**A GENETIC VARIANT IN THE CIRCADIAN GENE BMAL1 IS ASSOCIATED WITH HIGHER INCIDENCE OF CARDIOVASCULAR DISEASES**

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*Background*: The physiological functions of cardiovascular organs are closely related to circadian rhythm. The onset of cardiovascular diseases (CVD) such as acute coronary syndrome, atrial arrhythmia, etc exhibits diurnal oscillation suggesting that variations in clock genes may be very important in regulating these circadian rhythms and associated with CVD incidence. The Aryl hydrocarbon receptor nuclear translocator-like (ARNTL) gene, also called BMAL1, is, together with CLOCK, one of the most relevant clock genes. In mice it has been observed that BMAL1 influences critical heart functions, such as development of dilated cardiomyopathy, contractile function, as well as life span. However there are few studies that have related variations in this gene with CVD in humans. Aims: To study the association of polymorphisms in the BMAL1 and CVD incidence in a high-risk cardiovascular population.

*Methods*: We have carried out a prospective study in the PREDIMED-Valencia study participants (men and women aged 67+/-7 y). PREDIMED is a dietary intervention trial with Mediterranean diet (MedDiet). Participants (n=1055) were followed-up a median of approx. 5 years and incidence of CVD (including myocardial infarction, stroke and cardiovascular death were) was assessed. BMAL1 polymorphisms were determined by dense genotyping and the BMAL1-rs1982350 SNP (n=1007) was selected for associations. Multivariable Cox regression models were fitted.

*Results and Conclusions*: Prevalence of the BMAL1-rs1982350 was 51%GG, 39%GA and 10%AA. Carriers of the variant allele (A) had higher CVD incidence (2.7%, 5.6% and 8.2% in wild-type homozygous, heterozygous and homozygous for the variant allele, respectively; P=0.004). In the Cox model adjusted for age, sex, dietary intervention and diabetes, the HR for CVD per variant allele (additive model) was 1.56; 95%CI:1.07-2.37; P=0.023. We also found a significant association with higher risk of myocardial infarction, this being the first time that the association between this polymorphism and CVD incidence in humans has been reported.