Gene-by-Environment and Meta-Analysis

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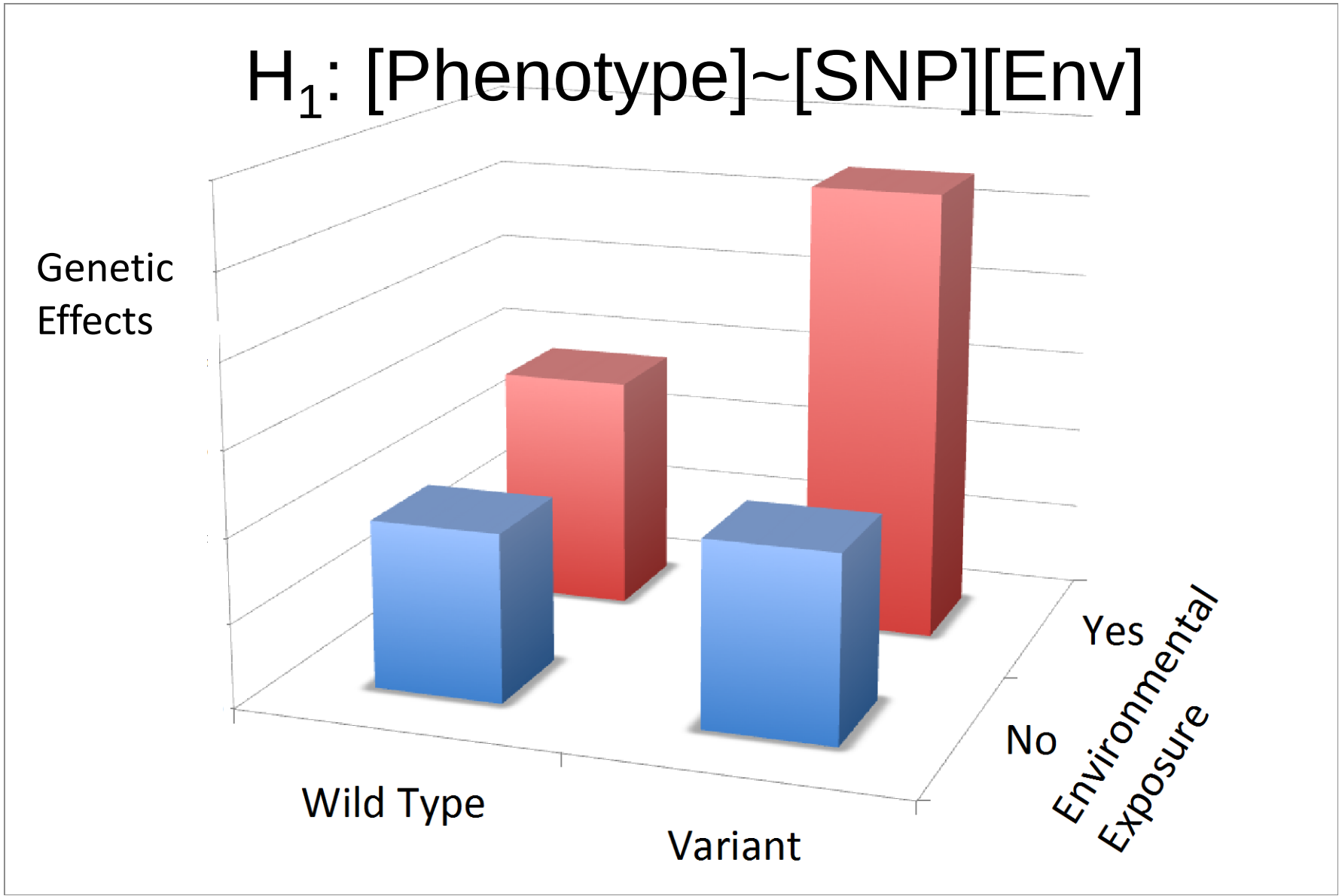
What I'm not talking about… (see the posters)

- Gene by Environment Interactions and Population Structure
  - *Accounting for population structure in gene-by-environment interactions in genome-wide association studies using mixed models*. Jae Hoon Sul, Michael Bilow, Wen-Yun Yang, Emrah Kostem, Nick Furlotte, Dan He, Eleazar Eskin.
- Fine Mapping Causal Variants
  - *Identification of causal genes for complex traits*. Farhad Hormozdiari, Gleb Kichaev, Wen-Yun Yang, Bogdan Pasaniuc and Eleazar Eskin
- New software: pylmm – python linear mixed model
  - "new" version of EMMA/EMMAX
  - http://genetics.cs.ucla.edu/pylmm/

Gene x Environment Interaction



Identifying GxE (Traditional Approach)

$$y = \mu + \alpha D + \beta X + \gamma X \cdot D + e$$

- α : main environmental effect
- D : n x 1 environmental status vector
- β : main genetic effect
- X : n x 1 genotype vector
- γ : GxE interaction effect
- e : residual error

Identifying GxE (Traditional Approach)

$$y = \mu + \alpha D + \beta X + \gamma X{\cdot}D + e$$

Two widely used GxE Hypothesis Test

1. Test GxE interaction effect only :
   the null hypothesis $\gamma = 0$
   vs the alternative hypothesis $\gamma \neq 0$

2. Test GxE interaction effect and genetic effect simultaneously :
   the null hypothesis $\beta = 0$ and $\gamma = 0$
   vs the alternative hypothesis $\beta \neq 0$ or $\gamma \neq 0$

Random Effect Meta Analysis

- Suppose we have n studies to combine

Env 1 Study 1 → $y_1 = \alpha_1 + \delta_1 X + e$

Env 2 Study 2 → $y_2 = \alpha_2 + \delta_2 X + e$

$$\vdots$$

Env n Study n → $y_n = \alpha_n + \delta_n X + e$

assume that $\delta_i \sim N(\mu, \tau^2)$

Random Effect Meta Analysis

assume that $\delta_i \sim N(\mu, \tau^2)$

performing likelihood ratio test

- the null hypothesis : $\mu = 0$ and $\tau^2 = 0$
- the alternative hypothesis : $\mu \neq 0$ or $\tau^2 \neq 0$

Relationship between RE meta-analysis and traditional GxE testing

For Study i

$$y_i = \alpha_i + \delta_i X + e$$

$$y_i = \alpha_i + \beta X + \gamma_i X + e$$

Common genetic effect

Environmental-specific effect

Relationship between RE meta-analysis and traditional GxE testing

For Study i $\longrightarrow$ $$y_i = \alpha_i + \delta_i X + e$$

$$y = \sum \alpha_i D_i + \beta X + \sum \gamma_i X \cdot D_i + e$$

Common genetic effect

Environmental-specific effect

Because RE meta analysis assumes $\delta_i \sim N(\mu, \tau^2)$

μ is analogous to β

The variation (τ^2) around μ is analogous to variation among γ_i due to different environments

Relationship between RE meta-analysis and traditional GxE testing

For Study i $\longrightarrow$ $y_i = \alpha_i + \delta_i X + e$

$$y = \sum \alpha_i D_i + \beta X + \sum \gamma_i X \cdot D_i + e$$

Common genetic effect

Environmental-specific effect

Given assumption $\delta_i \sim N(\mu, \tau^2)$

In random effect meta-analysis testing framework, we are testing $\mu = 0$ and $\tau^2 = 0$. This is equivalent to testing both common genetic effect ($\beta = 0$) and environmental-specific effect ($\gamma_i = 0$) simultaneously.

Proposed Approach

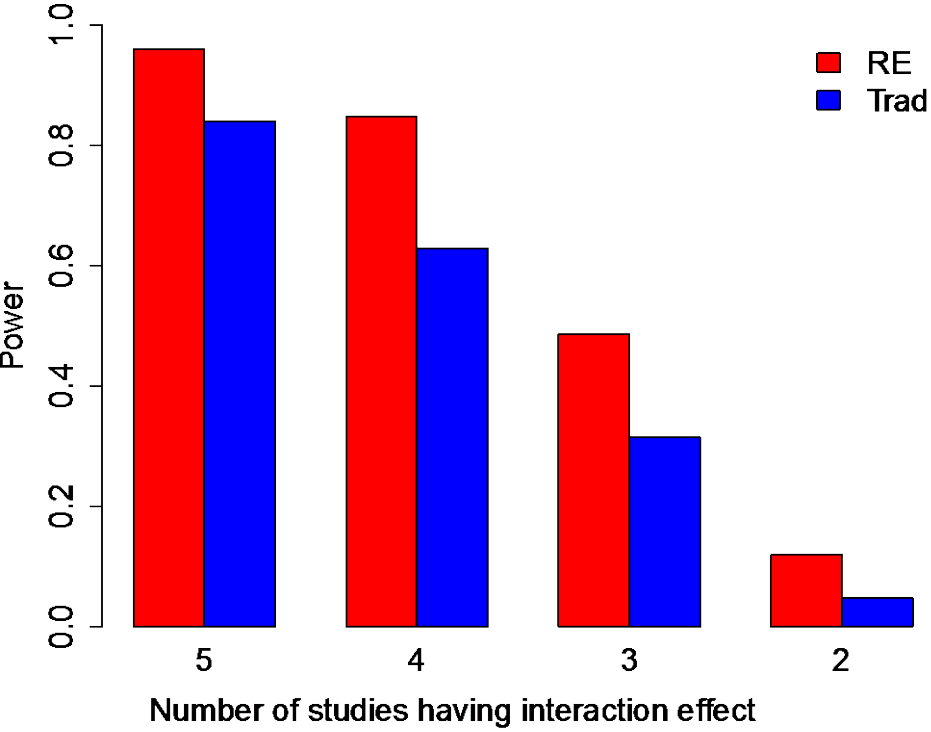
- Meta-GxE
  - a random-effects based meta-analytic approach to combine multiple studies conducted under varying environmental conditions
  - By making the connection between gene-by-environment interactions and random effects model meta-analysis, we show that GxE interactions can be interpreted as heterogeneity between effect sizes among studies.

