#CHAIR2017

10TH ANNUAL CHAIR SUMMIT

neuroscience CME

Master Class for Neuroscience Professional Development

November 16 - 18, 2017 | Hotel Monteleone | New Orleans, LA

Provided by CME Outfitters

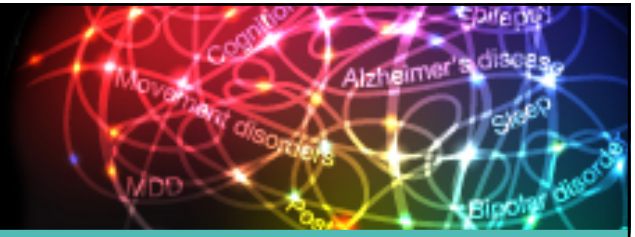
Genomic Insights About the Early Developmental Origins of Neurodevelopmental Disorders

Daniel R. Weinberger, MD
Johns Hopkins University
School of Medicine
Baltimore, MD

Learning Objective 1

Examine the implications of normal brain development for the pathogenesis of schizophrenia.

Daniel R. Weinberger, MD
Disclosures



- Dr. Weinberger has nothing to disclose.

Are Genes Related To Neurodevelopmental Disorders Preferentially Expressed During Fetal Life?

Disorders with likely developmental pathogenesis

- Schizophrenia
- Autism Spectrum Disorder (ASD)
- Intellectual Disability (ID)
- Syndromic Neurodevelopmental Disorders (SNDD)

Disorders "without" obvious developmental pathogenesis

- Bipolar Affective Disorder
- Neurodegenerative Disorders

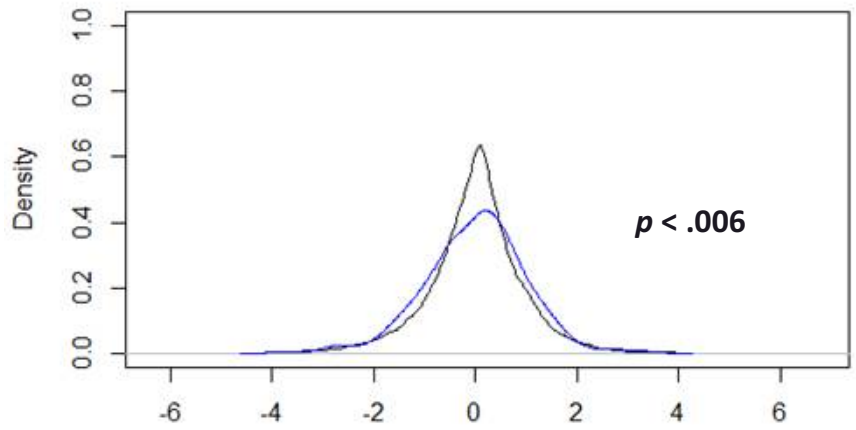
↓

Genes from the literature associated with the disorder

↓

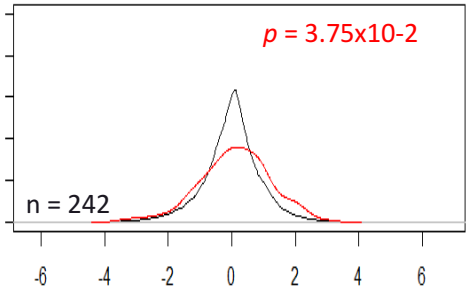
Are the composite set of genes associated with these disorders preferentially expressed during fetal life?

Schizophrenia Risk Associated Loci (287 Genes) Show a Pattern of Enriched Fetal Expression…

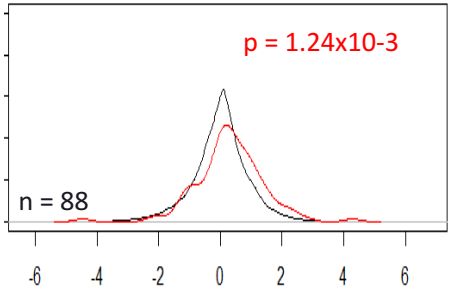


So do genes associated with autism and intellectual disability

Genome vs. ASD Database

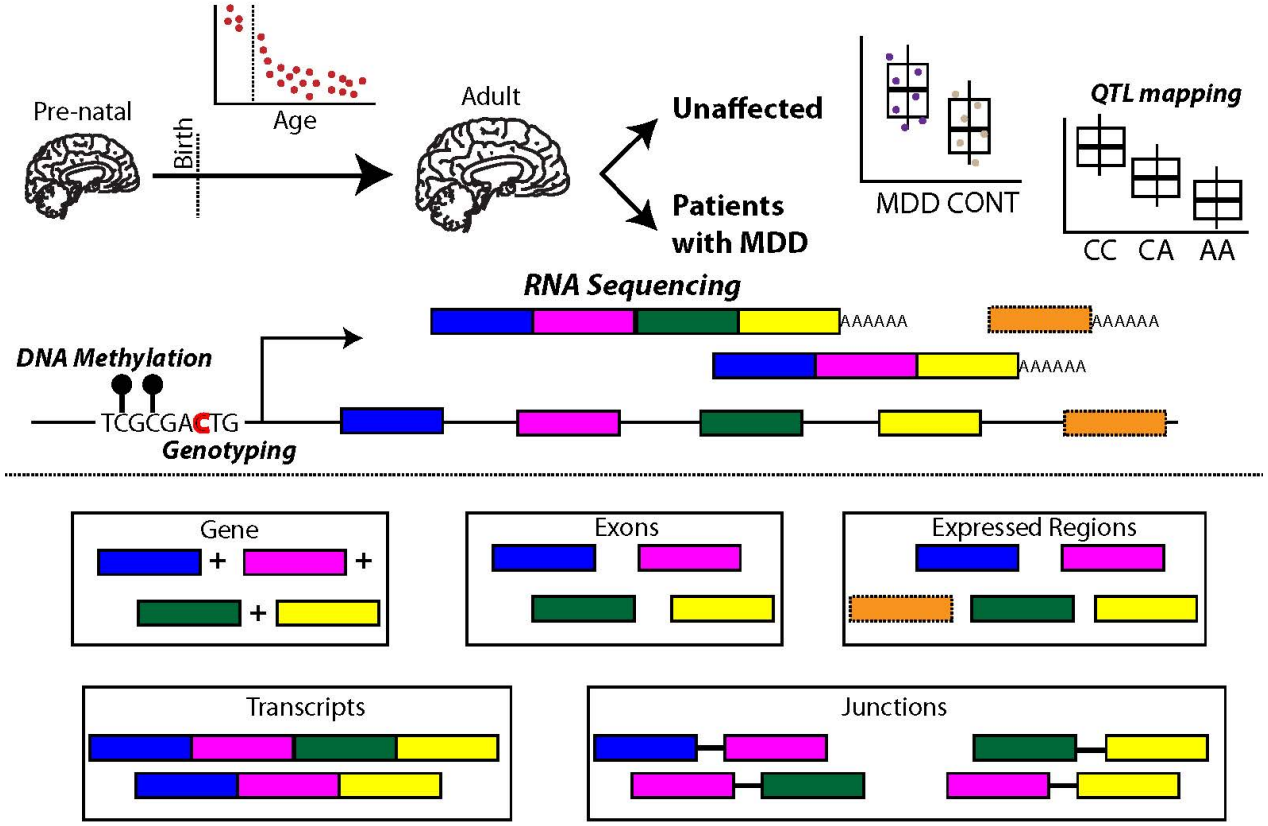


Genome vs. Intellectual Disability



Birnbaum R, et al. *Am J Psychiatry*. 2014;171(7):758-767.; Birnbaum R, et al. *Biol Psychiatry*. 2015;77(11):e43-51.

