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Master Class for Neuroscience Professional Development

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Convergence of Placenta Biology and Genetic Risk for Neuropsychiatric Illness

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Learning Objective

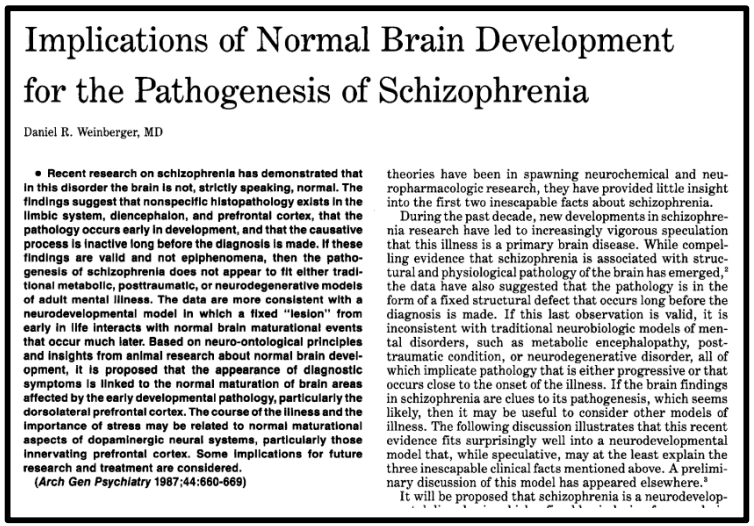
Examine the relationship between obstetrical complications and genetic risk for neuropsychiatric illness.

NEURODEVELOPMENT

Temperament Seems to be “Inborn” to a Considerable Degree

Are there early developmental components to mental illness?

Schizophrenia is Currently Viewed as a Neurodevelopmental Disorder



Implications of Normal Brain Development for the Pathogenesis of Schizophrenia

Daniel R. Weinberger, MD

• Recent research on schizophrenia has demonstrated that in this disorder the brain is not, strictly speaking, normal. The findings suggest that nonspecific histopathology exists in the limbic system, diencephalon, and prefrontal cortex, that the pathology occurs early in development, and that the causative process is inactive long before the diagnosis is made. If these findings are valid and not epiphenomena, then the pathogenesis of schizophrenia does not appear to fit either traditional metabolic, posttraumatic, or neurodegenerative models of adult mental illness. The data are more consistent with a neurodevelopmental model in which a fixed "lesion" from early in life interacts with normal brain maturational events that occur much later. Based on neuro-ontological principles and insights from animal research about normal brain development, it is proposed that the appearance of diagnostic symptoms is linked to the normal maturation of brain areas affected by the early developmental pathology, particularly the dorsolateral prefrontal cortex. The course of the illness and the importance of stress may be related to normal maturational aspects of dopaminergic neural systems, particularly those innervating prefrontal cortex. Some implications for future research and treatment are considered.

(*Arch Gen Psychiatry* 1987;44:660-669)

theories have been in spawning neurochemical and neuropharmacologic research, they have provided little insight into the first two inescapable facts about schizophrenia.

During the past decade, new developments in schizophrenia research have led to increasingly vigorous speculation that this illness is a primary brain disease. While compelling evidence that schizophrenia is associated with structural and physiological pathology of the brain has emerged,[2] the data have also suggested that the pathology is in the form of a fixed structural defect that occurs long before the diagnosis is made. If this last observation is valid, it is inconsistent with traditional neurobiologic models of mental disorders, such as metabolic encephalopathy, posttraumatic condition, or neurodegenerative disorder, all of which implicate pathology that is either progressive or that occurs close to the onset of the illness. If the brain findings in schizophrenia are clues to its pathogenesis, which seems likely, then it may be useful to consider other models of illness. The following discussion illustrates that this recent evidence fits surprisingly well into a neurodevelopmental model that, while speculative, may at the least explain the three inescapable clinical facts mentioned above. A preliminary discussion of this model has appeared elsewhere.[3]

It will be proposed that schizophrenia is a neurodevelop-

-"…lesion from early in life interacts with certain normal maturational events that occur much later…."

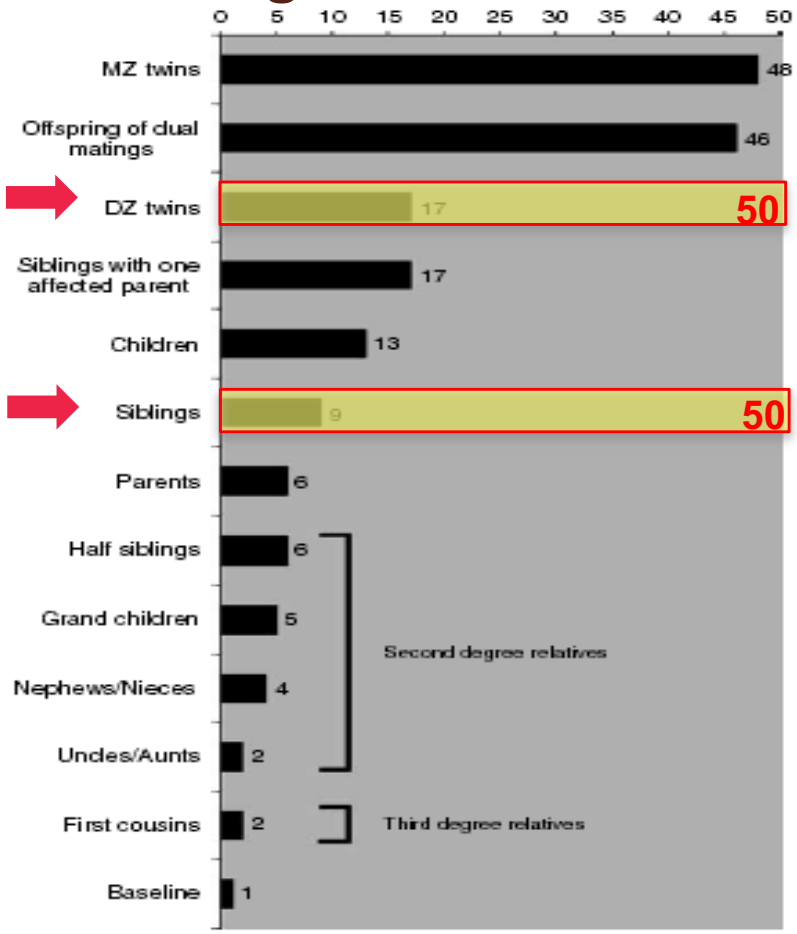
Schizophrenia may not be "the result of a discrete event or illness process at all, but rather one end of the developmental spectrum that for genetic and other reasons approximately 0.5% of the population will fall into."

	Pre-natal	Peri-natal	Post-natal	Adolescence
Epidemiological Evidence:	-Famine exposure -Maternal infection	-Obstetric Complications		-Cannabis
Other Observational/ Clinical Evidence:	→	→	-Delayed milestones -Minor Physical Anomalies -Motor Abnormalities -Social Abnormalities -Cognitive Deficits -Urbanicity	

→ Clinical Emergence of Schizophrenia

Weinberger DR. *Arch Gen Psychiatry* 1987;44:660-9.

Three Things We Know About Schizophrenia Risk…



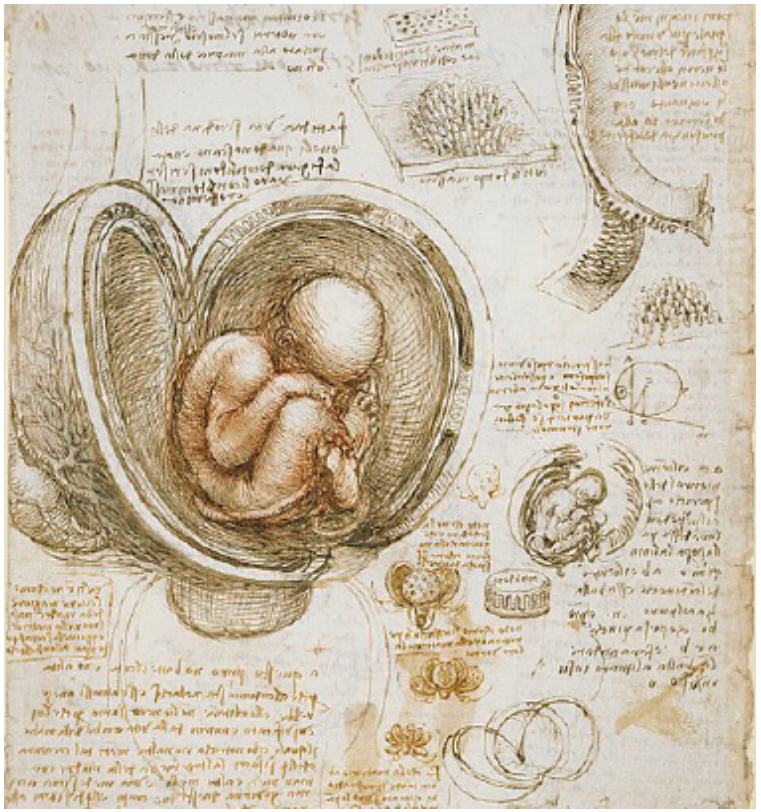
Degree of kinship with the affected relative

Risk for schizophrenia

- 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.

