Author's response to reviews

Title: Extensive Alterations of the Whole-Blood Transcriptome are associated with Body Mass Index: Results of an mRNA Profiling Study involving two large Population-based Cohorts

Authors:

Georg Homuth (georg.homuth@uni-greifswald.de)
Simone Wahl (simone.wahl@helmholtz-muenchen.de)
Christian Müller (christian_m@gmx.net)
Claudia Schurmann (claudia.schurmann@mssm.edu)
Ulrike Mäder (ulrike.maeder@uni-greifswald.de)
Stefan Blankenberg (s.blankenberg@uke.de)
Maren Carstensen (maren.carstensen@ddz.uni-duesseldorf.de)
Marcus Dör (mdoerr@uni-greifswald.de)
Karlhans Endlich (karlhans.endlich@uni-greifswald.de)
Christian Englbrecht (che74@gmx.de)
Stephan B Felix (felix@uni-greifswald.de)
Christian Gieger (christian.gieger@helmholtz-muenchen.de)
Harald Grallert (harald.grallert@helmholtz-muenchen.de)
Christian Herder (Christian.Herder@ddz.uni-duesseldorf.de)
Thomas Illig (Illig.Thomas@mh-hannover.de)
Jochen Krupa (Jochen.Kruppa@med.uni-goettingen.de)
Carola S Marzi (carola.marzi@helmholtz-muenchen.de)
Julia Mayerle (mayerle@uni-greifswald.de)
Thomas Meitinger (Meitinger@helmholtz-muenchen.de)
Andres Metspalu (andres.metspalu@ut.ee)
Matthias Nauck (matthias.nauck@uni-greifswald.de)
Annette Peters (peters@helmholtz-muenchen.de)
Wolfgang Rathmann (rathmann@ddz.uni-duesseldorf.de)
Eva Reinmaa (eva.reinmaa@ut.ee)
Rainer Rettig (rettig@uni-greifswald.de)
Michael Roden (Michael.Roden@ddz.uni-duesseldorf.de)
Arne Schillert (arne.schillert@imbs.uni-luebeck.de)
Katharina Schramm (katharina.schramm@helmholtz-muenchen.de)
Leif Steil (steil@uni-greifswald.de)
Konstantin Strauch (strauch@helmholtz-muenchen.de)
Alexander Teumer (ateumer@uni-greifswald.de)
Henry Völzke (voelzke@uni-greifswald.de)
Henri Wallaschofski (henri.wallaschofski@hotmail.com)
Philipp S Wild (philipp.wild@unimedizin-mainz.de)
Andreas Ziegler (ziegler@imbs.uni-luebeck.de)
Uwe Völker (voelker@uni-greifswald.de)
Holger Prokisch (Prokisch@helmholtz-muenchen.de)
Tanja Zeller (t.zeller@uke.de)
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To
The Editors, *BMC Medical Genomics*

Dear Editor,

We would like to submit the manuscript entitled “Extensive Alterations of the Whole-Blood Transcriptome are associated with Body Mass Index: Results of an mRNA Profiling Study involving two large Population-based Cohorts” for publication as a research article in *BMC Medical Genomics*.

Following an editorial suggestion, we transferred this manuscript to *BMC Medical Genomics* after it was initially submitted at *BMC Medicine*, because it might be more suited for a specialist journal and audience. The content has not been changed.

In this transcriptome-wide association study (TWAS) we analyzed global mRNA levels in whole blood samples from 1,979 participants of two large population-based cohorts (SHIP-TREND and KORA F4) using array-based transcriptome profiling and screened for associations between body mass index (BMI) and specific mRNA abundances. The analysis revealed extensive BMI-associated alterations of the whole-blood transcriptome with 3,538 annotated genes whose transcript levels were significantly correlated with BMI. Subsequent *in-silico* analyses identified several canonical pathways exhibiting significant association with BMI. The transcriptome profiles indicate three distinct mRNA signatures in whole-blood suggesting that increased BMI is associated with: i) a ratio shift from mature erythrocytes towards reticulocytes, ii) reduced expression of genes critically involved in insulin signaling and iii) down-regulation of key genes mediating protection against oxidative stress.

Our findings are in line with the well-known associations between increased BMI on the one hand and insulin resistance and enhanced systemic oxidative stress on the other hand, as well as between increased systemic oxidative stress and insulin resistance. While it is clear that obesity raises the risk for type 2 diabetes the pathophysiological mechanisms underlying this association are still not completely understood. Our data suggest that an important pathophysiological link between increased BMI and its detrimental consequences might be the decreased expression of genes encoding key proteins involved in transduction and amplification of the insulin signal as well as in systemic protection against oxidative stress on the mRNA level. These results may contribute to the development of new strategies to counteract obesity-related type 2 diabetes.

A major strength of our study is its non-interventional population-based design, which essentially precludes effects that may be caused by weight reduction or similar programs in clinical studies. Furthermore, our data are based on samples from two large independent population cohorts. Our novel findings fit well within the spectrum of and significantly extend the current knowledge about the relation between BMI and type 2 diabetes. Therefore, we think that this manuscript might be suitable for publication in *BMC Medical Genomics* as its content is of special interest to the readership of the journal.

Sincerely yours,

Georg Homuth, Ph. D.
Uwe Völker, Ph. D.

On behalf of the MetaXpress Consortium