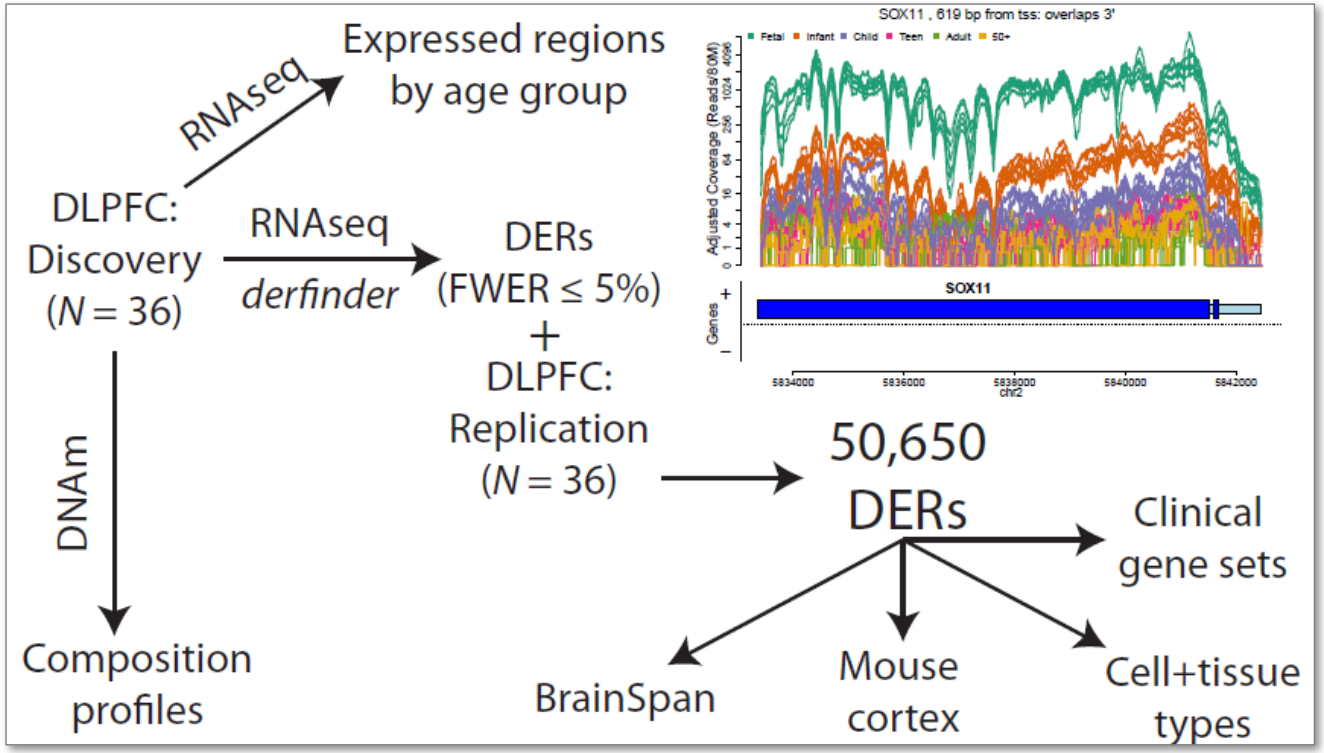
RNA Sequencing Analysis in Human Brain



nature neuroscience

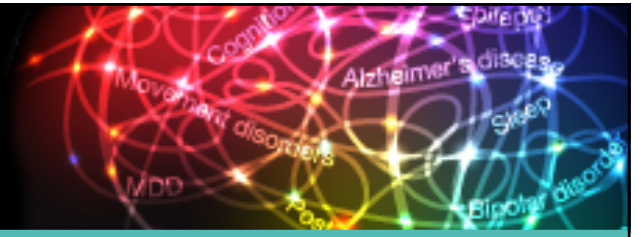
Developmental regulation of human cortex transcription and its clinical relevance at single base resolution

Andrew E Jaffe[1–3], Jooheon Shin[1], Leonardo Collado-Torres[1,2], Jeffrey T Leek[2,4], Ran Tao[1], Chao Li[1], Yuan Gao[1], Yankai Jia[1], Brady J Maher[1,5,6], Thomas M Hyde[1,5–8], Joel E Kleinman[1,9] & Daniel R Weinberger[1,4–7,9]



Jaffe AE, et al. *Nat Neurosci*. 2015;18(1):154-161.

Developmental DERs are Enriched with GWAS Positive Regions



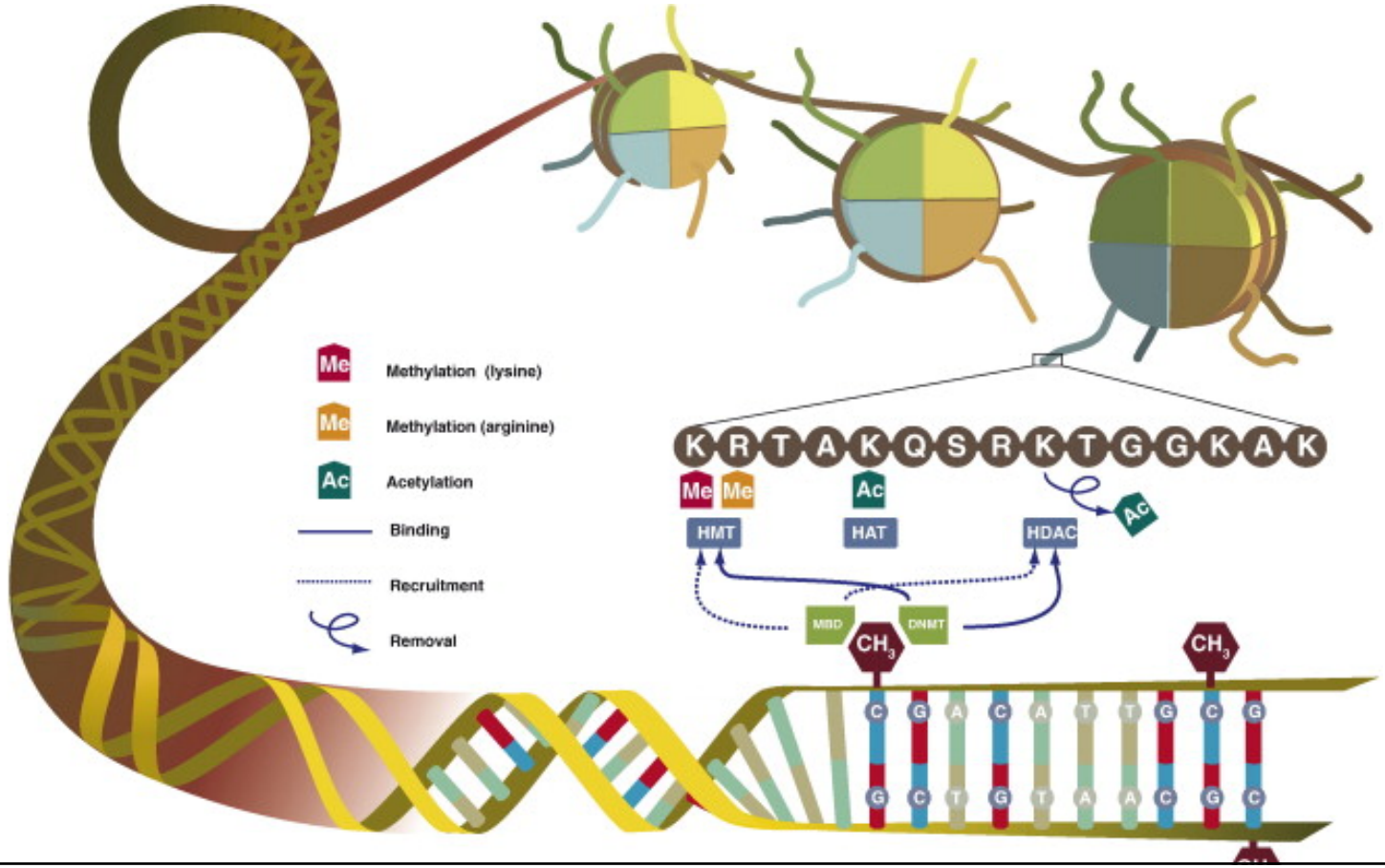
Trait	All	Exon	Intron	Intergenic
Schizophrenia	0.0013	0.0001	0.0003	0.0530
Alzheimer's disease	0.0385	0.2778	0.0117	0.6016
Parkinson's disease	0.0039	0.0100	0.0035	0.0882
Type 2 diabetes	0.2500	0.1029	0.4307	0.1200

- Shown are empirical *p* values determined by permutation assessing significant overlap between DERs and locations of GWAS-positive loci for schizophrenia, Alzheimer's disease, Parkinson's disease, and Type 2 diabetes
- DERs also overlap genes associated with intellectual disability ($p < 10^{-4}$), autism ($p = .017$), and syndromal neurodevelopmental disorders ($p = .027$).

GWAS = genome-wide association study

Jaffe AE, et al. *Nat Neurosci*. 2015;18(1):154-161.

Gene X Environment = Sequence X Epigenetic State

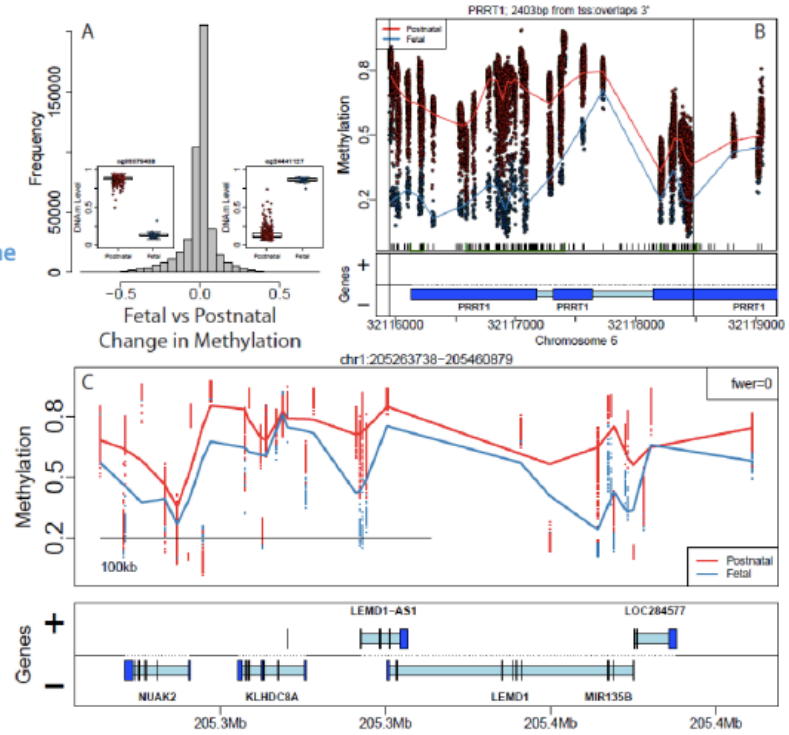


nature neuroscience

Mapping DNA methylation across development, genotype and schizophrenia in the human frontal cortex

Andrew E Jaffe[1–3], Yuan Gao[1], Amy Deep-Soboslay[1], Ran Tao[1], Thomas M Hyde[1,4,5], Daniel R Weinberger[1,4–7] & Joel E Kleinman[1,7]

231,415 CpGs (50.7%) at $p_{bonf} < 5\%$.
70% associated with nearby gene expression

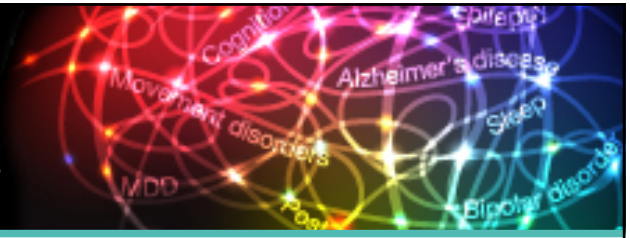


6,480 DMRs at $p_{fwer} < 5\%$.
87% associated with nearby gene expression

896 "blocks" at $p_{fwer} < 5\%$

Jaffe AE, et al. *Nat Neurosci*. 2016;19(1):40-47.