How Does Genetic Risk Relate to Pregnancy Complications?



Do genetic and environmental risk factors act independently or do they interact to modulate risk?

Do Genomes and Environmental Risk Factors Act Independently Or Do They Interact to Modulate Risk?

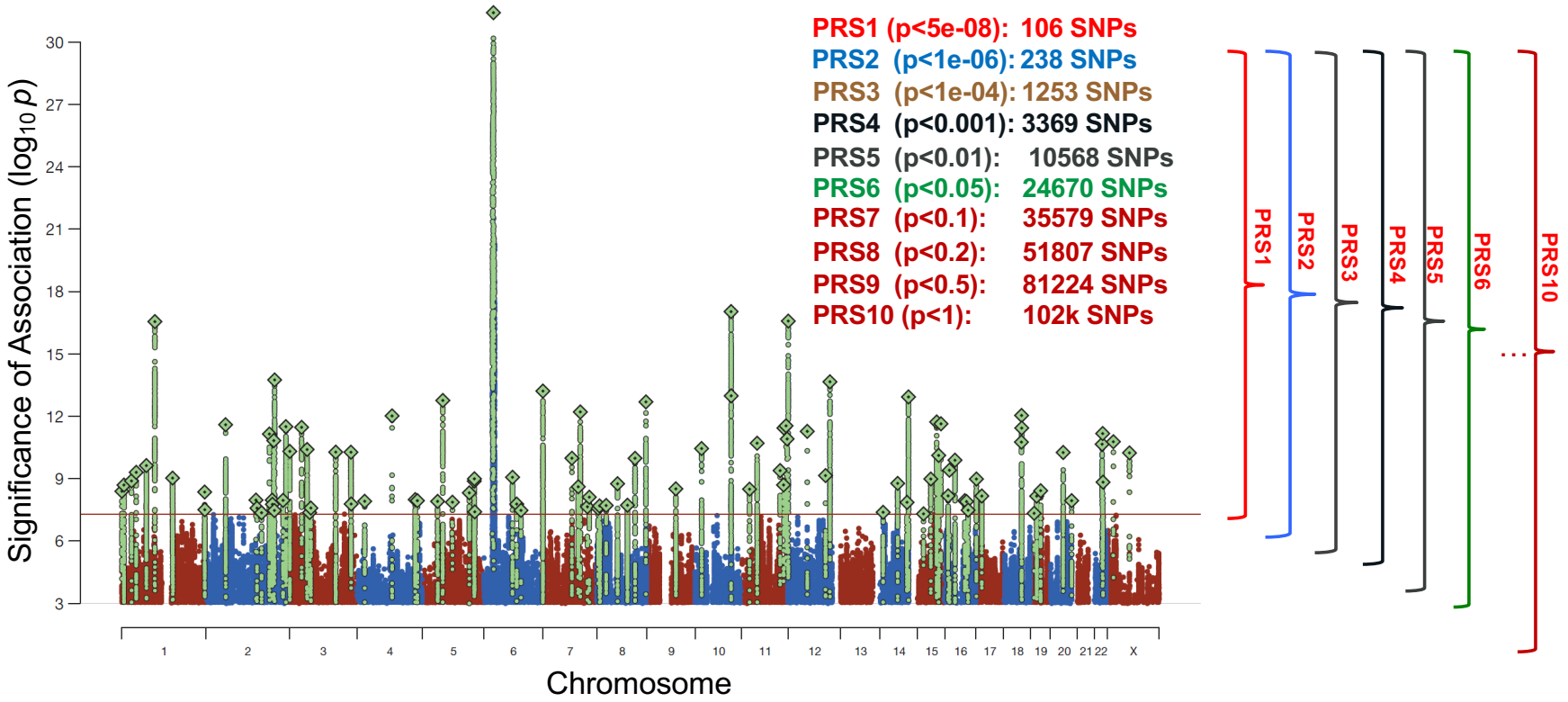
HYPOTHESIS:

GENOMIC RISK (PRS)

INTRAUTERINE ENVIRONMENT (OBSTETRIC COMPLICATIONS)

INCREASED RISK FOR SCHIZOPHRENIA

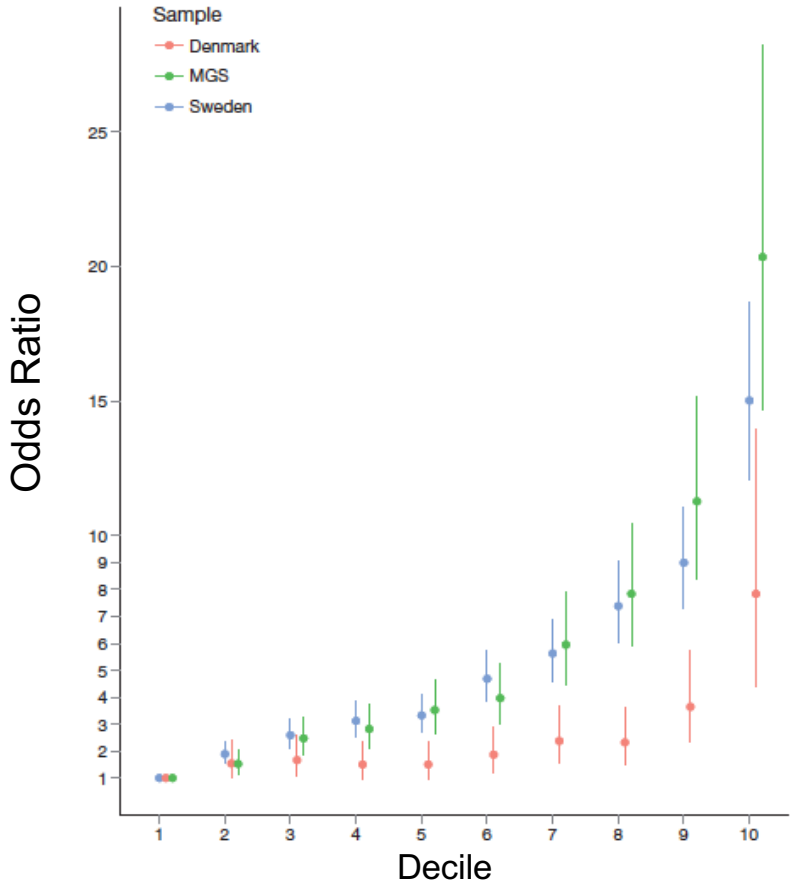
Polygenic Risk Scores (PRS) From Schizophrenia GWAS



GWAS = genome-wide association study

Wray NR, et al. *Genome Res*. 2007;17(10):1520-2528.; Schizophrenia Working Group of the Psychiatric Genomics Consortium. *Nature* 2014;511(7510):421-427.

