

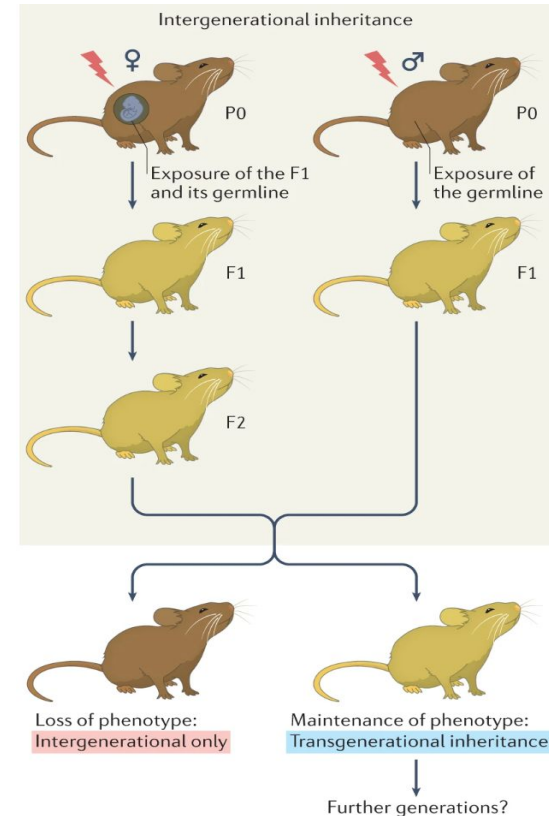


How Trauma Can Affect Future Generations Through Epigenetics

Ben Secord-Bacon, Emma Trotta, Parker Mills

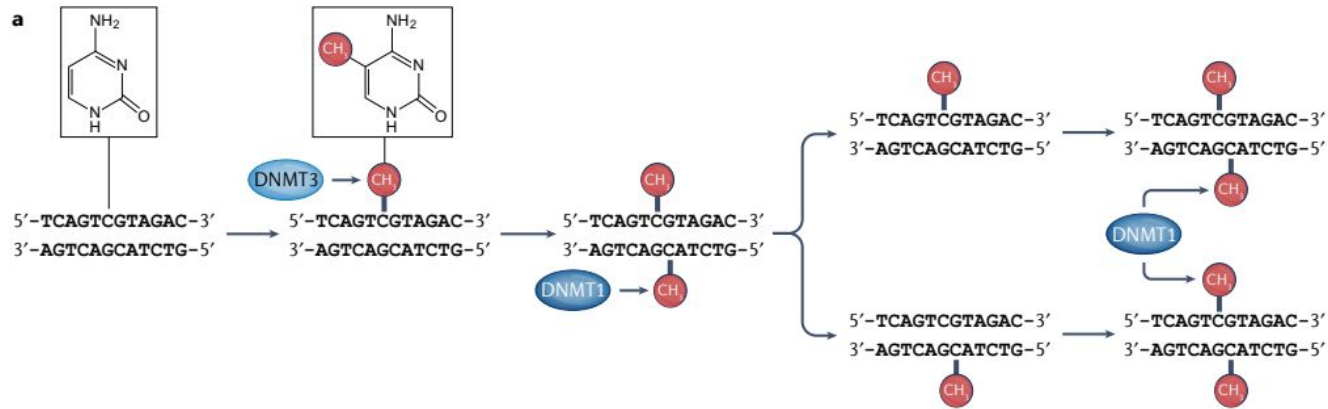
Transgenerational vs Intergenerational Inheritance

Epigenetics: The study of how cells control gene activity without changing the DNA sequence.



Epigenetic Mechanisms

DNA methylation via Cytosine phosphate Guanine (CpG) dinucleotides

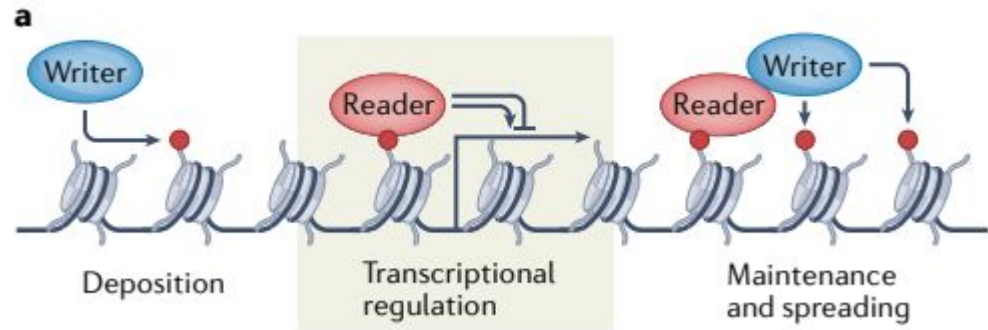


Epigenetic Mechanisms

Histone Modifications

Variants like H3.3 (Promoters and Enhancers), CENP-A (Centromeres), H2AZ (Open Chromatin)

Post-Translational Modifications:
H3 lysine trimethylation in transgene of fruit flies could regulate the expression of a gene for eye colour. Transmitted across generations (Ciabrelli et al., 2017).

