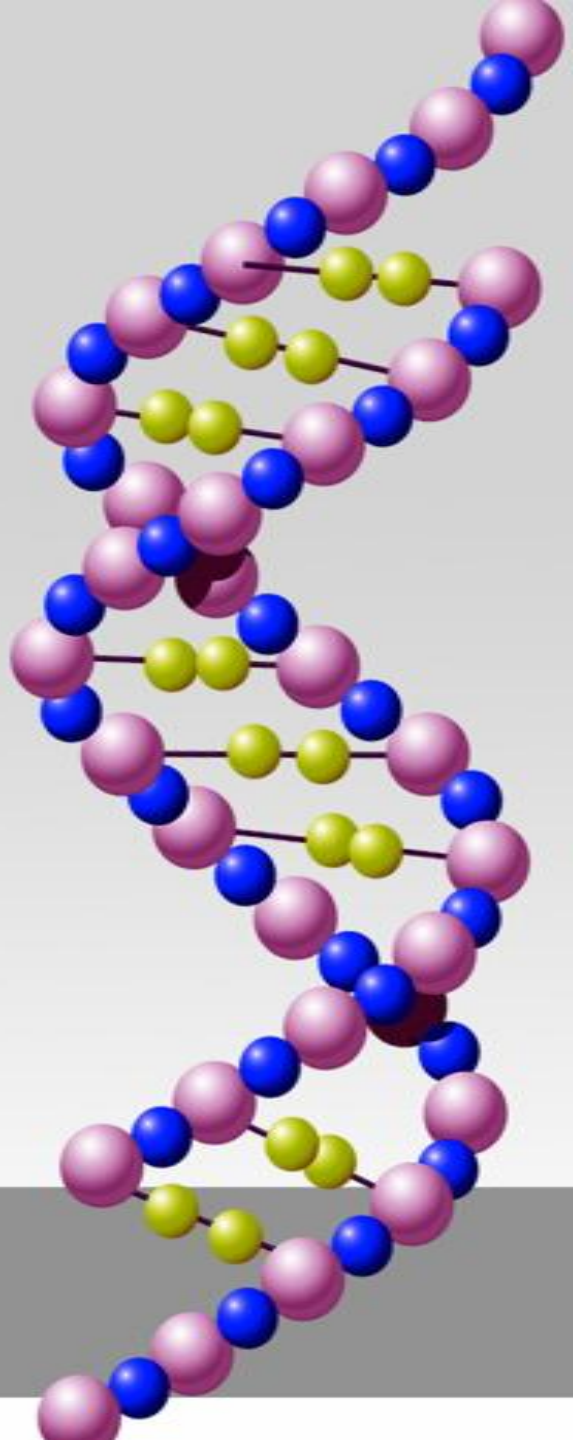
EPIGENETICS AND TREATMENT IN PSYCHIATRY



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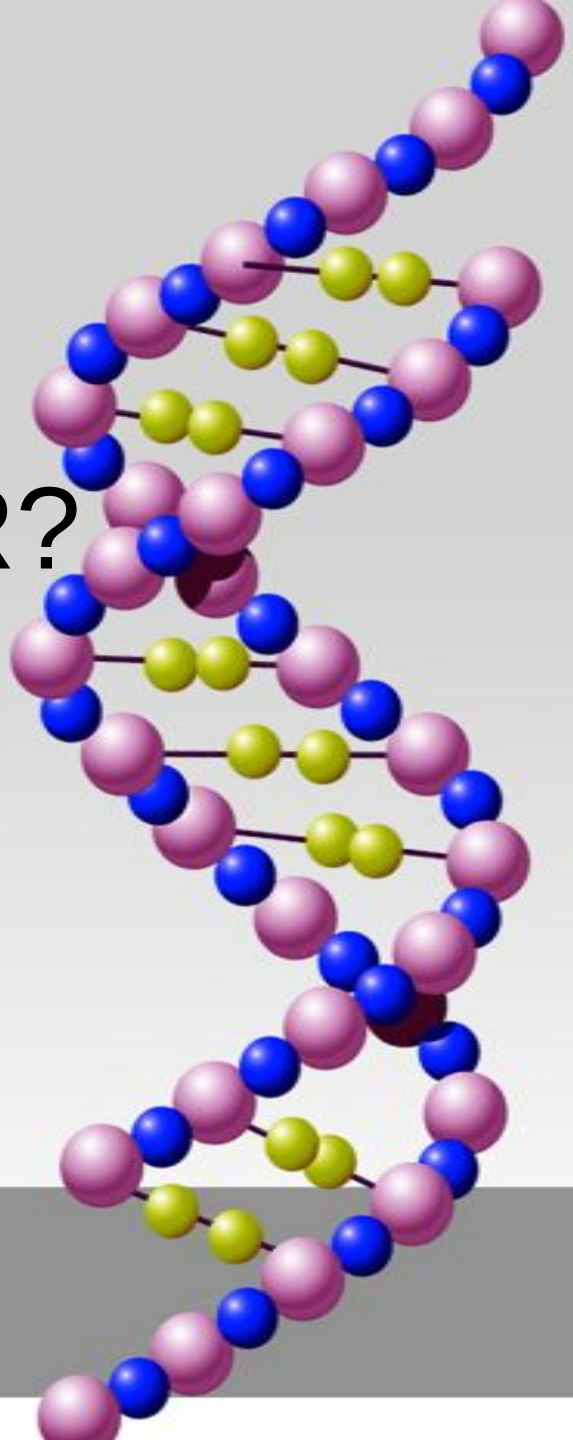
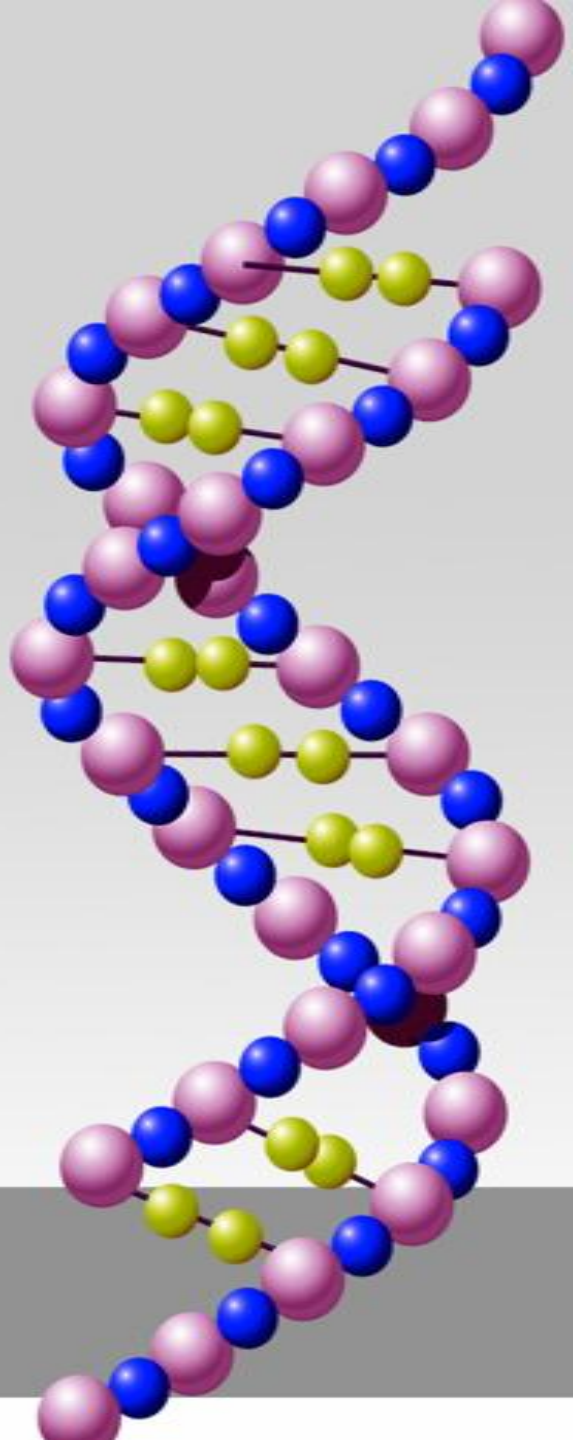
21st January, 2018, Bombay Psychiatric Society CME,

WHAT HAVE WE UNDERSTOOD SO FAR?



The Basics

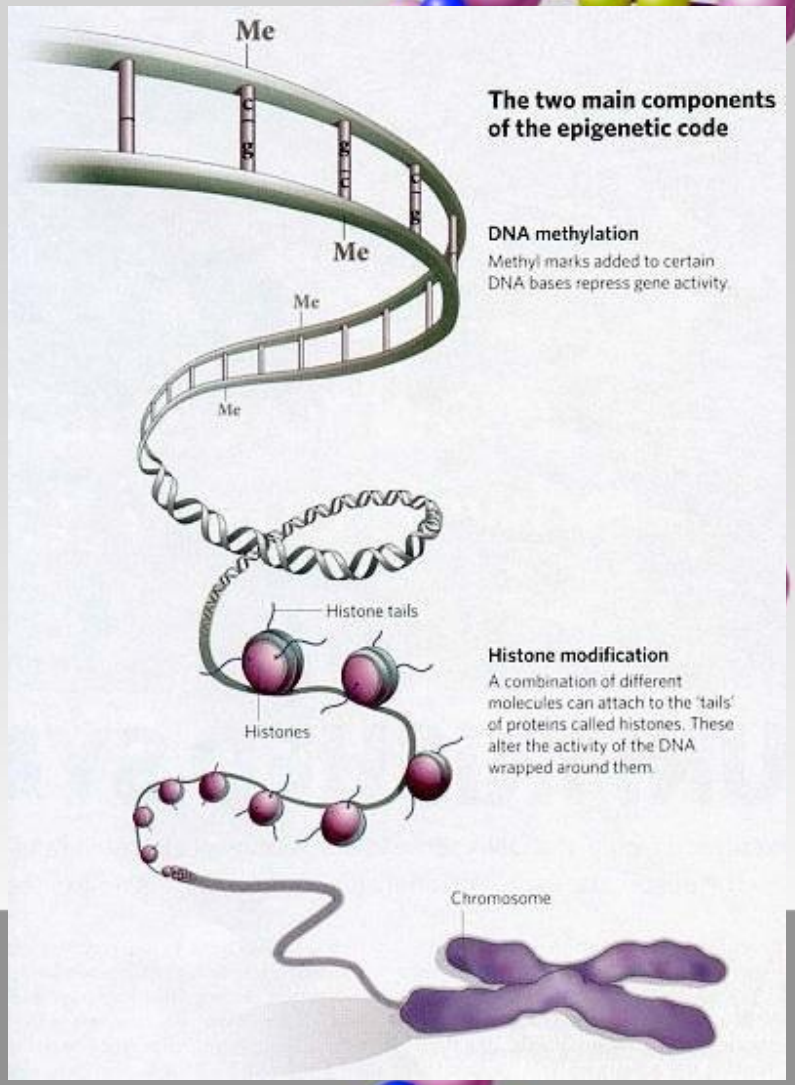
- DNA Methylation
- Histone acetylation
- mRNA splicing



Mechanisms

- DNA Methylation
  - Addition of methyl groups to DNA at CpG sites
- Chromatin/Histone modifications
  - Addition and removal of acetyl groups from DNA

