Genes, physical activity and obesity

actions and interactions

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Overview

- Where do genes fit in?
- Genetics epidemiology of physical activity
  - Heritability
  - Candidate gene approach
  - Genome-wide scans
- Gene-physical activity interaction
- Summary & conclusions
Genes & physical activity

Physical activity as an **outcome**
Genes & physical activity

Physical activity as an *intermediate factor*
Genes & physical activity

Physical activity as an *interactor*
Physical activity as a **effector**
Genes & physical activity

Physical activity as an outcome

Physical activity as an interactor
Overview

- Where do genes fit in?
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Is physical activity heritable?

**Heritability studies**

**Twin studies**
- Identical / MZ

**Fraternal / DZ**

**Family studies**
- Multi-generational
Is physical activity heritable?

**Heritability studies**

<table>
<thead>
<tr>
<th>Twin studies</th>
<th>Family studies</th>
</tr>
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<tbody>
<tr>
<td>$h^2 = 0 - 78%$</td>
<td>$h^2 = 0 - 57%$</td>
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</table>

**Reasons for the wide range**
- Difference in assessing physical activity
- Age of study population
- Methods for estimating heritability
- Sample size, and thus statistical power for analyses
The classical twin study design to assess heritability

**Basic assumptions**

MZ twins:  100% genes in common  
DZ twins:  50% genes in common

100% shared environment in common

**Basic statistic**

Intra-pair correlations

**Quick and simple:**  Falconer’s formula:  
$$h^2 = 2[r_{MZ} - r_{DZ}]$$

**More refined:**  structural equation modeling:  
$$V = V_a + V_c + V_e$$
A large twin study with objectively assessed physical activity

**TwinsUK**
- 419 pairs of MZ twins
- 352 pairs of DZ twins

**Physical activity assessment**
- 7-day monitoring (96% had >4 days)
- Heart rate monitors
- accelerometer

![Acceleration and Heart rate](image-url)
A large twin study with objectively assessed physical activity

Descriptives

<table>
<thead>
<tr>
<th>Trait</th>
<th>MZ-twins</th>
<th>DZ-twins</th>
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</thead>
<tbody>
<tr>
<td>N twins (pairs)</td>
<td>838 (419)</td>
<td>704 (352)</td>
</tr>
<tr>
<td>N women (pairs)</td>
<td>810 (405)</td>
<td>702 (351)</td>
</tr>
<tr>
<td>age (yrs)</td>
<td>56 ± 11</td>
<td>56 ± 10</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.8 ± 4.6</td>
<td>26.3 ± 4.9</td>
</tr>
<tr>
<td>PAEE (kJ/kg/day)</td>
<td>38.0 (29.0 - 47.6)</td>
<td>36.0 (27.9 - 45.2)</td>
</tr>
<tr>
<td>PAEE (kJ/day)</td>
<td>2550 (1923 - 3134)</td>
<td>2376 (1869 - 3063)</td>
</tr>
<tr>
<td>Sedentary (1 MET, min/d)</td>
<td>638 ± 108</td>
<td>646 ± 117</td>
</tr>
<tr>
<td>Light (1-3 METs, min/d)</td>
<td>725 ± 108</td>
<td>721 ± 113</td>
</tr>
<tr>
<td>MVPA (&gt;3 METs, min/d)</td>
<td>67 (39 - 104)</td>
<td>61 (38 - 96)</td>
</tr>
<tr>
<td>Actiheart wear time (d)</td>
<td>6.8 ± 1.2</td>
<td>6.8 ± 1.1</td>
</tr>
</tbody>
</table>

82% adhere to the physical activity guidelines
A large twin study with objectively assessed physical activity

Intra-pair correlations

<table>
<thead>
<tr>
<th>Trait</th>
<th>MZ_{ICC}</th>
<th>DZ_{ICC}</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAEE (kJ/day)</td>
<td>0.47</td>
<td>0.22</td>
</tr>
<tr>
<td>Sedentary (min/day)</td>
<td>0.42</td>
<td>0.14</td>
</tr>
<tr>
<td>Light (min/day)</td>
<td>0.42</td>
<td>0.14</td>
</tr>
<tr>
<td>MVPA (min/day)</td>
<td>0.45</td>
<td>0.20</td>
</tr>
</tbody>
</table>

\[ MZ_{ICC} = 0.47 \]
\[ DZ_{ICC} = 0.22 \]
A large twin study with objectively assessed physical activity

