

Project Report on:

“Effects of *PPARGC1A* gene polymorphism on metabolism and obesity”

Applicant: Sebastian Kalamajski

**Rationale:** Common genetic variant in *PPARGC1A* (rs8192678 C/T) associates with obesity and type 2 diabetes, but its causality and function in adipocytes is largely unexplored. Understanding the impact of this variant on the adipocyte phenotype can provide more clues on the adipose biology in individuals expressing the different *PPARGC1A* variants.

**Questions:** The genetic variant in question is a missense mutation, which could affect the function of the *PPARGC1A* gene product (called PGC-1alpha). We asked how the different mutations affect the activity of PGC-1alpha in adipocytes, and what their implications are for adipocyte differentiation and fat storage capacity.

**Conclusions:** We used CRISPR to generate the missense mutations in *PPARGC1A* in an isogenic background in human white adipocytes. We observed that the minor allele of the rs8192678 polymorphism conferred faster adipocyte differentiation, faster lipogenesis, as well as faster turnover and activity of PGC-1alpha. We also observed that each copy of the T allele has an apparent linear additive effect on lipogenesis and fat storage.

**Importance:** Our study shows how a common genetic variant causes a dramatically altered function of a gene involved in energy metabolism, and determines adipocyte differentiation and lipogenesis. This improves our understanding on how and why this genetic variation is associated with type 2 diabetes and obesity.

Our study was published in *Diabetologia* on May 12 2023. Please see below for full title, author list, and DOI number.

**Engineered allele substitution at *PPARGC1A* rs8192678 alters human white adipocyte differentiation, lipogenesis, and PGC-1 $\alpha$  content and turnover**

Mi Huang, Melina Claussnitzer, Alham Saadat, Daniel E Coral, Sebastian Kalamajski# Paul W Franks#

# Equal contribution

PMID: 37171500

DOI: 10.1007/s00125-023-05915-6