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Association of Nuclear – Mitochondrial Epistasis with BMI in Type 1 Diabetes Mellitus Patients

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Abstract : Obesity results from an imbalance between energy intake and its expenditure. Genome-Wide Association Study (GWAS) analyses have led to discovery of only about 100 variants influencing body mass index (BMI), which explain only a small portion of genetic variability. Analysis of gene epistasis gives a chance to discover another part. Since it was shown that interaction and communication between nuclear and mitochondrial genome are indispensable for normal cell function, we have looked for epistatic interactions between the two genomes to find their correlation with BMI. Methods: The analysis was performed on 366 T1DM patients using Illumina Infinium OmniExpressExome-8 chip and followed by imputation on Michigan Imputation Server. Only genes which influence mitochondrial functioning (listed in Human MitoCarta 2.0) were included in the analysis – variants of nuclear origin (MAF > 5%) in 1140 genes and 42 mitochondrial variants (MAF > 1%). Gene expression analysis was performed on GTex data. Association analysis between genetic variants and BMI was performed with the use of Linear Mixed Models as implemented in the package 'GENESIS' in R. Analysis of association between mRNA expression and BMI was performed with the use of linear models and standard significance tests in R. Results: Among variants involved in epistasis between mitochondria and nucleus we have identified one in mitochondrial transcription factor, TFB2M (rs6701836). It interacted with mitochondrial variants localized to MT-RNR1 (p=0.0004, MAF=15%), MT-ND2 (p=0.07, MAF=5%) and MT-ND4 (p=0.01, MAF=1.1%). Analysis of the interaction between nuclear variant rs6701836 (nuc) and rs3021088 localized to MT-ND2 mitochondrial gene (mito) has shown that the combination of the two led to BMI decrease (p=0.024). Each of the variants on its own does not correlate with higher BMI [p(nuc)=0.856, p(mito)=0.116)]. Although rs6701836 is intronic, it influences gene expression in the thyroid (p=0.000037). rs3021088 is a missense variant that leads to alanine to threonine substitution in the MT-ND2 gene which belongs to complex I of the electron transport chain. The analysis of the influence of genetic variants on gene expression has confirmed the trend explained above – the interaction of the two genes leads to BMI decrease (p=0.0308). Each of the mRNAs on its own is associated with higher BMI (p(mito)=0.0244 and p(nuc)=0.0269). Conclusıons: Our results show that nuclear-mitochondrial epistasis can influence BMI in T1DM patients. The correlation between transcription factor expression and mitochondrial genetic variants will be subject to further analysis.

Keywords : body mass index, epistasis, mitochondria, type 1 diabetes
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