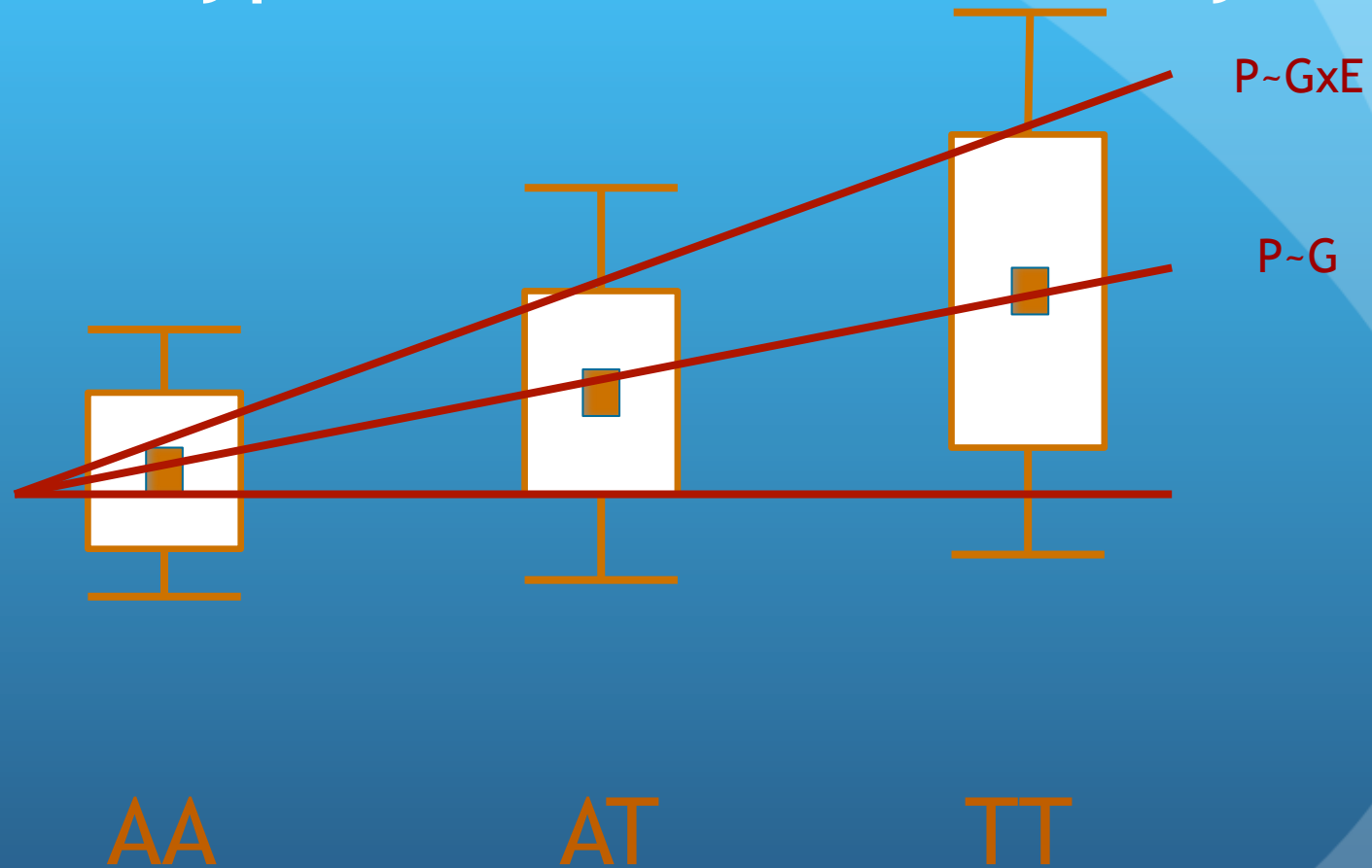


*FTO* genotype is  
associated with  
phenotypic variability of  
body mass index

Bioinfo JC

# Phenotype mean vs. variability



# Power issue

- Detection need very large sample sizes as variance has larger sampling error than mean!