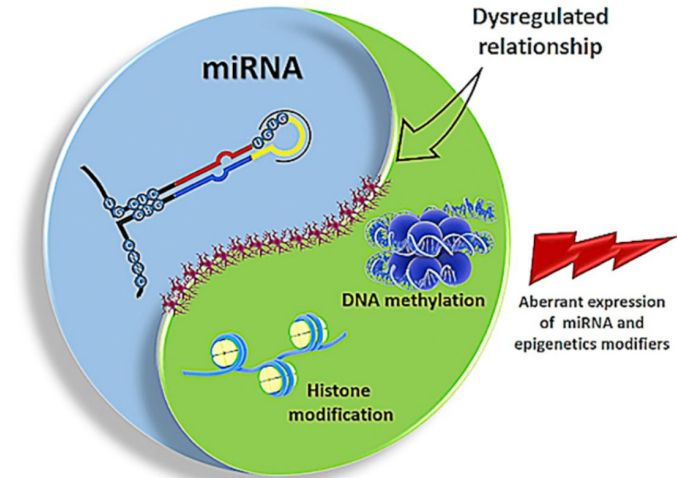


Fitz-James, M. H., & Cavalli, G. (2022). <https://doi.org/10.1038/s41576-021-00438-5>

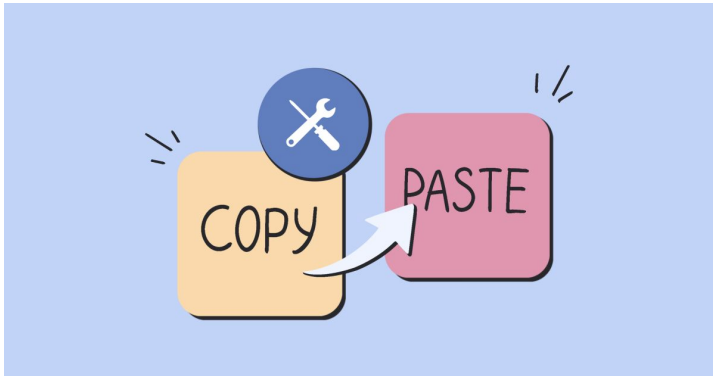
Epigenetic Mechanisms

DNA methylation and histone modifications can cause dysregulation of microRNA (miRNA) and other small RNA expression...

Secondary Epigenetic Mechanism



Replicative vs Reconstructive Transmission



VS



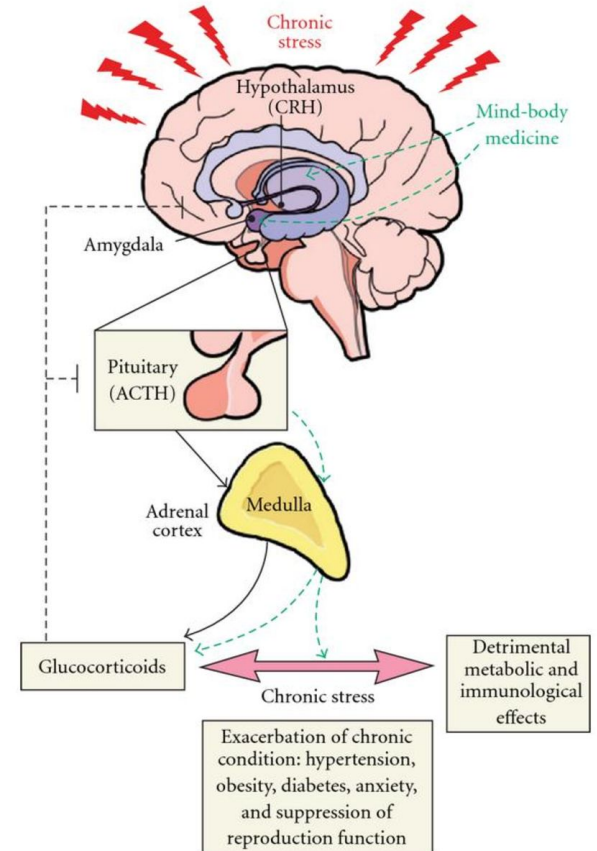
Eukaryotic Genomic Reprogramming → Likely Reconstructive Transmission (need secondary signals like non-coding RNA expression, transcription binding factors, 3-D spatial memory of hetero/ euchromatin)