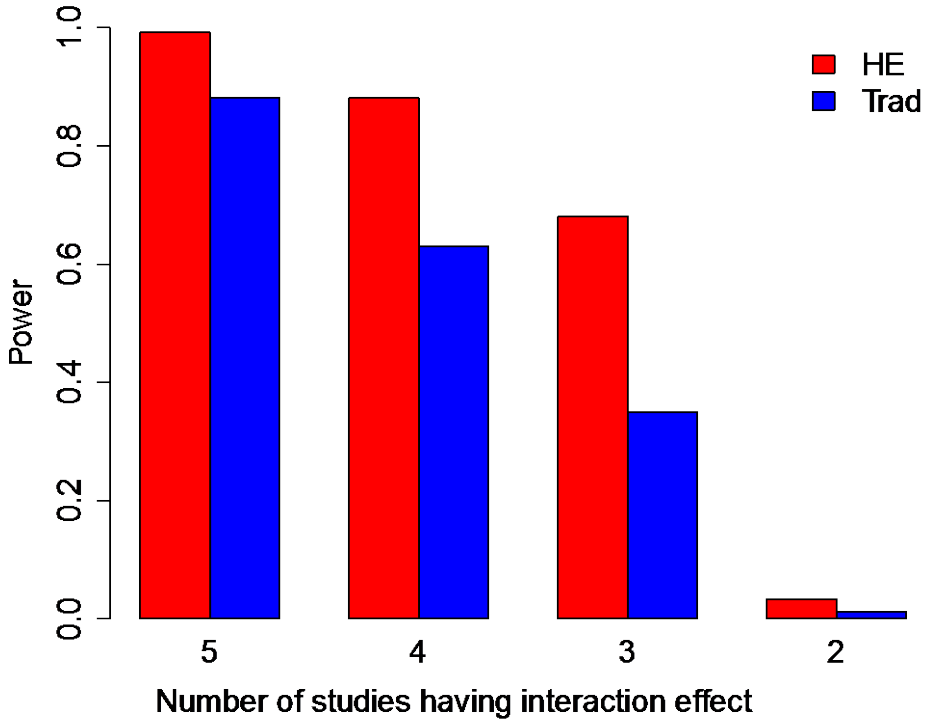
Simulation Experiments

- We generated 6 simulated genotype data sets with 1000 individuals assuming minor allele frequency of 0.3.
- And we simulated the phenotype using the following standard GxE model.

$$y = \mu + \alpha D + \beta X + \gamma X \cdot D + e$$

Statistical power comparison





Type I error is correctly controlled (Details in the paper)

Advantage of Meta-GxE compared to traditional approaches

- Meta-GxE is much more powerful than the traditional approach of treating the environment as a covariate. → Solve the power issue of identifying GxE in genome-wide scale.
- Meta-GxE does not requires prior knowledge about environmental variables. In many cases, it is hard to know about the environmental variables, which will have an interaction effect and how to encode in the model.

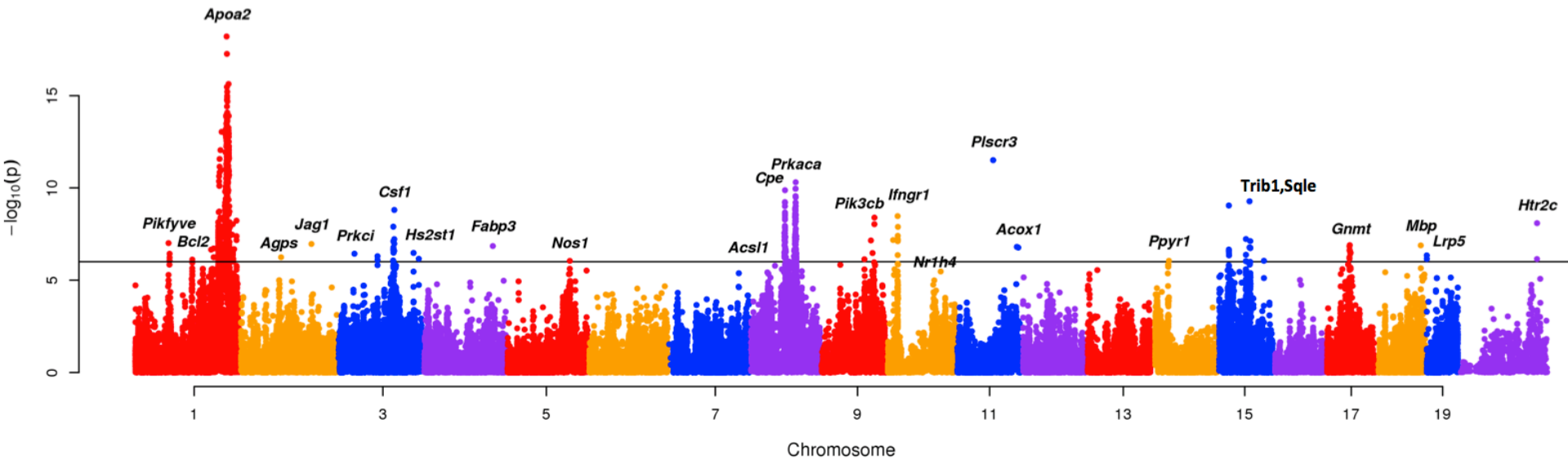
Application of Meta-GxE to 17 mouse studies with varying environments

- We apply our new method to combine 17 mouse studies of High-density lipoprotein (HDL) cholesterol, containing in aggregate 4,965 distinct animals.
- We search for GxE interactions with 17 HDL mouse studies.

17 HDL studies for meta analysis (~5000 animals)

Study ID	Strains	Conditions	Age	Sex	# Strains	# Samples	# Sig Loci	Ref
HMDPxB-chow(M)	(HMDP x BL/6) F1	Leiden/CETP TG,chow diet	8 weeks	M	97	516	1	U
HMDPxB-chow(F)	(HMDP x BL/6) F1	Leiden/CETP TG, chow diet	8 weeks	F	95	468	0	U
HMDPxB-ath(M)	(HMDP x BL/6) F1	Leiden/CETP TG, highfat diet	24 weeks	M	97	408	0	U
HMDPxB-ath(F)	(HMDP x BL/6) F1	Leiden/CETP TG, highfat diet	24 weeks	F	93	457	3	U
HMDP-chow(M)	HMDP	chow diet	12 weeks	M	111	749	6	[2]
HMDP-fat(M)	HMDP	highfat diet	16 weeks	M	106	586	0	[53]
HMDP-fat(F)	HMDP	highfat diet	16 weeks	F	92	475	0	[53]
BxD-db-12(M)	(DBA x BL/6) F2	BXD db/db, chow diet	12 weeks	M	125	125	0	[8]
BxD-db-12(F)	(DBA x BL/6) F2	BXD db/db, chow diet	12 weesk	F	122	122	0	[8]
BxD-db-5(M)	(DBA x BL/6) F2	BXD db/db, chow diet	5 weeks	M	109	109	1	[8]
BxD-db-5(F)	(DBA x BL/6) F2	BXD db/db, chow diet	5 weeks	F	139	139	0	[8]
BxH-apoe(M)	(C3H x BL/6) F2	BXH Apoe -/-	24 weeks	M	161	161	0	[68]
BxH-apoe(F)	(C3H x BL/6) F2	BXH Apoe -/-	24 weeks	F	174	174	0	[68]
BxH-wt(M)	(C3H x BL/6) F2	BXH wildtype, highfat diet	20 weeks	M	164	164	0	[66]
BxH-wt(F)	(C3H x BL/6) F2	BXH wildtype, highfat diet	20 weeks	F	144	144	0	[66]
CxB-ldlr(M)	(BALB/cJ x BL/6) F2	CXB LDLR -/-, highfat diet	12 weeks	M	124	124	0	U
CxB-ldlr(F)	(BALB/cJ x BL/6) F2	CXB LDLR -/-, highfat diet	12 weeks	F	64	64	0	U

