

Cross-cancer genome-wide pleiotropy analysis based on GAME-ON and GECCO across five common cancers: Lung, ovary, breast, prostate, and colorectal cancer

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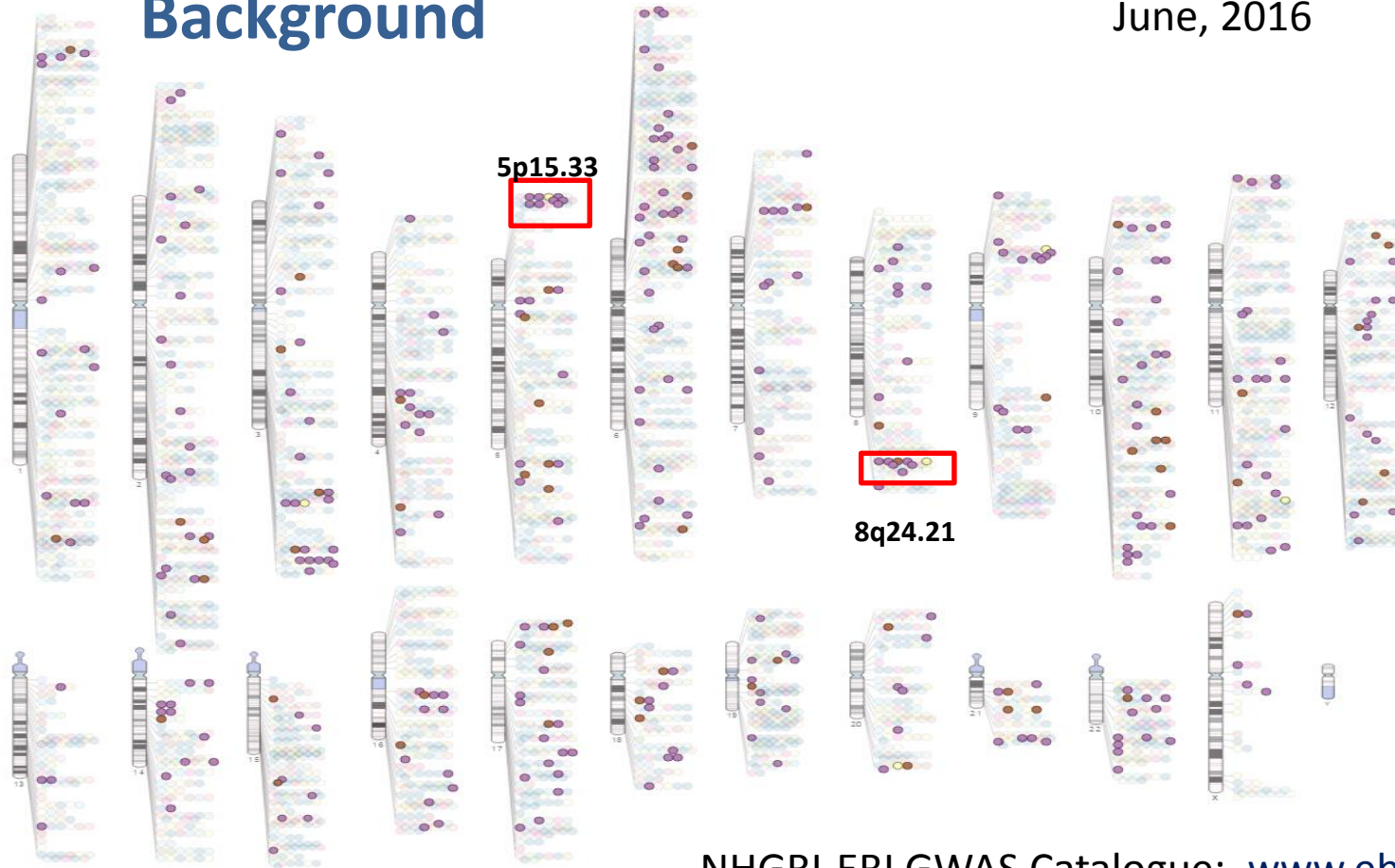
Cross-Cancer Pleiotropy: Background

➤ Why pleiotropy analysis?

- Pathways that are common across carcinogenesis of different tumor types
 - Cell cycle, DNA repair, Inflammation, etc
- Hypothesize that some genetic variants may exert modest effects in individual tumor types, and can only be detected when analyzing cancer as a whole.

Cross-Cancer Pleiotropy: Background

~552 loci related to cancer predisposition,
June, 2016



NHGRI-EBI GWAS Catalogue: www.ebi.ac.uk/gwas

Cross-Cancer Pleiotropy: Background

- NCI Cross-Cancer collaboration based on 5 funded research programs
 - Lung, Colorectal, Prostate, Breast and Ovary cancer
 - GAME-ON: Genetic Associations and Mechanisms in Oncology
 - Aim to promote post-GWAS cross-cancer collaborations