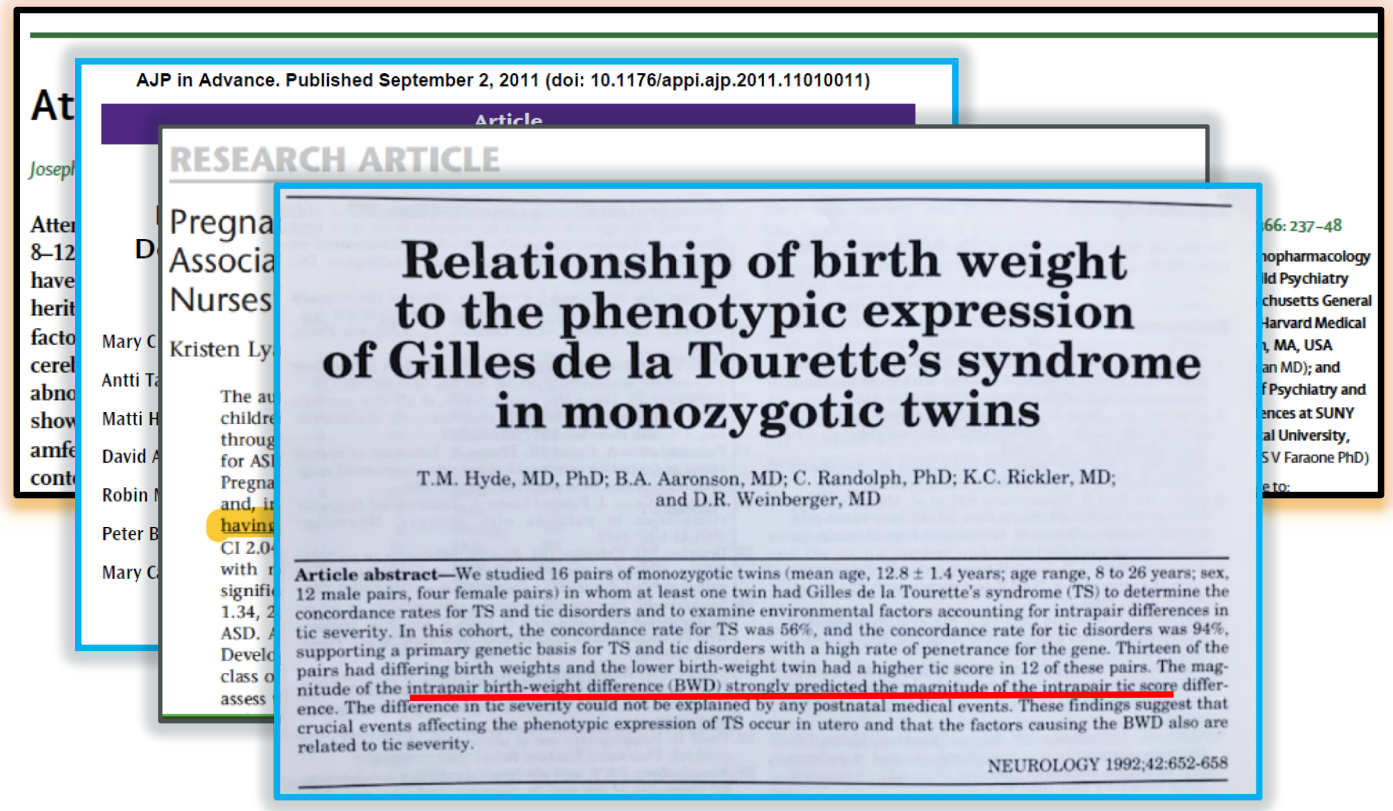
Odds of Developing Schizophrenia with Increasing Polygenic Risk Score



PRS is an additive count of all GWAS risk alleles in an individual

Schizophrenia Working Group of the Psychiatric Genomics Consortium. *Nature.* 2014;511(7510):421-427.

Obstetrical Complications are Risk Factors for Many Developmental Disorders



McNeil-Sjöström Scale for Grading Fetal Implications of Obstetric Complications

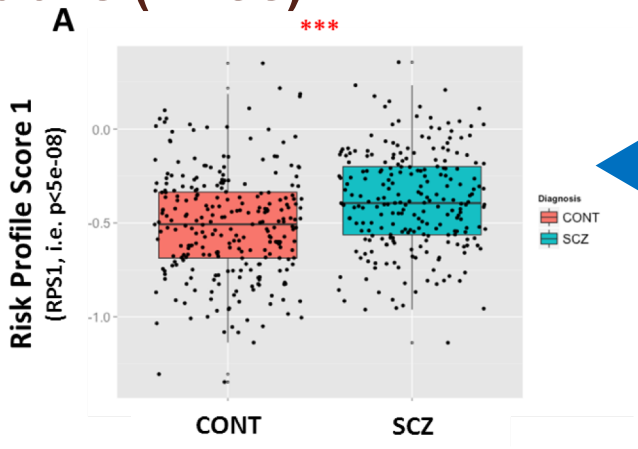
Severity level I: Not harmful or relevant (E.g. maternal Heartburn, maternal Fatigue)
Severity level 2: Not likely harmful or relevant (E.g. maternal Nose bleed, Headache, maternal Ischias)
Severity level 3: Potentially but not clearly harmful or relevant (E.g. maternal Febrile cystitis, maternal sinus infection, Induction of labor)

Severity level 4: Potentially clearly harmful or relevant (E.g. Mild preeclampsia, Breech delivery)
Severity level 5: Potentially clearly greatly harmful/relevant (E.g. Severe preeclampsia, Fetal asphyxia)
Severity level 6: Very great harm to or deviation in offspring (E.g. Eclampsia, Severe neonatal distress, offspring Hypoxic-ischemic cerebral injury)

McNeil, et al. *McNeil-Sjöström Scale for Obstetric Complications*. 1995;Version C:2007 06 01.

Genomic Risk for Schizophrenia in the Context of Early Life Complications (ELCs)

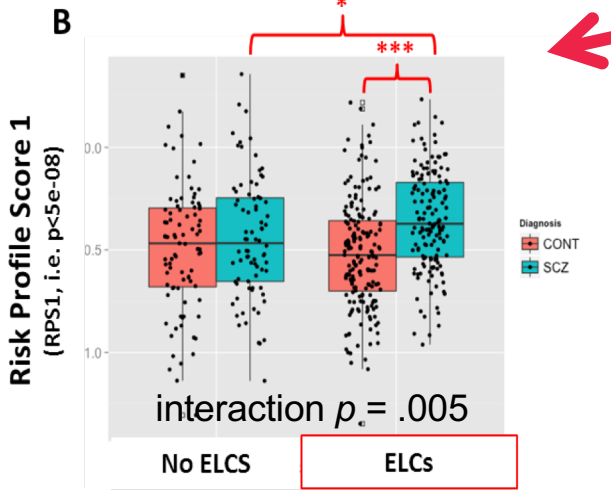
*: $p < .05$
**: $p < .01$
***: $p < .001$

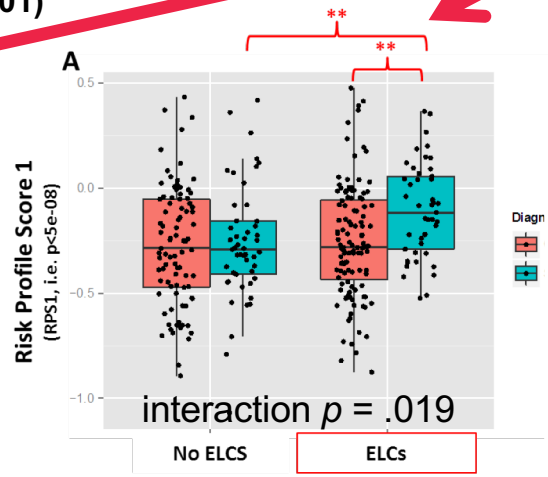


American sample (N=501)

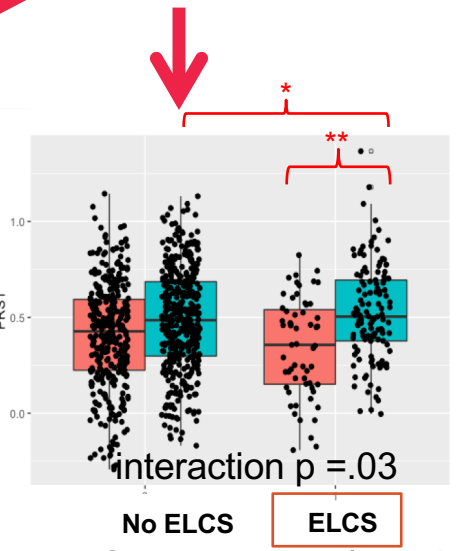
Polygene risk score (PRS1) is significantly different between patients with schizophrenia and controls

But especially in the context of Early Life Complications





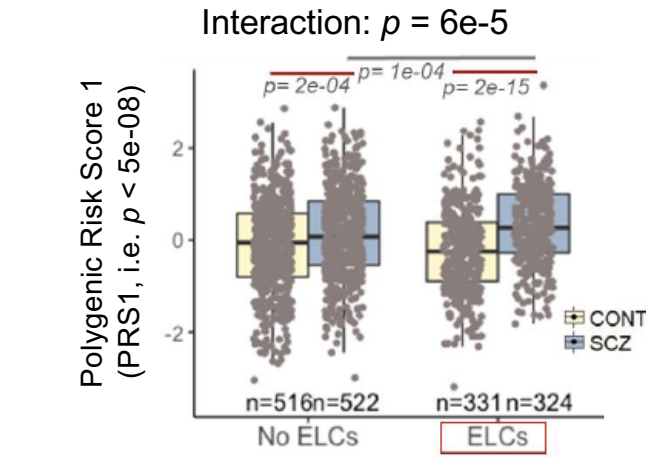
Italian sample (N = 273)

