**GENOME-WIDE ASSOCIATION SCREENING FOR TOTAL BILIRUBIN LEVELS IN PATIENTS WITH METABOLIC SYNDROME IN A MEDITERRANEAN POPULATION**

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**Background**: Bilirubin, a bile pigment with antioxidant and anti-inflammatory properties is emerging as a protective cardiovascular risk factor. Several studies have reported that bilirubin was negatively associated with oxidative stress-mediated diseases, including the metabolic syndrome and incident cardiovascular diseases (CVD). Likewise, Mendelian randomization studies have investigated the association between polymorphisms in genes related to bilirubin and CVD phenotypes. Although several genome-wide association studies (GWAs) have identified the UGT1A1 (UDP glucuronosyltransferase family 1 member A1) gene as the major locus controlling serum bilirubin, additional genetic heterogeneity has been described depending on the population. Our aim is to carry out a GWAs on a Mediterranean population with metabolic syndrome to detect the main genes associated with serum bilirubin concentrations

**Methods**: We analyzed 433 patients (aged 55-75 y) with metabolic syndrome that were consecutively recruited in the PREDIMED PLUS-Valencia study and had serum bilirubin and genotype data. Genotyping was undertaken with the Human OmniExpress Illumina array. PLINK was used for association analyses (adjusted for sex and age).

**Results and conclusions**: Bilirubin were 0.63+/-0.26 mg/dL in men and 0.53+/-0.20 mg/dL in women; P<0.001. Bilirubin was not correlated with age, fasting glucose, body mass index, liver or kidney enzymes. The only significant association (inverse) was found with fasting triglycerides. In this population the top-ranked gene associated with serum bilirubin was the UGT1A1 gene. For the UGT1A1-rs6742078 we observed a strong association at the genome-wide level (P=3.0x10E-28). The minor allele (allele 2) was associated with higher bilirubin concentrations (0.51+/-0.01 mg/dL for 11; 0.56+/-0.01 mg/dL for 12 and 0.91+/-0.05 mg/dL for 22). Genotype prevalence being: 11 (42%), 12 (46%) and 22 (13%). Although we also detected other top-ranked genes associated with serum bilirubin levels in this Mediterranean population, the UGT1A1-rs6742078 is a good proxy for its use in Mendelian randomization studies for CVD risk.