State of the Art: Genetics and Endometriosis

Peter AW Rogers[1], Sarah J Holdsworth-Carson[1], Jenny N Fung[2], Jane E Girling[1] & Grant W Montgomery[2]

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State of the Art: Genetics and Endometriosis

- **Introduction**
- Genetic regulation of endometrial transcription
- Genome-wide Association Studies (GWAS)
- Endometriosis genes LINC00339/CDC42/GREB1/VEZT
- Rare alleles/mutations
- Somatic mutations
- Epigenetics

DNA and Genes

- Human DNA has ~3 billion loci with different nucleotides
- Only 4 nucleotides : A, C, G, and T
  (adenine, cytosine, guanine, thymine)
- Only ~10 million loci have nucleotides that vary (ie: ~0.3%)
  Called **S**ingle **N**ucleotide **P**olymorphisms or SNP's
- Relatively few SNP's affect gene transcription
- Even fewer SNP's are associated with disease susceptibility
- **G**enome **W**ide **A**ssociation **S**tudy (GWAS)
  looks for SNPs associated with disease

Genetics of Endometriosis

First-degree relatives of women with endometriosis exhibit an increased risk of developing the disease (between 2 to 7 fold).

Additionally, disease severity is heightened in women with a family history

Treloar, S.A., et al., *Genetic influences on endometriosis in an Australian twin sample.* Fertil Steril, 1999. **71**(4):701-10.
Saha, R., et al., *Heritability of endometriosis.* Fertil Steril, 2015. **104**(4): 947-52.

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Human Reproduction, pp. 1–12, 2017
doi:10.1093/humrep/dex006

human reproduction

ORIGINAL ARTICLE *Reproductive biology*

The genetic regulation of transcription in human endometrial tissue

Jenny N. Fung[1,2,*], Jane E. Girling[3], Samuel W. Lukowski[1], Yadav Sapkota[2,4], Leanne Wallace[1], Sarah J. Holdsworth-Carson[3], Anjali K. Henders[1], Martin Healey[3], Peter A.W. Rogers[3,†], Joseph E. Powell[1,†], and Grant W. Montgomery[1,2,†]

[1]Institute for Molecular Bioscience, The University of Queensland, 306 Carmody Road, Building 80, St Lucia, Brisbane, QLD 4072, Australia [2]Genetics and Computational Biology Department, QIMR Berghofer Medical Research Institute, Brisbane, QLD 4006, Australia [3]Department of Obstetrics and Gynaecology, Gynaecology Research Centre, Royal Women's Hospital, University of Melbourne, Parkville, VIC 3052, Australia [4]Department of Epidemiology and Cancer Control, St. Jude Children's Research Hospital, Memphis, TN 38105, USA

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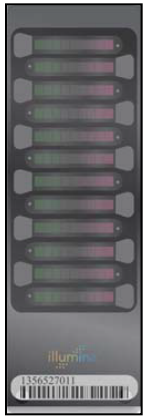
Submitted on October 7, 2016; resubmitted on November 18, 2016; accepted on January 5, 2017

STUDY QUESTION: Do genetic effects regulate gene expression in human endometrium?

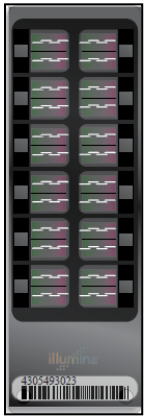
SUMMARY ANSWER: This study demonstrated strong genetic effects on endometrial gene expression and some evidence for genetic regulation of gene expression in a menstrual cycle stage-specific manner.

