

## Atherosclerosis and Inflammation

### 1.8 A Functional LDL Receptor-Related Protein 6 Gene Variant is an Independent Risk Factor For Early Carotid Artery Atherosclerosis in Hypertensive Patients

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**Introduction.** Low-Density Lipoprotein Receptor-Related Protein 6 (LRP6) is a co-receptor in the canonical Wnt/beta-catenin signalling pathway. Common (H1062V) and rare (R611C) variants display reduced activation Wnt/beta-catenin signalling. The rare gene variant causes hypertension, metabolic abnormalities, and early coronary artery disease.

**Aim.** To investigate whether a common V1062 LRP6 variant with similar functional consequences (nearly 5-fold lower signalling) was related to early carotid artery atherosclerosis (CAA) in hypertensive patients.

**Methods.** Cross-sectional study of 273 hypertensive patients (age <65 years) undergoing carotid artery ultra sonography. Hypertension, type 2 diabetes, dyslipidaemia, chronic kidney damage (CKD), and smoking habit were evaluated. Genotyping was carried out using realtime PCR. CAA was defined by the presence of atherosclerotic plaques (intima-media thickness >1.3 mm) at the level of common, bifurcation and/or internal carotid arteries. Logistic regression models were used to estimate the independent effect of V1062 allele controlling for CAA established risk factors.

**Results.** In our hypertensive patients, age, gender, dyslipidaemia, smoking habit, pulse pressure and CKD confirmed as risk factors for CAA. The V1062 LRP6 variant was a strong risk factor for CAA in both unadjusted (OR 1.75, 95%CI 1.02-3.02;  $p < 0.05$ ) and adjusted models (OR 2.07, 95%CI 1.05-4.11;  $p = 0.036$ ). When a more strict criterion to define CAA (atherosclerotic plaques with >15% lumen reduction, class C and above following Taylor and Strandness) was considered, the results were also stronger (unadjusted OR 2.14, 95% CI 1.2-3.84,  $p = 0.011$ ; adjusted OR 2.44, 95%CI 1.22-4.85,  $p = 0.011$ ).

**Conclusions.** Beside the role of established risk factors, V1062 LRP6 variant and CAA are strongly associated in hypertensive patients, making LRP6 a novel interesting candidate gene for early coronary and carotid artery atherosclerosis.