Structural equation modeling

Explained variance

- PAEE
- Sedentary
- Light
- MVPA

Heritability of daily physical activity 43-49%
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Candidate gene approach

= hypothesis-driven, based on the current understanding of the biology and pathophysiology of the trait/disease
Candidate gene approach

Animal studies

**DRD2**
(dopamine receptor D2)

**MC4R**
(melanocortin 4 receptor)

Reward and aversion


Craving and need

Candidate gene approach

Animal studies

Overexpression of the Cytosolic Form of Phosphoenolpyruvate Carboxykinase (GTP) in Skeletal Muscle Repatterns Energy Metabolism in the Mouse

Received for publication, July 25, 2007, and in revised form, August 21, 2007. Published, JBC Papers in Press, August 23, 2007. DOI 10.1074/jbc.M706127200

Parvin Hakimi†, Jiangqi Yang†, Gemma Casadesus§, Duna Massillon†, Fatima Tolentino-Silva**+, Colleen K. Nye‡, Marco E. Cabrera***, David R. Hagen†, Christopher B. Utter†, Yacoub Baghdy†, David H. Johnson†, David L. Wilson†, John P. Kirwan†,† Satish C. Kalhan†,† and Richard W. Hanson†

From the Departments of †Biochemistry, ‡Nutrition, **Pediatrics, §Neuroscience, and ††Biomedical Engineering. Case Western Reserve University School of Medicine, Cleveland, Ohio 44106-4935 and the ‡†Department of Gastroenterology/Hepatology and Pathobiology, Cleveland Clinic Foundation, Cleveland, Ohio 44195

Effect on ability, pain

Home cage activity

![Graph showing effect on ability, pain and home cage activity]
Common genetic variation - SNPs

SNP → Single Nucleotide Polymorphism
Genetic associations

The ‘additive’ model tests whether the A-allele increases PAEE significantly.

p-value = 0.###
beta (effect) = 1.4 kJ/kg/day

<table>
<thead>
<tr>
<th>Genotype</th>
<th>PAEE (kJ/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T/T</td>
<td>25.2</td>
</tr>
<tr>
<td>A/T</td>
<td>26.6</td>
</tr>
<tr>
<td>A/A</td>
<td>27.9</td>
</tr>
</tbody>
</table>
Candidate gene approach

Human studies

MC4R

Melanocortin-4 receptor gene and physical activity in the Québec Family Study

RJF Loos¹, T Rankinen¹, A Tremblay², L Pérusse², Y Chagnon³ and C Bouchard¹*

¹Human Genomics Laboratory, Pennington Biomedical Research Center, Baton Rouge, LA, USA; ²Physical Activity Sciences Laboratory, Laval University, Ste-Foy, Québec, Canada; and ³Genetic Psychiatry, Laval University Robert-Giffard Research Center, Béarport, Québec, Canada

- 669 individuals of the Québec Family Study
- Physical activity assessed by 3-day diary, every 15min
Candidate gene approach

Human studies

**MC4R**

![Graph showing physical activity counts](image)

- Total: p = 0.08
- Moderate-to-strenuous: p = 0.005
- Inactivity: p = 0.01

<table>
<thead>
<tr>
<th>Physical Activity Counts</th>
<th>C/C</th>
<th>C/T</th>
<th>T/T</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate-to-strenuous</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactivity</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>
Candidate gene approach

Human studies

\textit{PCK1}

- 2,101 boys and girls from European Youth Hearth Study
  - 1,255 9-y olds
  - 846 15-y olds
- Denmark and Estonia
- Physical activity - MTI accelerometer

\*sex, age, age-group, standardised height, maturity and country
Candidate gene approach

**Human studies**

**PCK1**

<table>
<thead>
<tr>
<th>PCK1 SNPs</th>
<th>Physical Activity counts</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs1042521</td>
<td>620</td>
<td>0.87</td>
</tr>
<tr>
<td>rs1042531</td>
<td>610</td>
<td>0.57</td>
</tr>
<tr>
<td>rs138756</td>
<td>620</td>
<td>0.68</td>
</tr>
<tr>
<td>rs207055</td>
<td>610</td>
<td>0.65</td>
</tr>
<tr>
<td>rs2071023</td>
<td>620</td>
<td>0.67</td>
</tr>
<tr>
<td>rs2179706</td>
<td>610</td>
<td>0.67</td>
</tr>
<tr>
<td>rs2859554</td>
<td>620</td>
<td>0.33</td>
</tr>
<tr>
<td>rs6025517</td>
<td>610</td>
<td>0.95</td>
</tr>
<tr>
<td>rs6070157</td>
<td>620</td>
<td>0.63</td>
</tr>
<tr>
<td>rs707555</td>
<td>610</td>
<td>0.07</td>
</tr>
</tbody>
</table>