Cross-Cancer Pleiotropy: Study Populations

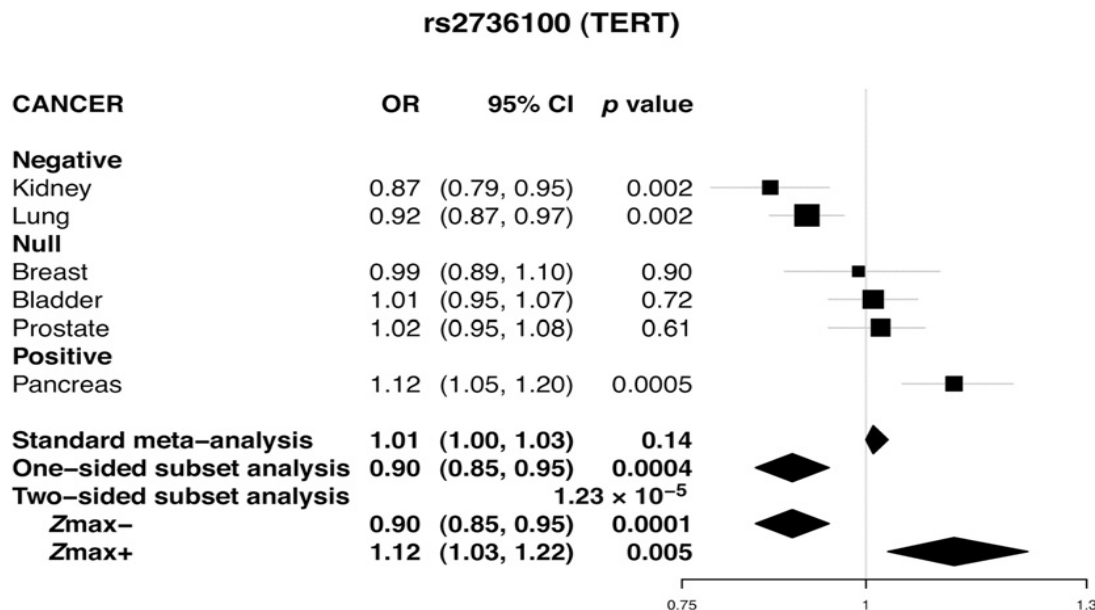
Cancer	Discovery (GAME-ON)		
	no.	Ca.	Con.
Lung	6	12160	16838
Adenocarcinoma	6	3718	15871
Squamous cell	6	3422	16015
Colorectal- GECCO	13	5100	4831
Colorectal- CORECT	6	10314	12857
Prostate	6	14160	12724
Aggressive	6	4450	12724
Breast	11	15748	18084
ER negative	8	4939	13128
Ovary	3	4369	9123
Serous	3	2556	9123
Endometrioid	3	715	9123
TOTAL	45	61,851	61,820

Cross-Cancer Pleiotropy: Study Populations

Cancer	Discovery (GAME-ON)			Replication			Generalizability		
	no.	Ca.	Con.	Study	Ca.	Con.	Study	Case	Control
Lung	6	12160	16838	deCODE	3865	196658	Nanjing	2331	3077
Adenocarcinoma	6	3718	15871	Harvard	984	970	Japan	1575	3363
Squamous cell	6	3422	16015						
Colorectal- GECCO	13	5100	4831	deCODE	3546	236404			
Colorectal- CORECT	6	10314	12857						
Prostate	6	14160	12724	deCODE iCOGS	4858 20219	83103 20440	LAPC/MEC JAPC/MEC	1034 980	1046 1005
Aggressive	6	4450	12724				AAPC	4853	4678
Breast	11	15748	18084	deCODE	5318	280808	Shanghai	2867	2285
ER negative	8	4939	13128				LABC/MEC AABC	1497 3015	3213 2743
Ovary	3	4369	9123	deCODE	716	111373			
Serous	3	2556	9123	iCOGS	16283	23491			
Endometrioid	3	715	9123						
TOTAL	45	61,851	61,820		55,789	330,490		18,152	21,410

Cross-Cancer Pleiotropy: Method

- What is the problem with the standard meta-analytical approach?
 - Cannot take associations with opposite directions into account
 - Sub-set based meta-analysis



Cross-Cancer Pleiotropy: Method

Cancer Site Specific Analysis

Logistic regression followed by meta-analysis at each cancer site
(lung, colorectal, prostate, breast and ovarian cancers and subtypes)
-> Summary results by variant and cancer site

