A Prospective Metabonomics Analysis Reveals New Pathways Involved In T2D Development

Background & Objectives:
Characterization of the metabolic disruptions that precede the onset of T2D is critical for the screening of high risk individuals and hence the implementation of effective early interventions to prevent/delay the onset of T2D and its complications. Currently available predictors fail to grasp the complex etiology of T2D. Metabolomics profiling opened new horizons for biomarkers discovery; and associations of metabolomics and genotyping studies offers new prospects for the understanding of the physiology of complex traits like T2D. The aim of this study was the screening for novel predictors for T2D and the identification of associations between metabolic SNPs and metabolites as functional intermediate phenotypes.

Methods:
We used plasma collected from 1214 subjects from a 9 years follow up cohort for Non-targeted metabolomics. For genotyping we used a metabochip that assays nearly 200,000 SNPs of interest for metabolic disorders.

Results, and Conclusions:
We identified 491 named metabolites that are involved in 65 metabolic pathways. With a false discovery rate set at 5% (q<0.05) and after adjusting for BMI, sex and age, 109 metabolites were found to significantly associate with incident T2D (p<0.05). After adjusting for fasting glucose, 23 out of the 109 metabolites remained strongly associated with incident T2D (p from 3.12x 10^-3 to 1.7x10^-6). Of these, 1-palmitoylglycerol, 1,5-anhydroglucitol, 1-oleoylglycerol, mannose, alpha-ketobutyrate and gamma-glutamylphenylalanine showed the strongest associations (p from 1.310^-5 to 1.7x10^-6). When using the metabolite ratios between year 9 and baseline after adjustment for fasting glucose, the metabolite 1,5-anhydroglucitol showed the strongest association with incident T2D (p=1.2x 10^-9). Moreover, our analysis revealed a strong association of the metabolite mannose with the rs1260326 in the GCKR locus (p=8.8 10^-40). The GCKR gene is considered a susceptibility gene candidate for T2D. We found associations of other metabolites with 8 different SNPs but none of them with known T2D loci.

Abstract
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