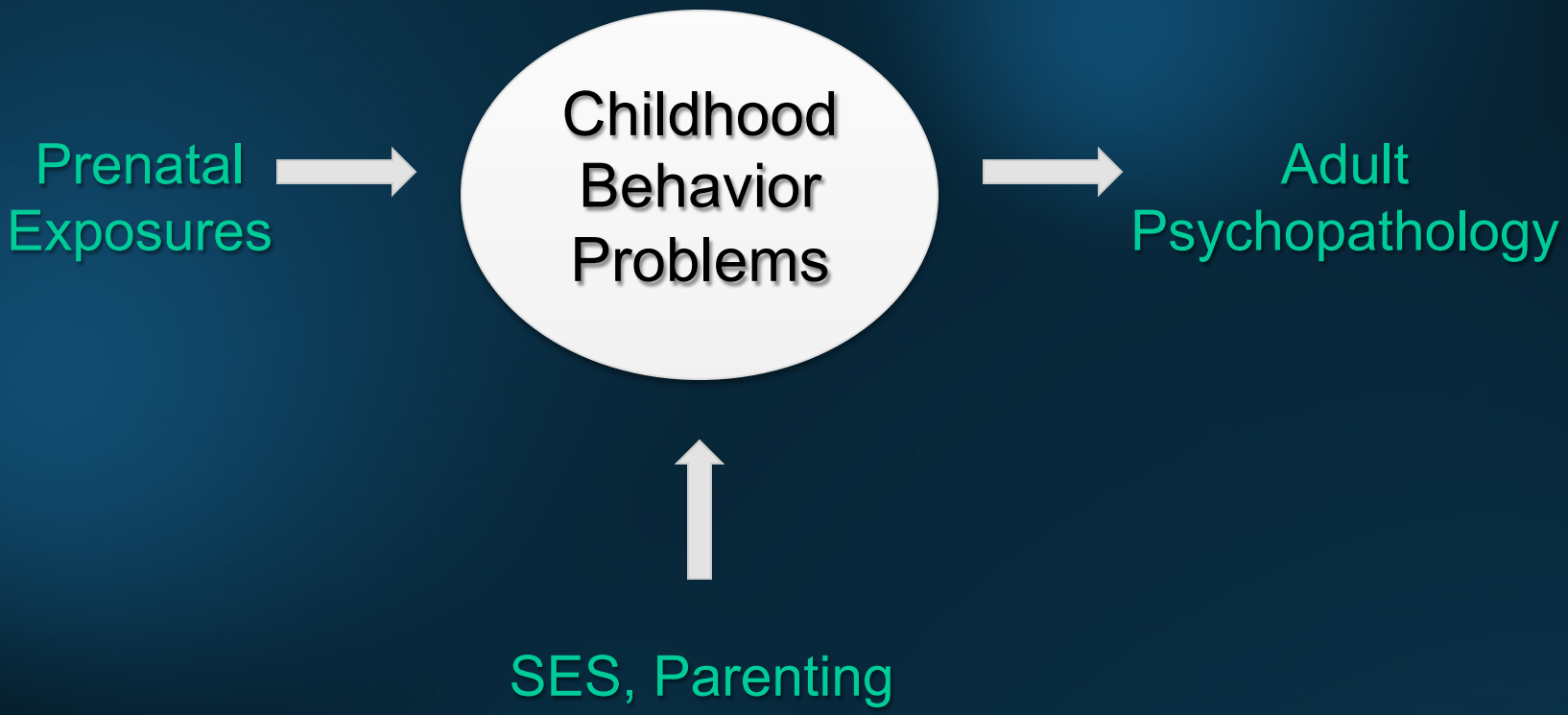
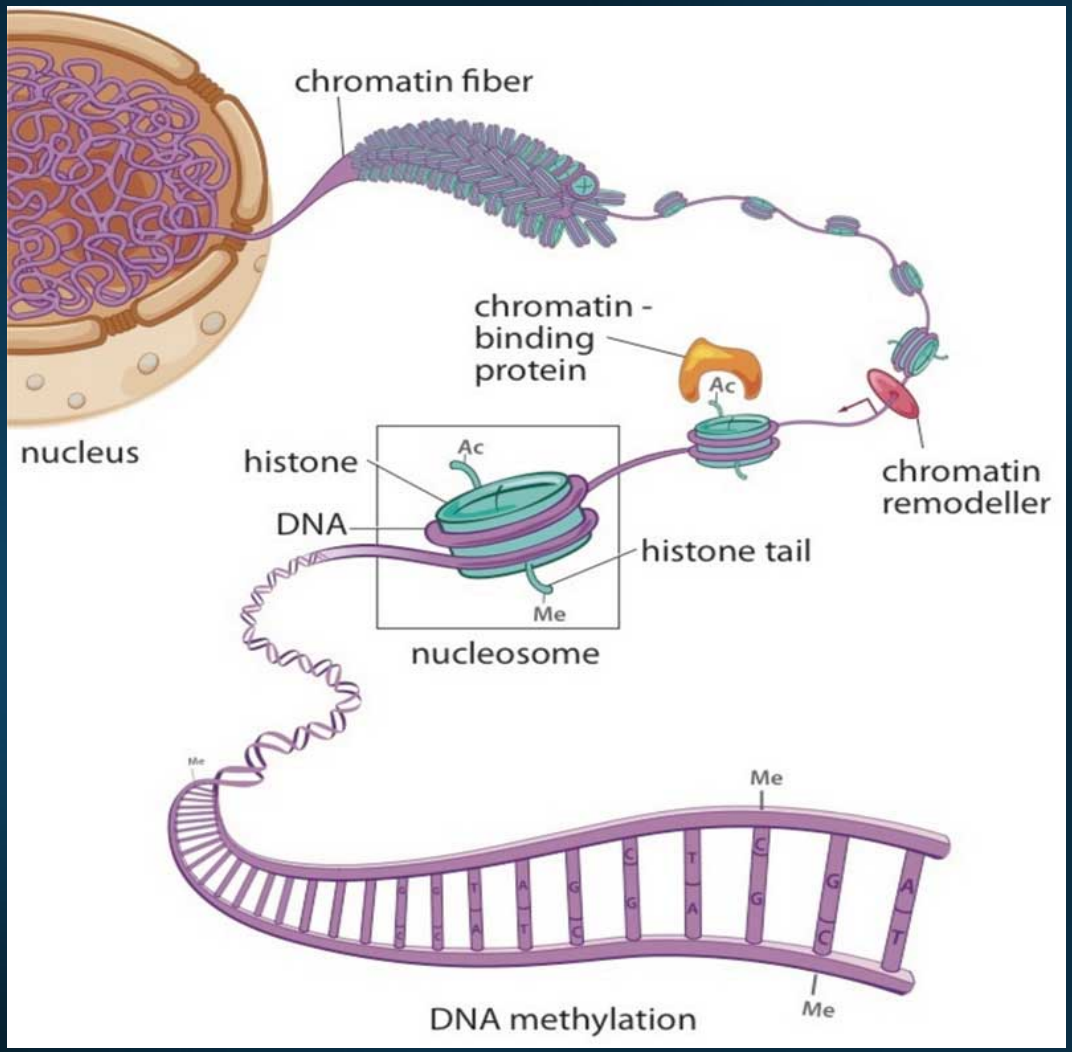
The Influence of Genetic and Epigenetic Patterns on Child Behaviors