26 significant loci identified



SNP Location	Meta GxE P (Male)	Meta GxE P (Female)	Meta GxE P (Male+Female)	# of Studies w/ Significant P	HE Meta P (Male+Female)	# Studies E/A/N	Genes in Region	Gene Refs
Chr1:64752822 (rs31078051)	1.12×10^{-6}	2.37×10^{-3}	$\mathbf{9.82\times10^{-8}}$	0	3.82×10^{-3}	2/14/1	**Pikfyve**	[62]
Chr1:107271282 (rs32203839)	6.69×10^{-4}	2.66×10^{-4}	$\mathbf{7.67\times10^{-7}}$	0	7.55×10^{-2}	6/0/11	**Bcl2**	[28]
Chr1:171199523 (rs32075748)	$\mathbf{3.45\times10^{-16}}$	$\mathbf{1.39\times10^{-7}}$	$\mathbf{4.41\times10^{-22}}$	1	5.80×10^{-5}	8/6/3	**Apoa2**	[55]
Chr2:77837584 (rs6273567)	1.55×10^{-4}	7.17×10^{-4}	$\mathbf{5.74\times10^{-7}}$	0	2.25×10^{-2}	3/14/0	**Agps**	[41]
Chr2:134421733 (rs27238693)	7.69×10^{-6}	1.66×10^{-3}	$\mathbf{1.09\times10^{-7}}$	0	1.63×10^{-2}	5/12/0	**Jag1**	[30]
Chr3:32944259 (rs29869794)	2.97×10^{-6}	2.49×10^{-2}	$\mathbf{3.68\times10^{-7}}$	0	2.36×10^{-5}	3/8/6	**Prkci**	[14]
Chr3:76066632 (rs31487078)	5.89×10^{-3}	2.29×10^{-5}	$\mathbf{5.03\times10^{-7}}$	0	6.56×10^{-2}	4/13/0	**Novel**	-
Chr3:107430396 (rs30013147)	9.59×10^{-6}	3.84×10^{-5}	$\mathbf{1.56\times10^{-9}}$	0	7.74×10^{-2}	7/10/0	**Csf1**	[57]
Chr3:143466942 (rs30206761)	1.82×10^{-3}	3.97×10^{-5}	$\mathbf{3.34\times10^{-7}}$	0	8.60×10^{-2}	7/10/0	**Hs2st1**	[60]
Chr4:131925523 (rs32595861)	1.72×10^{-4}	2.84×10^{-4}	$\mathbf{1.41\times10^{-7}}$	0	8.65×10^{-4}	6/8/3	**Fabp3**	[47]
Chr5:119034507 (rs33131194)	1.23×10^{-4}	2.59×10^{-3}	$\mathbf{9.00\times10^{-7}}$	0	3.94×10^{-1}	9/8/0	**Nos1**	[39, 49]
Chr8:46903188 (rs33272858)	$\mathbf{1.47\times10^{-7}}$	6.52×10^{-1}	1.66×10^{-6}	1	1.60×10^{-4}	2/11/4	**Acsl1**	[40]
Chr8:64150094 (rs31750594)	$\mathbf{1.96\times10^{-7}}$	1.89×10^{-4}	$\mathbf{1.33\times10^{-10}}$	0	8.34×10^{-1}	11/6/0	**Cpe**	[50]
Chr8:84073148 (rs33435859)	$\mathbf{1.95\times10^{-8}}$	4.53×10^{-4}	$\mathbf{4.94\times10^{-11}}$	0	8.33×10^{-1}	12/5/0	**Prkaca**	[51]
Chr9:101972687 (rs6333310)	1.22×10^{-4}	1.22×10^{-5}	$\mathbf{4.05\times10^{-9}}$	0	$\mathbf{1.98\times10^{-8}}$	2/1/14	**Pik3cb**	[5]
Chr10:21399819 (rs29363941)	9.07×10^{-4}	$\mathbf{3.64\times10^{-7}}$	$\mathbf{3.36\times10^{-9}}$	0	1.18×10^{-2}	3/12/2	**Ifngr1**	[23]
Chr10:90146088 (rs29370592)	$\mathbf{1.93\times10^{-7}}$	0.756	1.02×10^{-5}	1	8.94×10^{-4}	2/14/1	**Nr1h4**	[37]
Chr11:69906552 (rs29477071)	$\mathbf{5.77\times10^{-8}}$	1.35×10^{-5}	$\mathbf{3.17\times10^{-12}}$	0	$\mathbf{2.37\times10^{-9}}$	6/9/2	**Plscr3**	[71]
Chr11:114083173 (rs29416888)	0.00011	7.83×10^{-5}	$\mathbf{1.71\times10^{-7}}$	0	5.28×10^{-5}	3/13/1	**Acox1**	[13]
Chr14:33632464 (rs31061259)	1.96×10^{-4}	1.65×10^{-3}	$\mathbf{8.90\times10^{-7}}$	0	2.02×10^{-5}	3/10/4	**Ppyr1**	[58]
Chr15:21194226 (rs31670969)	$\mathbf{1.96\times10^{-8}}$	1.29×10^{-2}	$\mathbf{8.97\times10^{-10}}$	1	$\mathbf{5.65\times10^{-7}}$	3/2/12	**Novel**	-
Chr15:59860191 (rs3718217)	5.64×10^{-6}	1.45×10^{-5}	$\mathbf{5.31\times10^{-10}}$	0	9.92×10^{-5}	5/10/2	**Trib1, Sqle**	[12, 16]
Chr17:46530712 (rs33259313)	1.09×10^{-5}	0.0049	$\mathbf{3.26\times10^{-7}}$	0	3.53×10^{-5}	5/10/2	**Gnmt**	[43]
Chr18:82240606 (rs13483466)	2.05×10^{-4}	2.23×10^{-4}	$\mathbf{1.30\times10^{-7}}$	0	9.05×10^{-1}	5/12/0	**Mbp**	[3]
Chr19:3319089 (rs31004232)	5.58×10^{-2}	$\mathbf{8.53\times10^{-7}}$	$\mathbf{4.56\times10^{-7}}$	0	1.08×10^{-1}	3/14/0	**Lrp5**	[18]
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Male Specific Loci

