Biomarkers in bone metabolism & related organ systems: Common vitamin D-related genetic variants and vitamin D status in women and men

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Introduction

- Low 25-hydroxycholecalciferol (25(OH) vitamin D) status is known to play an important role in many diseases with focus on bone health.

Based on recently reported genetic determinants of vitamin D insufficiency, we investigate genetic variants of various vitamin D-associated genes for their potential role in predicting vitamin D levels during routine and research conditions.

- Genome wide association studies identified three common loci of genetic determinants for vitamin D insufficiency: group-specific component (GC, rs2282679), 7-dehydrocholesterol reductase (DHCR7, rs12785878) and cytochrome P450 IIR-1 (CYP2R1, rs10741657).

These loci are located near genes which are involved in vitamin D transport, cholesterol synthesis and hydroxylation.

Methods

- We investigate a panel of vitamin D-associated genetic variants in three cohorts.

- The “VitaGen Study” – outpatients of the Div. of Endocrinology and Diabetology, follow-up scenario (Fig. 1)

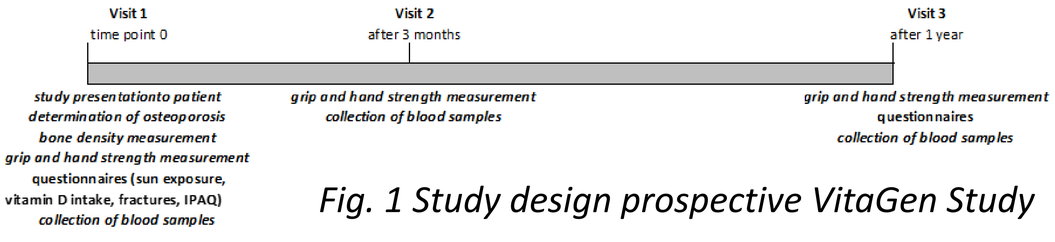
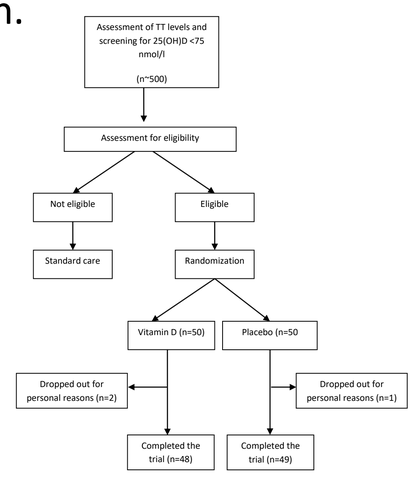


Fig. 1 Study design prospective VitaGen Study

- The “BioPersMed cohort” – 1025 volunteers with deep clinical phenotyping including bone density, muscle function, metabolic and cardiovascular characterisations and function tests – cross-sectional and follow-up design.

- The “Vitamin D RCT cohort” – ~100 male healthy men with 25(OH)vitamin D <30 ng/ml. Subjects were randomized to receive 20.000 IU of vitamin D3 per week (n=50) or placebo (n=50) for 12 weeks.



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Results

- Based on three actual and several previous studies and recent publications, we suggest a list of genetic variants for replication and clinical testing (Tab. 1):

Gene	Description	rs number
CYP2R1	Cytochrome P450 2R1, Vitamin-D-25-Hydroxylase	rs2228570
		rs10741657
CYP27B1	Cytochrome P450 27B1, 1α-Hydroxylase	rs10877012
		rs703842
		rs4646536
CYP24A1	Cytochrome P450 24A1, 24-Hydroxylase	rs2244719
		rs2296241
		rs17219315
DHCR7	7-Dehydrocholesterolreductase	rs12785878
GC	Group specific component	rs7041 oder rs4588
		rs1155563
		rs2282679
		rs12512631
VDR	Vitamin D Receptor	rs10735810
		rs10783219
LCT	Laktase gene (MCM6)	rs4988235

Persons in the study: n=1435

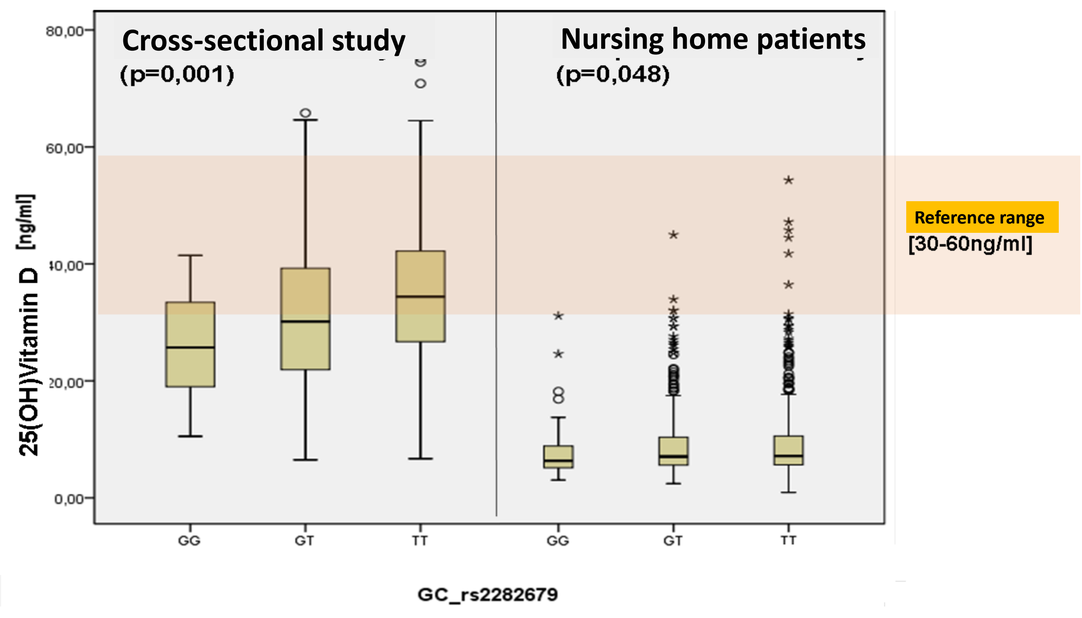

Fig. 2 Genetic variants of vitamin D-associated genes e.g. GC, CYP2R1 and DHCR7 have been tested in 1435 participants of previous studies in relation to vitamin D serum levels and prospective bone fractures. Trummer O, Obermayer-Pietsch B, JCEM 2014

Conclusions

Based on ongoing and recently performed clinical studies, we are able to replicate candidate variants of interest associated with vitamin D serum levels and secondary outcomes of vitamin D metabolism.

We plan in the last part of the project to assign a “risk allele” for each gene based on its association with lower 25(OH) vitamin D levels.

Our company partner is currently working on an easy-to-access system for these biomarkers.

The potential role of these risk alleles in clinical practice will help to better understand and support patients with vitamin D deficiency and may also serve as predictors for fracture risk or metabolic diseases and cancer.

funded by:

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