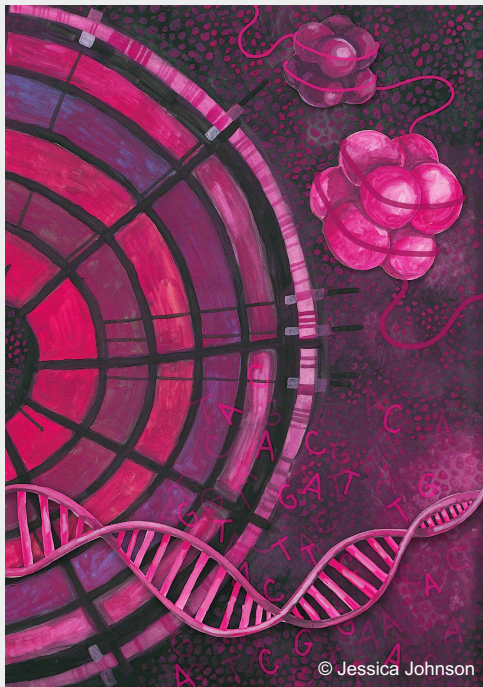




Schizophrenia

Sex Differences in Brain Disorders: Emerging Transcriptomic Evidence and Implications for Therapeutic Development

September 23rd, 2020

Panos Roussos, M.D., Ph.D.

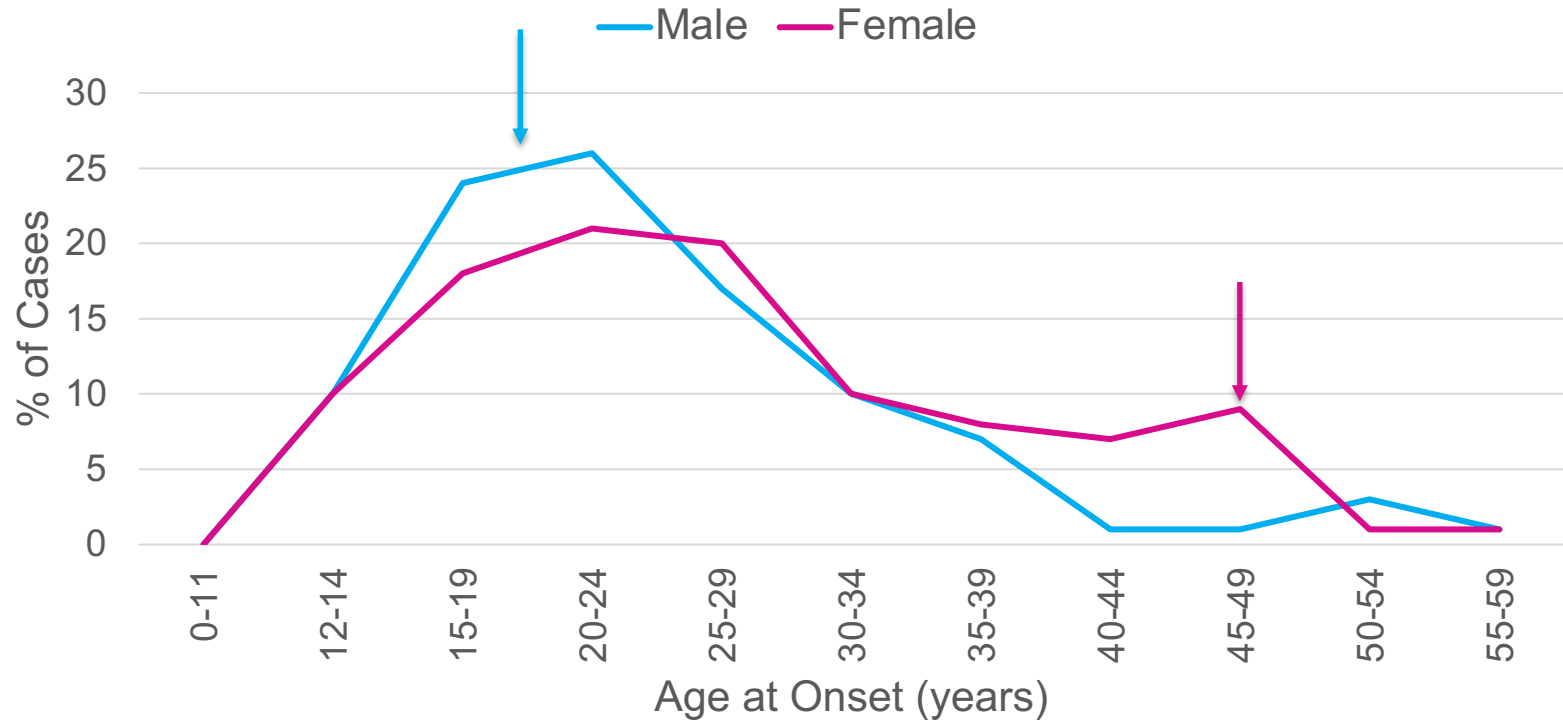
The Pamela Sklar Division of Psychiatric Genomics
Icahn Institute for Data Science and Genomic Technology
Friedman Brain Institute
Department of Genetics and Genomic Sciences
Department of Psychiatry
James J. Peters VA Medical Center



