Title: Does summation of alleles account for genetic risk and genotype-phenotype association in Type 2 Diabetes Mellitus?

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Abstract

Introduction: Type 2 diabetes (T2DM) and metabolic syndrome are common complex disorders with a high prevalence in the Maltese population. The aim of this study is to further define the genetic interplay between cognate genes from metabolic and inflammatory pathways on the likelihood of developing T2DM in adulthood and to relate the association of certain genetic profiles with defined biological and clinical endpoints.

Method: Eight hundred carefully characterised T2DM cases were recruited. Anthropometric and biochemical parameters, including serum high-sensitivity C-Reactive protein (hsCRP) levels were determined, and genotyping of 43 cognate genes carried out. Neonatal cord blood samples were used as the control reference population in this study.

Results: Ten polymorphisms in metabolic/inflammatory pathways showed significant association with T2DM. Three loci showed significant association with lipid profile, body weight and hsCRP levels. hsCRP levels demonstrated a strong positive correlation with body mass index. Genetic score analysis showed that combining multiple genetic markers results in higher relative risks. The functional significance of these polymorphisms is being further evaluated using targeted siRNA-mediated silencing in cultured monocytes.

Conclusion: A panel of ten candidate genes has consistently demonstrated significant association with type 2 diabetes and metabolic syndrome in the Maltese population. These gene variants serve functional roles in inflammation and adipose tissue function. A recruited cohort of untreated newly-diagnosed T2DM serves to identify and explore genotype-phenotype association. The strong effect sizes of these alleles could be used to develop personal genetic susceptibility profiles for T2DM leading to personalization of care and prevention of chronic complications.