Gene expression in endometrium

Genome-wide expression and genotyping

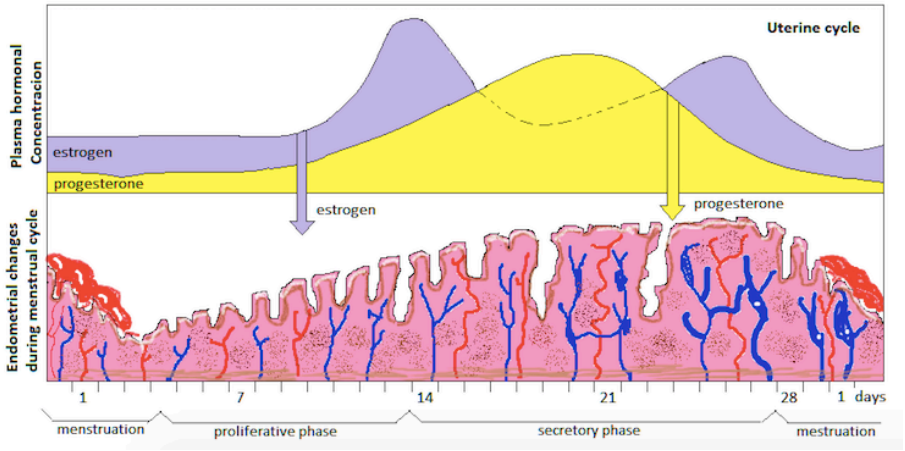


HT12 v4 GX chips
47,231 probes

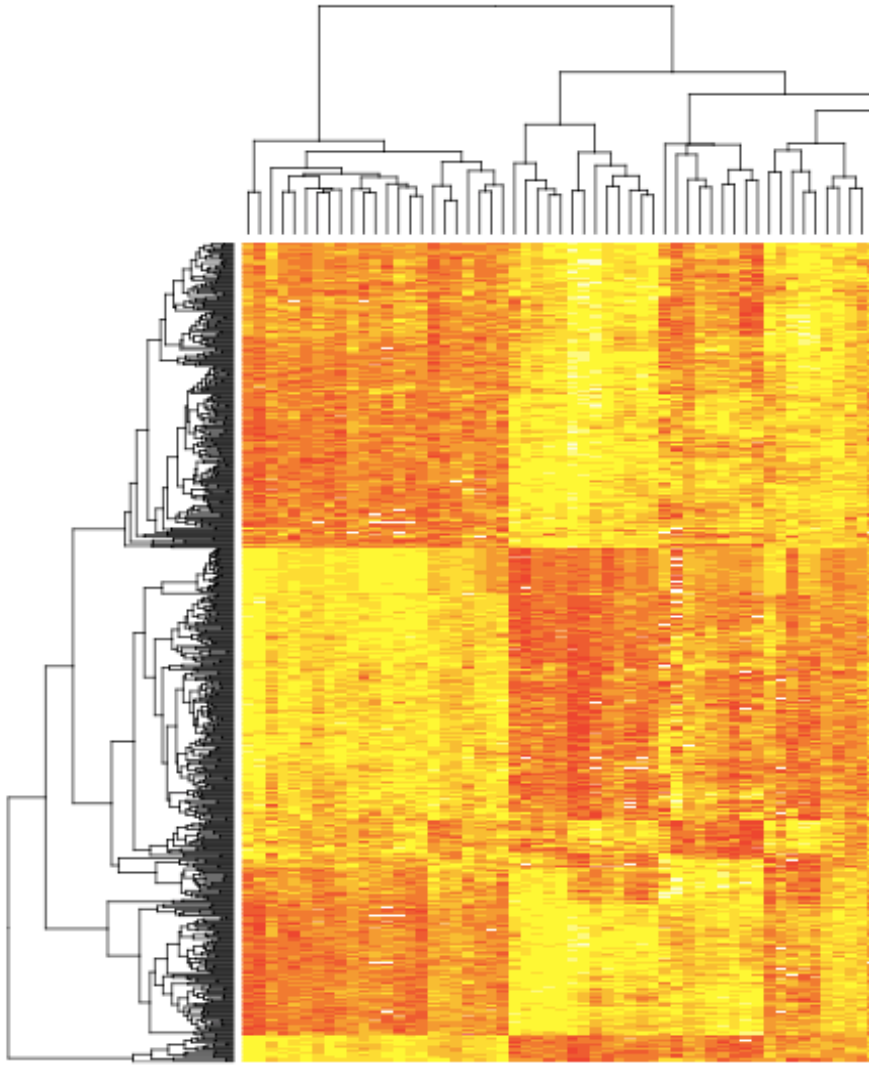


CORE/Exome GWAS chips
509,502 SNPs

Menstrual cycle



Proliferative Secretory

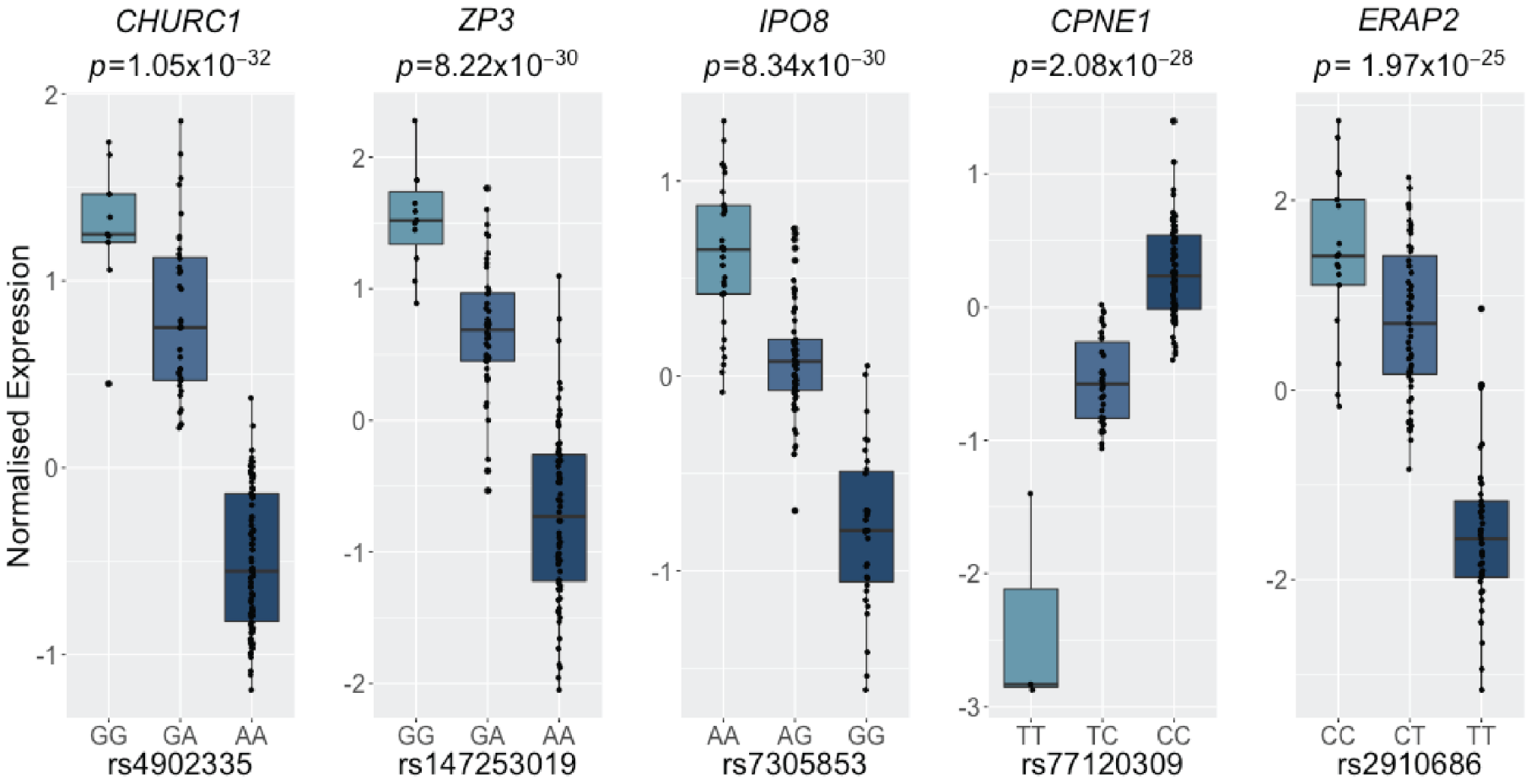


Proliferative Secretory

The genetic regulation of transcription in human endometrial tissue: cis-eQTL's

- 123 premenopausal women of European ancestry
- No hormone treatment in 3 months prior to surgery
- Endometrial biopsy and blood sample
- 15,226 endometrial probes and 8,613,031 SNPs for analysis
- Associations within +/-250kb from probe start site.
- Identified 18,595 cis-eSNPs at a Bonferroni significance threshold of $p<1.0x10^{-7}$.
- eSNPs corresponded to 211 independent eQTL, mapping to 198 unique genes

Fung et al., 2017 Hum Reprod



The relationship between genotypes of SNPs and gene expression levels of the top 5 study-wide significant cis-eQTLs for unique genes.

Fung et al., 2017 Hum Reprod

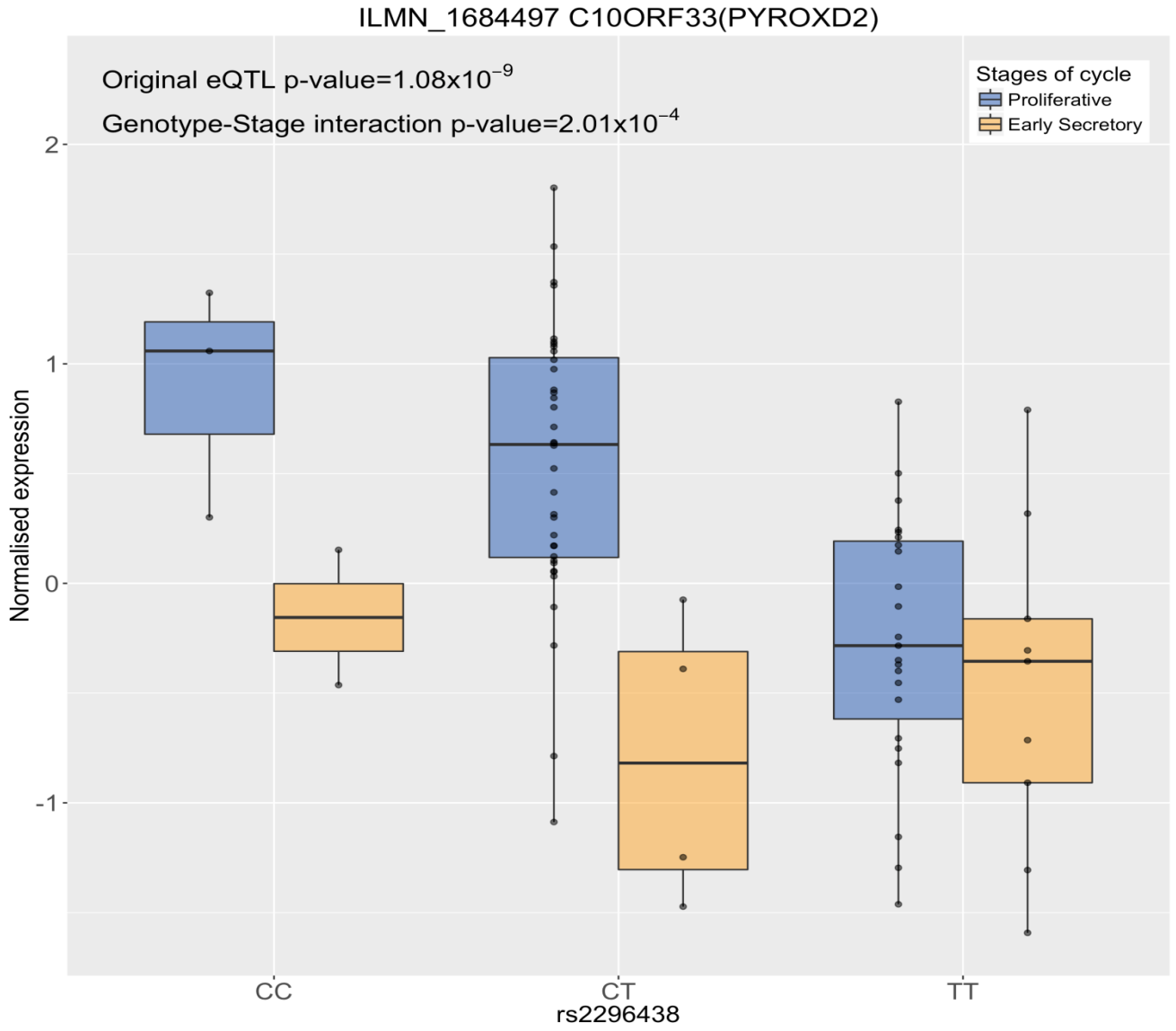


Figure 4. Genotype modulates the gene expression differences across to menstrual cycle stages in the endometrium. The blue boxplots represent the P samples and orange boxplots represent the ES samples.

Fung et al., 2017 Hum Reprod

- 229 women of European ancestry
- 12,321 endometrial genes in ≥ 90% of all samples
- 7,567 genes in at least one sample
- *cis*-eQTLs for 2,611 genes
- *trans*-eQTLs for 82 genes
- eQTLs in endometriosis GWAS loci: *LINC00339* (rs2501281), *VEZT* (rs10777680)
- eQTLs also in blood: effects may not be specific to endometrium

Fung et al., 2018 Submitted

Conclusion

There are strong genetic effects on gene expression in endometrium including control of gene expression levels in menstrual cycle stage-specific manner.