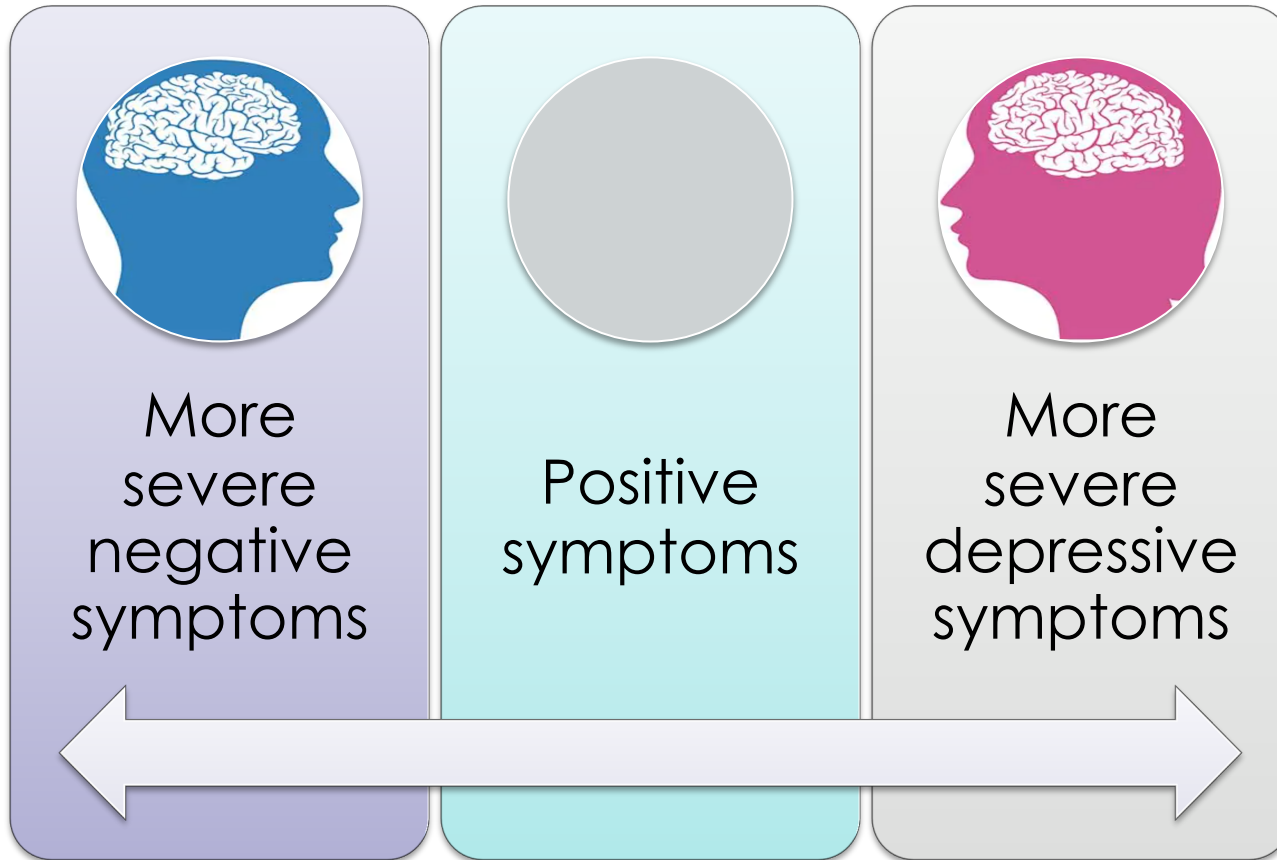
“The male sex appears in general to suffer somewhat more frequently and to be affected more severely by the dementia praecox”

Kraepelin 1919

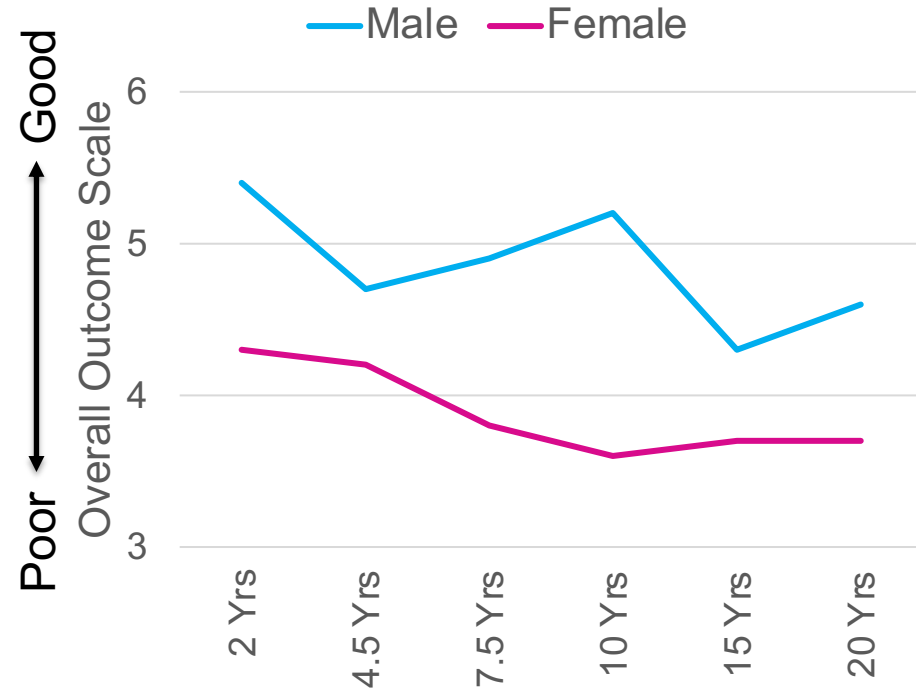
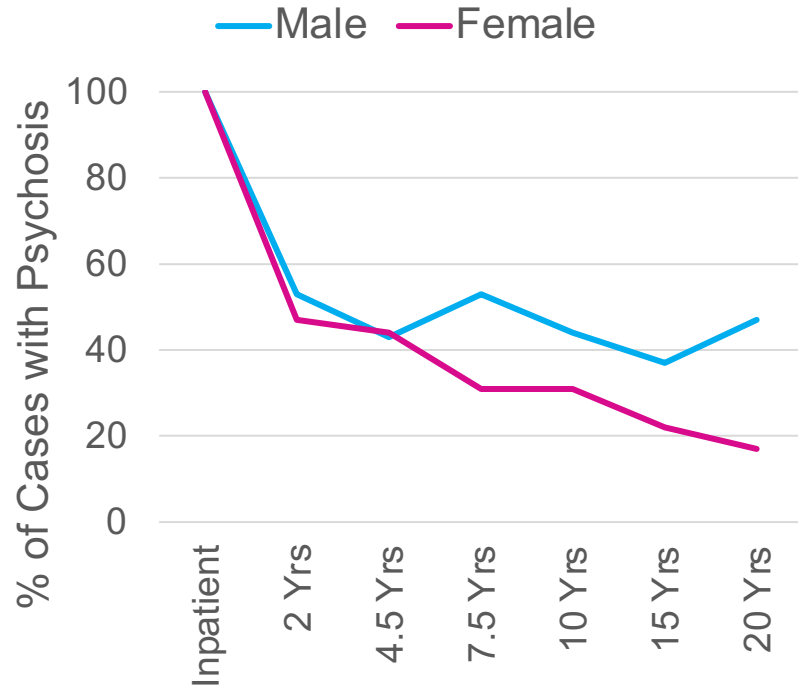
Incidence and prevalence of schizophrenia



