A Genome-wide meta-analysis of the combined influence of physical activity and genetic variants on body fat distribution in over 94,000 individuals of European descent

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On behalf of the GIANT consortium
03-21-2014

We have nothing to disclose.
Waist and Waist-to-Hip ratio (WHR) are measures of Central Adiposity

Central Adiposity:
- Waist circumference >102 cm in men and >88 cm in women
- Waist–hip ratio >0.9 for men and >0.85 for women

Insulin Resistance
High Triglycerides
High Blood Pressure
High cholesterol

Genes
Lifestyle factors

Central Adiposity:
Waist circumference >102 cm in men and >88 cm in women
Waist–hip ratio >0.9 for men and >0.85 for women
Meta-analysis identifies 13 new loci associated with waist-hip ratio and reveals sexual dimorphism in the genetic basis of fat distribution

Iris M Heid, Anne U Jackson, Joshua C Randall, Thomas W Winkler, Lu Qi, Valgerdur
Main Questions

1- Are there genome-wide differences between ACTIVE and INACTIVE Strata?
   -Does higher activity attenuate (or lower activity exacerbate) the associations between Genetic Loci and Waist-to-hip ratio?

2- Are there underlying differences by activity status that are masking unidentified loci associated with Waist-to-hip ratio?
The Genetic Investigation of ANthropometric Traits (GIANT) consortium

• Focuses on exploring the genetics of anthropometric traits.
  – Analyses have included over 90 genome-wide studies and 25 metabochip studies.
  – Primarily European Descent
**Study Design**

Genome-wide scan by activity status on waist-to-hip ratio **adjusted for BMI**

**Stage 1:**
38 GWAS: ACTIVE and INACTIVE individuals

- Meta-analyze ACTIVE and INACTIVE
- Compare ACTIVE vs. INACTIVE

**Stage 2:**
25 GWAS or Metabochip studies: ACTIVE and INACTIVE individuals

- Meta-analyze ACTIVE and INACTIVE
- Compare ACTIVE vs. INACTIVE

**Stage 1+2:**
ACTIVE and INACTIVE individuals

- Meta-analyze ACTIVE and INACTIVE
- Compare ACTIVE vs. INACTIVE
Standardization of Physical Activity

Qualitative or categorical data

INACTIVE:
• Sedentary occupation
• <1hr/wk of moderate-to-vigorous physical activity

ACTIVE: All Others

Quantitative or measured data

INACTIVE:
• 20% lowest age- and sex-specific physical activity levels

ACTIVE: All Others

Total Sample ACTIVE: 27,016 Men & 47,288 Women
Total Sample INACTIVE: 7,223 Men & 11,502 Women
Analytic Approach
1- Are there genome-wide differences between ACTIVE and INACTIVE Strata?

Z-test for differences

\[ \beta(\text{se}) \quad \text{INACTIVE} \quad \text{vs} \quad \beta(\text{se}) \quad \text{ACTIVE} \]

Genome-wide significance at \( p<5E-08 \)
Analytic Approach
2- Are the underlying differences masking unidentified loci associated with Waist-to-hip ratio?

Joint Test

Marginal Effect

β(se)
INACTIVE and ACTIVE

+ 

Activity Differences

β(se)
INACTIVE

vs

β(se)
ACTIVE

Genome-wide significance at p<5E-08
1- Are there genome-wide differences between ACTIVE and INACTIVE Strata?

![P-values for Difference
Active versus Inactive](chart.png)

- rs4235521
  - p = 5.1E-08
- p = 5E-06
- p = 5E-06

Women

Men
Effect sizes of loci with P-value $<5 \times 10^{-06}$ for difference between ACTIVE and INACTIVE Men

Per allele change in WHR

ACTIVE MEN

INACTIVE MEN

CD48
SPAG16
CDH12
EFNA5
DOCK4-ZNF277
PTER
FLT1
ANKRD5
Effect sizes of loci with P-value < 5e^-06 for difference between ACTIVE and INACTIVE Women

Per Allele Change in WHR
2- Are the underlying differences masking unidentified loci associated with Waist-to-hip ratio?
Joint P-value largely driven by SNP main effect

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<tr>
<th>Gene</th>
<th>P-value for Difference</th>
<th>Joint P-value</th>
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<tr>
<td>LYPLAL1</td>
<td>0.007</td>
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<td>CCDC92</td>
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<td>RSPO3</td>
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<td>VEGFA</td>
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<td>HOXC13</td>
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<td>ITPR2-SSPN</td>
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<td>GRB14</td>
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<td>DNM3-PIGC</td>
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<tr>
<th>Gene</th>
<th>P-value for Difference</th>
<th>Joint P-value</th>
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<tbody>
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<td>GDF5</td>
<td>0.011</td>
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Conclusions

• No loci reach genome-wide significant for difference of effect between INACTIVE and ACTIVE

  – Magnitude of effect sizes between loci at p<5e-06 appears larger in INACTIVE compared to ACTIVE

• Joint test did not reveal additional novel loci

  • Little difference in effect between INACTIVE and ACTIVE at strata.

• There are challenges in defining activity status across several studies.
Future Direction

• Stage 2 will include 25 additional GWAS and Metabochip studies.

• Compare results of differences in activity strata in European Cohorts only versus US cohorts only.

• Compare results of differences in activity strata for Cohorts with quantitative or measured data versus qualitative only data.
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GIANT GxE - Approach 2:

Model 3 SNPadjE Stage 1+2 results ($P_{\text{main}}$)

- $P_{\text{main}} < 1e-5$
- $P_{\text{main}} < 5e-8$

Test difference between strata

Power to detect difference between two strata:

- $N = 200K$
- 2 strata (equal size, e.g. men and women)

Fix effect size in women, using $R^2$ of PPARG in previous GIANT analyses on WHRadjBMI:

$R^2_{\text{women}} = 0.00057$

Thomas Winkler 14-03-06
1. Concordant direction but different magnitude: e.g. $\beta_m > \beta_w$, $\beta_{>50} < \beta_{\leq 50}$

Filter on combined P-Value $< 10^{-5}$
e.g. $+\beta_m = -\beta_w$,
$-\beta_{>50} = +\beta_{\leq50}$