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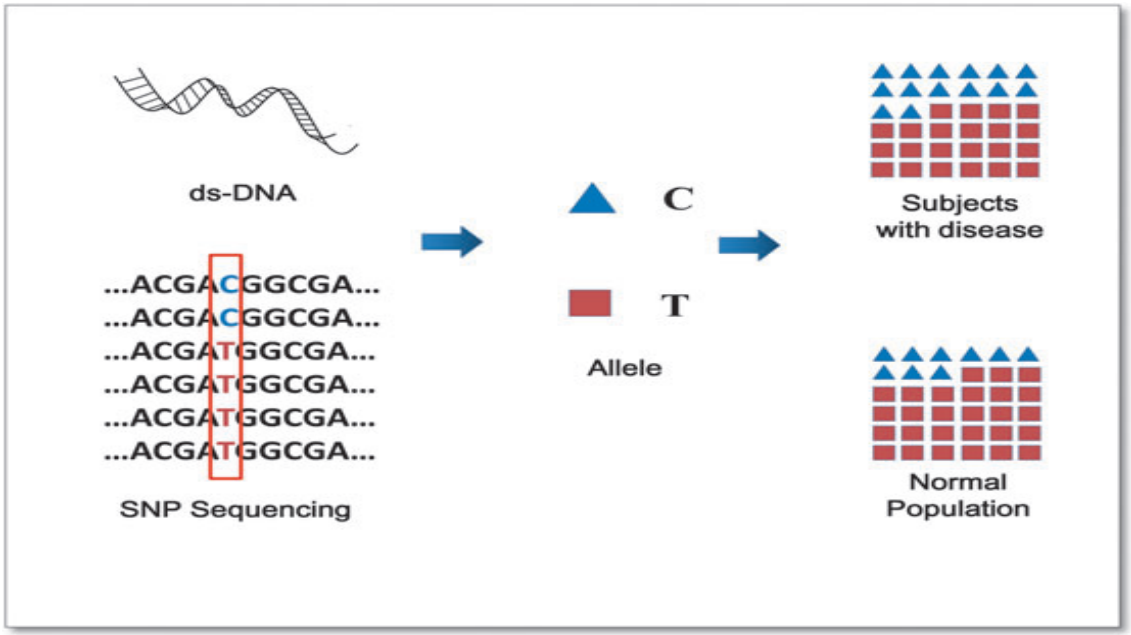
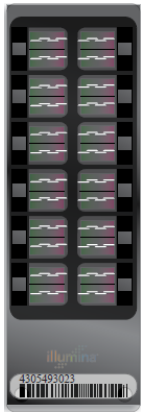
Genome-wide Association Studies (GWAS)

- Hypothesis-free approaches
- Population-based (typically case-control studies)
- Provide powerful approach for mapping disease genes
- Tag Single-Nucleotide Polymorphisms (SNPs) for known common variants in the genome



Zhao and Chen (2013), Molecular Human Reproduction, Vol.19, No.10



Illumina Genotyping Chip
509,502 SNPs

GWASs of Endometriosis

A genome-wide association study identifies genetic variants in the *CDKN2BAS* locus associated with endometriosis in Japanese

Satoko Uno[1,2], Hitoshi Zembutsu[1], Akira Hirasawa[3], Atsushi Takahashi[4], Michiaki Kubo[5], Tomoko Akahane[3], Daisuke Aoki[3], Naoyuki Kamatani[4], Koichi Hirata[2] & Yusuke Nakamura[1]

NATURE GENETICS VOLUME 42 | NUMBER 8 | AUGUST 2010

Meta-analysis of genome-wide association scans for genetic susceptibility to endometriosis in Japanese population

Sosuke Adachi[1], Atsushi Tajima[2], Jinhua Quan[1], Kazufumi Haino[1], Kosuke Yoshihara[1], Hideaki Masuzaki[3], Hidetaka Katabuchi[4], Kenichiro Ikuma[5,12], Hiroshi Suginami[6,13], Nao Nishida[7], Ryozo Kuwano[8], Yuji Okazaki[9], Yoshiya Kawamura[10], Tsukasa Sasaki[11], Katsushi Tokunaga[7], Ituro Inoue[2] and Kenichi Tanaka[1]

Journal of Human Genetics (2010) **55**, 816–821; doi:10.1038/jhg.2010.118; published online 16 September 2010

Genome-wide association study identifies a locus at 7p15.2 associated with endometriosis

Jodie N Painter[1,13], Carl A Anderson[2,3,13], Dale R Nyholt[4,13], Stuart Macgregor[5], Jianghai Lin[6], Sang Hong Lee[5], Ann Lambert[6], Zhen Z Zhao[1], Fenella Roseman[6], Qun Guo[7], Scott D Gordon[8], Leanne Wallace[1], Anjali K Henders[1], Peter M Visscher[5], Peter Kraft[9,10], Nicholas G Martin[8], Andrew P Morris[2], Susan A Treloar[1,11,14], Stephen H Kennedy[6,14], Stacey A Missmer[7,9,12,14], Grant W Montgomery[1,14] & Krina T Zondervan[2,6,14]

NATURE GENETICS VOLUME 43 | NUMBER 1 | JANUARY 2011 51

Genome-Wide Association Study Link Novel Loci to Endometriosis

Hans M. Albertsen, Rakesh Chettier, Pamela Farrington, Kenneth Ward*

Juneau Biosciences, LLC, Salt Lake City, Utah, United States of America

PLOS ONE | www.plosone.org 1 March 2013 | Volume 8 | Issue 3 | e58257

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

Dale R Nyholt[1,16], Siew-Kee Low[2,16], Carl A Anderson[3], Jodie N Painter[1], Satoko Uno[2,4], Andrew P Morris[5], Stuart MacGregor[1], Scott D Gordon[1], Anjali K Henders[1], Nicholas G Martin[1], John Attia[6,7], Elizabeth G Holliday[6,7], Mark McEvoy[6,8,9], Rodney J Scott[7,10,11], Stephen H Kennedy[12], Susan A Treloar[13], Stacey A Missmer[14], Sosuke Adachi[15], Kenichi Tanaka[15], Yusuke Nakamura[2], Krina T Zondervan[5,12,17], Hitoshi Zembutsu[2,17] & Grant W Montgomery[1,17]

NATURE GENETICS VOLUME 44 | NUMBER 12 | DECEMBER 2012

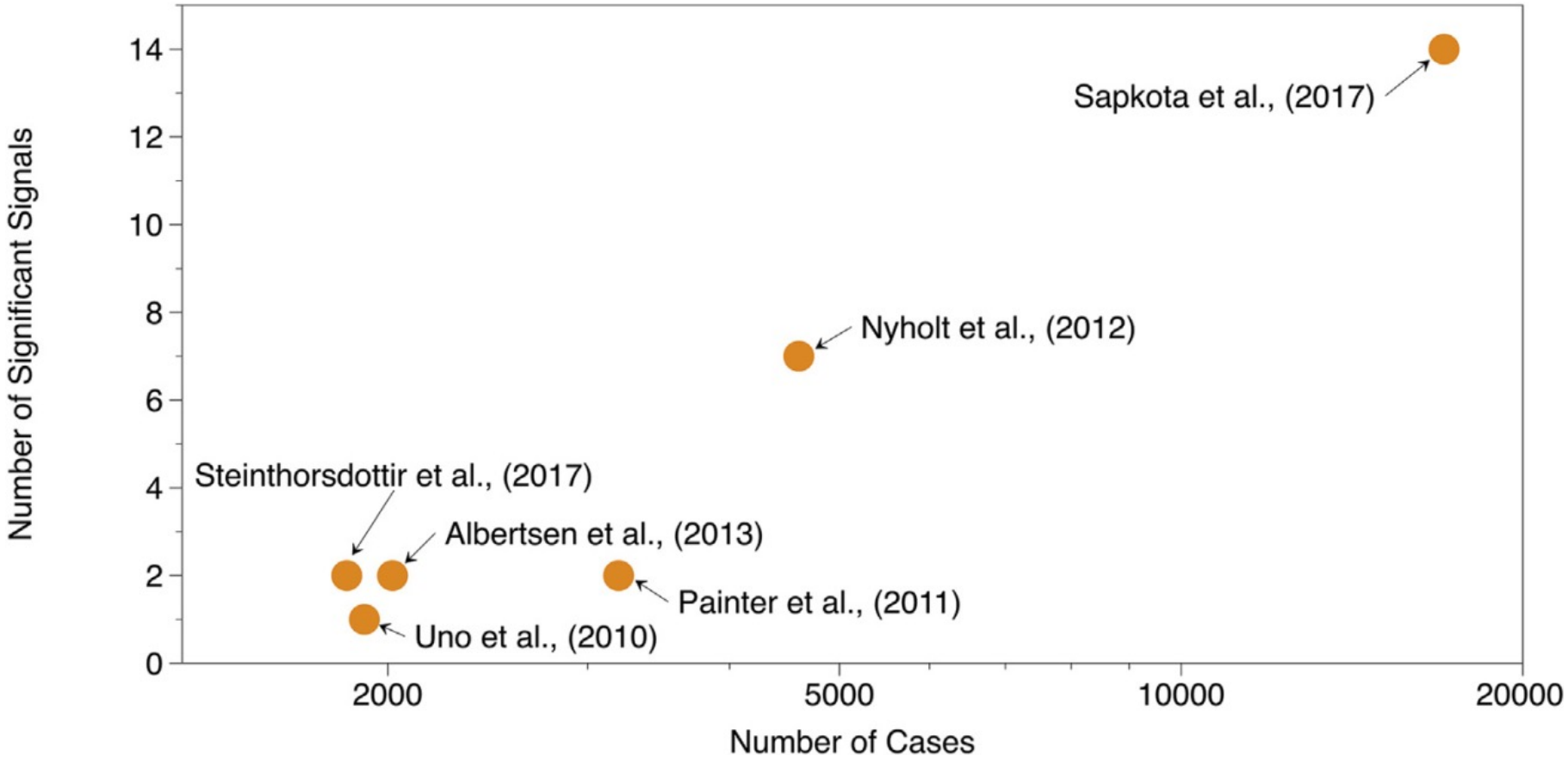
nature COMMUNICATIONS

ARTICLE

Received 11 Nov 2016 | Accepted 7 Apr 2017 | Published 24 May 2017 DOI: 10.1038/ncomms15539 OPEN

Meta-analysis identifies five novel loci associated with endometriosis highlighting key genes involved in hormone metabolism