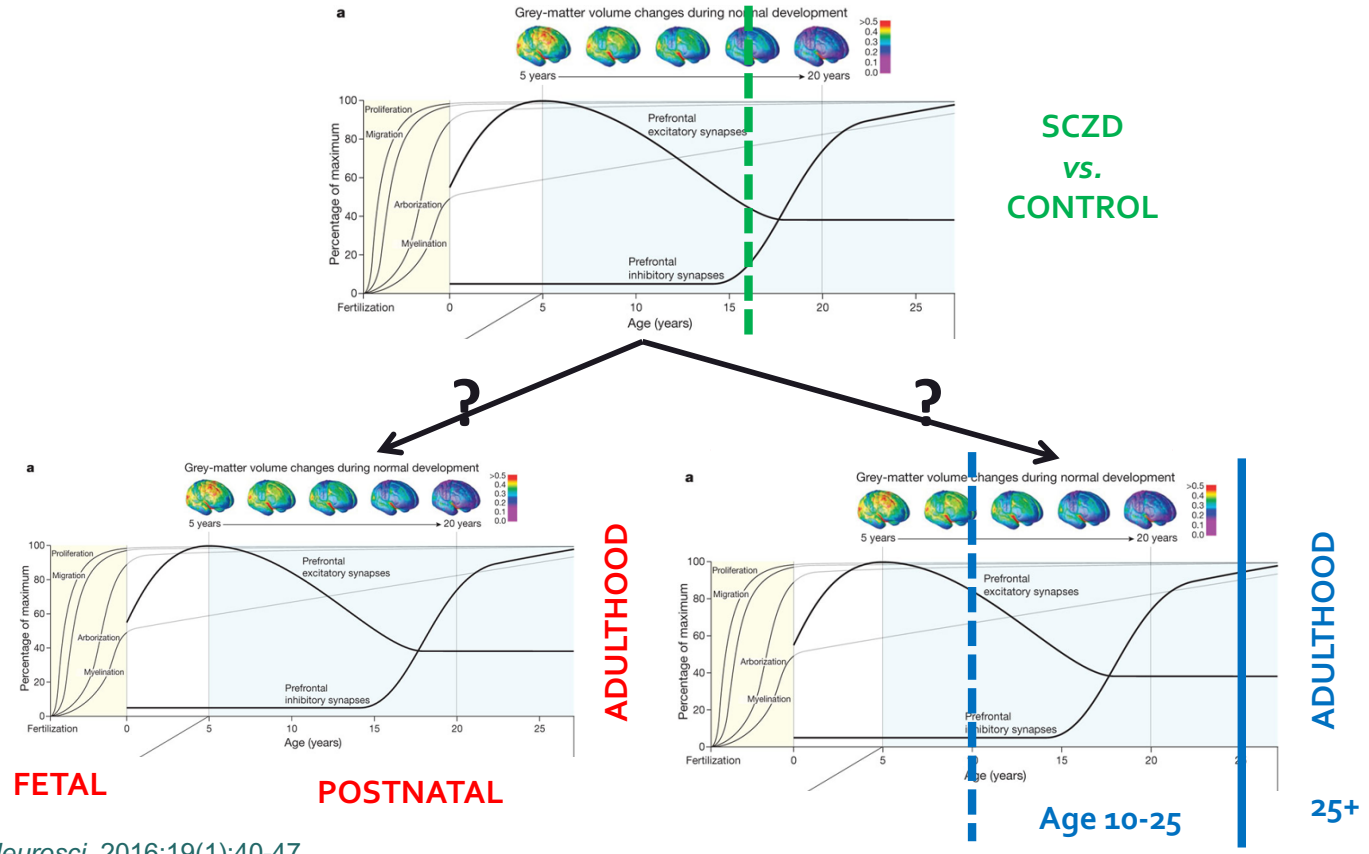
PGC2 Risk Regions are Enriched for Sites Showing Early DNAm Changes



- Significant enrichment of CpGs more highly methylated in fetal compared to post-natal life within the PGC2 risk regions for schizophrenia (51.2% within versus 46.5% outside regions, OR = 1.21, *p*-value = 2.03 x 10-8)
- Schizophrenia specificity: Non-significant association of AD or PD GWAS loci among birth-related changes
- Overall, DNAm changes associated with age of onset (10-25 vs 25+) are not enriched for PGC risk associated loci

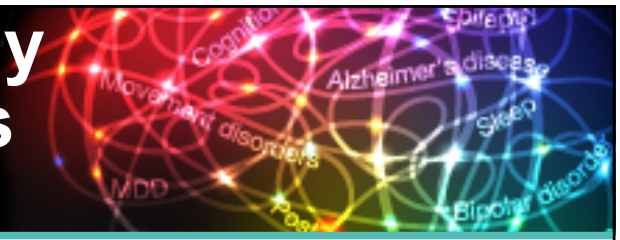
Jaffe AE, et al. *Nat Neurosci*. 2016;19(1):40-47.

CpGs Differentially Methylated in Schizophrenia Patients: Are They Enriched for Any Particular Time of Development?



Jaffe AE, et al. *Nat Neurosci*. 2016;19(1):40-47.

What About Those CpGs Differentially Methylated in Schizophrenia Patients Compared with Controls?

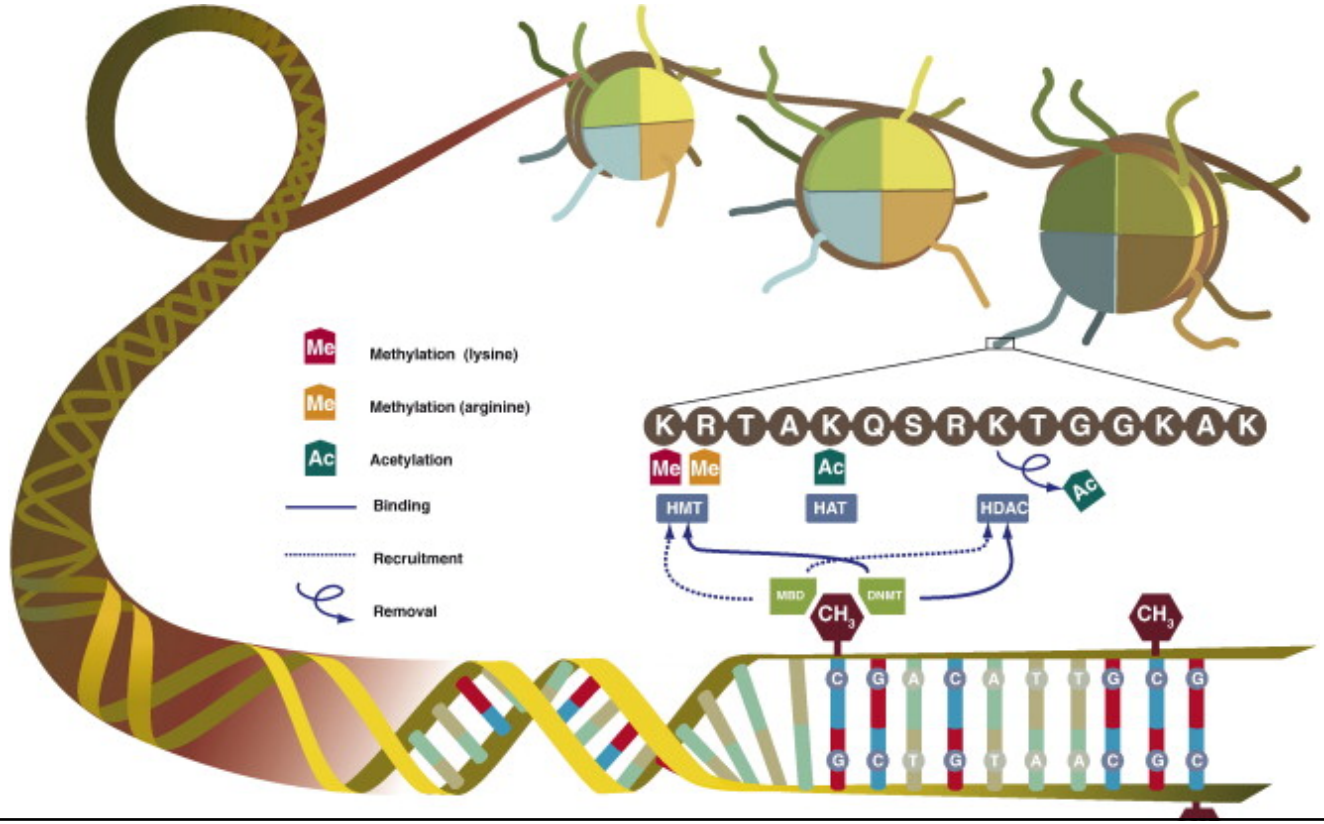


- Identified 2,104 slightly differentially methylated CpGs between 108 schizophrenia patients and 136 adult controls
  - (pbonf < 0.05)
- Schizophrenia-associated DNAm changes were:
  - Strongly enriched for fetal-postnatal transition DNAm changes (94.4%, OR = 16.5)
  - Depleted for DNAm changes near age-of-onset (1.5%, OR = 0.26)

CpG = *5′—C—phosphate—G—3′*

Jaffe AE, et al. Nat Neurosci. 2016;19(1):40-47.