Alicia K. Smith, PhD
Assistant Professor
Psychiatry & Behavioral Sciences
Emory University

Behavior is a Complex Trait

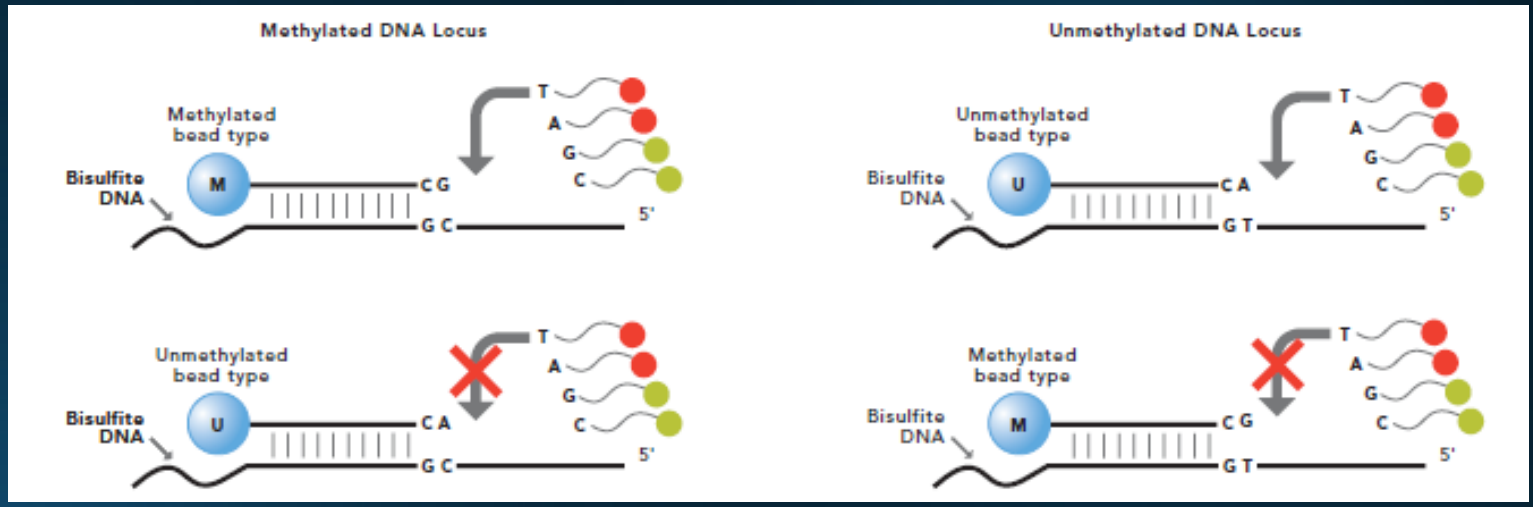


Epigenetics Overview



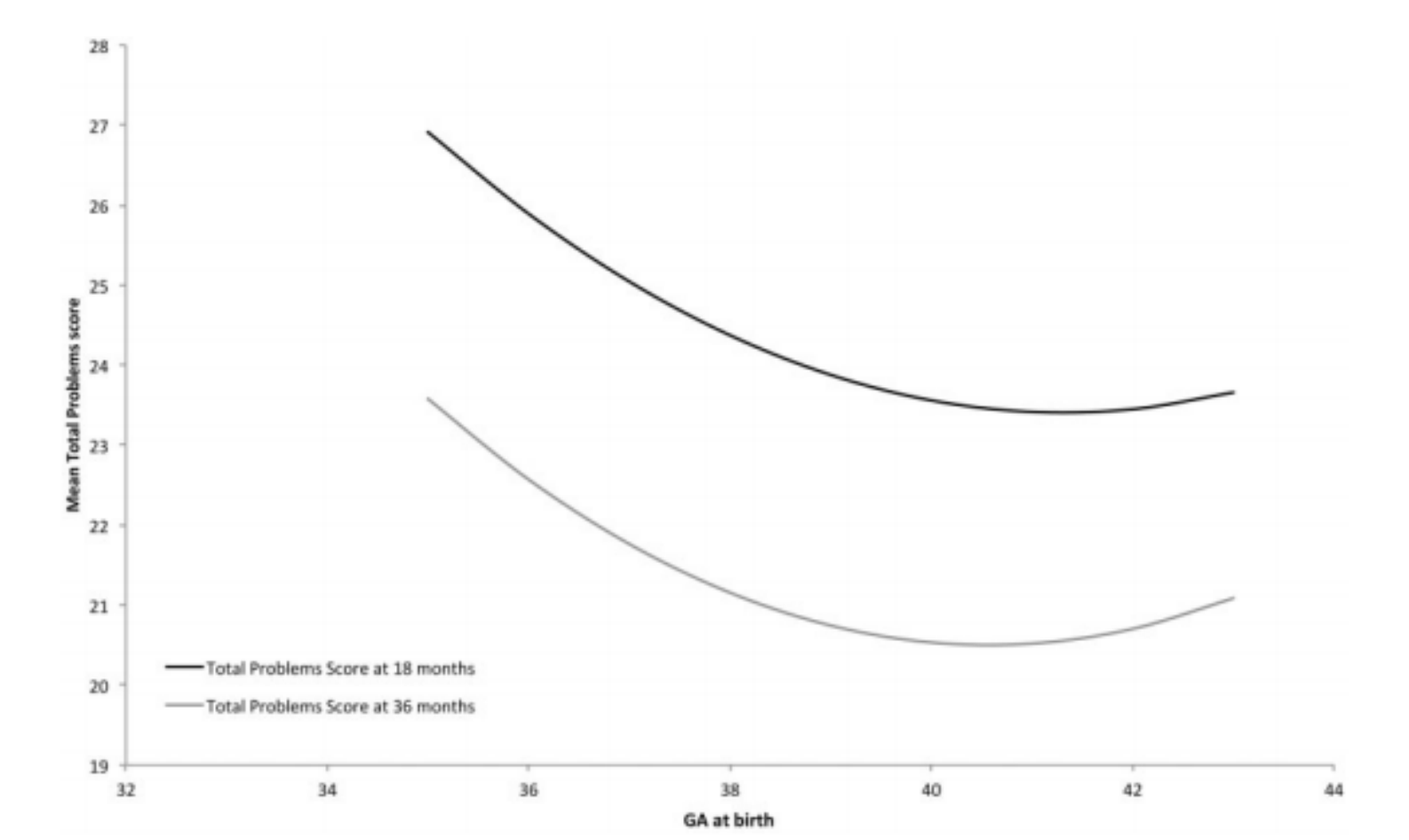
Methods

HumanMethylation27 Array



- Based bisulfite-converted DNA
- Interrogates 27,578 CpG sites in 14,495 genes