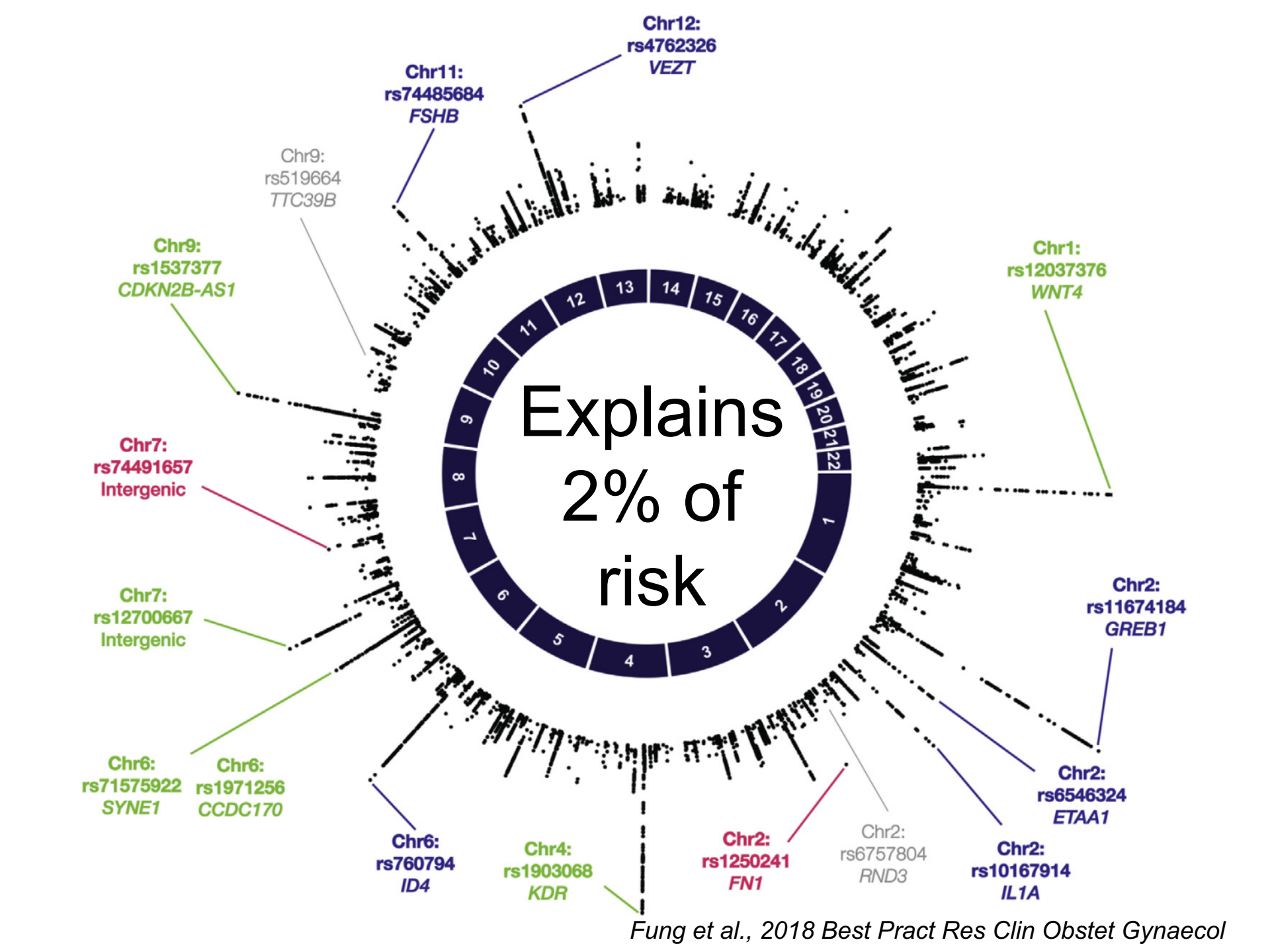
Yadav Sapkota[1,2], Valgerdur Steinthorsdottir[3], Andrew P. Morris[4,5], Amelie Fassbender[6,7], Nilufer Rahmioglu[5], Immaculata De Vivo[8,9], Julie E. Buring[8,10], Futao Zhang[11], Todd L. Edwards[12], Sarah Jones[13], Dorien O[6,7], Danielle Peterse[6,7], Kathryn M. Rexrode[8,10], Paul M. Ridker[8,10], Andrew J. Schork[14,15], Stuart MacGregor[1], Nicholas G. Martin[1], Christian M. Becker[16], Sosuke Adachi[17], Kosuke Yoshihara[17], Takayuki Enomoto[17], Atsushi Takahashi[18], Yoichiro Kamatani[18], Koichi Matsuda[19], Michiaki Kubo[18], Gudmar Thorleifsson[3], Reynir T. Geirsson[20,21], Unnur Thorsteinsdottir[3,21], Leanne M. Wallace[1,11], iPSYCH-SSI-Broad Group[1], Jian Yang[11], Digna R. Velez Edwards[22], Mette Nyegaard[23,24], Siew-Kee Low[18,*], Krina T. Zondervan[5,16,*], Stacey A. Missmer[8,9,*], Thomas D'Hooghe[6,7,25,*], Grant W. Montgomery[1,11,*], Daniel I. Chasman[8,10,*], Kari Stefansson[3,21,*], Joyce Y. Tung[26,*] & Dale R. Nyholt[1,27,*]



Fung et al., 2018 Best Pract Res Clin Obstet Gynaecol

International Endometriosis Genomic Consortium (IEGC)

IEGC: GWA Studies	Cases	Sub-Phenotypes			Controls
		Stage III/IV	Stage I/II	Infertile	
Adachi, Japan	696	-	-	-	825
Biobank Japan	1,423	-	-	-	1,318
DeCODE Genetics, Iceland	1,857	695	587	-	132,978
iPSYCH, Denmark	397	-	-	-	9,385
DBDS, Denmark	380	-	-	-	20,994
NFBC, Finland	184	-	-	-	9,194
EGCUT, Estonia	1,716	127	-	-	35,176
Katholieke Universiteit, Leuven	998	423	-	-	783
Crete, Greece	168	87	81	-	365
QIMRHCS, Australia	2,262	905	1,345	848	2,923
Melbourne, Australia	320	78	242	31	887
QSKIN, Australia	1,194	-	-	-	2,000
OXEGENE, Oxford U, UK	924	454	329	344	5,190
ENDOX/Edinburgh/Liverpool, UK	381	173	202	152	2,578
Generation Scotland, UK	323	-	-	-	9,788
UK-BIOBANK, Oxford U, UK	6,611	1,075	-	417	251,704
NHS2, Harvard University, USA	2,104	-	-	?	5,854
WGHS, USA	1,494	-	-	-	14,033
BioVu, USA	440	-	-	-	8,248
UCSF, USA	408	99	-	-	210
23andMe (Celmatix), USA	37,183	4,500	-	2,978	251,258
TOTAL	61,463	8,616	2,786	4,770	765,691



Fung et al., 2018 Best Pract Res Clin Obstet Gynaecol

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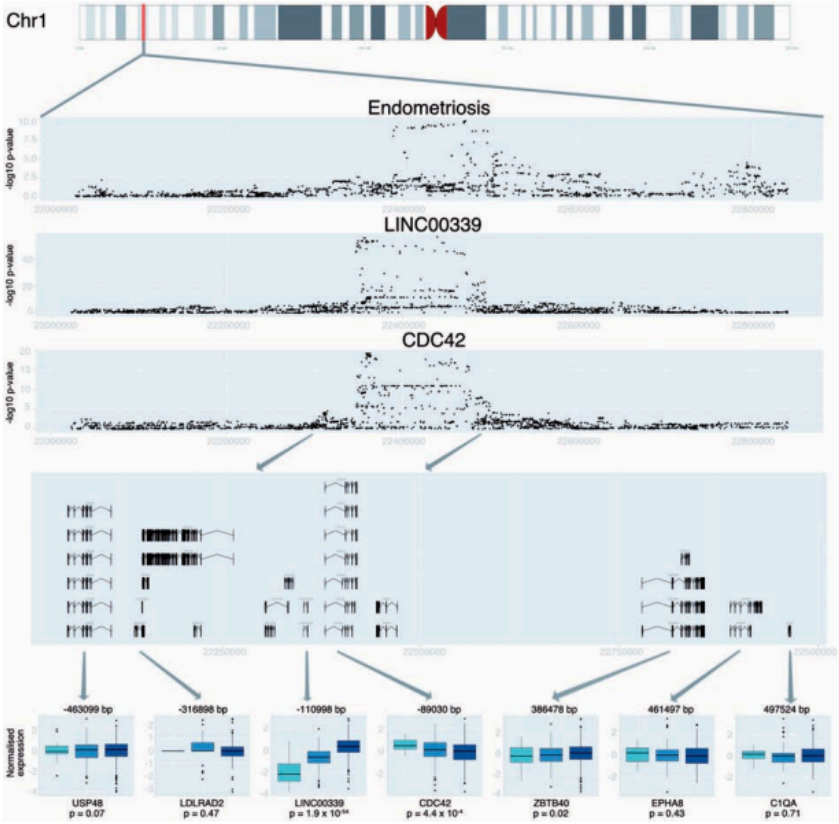
Volume 25 Number 22 15 November 2016

academic.oup.com/hmg

ASSOCIATION STUDIES ARTICLE

Endometriosis risk alleles at 1p36.12 act through inverse regulation of *CDC42* and *LINC00339*