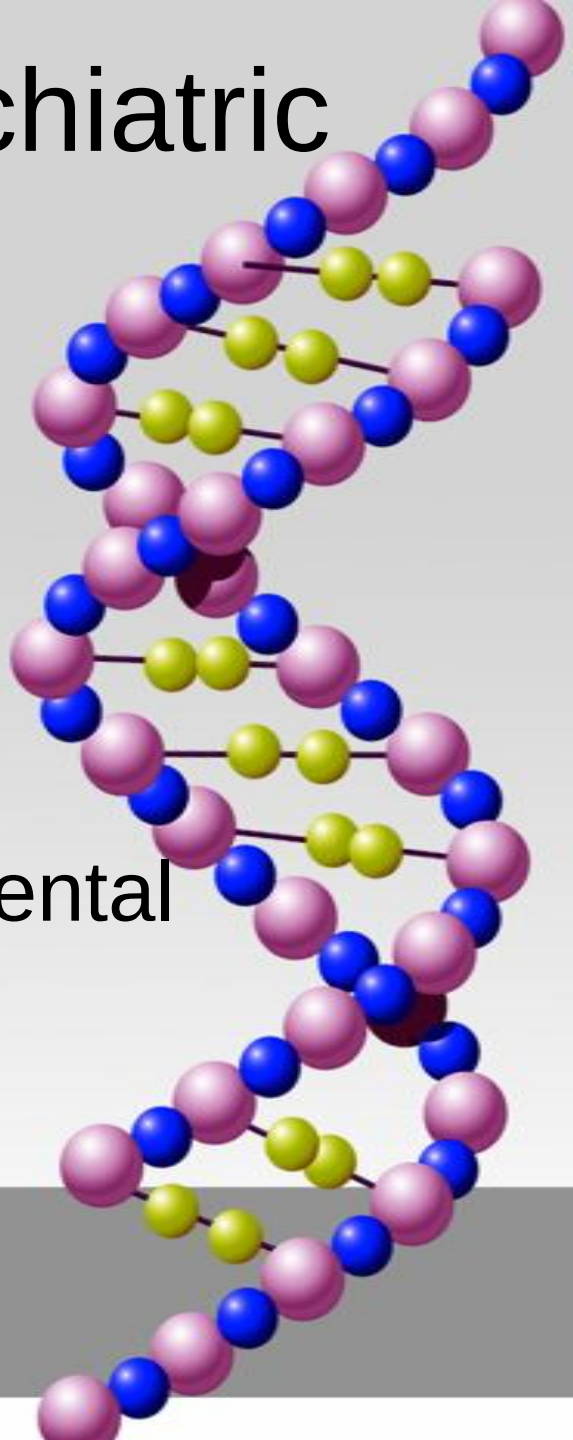
Epigenetic Mechanisms



http://www.universe-review.ca/F11-monocell.htm

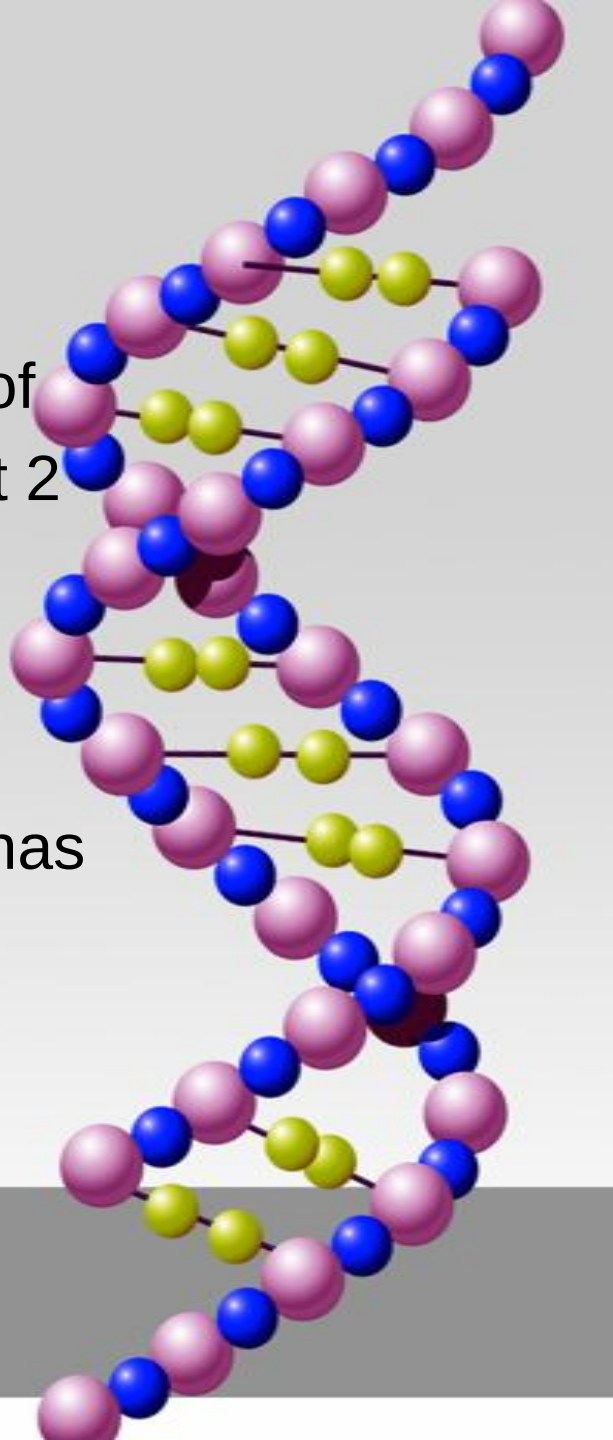
The Epochs of Psychiatric Illness

- Analytical-social
- Bio-psycho-social
- Genetic-Epigenetic-Environmental

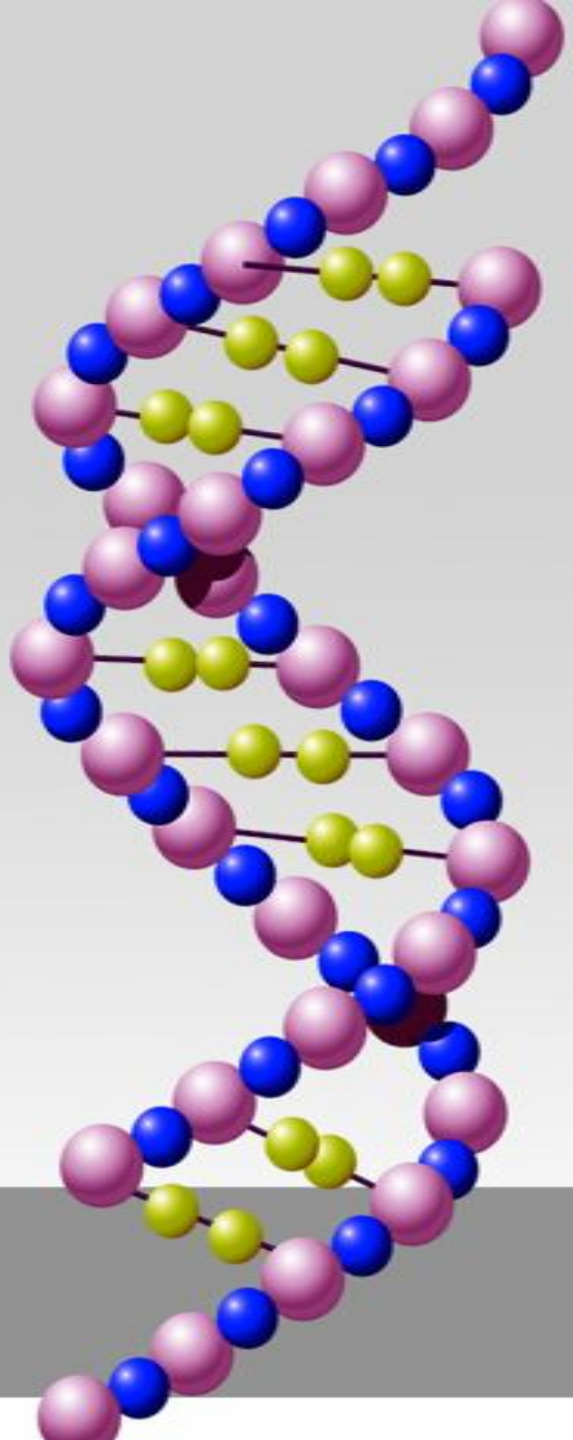


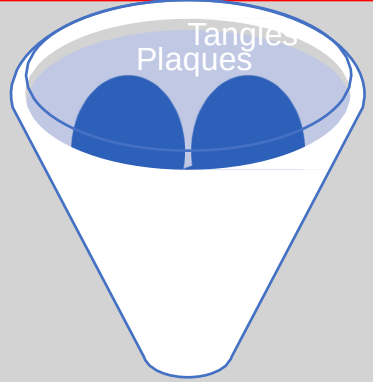
Case # 1

- Mr. A is a 72 year old man with history of progressive forgetfulness since the past 2 years. He is currently living with his son and daughter-in law,whom he does not recognize. He often wanders out of the house and has to be brought back. He has now also become incontinent.



- Clinical Diagnosis?
- Approach?





Alzheimer's Disease

Plaques	Deposition	Amyloid β
Neurofibrillary Tangles	Hyper-phosphorylation	Tau Protein
Cytokines	Oxidative Injury	TNF-α IL-1 β

Neugroschl J, Wang S. Alzheimer's Disease: Diagnosis and Treatment Across the Spectrum of Disease Severity. *The Mount Sinai Journal of*

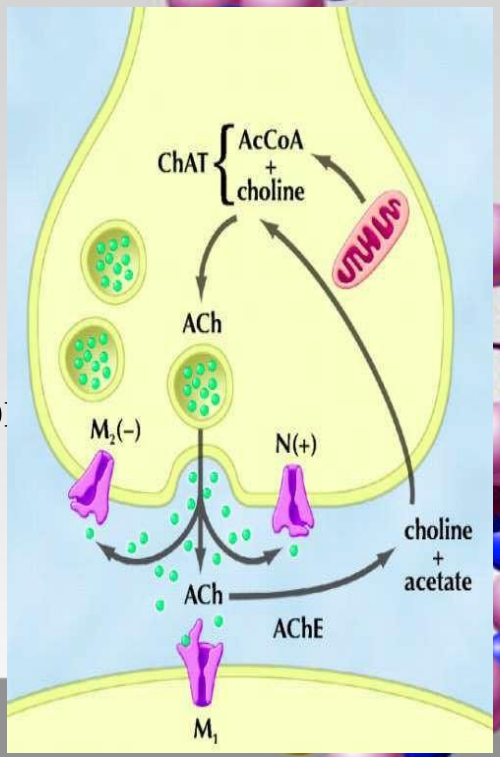
Genetic biomarkers for Alzheimer's Disease

Gene	Chromosome	Effect of mutation
APP: Amyloid Precursor Protein	21	Increased Aβ production
PSEN 1: Presenilin 1	14	-same-
PSEN 2: Presenilin 2	1	-same-
Apo E_4	19	Increased Aβ deposition
LOX gene	18	Neuro-inflammatory insult

Neugroschl J, WaŶg S. Alzheiŵer's Disease: DiagŶosis aŶd TreatŵeŶt Across the Spectrum of Disease Severity. *The Mount Sinai Journal of Medicine, New York*. 2011

Influence of ApoE on AD therapeutics

- 40 % of AD patients don't respond to cholinesterase inhibitors.
- $ApoE_4$ genotype +ve: Decreased levels of Choline Acetyl Transferase (ChAT) in cortex and hippocampus
- Farlow et al.
  - 80 % $ApoE_4$ –ve: High performance status fo
  - 60 % $ApoE_4$ +ve: Deteriorated



Farlow MR, Lahiri DK, Poirier J, Davignon J, Schneider L, Hui SL. Treatment outcome of tacrine therapy depends on apolipoprotein genotype and gender of the subjects with Alzheimer's disease. Neurology.

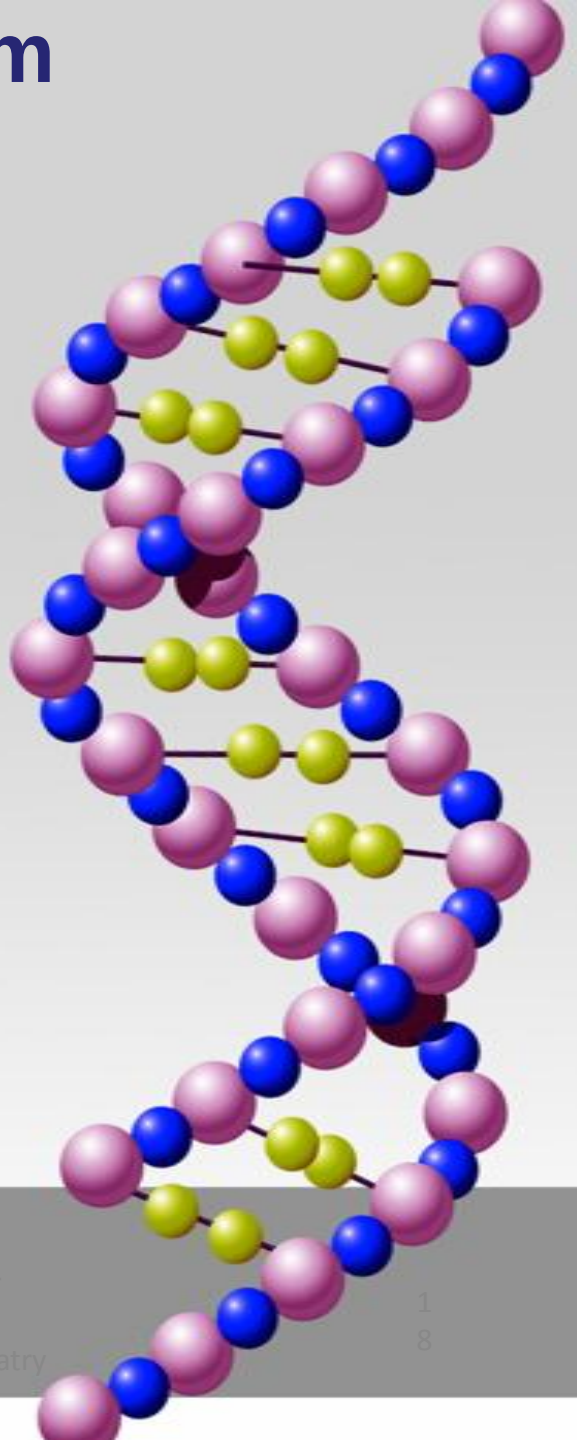
Influence of 5-LOX polymorphism on AD therapeutics

- Inflammatory molecules and mechanisms also play a major role in the onset and progression of clinical symptoms of Alzheimer's disease.

