Original Article

Variant on chromosome 9p is associated with left ventricular mass: results from two cohorts of essential hypertensive individuals

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Objectives: It is well known that among hypertensive patients, an increased left ventricular mass (LVM) is a powerful predictor of cardiovascular morbidity and mortality. However, the mechanisms underlying LVM in hypertension are not completely understood, as the absolute value of blood pressure and other risk factors associated do not predict alone a definite LVM progression. Recently, the 9p21 chromosomal region has been consistently associated with coronary heart disease.

Methods and results: We examined the association of 384 single nucleotide polymorphisms (SNPs) in the short arm of chromosome 9 with LVM in 821 hypertensive individuals from northern Italy. We identified a SNP (rs894379) in the intronic region of the centlein, centrosomal protein (*CNTLN*) gene on chromosome 9p22, whose minor allele G is associated with an increased LVM. We performed a follow-up validation analysis for the top SNP in 1038 hypertensive individuals from southern Italy. We then combined the results and found a nominal association for rs894379 ($\beta = 2.46$, $P = 0.0026$).

Conclusion: We describe a new variant associated with echocardiography LVM. This result, though it needs to be further investigated, may improve our understanding of the genetic determination of this prognostically relevant trait.

Keywords: association, chromosome 9p21, genetics, left ventricular mass

Abbreviations: BP, blood pressure; BSA, body surface area; CNTLN, centlein centrosomal protein; ELN, elastin; ET-A, endothelin receptor type A; FC-ECG, cardiac frequency ECG; FDR, false discovery rate; GWAS, genome-wide association study; LVEDD, left ventricular end-diastolic diameter; LVM, left ventricular mass; LVMI, LVM index; LVH, left ventricular hypertrophy; MAF, minor allele frequency; MMP9, matrix metallopeptidase 9; SNP, single nucleotide polymorphism

INTRODUCTION

Increased left ventricular mass (LVM) is a strong and independent risk factor for cardiovascular morbidity and mortality [1,2]. Even though demographic characteristics, such as sex and BMI, and hemodynamic variables, such as blood pressure (BP) values, volume load and contractile efficiency, are known to be associated with LVM, nearly half of the LVM variability remains unexplained [3]. LVM heritability is found to be between 0.17 and 0.59, thus suggesting that LVM has a clear genetic component [4–8]. Candidate genes studies have shown a potential role of genetic polymorphisms located in angiotensin-converting enzyme [9] and aldosterone synthase (CYP11B2) [10], insulin-like growth factor [11], neuropeptide Y [12], guanine nucleotide-binding protein 3 [13], endothelial nitric oxide synthase [14] and peroxisome proliferator-activated receptor-α (*PPARα*) [15] genes. Genome-wide linkage and association studies (GWASs) have shown an association between LVM, assessed especially with ECG criteria, and several loci located in different chromosomes (3, 5, 6, 7, 10, 12, 15, 17 and 19) [16–18]. Particularly, in a whole genome linkage study of hypertensive families, three regions (10q23.1, 12q14.1 and 17p13.3) were found to approach suggestive evidence of linkage for particular measures of

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