A Genome-wide Meta-analysis of the Combined Influence of Physical Activity and Genetic Variants on Body Fat Distribution in 94,779 Individuals of European Descent

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Central adiposity, assessed by waist-to-hip ratio (WHR), has been associated with increased risk for cardiovascular disease. Both genetic and lifestyle factors, including physical inactivity, have been independently associated with WHR adjusted for BMI (WHRadjBMI). Physical activity (PA) is an important component of interventions for reducing or preventing central adiposity and has been shown to attenuate genetic influences on adiposity. However, the influence of PA on loci associated with central fat, independent of total body fat, is unknown. Our objective was to identify genetic variants whose effects on WHRadjBMI are modified by PA. To this end, we performed a meta-analysis of 36 genome-wide association studies, including 94,779 individuals of European ancestry. PA was standardized within each study (physically active and inactive) with the lowest quintile being defined as inactive. WHR was adjusted for BMI, age, and age² in men and women separately. Each study tested the SNP x PA interaction alone, and also tested the joint effects of both the interaction and SNP main effect using a two degree of freedom (2df) test. We pooled the results from individual studies using fixed-effects inverse variance weighted meta-analysis in men and women combined and separately. The 2df joint test reached genome-wide significance (p<5e⁻⁸) for 23 loci, which included 11 novel loci for WHRadjBMI. Of these 11 loci, 7 were identified in women only, and one in men only. For each of the 23 loci, the association of the joint test was primarily driven by the SNP main effect on WHRadjBMI, rather than its interaction with PA. When we examined the interaction effects of the 23 loci, separately from main effect, the interaction reached nominal significance for 11 loci (5 of these were novel): e.g. established loci in/near LYPLAL1 (p=1.0e⁻⁷), VEGFA (p=3.8e⁻⁵), TBX15 (p=2.1e⁻⁵ in women), and RSPO3 (p=5.6e⁻³), and novel (in women only), in/near TMEM131 (p=3.2e⁻⁴), FAM186A (p=4.1e⁻⁴), and FLJ45974 (p=1.9e⁻³). In each case, the effect of the WHRadjBMI-increasing allele was smaller in the active group than in the
inactive group; e.g. for the SNP near \textit{LYPLAL1}, in the active versus inactive: $\beta[SE] = 0.024(0.036)$ vs $0.215(0.084)$, respectively. For the interaction term alone, no loci reached genome-wide significance, but a search at $P<1e^{-6}$ revealed 3 additional novel loci; 2 in men and women combined (in/near \textit{MYO18B} and \textit{COX11P}) and 1 in men only (in \textit{SNW1}). Our findings suggest that joint tests of main and interaction effects help elucidate the genetic basis of abdominal obesity and that genetic effects are larger in physically inactive compared to active individuals. To follow-up our initial findings, we are currently collecting data from 25 additional studies with genome-wide or MetaboChip data.

\textbf{Author Disclosure Block:}