Subset Meta-Analysis

Cross-cancer association tests
Threshold: $P \leq 5 \times 10^{-7}$

Fixed Effects Meta-Analysis

Cross-cancer association tests
Threshold : $P \leq 5 \times 10^{-7}$

Variant-Cancer Site Associations

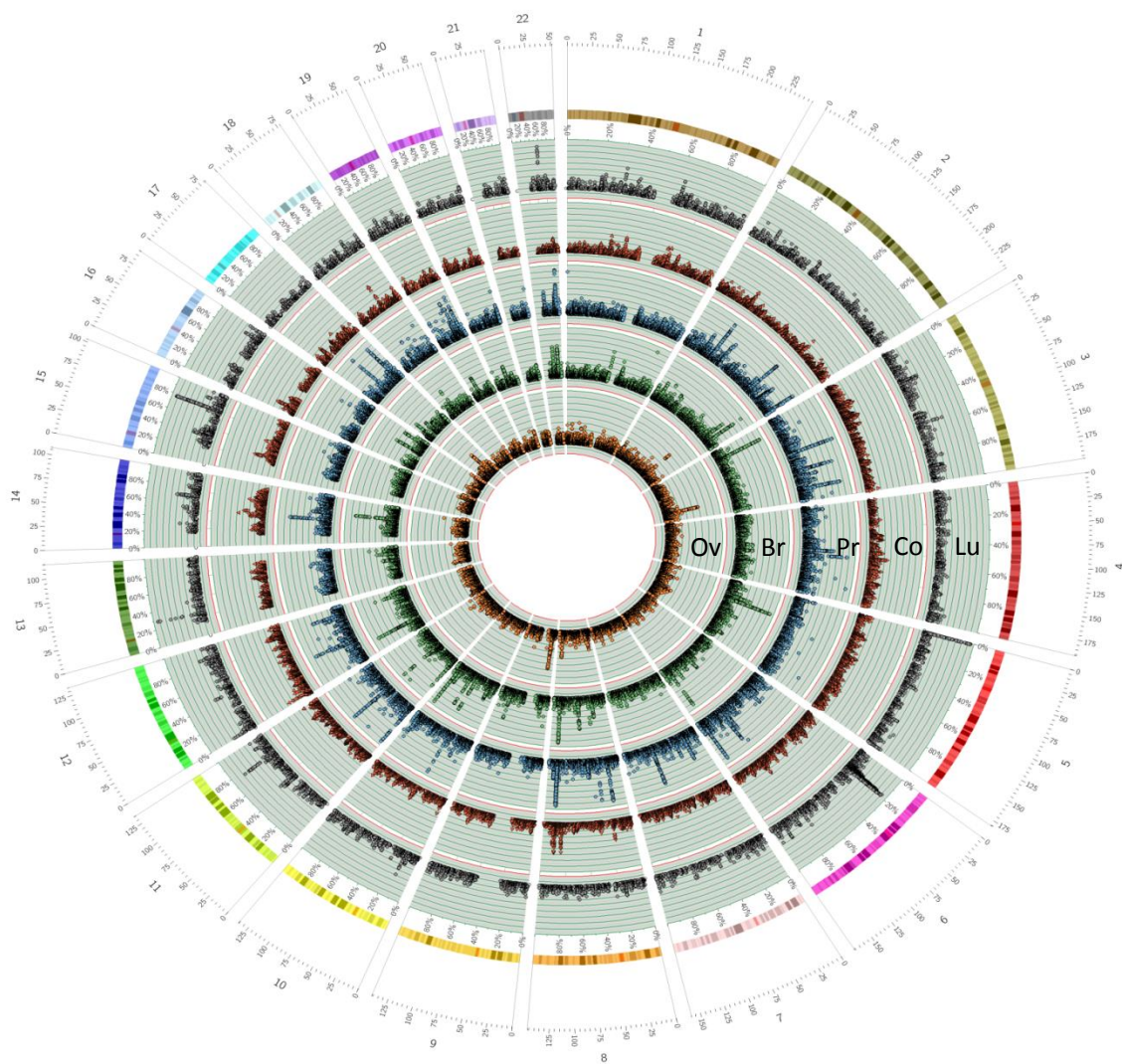
Threshold: Associations at two cancer sites ($P \leq 5 \times 10^{-3}$)

Replication of variant-cancer site associations

Replication of specific variant -cancer site associations that contributed to the pleiotropic signal in populations of European descent.
Further investigation for cross-ethnic group generalizability

Cross-Cancer Pleiotropy: Results

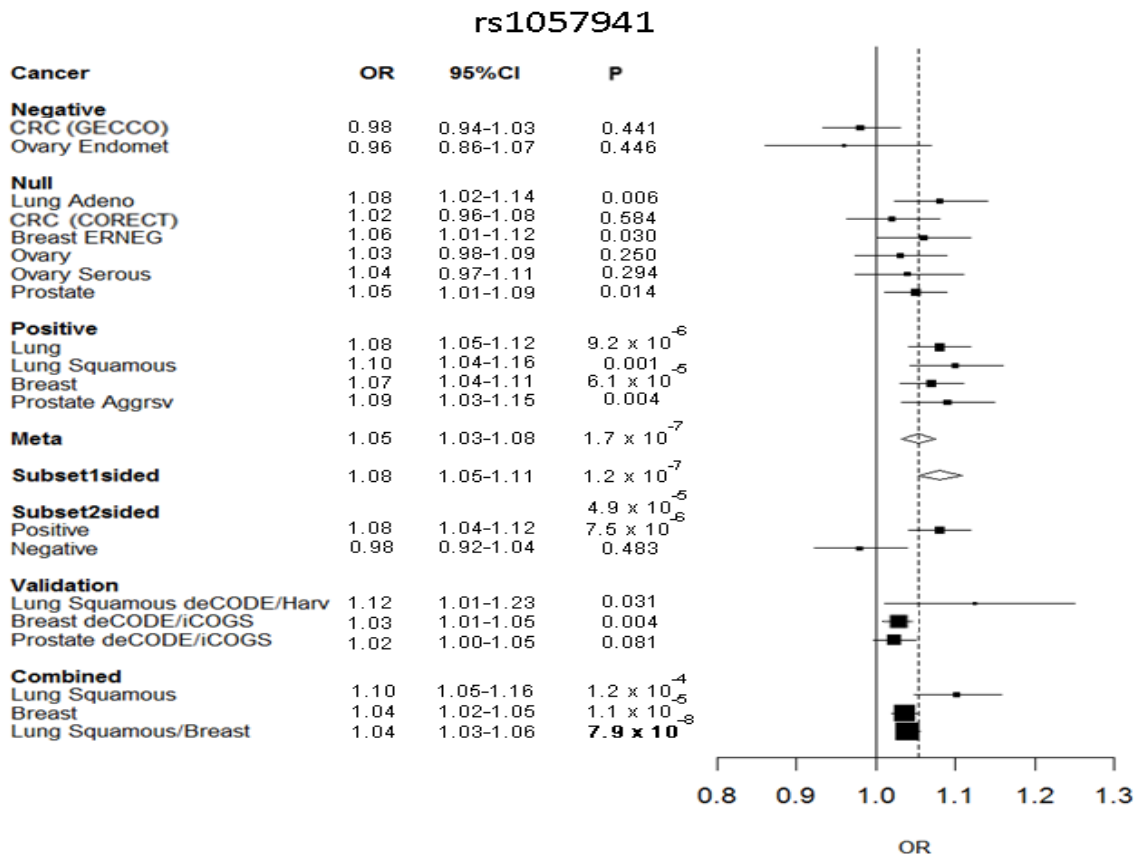
- Prioritized 190 variants in 33 regions for validations
 - Harvard, deCODE, iCOGS
 - N= 55,789 cases, 330,490 controls
- 4 regions replicated
 - 1q22
 - 2q33
 - 9p21.3
 - 13q13.1