- The signals from methylated (*M*) and unmethylated (*U*) bead types are used to calculate a β value where $\beta = M/(U+M)$

Gestational Age Associates with Child Behavior Problems



ADD CITATION

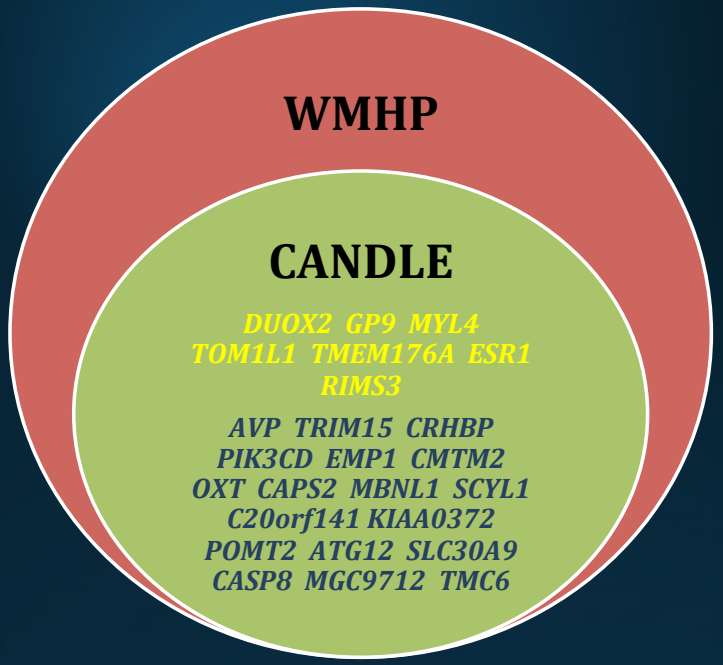
DNA methylation varies with Gestational Age (GA)

- Women's Mental Health Program (WMHP)
- DNA methylation was examined in the umbilical cord blood of 259 subjects
  - 49% male
  - 89.6% Caucasian
- Average GA 38.8 (1.2)

