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Whole exome sequencing on a large cohort of severely-obese individuals to investigate pancreatic β-cell function related protein-coding variants potentially protective against type 2 diabetes in the metabolically healthy non-diabetic group

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Objective: A non-trivial population of individuals manages to maintain non-diabetic range euglycemia despite being severely obese i.e. metabolically healthy obese (MHO). Our objective is to investigate protein-coding variants related to β-cell function that are potentially protective against type 2 diabetes (T2D) in a large group of severely obese individuals with and without T2D.

Materials and methods: Whole exome sequencing was performed on 186 subjects (104 non-T2D and 82 T2D; Age:41±10 years; 54.3% females; BMI:42.3±9.2kg/m²). Mutations in 16 β-cell-related genes (HNF1α, HNF1β, HNF4α, GCK, NEUROD1, PDX1, ABCC8, PPARG, KLF11, PAX4, INS, INSR, CEL, BLK, LMNA, and KCNJ11) known to cause monogenic diabetes were analyzed, stratified by diabetes status. Additionally, individual risk scores assigned to 8 variants in 5 β-cell genes encoding transcription factors (HNF1α/HNF1β/HNF4α/PAX4/PDX1) were combined into a single genetic risk score. Test for association was performed using Chi-square and Mann-Whitney tests.

Results: Non-T2D obese subjects showed robust β-cell compensation with declining insulin sensitivity, accounting for the higher glucose disposition index ($p<0.001$) compared to their T2D counterparts. There was no significant difference in the frequency of mutations in the 16 genes between subjects with and without T2D (all $p>0.05$). Twenty-six non-T2D and 19 T2D subjects had at least one potentially functional variant in the 5 transcription factor genes (prevalence $p=0.772$), and produced an aggregate risk score of 16.5 and 11 ($p=0.697$), respectively.

Conclusion: Non-T2D subjects demonstrated robust β-cell compensation in face of deteriorating insulin sensitivity. However, this cannot be explained by difference in protein-coding variants related to β-cell function candidate genes.