- Qu T et al., 2001
  - Alzheimer's disease will be delayed in subjects who display a mutation in the 5-LOX gene promoter, and that consequently the frequency of occurrence of the three known 5-LOX mutated alleles will be greater in subjects with onset of Alzheimer's at a very old age than in subjects with an earlier onset.

- Other Clinical trials :

1. Zileuton , NSAIDS, Etarnacept, Steroids



Qu T, Manev R, Manev H. 5-Lipoxygenase (5-LOX) promoter polymorphism in patients with [illegible] disease. J Neuropsychiatry Clin Neurosci. 2001

Epigenetics in Alzheimers Disease

- Animal post-mortem studies show:

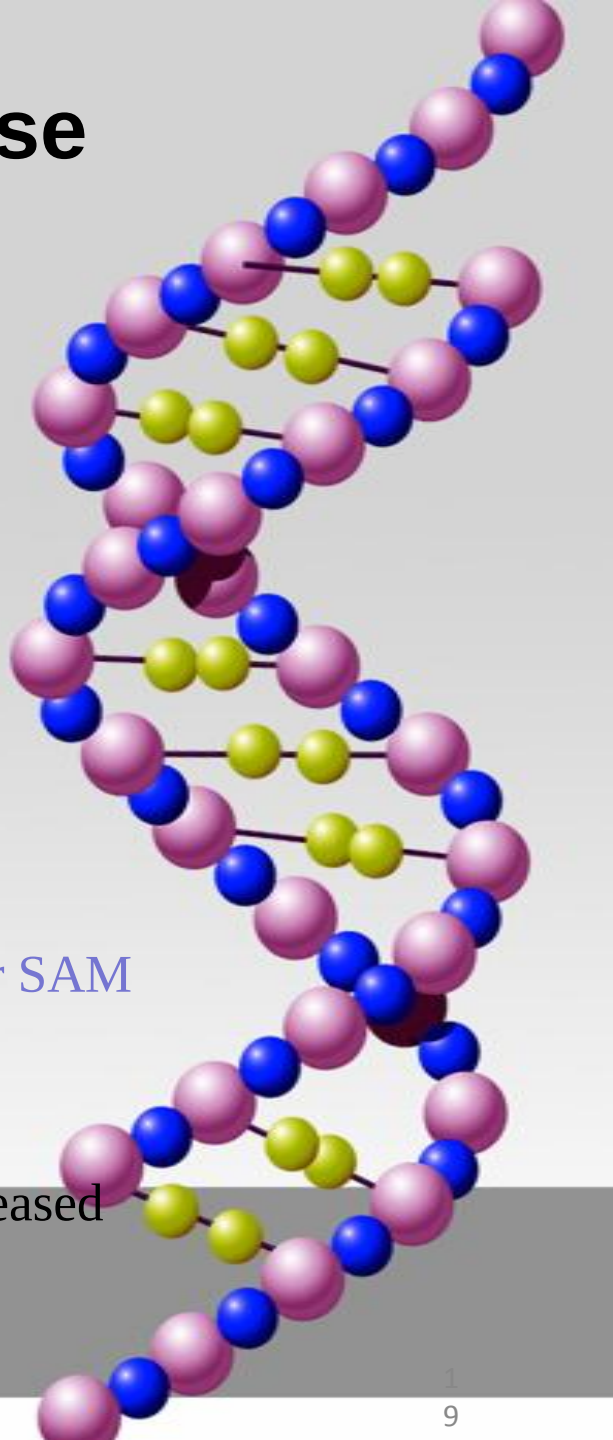
Pathology	Effect
Decreased global levels of 5'-mC in brain	Increased Tau phosphorylation
Decreased level of H3 acetylation in Temporal lobe	Decreased synaptic plasticity leading to decreased learning and memory

Hypothesis:

- Folate participates in 1 carbon metabolism required for SAM production.

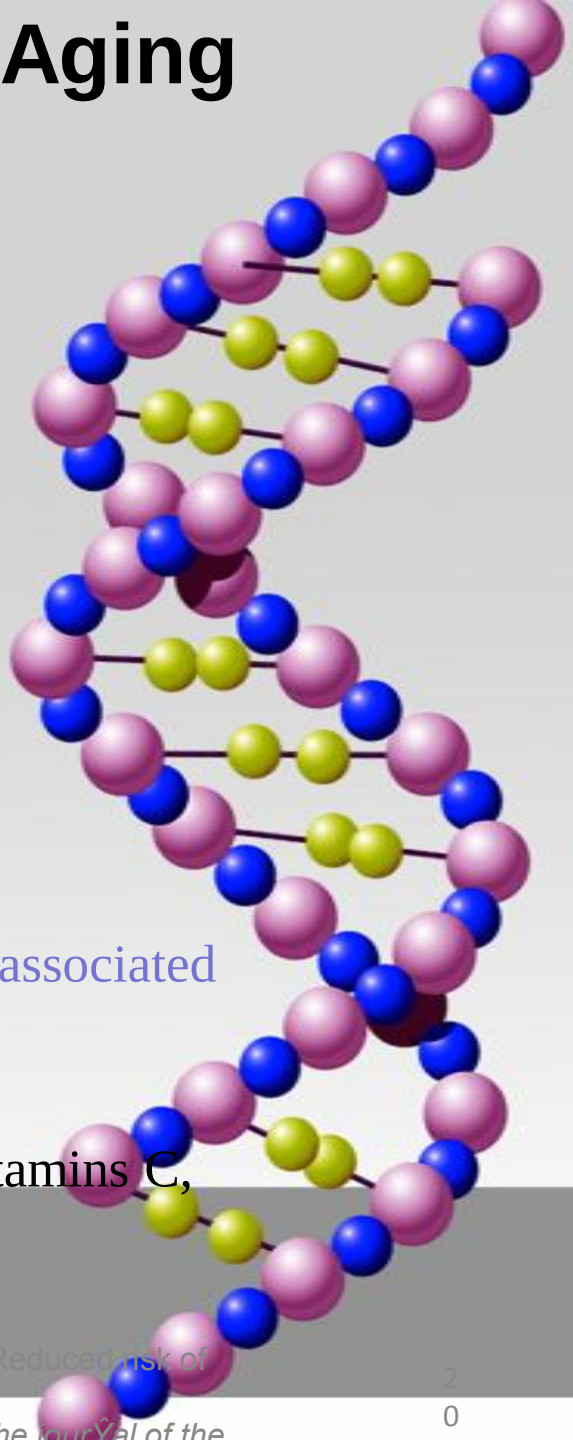
Transgenic mice (AD) studies:

- Groups kept under folate deficient conditions had increased production of BACE-1 and Aβ deposition



Baltimore Longitudinal Study of Aging (2005)

- 579 non-demented elderly
- Recorded dietary supplemental intake
- Follow-up of 9.3 years
- 57 subjects developed AD
- Conclusion:
  1. Only total intake of folate at or above the RDA was associated with a significant decreased risk of AD.
  2. No association was found between total intake of vitamins C, carotenoids, or vitamin B12 and risk of AD.



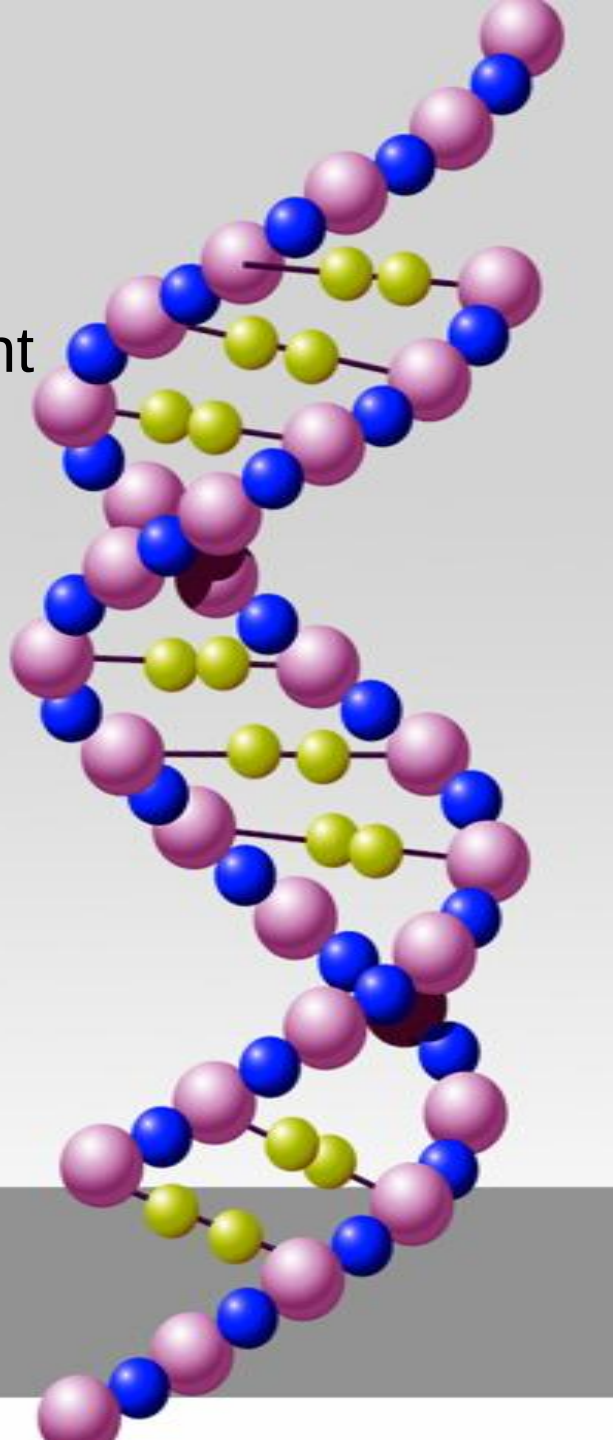
Corrada MM, Kawas CH, Hallfrisch J, Muller D, Brookmeyer R. Reduced risk of Alzheimer's disease with high folate intake: The Baltimore Longitudinal Study of Aging. *Alzheimer's & dementia : the journal of the*