Schroeder et al, Epigenetics 2011

DNA methylation varies with Gestational Age

- CANDLE is a community-based cohort assessing cognitive development in the neonates of Shelby County, TN
- 194 subjects
  - 52.1% male
  - 43.3% caucasian
- Average GA 39.0 (1.3)



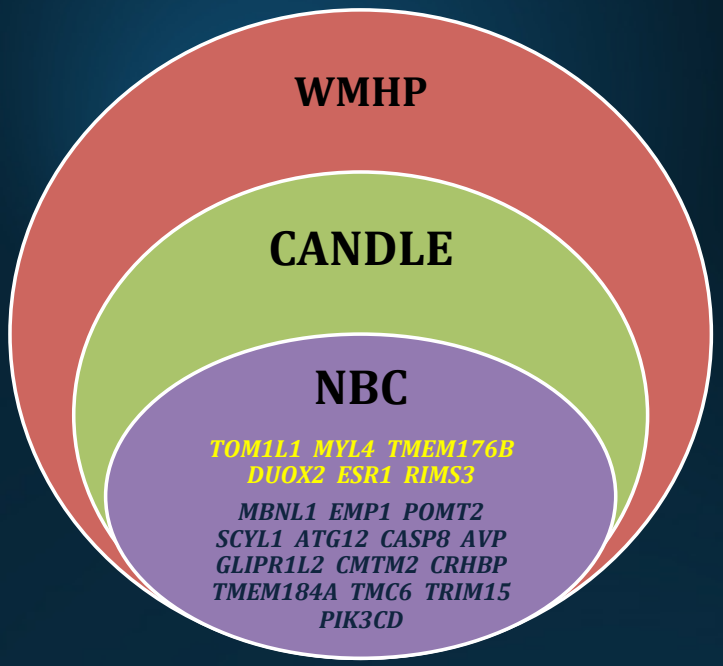
Schroeder et al, Epigenetics 2011

DNA methylation varies with Gestational Age

- The Nashville Birth Cohort (NBC) was developed to examine genetic predictors of spontaneous PTB

- 52 subjects
  - 50.0 % male
  - 100% African American

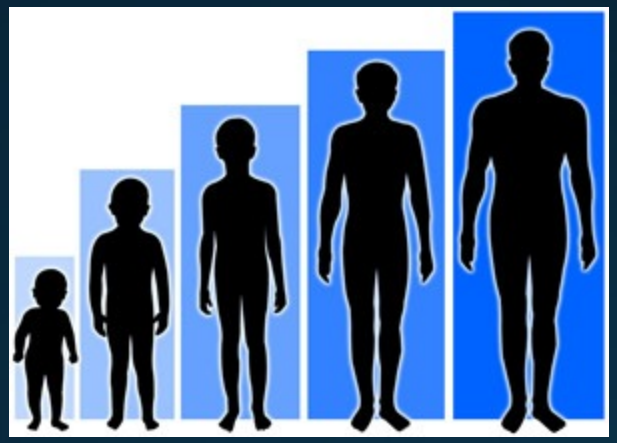
- Average GA 35.8 (5.3)



Schroeder et al, Epigenetics 2011
Parets et al, Under Review

Developmental Programming

- DNA methylation patterns are relatively stable between birth and the 2nd year of life.
- Epigenetic patterns established during development may influence gene expression over the lifetime



Wang et al. 2012

Prenatal Medication Exposure

- Antiepileptic drugs (AEDs) are used to treat epilepsy, bipolar disorder, migraines, fibromyalgia and other pain syndromes
- AED exposure during pregnancy may limit IQ, motor function, cognition and increase the risk of developing ADHD

- In 201 subjects, we identified DNA methylation differences in AED-exposed neonates

Decrease in methylation of genes with increased exposure to AED

- Global methylation levels decreased (p=.0045)
- CpG sites in 14 genes were associated with number of weeks of prenatal exposure to anti-epileptic medications
- Some were also differentially methylated in placental tissue from these neonates