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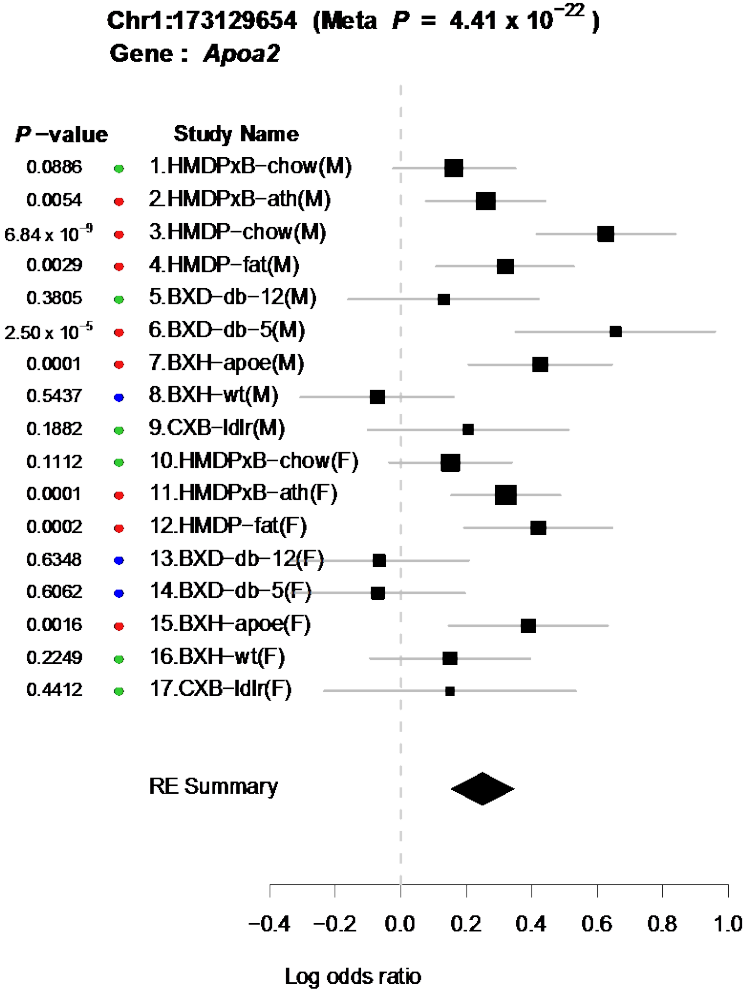
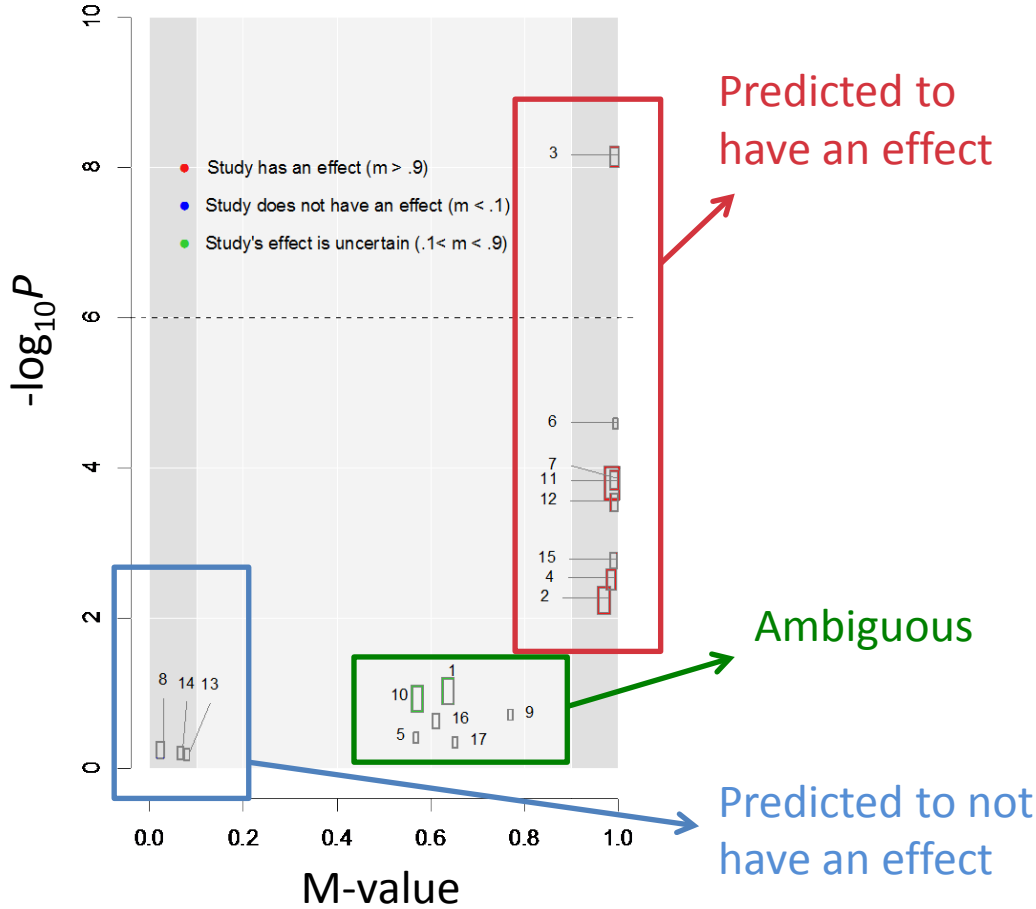
Chr10:90146088 (rs29370592)	$\mathbf{1.93\times10^{-7}}$	0.756	1.02×10^{-5}	1	8.94×10^{-4}	2/14/1	**Nr1h4**	[37]
Chr11:69906552 (rs29477071)	$\mathbf{5.77\times10^{-8}}$	1.35×10^{-5}	$\mathbf{3.17\times10^{-12}}$	0	$\mathbf{2.37\times10^{-9}}$	6/9/2	**Plscr3**	[71]
Chr11:114083173 (rs29416888)	0.00011	7.83×10^{-5}	$\mathbf{1.71\times10^{-7}}$	0	5.28×10^{-5}	3/13/1	**Acox1**	[13]
Chr14:33632464 (rs31061259)	1.96×10^{-4}	1.65×10^{-3}	$\mathbf{8.90\times10^{-7}}$	0	2.02×10^{-5}	3/10/4	**Ppyr1**	[58]
Chr15:21194226 (rs31670969)	$\mathbf{1.96\times10^{-8}}$	1.29×10^{-2}	$\mathbf{8.97\times10^{-10}}$	1	$\mathbf{5.65\times10^{-7}}$	3/2/12	**Novel**	-
Chr15:59860191 (rs3718217)	5.64×10^{-6}	1.45×10^{-5}	$\mathbf{5.31\times10^{-10}}$	0	9.92×10^{-5}	5/10/2	**Trib1, Sqle**	[12, 16]
Chr17:46530712 (rs33259313)	1.09×10^{-5}	0.0049	$\mathbf{3.26\times10^{-7}}$	0	3.53×10^{-5}	5/10/2	**Gnmt**	[43]
Chr18:82240606 (rs13483466)	2.05×10^{-4}	2.23×10^{-4}	$\mathbf{1.30\times10^{-7}}$	0	9.05×10^{-1}	5/12/0	**Mbp**	[3]
Chr19:3319089 (rs31004232)	5.58×10^{-2}	$\mathbf{8.53\times10^{-7}}$	$\mathbf{4.56\times10^{-7}}$	0	1.08×10^{-1}	3/14/0	**Lrp5**	[18]
ChrX:151384614 (rs31202008)	2.59×10^{-4}	4.72×10^{-6}	$\mathbf{8.09\times10^{-9}}$	0	1.22×10^{-1}	5/5/0	**Htr2c**	[36]

Interpretation and prediction

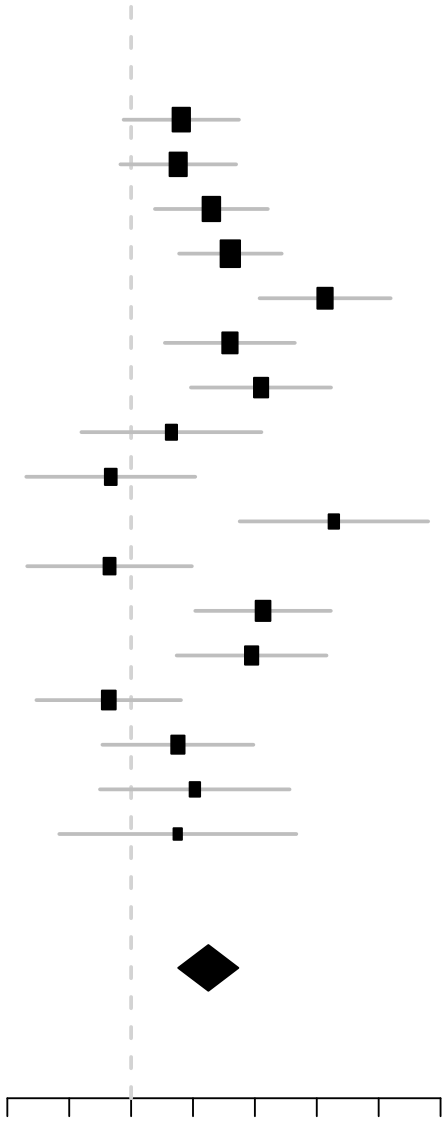
- Under a model that effect either exists or not
- Estimate posterior probability that effect will exist (m-value)
- Analytical calculation ($O(2^n)$) and MCMC

