Genetics of fasting and postprandial metabolite levels are overlapping

Li-Gao, R.; Mutsert, R. de; Rosendaal, F.R.; Dijk, K.W. van; Mook-Kanamori, D.O.

Genetics of fasting and postprandial metabolite levels are overlapping

**Ruifang Li-Gao,[1] Renée de Mutsert,[1] Frits R. Rosendaal,[1] Ko Willems van Dijk,[2,3]
and Dennis O. Mook-Kanamori[1,4]**

[1]*Department of Clinical Epidemiology; Leiden University Medical Center, Leiden, the Netherlands;* [2]*Department of Human
Genetics, Leiden University Medical Center, Leiden, the Netherlands;* [3]*Department of Medicine, Division of Endocrinology,
Leiden University Medical Center, Leiden, the Netherlands;* and [4]*Department of Public Health and Primary Care, Leiden
University Medical Center, Leiden, the Netherlands*

Li-Gao R, de Mutsert R, Rosendaal FR, Willems van Dijk K,
Mook-Kanamori DO. Genetics of fasting and postprandial metabo-
lite levels are overlapping. *Physiol Genomics* 50: 235–236, 2018. First
published January 26, 2018; doi:10.1152/physiolgenomics.00101.
2017.—In 2015, a genome-wide association study described 59 inde-
pendent signals that showed strong associations with 85 fasting
metabolite concentrations as measured by the Biocrates AbsoluteIDQ
p150 kit. However, the human body resides in a nonfasting state for
the greater part of the day, and the genetic basis of postprandial
metabolite concentrations remains largely unknown. We systemati-
cally examined these previously identified genetic associations in
postprandial metabolite concentrations after a mixed meal. Of these
85 metabolites, 23 were identified with significant changes after the
meal, for which 38 gene-metabolite associations were analyzed. Of
these 38 associations, 31 gene-metabolite associations were replicated
with postprandial metabolite concentrations. These data indicate that
the genetics of fasting and postprandial metabolite levels are signifi-
cantly overlapping.

metabolites; postprandial; replication; SNPs

BACKGROUND/MOTIVATION FOR THE STUDY

In 2015, a genome-wide association study described 59
independent signals that showed strong associations with a
wide range of metabolite concentrations as measured by the
Biocrates AbsoluteIDQ p150 kit (1). However, this study was
limited to metabolite concentrations in the fasting state, and the
human body resides in a nonfasting state for the greater part of
the day. Therefore, our objective was to examine these asso-
ciations within postprandial metabolite concentrations.

PHENOTYPE

Fasting blood samples were drawn in 478 middle-aged men
and women. Within the next 5 min after the fasting blood draw,
a liquid mixed meal [400 ml, 600 kcal, with 16% of energy
(En%) derived from protein, 50 En% carbohydrates, and 34
En% fat] was consumed, and subsequent blood samples were
drawn 150 min after the meal. Metabolomic measurements
were performed in the postprandial EDTA-plasma samples
with the Biocrates AbsoluteIDQ p150 assay. The metabolite
concentrations were logarithm-transformed to obtain normal
distributions.

Cohort details. This study was embedded in the Netherlands
Epidemiology of Obesity (NEO) study, a population-based
prospective cohort with 6,671 participants from the greater
area of Leiden (in the west of the Netherlands) (2). In 478
participants [56% men, mean (SD) body mass index (BMI)
30.4 (5.0) kg/m^2] the metabolite concentrations were measured
150 min after a mixed meal.

Type of study. Candidate single nucleotide polymorphisms
(SNPs).

Details of the SNPs studied. We set out to examine 123
genetic associations (59 independent signals with 85 unique
metabolites) with fasting metabolites reported in Draisma et.al
(1). on postprandial metabolite concentrations. After we
dropped the variants with low imputation quality (imputation
info <0.4) and/or minor allele frequency <0.01, 75 gene-
metabolite associations remained between 54 postprandial me-
tabolites and 47 unique SNPs for analysis (Supplemental Table
S1). (The online version of this article contains supplemental
material.)

Analysis model. We used paired *t*-tests to identify the me-
tabolites with significant changes ($P < 0.05$) after the meal.
Additive genetic models were used to assess the associations to
the postprandial metabolite concentrations by linear regres-
sions, adjusted for age, sex, BMI, and the first four principal
components. A *P* value<1.3E-3 (0.05/38, by Bonferroni cor-
rection of multiple testing) was considered as a successful
replication.

RESULTS

Of the 54 postprandial metabolites, 23 changed significantly
in concentration after the meal, involving 38 gene-metabolite
associations. Half of these 38 associations ($n = 19$) previously
identified based on fasting metabolites also revealed pro-
nounced associations to postprandial metabolites. For some
gene-metabolite associations the effect size was much larger
for the postprandial concentration than for the fasting concen-
tration, e.g., rs1171614 with acetyl-L-carnitine (C2)
($\beta_{postprandial} = -0.14$, *P* value = 8.45E-12 vs. $\beta_{fasting} =
-0.07$) and rs2238732 with proline ($\beta_{postprandial} = 0.24$, *P*
value = 3.64E-11 vs. $\beta_{fasting} = 0.18$) (Supplemental Table S2).

INTERPRETATION

In this study, we replicated half of the previously described
gene fasting-metabolite associations in postprandial metabo-
lites after a mixed meal with very high levels of significance.

Interestingly, some of the genetic signals were stronger as compared with fasting metabolite concentrations.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

R.L.-G. and D.O.M.K. analyzed data; R.L.-G. and D.O.M.K. interpreted results of experiments; R.L.-G. prepared figures; R.L.-G. drafted manuscript; R.L.-G., R.d.M., K.W.v.D., and D.O.M.K. edited and revised manuscript; R.L.-G., R.d.M., F.R.R., K.W.v.D., and D.O.M.K. approved final version of manuscript; R.d.M., F.R.R., and K.W.v.D. conceived and designed research.

REFERENCES

1. **Draisma HHM, Pool R, Kobl M, Jansen R, Petersen AK, Vaarhorst AAM, Yet I, Haller T, Demirkan A, Esko T, Zhu G, Böhringer S, Beekman M, van Klinken JB, Römisch-Margl W, Prehn C, Adamski J, de Craen AJM, van Leeuwen EM, Amin N, Dharuri H, Westra HJ, Franke L, de Geus EJC, Hottenga JJ, Willemsen G, Henders AK, Montgomery GW, Nyholt DR, Whitfield JB, Penninx BW, Spector TD, Metspalu A, Slagboom PE, van Dijk KW, 't Hoen PAC, Strauch K, Martin NG, van Ommen GB, Illig T, Bell JT, Mangino M, Suhre K, McCarthy MI, Gieger C, Isaacs A, van Duijn CM, Boomsma DI.** Genome-wide association study identifies novel genetic variants contributing to variation in blood metabolite levels. *Nat Commun* 6: 7208, 2015. doi:10.1038/ncomms8208.

2. **de Mutsert R, den Heijer M, Rabelink TJ, Smit JW, Romijn JA, Jukema JW, de Roos A, Cobbaert CM, Kloppenburg M, le Cessie S, Middeldorp S, Rosendaal FR.** The Netherlands Epidemiology of Obesity (NEO) study: study design and data collection. *Eur J Epidemiol* 28: 513–523, 2013. doi:10.1007/s10654-013-9801-3.