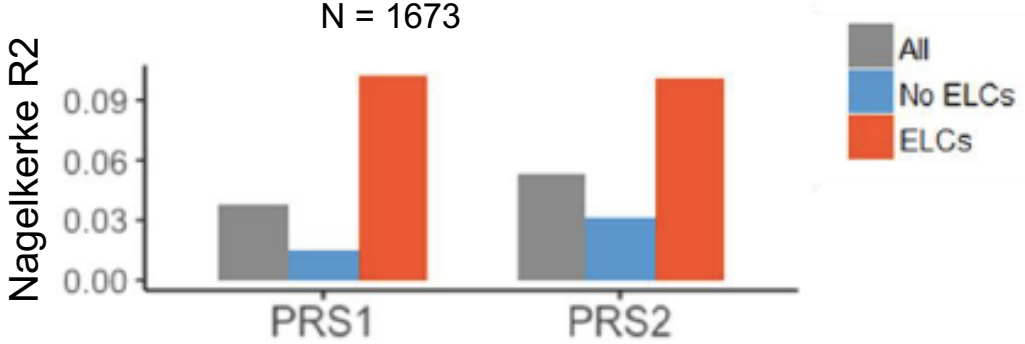


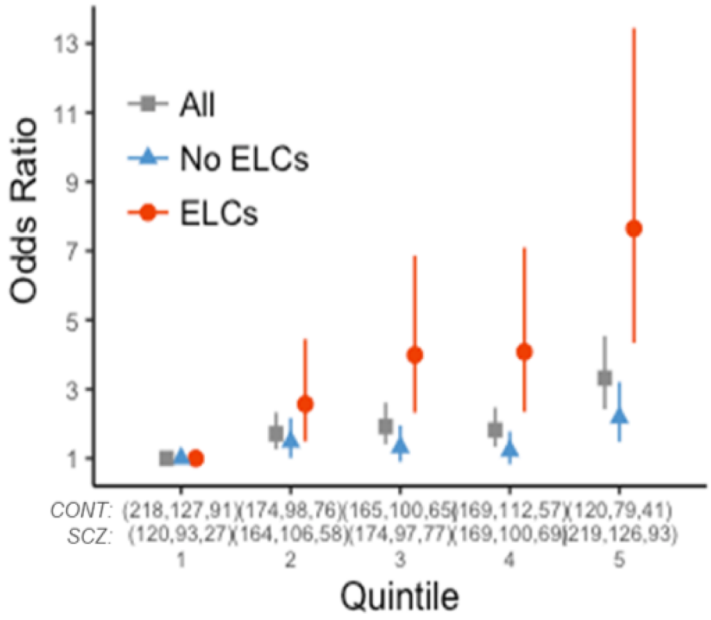
German sample (N = 919)

Ursini G, et al. *Nat Med*. 2018;24(6):792-801.

Interaction Between Prs1 and ELCs in the Merged Samples (N = 1693) and the Change in Risk Prediction

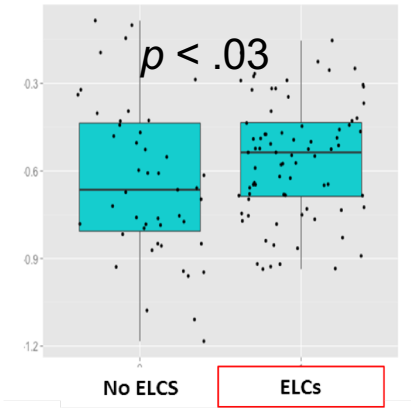




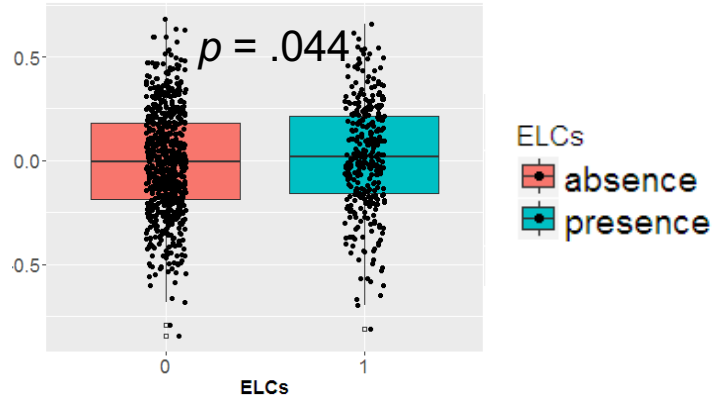


Ursini G, et al. *Nat Med*. 2018;24(6):792-801.

PRS1 Are Greater in Probands with a History of ELCs: Two More Datasets (Five in All)



Japanese patient only sample
(N = 172)



German patient only sample
(N = 990)

RPS	t	p
RPS1	3.893	0.000102
RPS2	2.132	0.033158
RPS3	0.656	0.512097
RPS4	0.028	0.977935
RPS5	0.455	0.648935
RPS6	0.938	0.348370
RPS7	0.746	0.455812
RPS8	0.904	0.366344
RPS9	0.812	0.416777
RPS10	0.808	0.419370