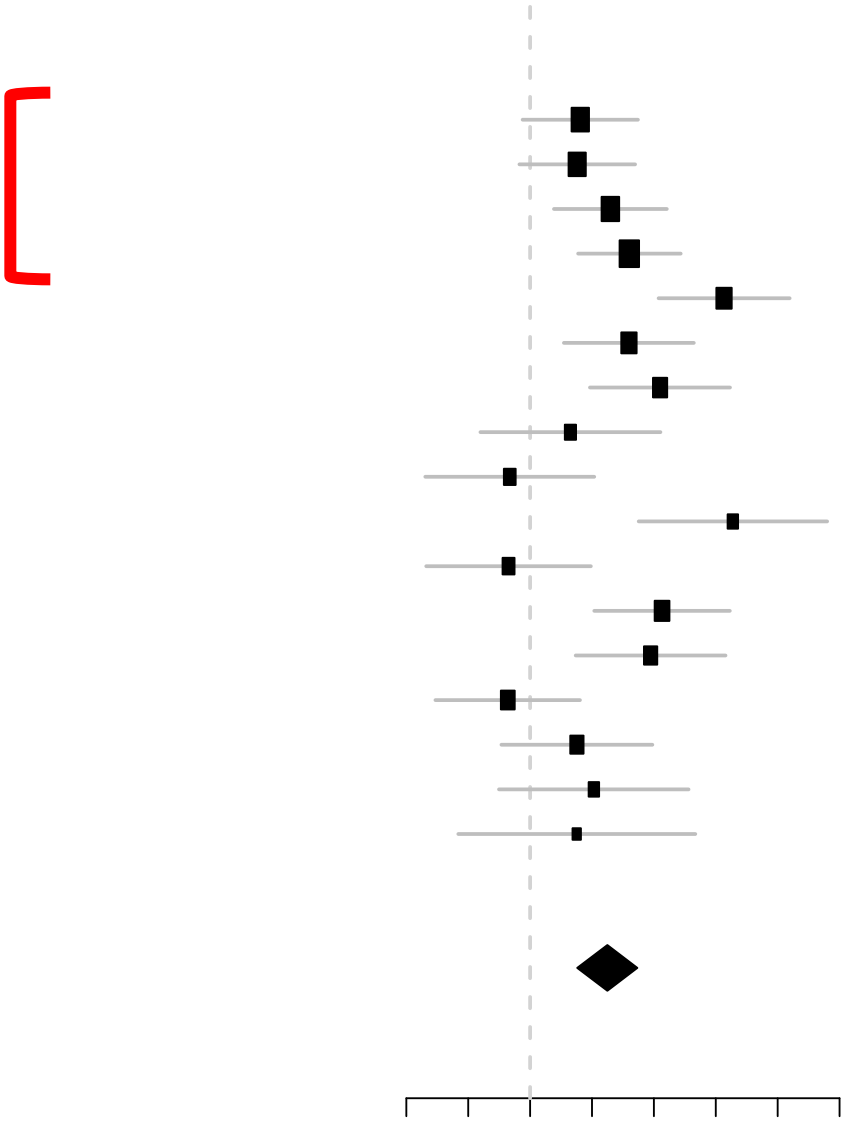


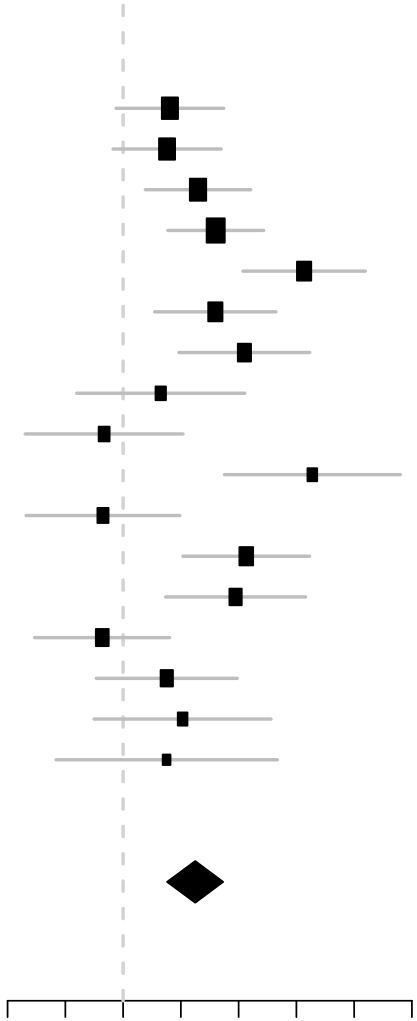
PM-plot



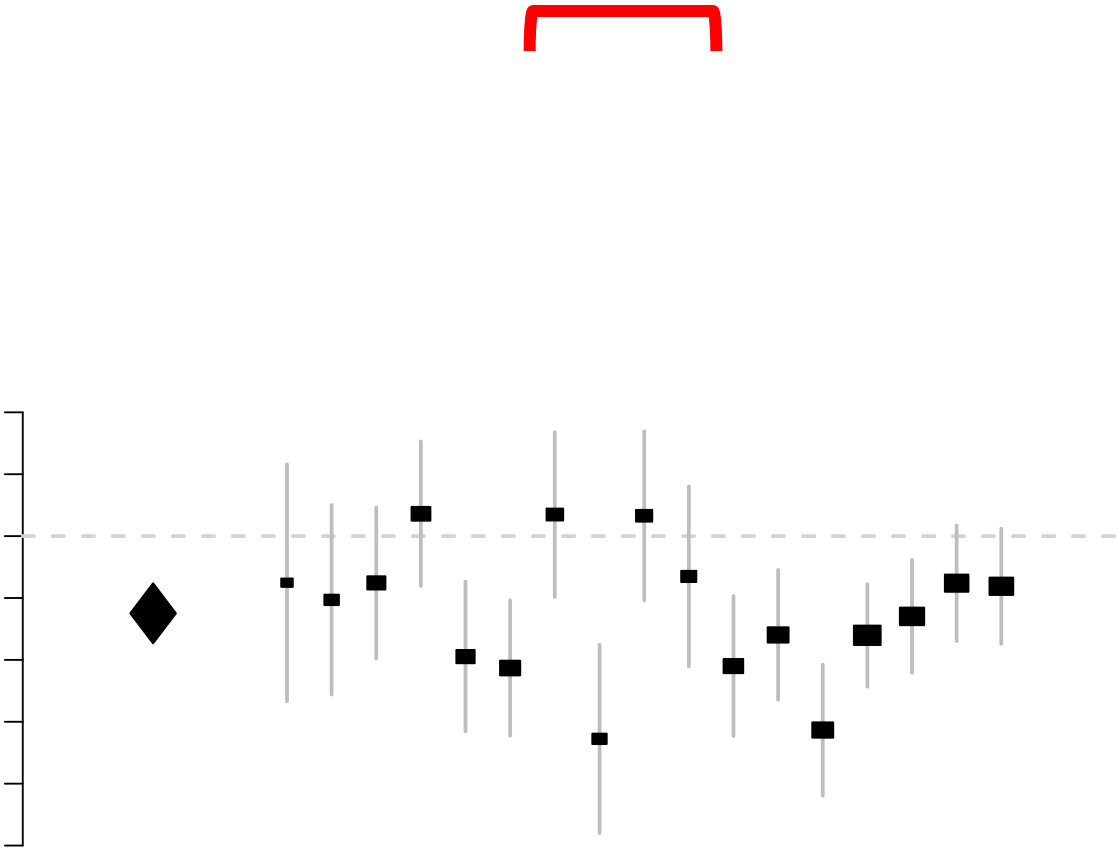
Han and Eskin, PLOS Genetics 2012

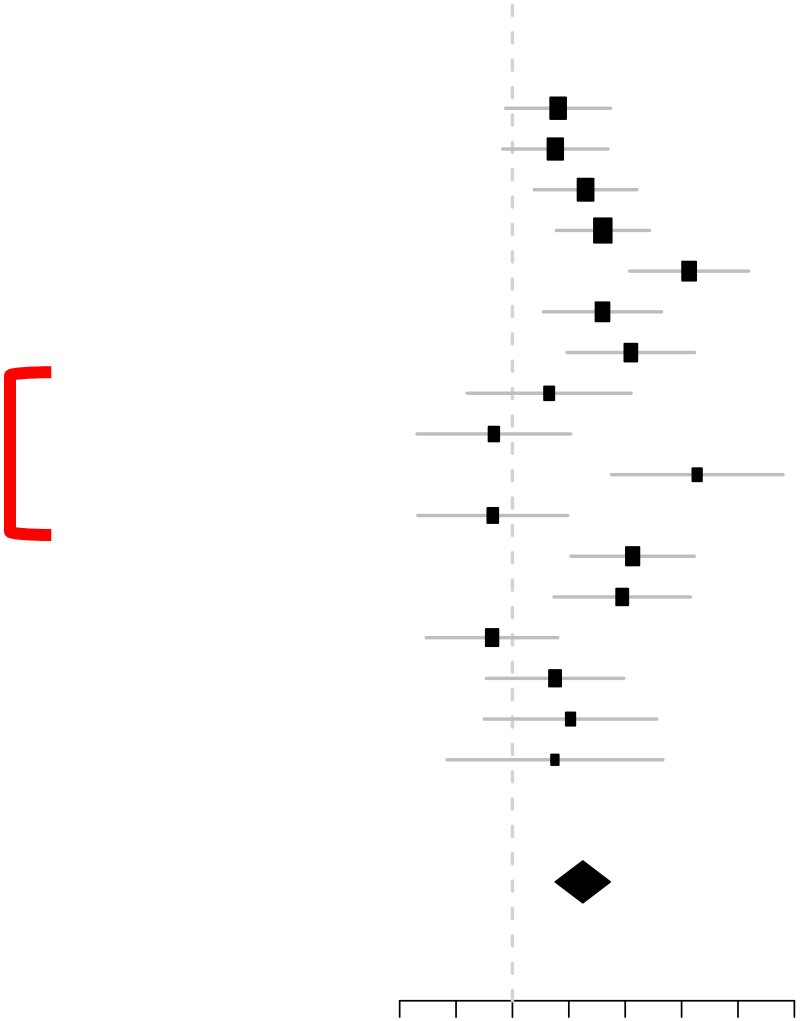




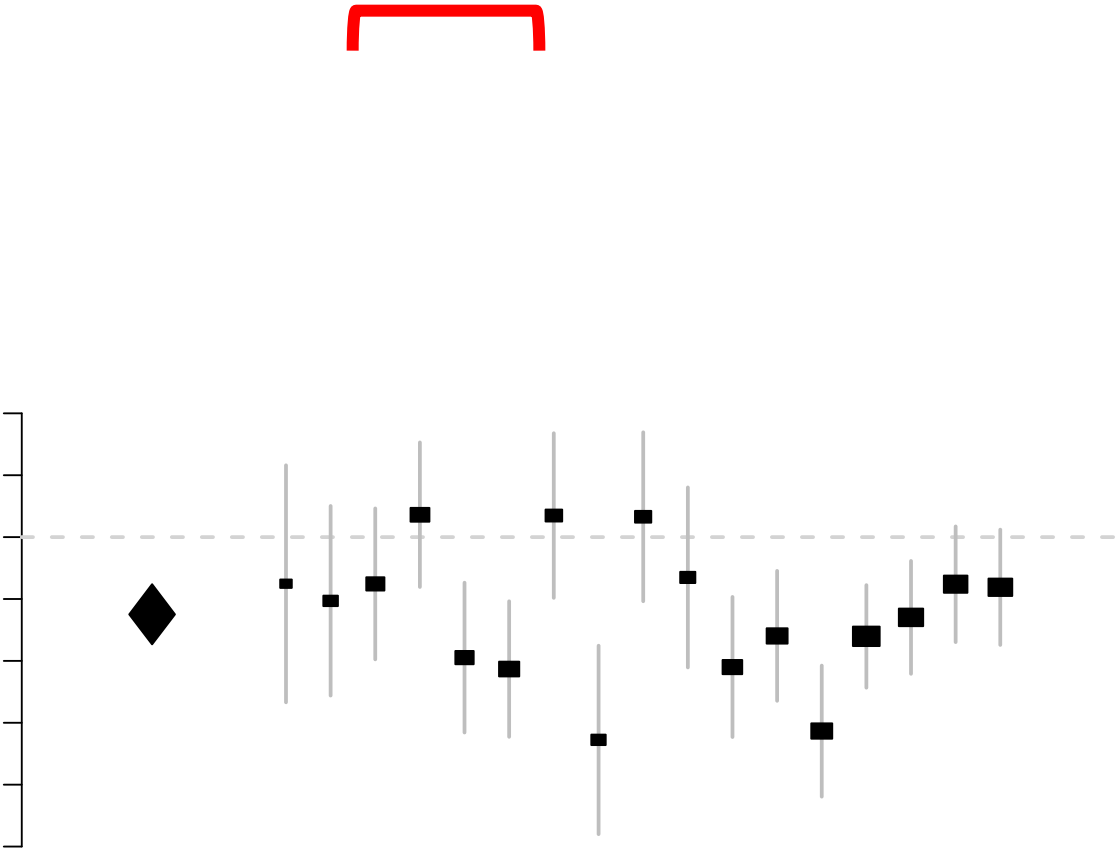


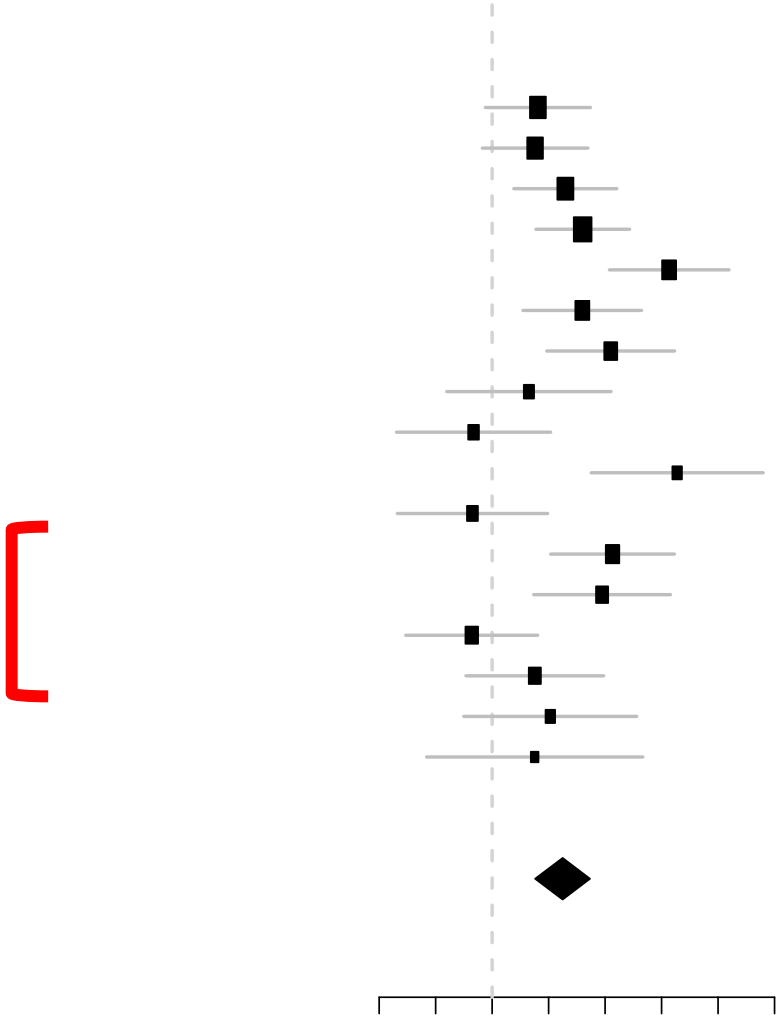
Gene x Diet Interaction



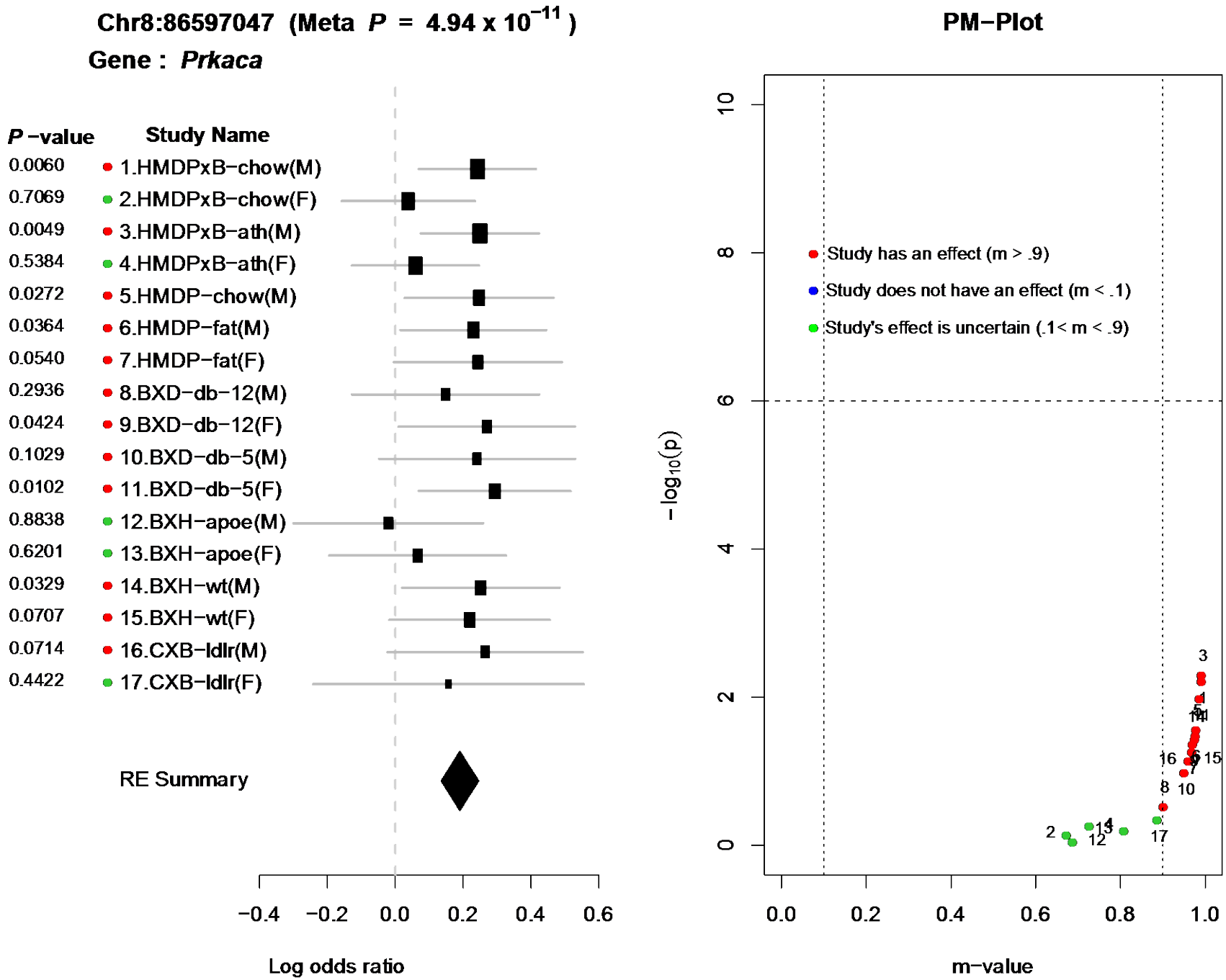


Gene x Sex Interaction





Gene x Apoe Knockout Interaction


Chr8:86597047 (Meta P = 4.94 x 10^-11)
Gene : Prkaca
P −value
Study Name
0.0060 1.HMDPxB−chow(M)
0.7069 2.HMDPxB−chow(F)
0.0049 3.HMDPxB−ath(M)
0.5384 4.HMDPxB−ath(F)
0.0272 5.HMDP−chow(M)
0.0364 6.HMDP−fat(M)
0.0540 7.HMDP−fat(F)
0.2936 8.BXD−db−12(M)
0.0424 9.BXD−db−12(F)
0.1029 10.BXD−db−5(M)
0.0102 11.BXD−db−5(F)
0.8838 12.BXH−apoe(M)
0.6201 13.BXH−apoe(F)
0.0329 14.BXH−wt(M)
0.0707 15.BXH−wt(F)
0.0714 16.CXB−ldlr(M)
0.4422 17.CXB−ldlr(F)
RE Summary
−0.4 −0.2 0.0 0.2 0.4 0.6
Log odds ratio
PM−Plot
Study has an effect (m > .9)
Study does not have an effect (m < .1)
Study's effect is uncertain (.1< m < .9)
−log10(p)
0 2 4 6 8 10
0.0 0.2 0.4 0.6 0.8 1.0
m−value

Study Results Summary

- We found 26 significant loci, many of which shows interesting GxE interactions by applying Meta-GxE to 17 mouse HDL genetic studies of 4,965 distinct animals.
- We make the connection between random effects meta-analysis and gene-by-environment interactions.
- Traditional approach requires prior knowledge including kinds of variable (e.g. sex, age, gene knockouts) and encoding of the variables (e.g. binary values, continuous values). Our method does not require explicit modeling of environmental variables.