Cross-Cancer Pleiotropy: 1q22 Results

➤ Novel region at 1q22, not previously implicated in cancer

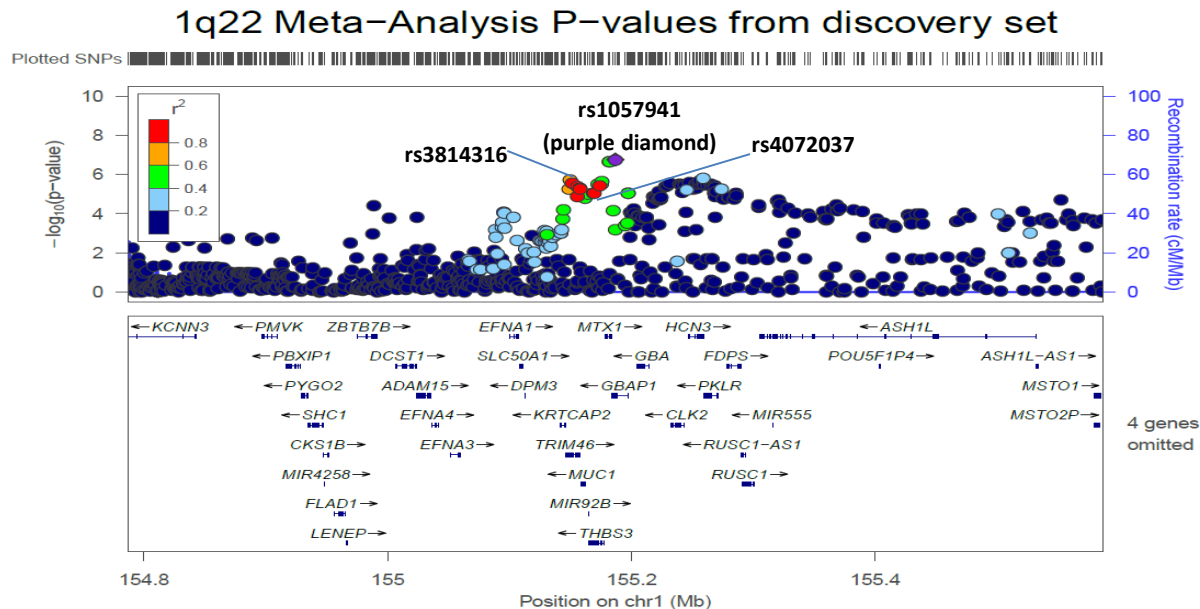
- Associated with lung, breast and prostate
- Validated in deCODE, Harvard, and iCOGS
- Combined p-value = 7.9×10^{-8}



Cross-Cancer Pleiotropy: 1q22 Results

➤ Novel region at 1q22, not previously implicated in cancer

- Associated with lung, breast and prostate
- Validated in deCODE, Harvard, and iCOGS
- Combined p-value = 7.9×10^{-8}
- A cluster of genes related to connective tissue growth factors and glycoproteins



ADAM15, Metalloproteinase Domain 15

THBS3, thrombospondin 3

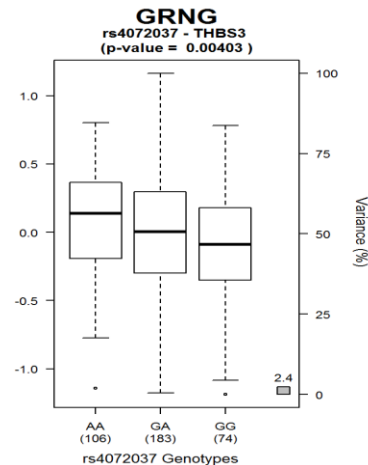
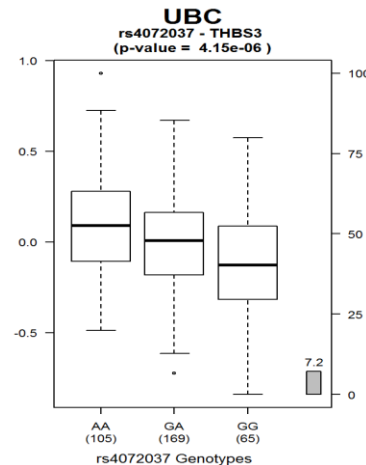
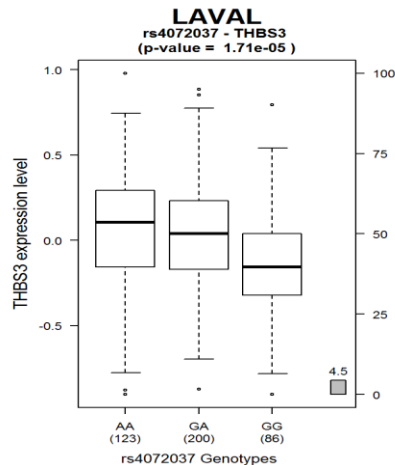
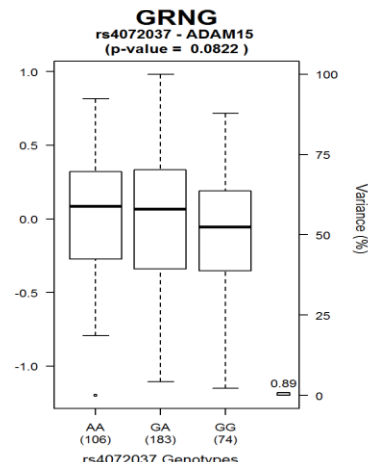
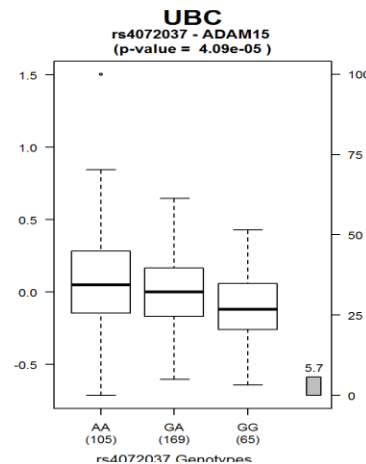
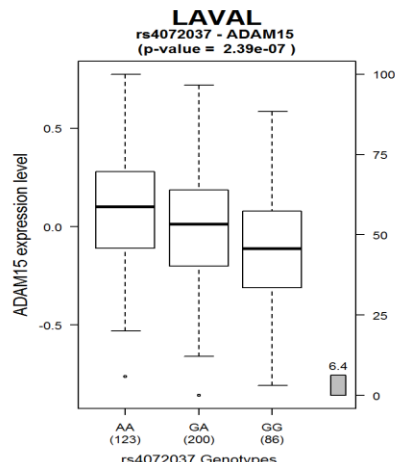
Cross-Cancer Pleiotropy: 1q22 Results