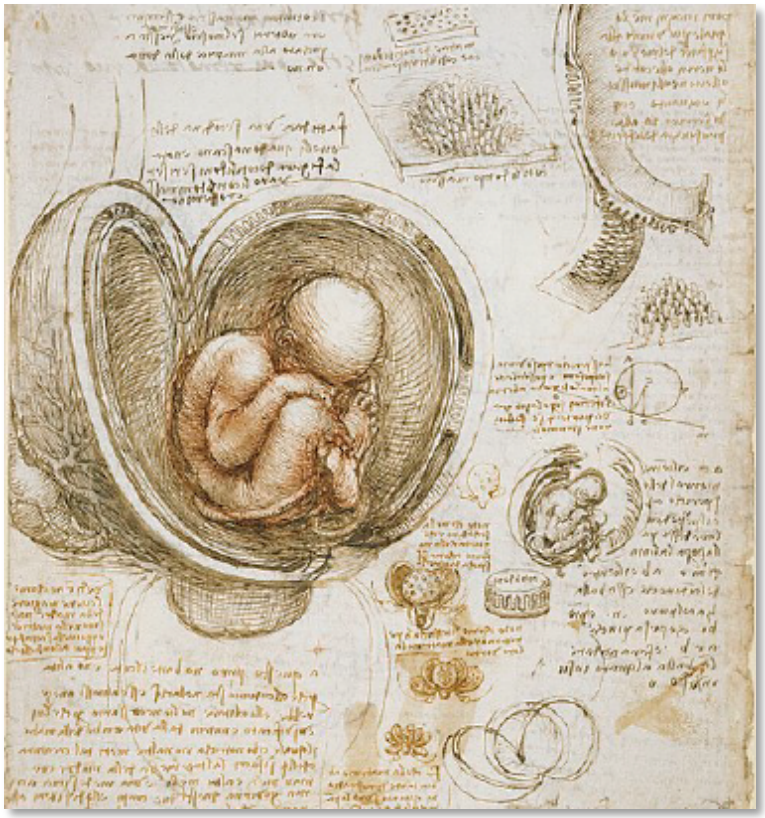
Meta-analysis
N = 2038 patients in all

Gianluca Ursini

Giovanna Punzi

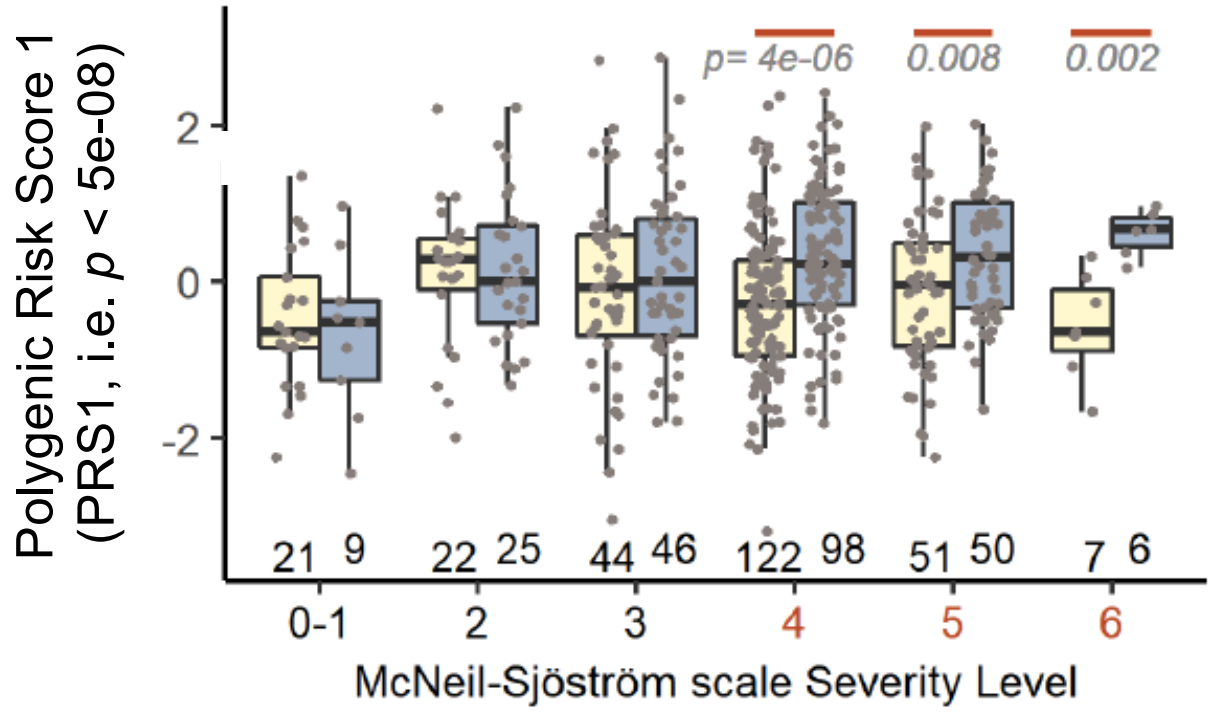
Ursini G, et al. *Nat Med*. 2018;24(6):792-801.

How Important is the Severity of the ELC?



If ELCs modulate the impact of genomic risk (and vice versa), it would be expected that this interaction would scale with the severity of the ELC….

PRS X ELC Interaction is Driven by Potentially Serious ELCs



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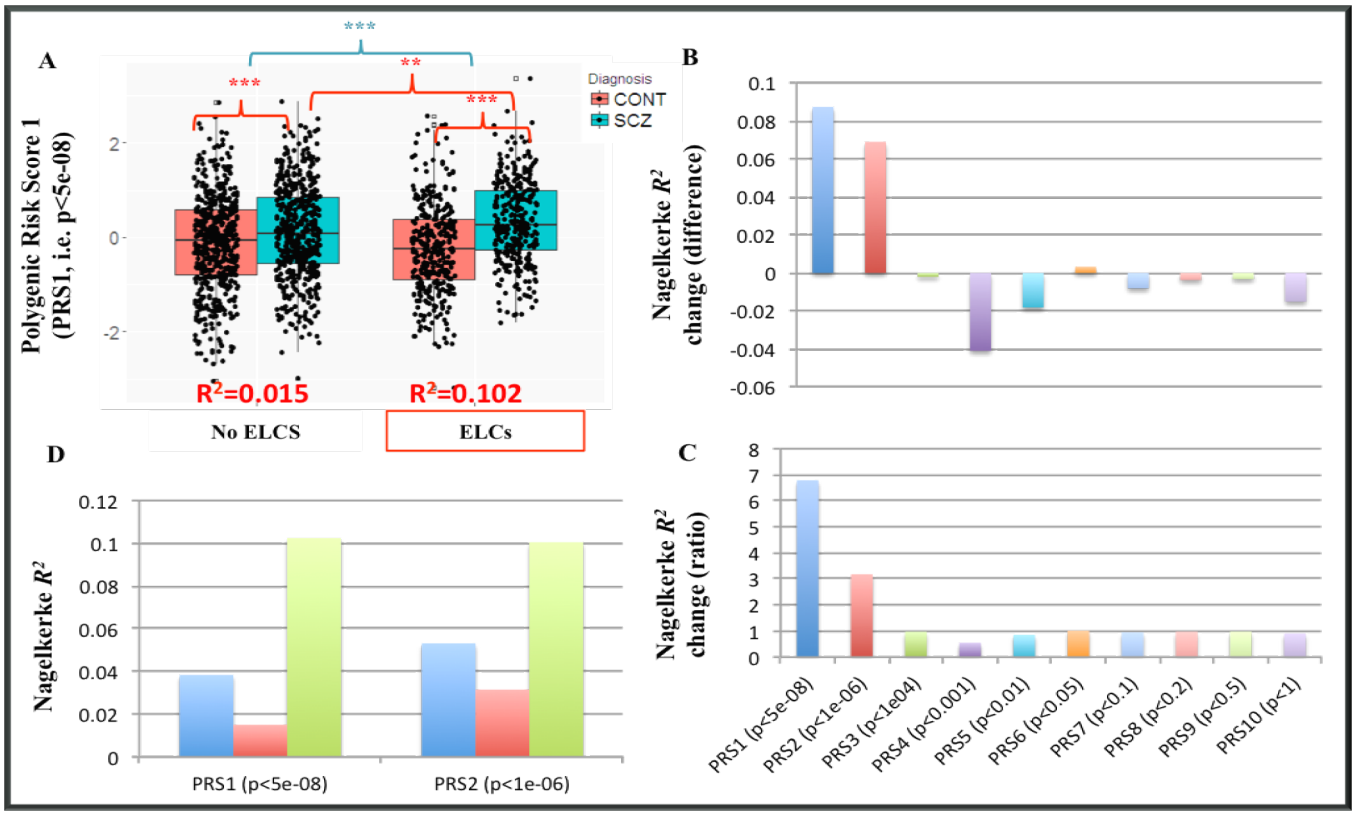
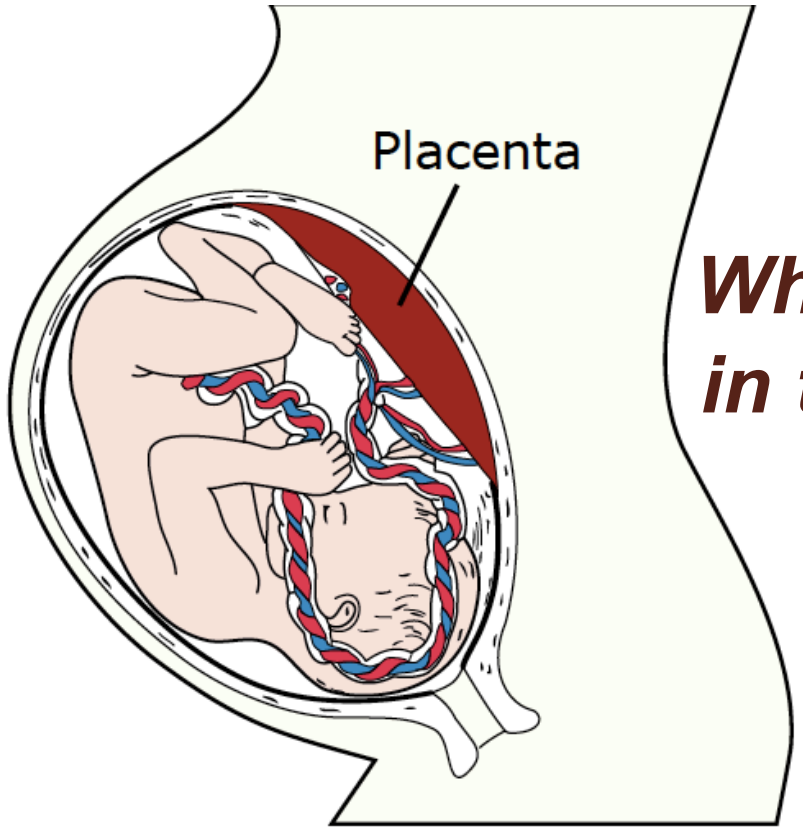
Only PRS1 and PRS2, Constructed with the Most GWAS-Significant SNPs, Interact with ELCs History to Increase Liability



Ursini G, et al. *Nat Med*. 2018;24(6):792-801.

