvitamin D concentrations were measured by radioimmunoassay, chemiluminescent assay, ELISA, or mass spectrometry. Vitamin D insufficiency was defined as concentrations lower than 75 nmol/L or 50 nmol/L. We combined results of genome-wide analyses across cohorts using Z-score-weighted meta-analysis. Genotype scores were constructed for confirmed variants.

FINDINGS: Variants at three loci reached genome-wide significance in discovery cohorts for association with 25-hydroxyvitamin D concentrations, and were confirmed in replication cohorts: 4p12 (overall $p=1.9 \times 10^{-109}$ for rs2282679, in GC); 11q12 ($p=2.1 \times 10^{-27}$ for rs12785878, near DHCR7); and 11p15 ($p=3.3 \times 10^{-20}$ for rs10741657, near CYP2R1). Variants at an additional locus (20q13, CYP24A1) were genome-wide significant in the pooled sample ($p=6.0 \times 10^{-10}$ for rs6013897). Participants with a genotype score (combining the three confirmed variants) in the highest quartile were at increased risk of having 25-hydroxyvitamin D concentrations lower than 75 nmol/L (OR 2.47, 95% CI 2.20-2.78, $p=2.3 \times 10^{-48}$) or lower than 50 nmol/L (1.92, 1.70-2.16, $p=1.0 \times 10^{-26}$) compared with those in the lowest quartile.

INTERPRETATION: Variants near genes involved in cholesterol synthesis, hydroxylation, and vitamin D transport affect vitamin D status. Genetic variation at these loci identifies individuals who have substantially raised risk of vitamin D insufficiency.

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