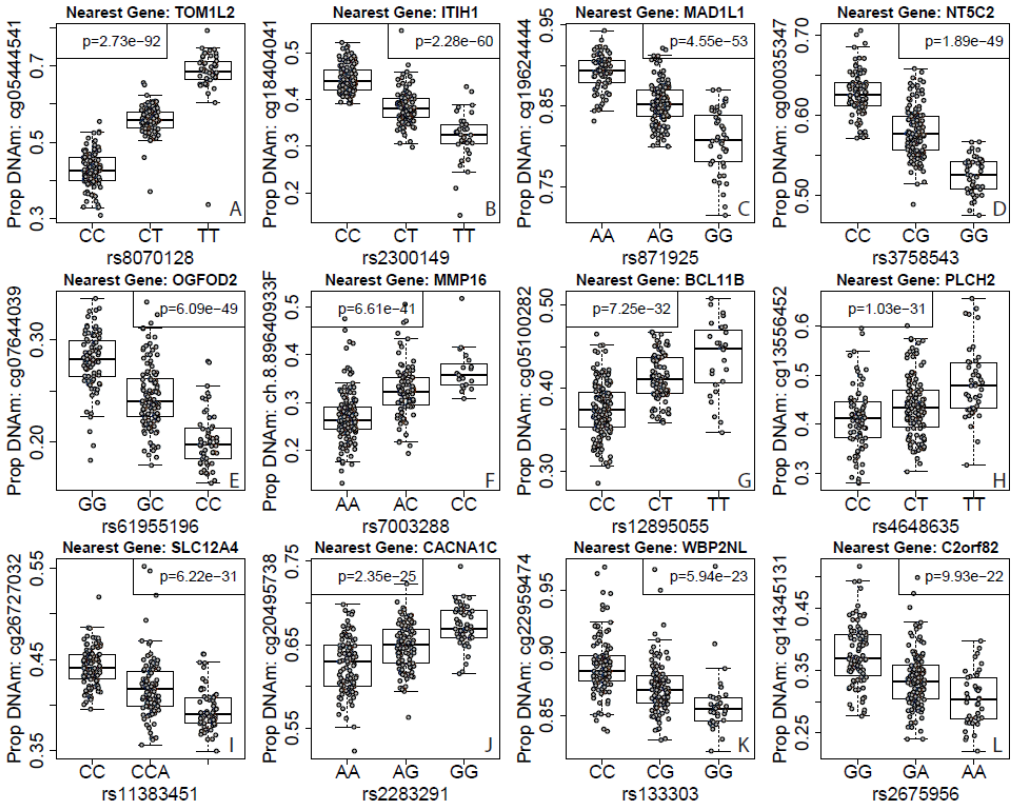
These results suggest that risk factors for schizophrenia, both genetic and those environmental factors that leave a mark in adult brain, are principally related to early brain development and not to the tumultuous time of clinical diagnosis.



Many PGC-Positive Risk SNPs Associated With Nearby DNAm Levels

- 62/104 (59.6%) PGC2-positive index SNPs or their highly correlated proxies were associated with nearby DNAm levels ("meQTL")

Schizophrenia risk variants appear to be about environmental sensitivity!



PGC = pepsinogen C gene, DNAm = DNA methylation

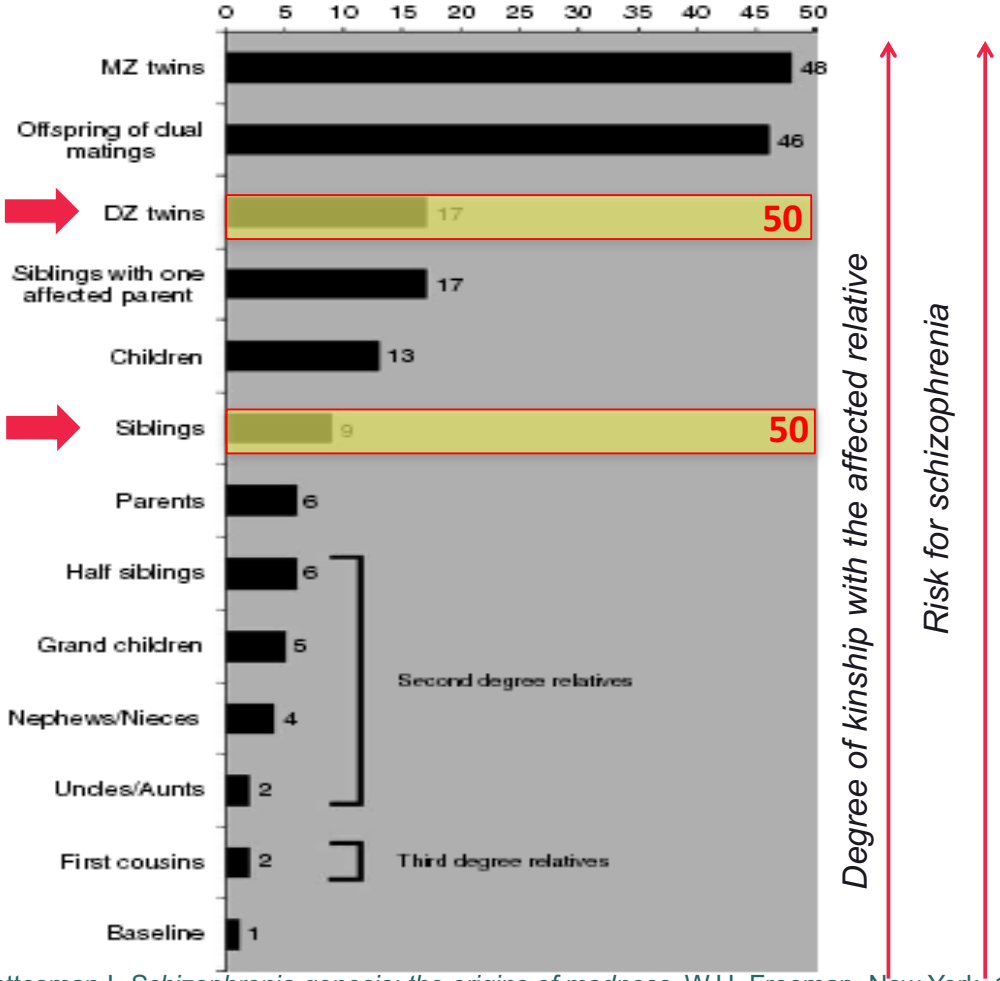
Jaffe AE, et al. *Nat Neurosci.* 2016;19(1):40-47.

Interesting biology, but still very little clinical risk explained…. what's missing?

How about GxE?

GxE = genetics by environment

Three Things We Know About Schizophrenia Risk…



Polygenic Architecture[1]

Role Of Early Life Environment[2]

Higher Incidence In Males[3]

1. Gottesman I. *Schizophrenia genesis: the origins of madness.* W.H. Freeman. New York, 1990.; 2. Cannon M, et al. *Am J Psychiatry*. 2002;159(7):1080-1092.; 3. McGrath J, et al. *Epidemiol Rev.* 2002;30:67-76.

Genetic Risk and Environmental Risk

HYPOTHESIS:

GENOMIC RISK (PRS)

INTRAUTERINE ENVIRONMENT
(OBSTETRIC COMPLICATIONS)

INCREASED RISK FOR
SCHIZOPHRENIA

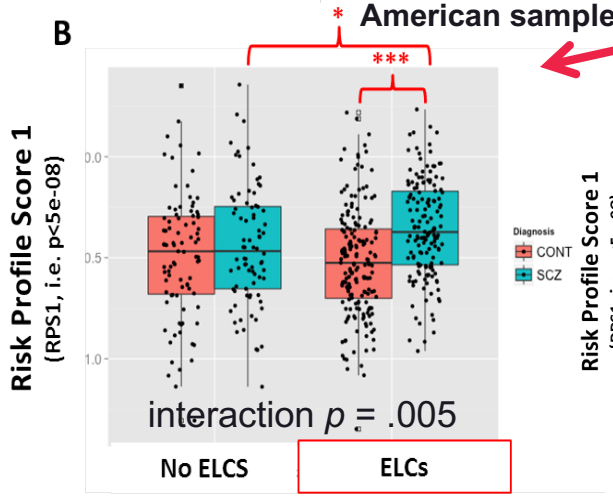
Genomic Risk For Schizophrenia In The Context Of Early Life Complications (ELCs)

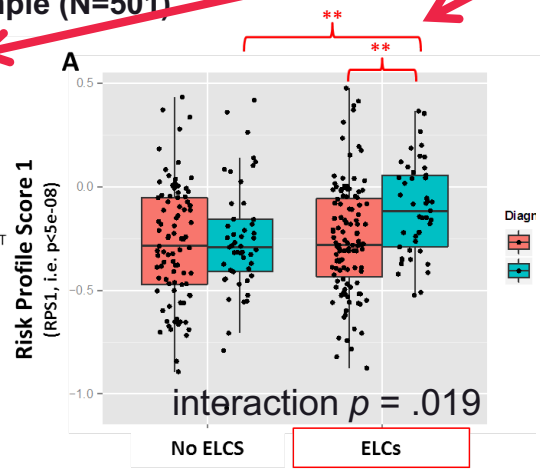
*: $p < .05$
**: $p < .01$
***: $p < .001$