Histone Tail modifications (HDACi) in Pre-clinical studies

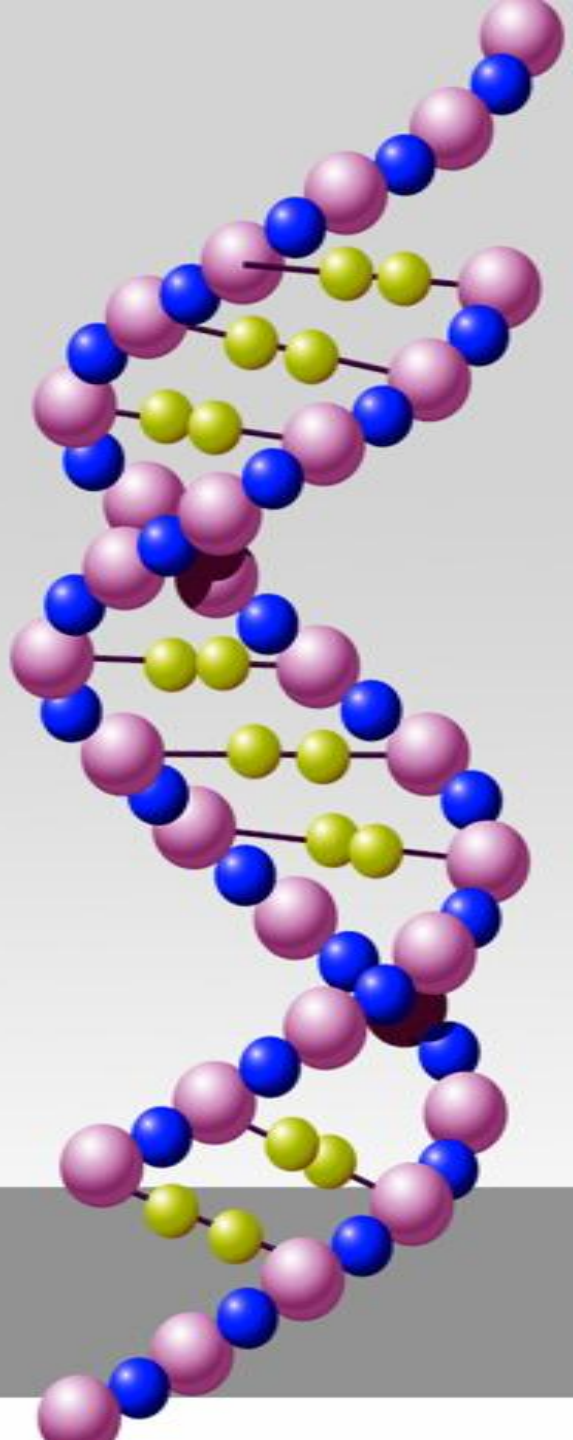
Reference	Compound	Experimental Model	Results
Fischer et al., 2010	Sodium butyrate	Transgenic AD mice (CK-p25)	4 week intra-peritoneal administration improved learning and memory
Francis et al., 2009	Trichostatin A	Transgenic AD mice (APP/PS1)	Acute treatment prior to fear conditioning training rescued hippocampal H4 acetylation levels and contextual freezing performances
Kilgore et al., 2010	Sodium butyrate, sodium valproate, or vorinostat	Transgenic AD mice (APP/PS1)	2–3 weeks intra-peritoneal injection reversed contextual memory deficits
Zhang and Schluesener, 2013	MS-275 (entinostat)	Transgenic AD mice (APP/PS1)	10 days oral administration ameliorated neuroinflammation and cerebral amyloidosis and improved behavior

CASE # 2

Master B is a 4 year old who has been brought to you, by his worried parents for ‘speech delay’. You find that the child is very restless, has no eye contact, and repeatedly plays with the paperweight on your desk. Further, on conversing with him, he repeats whatever you say.



- Clinical Diagnosis?
- Other details?
- How will you manage him?



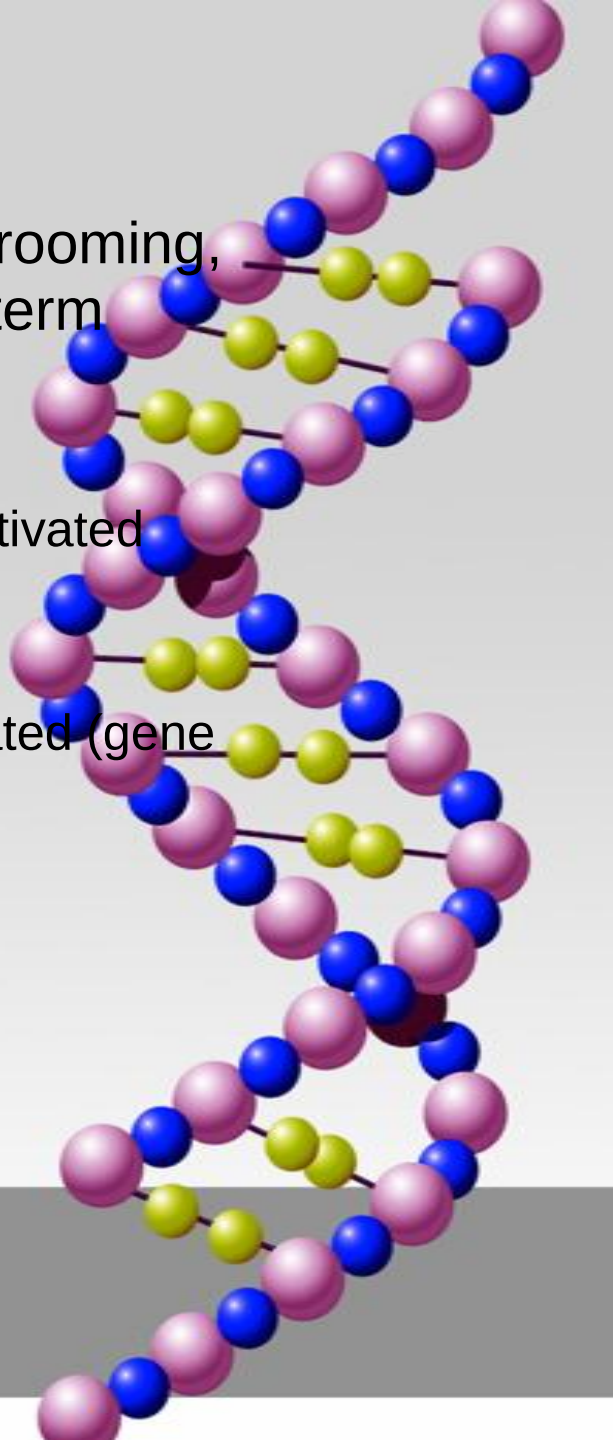
Single nutrients

A pup of a different color.

- Study by Dr. Jirtle (2006) concerning epigenetic changes by dietary supplements
  - Epigenetic regulation of agouti gene
  - pregnant mothers diet
    - Vitamin B12, folic acid, choline and betaine.
    - brown coat color in offspring
    - inherited by next generation
  - pregnant mother diet
    - BPA
    - yellow coat color in offspring

Supplementation of maternal diet with genistein and other compounds induced alterations in DNA methylation that were reflected in offspring coat color changes. Environ Health Perspect. 2006 March; 114(3): A160–A167.

- Study by Dr. Moshe Szyf (2004) showed that grooming, nursing, and licking of a rat pup can affect long-term behavior of offspring .
  - Rats pups receiving high nurturing
    - methyl groups removed by nurturing signals, activated GR receptor gene-calm adults
  - Rats pups receiving low nurturing
    - methyl groups remain attached to DNA, inactivated (gene silenced) GR receptor gene-anxious adults
- Hippocampus in pups
  - Production of GR protein (glucocorticoid receptor)
  - Cortisol (stress hormone) binds to these receptors
- Affects more than just GR gene



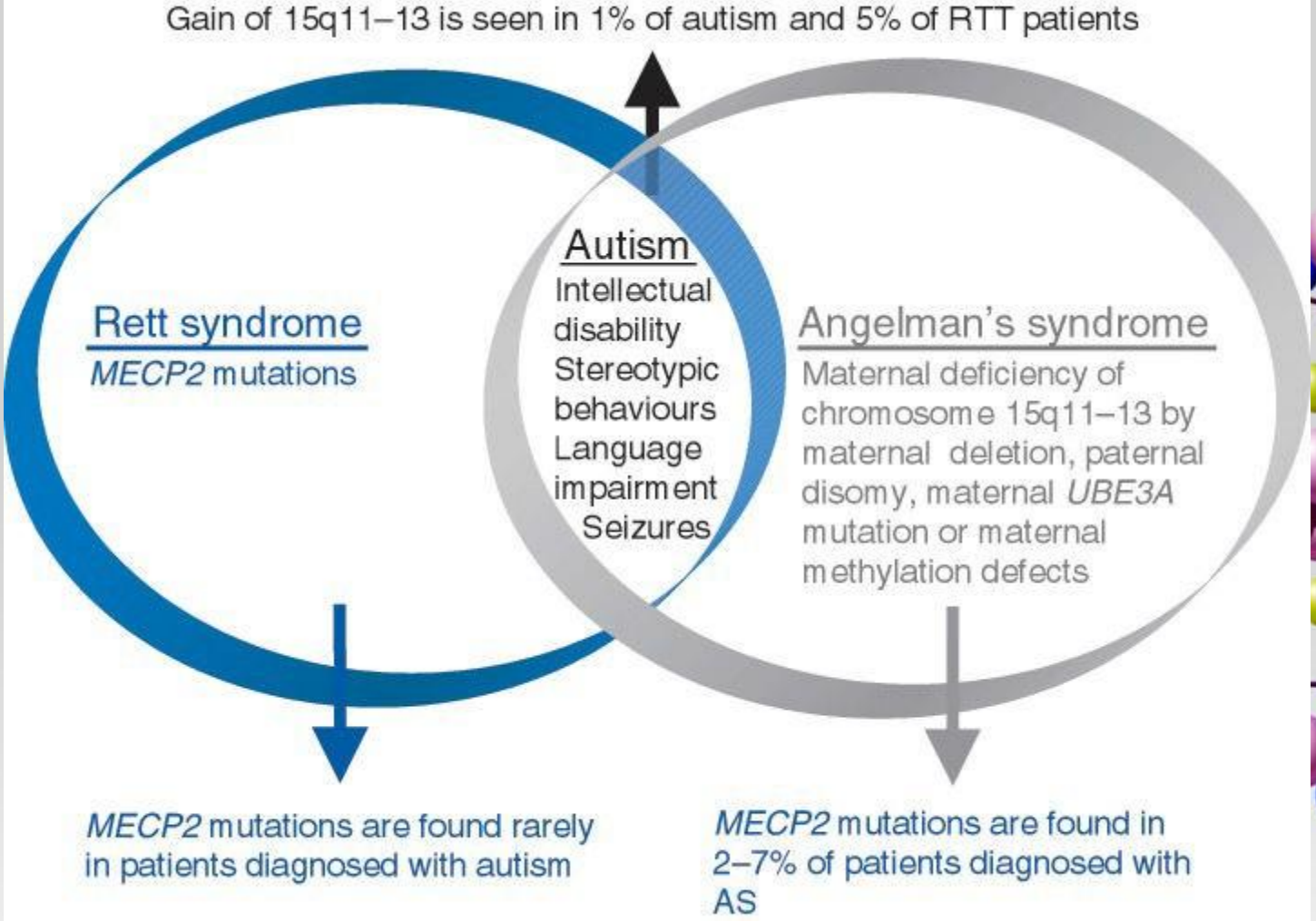
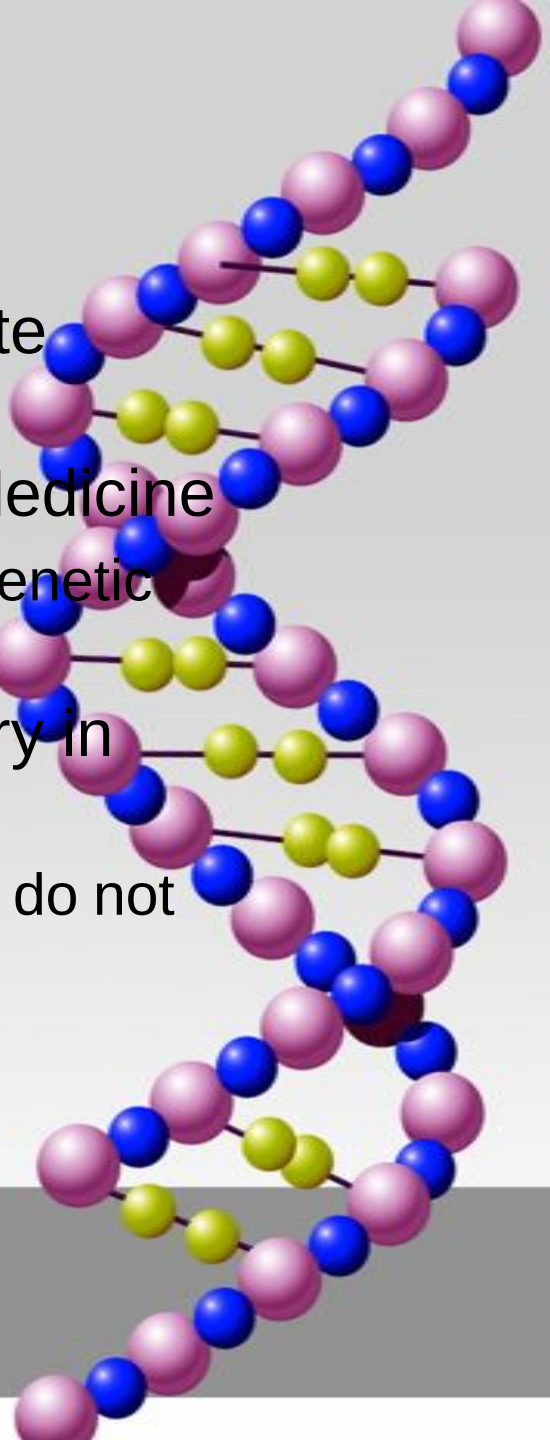


Fig. 1. The overlapping disorders, phenotypes and genotypes regulated by MECP2/MeCP2 through epigenetic mechanisms. AS, Angelman's syndrome; RTT, Rett syndrome.