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eQTL analysis (M. Obeidat, Y. Bosse)(N=1,111)

- Risk allele (A) is associated with increased expression of *ADAM15* and *THBS3*
- ADAM15* is over-expressed in both lung and breast cancer



ADAM15, Metallopeptidase Domain 15

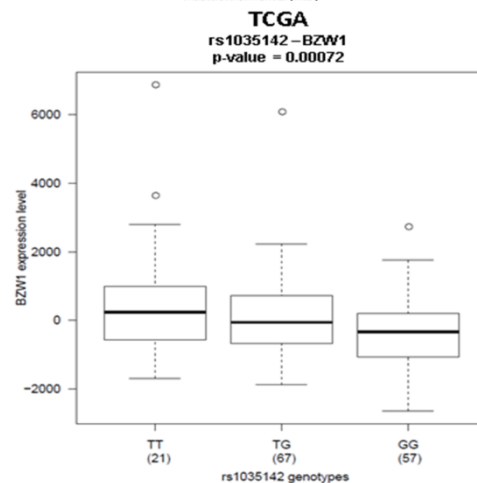
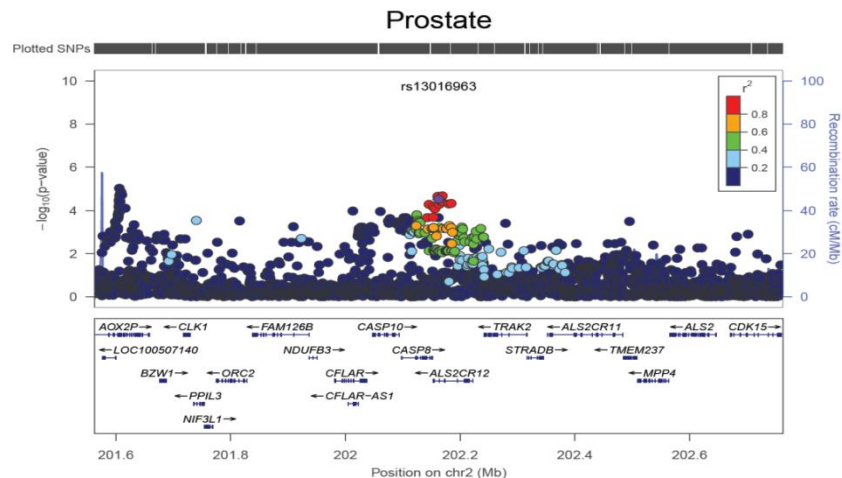
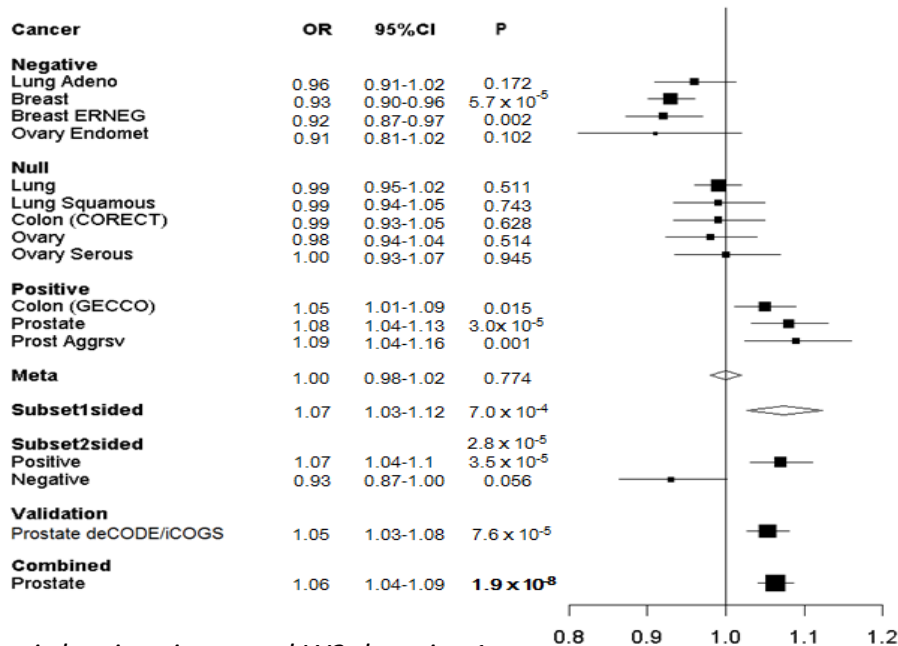
THBS3, thrombospondin 3