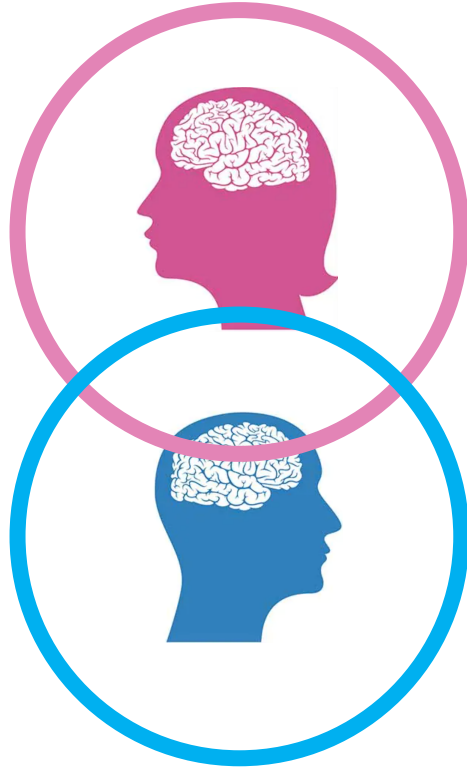
Clinical presentation



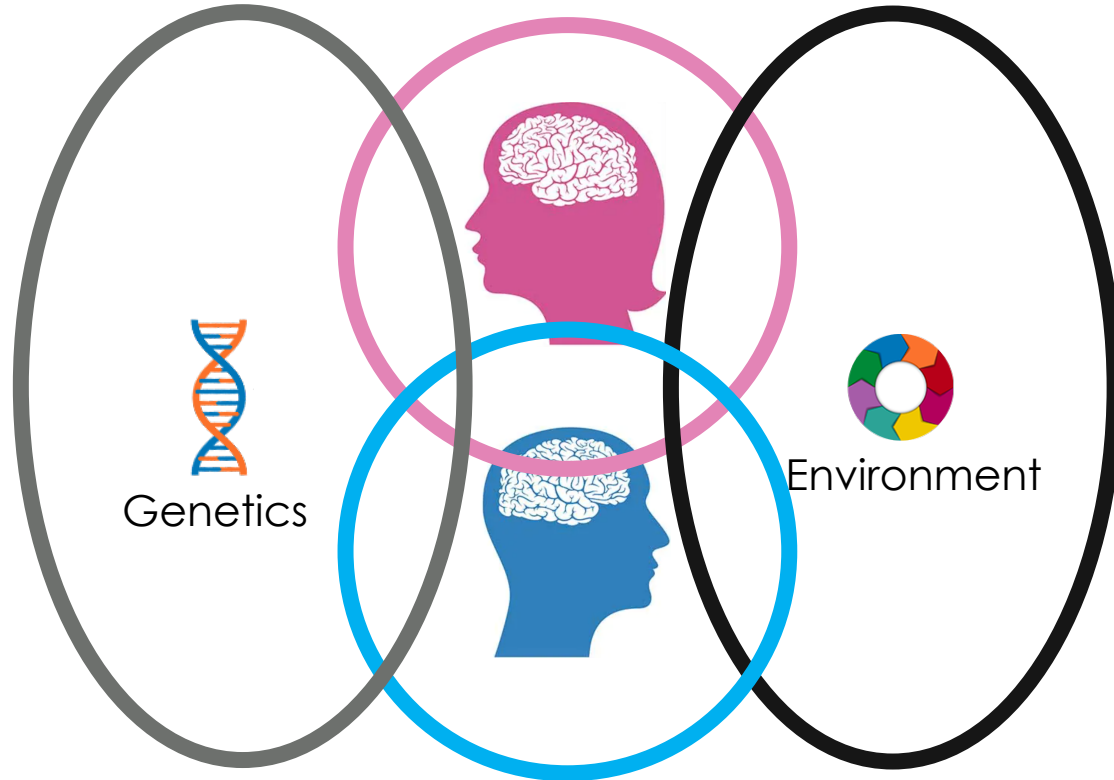
Course of illness



Etiology of schizophrenia

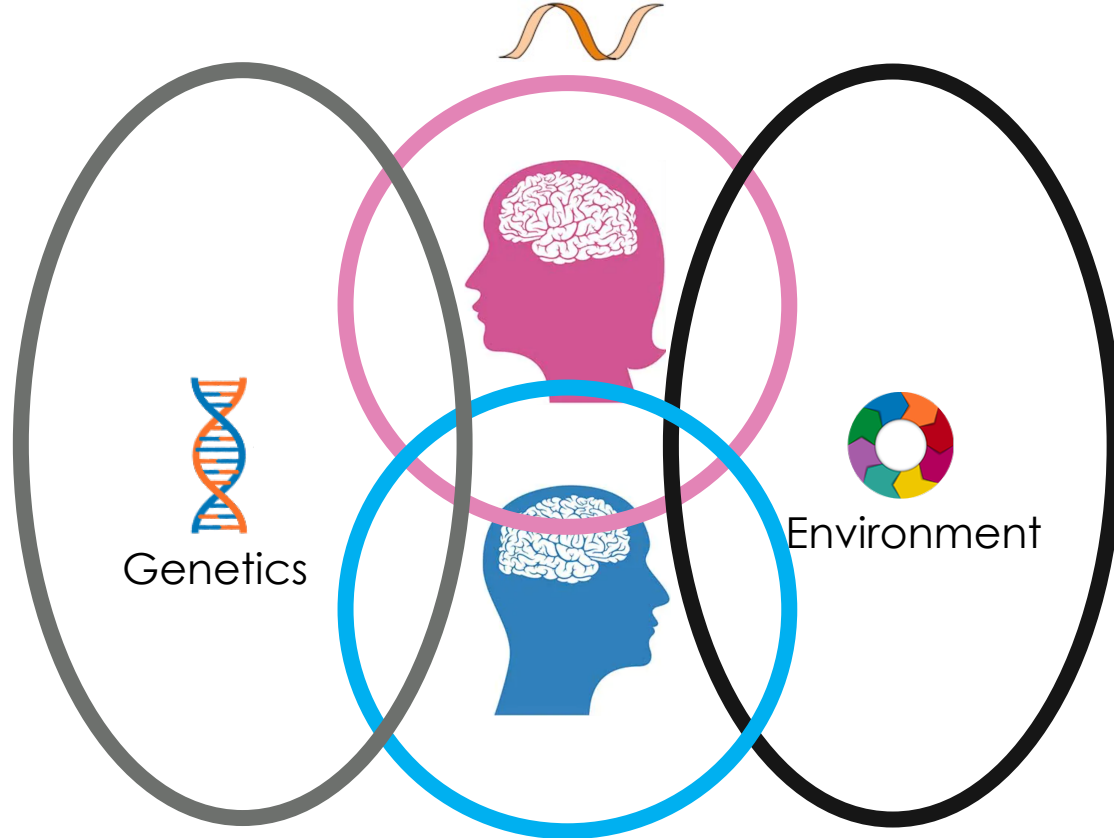


Etiology of schizophrenia



Etiology of schizophrenia

Gene expression in brain tissue



Lack of gene expression studies on sex differences in schizophrenia



"sex differences" AND "schizophrenia" AND "gene expression"

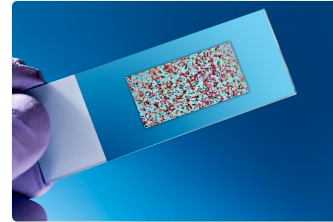
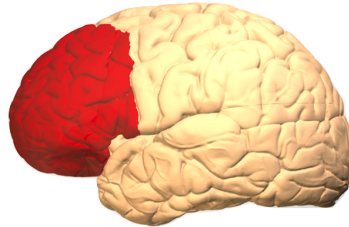


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	Controls	SCZ
Male	89	90
Female	35	32



6 studies across 3 regions: Brodmann area 9, 10 and 46