- *COL21A1*
- *ANP32D*
- *PPFIA3*
- ***PGC***
- *ATP1B4*
- ***C15orf2***
- ***ZNF384***
- *PDGFRB*
- *NDUFS5*
- *GATA1*
- *CBX7*
- *MS4A12*
- *GUCA1B*
- *SDS*

Smith et al, Epigenetics 2012

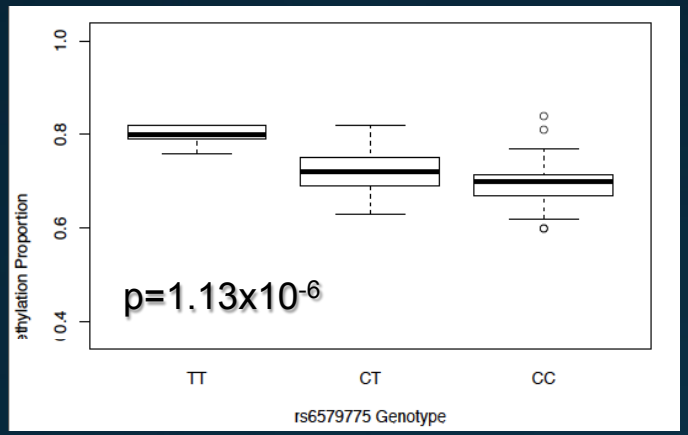
Decreased DNA methylation with AED exposure

- Changes were not attributable to diagnosis of epilepsy, number of seizures or maternal psychiatric diagnosis
- Changes were not more extreme in those exposed to more than one type of AED
- >77% of the subjects were exposed to lamotrigine (LTG)

Smith et al, Epigenetics 2012

Genetic & Epigenetic Correlation in Blood & Brain

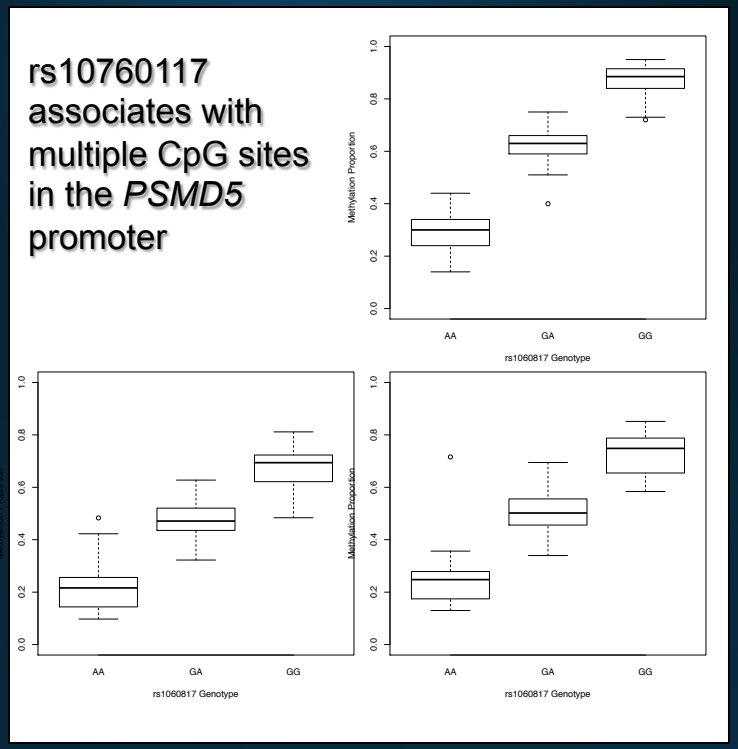
- Platelet-derived growth factor receptor beta (*PDGFRB)*
- Associated with schizophrenia & autism
- CNS knock out mice exhibit cognitive and socioemotional deficits



Genetic & Epigenetic Correlation in Blood & Brain

- DNA methylation patterns vary substantially between different tissues, but they can be consistent across tissues