American sample (N=501)

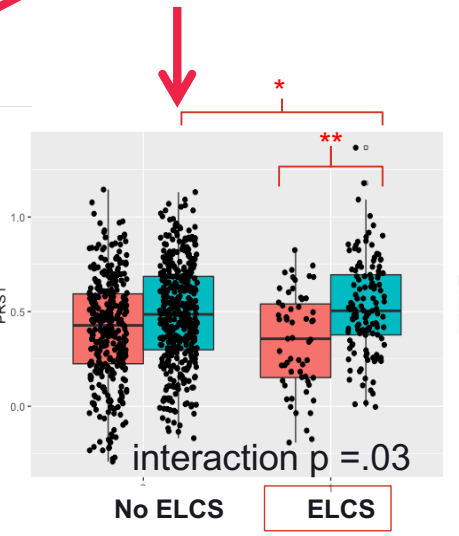
Polygene risk score (PRS1) is significantly different between patients with schizophrenia and controls

But especially in the context of Early Life Complications





Italian sample (N = 273)

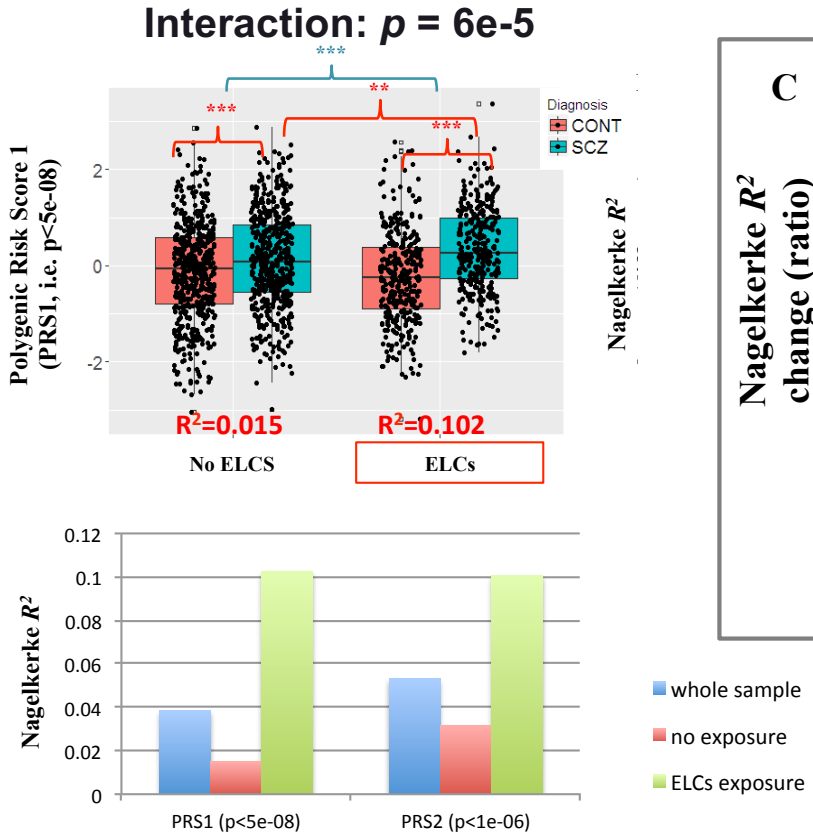


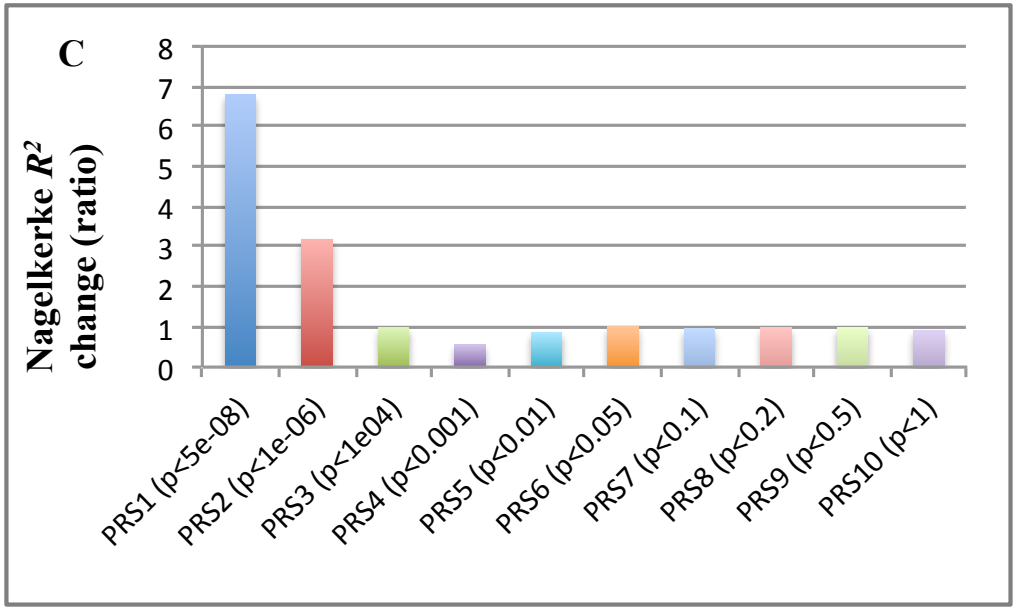
German sample (N = 919)

Ursini G, et al. bioRxiv. Published Jun. 7, 2017; doi: http://dx.doi.org/10.1101/147207.

Interaction Between PRS1 and ELCs in the Merged Samples and the Change in Risk Prediction

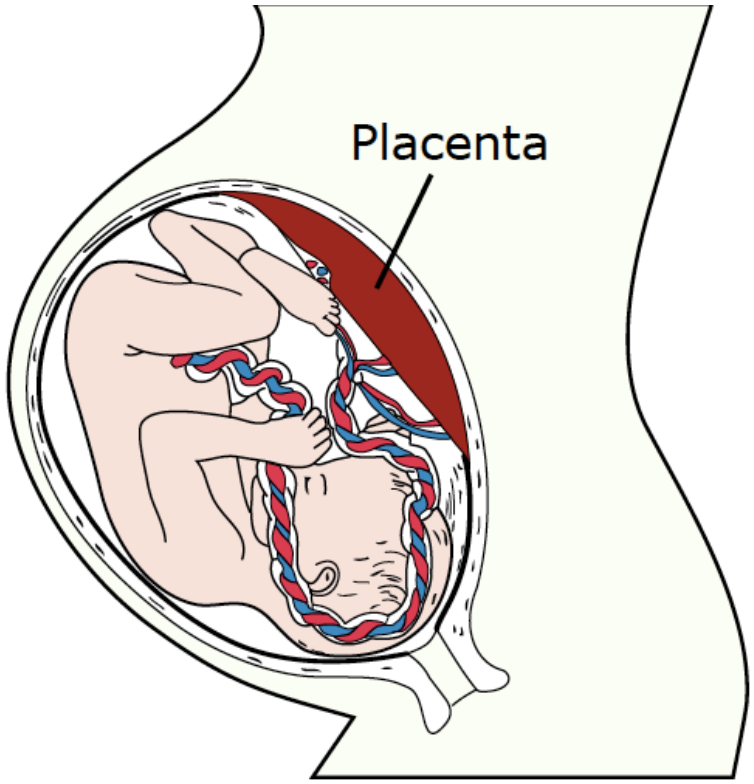
N = 1693





Ursini G, et al. *bioRxiv*. Published Jun. 7, 2017; doi: http://dx.doi.org/10.1101/147207.

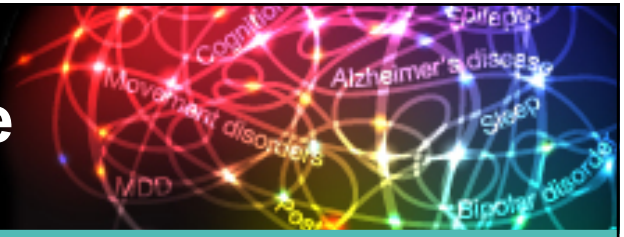
How Do Genomic Risk and ELCs Interact?



What's going on in the placenta?