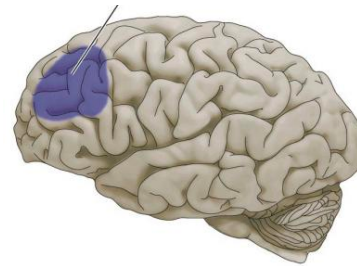
- Sex by diagnosis interaction on gene expression showed 46 disease genes only in males. No significant signal was found in females.
- No significant biological process (GO term Biological Process and KEGG pathway databases) was found.

Resources to study gene expression in the human brain

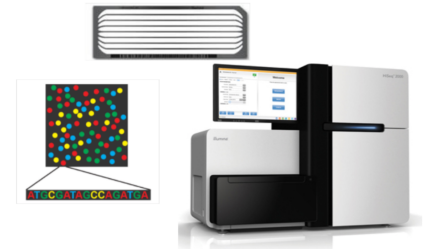


Cohort	Institution	Female		Male	
		Controls	SCZ	Controls	SCZ
CMC	MSSM	77	46	84	97
	Penn	19	34	18	22
	UPitt	23	13	59	41
HBCC	NIMH	40	29	117	59
Total		159	122	278	219
Control:Case ratio		1.30		1.27	
Male:Female ratio		1.77			

Dorsolateral Prefrontal cortex
(Brodmann area 9 and 46)