# Contributing cohort information

- 51 studies (~150,000 samples)
- European descent
- HapMap II imputation
- Standard QC

# Phenotypes

- Height and BMI
- Residuals calculated using age and age<sup>2</sup> as covariate, then

inverse-normal transformation

# Method

- Additive genetic model:

$$y = \alpha + \beta x + e$$

$$y = z^2$$

$\alpha$  = intercept

$\beta$  = additive snp effect on  $z^2$

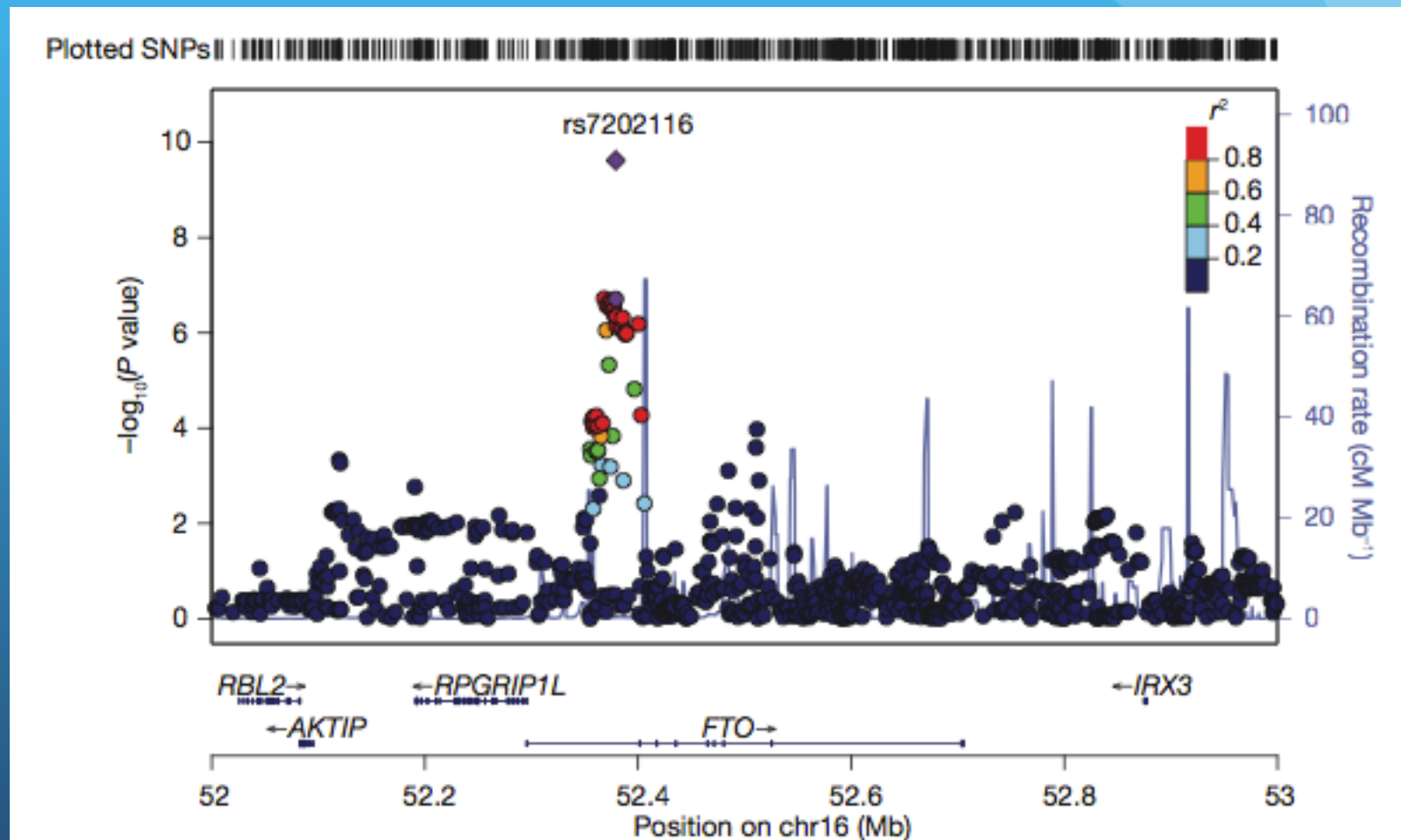
$e$  = residual

# Discovery & Combined top results

Nearest gene	CA	Discovery				Combined	
		Freq.	$\beta$	SE	$P$	$P$	$n$
<i>PRDM2</i>	G	0.196	-0.035	0.0071	$1.0 \times 10^{-6}$	$1.0 \times 10^{-5}$	161,555
<i>KYNU</i>	T	0.180	-0.036	0.0074	$1.0 \times 10^{-6}$	$1.0 \times 10^{-5}$	161,668
<i>SIX3</i>	T	0.175	-0.038	0.0075	$4.0 \times 10^{-7}$	$3.0 \times 10^{-6}$	161,171
<i>INHBA</i>	C	0.339	0.029	0.0060	$1.0 \times 10^{-6}$	$6.0 \times 10^{-5}$	161,250
<i>CSMD1</i>	G	0.444	-0.029	0.0059	$1.0 \times 10^{-6}$	$7.0 \times 10^{-6}$	158,200