Initial Epigenetic Changes in DNA due to Childhood Trauma

Trauma Induced Epigenetic Changes - DNA Methylation

- Hyper vs Hypo Methylation
- Chronic exposure to stress hormones
- Dysregulation of the hypothalamic-pituitary-adrenal Axis (HPA Axis)
- Glucocorticoid Receptor




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Glucocorticoid Receptor

- Glucocorticoids
 - Primary Stress Hormones
 - Regulate numerous physiologic processes to maintain homeostasis
- Found in the **Cytoplasm** or **Nucleus** of virtually all human cells.
- Ligand Occupied GR induces or represses the transcription of many different genes.
 - GREs (Glucocorticoid Responsive Elements)
- *NR3C1* and *FKBP5* and related genes affected by early life trauma
 - Exon 1 Variants of *NR3C1*



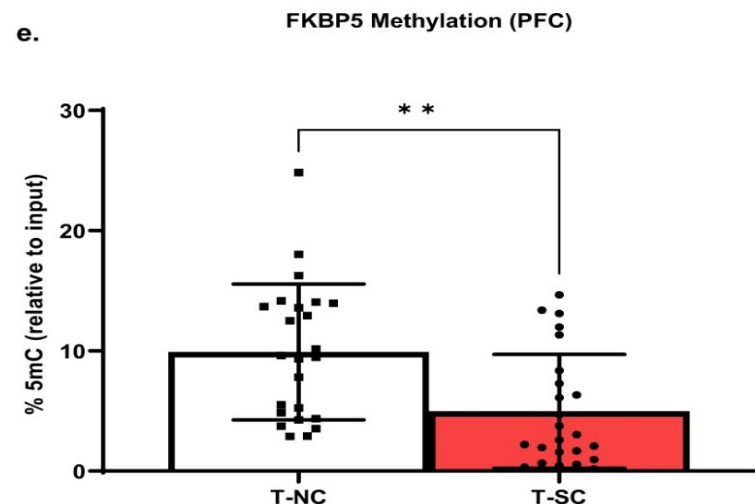
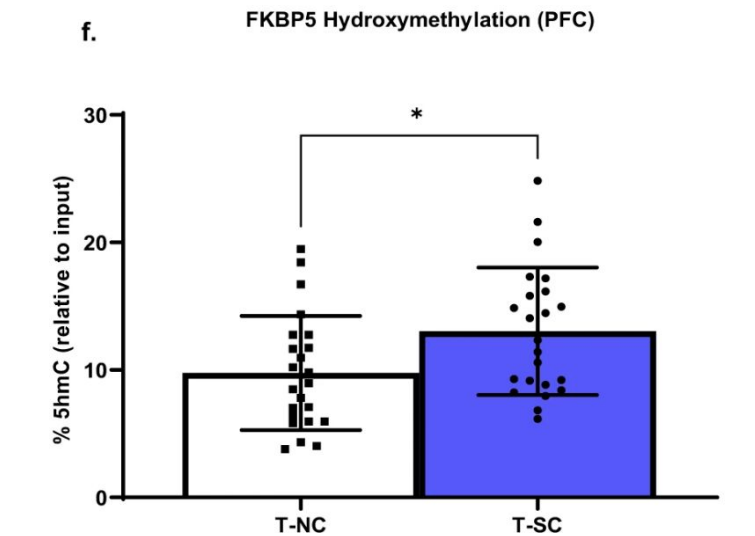
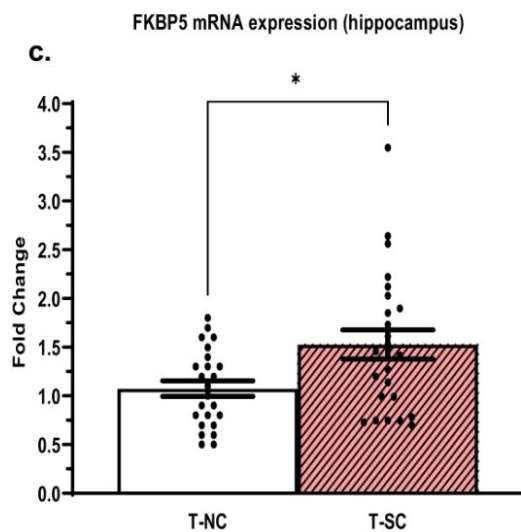
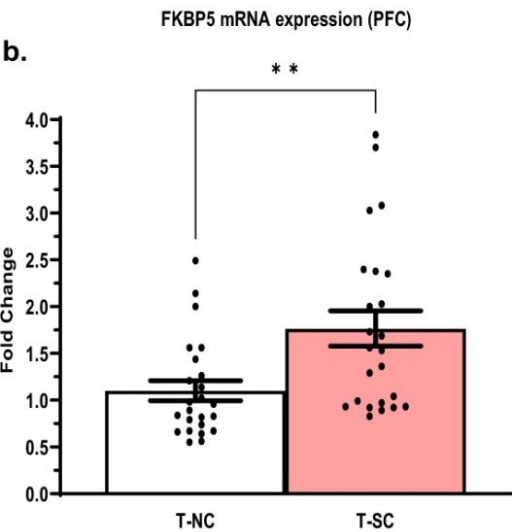
Rizavi et al. (2023) *NR3C1* + *FKBP5* Methylation at Exon-1 Variants in Suicide-Completers