Cross-Cancer Pleiotropy: 2q33.1 Results

- 2q33.1 *CASP8* (known for breast cancer and melanoma) and prostate cancer
- eQTL analysis showed association with *BZW1* expression

- *BZW1*: activate H4 gene transcription, server as co-regulator of transcription factors involved in cell cycles
- Implicated in the mucoepidermoid carcinoma tumor growth

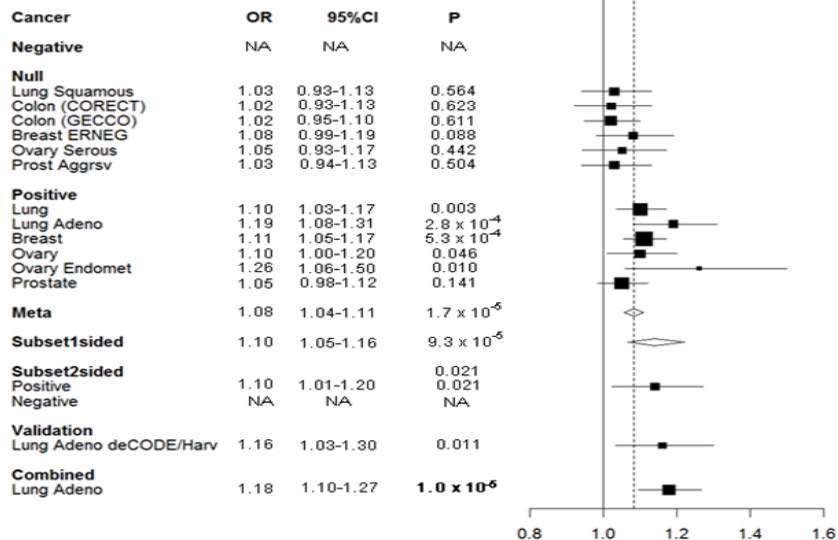
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BZW1, basic leucine zipper and W2 domains 1

Cross-Cancer Pleiotropy: 9p21.3 Results

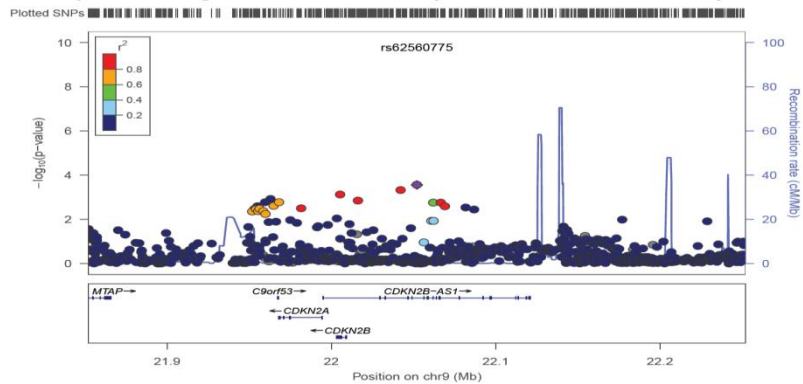
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➤ 9p21.3 *CDKN2B-AS1*

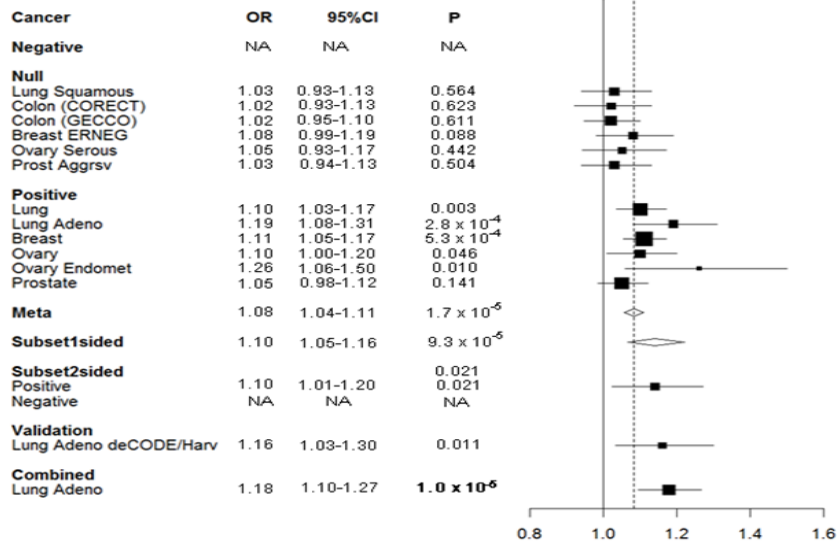
- *CDKN2B*-Antisense RNA1
- Displays a complex nature of associations with multiple cancer sites
- Previously known for breast cancer, lung squamous cell carcinoma and melanoma
- Identified new associations with lung adenocarcinoma and prostate cancer
- However most of variants are associated with only 1 tumor type
- Suggesting multiple causal variants in this region, akin to 8q24

