Common genetic variations in the CYP2R1 and GC genes are determinants of vitamin D status in Danes

Vitamin D is considered a key fat-soluble vitamin critically important for good bone- and overall health throughout life. Vitamin D deficiency increases the risk of developing rickets, osteomalacia and osteoporosis, and moreover increases the risk of various non-skeletal adverse health outcomes including cardiovascular diseases, autoimmune diseases, some cancers and overall mortality. In humans, vitamin D is mainly synthesized in the skin after solar exposure and only a small amount is obtained through the diet.

An inter-individual variation in vitamin D status exists, which may be explained by genetic variation in vitamin D modulating genes. Twin and family-based studies indicate that genetic variation may have an appreciable influence on vitamin D status. Moreover, several candidate gene studies including two genome-wide association studies (GWAS) have found single nucleotide polymorphisms (SNPs) in CYP2R1, CYP24A1, CYP27B1, C10orf88, DHCR7/NADSYN1, GC and VDR genes to be associated with vitamin D status. The main hypothesis of this work was that genetically determined variation in vitamin D metabolism would influence the effect of vitamin D sources (vitamin D-supplementation and ultraviolet (UV)-B) on vitamin D status.

This was done by assessing the association between 25 SNPs located in the CYP2R1, CYP24A1, CYP27B1, C10orf88, DHCR7/NADSYN1, GC and VDR genes and vitamin D status in 756 participants in the VitmaD study in late summer (paper I), at the end of a winter season (paper II), after 6 months intake of vitamin D3-fortified bread and milk (paper II) and in 92 participants in the VitDgen study after artificial UVB irradiation during winter (paper III).

Common genetic variations in the CYP2R1 and GC genes were found to be important determinants of vitamin D status in three out of four scenarios: in late summer, after 6 months intake of vitamin D3-fortified bread and milk and after artificial UVB irradiation, but not at the end of winter when no artificial vitamin D sources (vitamin D3-fortification or UVB irradiation) had been given.

Overall, a general negative gene-dose dependent relationship was observed between increasing numbers of risk alleles of CYP2R1 and GC and lower vitamin D status, and moreover an additive effect of CYP2R1 and GC polymorphisms on vitamin D status was observed. Genetically predisposed individuals carrying all risk alleles of CYP2R1 and GC had the lowest vitamin D status in late summer, the largest decrease in vitamin D status after intake of vitamin D3-fortified bread and milk during winter and the smallest increase in vitamin D status after artificial UVB irradiation compared to individuals carrying fewer or no risk alleles of CYP2R1 and GC.

Based on the studies included in this thesis, it is concluded that genetically predisposed individuals, with a genetic profile of CYP2R1 and GC leading to low vitamin D status, had the lowest vitamin D status in late summer and responded the least to increased exposure of the vitamin D sources, vitamin D3-fortification and UVB irradiation. Genetically determined variation in CYP2R1 and GC may potentially be used as a biomarker to identify at-risk individuals who have substantially increased risk of having low vitamin D status.

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