Future Studies

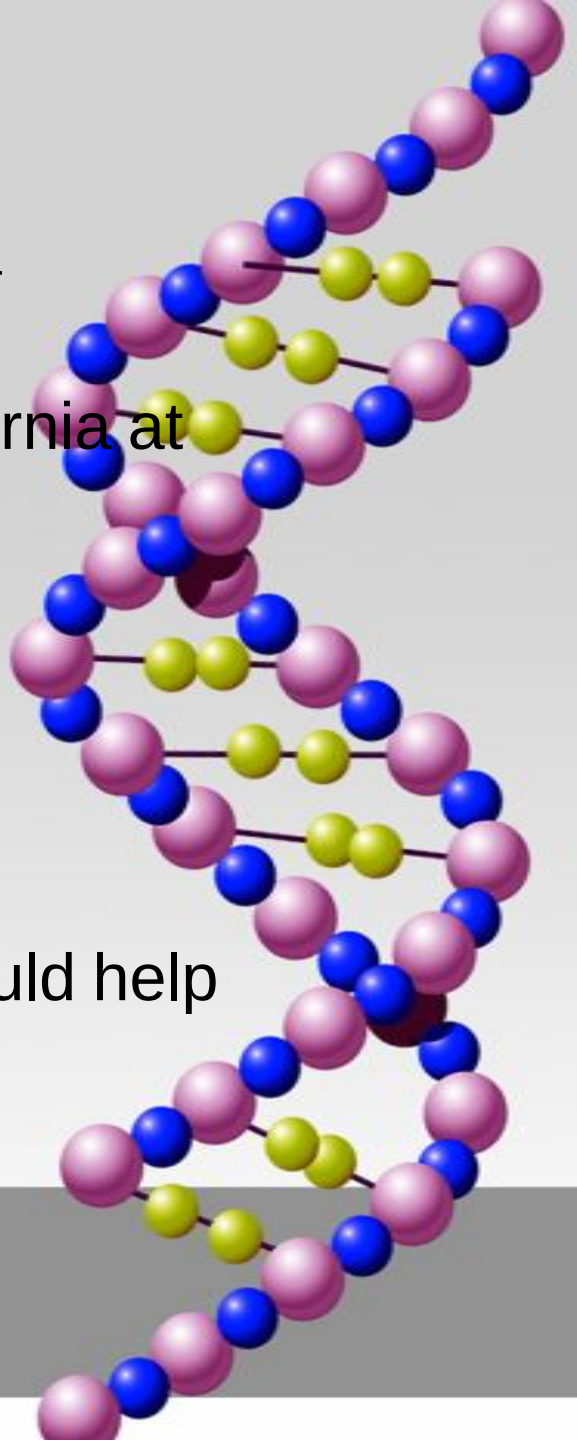
- Recent attention of epigenetics in ASD
- Autism Speaks: $3.6 million to investigate environmental risk factors for autism
- Dr. Yong-hui Jiang at Baylor College of Medicine
  - how folic acid supplementation affects epigenetic modulation of SHANK3 protein expression
- Dr. Robert Plomin at Institute of Psychiatry in London
  - Looking at epigenetic markers in twins who do not share diagnosis of autism.



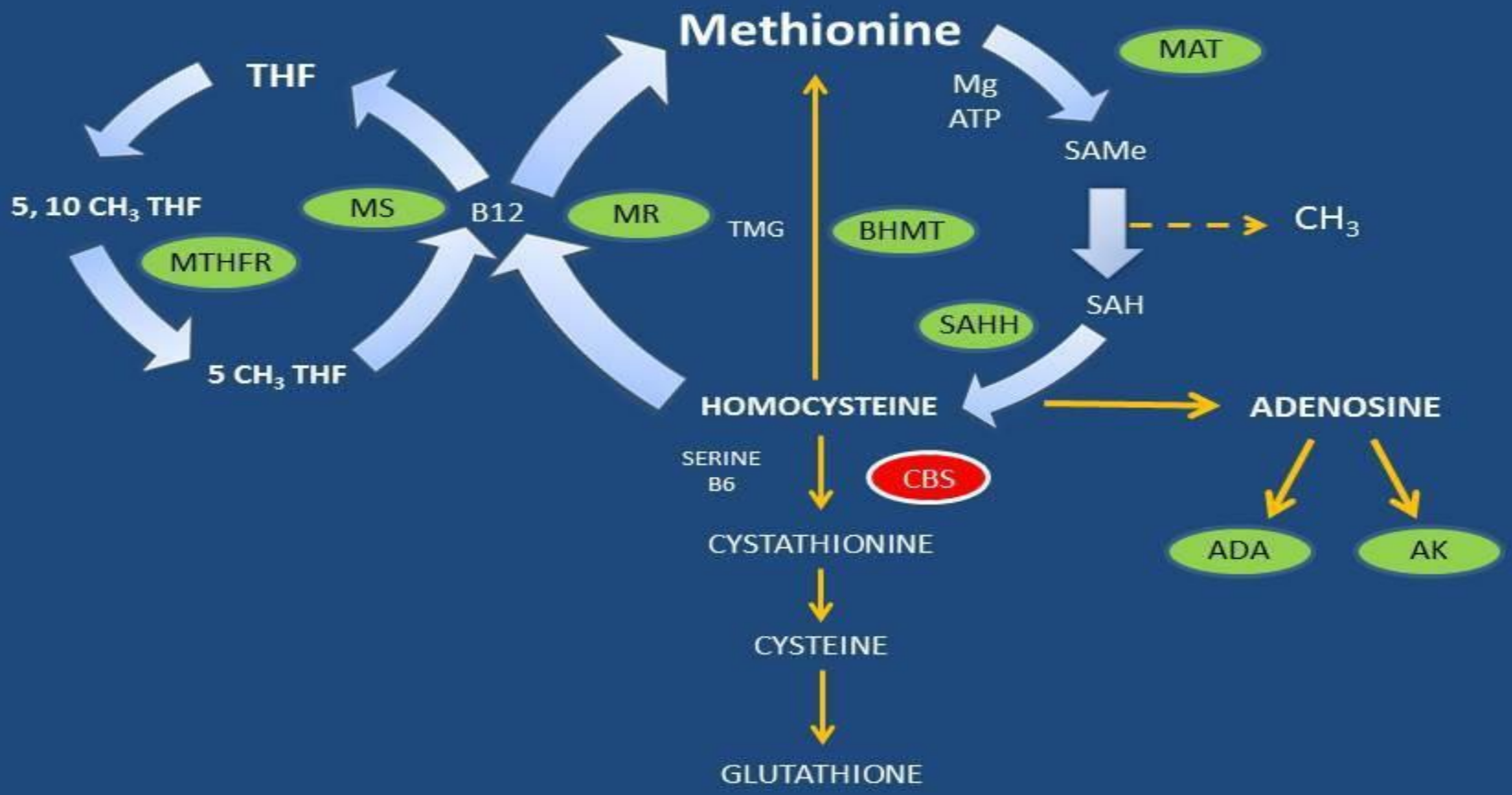
Future Studies (cont.)

- Dr. Emile Rissman at University of Virginia
  - BPA (Bisphenol A)
- Dr. Bruce Hammock at University of California at Davis
  - Vitamin D levels
    - lack of Vitamin D could influence brain development and function

- It's too early to speculate on treatment for epigenetic factors, but mouse models should help evaluate treatment. **Aripiprazole shows promise**.



Methylation Cycle Enzymes

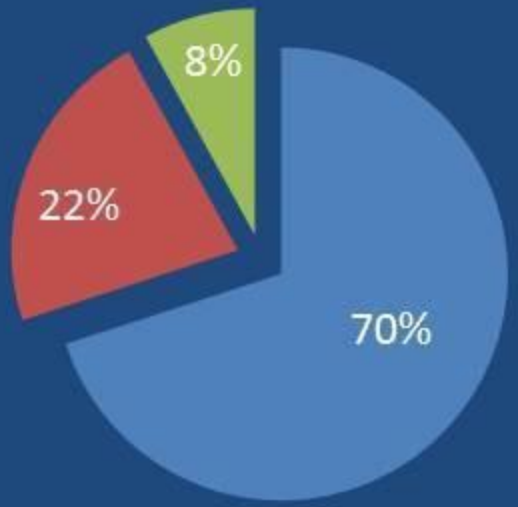


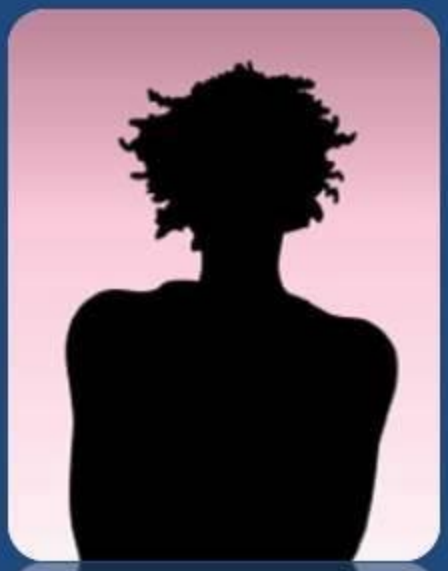
Methylation Disorders – Two Types

UNDERmethylation

OVERmethylation

Incidence of Methylation Disorders in the General Population





Normal Methylation = 70%

Under Methylation = 22%

Over Methylation = 8%

Incidence of UNDERmethylation

Autism-Spectrum	98%
Antisocial Personality Disorder	95%
Schizoaffective Disorder	90%
Oppositional-Defiance	85%
Anorexia	82%
Depression	38%

Incidence of OVERmethylation

Panic/Anxiety Attacks	64%
Paranoid Schizophrenia	52%
ADHD	28%
Behavior Disorders	23%
Depression	18%

Under Methylation: Symptoms & Traits

Partial List

- Very strong willed; oppositional to authority
- Seasonal inhalant allergies
- Competitive in sports or games
- Calm demeanor but high inner tension
- High fluidity (tears, saliva, etc.)
- OCD tendencies; controlling behavior
- Good response to SSRI's
- High libido

