Supplemental Text

OVERLAP OF EWAS RESULTS AND PUBLISHED GWAS AND EWAS

To further examine the role of candidate genes in metabolic syndrome, we queried published GWAS results in the GWAS catalog (1) to determine if any of our candidate genes had been previously bookmarked a candidate gene in a GWAS for cardiovascular or metabolic traits. Overall, we found 7 candidate genes associated with EWAS hits in the current study have been previously associated with metabolic or cardiovascular. For example, we found that *LINC01317* is associated with insulin sensitivity index (MATSUDA) using EWAS, and a GWAS to Glomerular filtration rate reported a significant association with a SNP (rs10495809) in an intron of *LINC01317* (2). *CPEB4* is associated OGTT plasma insulin levels, insulin sensitivity index (MATSUDA), and insulin resistance index (HOMAIR) in the current EWAS, and was previously reported as a bookmark gene for a SNP ((s7705502) reported in a GWAS to waist-to-hip ratio adjusted for body mass index (3). *CPEB4* is also a strong *cis*-eQTL in adipose tissue (Table1, p=2.4x10^{-174}), making it an excellent candidate gene associated with diabetes in humans. Although the traits associated with the candidate genes are different in the current EWAS and published GWAS, these findings lend additional support to the involvement of these candidate genes in diabetes traits. Results for all candidate genes are summarized in Table S2.

In addition, to published GWAS associations, four of the candidate genes have been previously shown to influence diabetes and/or obesity, including the fatty acid synthase gene *FASN* and the transcription factor *RXRA,* a well-known regulator of metabolism. The mismatch repair genes *MSH2* and *MSH6* were previously linked to BMI in humans (4), and in the current study they are associated with BMI, waist circumference, and percent fat mass.

A recent EWAS study examined association of BMI and DNA methylation levels measured from blood using methylation arrays, in a human population of 10,774 individuals (5). They identified 278 in CpG sites associated with BMI at ($p< 1\times10^{-7}$), distributed across 207 loci, and replicated 187 of these. The published EWAS and the current study both examine BMI as a trait, however we used both different cell-types (blood in the published work, and adipose tissue in our study), and different methods of measuring methylation levels (microarrays versus bisulfite sequencing in our study). Hence to be able to compare our EWAS results with this published study, we focused on the overlap of the nearest candidate gene to each locus, and found that *SBNO2*

was associated with BMI in the published EWAS by Wahl and colleagues, and was associated with both BMI and body weight. Additionally, the disparity in sample size (201 vs 10,774) suggest the current study is underpowered to detect all overlapping signals.

REFERENCES

1. MacArthur, J., Bowler, E., Cerezo, M., Gil, L., Hall, P., Hastings, E., Junkins, H., McMahon, A., Milano, A., Morales, J., *et al.* (2017) The new NHGRI-EBI Catalog of published genome-wide association studies (GWAS Catalog). *Nucleic Acids Research* , **45**, D896–D901.
2. Wuttke, M., Wong, C.S., Wuhl, E., Epting, D., Luo, L., Hoppmann, A., Doyon, A., Li, Y., Sozeri, B., Thurn, D., *et al.* (2016) Genetic loci associated with renal function measures and chronic kidney disease in children: the Pediatric Investigation for Genetic Factors Linked with Renal Progression Consortium. *Nephrol. Dial. Transplant* , **31**, 262–269.
3. Shungin, D., Winkler, T.W., Croteau-Chonka, D.C., Ferreira, T., Locke, A.E., Magi, R., Strawbridge, R.J., Pers, T.H., Fischer, K., Justice, A.E., *et al.* (2015) New genetic loci link adipose and insulin biology to body fat distribution. *Nature* , **518**, 187–196.
4. Joehlin-Price, A.S., Perrino, C.M., Stephens, J., Backes, F.J., Goodfellow, P.J., Cohn, D.E., and Suarez, A.A. (2014) Mismatch repair protein expression in 1049 endometrial carcinomas, associations with body mass index, and other clinicopathologic variables. *Gynecol. Oncol.* , **133**, 43–47.
5. Wahl, S., Drong, A., Lehne, B., Loh, M., Scott, W.R., Kunze, S., Tsai, P.C., Ried, J.S., Zhang, W., Yang, Y., *et al.* (2017) Epigenome-wide association study of body mass index, and the adverse outcomes of adiposity. *Nature* , **541**, 81–86.