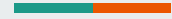
Methods:

- Tissue samples from the Prefrontal Cortex and Hippocampus
- Measured mRNA concentrations as well as DNA 5mC and 5hmC of GR related genes at CpG sites. (*NR3C1* and *FKBP5*)
- HPA axis dysfunction in teen Suicide-Completers
- Results revealed:
 - Decreased GR mRNA from certain (5 of 7) first exon variants in the prefrontal cortex but not the hippocampus of suicide completers.
 - Increased expression of *FKBP5* mRNA with reduced 5mC and Increased 5hmC near the transcriptional start site at both the prefrontal cortex and hippocampus.
 - Increased expression of *FKBP5*, a gene coding for a co-chaperone of GR proteins, results in the decreased expression of *NR3C1*.

Rizavi et al. (2023)

<https://doi.org/10.1038/s41398-023-02345-1>





Maternal Childhood Trauma and Epigenetic Transmission



Pilkay et al. (2024) Maternal Childhood Trauma and its Effects on Child's DNA Methylation and Mental Health

- Examined DNA methylation at specific sites in children which has been previously associated with maternal childhood physical abuse by her father.
- Prior study:
 - Also conducted by Pilkay et al. in which they found epigenome-wide associations between newborn DNA methylation and maternal childhood physical abuse according to her relationship with her abuser.
- Used a questionnaire at the beginning of the study in which mothers reported the type of physical abuse they endured as children as well as the relation to them of their abuser.
 - This study focuses on mothers who were physically abused by their father



Methods and Findings

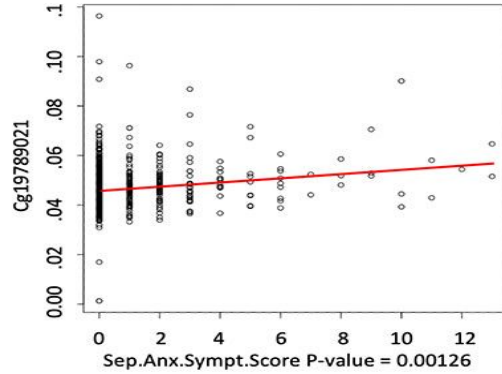
Methods

- Cord blood at the birth of each child was sampled and measured for DNA methylation using the HumanMethylation 450 BeadChip
 - A DNA array which can assess 450,000 CpG sites for methylation.
- Mental health of children measured via parent and school reports on separation anxiety, overall anxiety, fear, worry, and tearfulness on a scale from 0-2.

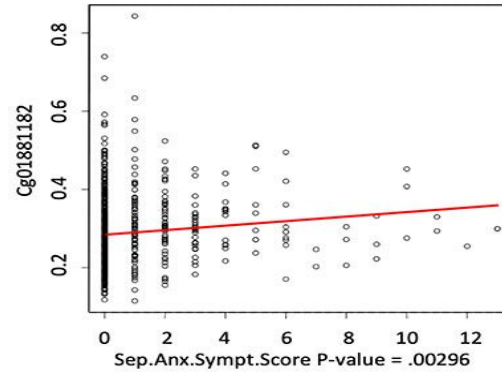
Findings

- DNA methylation at specific sites in the ABAT and GRLX genes identified in their previous study as being connected to maternal physical abuse by her father is also associated with child separation anxiety at age 7 regardless of the child's sex.
- Found methylation of DAXX in males had a positive relationship with overall fearfulness, while methylation of HSPA2 in females resulted in the opposite.