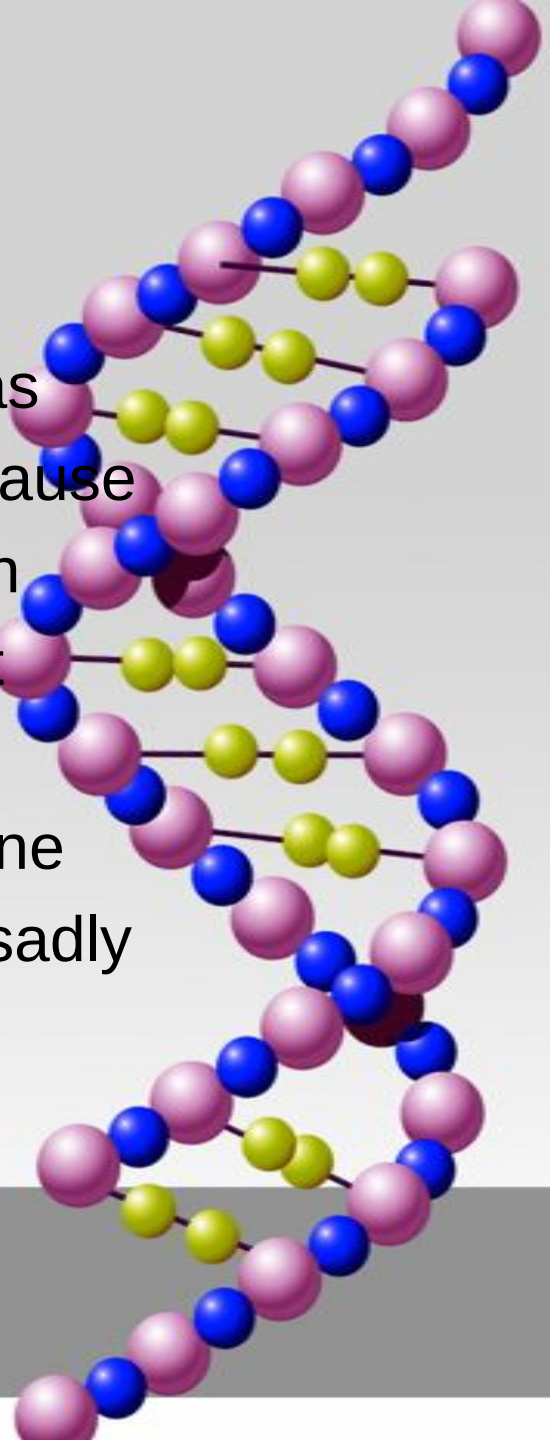
Over Methylation: Symptoms & Traits

Partial List

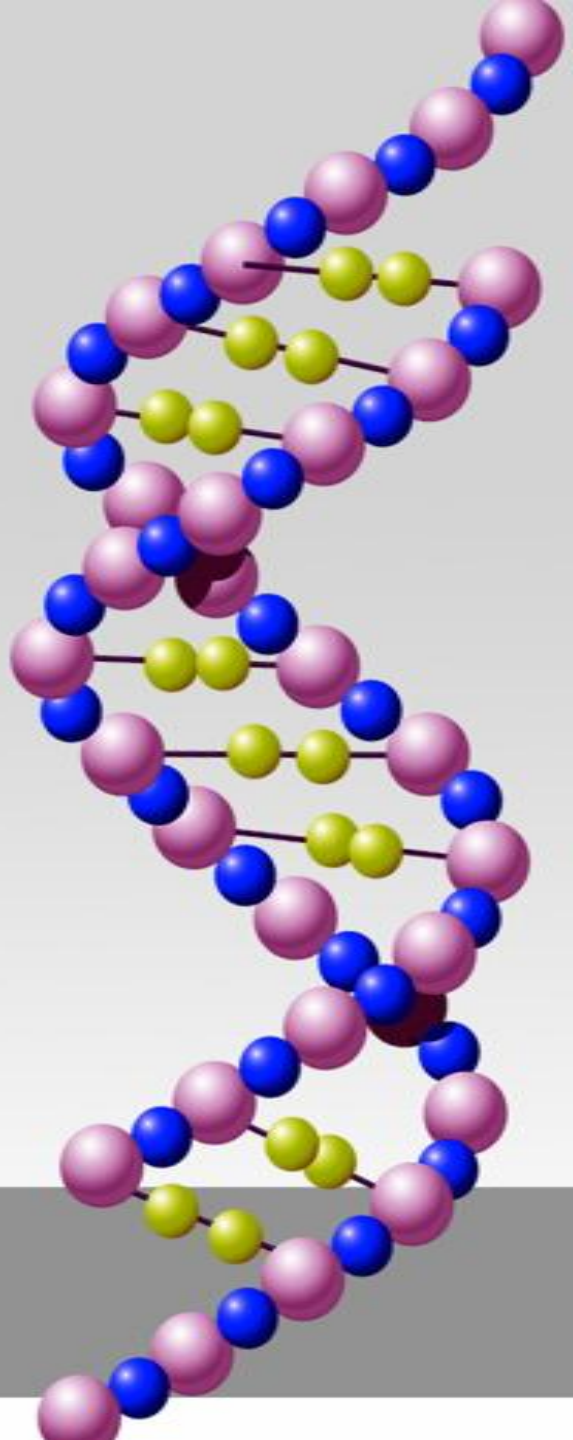
- High anxiety; panic tendency
- Hyperactivity; nervous legs; pacing
- Sleep disorder
- Low libido
- Absence of seasonal allergies
- Food, chemical sensitivities
- Dry eyes and mouth
- Excellent socialization, empathy
- Non-competitiveness in sports, academics
- Adverse reaction to SSRIs, anti-histamines

CASE # 3

Ms. C is a 29 year old married lady who was brought to the hospital by her husband because she had become increasingly irritable, often abusive, and very suspicious. She wouldn't let her children go to school out of fear that someone will harm them. She often sat alone and muttered to herself. Her self care had sadly deteriorated.

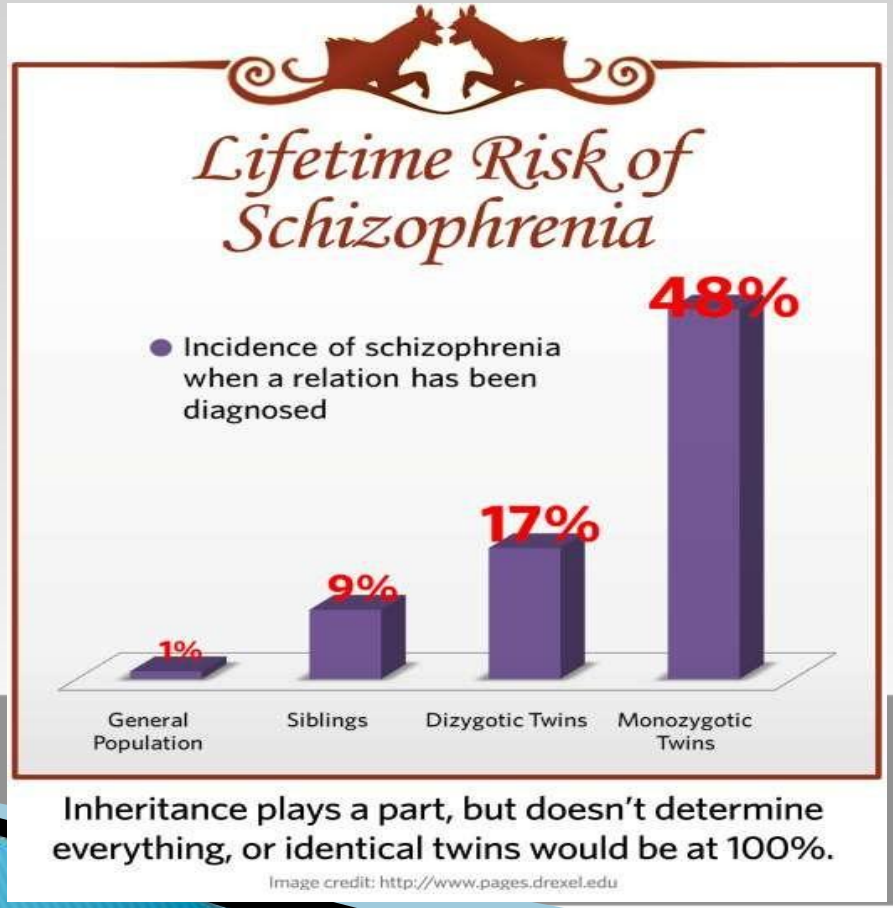


- Clinical Diagnosis?
- Will you advise any tests?
- How will you manage her?

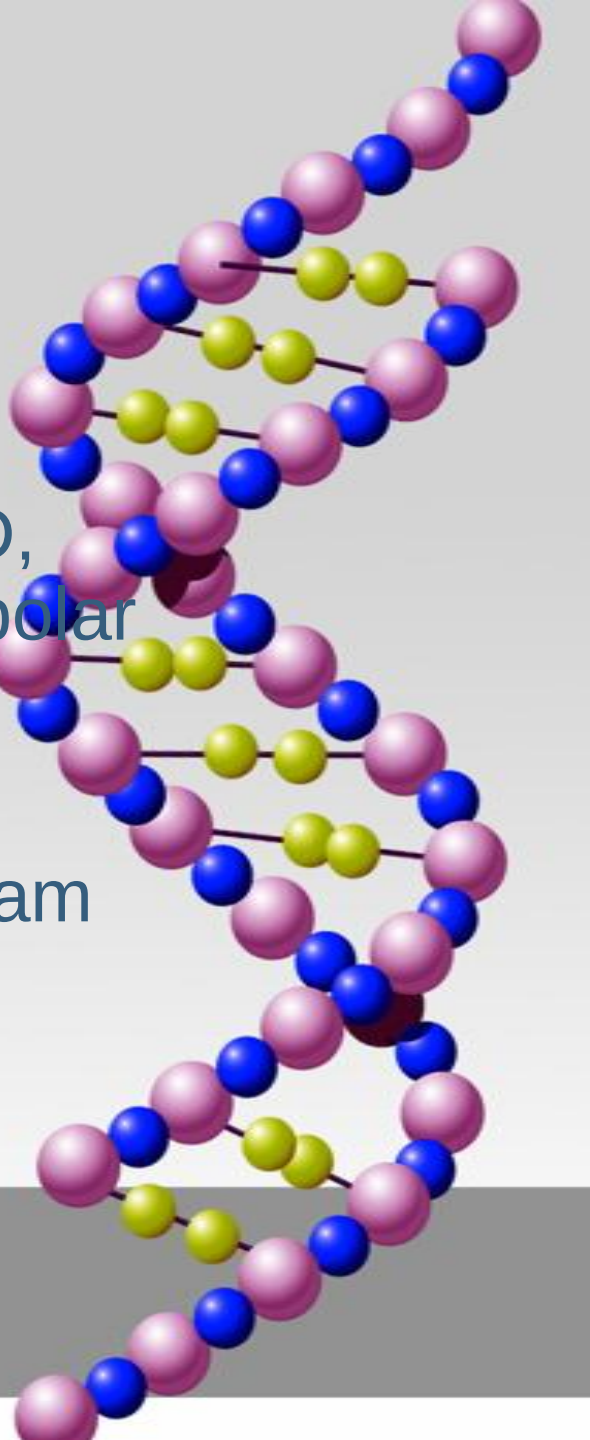


Epigenetic Factors Can Explain Lower Than 100% Transmission of Schizophrenia in Identical Twins

- Identical twin studies show a schizophrenia concordance rate of 48–60%.
- If schizophrenia were a genetic disorder the concordance rate should be 100% .



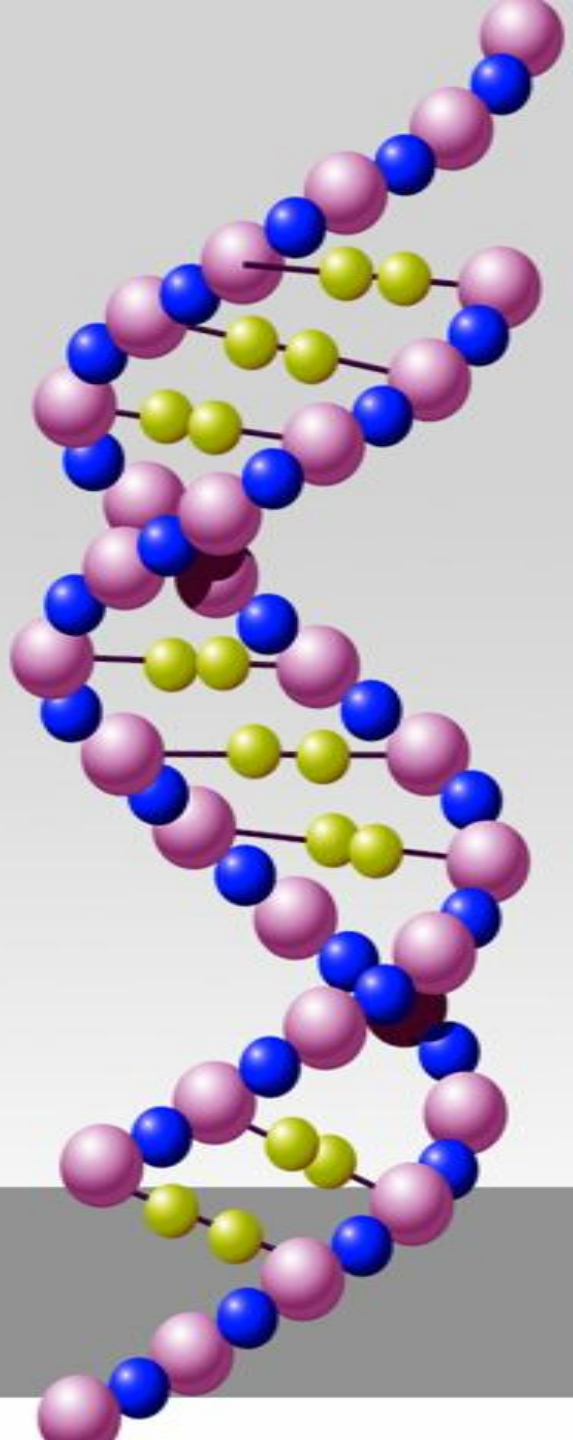
Walsh Research Institute
Naperville, Illinois