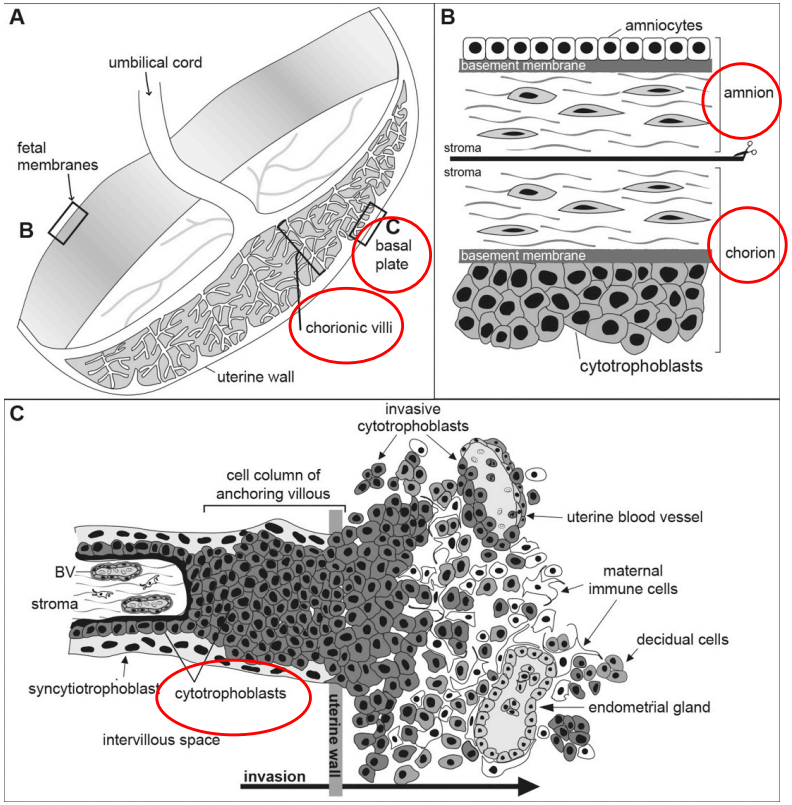
How Do Genomic Risk and ELCs Interact?



What's going on in the placenta?

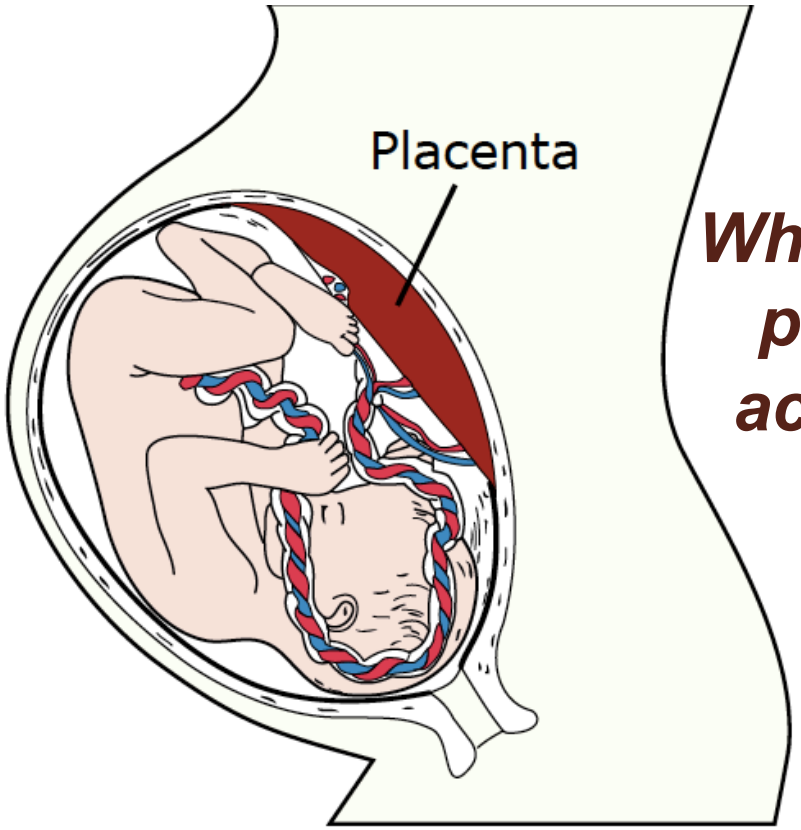
Schizophrenia PRS 1/2 Risk Loci Genes are Highly Expressed in Placenta Compared with Other PRS Loci Genes

Placental Tissue Compartment	n	P-value of the Gene-Set Test
Amnion	4	1e-04
Basal plate	4	1e-04
Chorion	4	3e-04
Villi	4	1e-05
Trophoblast	4	1e-05
Trophoblast – 2nd TR.	2	3e-05
Trophoblast – 3rd TR.	2	1e-06



http://www.roadmapepigenomics.org.; Ursini G, et al. *Nat Med*. 2018;24(6):792-801.

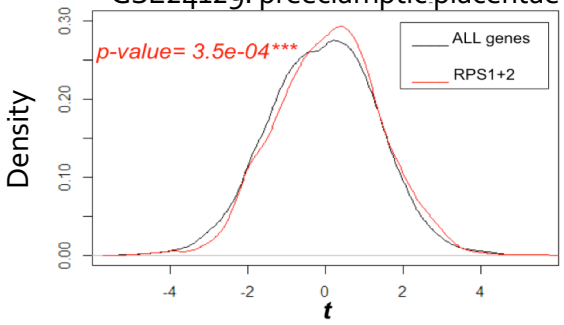
How Do Genomic Risk and ELCs Interact?



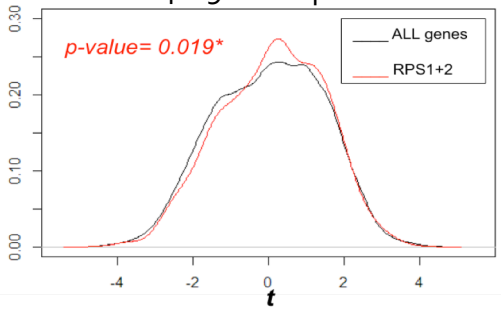
What happens in the placenta from an actual complicated pregnancy?

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

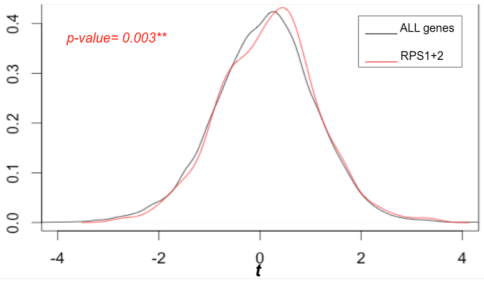
GSE24129: preeclamptic placentae



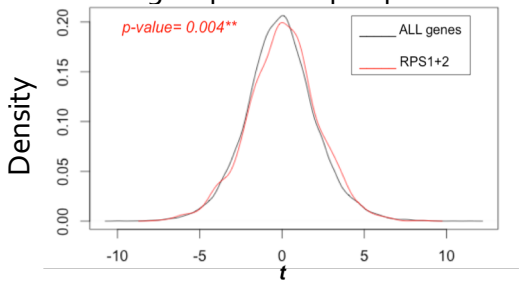
GSE24129: IUGR placentae



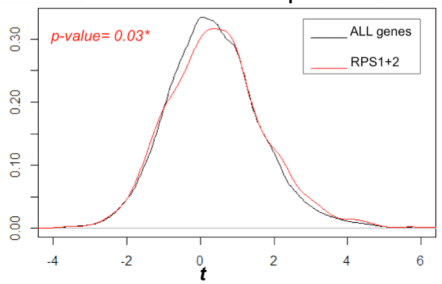
GSE12767: preeclamptic chorionic villi (1st tr.)



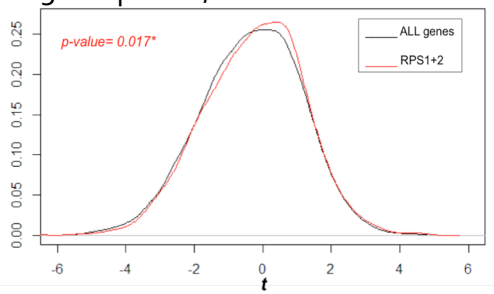
GSE10588: preeclamptic placentae



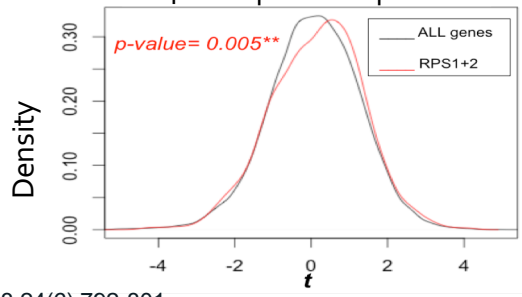
GSE12216: IUGR placentae



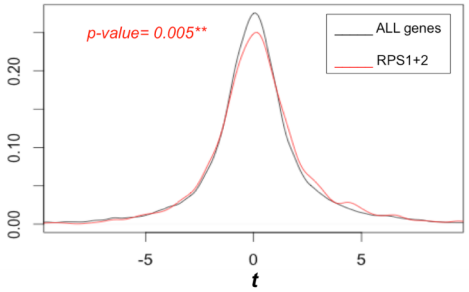
GSE25861: preecl./IUGR microvasc. endothelium