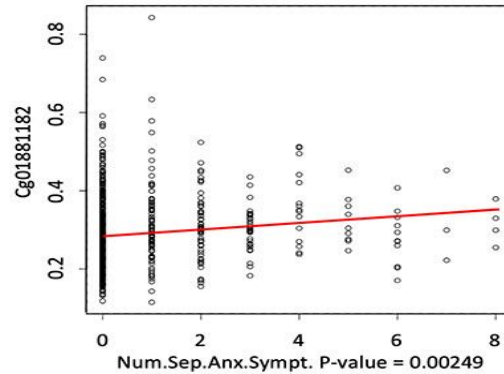
b. Cg19789021 and Separation Anxiety Symptom Score



c. Cg01881182 and Separation Anxiety Symptom Score

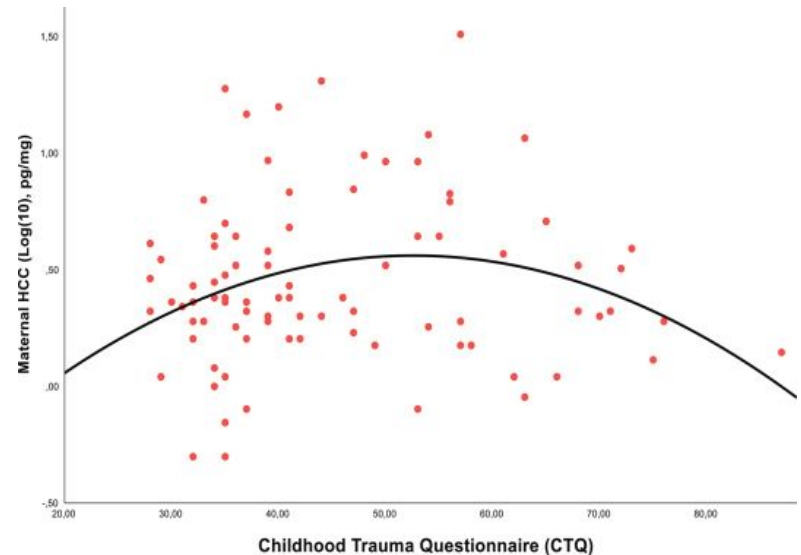


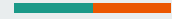
e. Cg01881182 and Number of Separation Anxiety Symptoms



Broeks et al. (2023) Intergenerational Impact of Childhood Trauma on Hair Cortisol Concentrations in Mothers and their Infants

- Examined the relationship between hair cortisol concentrations (HCC) in mothers and their infants 3 months postpartum depending on childhood trauma, lifetime depressive or anxiety disorders, or traumatic/stressful recent life events.
- Found a significant curvilinear relationship between maternal HCC and childhood trauma
- Interestingly found a negative relationship between childhood trauma and infant HCC, suggesting intergenerational effects on the HPA axis in the children.