RNA-seq

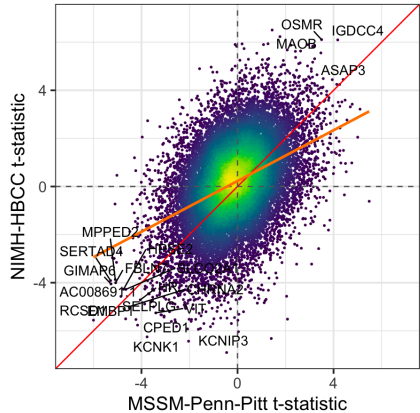


Questions we would like to address

1. *Identify sex biased transcripts in human brain*
2. *Identify schizophrenia-by-sex biased transcripts*
3. *identify schizophrenia-by-sex biased molecular pathways and co-expression modules*

Schizophrenia differential expression

Concordance of SCZ

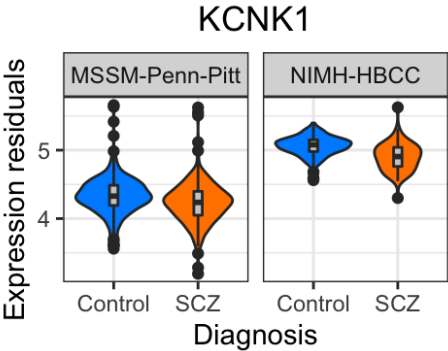
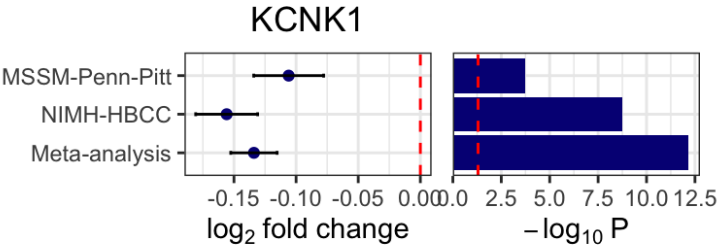
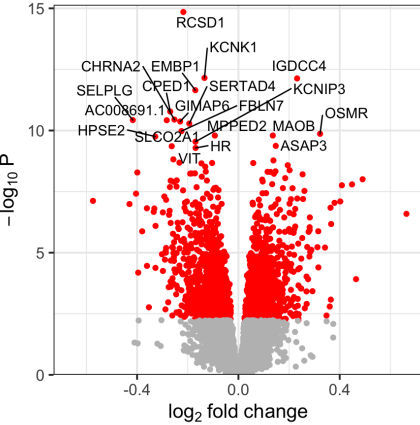


Discovery	pi1
MSSM-Penn-Pitt	0.9
NIMH-HBCC	0.5

Rho spearman	P
0.34	0

Analysis	N genes
MSSM-Penn-Pitt	217
NIMH-HBCC	1,706
Meta-analysis	2,209

Meta-analysis: DxSCZ



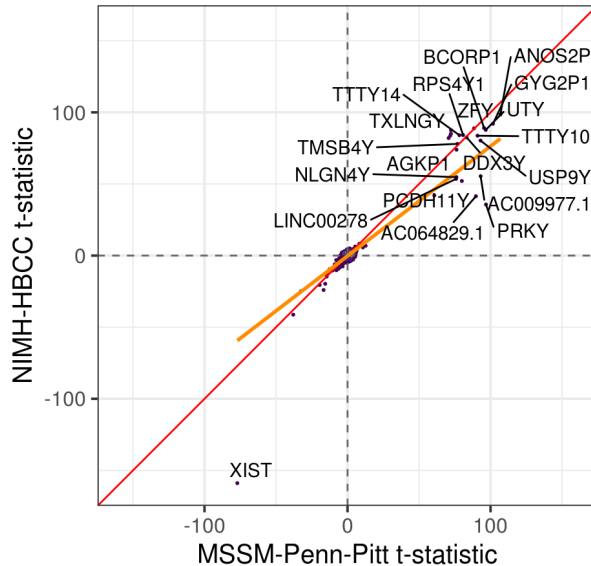
Sex differential expression (1)

Rho spearman	P
0.15	1.2×10^{-96}

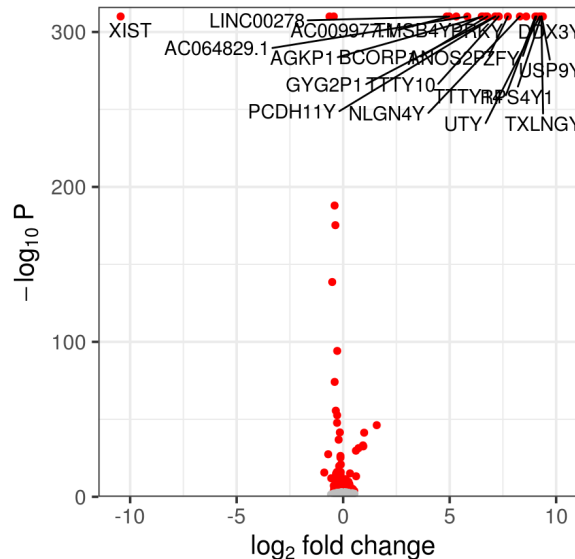
Discovery	pi1
MSSM-Penn-Pitt	0.5
NIMH-HBCC	0.5

