00466 A Network Genetics Approach to Elucidate Causal Mechanisms Underlying Body Fat Distribution

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Aims: Although genome-wide association studies (GWAS) have identified a large number of traitassociated genetic variants, our understanding of the functional impact and site of action of disease-associated variants remains poor. Tissue level investigation of the associations can generate insight into the functional effects of the disease associated loci. Here we have conducted tissue specific network analysis of BMI-adjusted Waist to Hip ratio (WHRadjBMI), an index of body fat distribution and a marker of cardiometabolic risk, in up to 224,459 individuals of largely European descent.

Methodology: Summary statistics (p-values) from a GWAS meta-analysis of WHRadjBMI were converted to gene-level statistics via the maximum of chi-squared method in Pascal. Nominally significant genes (p<1E-07) were queried for connectivity enrichment in 145 tissue-specific networks (NetWAS scores) from GIANT (giant.princeton.edu). Tissues showing higher overall connectivity to GWAS genes were identified via area receiver operating curve (ROC-AUC) method. An adipose tissue specific network was further queried via weighted key driver analysis (wKDA) to identify putative causal drivers of the tissue network.

Result: 91 genes were nominally significant to WHadjBMI (association P <1e-07). AUC analysis of tissue-specific networks identified adipose tissue, adrenal gland, kidney, brain and intestine to be of higher relevance to WHRadjBMI. Subnetwork analysis demonstrated high network connectivity for HOXA5 and TBX15 in adipose tissue, brain and kidney, CEBPA in brain, and HOXC10 in adipose tissue and kidney. wKDA analysis on an adipose tissue functional interaction network identified the transcription factors HLF, NFIL3, DBP, TEF and the MHC Class II genes HLA-DQA1 and HLA-DQB1 as potential key network regulators (FDR<0.001).

Conclusion: Network genetics of WHRadjBMI sheds light on the inter-connectivity of several traitassociated genes in key metabolic tissue and helps formulate testable hypothesis for the validation for functional effects. Thus network based approaches provide a path forward for efficient prioritization of GWAS hits.