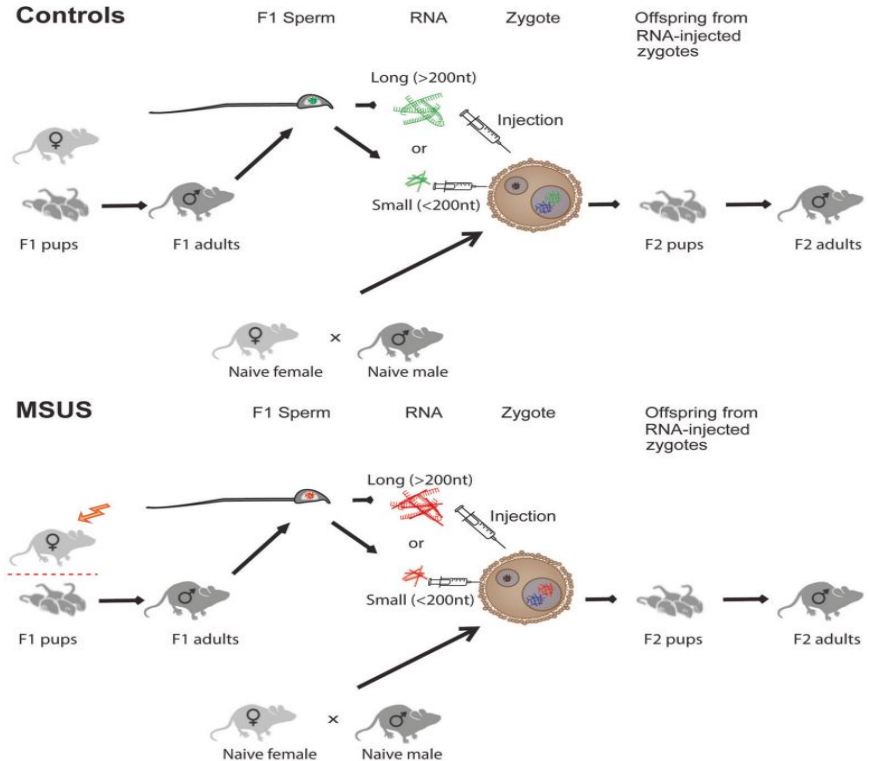


Paternal Childhood Trauma and Epigenetic Transmission

Trauma Affects Future Generations via Sperm RNA

Two Studies: Compare to a Control (no stress)

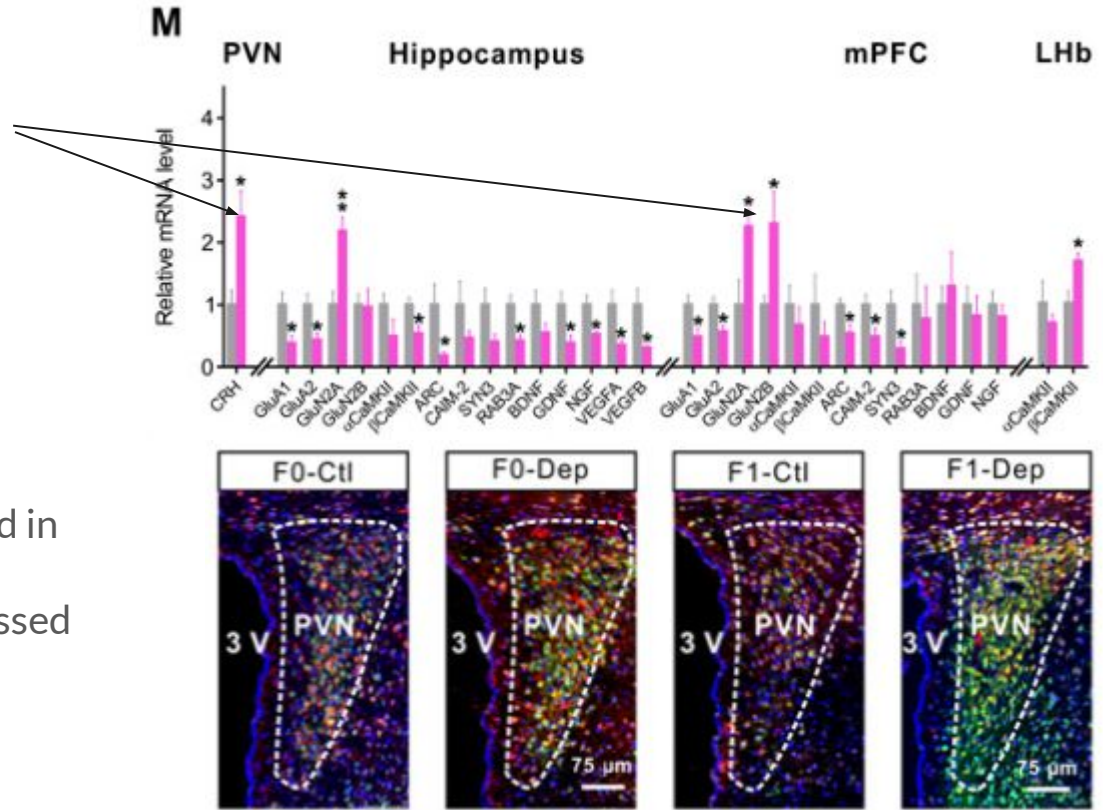
- Young mice subjected to stress
- Test to see if they exhibit depressed behaviours and altered gene expression
- Breed with naive mother and observe offspring, or extract sperm and implant in naive zygote and observe offspring.
- Observe next generations, and run transcriptomic analyses to view differences in gene expression



Wang et al. (2021) → small RNA (sRNA) and miRNA

Pink shows altered mRNA expression for proteins associated with HPA axis hyperactivation and depression in F1-Depressed mice compared to Control.