- .

Fixed vs. Random effects models

Fixed effects model	Random effects model
Cochran 1954 Mantel and Haenszel 1959	DerSimonian and Nan Laird 1986
Assumes no heterogeneity	Explicitly accounts for heterogeneity
Variance of effect sizes $\tau^2 = 0$	Variance of effect sizes $\tau^2 \geq 0$

Statistics of Fixed and Random

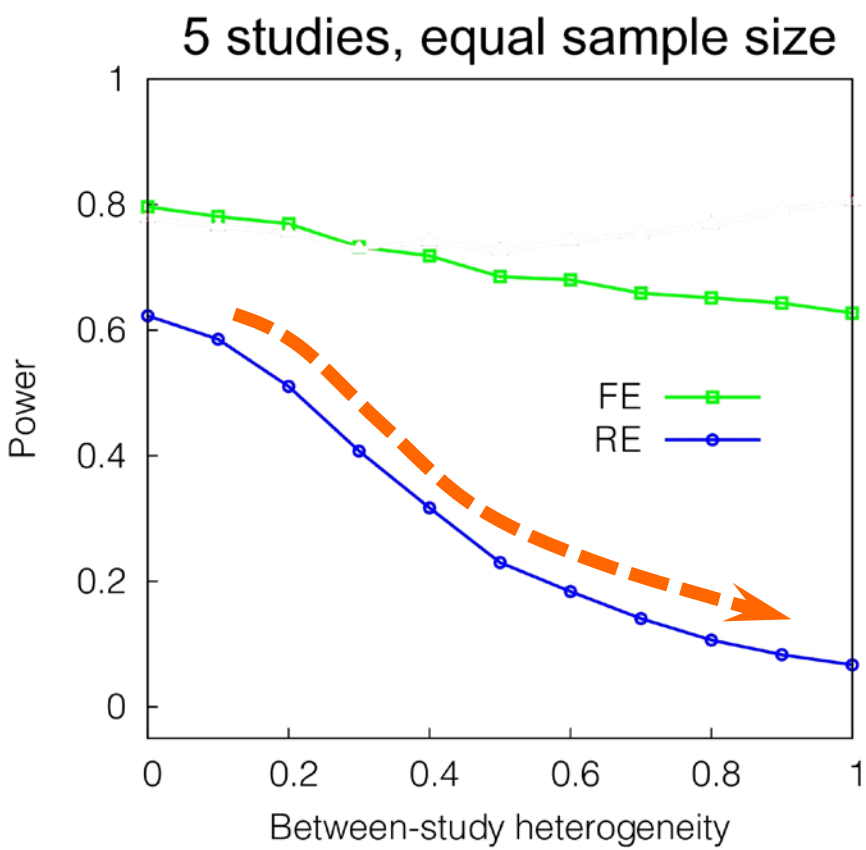
	Fixed effects model	Random effects model
Summary effect size	$X_{\mathrm{FE}} = \frac{\sum V_i^{-1} X_i}{\sum V_i^{-1}}$	$X_{\mathrm{RE}} = \frac{\sum (V_i + \tau^2)^{-1} X_i}{\sum (V_i + \tau^2)^{-1}}$
Z-score	$Z_{\mathrm{FE}} = \frac{X_{\mathrm{FE}}}{SE(X_{\mathrm{FE}})}$	$Z_{\mathrm{RE}} = \frac{X_{\mathrm{RE}}}{SE(X_{\mathrm{RE}})}$

X_i : Effect size estimate in study *i*

V_i : Variance of X_i

Random effects model is severely underpowered

- Expectation
  - $\tau^2=0$: Fixed>Random
  - $\tau^2>0$: Fixed<Random
- Observation
  - $\tau^2=0$: Fixed>Random
  - $\tau^2>0$: Fixed>>Random
- Why?



Implicit assumption of traditional RE

- Using z-score is equivalent to LRT assuming heterogeneity under the null

$$L_0 = \prod_i \frac{1}{\sqrt{2\pi(V_i + \hat{\tau}^2)}} \exp\left(-\frac{X_i^2}{2(V_i + \hat{\tau}^2)}\right)$$

$$L_1 = \prod_i \frac{1}{\sqrt{2\pi(V_i + \hat{\tau}^2)}} \exp\left(-\frac{(X_i - \mu)^2}{2(V_i + \hat{\tau}^2)}\right)$$

X_i : Effect size estimate in study *i*
V_i : Variance of X_i

$$Z_{\mathrm{RE}} = \frac{X_{\mathrm{RE}}}{SE(X_{\mathrm{RE}})}$$

Heterogeneity in GWAS

Does heterogeneity exist under the null? **O** / □

- Causes:
  - Different populations
    - Same effects, different LD □
    - Different effects due to GxG □
  - Different phenotypic definitions (different cutoffs) □
  - Different environmental factors (GxE) □
  - Different usage of covariates □
  - Different genetic structure (cross-disease) □
  - Different imputation quality □

New Random Effects Model

- LRT assuming $\tau^2=0$ under the null

$$L_0 = \prod_i \frac{1}{\sqrt{2\pi V_i}} \exp\left(-\frac{X_i^2}{2V_i}\right)$$

No heterogeneity

$$L_1 = \prod_i \frac{1}{\sqrt{2\pi(V_i+\tau^2)}} \exp\left(-\frac{(X_i-\mu)^2}{2(V_i+\tau^2)}\right)$$

Heterogeneity

$$S_{\text{New}} = -2\log(\lambda) = \sum \log\left(\frac{V_i}{V_i+\hat{\tau}^2}\right) + \sum \frac{X_i^2}{V_i} - \sum \frac{(X_i-\hat{\mu})^2}{V_i+\hat{\tau}^2}$$

- Asymptotically follow 50:50 mix of 1 and 2 df. χ^2
- Sample size is small (#study) → Tabulated p-values

Han and Eskin, American Journal of Human Genetics 2011

Decomposition

$$
\begin{aligned}
S_{\text{New}} &= \sum \log\left(\frac{V_i}{V_i+\hat{\tau}^2}\right) + \sum \frac{X_i^2}{V_i} - \sum \frac{(X_i-\hat{\mu})^2}{V_i+\hat{\tau}^2} \\
&= \left\{\sum \frac{X_i^2}{V_i} - \sum \frac{(X_i-\hat{\mu}')^2}{V_i}\right\} + \left\{\sum \log\left(\frac{V_i}{V_i+\hat{\tau}^2}\right) + \sum \frac{(X_i-\hat{\mu}')^2}{V_i} - \sum \frac{(X_i-\hat{\mu})^2}{V_i+\hat{\tau}^2}\right\} \\
&= S_{\text{FE}} + S_{\text{Het}}
\end{aligned}
$$

Squared FE statistic

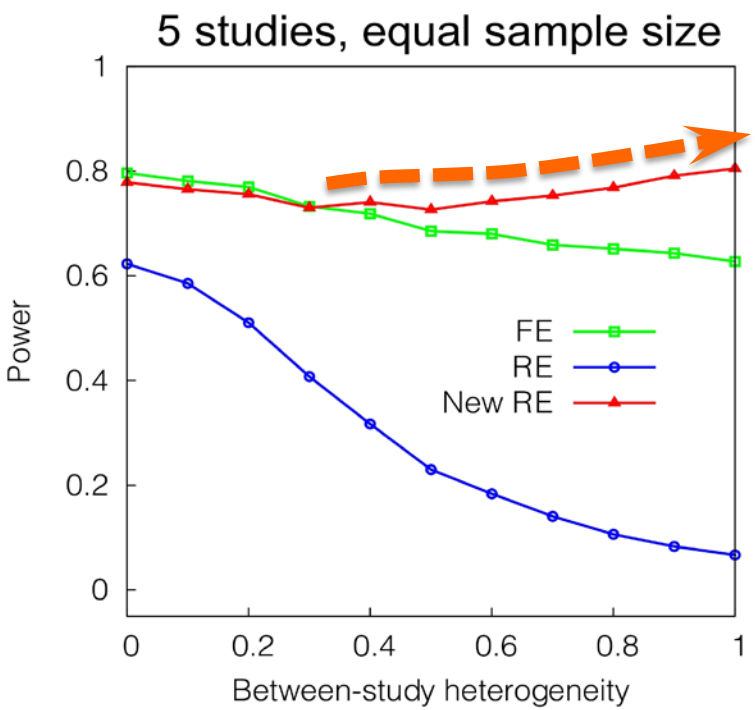
LRT statistic testing for heterogeneity (asymptotically the same as Cochran's Q)