9p21.3 Lung Adenocarcinoma p-values from discovery set

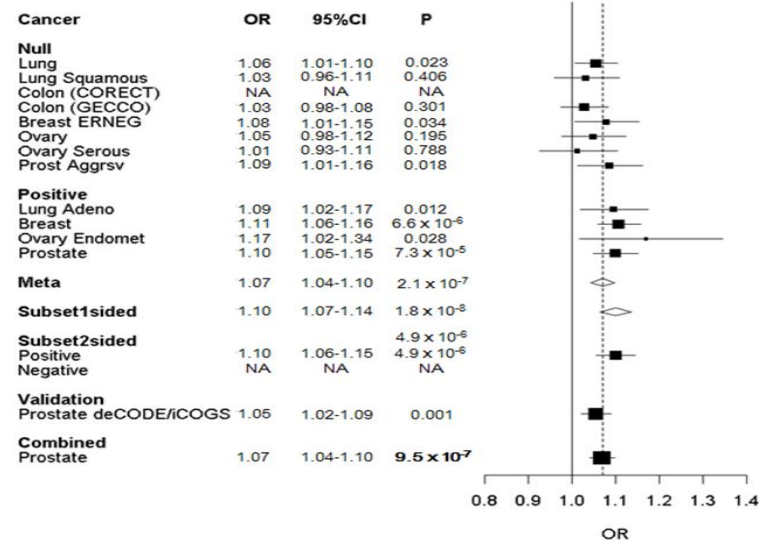


Cross-Cancer Pleiotropy: 9p21.3 Results

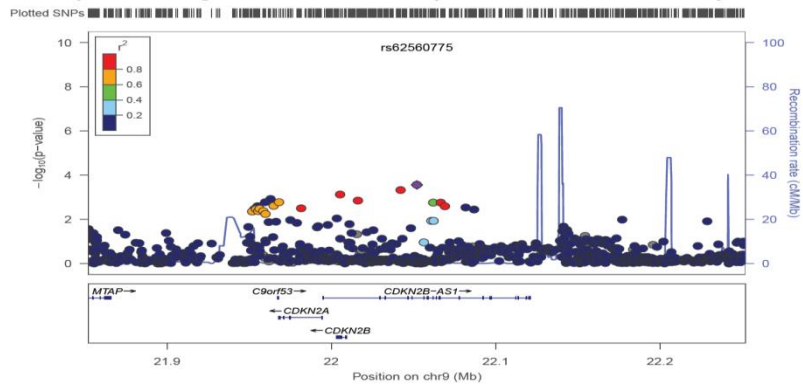
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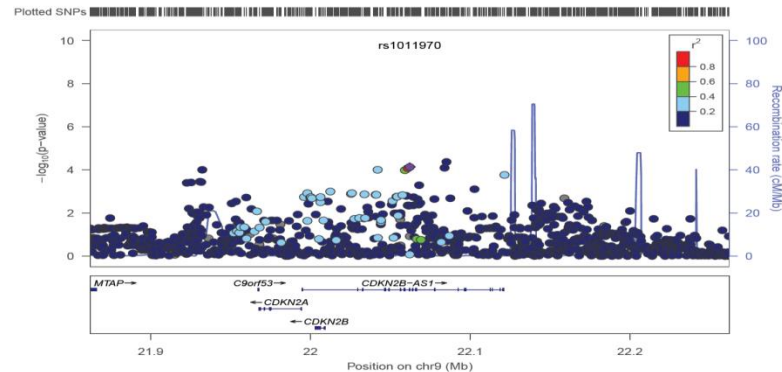
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9p21.3 Lung Adenocarcinoma p-values from discovery set