Analysis	N genes
MSSM-Penn-Pitt	482
NIMH-HBCC	148
Meta-analysis	686

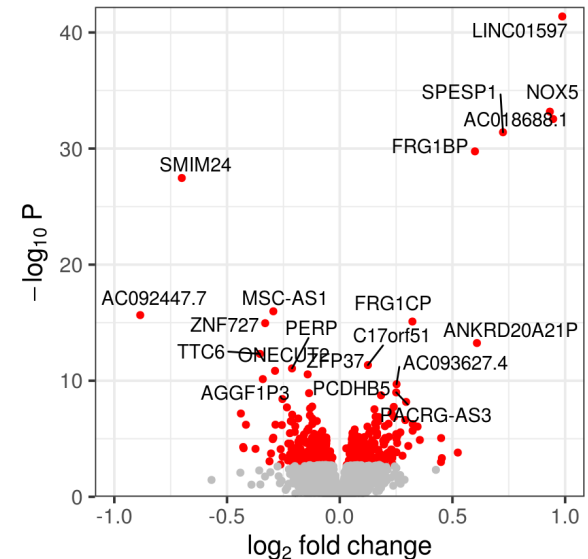
Concordance of Sex



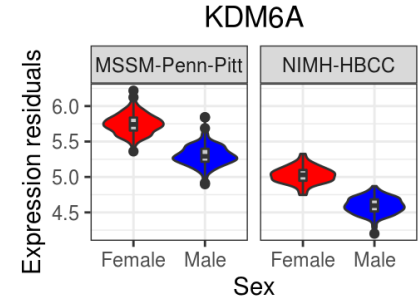
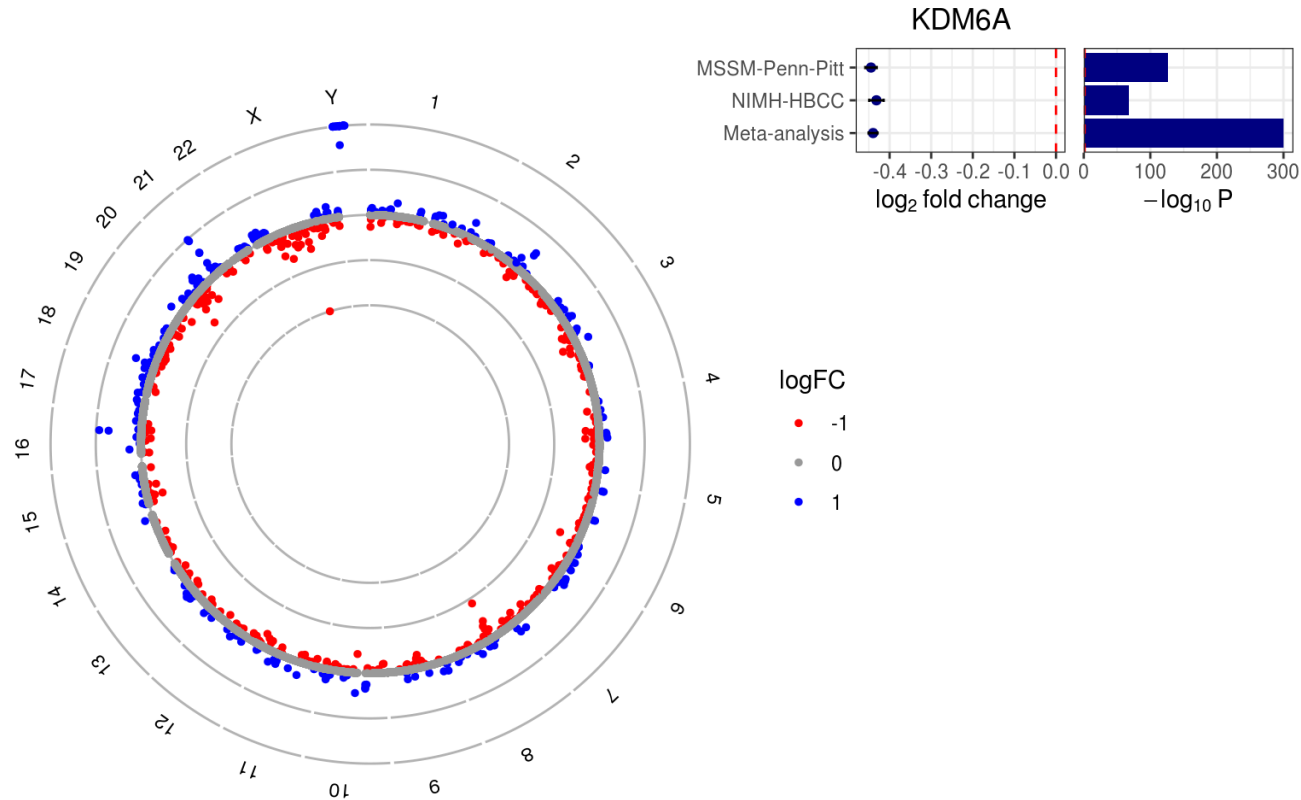
Meta-analysis: Sex