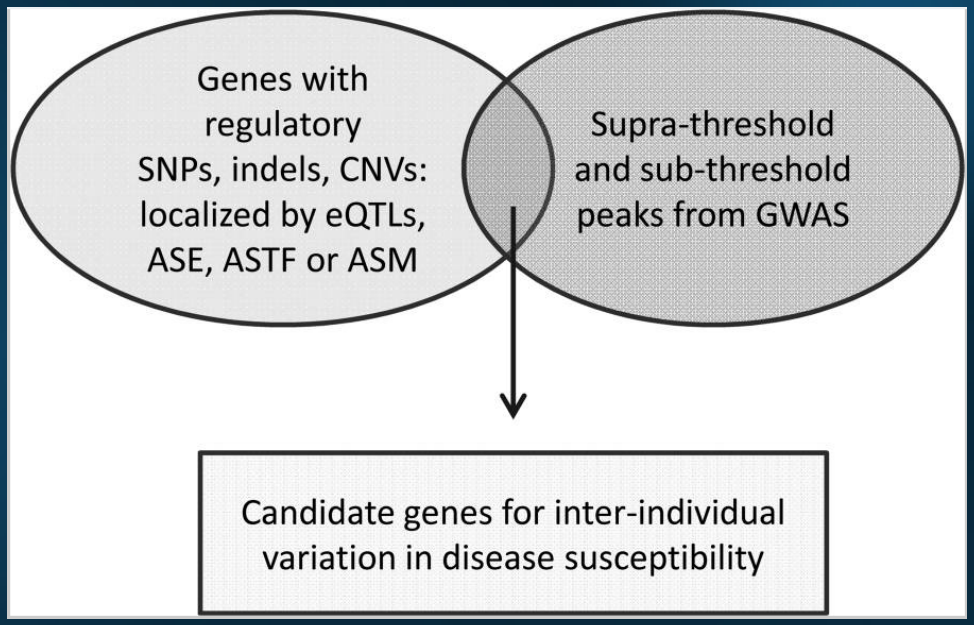
- mQTLs in cord blood samples are likely to be detected in brain tissues
  - 8.6-30.9%
  - $p<1\times10^{-308}$



$8.05\times10^{-57}<p<5.37\times10^{-10}$

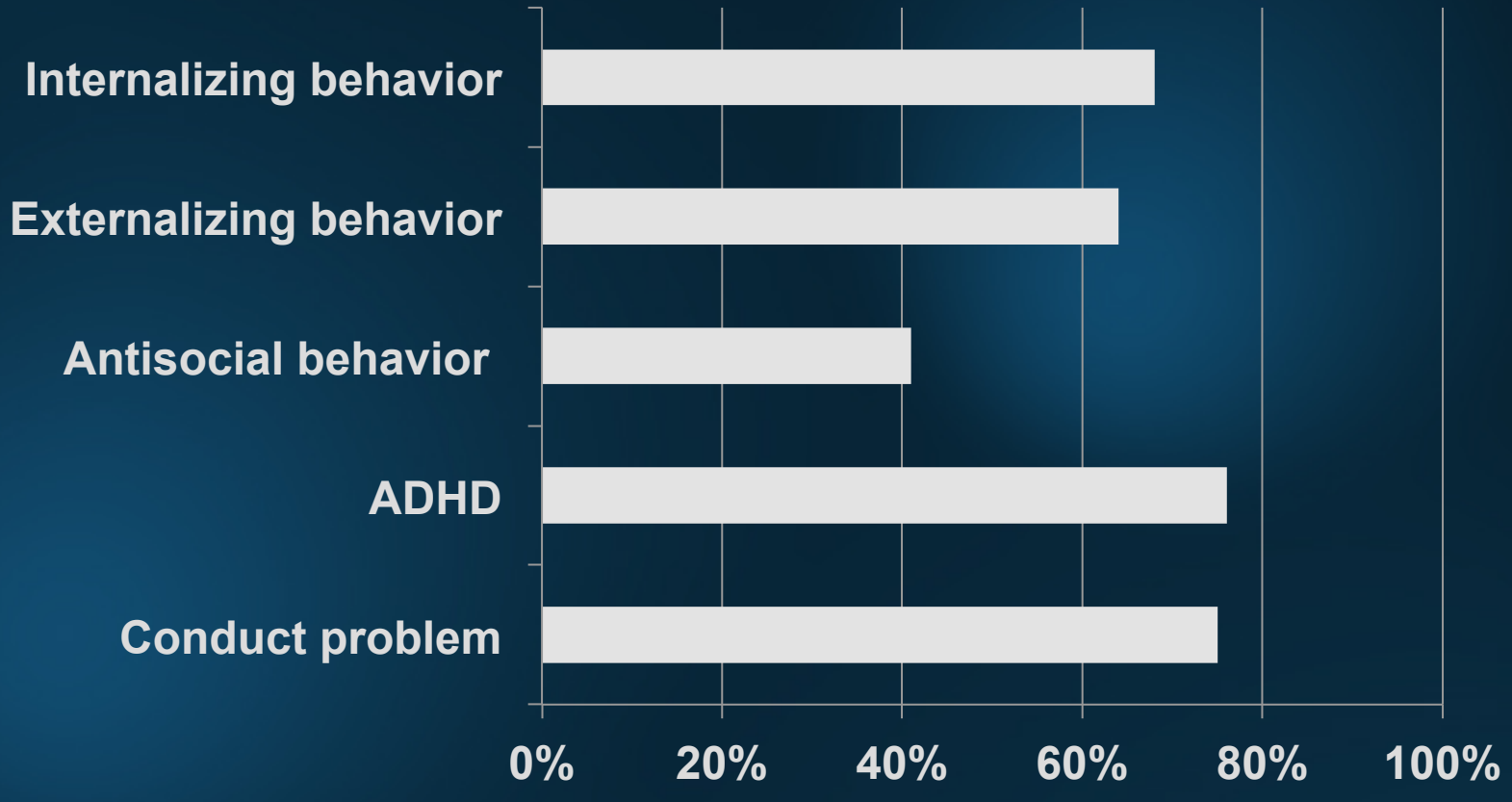
mQTLs can be used to harness the power of GWAS

