Vandenõuteooriad I

# Erinevused kaksikute ja ülegenoomsete uuringute vahel

ehk

# kes varjab geneetilist päritavust?

# Kus on peidus puuduv 86,3%?

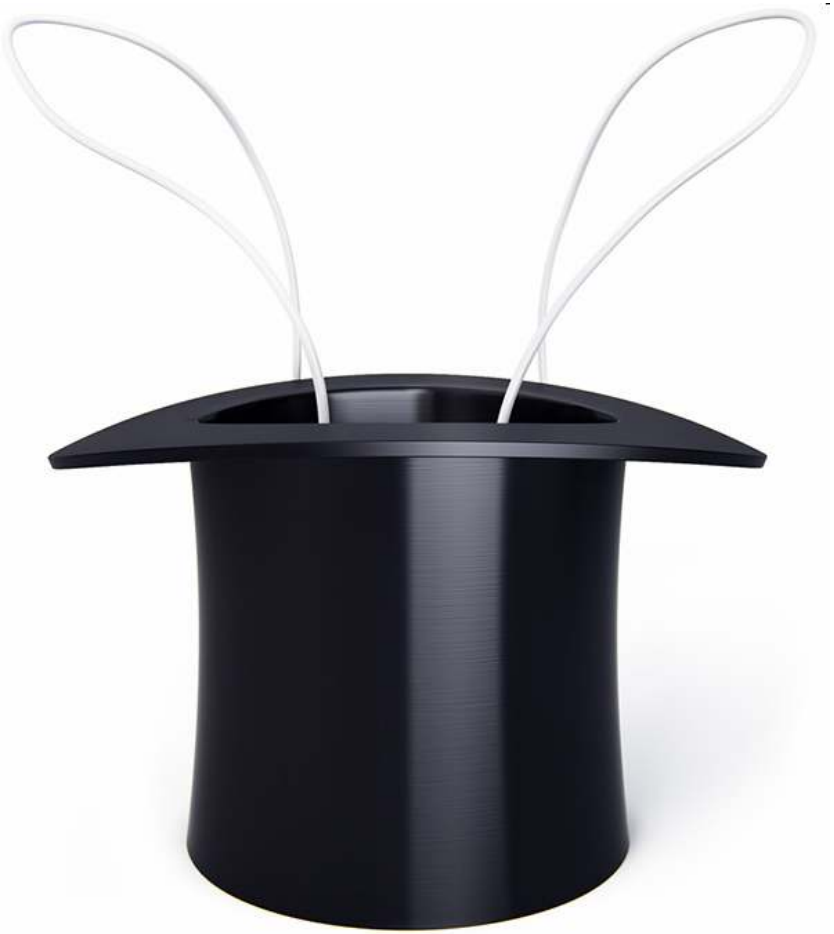
Twin Studies: “Adult height is a model polygenic trait. It is easily and accurately measured and highly heritable, with up to 90% of variation in adult height within a population explained by genetic variation“

Nat Genet. 2008 May; 40(5): 575–583.

GWAS: We identified 27 regions of the genome ... showing significant association with height. ... taken together, they explain around 3.7% of the population variation in height.

Nature Genetics 40, 609 - 615 (2008), 39509

# Kas õnnestub üles leida kadunud päritavus?



Kes varjab meie eest päritavust?

Miks?

Kuhu on puuduv osa päritavusest peidetud?

# Mis üldse on päritavus(koefitisient)?

Height = G + K + e + G*K + D + ...

D(Height) = D(G) + D(K) + D(e) +
+ cov(G,K)+...

Päritavuskordaja:

$$h^2 = \frac{D(G)}{D(Height)} = \frac{D(G)}{D(G)+D(K)+D(e)}$$

# Päritavuskordaja hindamisest kaksikute uuringu korral

$$r_{MZ1,MZ2} = \frac{\mathrm{cov}(MZ1, MZ2)}{\sqrt{D(MZ1, MZ2)}} = \frac{D(G) + D(K) + \mathrm{cov}(G, K)}{D(G) + D(K) + D(e)}$$

$$r_{HZ1,HZ2} = \frac{0.5D(G) + D(K) + 0{,}5\,\mathrm{cov}(G, K)}{D(G) + D(K) + D(e)}$$

$$r_{MZ1,MZ2} - r_{HZ1,HZ2} = \frac{0.5D(G) + 0{,}5\,\mathrm{cov}(G, K)}{D(G) + D(K) + D(e)}$$

$$h^2 = 2(r_{MZ1,MZ2} - r_{HZ1,HZ2})$$

# Näide: Silventoinen jt, 2000

| | No. of Pairs | Mean | Variance | Intraclass Correlation |
|---|---|---|---|---|
| Men | | | | |
| 1928 or earlier | | | | |
| MZ | 311 | 171.3 | 6.00 | 0.86 |
| DZ | 654 | 171.6 | 6.30 | 0.48 |
| *P* | | .396 | .264 | |
| 1929–1938 | | | | |
| MZ | 250 | 173.0 | 6.07 | 0.90 |

| | A | C | E | $h^2$ | $\chi^2$ | *df* | *P* |
|---|---|---|---|---|---|---|---|
| Men | | | | | | | |
| 1928 or earlier | 5.417 (0.2109) | 2.058 (0.5560) | 2.282 (0.0915) | 0.76 | 9.4 | 3 | .024 |
| 1929–1938 | 5.700 | 2.023 | 1.965 | 0.80 | 2.1 | 3 | .554 |