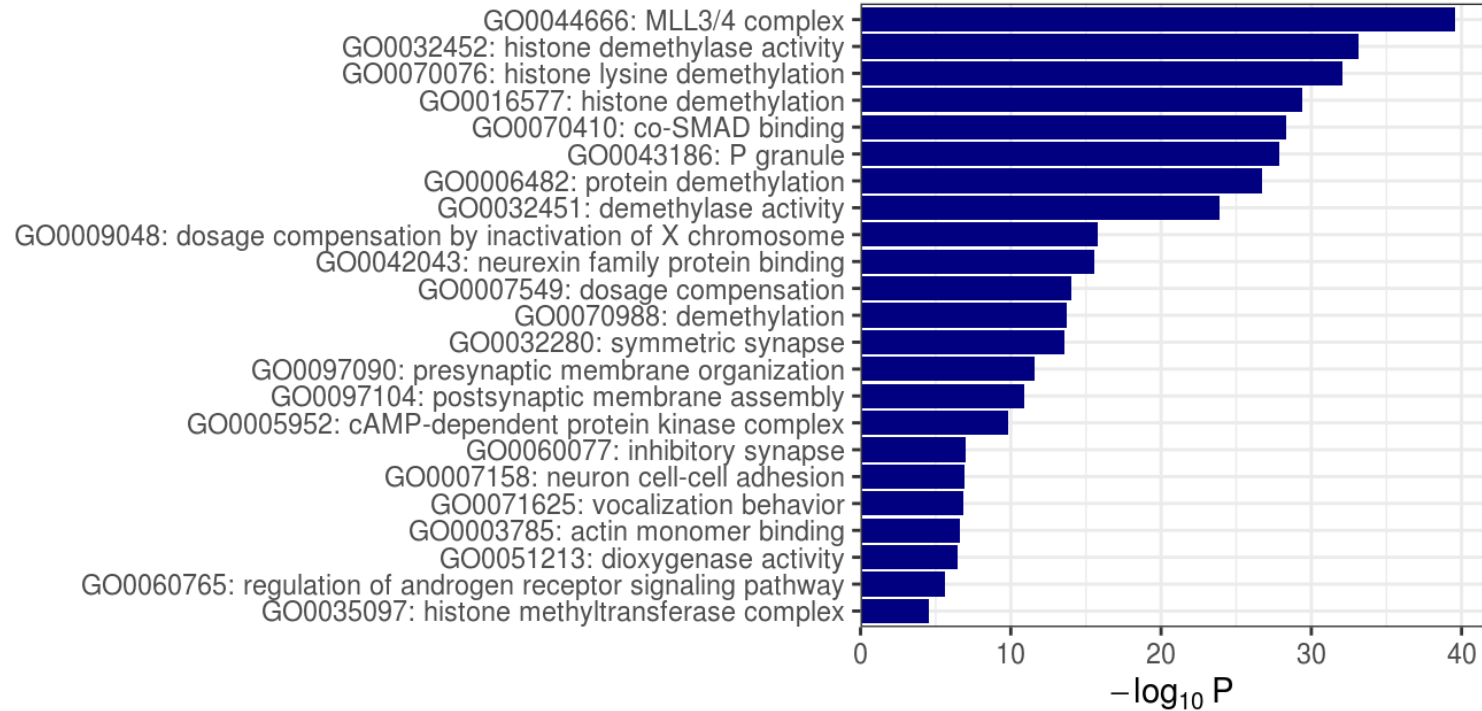
Meta-analysis: Sex autosome

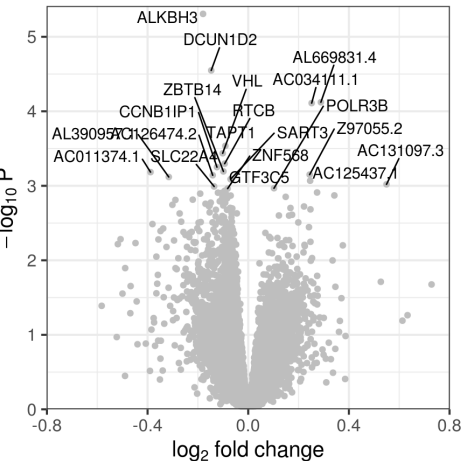


Sex differential expression (2)



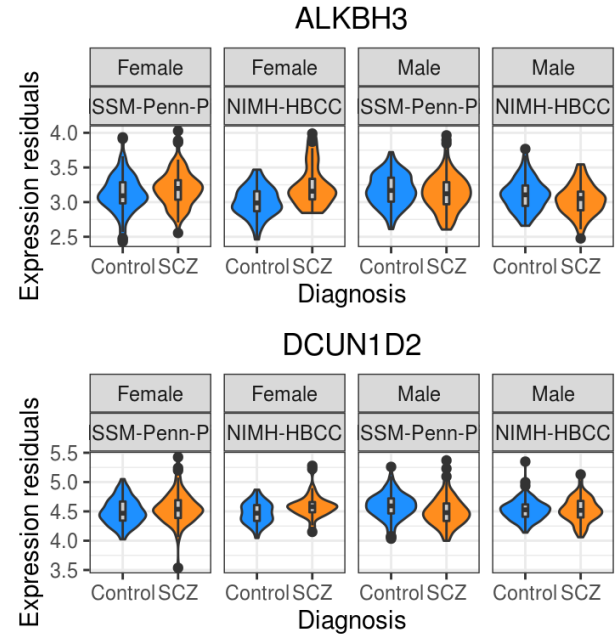
Sex differential expression (3)