ELC = early-life complications

Schizophrenia Risk Genes (PRS1+2) are Enriched in Placenta, Compared With the Remaining PRS Genes

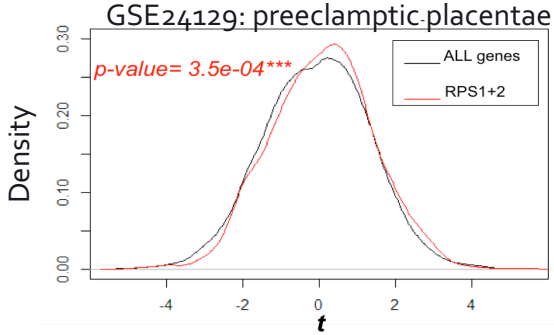


Placental Tissue Compartment	P-value of the Gene-Set Test
Amnion	1e-04***
Basal plate	1e-04***
Chorion	3e-04***
Villi	1e-05***
Trophoblast	1e-05***
Trophoblast – 2nd trimester	3e-05***
Trophoblast – 3rd trimester	1e-06***

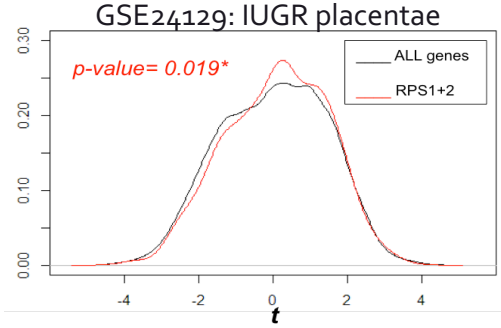
Ursini G, et al. *bioRxiv*. Published Jun. 7, 2017; doi: http://dx.doi.org/10.1101/147207

Schizophrenia Risk Genes are Enriched in Placental Samples from Complicated, Compared With Normal Pregnancies

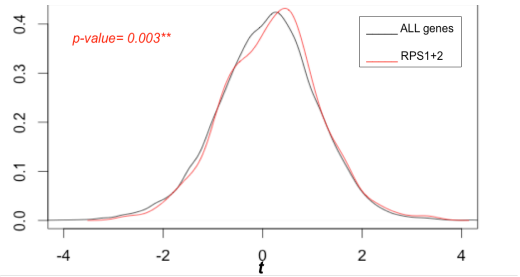
GSE24129: preeclamptic placentae



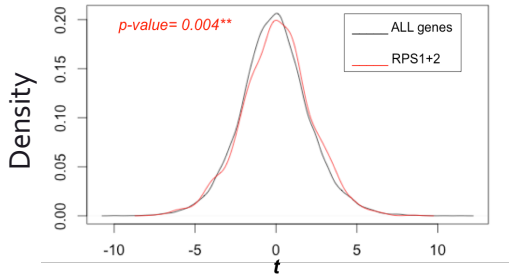
GSE24129: IUGR placentae



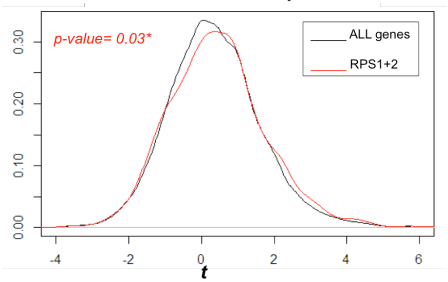
GSE12767: preeclamptic chorionic villi (1st tr.)



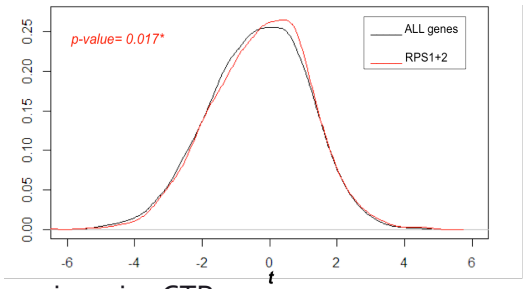
GSE10588: preeclamptic placentae



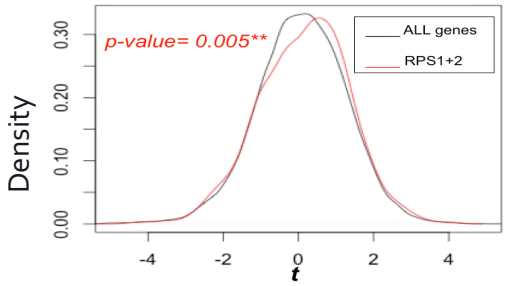
GSE12216: IUGR placentae



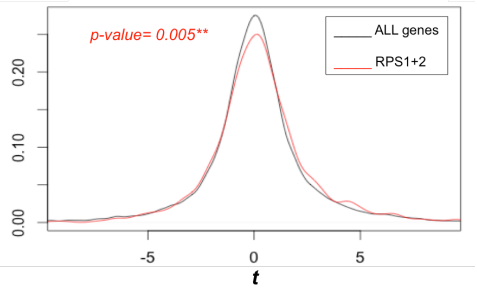
GSE25861: preecl./IUGR microvasc. endothelium



GSE40182: preeclamptic CTBs



GSE25861: invasive vs. non invasive CTBs



Ursini G, et al. *bioRxiv*. Published Jun. 7, 2017; doi: http://dx.doi.org/10.1101/147207.

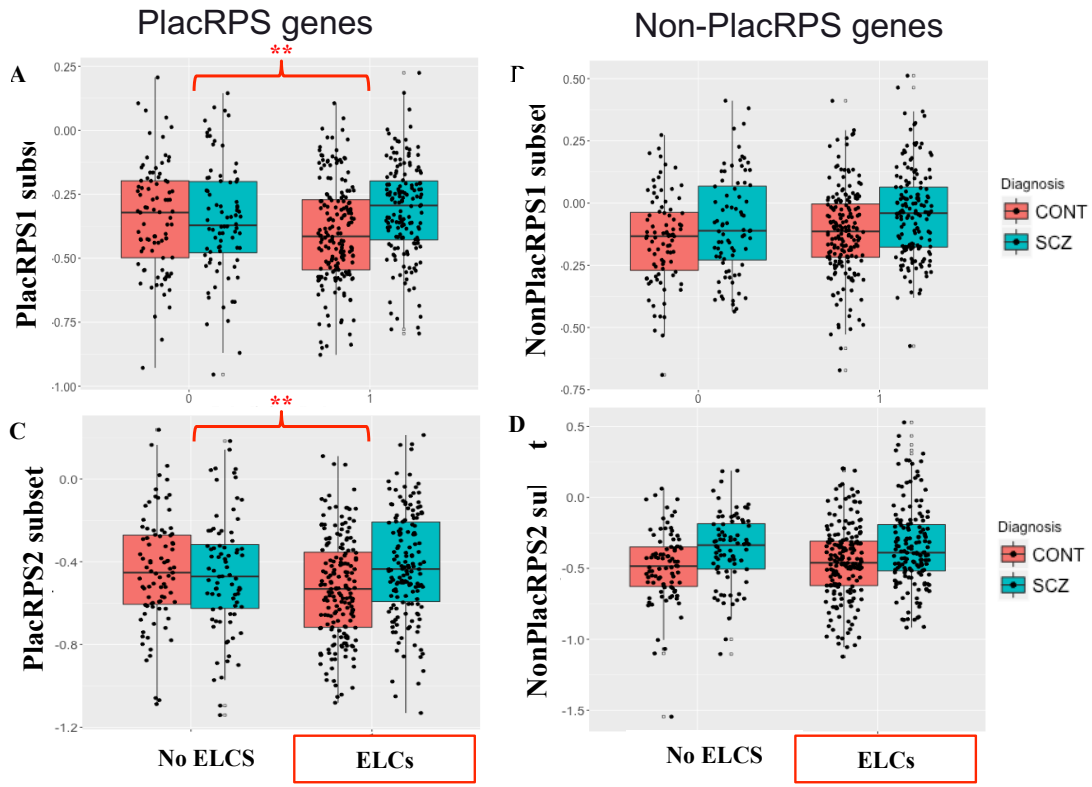
Is PlacPRS Gene Expression a Nonspecific Response to Organ Pathology, Per Se?

Dataset	Condition	Tissue	p-value of Gene-Set Test	χ^2 test	
				p-value	χ^2
GSE24129	Preeclampsia	whole placentae	3.5e-04***	0.002**	7.670
GSE24129	IUGR	whole placentae	0.019*	0.02*	3.97
GSE35574	Preeclampsia	whole placentae	0.04*	0.03*	3.21
GSE35574	IUGR	whole placentae	0.007**	0.04*	2.76
GSE10588	Preeclampsia	whole placentae	0.004**	0.04*	3.03
GSE25906	Preeclampsia	whole placentae	0.02*	0.003**	7.13
GSE12216	Preeclampsia	whole placentae	0.03*	0.01*	4.53
GSE40182	Preeclampsia	CTB	0.005**	0.04*	2.87
GSE12767	Preeclampsia	1st trimester chorionic villi	0.003**	0.007**	6.15
GSE25861	Preeclampsia/IUGR	microvascular endothelium	0.017*	0.02*	4.13
GSE65271	CTB invasiveness	CTB	0.005**	0.002**	7.883
GSE28619	Hepatitis (liver)	liver	0.11	0.12	1.4
GSE41804	Hepatitis (liver)	liver	0.13	0.35	0.16
GSE27411	HP gastritis (corpus)	stomach corpus	0.46	0.25	0.48
GSE27411	HP gastritis (antrum)	stomach antrum	0.63	0.37	0.11
GSE42955	Dilatative cardiomiopathy	heart	0.37	0.37	0.11
GSE3586	Dilatative cardiomiopathy	heart	0.3	0.02 (opposite direction)	4.2
GSE4172	Dilatative cardiomiopathy	heart	0.92	0.46	0.01