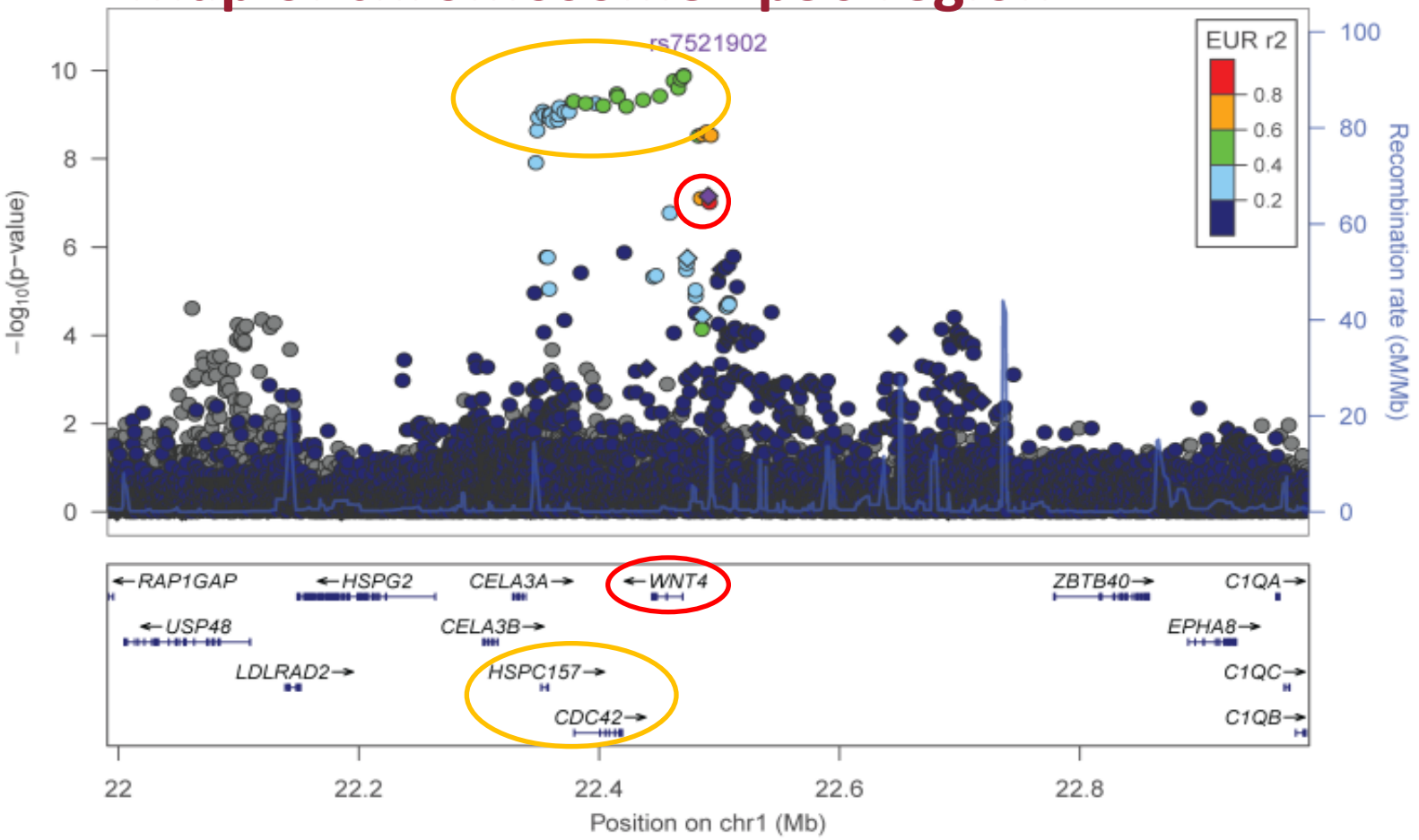
Joseph E. Powell[1,2,*,†], Jenny N. Fung[3,†], Konstantin Shakhbazov[2], Yadav Sapkota[3], Nicole Cloonan[3], Gibran Hemani[2,4], Kristine M. Hillman[3], Susanne Kaufmann[3], Hien T. Luong[3], Lisa Bowdler[3], Jodie N. Painter[3], Sarah J. Holdsworth-Carson[5], Peter M. Visscher[2], Marcel E. Dinger[6,7], Martin Healey[5], Dale R. Nyholt[3,8], Juliet D. French[3], Stacey L. Edwards[3], Peter A. W. Rogers[5,†] and Grant W. Montgomery[3,†]



OXFORD OPEN

OXFORD UNIVERSITY PRESS

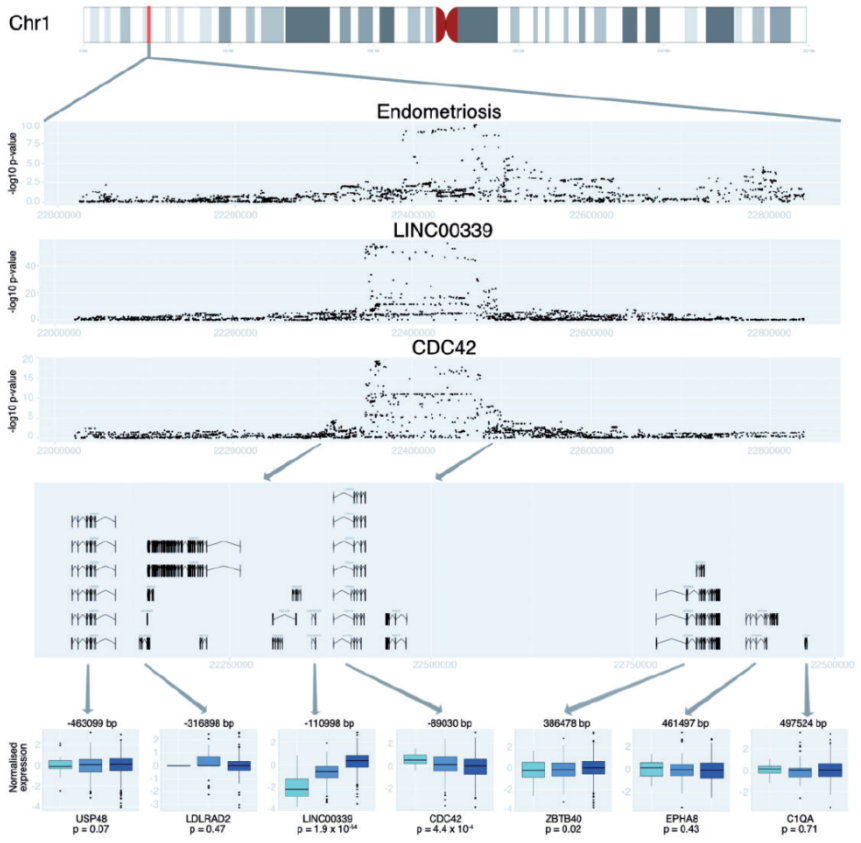
Map of chromosome 1p36 region



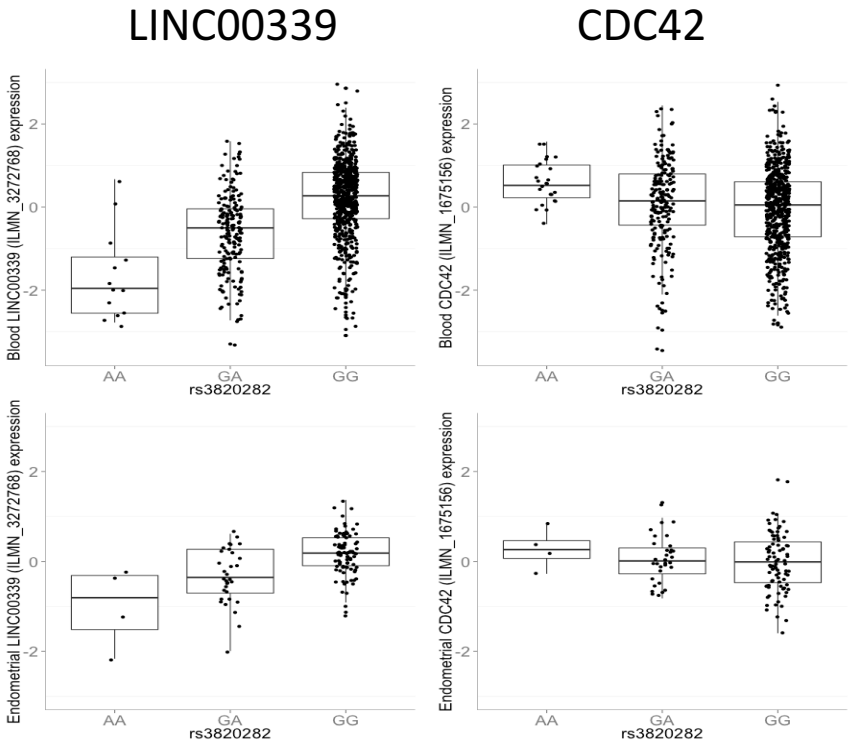
- WNT4 – development of the uterus and human endometrial stromal cell differentiation
- HSPC157 - increased expression in lesion vs eutopic endometrium (Hu et al, 2006, JCEM 91: 228)
- Cell division cycle 42 (CDC42) – increased expression in secretory phase and endometriosis (Goteri et al, 2006, F&S 86: 559)

Effect of key SNPs on expression of *LINC00339* and CDC42 in blood and from endometrium

Chromosome 1 eQTL in blood



eQTLs in blood and endometrium



Powell et al., 2016 Human Molecular Genetics 25: 5046

Conclusions

- A block of ‘risk’ SNPs at chromosome 1p36.12 span genes WNT4, CDC42, and LINC00339
- The key SNP on chromosome 1 is located within an intron of WNT4
- **BUT**: There is chromatin looping between SNPs associated with endometriosis risk and promoter regions for both CDC42 and LINC00339, but **NOT** WNT4
- Results strongly implicate variation in expression of CDC42 and LINC00339 in endometriosis risk.
- Additional expression and functional studies will be necessary.

