Genetics and Pharmacogenomics

4.1 The B Allele of the BsmI Vitamin D Receptor (VDR) Gene Polymorphism is Independently Associated to LVH and to Higher Progression Rate of LVH in End-Stage Renal Disease (ESRD) Patients

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Introduction. Left ventricular hypertrophy (LVH) is a strong risk marker for death and cardiovascular complications in ESRD patients. Vitamin D treatment is associated with reduced death risk in these patients and a causal role of vitamin D deficiency and/or disturbed vitamin D signalling in the high risk of ESRD is suggested by the observation that Vitamin D Receptor (VDR) knock-out mouse displays marked cardiac hypertrophy.

Aim. Because the BsmI VDR gene polymorphism may alter the VDR function, we performed a longitudinal study to establish: (1) the relationship between BsmI VDR gene polymorphism (high-throughput TaqMan allelic discrimination assay) and LV mass index (LVMI) measured by echocardiography; (2) The predictive power of this polymorphism for progression in LV hypertrophy (LVH).

Methods. One hundred and eighty two dialysis patients (age 59±15 years; 104 M and 78 F, all Caucasians) participated into the study and each patient underwent echocardiography twice, 18±2 months apart.

Results. The distribution of BsmI genotypes did not significantly deviate from Hardy-Weinberg equilibrium either in patients (bb genotype: 33.5%; Bb genotype: 52.2% and BB genotype 14.3%) or in an age and sex matched group of healthy subjects (bb genotype: 37.8%; Bb genotype: 47.4% and BB genotype: 14.9 %). The frequency of the B allele (40.4%) in dialysis patients was similar to that of healthy control subjects (38.6%). The numbers of B-alleles of BsmI polymorphism were directly and significantly related to LVMI ($r=0.20$, $P=0.007$). This relationship was quite robust because it remained unmodified ($r=0.20$, $P=0.005$) in a multivariate analysis adjusting for traditional risk factors (age, sex, smoking, systolic pressure, diabetes, cholesterol), previous CV events, factors peculiar to ESRD (haemoglobin, albumin, calcium*phosphate, KTV and duration of RDT), emerging risk factors (CRP, homocysteine and ADMA) and anti-hypertensive and calcitriol treatment. In the longitudinal study LVMI rose from 60.1±17.9 g/m^{2.7} to 64.2±19.3 g/m^{2.7} ($P<0.001$). Interestingly, patients carrying the B allele showed a higher progression rate of LVMI (LVMI: +0.30±0.53 g/m^{2.7}/month) when compared to patients without the B allele (LVMI: +0.08±0.49 g/m^{2.7}/month) ($P=0.019$) and this difference remained significant ($P=0.03$) also after data adjustment for all potential confounders including LVMI at baseline.

Conclusions. In dialysis patients, the B allele of the BsmI VDR gene polymorphism is coherently related to LVH and to higher progression rate of LVH in these patients. Since these associations are not influenced by the presence by traditional and non-traditional risk factors and since genes are randomly transmitted (Mendelian randomization), our cross-sectional and longitudinal observations consistently support the hypothesis that altered Vitamin D signalling in vivo, in ESRD patients is implicated in LVH in ESRD patients