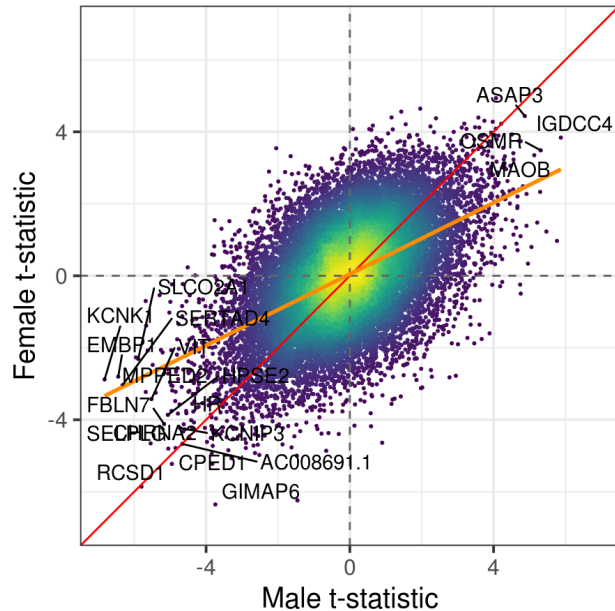


ALKBH3

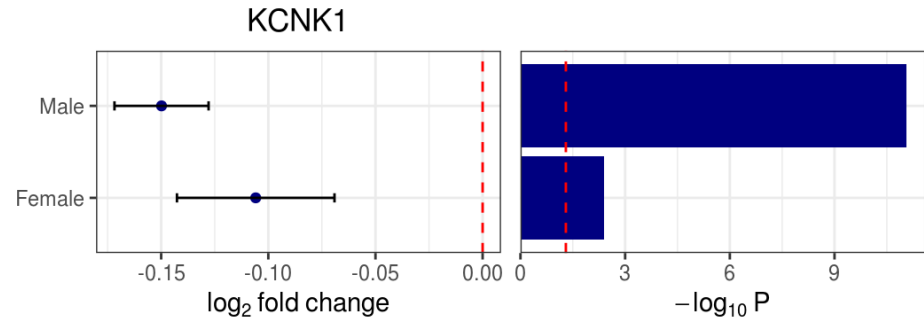
Study	log ₂ fold change (Forest Plot)	-log ₁₀ P (Bar Chart)
MSSM-Penn-Pitt	-0.12	1.6
NIMH-HBCC	-0.31	4.8
Meta-analysis	-0.18	5.1



Schizophrenia differential expression analysis in Males and Females



Rho spearman	P
0.45	0



Based on the slope, the effect size on Females is 71% of the effect size in Males ($p < 1e-16$)

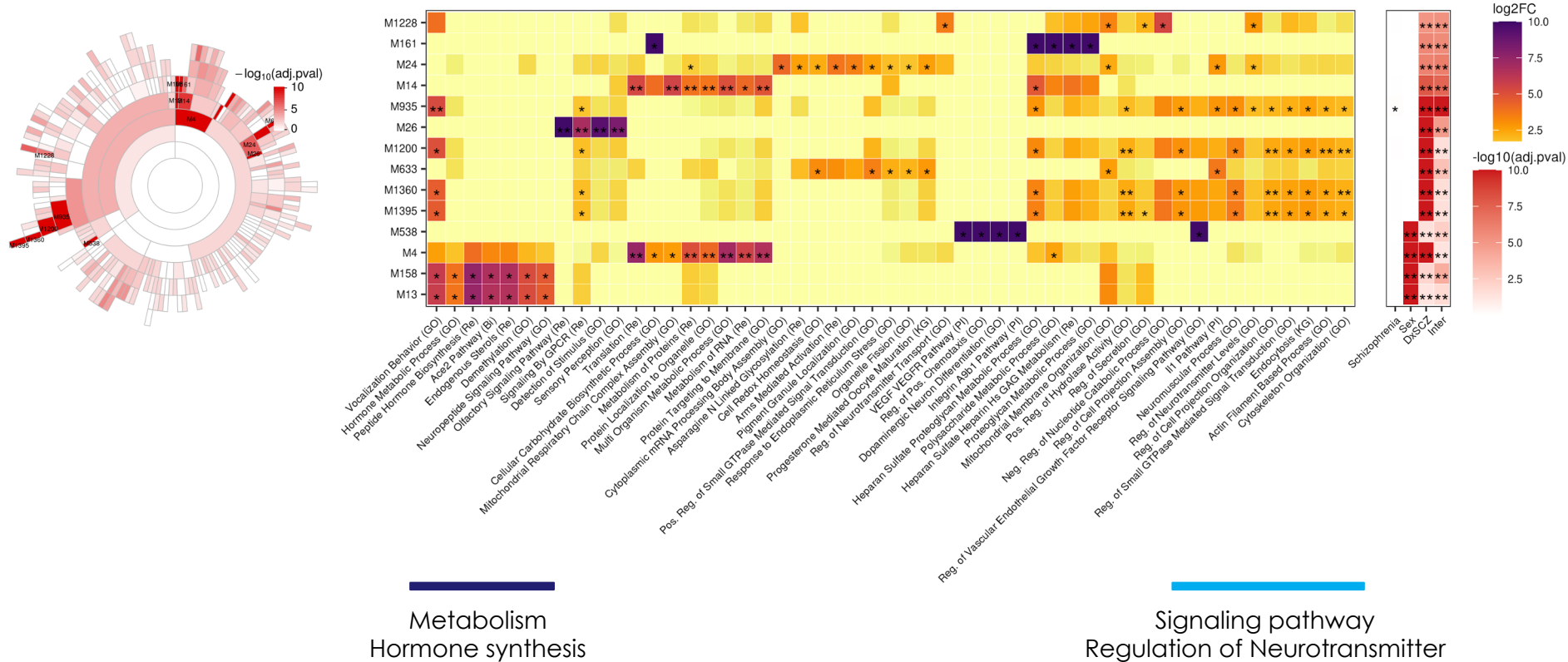
Performing co-expression analysis

Organize transcriptome into co-expression modules to identify group of genes (modules) affected by diagnosis, sex and/or diagnosis by sex comparison



Multiscale Embedded Gene coExpression Network Analysis (MEGENA)

Sex differences in schizophrenia affect different molecular pathways



Summary

1. Sex differences affect molecular pathways related to epigenome regulation, synaptic transmission and hormone regulation
2. Gene expression in schizophrenia is less affected in females compared to males
3. Co-expression analysis identifies modules related to hormone synthesis and synaptic transmission that are associated with diagnosis-by-sex signatures

Overall, our analysis identifies robust sex differences in the schizophrenia transcriptome analysis pointing to different molecular pathways affected by the disease in males and females.

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