- mQTLs are enriched in GWAS studies of bipolar disorder



Gamazon et al, Molecular Psychiatry 2011
Tycko, Human Mol Gen 2010

Heritability of Behavior



Genome-wide Association Studies

- Neale et al (2008). **Genome-wide association scan of attention deficit hyperactivity disorder**: Am J Med Genet B Neuropsychiatr Genet, 147B, 8, 1337-44.
- Lasky-Su et al (2008). **Genome-wide association scan of quantitative traits for attention deficit hyperactivity disorder identifies novel associations and confirms candidate gene associations**: Am J Med Genet B Neuropsychiatr Genet, 147B, 8, 1345-54.
- Mick et al (2011). **Genome-wide association study of the child behavior checklist dysregulation profile**: J Am Acad Child Adolesc Psychiatry, 50, 8, 807-17 e8.
- Neale et al (2010). **Meta-analysis of genome-wide association studies of attention-deficit/hyperactivity disorder**: J Am Acad Child Adolesc Psychiatry, 49, 9, 884-97. PMCID: 2928252.

Genome-wide Association Studies

- Phenotypic & genotypic heterogeneity
- Loss of power inherent in dichotomizing complex childhood behavioral patterns into presence or absence of a diagnosis
- GWAS studies rarely account for gene-environment interactions or environmental predictors
- More efficient methods will be necessary

Conclusions

- DNA methylation differences associate with prenatal exposures and developmental outcomes
- mQTLs may be used to provide insight into regulation of gene expression in the brain
- Examining behavior requires a comprehensive strategy that incorporates genetic, epigenetic and environmental risk factors

Acknowledgments

- Emory University
  - Karen Conneely
  - Patricia Brennan
  - Katrina Johnson
  - Julie Carrol
  - James Schroeder
  - Varun Kilaru
  - Sasha Parets
- Nashville Birth Cohort
  - Ramkumar Menon
- CANDLE
  - Frances Tylavsky
  - Ronald Adkins
  - Julia Krushkal
  - Mehmet Kocak
  - Amy Scheck
- Women's Mental Health Program
  - Zachary Stowe
  - D. Jeffrey Newport
  - Bettina Knight