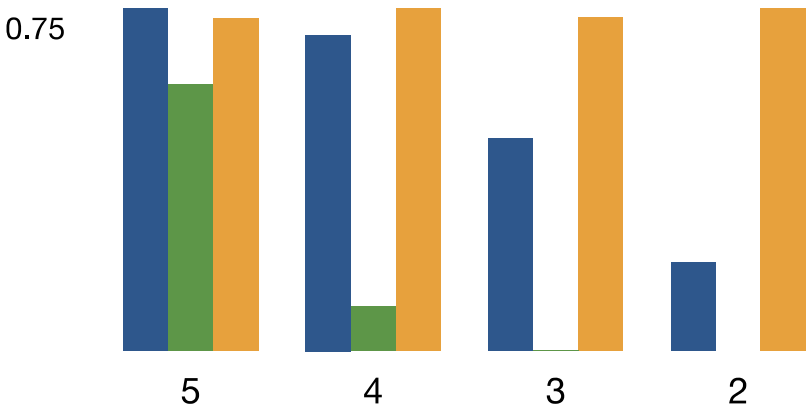
- Shows heterogeneity is working as "signal" in addition to main affect

Han and Eskin, American Journal of Human Genetics 2011

Power of new method

- Expectation
  - $\tau^2=0$: Fixed>Random
  - $\tau^2>0$: Fixed<Random
- Observation
  - $\tau^2=0$: Fixed>Random
  - $\tau^2>0$: Fixed<Random
- False positive rate is controlled.





Many studies use new RE

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NATURE GENETICS | LETTER

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Identification of common variants associated with human hippocampal and intracranial volumes

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Human Molecular Genetics

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CD33: increased inclusion of exon 2 implicates the Ig V-set domain in Alzheimer's disease susceptibility

Towfique Raj[1,3,4], Katie J. Ryan[1,3,4,5], Joseph M. Replogle[1,4], Lori B. Chibnik[1,3,4], Laura Rosenkrantz[1], Anna Tang[1], Katie Rothamel[2], Barbara E. Stranger[6,7], David A. Bennett[8], Denis A. Evans[9], Philip L. De Jager[1,3,4,5,†,*] and

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Published: May 31, 2012 • DOI: 10.1371/journal.pgen.1002741

Human Molecular Genetics

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Genome-wide association study of ancestry-specific TB risk in the South African Coloured population

Emile R. Chimusa[1,†,*], Noah Zaitlen[7,†], Michelle Daya[6], Marlo Möller[6],

Molecular Psychiatry

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Original Article

Molecular Psychiatry (2013) **18,** 195–205; doi:10.1038/mp.2011.157; published

There is a Corrigendum (1 February 2013) associated wit

Genome-wide association study meta-analys European and Asian-ancestry samples identi novel loci associated with bipolar disorder

D T Chen[1], X Jiang[1], N Akula[1], Y Y Shugart[1], J R Wendland[1], C L Kassem[1], J-H Park[2], N Chatterjee[2], S Jamain[3], A Cheng[4], M L T G Schulze[1,5], S Cichon[7], M M Nöthen[7], M Rietschel[8], BiGS[9] an

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Oxford Journals › Life Sciences & Medicine › Human Molecular Genetics › Volume 21, Issue

A genome-wide association study of COPD identifies a susceptibility locus on chromosome 19q13

Michael H. Cho[1,2,*], Peter J. Castaldi[1], Emily S. Wan[1,2], Mateusz Siedlinski[1], Craig P. Hersh[1,2], Dawn L. Demeo[1,2], Blanca E. Himes[1], Jody S. Sylvia[1], Barbara J. Klanderman[1], John P. Ziniti[1], Christoph Lange[3], Augusto A. Litonjua[1,2], David Sparrow[4,5,6], Elizabeth A. Regan[7], Barry J. Make[7], John E. Hokanson[8], Tanda Murray[9], Jacqueline B. Hetmanski[9], Sreekumar G. Pillai[10,†], Xiangyang Kong[11], rson[10], Ruth Tal-Singer[11], David A. Lomas[12], Harvey O. Coxson[13], s[10], William MacNee[14], Jørgen Vestbo[15], Julie C. Yates[10], Alvar Agusti[16], erley[17], Bartolome Celli[2], Courtney Crim[10], Stephen Rennard[18], .9, Per Bakke[20], Amund Gulsvik[20], James D. Crapo[7], Terri H. Beaty[9], man[1,2] and on behalf of the ICGN, ECLIPSE, and COPDGene Investigators iations

nature genetics

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NATURE GENETICS | LETTER

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Genome-wide association meta-analysis identifies new endometriosis risk loci

Dale R Nyholt, Siew-Kee Low, Carl A Anderson, Jodie N Painter, Satoko Uno, Andrew P Morris, Stuart MacGregor, Scott D Gordon, Anjali K Henders, Nicholas G Martin, John Attia Elizabeth G Holliday, Mark McEvoy, Rodney J Scott, Stephen H Kennedy, Susan A Treloar, Stacey A Missmer, Sosuke Adachi, Kenichi Tanaka, Yusuke Nakamura, Krina T Zondervan, Hitoshi Zembutsu & Grant W Montgomery

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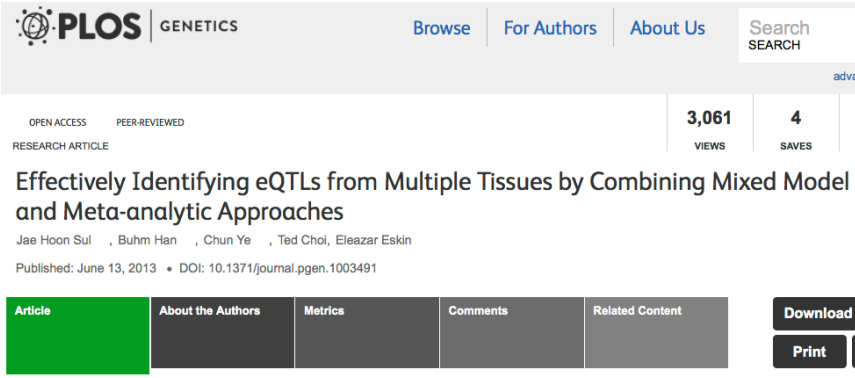
Krzysztof Kiryluk, Yifu Li, Simone Sanna-Cherchi, Mersedeh Rohanizadegan, Hitoshi Suzuki, Frank Eitner, Holly J. Snyder, Murim Choi, Ping Hou, Francesco Scolari, Claudia Izzi, Maddalena Gigante, Loreto Gesualdo, [...], Ali G. Gharavi, [view all]

Published: June 21, 2012 • DOI: 10.1371/journal.pgen.1002765

Extensions

- **Multi-tissue expression quantitative loci (eQTL) analysis**
  - Combining multiple tissues gives better power
  - RE + Linear mixed model + decoupling



- **Gene-environmental interaction analysis**
  - Meta-analyze studies with different environments
  - Heterogeneity = interaction

Sul*, Han*, Ye* et al. PLOS Genetics, 2013
Kang*, Han*, Furlotte* et al. PLOS Genetics, 2013

Other Methods Projects

- Meta-Analysis
  - Random Effects (Buhm Han, AJHG 2011)
  - Interpreting (Buhm Han, PLoS Genetics 2011)
  - Imputation Errors (Noah Zaitlen, GenEpi 2010)
  - Population Structure (Nick Furlotte, Genetics 2012)
  - Meta-GxE (Eun Yong Kang, PLoS Genetics 2014)
  - Meta-Sex Specific (Kang, unpublished, 2014)
- eQTL Methods
  - Multi-Tissue eQTLs (Jae Hoon Sul, PLoS Genetics 2013)
  - Speeding up computation (Emrah Kostem, JCB 2013)
  - Correcting for confounding (Joo, Genome Biology, 2014)
- Mixed Models
  - Longitudinal data (Furlotte, Gen Epi 2012)
  - Population Structure and Selection (Jae Hoon Sul, NRG 2013)
  - GxE Mixed Models (Jae Hoon Sul, unpublished)
  - Heritability Partitioning (Emrah Kostem, AJHG 2013)
- Spatial Ancestry (Wen-Yun Yang, Nature Genetics 2012)
- Rare Variants Association (Jae-Hoon Sul, Genetics 2011, JCB 2012)
- Identification of Relatives without Compromising Privacy (He, Genome Research, 2014)
- Gene-Gene Interaction Detection (Wang, JCB 2014)
- Virus Quasispecies Assembly (Bioinformatics, 2014)
- IBD Association Mapping (Bioinformatics, 2013)
- Finw Mapping (Farhad Hormozdiari, 2014)

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- Eun Yong Kang
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- Richard Davis
- Diana Shih

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