<i>BAZ1A</i>	T	0.227	0.031	0.0068	$5.0 \times 10^{-6}$	$6.0 \times 10^{-6}$	164,875
<i>LRP1B</i>	G	0.263	-0.038	0.0078	$1.2 \times 10^{-6}$	$1.1 \times 10^{-3}$	137,043
<i>CRYGD</i>	C	0.407	0.028	0.0059	$2.9 \times 10^{-6}$	$5.6 \times 10^{-5}$	156,238
<i>FAT</i>	A	0.140	-0.043	0.0085	$4.3 \times 10^{-7}$	$6.2 \times 10^{-6}$	153,026
<i>IBTK</i>	G	0.496	-0.026	0.0057	$3.3 \times 10^{-6}$	$1.2 \times 10^{-4}$	164,332
<i>RCOR1</i>	C	0.057	0.061	0.0126	$1.3 \times 10^{-6}$	$7.9 \times 10^{-8}$	159,378
<b><i>RCOR1</i></b>	<b>G</b>	<b>0.057</b>	<b>0.059</b>	<b>0.0126</b>	<b><math>2.4 \times 10^{-6}</math></b>	<b><math>4.1 \times 10^{-8}</math></b>	<b>155,120</b>
<i>FTO</i>	C	0.403	0.030	0.0058	$1.9 \times 10^{-7}$	$5.4 \times 10^{-8}$	159,986
<b><i>FTO</i></b>	<b>G</b>	<b>0.402</b>	<b>0.035</b>	<b>0.0067</b>	<b><math>2.0 \times 10^{-7}</math></b>	<b><math>2.4 \times 10^{-10}</math></b>	<b>131,233</b>
<i>PIK3C3</i>	G	0.378	0.033	0.0069	$1.6 \times 10^{-6}$	$3.5 \times 10^{-4}$	130,639