*p* = 0.87, 0.57, 0.68, 0.65, 0.67, 0.33, 0.95, 0.63, 0.07

*Sex, age, age-group, standardised height, maturity and country*
Candidate gene approach - literature overview

**Human studies**

### Craving and need
- Melanocortin 4 receptor (*MC4R*)
- Leptin receptor (*LEPR*)

- Loos *et al.* (IJO, 2005): Association with moderate-to-strenuous PA (p=0.005) in the QFS.
- Stefan *et al.* (IJO, 2002): Association with total PA in Pima Indians (p=0.007)
- de Moor *et al.* (MSSE, 2009) Association with leisure time PA in Americans (p=0.0005)

### Reward and aversion
- Dopamine 2 receptor (*DRD2*)

- Simonen *et al.* (Physiology & Behavior, 2009): Association with physical activity, sports participation, and occupational activity (p=0.05) in the QFS and HERITAGE.

### Effect on ability, pain
- Calcium sensing receptor (*CASR*)
- Angiotensin-converting enzyme (ACE)

- Lorentzon *et al.* (EJE, 2009): Association with hours spent on physical activity per week in adolescent girls (p=0.01)
- Winnicki *et al.* (AJMG, 2004): Association with leisure time physical activity per week in hypertensives (p=0.001)
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• Where do genes fit in?

• Genetics epidemiology of physical activity
  • Heritability
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  • Genome-wide scans

• Gene-physical activity interaction

• Summary & conclusions
Genome-wide scans

= hypothesis-generating, to identify new, unanticipated, genes and thus expand view of biology and physiology of disease/trait
Genome-wide scans

Genome-wide analyses

Genome-wide linkage analyses
aim to identify a *crude* chromosomal location of the
gene or genes associated with a phenotype of interest

Genome-wide association analyses
aim to identify an *exact* chromosomal location of
the genetic variant associated with a phenotype of
Genome-wide linkage studies

A Quantitative Trait Locus on Chromosome 18q for Physical Activity and Dietary Intake in Hispanic Children

Guowen Cai,* Shelley A. Cole,† Nancy Butte,* Carlos Bacino,* Vincent Diego,† Karen Tan,‡ Harald H. Göring,† Stephen O’Rahilly,‡ I. Sadaf Farooqi,‡ and Anthony G. Comuzzie†

- 1,030 sibling of 319 Hispanic families
- Physical activity - accelerometer
Genome-wide *linkage* studies

*Figure 1*: The genome-wide screening of sedentary activity (percentage of awake time) in Hispanic children.

*Figure 2*: The multipoint linkage analyses of physical activity levels on chromosome 18.
Genome-wide association studies

STAGE 1 - Discovery stage
- Determine genotype of up to 2,500,000 genetic variants (SNPs)
- Case-control or cohort studies
- Large amount of tests → significance threshold $p < 0.000001$

STAGE 2 - Replication/follow-up stage
- 1-100 SNPs that represent top loci
- Case-control or cohort studies – at least equal size of discovery panel
- Meta-analysis of stage 1 & 2 results
Published Genome-wide Associations

>1,700 published GWA at $p<5 \times 10^{-8}$

NHGRI GWA Catalog
www.genome.gov/GWAStudies

06/2012
Genome-wide *association* for physical activity

**Aim:** Large-scale genome-wide meta-analysis on five physical activity traits

**Outcomes of interest:**
1. Moderate-to-vigorous intensity leisure time activities
2. Sedentary behavior during commuting
3. Sedentary behavior at work
4. TV viewing
5. Other sedentary behavior at home

**Genome-wide genotypes:**
2.5 million genetic variations across the autosomal genome

**Study design Stage 1 (discovery):**
33 studies with required data were invited, up to 82,000 individuals
Study-specific analyses plans sent out (customized by questionnaire)
Meta-analyses of summary statistics (for each of the 2.5 million variants)

**Study design Stage 2 (follow-up):**
>40 studies with required data have been invited, expect data from up to 80,000 individuals
Follow-up of 56 genetic variants with promising association (p < 10^-6) in stage 1
Genome-wide association for physical activity

Sedentary commuting to work (vs active commuting to work)
Genome-wide association for physical activity

TV viewing
Genes for physical activity

Candidate gene studies
Even though animal studies have identified credible proteins that affect physical activity, genetic variants in the encoding genes are not (yet) convincingly associated with daily physical activity levels in humans.