Powell et al, 2016 Hum Mol Gen

Human Reproduction, Vol.30, No.5 pp. 1263–1275, 2015
Advanced Access publication on March 18, 2015 doi:10.1093/humrep/dev051

human reproduction ORIGINAL ARTICLE *Reproductive genetics*

Functional evaluation of genetic variants associated with endometriosis near *GREB1*

Jenny N. Fung[1,*,†], Sarah J. Holdsworth-Carson[†,2], Yadav Sapkota[1], Zhen Zhen Zhao[1], Lincoln Jones[1], Jane E. Girling[2], Premila Paiva[2], Martin Healey[2], Dale R. Nyholt[1], Peter A. W. Rogers[2], and Grant W. Montgomery[1]

- GREB1 is an estrogen-regulated gene first identified in breast cancer cell lines and tumours
- Knock down of GREB1 inhibits estrogen induced growth in MCF-7 breast cancer cell lines
- ER-regulated transcription involves over 100 ER-associated proteins.
- GREB1 is the most estrogen-dependent ER interactor: functions as an essential component of the ER transcription complex

Human Reproduction, Vol.31, No.5 pp. 999–1013, 2016
Advanced Access publication on March 22, 2016 doi:10.1093/humrep/dew047

human reproduction

ORIGINAL ARTICLE *Gynaecology*

Endometrial vezatin and its association with endometriosis risk

Sarah J. Holdsworth-Carson[1,†], Jenny N. Fung[2,†], Hien T.T. Luong[2], Yadav Sapkota[2], Lisa M. Bowdler[2], Leanne Wallace[2], Wan Tinn Teh[1], Joseph E. Powell[3,4], Jane E. Girling[1], Martin Healey[1], Grant W. Montgomery[2,‡], and Peter A.W. Rogers[1,‡*]

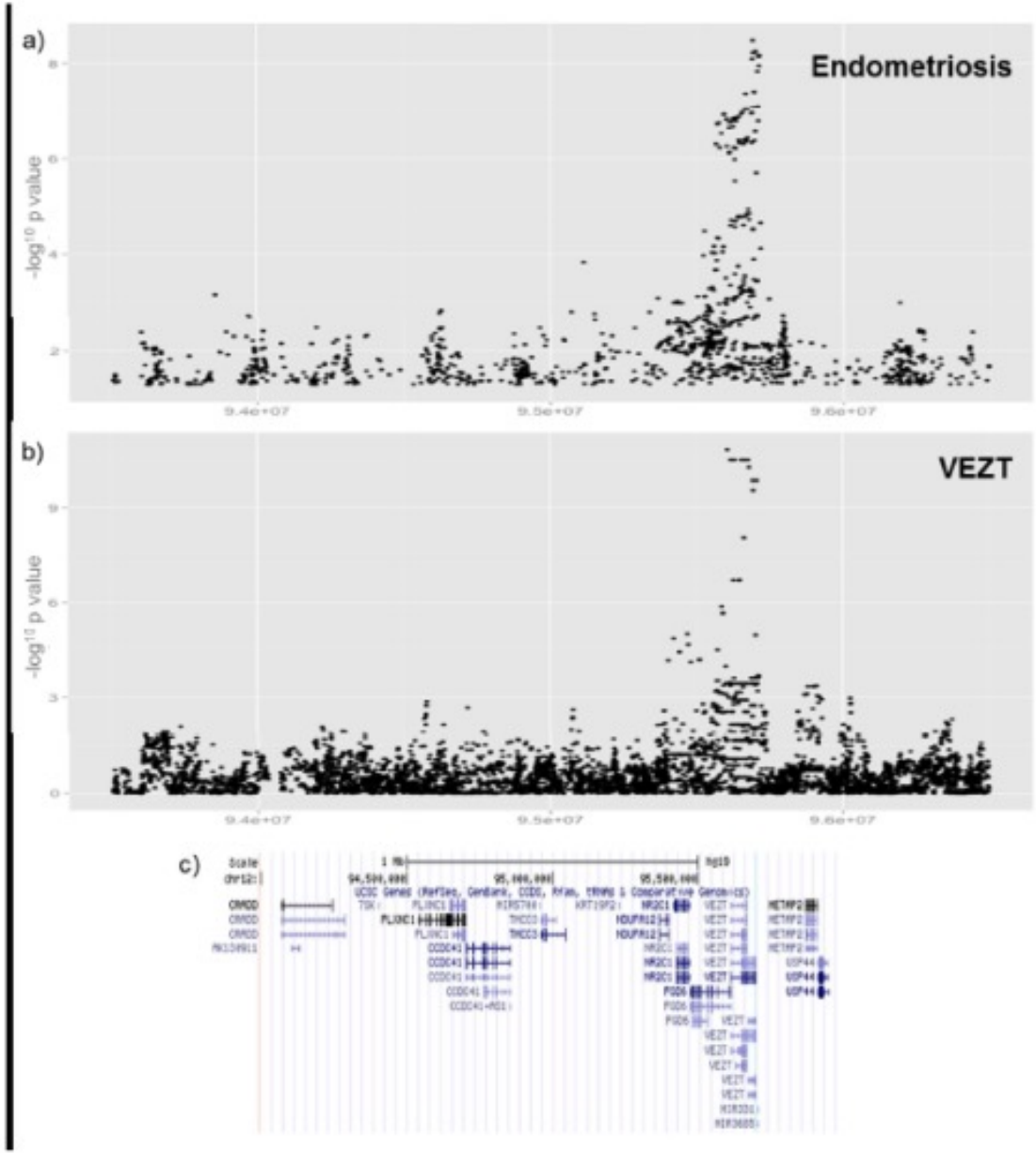
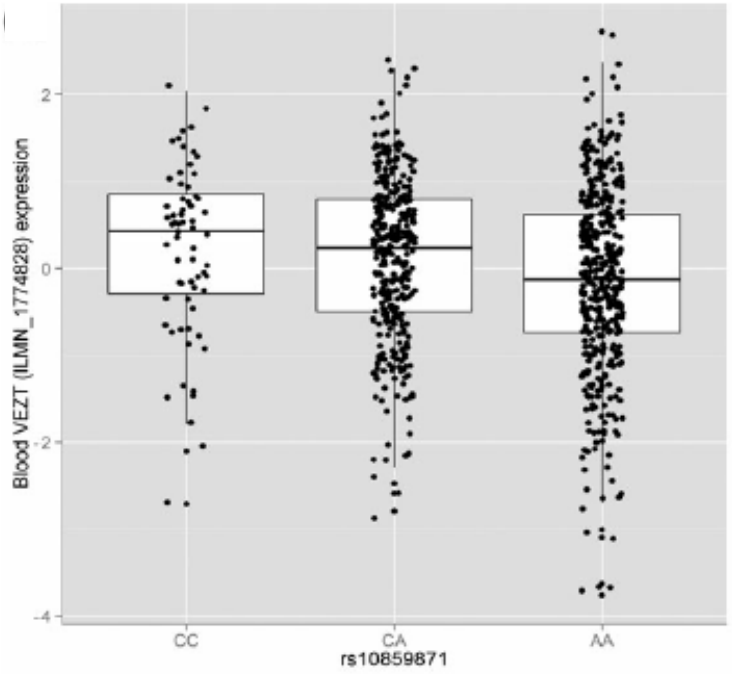
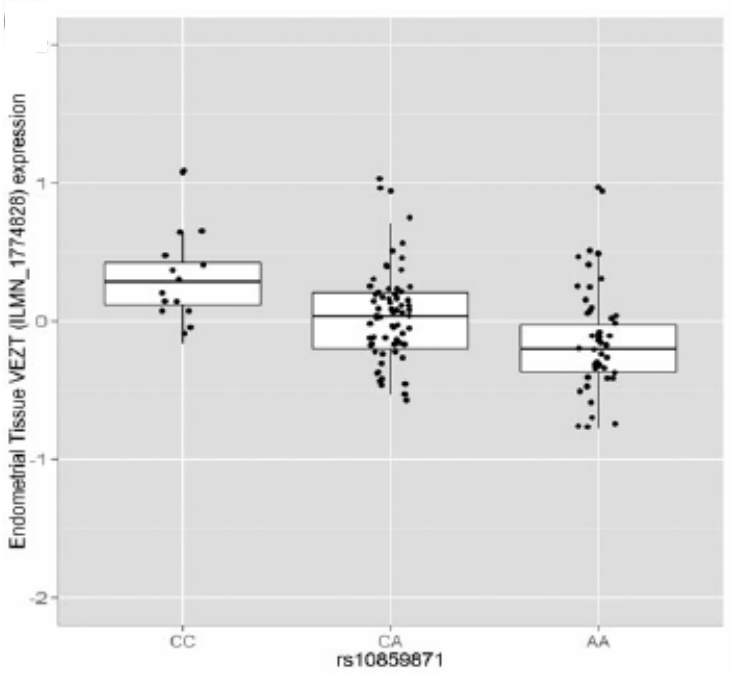
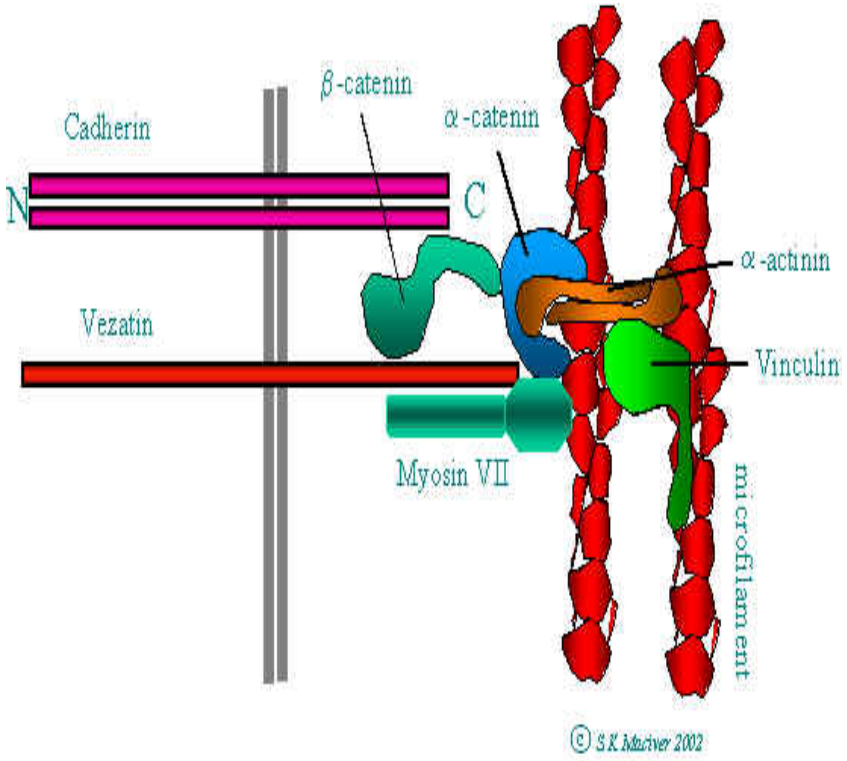


