PHYSIOGENOMICS OF THIAZOLIDINEDIONE EFFICACY AND SAFETY

i2 Poster Contributions
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Background: Optimizing the effect on HbA1c while avoiding weight gain and edema are keys to successful thiazolidinedione therapy. Previously we identified physiogenomic associations of SNPs in ADORA1 to weight gain and NPY to edema (Ruano et al., Clin Chim Acta 400:48-55, 2009). Here we apply physiogenomic analysis to HbA1c lowering.

Methods: 87 outpatients treated with pioglitazone or rosiglitazone at a Joslin Center Clinic (New Britain, CT) were characterized for HbA1c in addition to body mass index (BMI), and presence/absence of edema. We genotyped 347 SNPs (single nucleotide polymorphism) from our PhysioGenomic (PG) Array of 222 cardiometabolic and neuroendocrine genes.

Results: We discovered significant associations between the efficacy phenotype HbA1c and SNPs in five genes, of which the strongest association was to rs706713 in the gene PIK3R1 (phosphatidylinositol 3-kinase, regulatory subunit 1, p<0.001), a haplotype tagging synonymous SNP located in exon 1. Other associations were to ACACA (acetyl-Coenzyme A carboxylase alpha) rs8081866 (p<0.012), GNAO1 (G protein, alpha activating activity polypeptide-O rs4784642 (p<0.013), EDN1 (endothelin 1) rs5369 (p<0.014), and INSR (insulin receptor) rs4804103 (p<0.016), none of which were linked to BMI or edema. UCP3 (uncoupling protein 3) was moderately associated to both HbA1c and BMI.

Conclusions: We have found additional evidence supporting thiazolidinedione response phenotypes being modulated by separate pathways. The findings permit the construction of a safety/efficacy model that combines BMI, edema, and HbA1c reduction components. Pending further validation, we predict that such models can help clinicians minimize side effects and maximize efficacy in prescribing thiazolidinediones.