GSE40182: preeclamptic CTBs

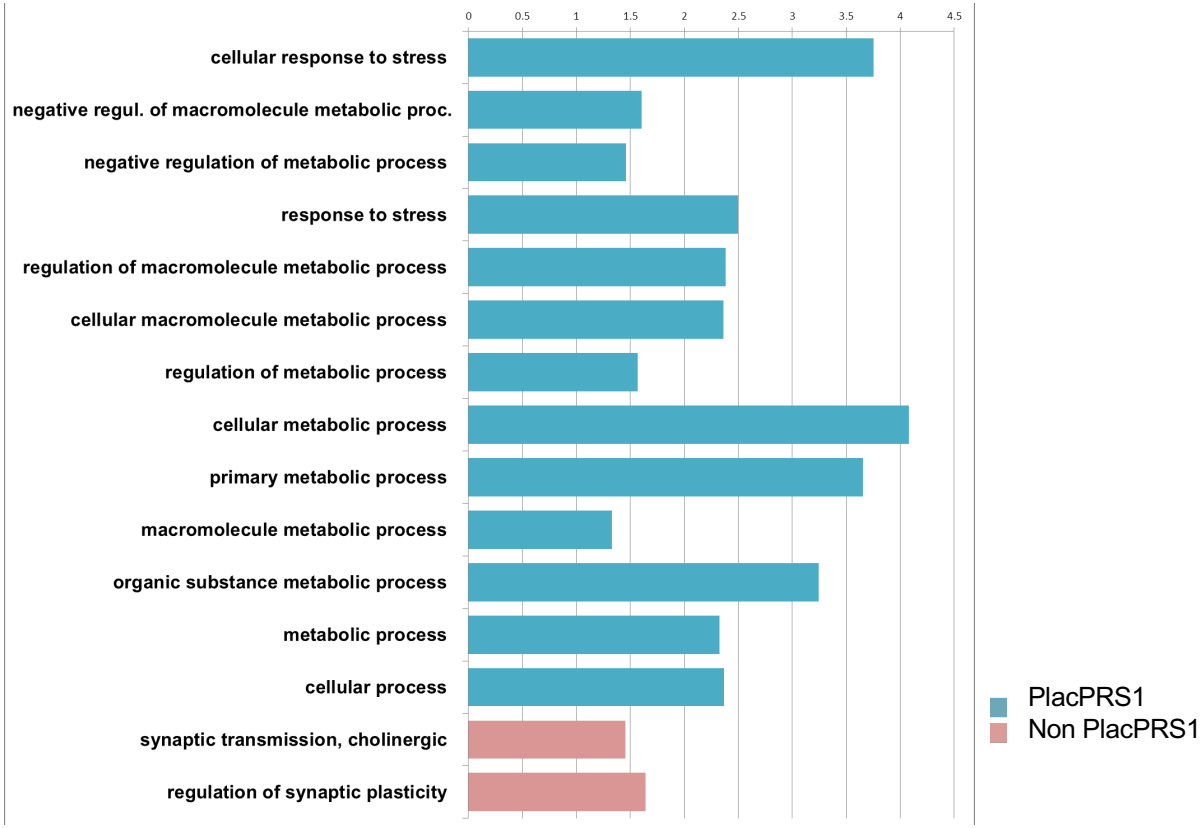


GSE25861: invasive vs. non invasive CTBs



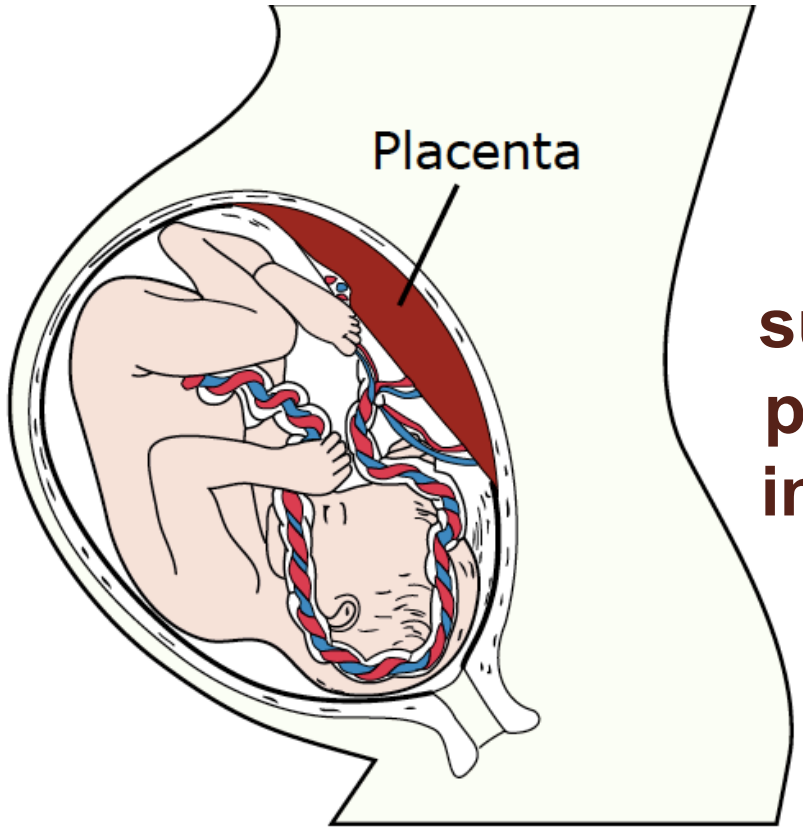
Ursini G, et al. *Nat Med*. 2018;24(6):792-801.

Biological Processes (*GO* Terms) Enriched for PlacPRS1 and NonPlacPRS1 Genes



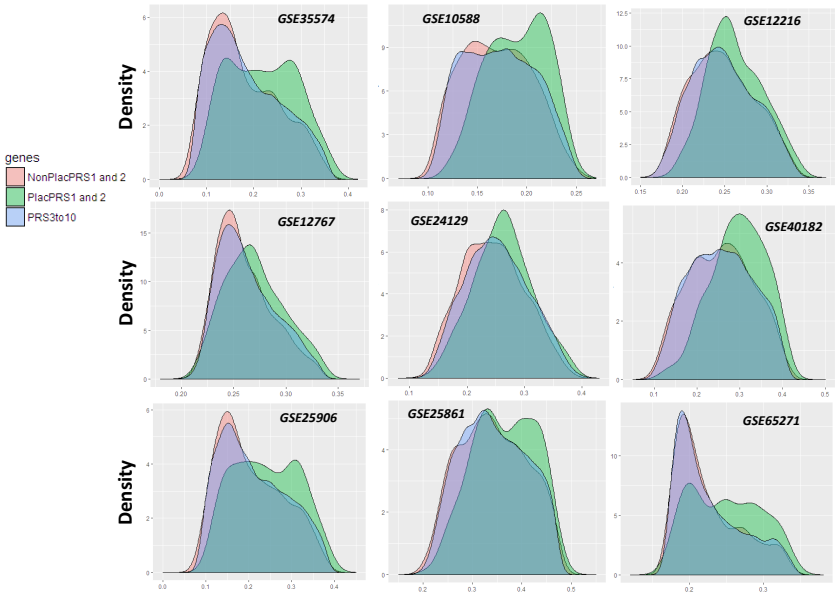
Ursini G, et al. *Nat Med*. 2018;24(6):792-801.

How Do PlacPRS Genes Influence Placenation?



