Lecture 4.3 - The Epigenetic Landscape of PTSD

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Daniel Rawrio - The Zebrafish

Learning Objectives

1. **Explain the mechanism and detection procedure for DNA Methylation marks.**
2. Discuss the role of epigenomics in PTSD research.
3. Answer a figure-related question from PTSD research and identify what role DNA Methylation has.

DNA Methylation Is A Key Epigenetic Modification

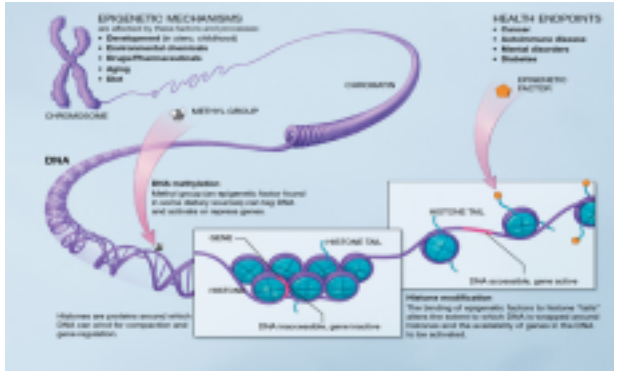
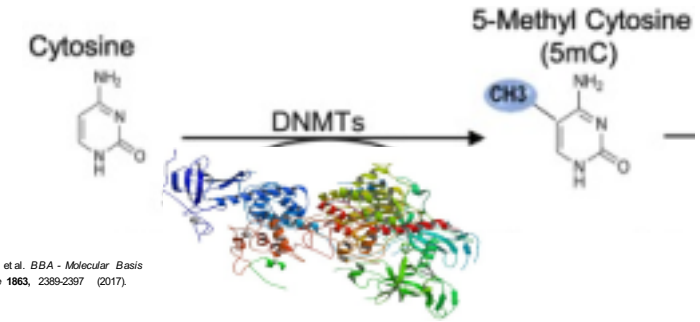


Image from: NIH

DNA Methyltransferase Is Responsible For Methylation of CpG Islands



Images:
X. Zhang, et al. *BBA - Molecular Basis of Disease* **1863,** 2389-2397 (2017).

PDB

DNA Methylation is Categorized By Method

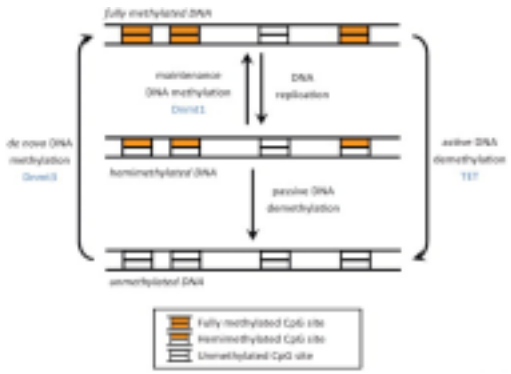


Image from:
A. Jeltsch, R. Z. Jurkowska. *Trends in Biochemical Sciences* **39**, 310-318 (2014).

DNA Methylation in CpGI Promoters Decreases Transcription

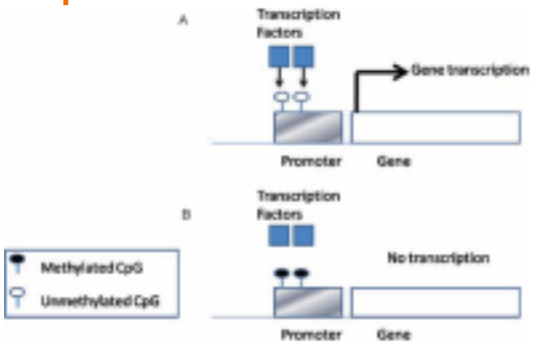


Image from: D. H. K. Lim, E. R. Maher. *The Obstretician & Gynecologist* **12**, 37-42 (2010).

http://www.beatricebiology.com/2016/06/gene-silencing/

Bisulfite Treatment of Non-Methylated Cytosines Causes Conversion to Uracil

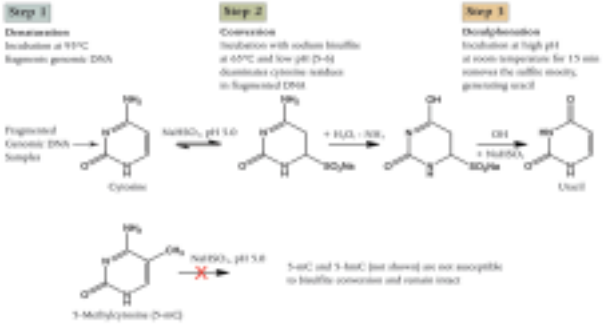


Image from: New England BioLabs

Bisulfite Sequencing Is A High Resolution Technique for DNA Methylation Detection