- Expertise in behavior disorders, ADHD, autism, depression, schizophrenia, bipolar disorder, and Alzheimer's
- International Physician-Training Program
- Research

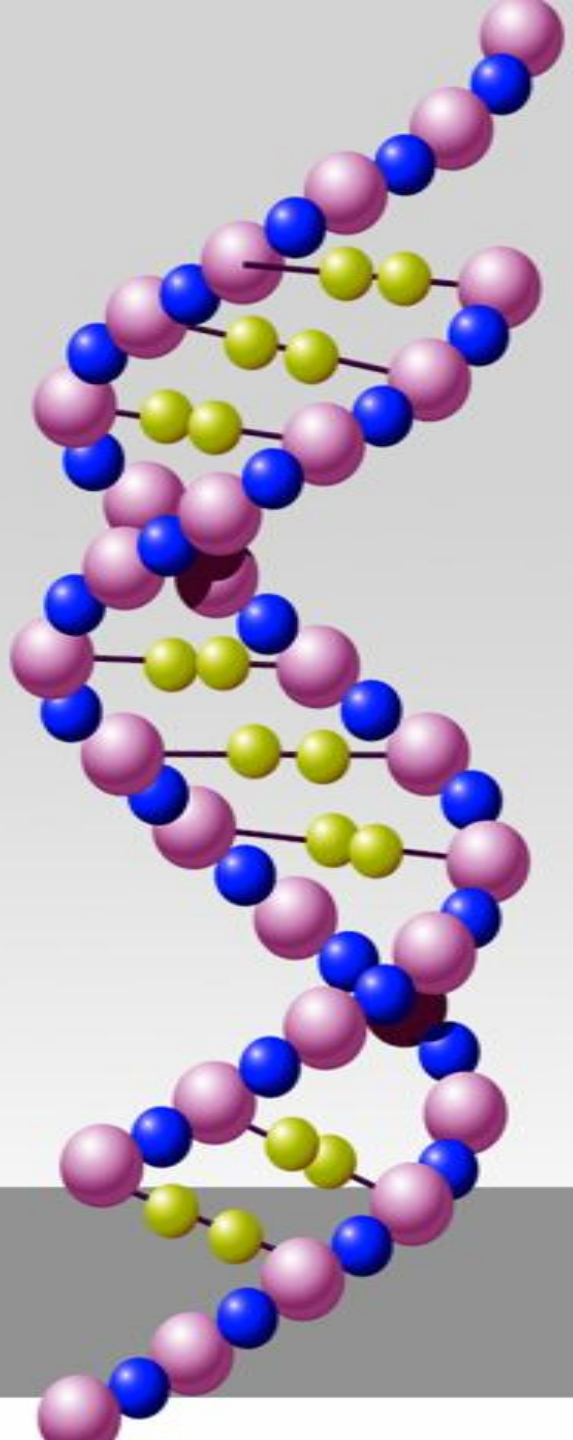
Massive Chemistry Database

- Laboratory testing of 30,000 mental health patients and controls.
- More than 3 million chemical test results for patients diagnosed with schizophrenia, depression, ADHD, depression, autism, etc.
- More than 2 million medical history factors for these populations.

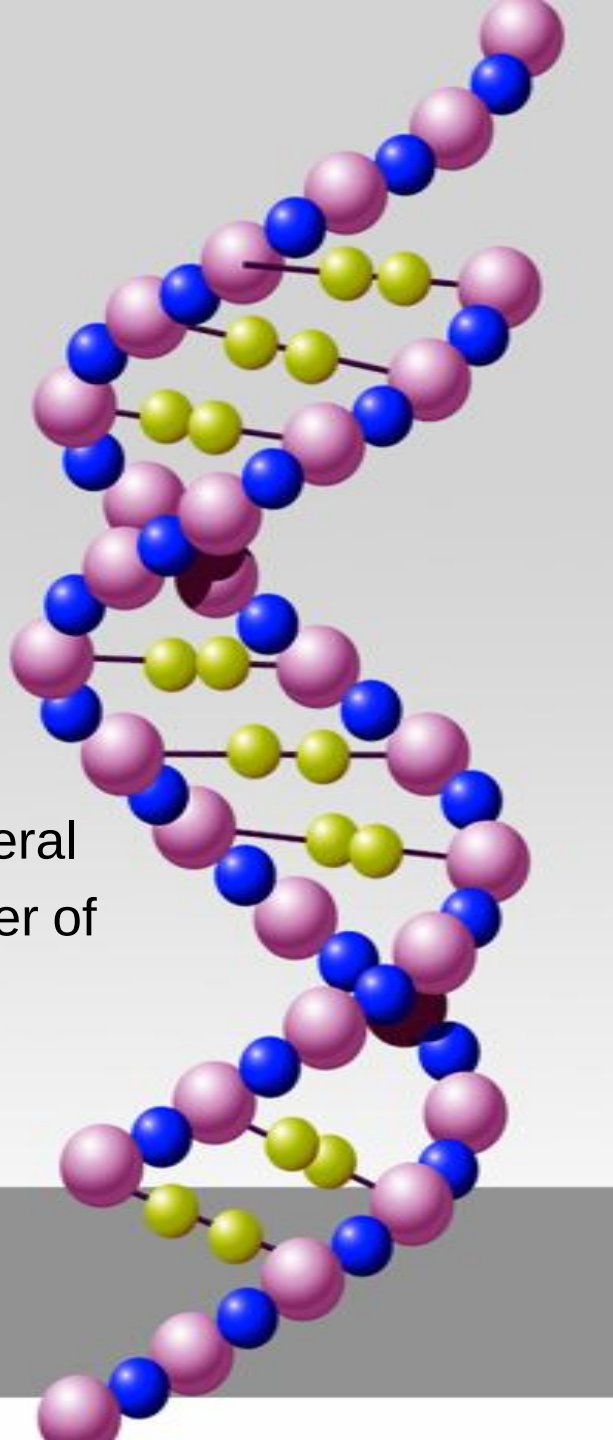


Single Nucleotide Polymorphisms

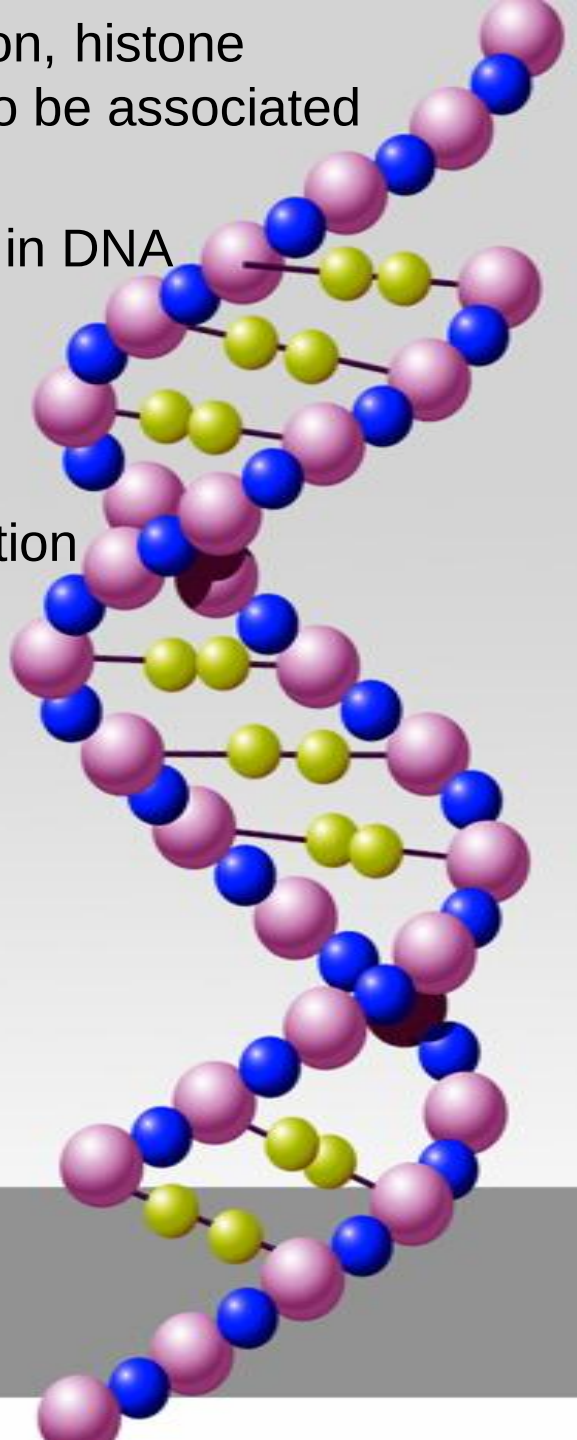
- We share 99.9% of our DNA with everyone of the same gender -- It's the 0.1% that makes us different.
- SNPs are gene mutations that developed over thousands of years.
- More than 10 million SNPs have been identified in the human genome. Most humans have more than 1,000 SNPs.



- Recently, it was shown that levels of VLDLR mRNA in peripheral lymphocytes in drug-naïve patients with schizophrenia were significantly lower than those of controls, indicating decreased expression of VLDLR in these cells in such patients (Suzuki et al., 2008). The authors of this study suggested that peripheral VLDLR mRNA may serve as a reliable biomarker of schizophrenia



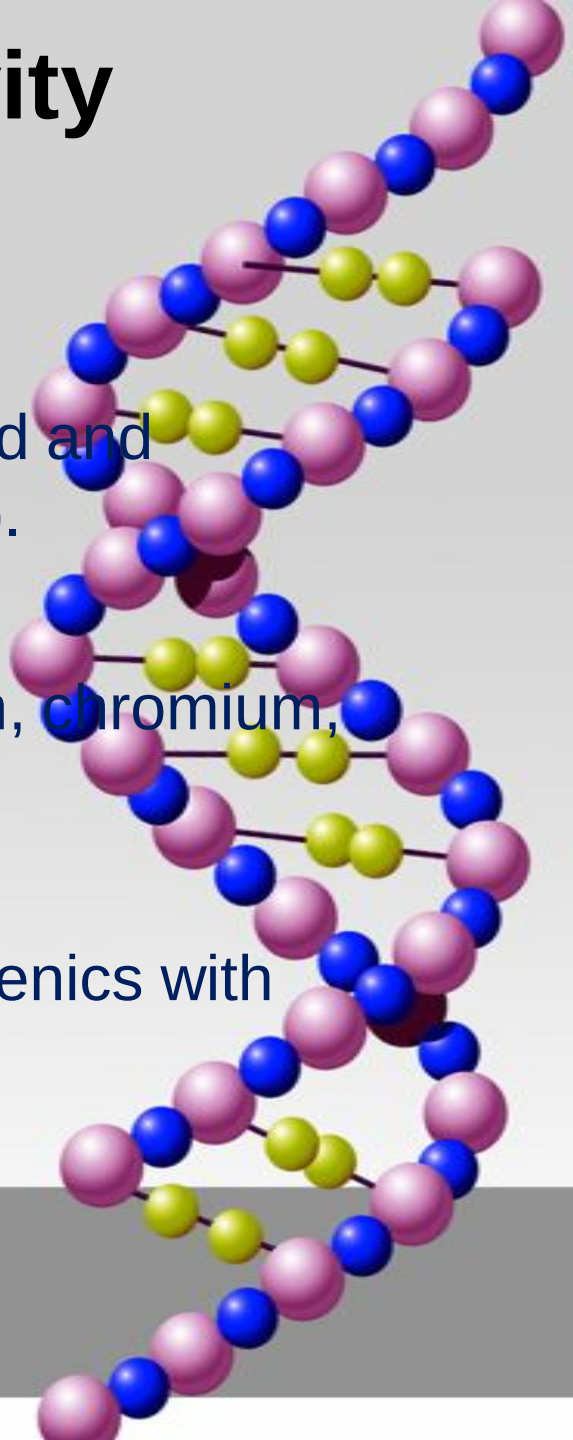
- Epimutations in the form of aberrant DNA methylation, histone modifications and miRNA expression are reported to be associated with SCZ.
- Differential global as well as gene-specific changes in DNA methylation have been reported in SCZ with contradictions.
- Histone modifications in few candidate genes may contribute to the pathogenesis of prefrontal dysfunction in SCZ.
- Increased expression of histone methyltransferases has reported to being a significant predictor for diagnosis of SCZ.



