Molecular SNPlotypes™ with Common Alleles Reflects Expression Profile in Diabetes Mellitus Type 2 in two Mediterranean populations (Maltese and Libyans)

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**Introduction:** Type 2 Diabetes Mellitus (T2DM) is a complex and a heterogeneous group of metabolic conditions characterized by elevated levels of blood glucose, caused mainly by impairment of insulin action or insulin secretion, or both. The pathophysiology of T2DM is related to underling multiple genes.

**Objectives:** The objectives of the research where to explore the extent of the underlying genetic risk due to metabolic or inflammatory alleles in the comparative T2DM population of two Mediterranean countries (Malta and Libya). Furthermore, to evaluate the significance of genetic profiles expressed as SNPlotypes or SNPlotype score in diagnosis and therapeutics of T2DM and at the same time evaluating the possible pathophysiological and pharmacological significance of the alternate genetic profiles in cultured monocytes.

**Methods:** In this study 20 Single Nucleotide Polymorphisms (SNPs), originally that have been associated with T2DM in other populations, were characterized after PCR and RFLP using DNA samples from Maltese and Libyan T2DM patients, and their respective reference populations. Blood was also obtained from eight Maltese T2DM patients for use in monocyte cell culture experiments. The response to drugs (Insulin, Metformin and Glibenclamide) by the selected Maltese T2DM patients representing the different SNPlotypes was measured as a function of differential expression of a gene using RT-PCR on mRNA extracted from monocyte of Maltese T2DM patients.

**Results:** 7/20 cognate SNPs at different loci representing different genes (ADRAB2 [nt46 A→G], FABP2 [codon 54 G→A], UCP1 [nt3826 A→G], LEPTIN [nt -2549 C→A], IPF1 [codon 18 T→C], IL-6 [-174 G→C], TCF7L2 [IVS3 T→G]) showed significant association with T2DM having a significant odds ratio of 1.7 to 4.2. When the genetic data of the seven cognate SNPs was combined together in the form of a SNPlotype™, this enhanced the association with T2DM patients in the 2 populations.

**Discussion:** The seven selected genes represent inflammatory response genes, metabolic syndrome genes and MODY genes. The distribution of SNPs in the different SNPlotypes™ indicates that β2 adrenergic receptor is highly represented (44%) followed by FABP2 (44%), TCF7L2 (41%), Leptin (35%), IL6 (27%) and UCP1 (24%). The SNPlotype with the highest association in the population study was found to be significant and inherited together with the disorder in a family study. Only β2 adrenergic receptor (ADRAB2) transcripts were detected in the untreated and treated monocytes. The differential expression of ADRABβ2 indicates that there is a relation between the response to the drug and the SNPlotype of the patient. Interestingly, the expression of ADRABβ2 was downregulated in response to Insulin and Metformin in patients with SNPlotypes lacking the ADRABβ2 mutation, while the expression was upregulated in the other SNPlotypes. The outcome of ADRABβ2 mRNA transcript was dependent on patient SNPlotype™, when ranked by wildtype and mutant UCP1 and ADRABβ2 polymorphisms. In conclusion some metabolic and inflammatory alleles where characterized in the Maltese and Libyan populations. SNPlotype™ enhances the association to measure the risk for a particular disorder and we give evidence that it can be used to classify patients into potentially therapeutic groups.