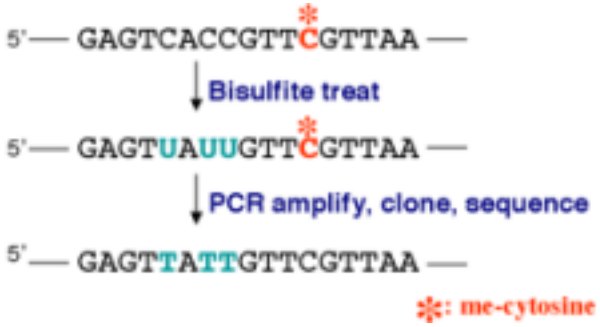


Image from: Alpha BioLaboratory

Bisulfite-DNA Pyrosequencing Technology Is Able To Accurately Help Detect Methylated Cytosines

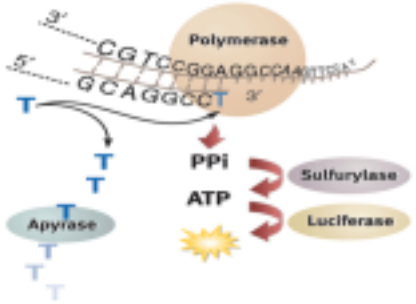


Image from: Center for Genomic Sciences, University of Hong Kong

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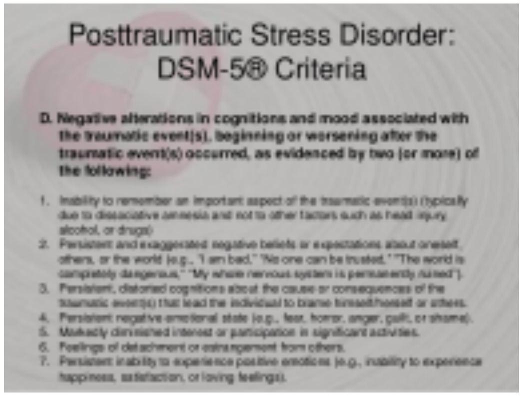
Posttraumatic Stress Disorder (PTSD)

Image from: psychcentral

Posttraumatic Stress Disorder is a DSM-5-Classified Mental Disorder



Posttraumatic Stress Disorder: DSM-5® Criteria

D. Negative alterations in cognitions and mood associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:

1. Inability to remember an important aspect of the traumatic event(s) (typically due to dissociative amnesia and not to other factors such as head injury, alcohol, or drugs).
2. Persistent and exaggerated negative beliefs or expectations about oneself, others, or the world (e.g., "I am bad," "No one can be trusted," "The world is completely dangerous," "My whole nervous system is permanently ruined").
3. Persistent, distorted cognitions about the cause or consequences of the traumatic event(s) that lead the individual to blame himself/herself or others.
4. Persistent negative emotional state (e.g., fear, horror, anger, guilt, or shame).
5. Markedly diminished interest or participation in significant activities.
6. Feelings of detachment or estrangement from others.
7. Persistent inability to experience positive emotions (e.g., inability to experience happiness, satisfaction, or loving feelings).

Image from: slideshare

Altered DNA Methylation is Suspected in Many PTSD-Associated Genes

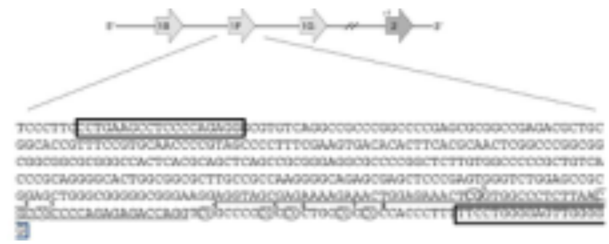
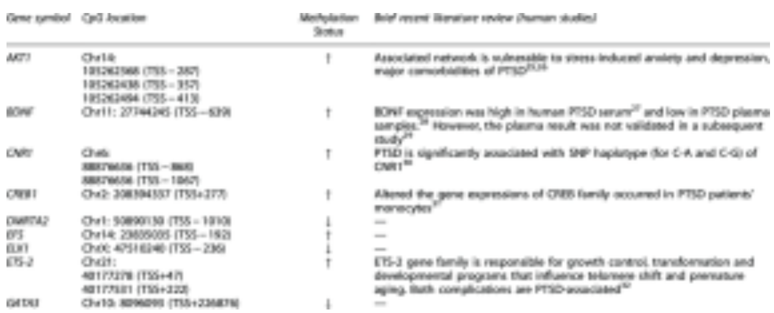