Answer: *NO*

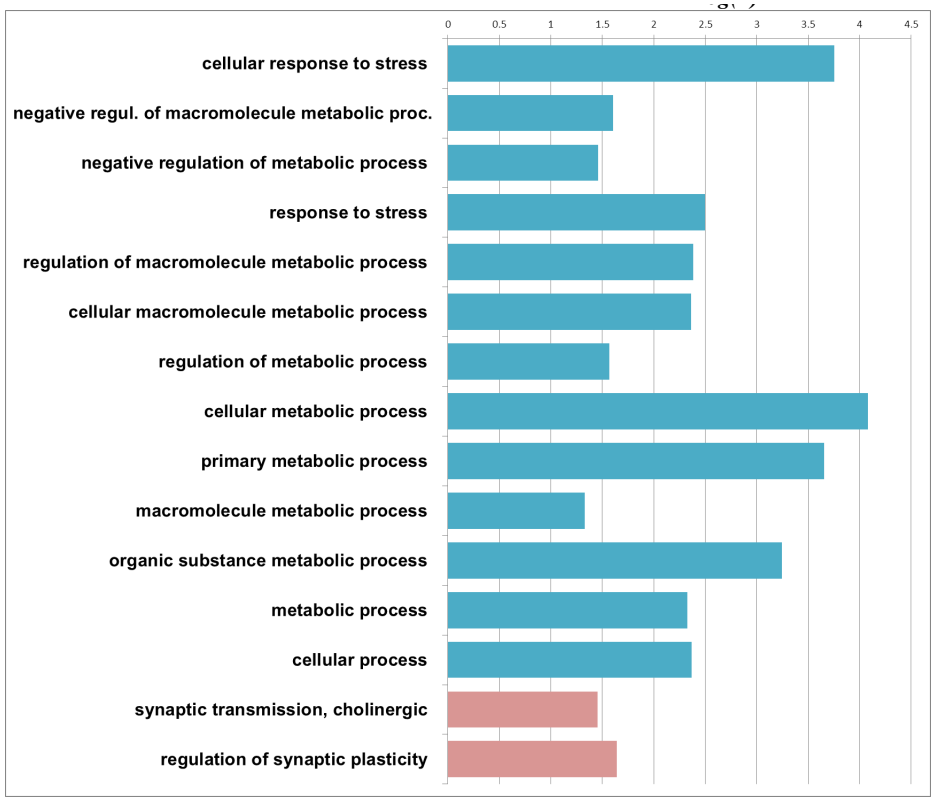
Ursini G, et al. *bioRxiv*. Published Jun. 7, 2017; doi: http://dx.doi.org/10.1101/147207

Schizophrenia Risk Genes Dynamically Modulated in Placenta Drive the Interaction Between PRS and ELCs



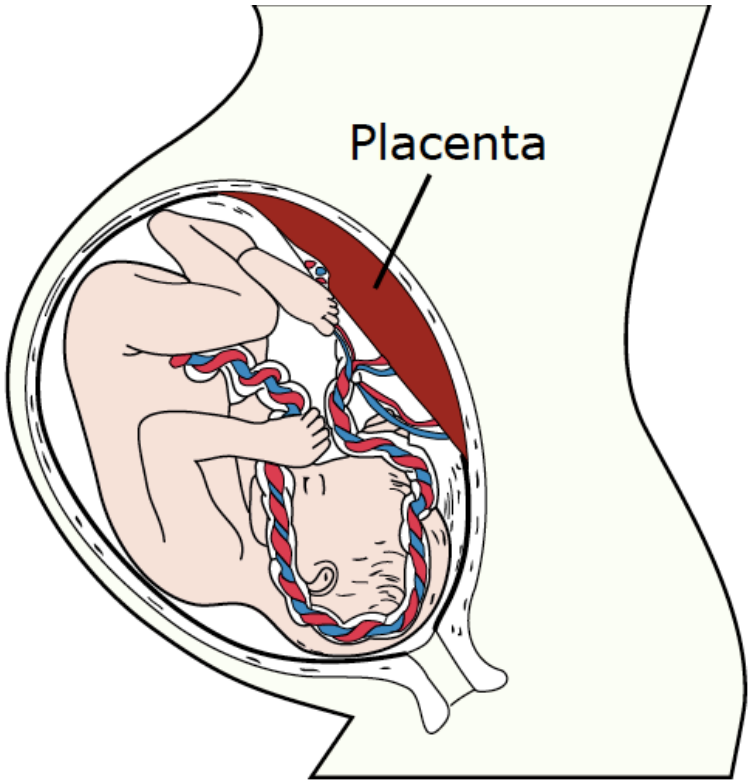
Ursini G, et al. *bioRxiv*. Published Jun. 7, 2017; doi: http://dx.doi.org/10.1101/147207

Biological Processes (*GO* Terms) Enriched for PlacPRS1 and NonplacPRS1 Genes



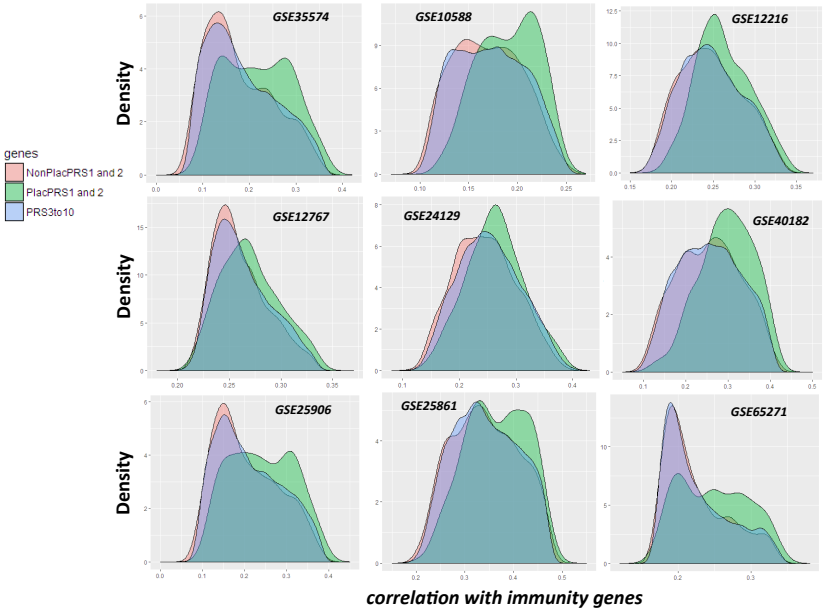
Ursini G, et al. *bioRxiv*. Published Jun. 7, 2017; doi: http://dx.doi.org/10.1101/147207

How Do PLACPRS Genes Influence Placentation?



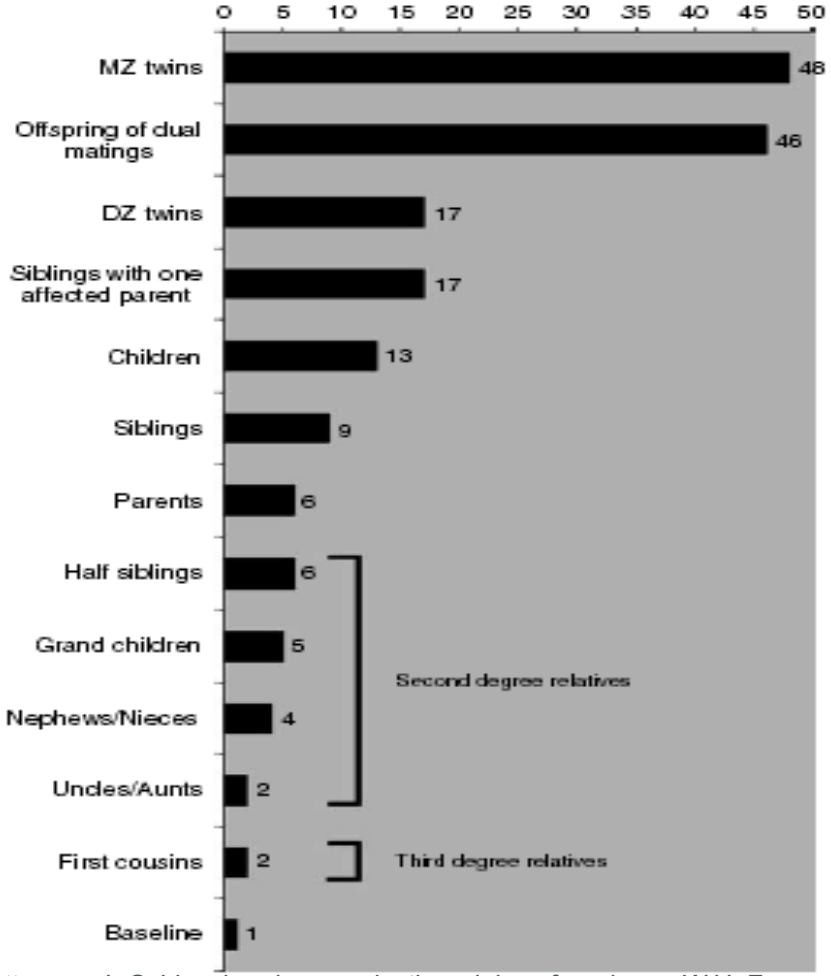
PLACPRS = PRS placental subset, PRS = polygenic risk scores

Strong Co-Expression of PlacPRS Genes with Immunity Genes



	all Immunity genes	Complement	Heat Shock Proteins
GSE24129	1.68E-03	0.1248927	7.82E-10
GSE35574	5.85E-12	8.99E-10	7.34E-12
GSE10588	3.62E-14	4.29E-09	5.07E-14
GSE25906	2.64E-09	6.38E-07	1.07E-09
GSE12216	1.14E-08	9.72E-08	1.35E-12
GSE40182	7.60E-16	1.86E-10	4.95E-18
GSE12767	2.95E-05	0.4534849	6.06E-05
GSE25861	1.16E-06	2.51E-06	1.13E-08
GSE65271	1.10E-13	2.90E-11	1.08E-12

Three Things We Know About Schizophrenia Risk…



Polygenic Architecture[1]