Concluded: sperm sRNA, primarily miRNA was differentially expressed in depressed mice, and when injected into zygotes, this resulted in depressed phenotype and gene expression patterns. → Intergenerational



Gapp et al. (2018) → long non-coding RNA and sRNA



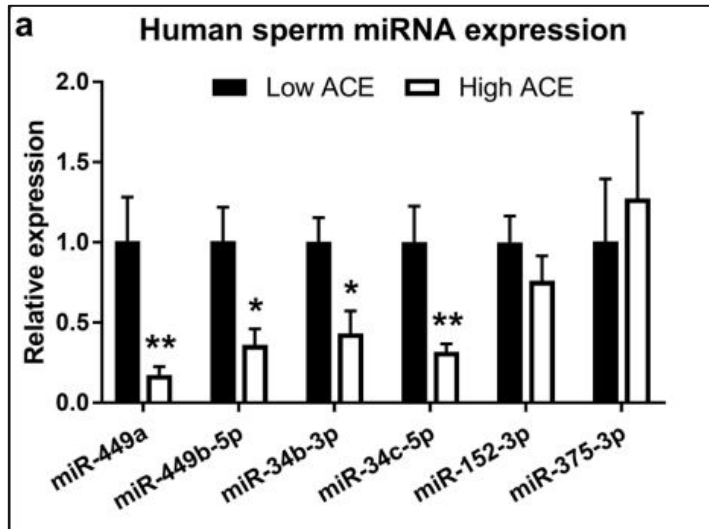
- Total ncRNA = Transgenerational (3 generations)
- all epigenetic changes inherited in response to trauma

sRNA = alterations in body weight and behavioural despair

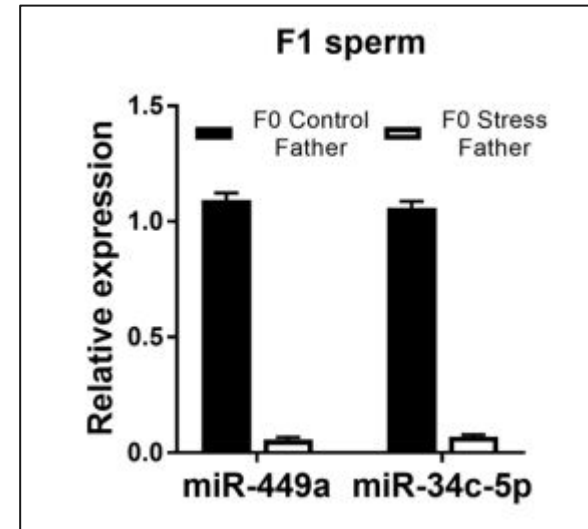
Long ncRNAs = changes in food intake, glucose metabolism, and risk-taking behaviour

Mice and Humans (Dickson et al., 2018)

- Stressed mouse sperm compared to sperm of men with high Adverse Childhood Experience scores
- Isolate sperm RNA and use qPCR to quantify miRNA levels
- Validates mice as model to explain human mechanisms... we can affect our offspring in the same way



Human



Mice



Correlation Studies



Limitation to current studies

- Few direct parent and offspring studies
- Small sample size
- Little resources for long term studies
- Complexity of DNA modification pathways and our understanding of them is not complete

