Epigenetics across neurodevelopmental disorders

POND Family Day

Dr. Michelle T. Siu, Research Associate
(PI, Platform Lead: Dr. Rosanna Weksberg)

What is EPIGENETICS?
Epigenetics reflects the interaction between genes and environment.

Neurodevelopmental disorders (NDDs) are heterogeneous, and so are their causes.

- Autism spectrum disorder (ASD) is highly heritable
  - Mutations are rare (each account for <1% of cases)
  - Only 25-40% of cases have a known genetic cause

- Attention deficit hyperactivity disorder (ADHD) is highly heritable, but very few strong, consistent risk genes identified

- Obsessive compulsive disorder (OCD) has even fewer risk genes identified

EPIGENETICS = Your genes + Your environment & lifestyle
Epigenetics regulates how genes are read (gene expression)

When I sing well, ladies get sick

When I sing, well ladies get sick

When I sing, well ladies get sick

Normal variation

When I sing well, ladies get sick

When I sing well, ladies get sick

ASD features

ADHD features

When I sing, well ladies get sick

When I sing, well ladies get sick

ASD diagnosis

ADHD diagnosis
Our Goal: Use epigenetics to identify new biomarkers of NDDs, and to understand disease mechanisms

Development of new diagnostic biomarkers
Complement existing tools to improve diagnosis
Improve drug development
Identify and test new drug targets

https://www.metanomics-health.com

Are there some epigenetic profiles that are distinct for ASD, ADHD, OCD, and/or are there some that overlap across disorders?
Using epigenetics to molecularly profile individuals with NDDs

NDDs: e.g. ASD, ADHD, OCD

Groups could represent:
- Subgroups within a disorder
- Across disorders with similar presentation/features

Comparisons of:
- Biochemical biomarkers
- Brain structure and function
- Cognitive profile
- Clinical profile

Loth et al., 2016 Nat Rev
Our favourite epigenetic tags: DNA Methylation (DNAm)

DNA methylation (DNAm)
- DNA is methylated at specific sites
- Stable tag, extensively studied in research
- Found throughout the genome, not evenly distributed, highly specific regulation
Method: How we measure DNAm in human tissues

Illumina DNAm microarray chip

NDDs
ASD, ADHD, OCD

Healthy control

Gene X
ATTCGAAATCGGCCCGCGAAACGATTTCG

Gene Y
TTCTCGCGATCGACCAGACACGGATGA

SIMILARLY METHYLATED

DIFFERENTLY METHYLATED
POND data: DNAm profiles across NDDs

Mixed group of individuals with an NDD

- SIMILARLY METHYLATED

Healthy control

Subgroups:
- Same genetic mutation (e.g. CHD8 in ASD)
- Symptom severity (e.g. CYBOCS for OCD)

Healthy control

- DIFFERENTLY METHYLATED
POND data: DNAm profiles help us understand biology

- Immune
- Brain development and function
- Other epigenetic mechanisms
- Metabolic
We can use this approach to apply to:
E.g. all individuals with ASD and
• Specific genetic changes
• Sleep, GI issues
• Certain exposures to fetus during pregnancy, in early childhood

https://sites.jmu.edu/gbio103/bbq4b-final-what-causes-gene-mutations-leading-to-cancer/
How will epigenetics help patients with NDDs?

Some of the questions we are asking and pursuing through POND:
• Predictive biomarkers—earlier and more accurate diagnosis
• Help to complement/interpret unclear genetic results
• Predict response to medication?
• Identify new druggable pathways/targets
• Can the improper molecular marks (DNAm) be corrected/altered for improved outcome? i.e. drugs that target epigenetic mechanisms themselves

https://www.metanomics-health.com
Weksberg Lab
Dr. Rosanna Weksberg
Dr. Jack Brzezinski
Dr. Eric Chater-Diehl
Dr. Sanaa Choufani
Youliang Lou
Chunhua Zhao

Former Members
Dr. Darci Butcher
Yi-an Chen
Dr. Daria Grafodatskaya
Fatemeh Heshmati
Dr. Jung-Min Ko
Dr. Raymond Lo
Thanuja Selvanayagem

SickKids
Cheryl Cytrynbaum
Cheryl Shuman
Ny Hoang
Dr. Jim Stavropoulos
Dr. Susan Walker
Matt Gazzellone
Barbara Kellam

POND Network
Dr. Evdokia Anagnostou
Dr. Stelios Georgiades
Dr. Rob Nicolson
Dr. Peter Szatmari

Acknowledgements
Thank you for being a part of our research!