$h^2 = 2*(0,86-0,48)=0,76$

# “Päritavus” GWAS-uuringus

Determinatsioonikordaja:

$$R^2 = \frac{D(Y) - D(Y \mid X_1, X_2, ...)}{D(Y)}$$

Coefficient of partial determination:

$$R^2_{G|K} = \frac{D(Y \mid K) - D(Y \mid G, K)}{D(Y)}$$

# Päritavus GWAS-is

$$
\begin{aligned}
R^2_{G|K} &= \frac{D(Y \mid K) - D(Y \mid G, K)}{D(Y)} \\
&= \frac{D(G + K + E \mid K) - D(G + K + E \mid G, K)}{D(G + K + E)} \\
&= \frac{D(G) + D(E) - D(E)}{D(G + K + E)} \\
&= \frac{D(G)}{D(G + K + E)}
\end{aligned}
$$

# Kui suur on D(*Height*)?

National Health Statistics Reports: Anthropometric Reference Data for Children and Adults: United States, 2003-2006.

Täiskasvanud inimesed (20+), pikkus:

SD = 13,28...

D(Height)=176,...

Silventoinen et al (2003). Heritability of adult body height: A comparative study of twin cohorts in eight countries. *Twin Research*, *6,* 399–408.

**Table 2**

Mean (and *SD*) Height by Country and Zygosity Group

| | Australia | Denmark | Finland |
|---|---|---|---|
| MZm | 178.4 (6.92) | 180.9 (6.62) | 179.3 (6.73) |
| DZm | 178.9 (6.67) | 181.7 (6.65) | 179.5 (6.68) |
| DOSm | 179.4 (6.47) | 181.8 (6.83) | 179.7 (6.31) |
| MZf | 166.5 (6.83) | 167.8 (6.07) | 165.3 (5.80) |
| DZf | 166.8 (6.92) | 168.2 (6.56) | 166.3 (5.95) |
| DOSf | 166.3 (6.79) | 168.5 (6.15) | 166.2 (5.49) |

D(Height) = $6{,}73^2$ = 45,...

Kadu: (176-45)/176*100% = 75%

# Millest ikkagi koosneb D(*Height*)?

D(Height)=176,...

D(Height|Race=Non-Hispanic white)=118,...
(sd=10,86...)

D(Height|white, male)=93,...
(sd=9,66...)

D(Height|white, male,40-59)=87,...
(sd=9,32...)

D(Height)=D(race)+D(culture)+D(gender)+D(age)+....

# Millest koosneb D(Height) kaksikute uuringus?

| | A | C | E | $h^2$ | $\chi^2$ | *df* | *P* |
|---|---|---|---|---|---|---|---|
| Men | | | | | | | |
| 1928 or earlier | 5.417 (0.2109) | 2.058 (0.5560) | 2.282 (0.0915) | 0.76 | 9.4 | 3 | .024 |
| 1929–1938 | 5.700 | 2.023 | 1.965 | 0.80 | 2.1 | 3 | .554 |

D(Height)=D(race)+D(culture)+D(gender)+D(age)+....

$D(Height_{TWIN\ STUDY})=$

=D(race)+D(culture)+D(gender)+D(age)+....

=0 =0 =0 ≈0

# Millest koosneb D(Height) GWAS-uuringus?

We used GWA data from five studies that ranged in size from 1,437 to 3,560 people of European ancestry from the UK and a sixth study of 2,978 Scandinavian individuals....

We searched for sequence variants that affect height by scanning the genomes of 25,174 Icelanders, 2,876 Dutch, 1,770 European Americans and 1,148 African Americans. We then combined these results with previously published results from the Diabetes Genetics Initiative on 3,024 Scandinavians and tested a selected subset of SNPs in 5,517 Danes...

# Millest koosneb D(Height) GWAS-uuringus?

Mudel:

Height = c0 + gender + age+ age^2+

+SNP1+SNP2+... + population stratification+

D(Height)=D(race)+D(culture)+D(gender)+D(age)+....

$D(Height_{GWAS})$=

=D(race)+D(culture)+D(gender)+D(age)+....

vahel olemas olemas olemas olemas

# Mis jääb murrujoone peale GWAS-uuringus?

GWAS:

$$R^2_{G|K} = \frac{D(Y \mid K) - D(Y \mid G, K)}{D(Y)}$$

$$= \frac{D(Y \mid gender, race, age) - D(Y \mid gender, race, age, SNP1, SNP2, ...)}{D(Y)}$$

$$\frac{D(G \mid race, gender, age)}{D(race) + D(culture) + D(gender) + D(age) + ....}$$

TWINS:

$$h^2 = \frac{D(G \mid race, gender)}{....}$$

$$D(race) + D(culture) + D(gender) + D(age) + D(....) \approx 4D(....)$$

Seega:

Päritavuskordajad kaksikute uuringute ja ülegenoomsete uuringute vahel erinevad ca 4x juba ainult nimetaja erinevuse tõttu (erinev uuritava tunnuse hajuvuse definitsioon...)

Lisaks:

Kaksikute uuringutes lugejas $D(G)+COV(G,K)+COV(G,E)$

GWAS uuringus lugejas $D(G)+COV(G,E)$

# Ühesõnaga:
# kõiges on süüdi naised!