Image from: Nature

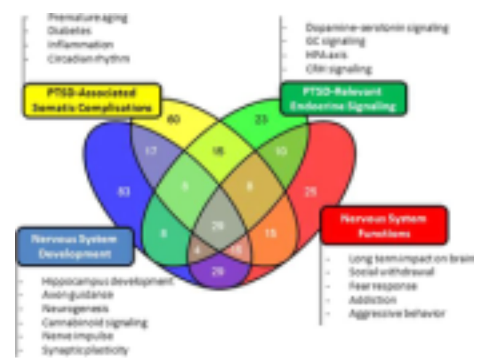
Genes Correlated With PTSD Were Identified From Differentially Methylated CpG Islands



Gene symbol	CpG location	Methylation Status	Brief recent literature review (human studies)
AKT1	Chr14: 105262568 (TSS − 287) 105262438 (TSS − 357) 105262494 (TSS − 413)	↑	Associated network is vulnerable to stress-induced anxiety and depression, major comorbidities of PTSD[23,24]
BDNF	Chr11: 27744245 (TSS − 639)	↑	BDNF expression was high in human PTSD serum[27] and low in PTSD plasma samples.[28] However, the plasma result was not validated in a subsequent study[29]
CNR1	Chr6: 88876606 (TSS − 868) 88876656 (TSS − 1067)	↑	PTSD is significantly associated with SNP haplotype (for C-A and C-G) of CNR1[30]
CREB1	Chr2: 208394337 (TSS+277)	↑	Altered the gene expressions of CREB family occurred in PTSD patients' monocytes[31]
DMRTA2	Chr1: 50890150 (TSS − 1010)	↓	—
EFS	Chr14: 23835005 (TSS − 192)	↑	—
ELK1	ChrX: 47510240 (TSS − 236)	↓	—
ETS-2	Chr21: 40177278 (TSS+47) 40177501 (TSS+222)	↑	ETS-2 gene family is responsible for growth control, transformation and developmental programs that influence telomere shift and premature aging. Both complications are PTSD-associated[32]
GATA3	Chr10: 8096095 (TSS+236876)	↓	—

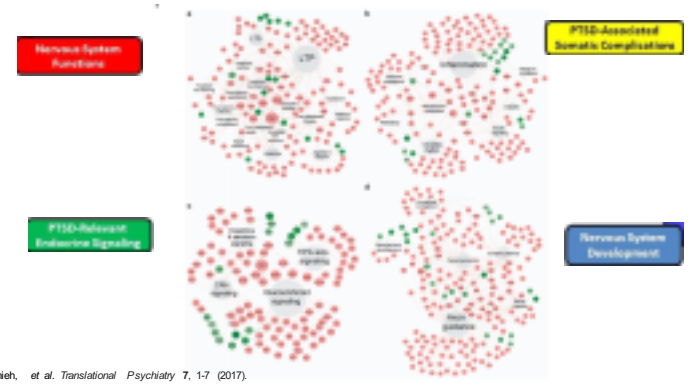
R. Hammamieh, *et al.* *Translational Psychiatry* **7**, 1-7 (2017).

Four Clusters of PTSD-Related Gene Networks Were Derived From DMGs



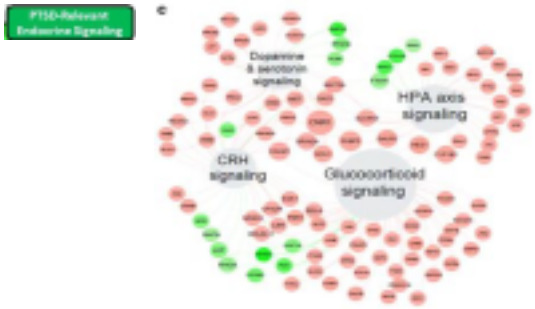
R. Hammamieh, *et al.* *Translational Psychiatry* **7**, 1-7 (2017).

Hypermethylation is Enriched in All Four Clusters in PTSD+ Veterans



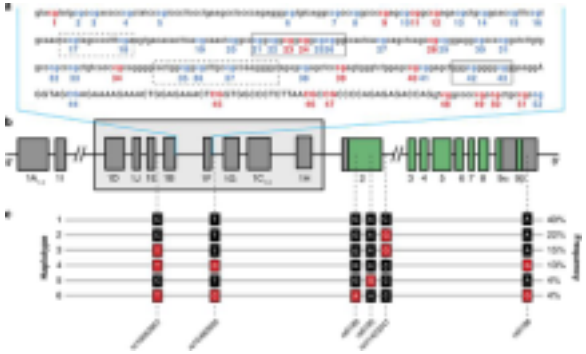
R. Hammamieh, *et al. Translational Psychiatry* **7**, 1-7 (2017).

Endocrine Signaling Cluster Shows Hypermethylation of Glucocorticoid Genes



R. Hammamieh, *et al. Translational Psychiatry* **7**, 1-7 (2017).

Cortisol Pathways are Less Effective in PTSD Sufferers, Increasing the Feelings of Stress



Schur, R.R., *et al.* Translational Psychiatry, 1-8 (2017)

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