Figure 2. SNPs within the 12q22 locus are associated with both endometriosis risk and the expression levels of VEZT. Association results for individual SNPs are plotted by position on chromosome 12 (hg19; X-axis) and as −log10 p values (Y-axis) for endometriosis risk a) and VEZT expression in the BSGS b). The relative locations of genes (RefSeq genes) within the 12q22 locus are shown in c).
177x194mm (150 x 150 DPI)





VEZT expression quantitative trait loci (eQTL) effects in blood and eutopic endometrium. The expression levels of VEZT probe (ILMN_1774828) with eQTL effects for the relationship between rs10859871 and gene expression in blood (top panel) and in endometrium (bottom panel). Risk allele (CC), heterozygotes (CA) and other not-at-risk allele (AA).



- Vezatin is a ubiquitous protein of adherens cell-cell junctions
- Contributes to creating a tension between adherens junctions and actin cytoskeleton to strengthen cell-cell adhesion (Kussel-Andermann, El-Amraoui et al. 2000)
- Unclear how/if VEZT increases susceptibility to endometriosis

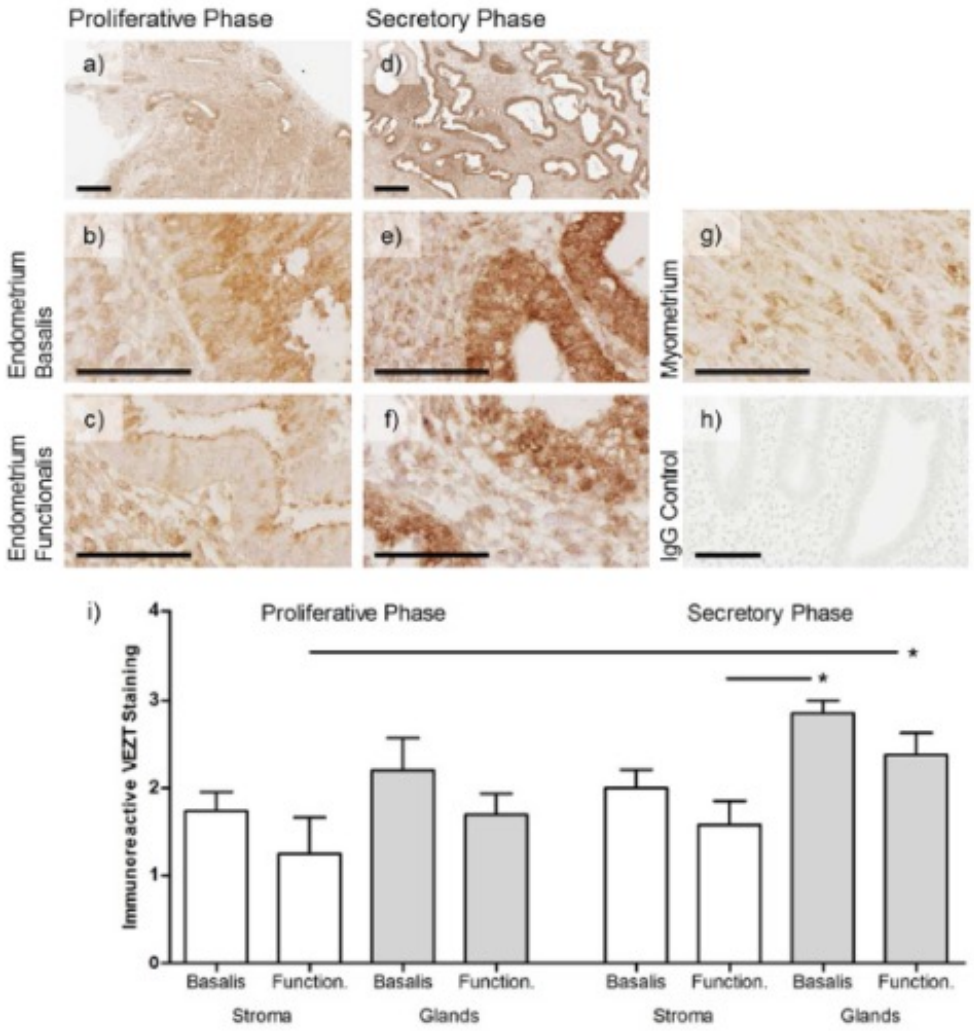


Figure 1. Representative micrographs of the immunolocalisation of VEZT (brown) in a) proliferative phase endometrium (low power), b) proliferative phase basalis endometrium, c) proliferative phase functionalis endometrium, d) secretory phase endometrium (low power), e) secretory phase basalis endometrium, f) secretory phase functionalis endometrium and g) myometrium. h) A mouse IgG isotype-specific control, with no brown staining observed. Scale bar is equal to 200 μm (a and d) and 50 μm in the remaining images. Staining was carried out on n=6 women from each proliferative and secretory phases of the menstrual cycle. i) VEZT staining intensity was scored between 0 and 3 (where 0 = none and 3 = strong) by three independent scorers separately for endometrial stroma and glands (basalis and functionalis). Semi-quantitative data was analysed by two-way ANOVA (significance denoted by * ($P < 0.05$)).

174x188mm (150 x 150 DPI)

What does VEZT result mean for understanding endometriosis?

No published data on function of VEZT in endometrium despite reasonable expression levels.

VEZT functions in other tissues related to role in adherens junctions.

Role of VEZT in endometriosis will require considerable new work.