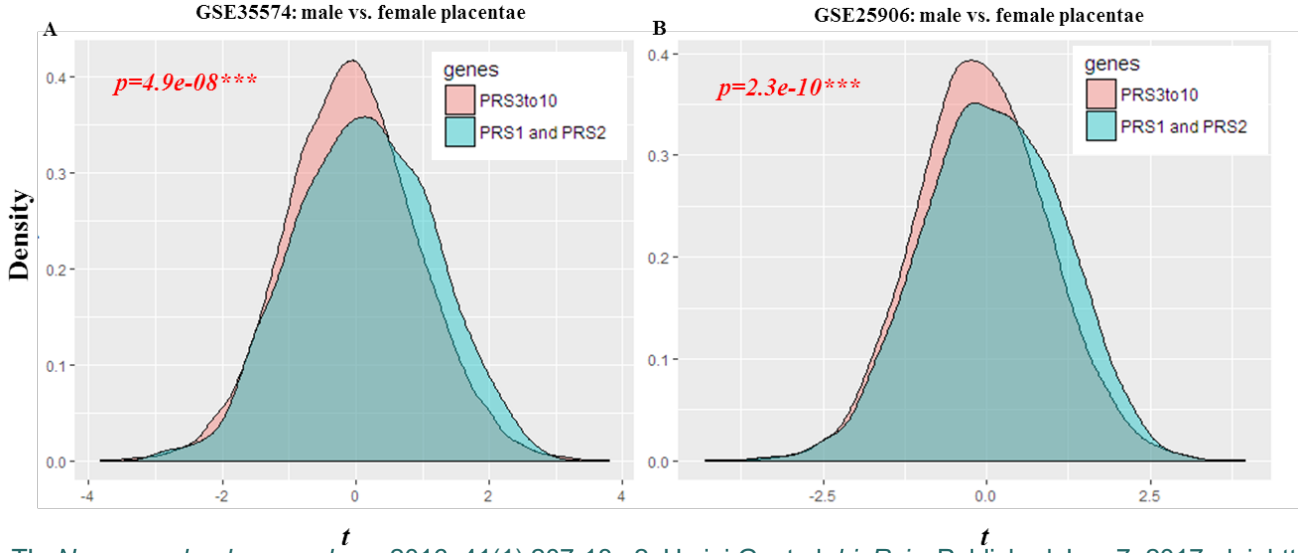
Role of Early Life Environment[2]

Higher Incidence In Males[3]

1. Gottesman I. *Schizophrenia genesis: the origins of madness.* W.H. Freeman. New York, 1990.; 2. Cannon M, et al. *Am J Psychiatry*. 2002;159(7):1080-1092.;
3. McGrath J, et al. *Epidemiol Rev.* 2002;30:67-76.

Is Expression of Schizophrenia PRS Genes Higher in Placentae of Male Compared With Female Offspring?

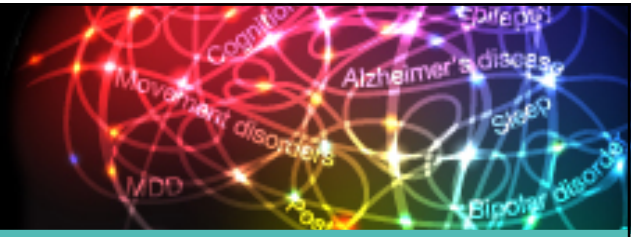
- Animal studies show that the outcomes of altered placental functioning on brain development are sex-specific, with males more vulnerable than female to prenatal adversities[1]
- Is there a link with the greater incidence of developmental disorders like schizophrenia in males?



1. Bronson SL, Bale TL. *Neuropsychopharmacology*. 2016; 41(1):207-18.; 2. Ursini G, et al. *bioRxiv*. Published Jun. 7, 2017; doi: http://dx.doi.org/10.1101/147207.

ACKNOWLEDGEMENTS

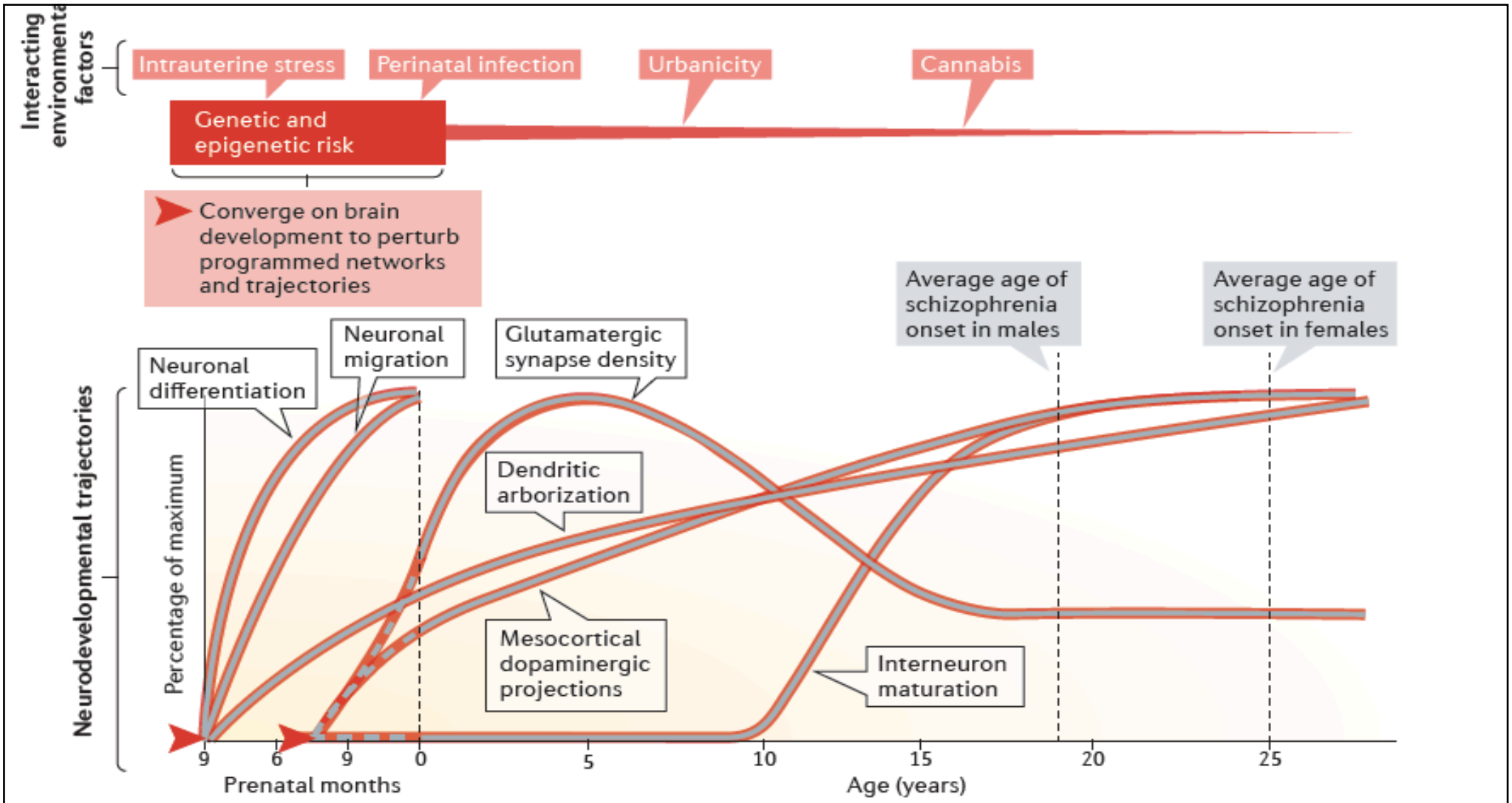
LIBD Acknowledgements



Postmortem human brain
Amy Deep-Salobslay
Thomas Hyde
Joel Kleinman

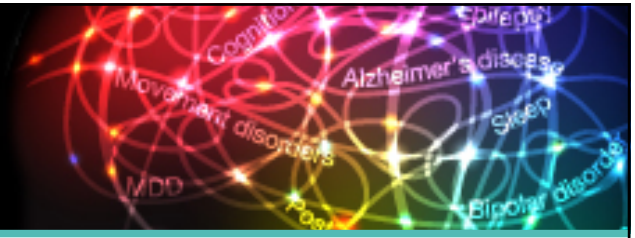
Genetic association and RNA Seq
Gianluca Ursini
Giovanna Punzi
Joo Heon Shin
Richard Straub
Danny Chen
Andrew Jaffe

Stefano Marenco, NIMH
Karen Berman, NIMH
Ryota Hashimoto, Osaka Univ, Japan
Allessandro Bertolino, Univ of Bari, Italy
Michael Egan, Merck
Dan Rajescu, Ludwig-Maximilians University, Germany
Hannelore Ehrenreich, Max Planck Institute, Germany



Birnbaum R, Weinberger DR. *Nat Rev Neuroscience*. 2017 Oct 26 doi:10.1038/nrn.2017.125.

Call to Action



- Genes associated with developmental disorders are preferentially expressed during fetal life
- GWAS loci for schizophrenia are enriched for genes showing transcriptional and epigenetic changes related to early fetal life and not for changes around the time of clinical diagnosis
- The most significant genetic variants detected by current GWAS contribute to risk of schizophrenia at least partly by converging on a developmental trajectory sensitive to intrauterine and perinatal adversity and linked with abnormal placentation
- Gene-environment interactions influencing placental biology may account for the higher incidence of schizophrenia in males compared with females
- **Preserving prenatal health may represent a primary form of prevention of schizophrenia, especially in male individuals with high genetic risk**

Questions & Answers

Don’t forget to fill out your evaluations to collect your credit.