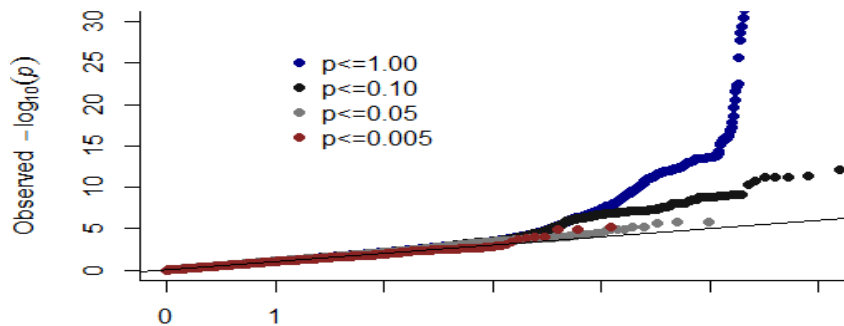


9p21.3 Prostate cancer p-values from discovery set

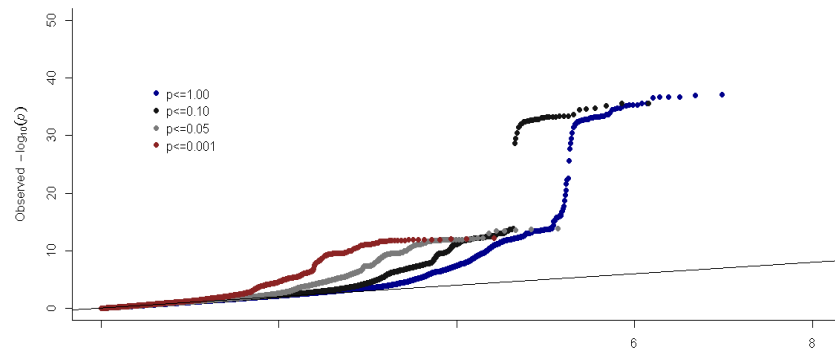


Cross-Cancer Pleiotropy: Conditional Q-Q Plots

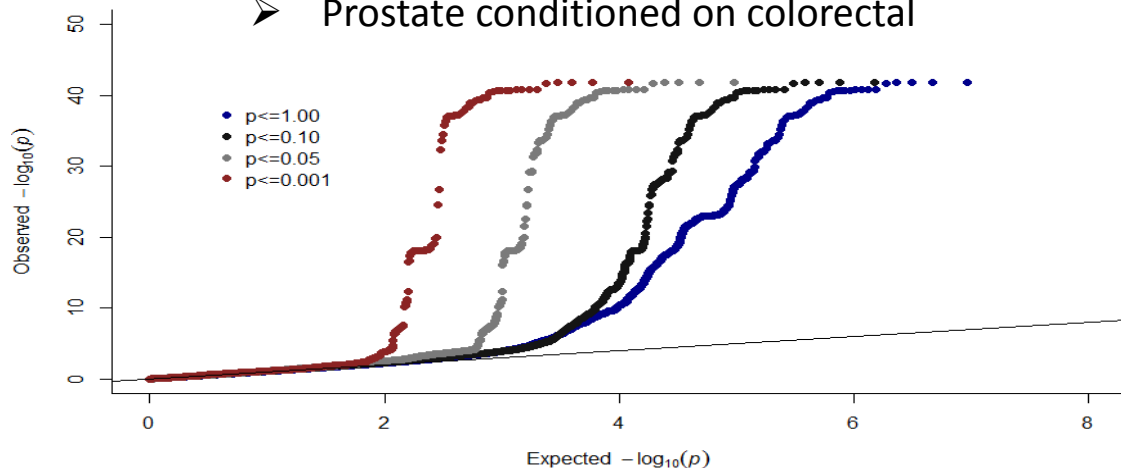
➤ Breast conditioned on colorectal



➤ Breast conditioned on prostate



➤ Prostate conditioned on colorectal



Summary

- It is one of the largest cross-cancer pleiotropy analysis conducted with 117,640 cancer patients, 392,310 controls combining both discovery and replication stage
- Main findings
 - 1q22 : new cancer locus, breast and lung cancer, supported by eQTL analysis. Has also been identified as a gastric cancer locus since
 - 2q33.1: Known for breast cancer and melanoma, new associations with prostate cancer
 - 9p21.3: known for lung squamous cell carcinoma and breast cancer, new associations with lung adenocarcinoma and prostate cancer
- Since our replication set is smaller than the discovery set, we cannot preclude the possibility of more pleiotropic regions
- These results underline the importance of pleiotropy analysis

Acknowledgement



Lunenfeld-Tanenbaum
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Transdisciplinary Research in Cancer of the Lung

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Southern California

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UNIVERSITY OF
CAMBRIDGE

MOFFITT
CANCER CENTER

FRED HUTCHINSON
CANCER RESEARCH CENTER

National Cancer Institute
at the National Institutes of Health

- **LTRI:** Gord Fehringer, Xuchen Zong, Yonathan Brhane
- **TRICL:** C. I. Amos, P. Brennan, H. Bickeböllner, R. Houlston, M. T. Landi, N. Caporaso, A. Risch
- **ELLIPSE:** B. E. Henderson, C. A. Haiman, F. Schumacher, A. Amin Al Olama, S.I Berndt, E. Giovannucci, H. Grönberg, Z. Kote-Jarai, J. Ma, K. Muir, M. Stampfer, V. L. Stevens, F. Wiklund, W. Willett
- **FOCI and eQTL ovary:** T. A. Sellers, E. L. Goode, J. Permuth-Wey, H. Risch, B. M. Reid, S. Bezieau, H. Brenner, A. T. Chan, J. Chang-Claude, T. J. Hudson, J.K Kocarnik, P. A. Newcomb, R. E. Schoen, M. L. Slattery, E. White, J. Schildkraut
- **DRIVE:** D. J. Hunter, P. Kraft, D. Easton, S. Lindström, M. Adank, H. Ahsan, K. Aittomäki, L. Baglietto, S. Berndt, C. Blomquist, F. Canzian, K. Czene, I. dos-Santos-Silva, A. H. Eliassen, J. Figueroa, Dieter Flesch-Janys, O. Fletcher, M. Garcia-Closas, M. M. Gaudet, Per Hall, A. Hazra, HEBON, R. Hein, A. Hofman, J. L. Hopper, A. Irwanto, M. Johansson, N. Johnson, R. Kaaks, M. G. Kibriya, P. Lichtner, J. Liu, E. L. Lund, E. Makalic, A. Meindl, B. Müller-Myhok, Taru A. Muranen, Heli Nevanlinna, P. H. Peeters, J. Peto, R. L. Prentice, N. Rahman, M. J. Sanchez, D. F. Schmidt, R. K. Schmutzler, M. C. Southey, R. Tamimi, R. C. Travis, C. Turnbull, A. G. Uitterlinden, Z. Wang, A. S. Whittemore, R. Yang, W. Zheng
- **CORECT:** S. Gruber, F. Schumacher, D.D. Buchanan, G. Casey, D. V. Conti, C. K. Edlund, S. Gallinger, R. W. Haile, M. Jenkins, L. Le Marchand, L. Li, N. M. Lindor, S. L. Schmit, S. N. Thibodeau
- **GECCO:** Jian Gong, Ulrike Peters on behalf of Genetics and Epidemiology of Colorectal Cancer Consortium
- **deCODE replication:** Thorunn Rafnar, Julius Gudmundsson, Simon N Stacey, Kari Stefansson, Patrick Sulem
- **The PRACTICAL consortium:** Rosalind Eeles; **Ovarian Cancer Association Consortium (OCAC):** Paul Pharoah Y. Ann Chen, Jonathan P. Tyrer
- **Harvard replication:** David C. Christiani, Yongyue Wei; **MEC:** African American Breast Cancer GWAS Consortium, African Ancestry Prostate Cancer GWAS Consortium
- **Chinese lung cancer:** Hongbing Shen, Dr Zhibin Hu, Xiao-Ou Shu; **Japanese lung cancer:** Kouya Shiraishi, Atsushi Takahashi
- **eQTL Lung:** Yohan Bossé, Ma'en Obeidat, David Nickle, Wim Timens; **eQTL prostate:** Matthew L. Freedman, Qiyuan Li
- **NCI:** Daniela Seminara, Stephen J. Chanock, Nilanjan Chatterjee