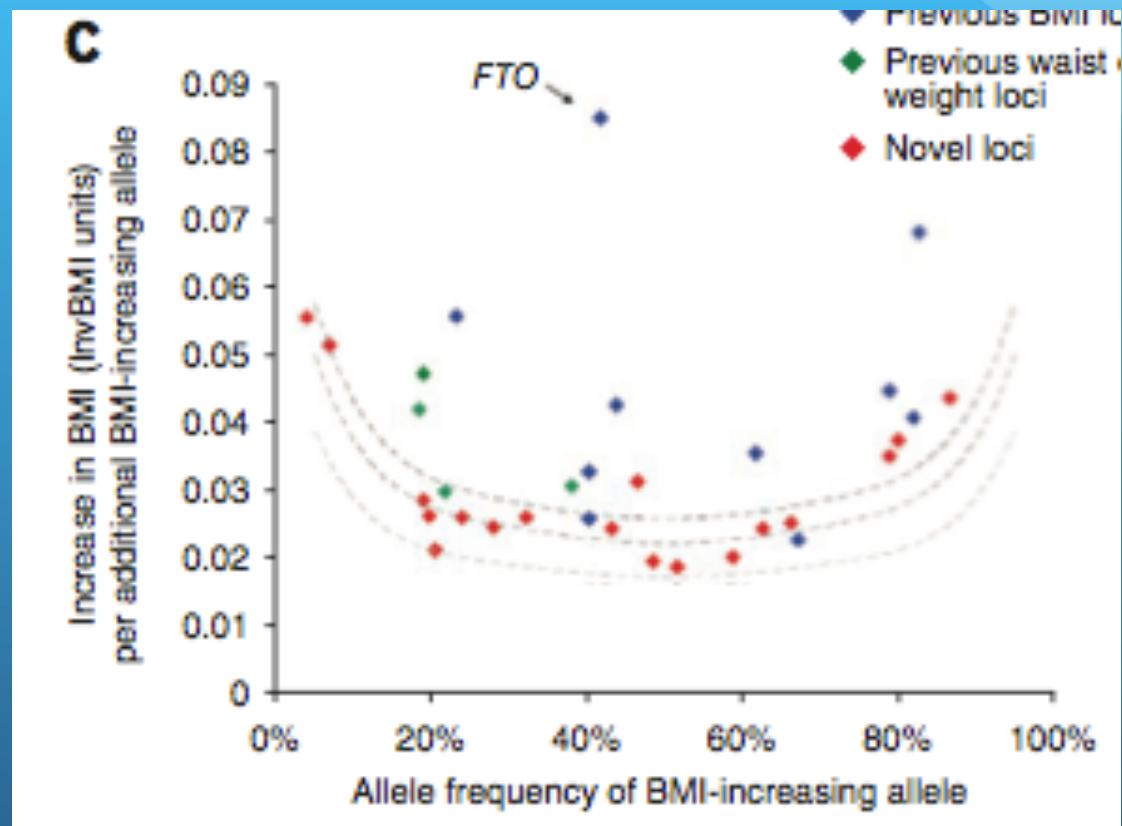
GWAS  $\alpha=5 \times 10^{-8}$ , current experiment  $\alpha=2.5 \times 10^{-8}$

# FTO locuszoom





# FTO



# FTO var(G | P)

- Difference in variance among individuals with opposite homozygous genotypes ~7% (0.5 kg)

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PLoS MEDICINE

## Physical Activity Attenuates the Influence of *FTO* Variants on Obesity Risk: A Meta-Analysis of 218,166 Adults and 19,268 Children

Tuomas O. Kilpeläinen<sup>1</sup>, Lu Qi<sup>2\*</sup>, Soren Brage<sup>1</sup>, Stephen J. Sharp<sup>1</sup>, Emily Sonestedt<sup>3</sup>, Ellen Demerath<sup>4</sup>, Tariq Ahmad<sup>5</sup>, Samia Mora<sup>6</sup>, Marika Kaakinen<sup>7</sup>, Camilla Helene Sandholt<sup>8</sup>, Christina Holzapfel<sup>9,10</sup>, Christine S. Autenrieth<sup>11</sup>, Elina Hyppönen<sup>12</sup>, Stéphane Cauchi<sup>13</sup>, Meian He<sup>14</sup>, Zoltan Kutalik<sup>15</sup>, Meena Kumari<sup>16</sup>, Alena Stancáková<sup>17</sup>, Karina Meidtner<sup>18</sup>, Beverley Balkau<sup>19,20</sup>, Jonathan T. Tan<sup>21</sup>, Massimo Mangino<sup>22</sup>, Nicholas J. Timpson<sup>23</sup>, Yiqing Song<sup>24</sup>, M. Carola Zillikens<sup>25,26</sup>, Kathleen A. Jablonski<sup>27</sup>, Melissa E. Garcia<sup>28</sup>, Stefan Johansson<sup>29,30</sup>, Jennifer L. Bragg-Gresham<sup>31</sup>, Ying Wu<sup>32</sup>, Jana V. van Vliet-Ostaptchouk<sup>33</sup>, N. Charlotte Onland-Moret<sup>34,35</sup>, Esther Zimmermann<sup>36,37</sup>, Natalia V. Rivera<sup>38</sup>, Toshiko Tanaka<sup>39,40</sup>, Heather M. Stringham<sup>31</sup>, Günther Silbernagel<sup>41</sup>, Stavroula Kanoni<sup>42</sup>, Mary F. Feitosa<sup>43</sup>,

# Conclusions

- *FTO* (and *RCOR1*) influence phenotypic variance of BMI
- This might be due to GxE interactions (e.g. physical activity)
- Nothing was found for height (GxG?)
- No wide-spread genotype-by-environment interaction effects
- No common genetic variants that account for large porportion of phenotypic variability
- There might be need for even larger sample size

