Common variants in MTNR1B (melatonin receptor 1B) influence fasting glucose and type 2 diabetes risk

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Fasting glucose (FG) levels usually are tightly regulated within a narrow physiologic range, and disruption of normal glucose homeostasis and elevation of FG are hallmarks of insulin resistance and type 2 diabetes (T2D). To identify novel loci that impact on FG we established MAGIC (Meta-Analyses of Glucose and Insulin-related traits Consortium), a collaborative effort of 10 individual studies represented by four consortia: ENGAGE (deCODE, NFBC66, NTR/NESDA, Rotterdam Study), GEM (CoLaus, TwinsUK), DFS (DGI, FUSION, SardiNIA) and the Framingham Heart Study. We initially exchanged the identities of 10-20 SNPs most prominently associated with FG from GWA scans in each study. All four groups (n=6,828-12,390) independently identified strong evidence for association at MTNR1B (melatonin receptor 1B), confirmed by meta-analysis of the 1Mb region flanking the gene (n=36,610; 381 SNPs). The risk allele of the SNP most strongly related to higher FG levels (per allele increase in FG 0.07 mmol/L [95% CI: 0.06-0.08]; P=1.1x10-41) also showed evidence of association with HOMA-B (P=1.0 x 10-15), as well as an increased risk of T2D (per allele odds ratio = 1.12 [95% CI: 1.07-1.18]; P=5.2 x 10-6) in a meta-analysis of six case-control studies totalling 7,625 cases and 45,419 controls. In addition, we confirm the previously reported associations of variants at the G6PC2 (P=7.1 x 10-49) and GCK (P=4.8 x 10-20) loci and FG levels. We conclude that MTNR1B is a novel candidate gene involved in FG regulation and T2D risk.