Genome-wide linkage studies
Even though one study provided suggestive confirmation for the MC4R locus, results have not been firmly confirmed.

Genome-wide association studies
Large-scale meta-analysis is on-going;
- stage 1 results are promising
- stage 2 results will soon be available!

First results are emerging, but much more work is needed!
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Genes & physical activity

Does physical activity attenuate the association between genotype and outcome?

Does genotype attenuate the association between physical activity and outcome?
Physical activity, FTO and obesity-susceptibility

Physical activity attenuates the body mass index–increasing influence of genetic variation in the FTO gene\(^1-^3\)

Karani S Vinaleswaran, Shengxi Li, Jing Hua Zhao, Jian’an Luan, Sheila A Bingham, Kay-Tee Khaw, Ulf Ekelund, Nicholas J Wareham, and Ruth JF Loos


- 17,619 men and women of the EPIC-Norfolk study (40-75y), with self-reported physical activity levels.
Overview of the literature on FTOxPA interaction and BMI

<table>
<thead>
<tr>
<th>Interaction</th>
<th>No interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPIC-Norfolk (n=20,374)</td>
<td>Malmö PP (n=15,925)</td>
</tr>
<tr>
<td>KSNP (n=8,842)</td>
<td>DESIR (n=4,640)</td>
</tr>
<tr>
<td>Inter 99 (n=5,922)</td>
<td>NHS98 (n=4,210)</td>
</tr>
<tr>
<td>MDC (n=4,810)</td>
<td>NFBC66 (n=4,022)</td>
</tr>
<tr>
<td>NFBC86 (n=4,780)</td>
<td>Botnia PP (n=2,511)</td>
</tr>
<tr>
<td>BCAMS (n=3,503)</td>
<td>TRAILS (n=1,230)</td>
</tr>
<tr>
<td>ULSAM (n=1,115)</td>
<td>Liu G, et al.</td>
</tr>
<tr>
<td>HAPI Heart (n=702)</td>
<td>Obesity 2009;17:832-6</td>
</tr>
<tr>
<td>Rampersaud E, et al.</td>
<td></td>
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<tr>
<td>Arch Intern Med 2008;168:1791-7</td>
<td></td>
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<tr>
<td>HELENA (n=752)</td>
<td></td>
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<tr>
<td>Ruiz JR, et al.</td>
<td></td>
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<tr>
<td>Arch Pediatr Adolesc Med 2010;164:328-33</td>
<td></td>
</tr>
<tr>
<td>Greek adol. (n=499)</td>
<td></td>
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<tr>
<td>Scott RA, et al.</td>
<td></td>
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<tr>
<td>Eur J Hum Genet 2010 Aug 18</td>
<td></td>
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</tbody>
</table>
De novo meta-analysis of all available data

Study design

- Contact all cohorts that have published on the FTO locus (and that are known to have physical activity data).
- ‘Harmonise’ physical activity data across cohorts (i.e. questionnaire, diary, accelerometry, ...).
  → Dichotomise: active vs sedentary – custom definition for each cohort
- Ask cohorts to (re-)analyse data according to detailed analysis plan.

Data collection & analysis

- 45 studies – 218,166 individuals
- Meta-analyses of the interaction term
- Stratified meta-analyses of active and sedentary individuals

### Results

**North America** (n=47,938)

- DPP Asian: 0.70 (-3.10, 4.50)
- WHI-OS Asian: -1.15 (-3.40, 1.09)
- WHI-OS Hispanic: 1.40 (-0.85, 3.45)
- DPP Hispanic: -0.16 (-1.82, 1.51)
- DPP African American: -0.16 (-1.88, 1.57)
- BLSA: 0.15 (-0.74, 1.05)
- GFS: -1.20 (-3.42, 1.02)
- HAPI: -0.91 (-1.57, 0.16)
- FAMHS: 0.19 (-1.04, 1.43)
- WHI-OS African American: -1.25 (-2.63, 0.13)
- WHI-OS White: -0.55 (-1.62, 0.51)
- DPP White: -0.32 (-1.28, 0.64)
- NHS & HPFS cases: -0.83 (-1.51, -0.14)
- NHS & HPFS controls: -0.26 (-0.84, 0.33)
- ARIC: -0.37 (-0.71, -0.03)
- WHGS: -0.61 (-0.84, -0.38)
- P for interaction = 1.6x10^-6, P = 0%