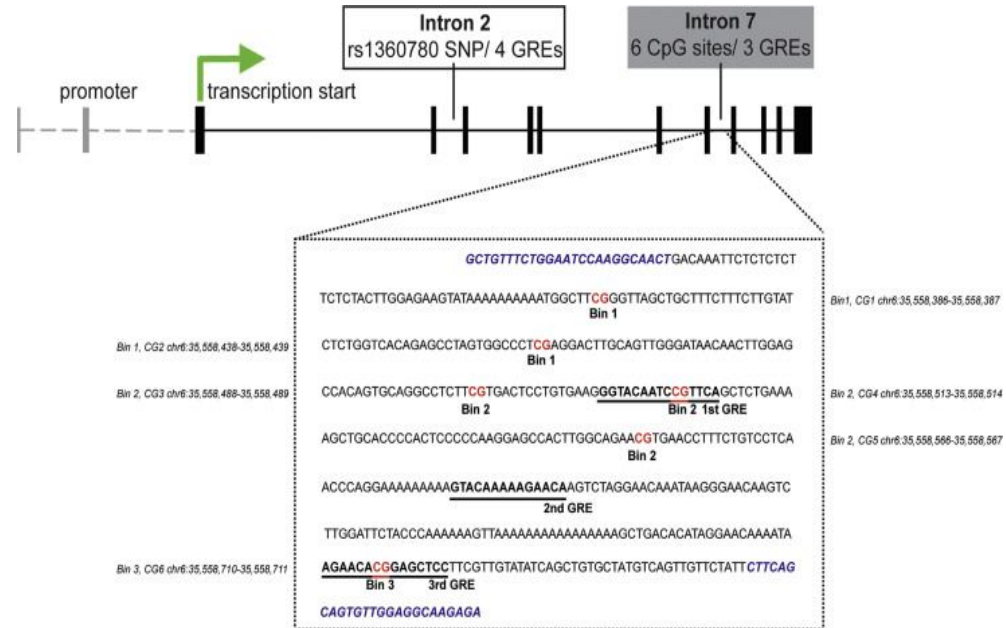


Benefits of Correlation Studies

- Compile research done in epigenetics
- Able to link known DNA modifications that result in different diseases like PTSD or obesity
- These studies are usually based on Childhood Trauma Questionnaires (CTQ) to get a psychological evaluation of how the participant have been affected by trauma in their past

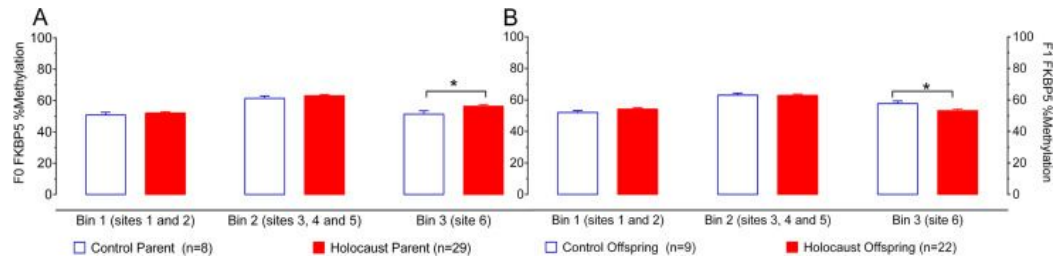
PTSD in Holocaust Survivors Yehuda et al. (2016)

- Determine if PTSD has been epigenetically passed down from survivors of the Holocaust
- Methylation of the FKBP5 gene
- FKBP5 is a co-chaperone proteins that bind and inhibits glucocorticoid to its receptor
- Differential activities of the GC receptor is associated with PTSD and other major depressive disorders
- Methylation at 6 different CpG sites on intron 7 of the FKBP5 gene was the primary focus
- Intron 7 is in direct physical contact with FKBP5 transcription start site and it contain glucocorticoid response elements which regulates FKBP5 expression



PTSD in Holocaust Survivors Yehuda et al. (2016)

- Compared methylation of intron 7 from Holocaust survivors to demographically match Jewish control population
- Not all of the offspring and the parents were direct biological matches
- Found that methylation of Holocaust survivors and their offspring differed from control population at bin 3 site 6 of Intron 7
- Lower methylation in the offspring
- CTQ results:
 - Manipulate the results to look at only the effect of physical and sexual abuse
 - Holocaust survivors who were physically and sexual abuse, caused significant changes in the methylation of bin 2





Obesity in Indigenous Populations Schaffe & Bruna (2023)

- Long history of trauma associated oppression, discrimination, systematic racism, and colonialism
- Study the correlation of increased obesity, hypertension, insulin resistance, diabetes, stroke, and coronary heart disease
- Focuses on historic and intergenerational trauma
 - Historic: psychological and social issues in the community
 - Intergenerational: epigenetics during pregnancy

Obesity in Indigenous Populations Schaffe & Bruna (2023)

Epigenetics results from trauma

- Obesity is an epigenetic disease!
- Affects the genes responsible for placental, embryonic and fetal growth, adiposity and energy metabolism during embryogenesis
- Nutritional imprint



Behavioural results of trauma

- Lack access to healthier environment
- Improper coping strategies
- Food as a form of love





Obesity in Indigenous Populations Schaffe & Bruna (2023)

- Allostasis
- Allosteric Load
- The allosteric load scale was based on specific biomarkers for obesity
- 5 times more likely to have high-mid allosteric load level
- Offspring's allosteric load was more so due to the material experience in residential school and not due to external behaviours as the child grew up



Obesity in Indigenous Populations Schaffe & Bruna (2023)

- Caution in how future research is presented is key
- Can't put the blame on mother for something that is out of their control
- Diminishes the responsibility of society to solve the issues of historic trauma



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