SCIENTIFIC REPORTS

OPEN

Analysis of potential protein-modifying variants in 9000 endometriosis patients and 150000 controls of European ancestry

Received: 3 February 2017
Accepted: 9 August 2017
Published online: 12 September 2017

Yadav Sapkota[1,2], Immaculata De Vivo[3,4], Valgerdur Steinthorsdottir[5], Amelie Fassbender[6,7], Lisa Bowdler[1], Julie E. Buring[3,8], Todd L. Edwards[9], Sarah Jones[10], Dorien O[6,7], Daniëlle Peterse[6,7], Kathryn M. Rexrode[3,8], Paul M. Ridker[3,8], Andrew J. Schork[11,12], Gudmar Thorleifsson[5], Leanne M. Wallace[1], iPSYCH-SSI-Broad Group[*], Peter Kraft[13], Andrew P. Morris[14], Dale R. Nyholt[1,15], Digna R. Velez Edwards[16], Mette Nyegaard[17,18], Thomas D'Hooghe[6], Daniel I. Chasman[3,8], Kari Stefansson[5,19], Stacey A. Missmer[3,4] & Grant W. Montgomery[1,20]

- Exome-array for protein-modifying variants in endometriosis
- 7164 cases and 21005 controls. Replication 1840 cases and 129016 controls of European ancestry.
- Evidence for association with coding variants in (rs1801232-*CUBN*) (*CIITA* and *PARP4*) (did not survive replication).
- Genome-wide significant evidence for rs13394619 ($P = 2.3 \times 10^{-9}$) in *GREB1*

State of the Art: Genetics and Endometriosis

- Introduction
- Genetic regulation of endometrial transcription
- Genome-wide Association Studies (GWAS)
- Endometriosis genes LINC00339/CDC42/GREB1/VEZT
- **Rare alleles/mutations**
- Somatic mutations
- Epigenetics

S-109

Large Effect Mutations Found in Endometriosis Genes Implicated by GWAS. Rakesh Chettier, Hans M Albertsen, Kenneth Ward. *Juneau Biosciences, LLC, Salt Lake City, UT, United States.*

- 1019 Women with confirmed endometriosis
- Sequenced exons of 16 endometriosis GWAS genes to search for causative mutations
- 333/571 rare genetic variants alter protein coding
- 5 mutations have high odds ratios for endometriosis
- Stop mutations more prevalent in endometriosis cohort for 5 genes GREB1, NFE2L3, FN1, SYNE1, VEZT ($p=1.7 \times 10^{-13}$)

Reprod Sci 25: Suppl. 1 March 2018

S-086

A Family with over 200 Women with Confirmed Endometriosis Suggesting Autosomal Dominant Inheritance. Kenneth Ward*, VeeAnn Argyle. *Juneau Biosciences, Salt Lake City, UT, United States.*

- Database of 32 million ancestors of current Utah population
- Identified 218 surgically affected women related through 19 generations to a single founder born in 1508 in England
- Suggests an autosomal dominant gene for endometriosis with high but incomplete penetrance

Reprod Sci 25: Suppl. 1 March 2018

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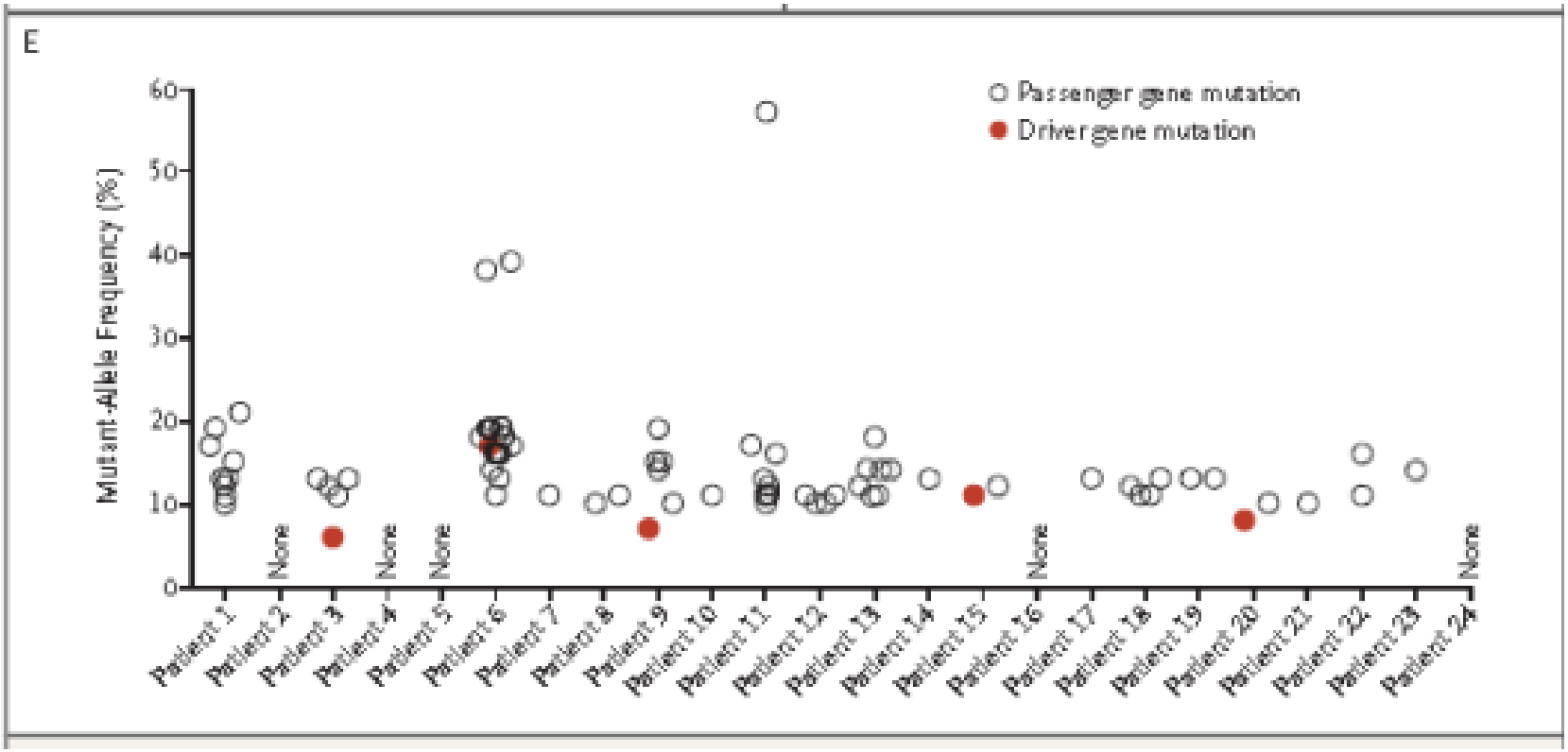
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cancer-Associated Mutations in Endometriosis without Cancer

M.S. Anglesio, N. Papadopoulos, A. Ayhan, T.M. Nazeran, M. Noë, H.M. Horlings, A. Lum, S. Jones, J. Senz, T. Seckin, J. Ho, R.-C. Wu, V. Lac, H. Ogawa, B. Tessier-Cloutier, R. Alhassan, A. Wang, Y. Wang, J.D. Cohen, F. Wong, A. Hasanovic, N. Orr, M. Zhang, M. Popoli, W. McMahon, L.D. Wood, A. Mattox, C. Allaire, J. Segars, C. Williams, C. Tomasetti, N. Boyd, K.W. Kinzler, C.B. Gilks, L. Diaz, T.-L. Wang, B. Vogelstein, P.J. Yong, D.G. Huntsman, and I.-M. Shih

- Analyzed deep infiltrating endometriotic lesions from 27 patients
- Exome sequencing revealed somatic mutations in 19 of 24 patients (79%)
- Five patients had cancer driver mutations in epithelium: *ARID1A*, *PIK3CA*, *KRAS*, or *PPP2R1A*



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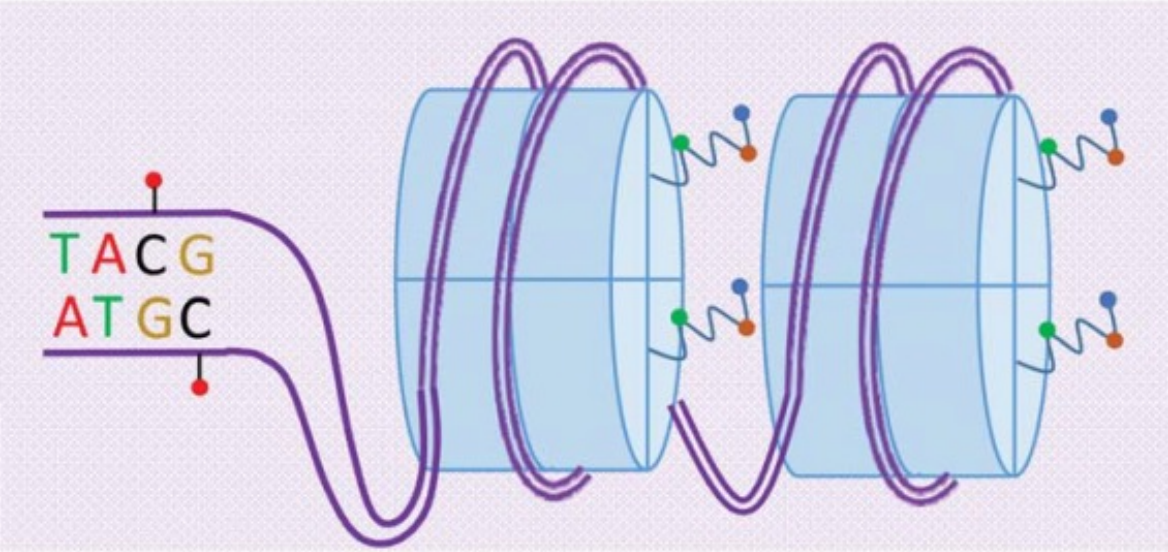
Epigenetics

- Epigenetics can be broadly defined as changes in gene function that do not involve changes in DNA sequence
- Cellular machineries that regulate genome function
- DNA methylation, hydroxymethylation and demethylation of enzymes able to post-translationnaly modify histones.



- Extensive cross-talk between different epigenetic layers maintains and regulates complex transcriptional networks in cells

G. Zhang et al 2014. IUBMB Life

Conclusions

- Huge amount of complex data
- Need large numbers to stratify for:
  - Genotype
  - Menstrual cycle stage
  - Cell type
  - Clinical data (disease symptoms, type, location, outcome etc)
  - Environmental influences
- Functional studies challenging
- Will ultimately start to define biological processes that increase risk for endometriosis

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