**Europe** (n=164,307)

- Fusion Stage 2 controls: 0.49 (-1.27, 2.25)
- DPS: -0.04 (-1.46, 1.38)
- Fusion Stage 2 cases: 0.35 (-1.17, 1.86)
- Segovia: 0.79 (-0.55, 2.12)
- ORGGG cases: 0.64 (-1.01, 2.10)
- RISC: 0.65 (-0.26, 1.56)
- MRC Ely cases: -1.54 (-2.54, -0.54)
- HUNT2-DiaB cases: 1.03 (-0.06, 2.05)
- ORGGG controls: -0.21 (-1.40, 0.98)
- Fusion Stage 1 controls: -0.51 (-1.80, 0.77)
- TUEF & TULIP: -0.10 (-1.46, 1.28)
- GOOD: 0.30 (-0.32, 0.91)
- Fusion Stage 1 cases: -0.16 (-1.07, 0.76)
- InCHIANTI: -1.05 (-2.02, -0.08)
- ERF: 0.61 (-0.93, 2.14)
- EPIC-NL: -0.00 (-0.96, 0.95)
- HUNT2-DiaB controls: 0.62 (-0.12, 1.35)
- YFS: -0.48 (-1.10, 0.13)
- PPP-Botnia: 0.36 (-0.22, 0.94)
- BVWWHS: -0.27 (-0.77, 0.23)
- AGES-Roykjavik: 0.17 (-0.26, 0.53)
- Rotterdam: 0.30 (-0.18, 0.78)
- TwinsUK: 0.07 (-0.41, 0.55)
- NFBC1986: -0.14 (-0.58, 0.30)
- DESIR: -0.08 (-0.38, 0.22)
- EPIC-Rotsdam: -0.26 (-0.74, 0.18)
- METSIM: 0.01 (-0.44, 0.47)
- ELSA: -0.07 (-0.66, 0.52)
- CoLaus: -0.33 (-0.86, 0.19)
- Birth Cohort 1956: 0.03 (-0.44, 0.49)
- Infor99: -0.48 (-0.83, -0.14)
- MONICA/KORA: -0.03 (-0.37, 0.30)
- GLACIER: -0.05 (-0.23, 0.14)
- MPP: 0.03 (-0.14, 0.21)
- EPIC-Norfolk: -0.18 (-0.34, -0.02)
- MDC: -0.12 (-0.29, 0.05)
- P for interaction = 0.18, I^2 = 26%

**Asia** (n=5,921)

- Singapore NHS98 Indian Asian: 0.73 (-0.75, 2.22)
- Singapore NHS98 Malay: -0.26 (-1.80, 1.22)
- CUHNS: -0.26 (-1.18, 0.66)
- Singapore NHS98 Chinese: -0.65 (-1.40, 0.02)
- P for interaction = 0.15, I^2 = 0%

**Overall P for interaction = 0.0049, P = 36%**

-0.14 (-0.23, -0.04)
Overall interaction term:

\[ b3 = -0.14 \text{ kg/m}^2 \quad [95\% \text{CI } -0.23 \text{ to } -0.04] \]

\[ P = 0.005 \]

→ The BMI-increasing effect of FTO is less pronounced in active individuals than in sedentary individuals; i.e., for each additional risk allele the increase is 0.14kg/m\(^2\) less.
Twelve obesity-susceptibility loci - interaction with physical activity

Genetic predisposition score on BMI in 20,000 individuals of the EPIC-Norfolk study

0.15 kg/m²/allele or 444 g/allele

\( p = 1.54 \times 10^{-22} \)
Genetic predisposition score on BMI in 20,000 individuals of the EPIC-Norfolk study

Twelve obesity-susceptibility loci - interaction with physical activity

Li et al AJCN 2010 & PLoS Medicine 2010
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Summary

**Heritability**
Based on a large-scale twin study with objective PA measurements, 43-49% of the inter-individual variation can be explained by genetic difference.

**Candidate gene approach**
Animal studies have identified genes that play a role in PA (reward, craving, ability). However, these variation in these candidate genes does not (yet) associate with PA in humans.

→ Study more variants, in larger studies

**Genome-wide scans**
On-going large scale genome-wide association studies have identified loci that show promising association with PA (in particular sedentary behavior). These results need to be confirmed.

**Gene-physical activity interaction**
Physical activity attenuates the BMI-increasing effects of obesity-susceptibility loci by 30-40%

→ Even those genetically predisposed to obesity benefit from physical activity.
Collaborators and acknowledgements

**Marcel den Hoed, PhD**
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