Animal studies suggest that many placental stresses initiate an immune response

Strong Co-Expression of PlacPRS Genes with Immunity Genes



correlation 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

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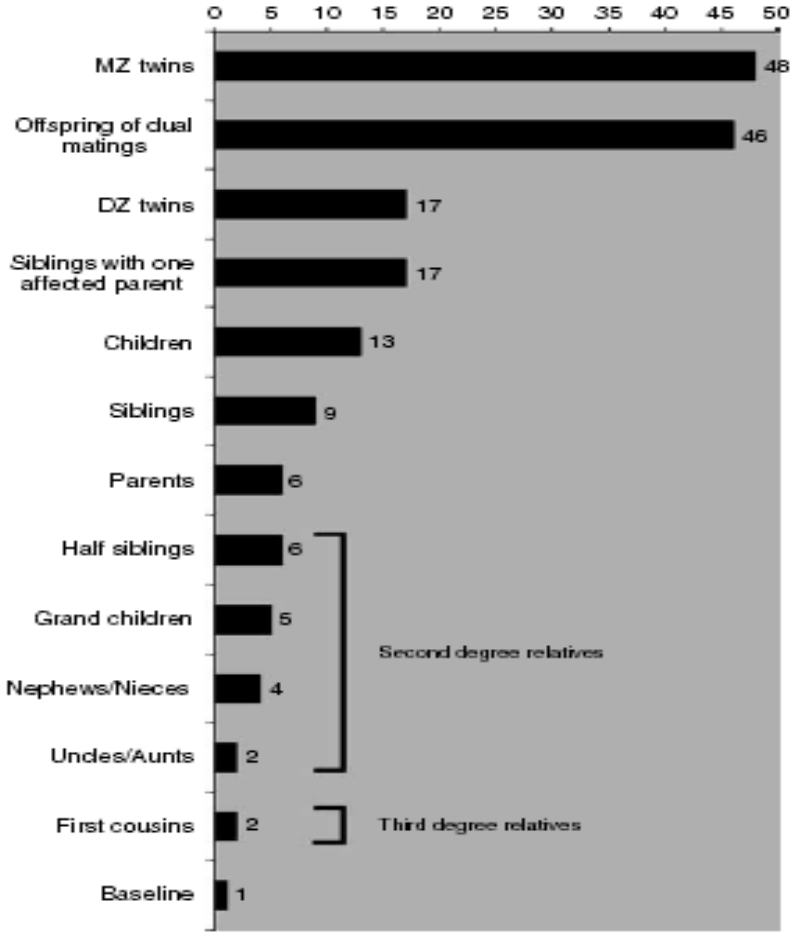
Three Things We Know About Schizophrenia Risk…

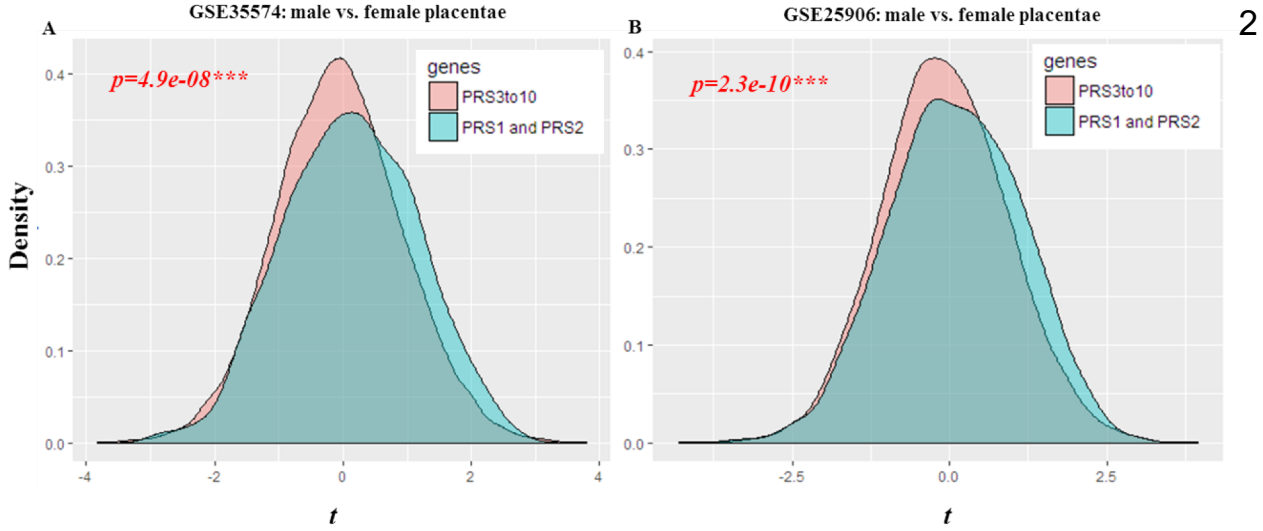


- Polygenic Architecture[1]
- Role Of Early Life Environment[2]
- Higher Incidence In Males[3]

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?



2

1. Bronson SL, Bale TL. *Neuropsychopharmacology*. 2016;41(1):207-18.; 2. Ursini G, et al. *Nat Med*. 2018;24(6):792-801.

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Susan J. Fisher

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Jan Seidel
Hannelore Ehrenreich

University of Bari
Annamaria Porcelli
Giancarlo Maddalena
Giuseppe Blasi
Allessandro Bertolino

NIMH
Stefano Marenco
Karen F. Berman

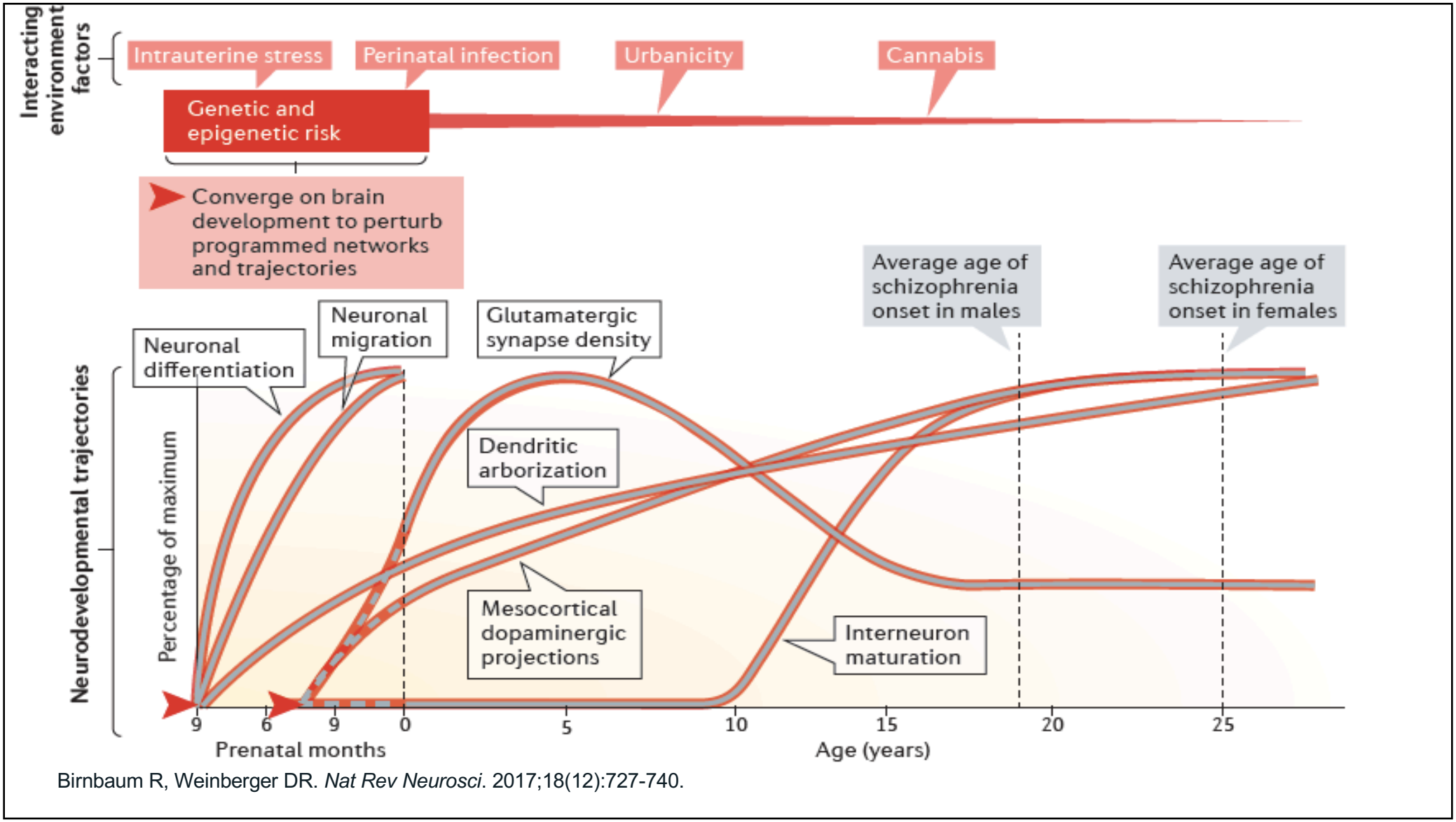
Michael F. Egan (currently at MERCK)

University of Osaka
Hidenaga Yanamori
Ryota Hashimoto

Martin Luther University of Wittenberg
Dan Rujescu

Call to Action

- 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**



Birnbaum R, Weinberger DR. *Nat Rev Neurosci*. 2017;18(12):727-740.

Questions & Answers

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