**CHRONOLOGICAL AGE-GENE INTERACTIONS IN DETERMINING THE EFFECTS OF THE CIRCADIAN MTNR1B GENE ON FASTING GLUCOSE**

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**Background and Objectives**: Age-dependent effects on fasting glucose have not been systematically investigated in genomic studies analyzing the effects of relevant genetic variants on cardiovascular risk phenotypes. We focused on the MTNR1B (Melatonin receptor 1B)-rs10830963 variant that has been associated with fasting glucose in several studies. This gene encodes a high affinity form of a receptor for melatonin, the primary hormone secreted by the pineal gland, under the control of the suprachiasmatic nucleus and consequently has a profound circadian rhythm. Aging is typically associated with both impairments of the circadian system and decreases in melatonin secretion. Our aim was to analyze whether the association between the MTNR1B-rs10830963 polymorphism and fasting glucose is age-dependent.

**Methods**: We carried out a cross-sectional study in 1378 participants (median age 41 years; 543 males and 835 females) in the OBENUTIC study, a case-control study in a Mediterranean population. Cases (n=301) were obese subjects and controls, non-obese subjects recruited from the general population. The MTNR1B-rs10830963 C>G polymorphism (665 CC, 565 CG and 148 GG) and fasting glucose were determined.

**Results**: As expected, the minor allele G was significantly associated with higher fasting glucose levels in the whole population. However, when the modulation by age (less or over 41 y), was analyzed we observed a strong gene-age interaction, in such a way that the increasing effect of the minor allele was only present in subjects aged less than 41 y (P-gene-age-interaction=0.004; multivariable adjusted). In non-diabetic subjects (n=1327), the adjusted means (mg/dL) for CC, CG and GG subjects were: 86.2+/-0.6, 88.7+/-0.6 and 92.4+/-1.1; P<0.05 in less than 41 y versus 95.1+/-0.6, 96.4+/-0.6 and 96.5+/-1.1; P>0.05 over 41 y).

**Conclusions**: The effect of the rs10830963 polymorphism on fasting glucose is age-dependent. Identification of gene-age interactions can provide insight into the biology and temporal regulation underlying gene-risk associations.