Excessive Dopamine Activity

Nutrient Therapy Approach

- Support acetylation of histones with folic acid and niacinamide (powerful deacetylase inhibitors).
- Augmenting nutrients DMAE, zinc, selenium, chromium, Vitamins B-6, B-12, C, D, E.
- Especially promising for paranoid schizophrenics with excessive dopamine activity.

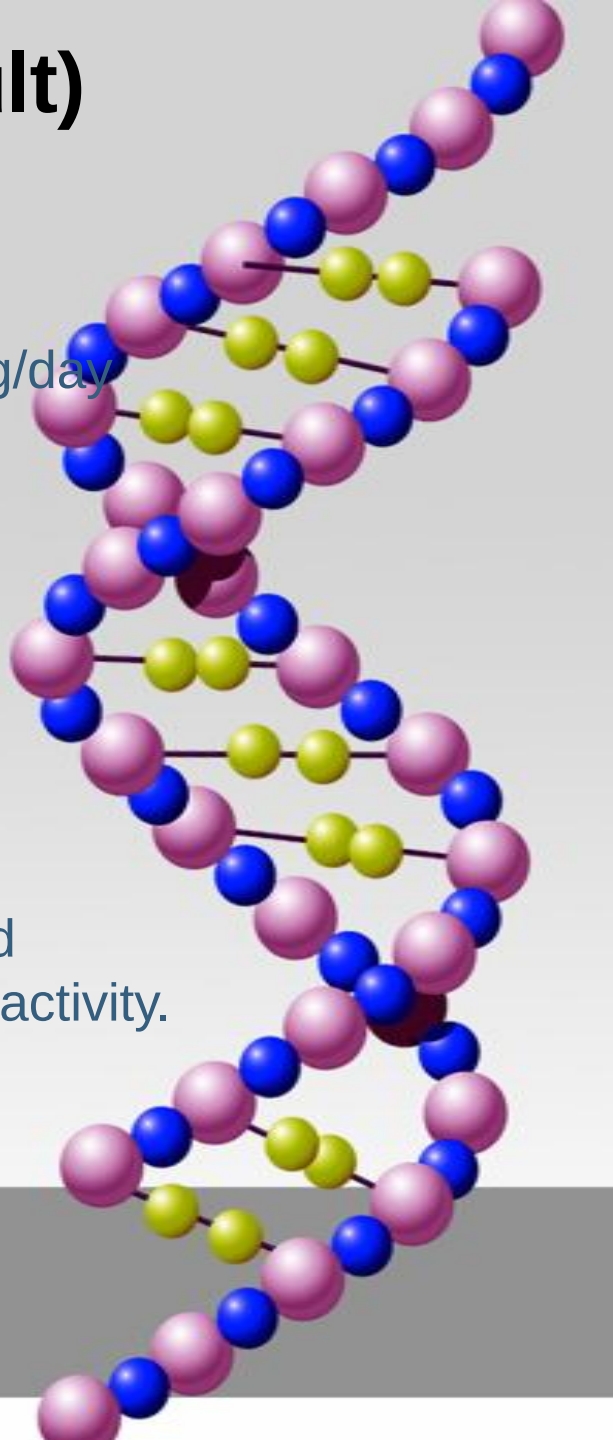


Treatment Example (160 lb adult)
Excessive Dopamine Activity

- Folic Acid, 2400 mcg/day, and Niacinamide, 1000 mg/day to support acetylation of histones and promote reuptake of dopamine.

- Augmenting nutrients DMAE, zinc, manganese, selenium, chromium, Vitamins B-6, B-12, C, D, E.

- Especially promising for paranoid schizophrenics and anxiety/depression patients with excessive dopamine activity.

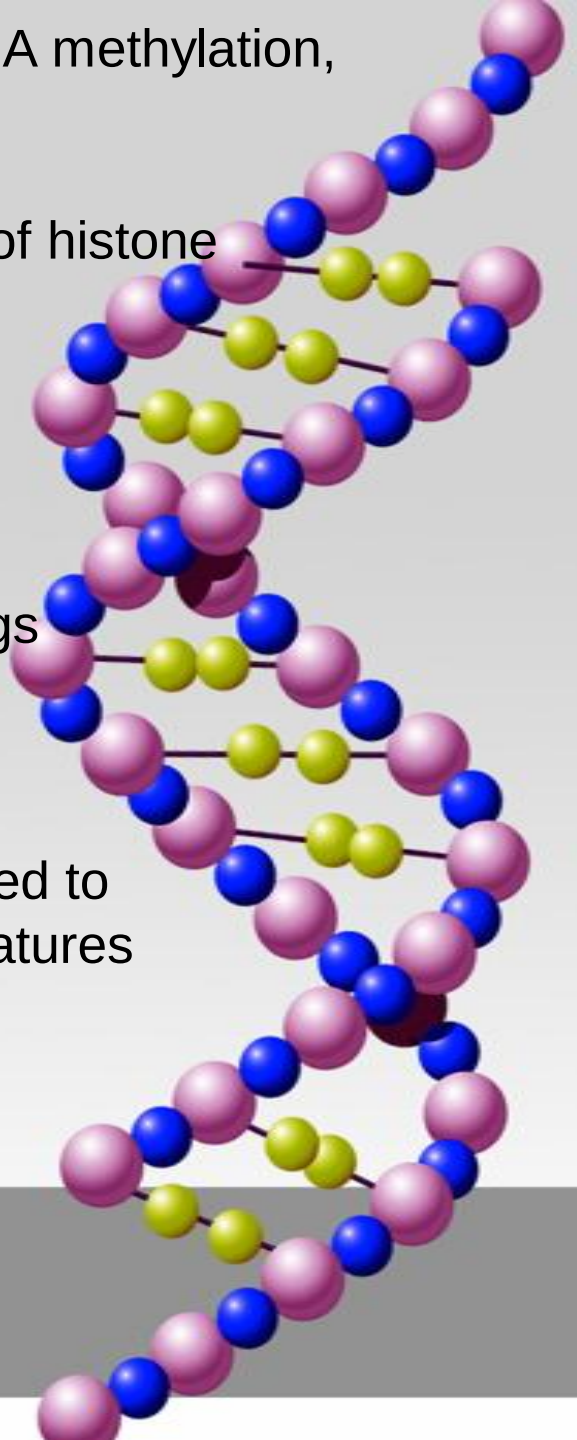


Haloperidol has been shown to induce changes in DNA methylation, histone modifications and miRNA expressions.

Clozapine has also been reported to alter expression of histone modifier genes, gene-specific methylation and miRNA expressions.

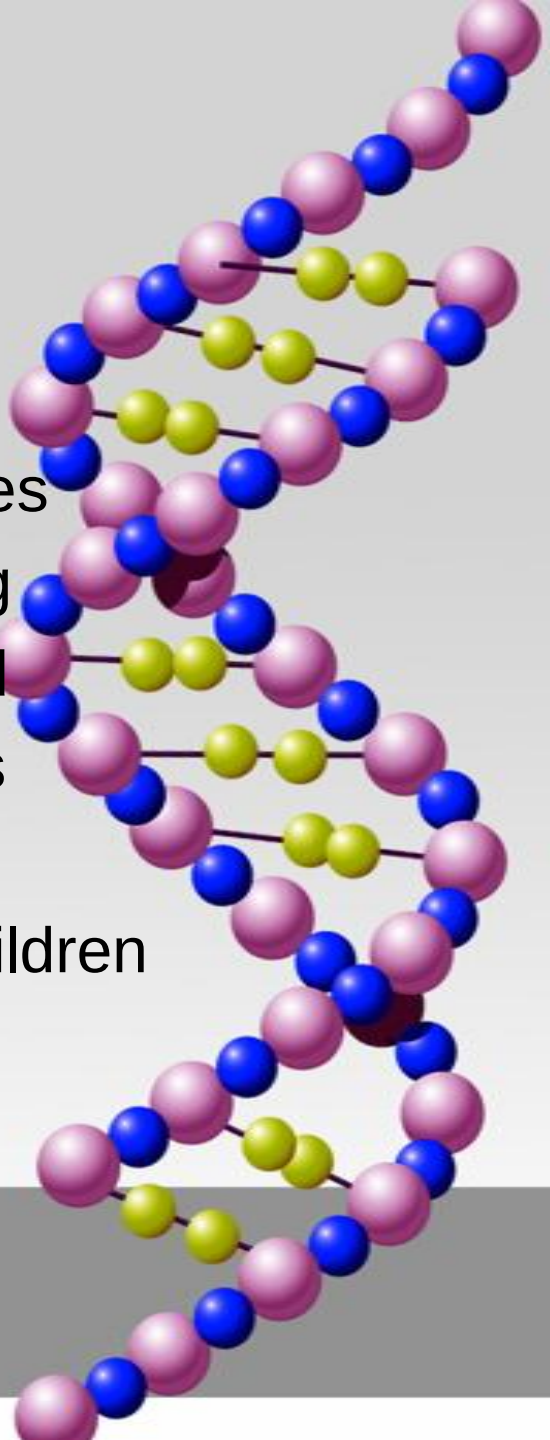
Similar observations have been made with **risperidone, olanzapine and quetiapine**, indicating epigenetic effects of these antipsychotic drugs

Valproic Acid is a histone deacetylator. Often it is added to anti-psychotics and seems to play a role in affective features and through BDNF



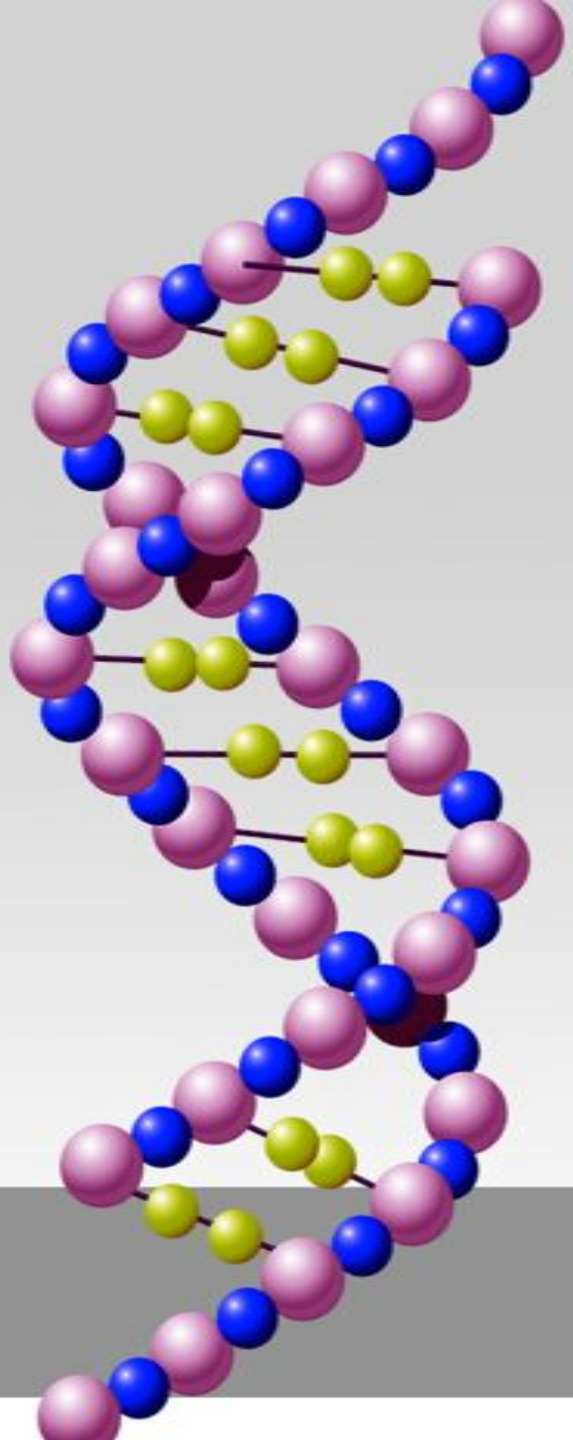
CASE # 4

Ms. D is a 30 year old working woman who has approached you because she is having frequent problems at work due to the mistakes she is making. She does not feel like working at all; in fact has even started getting irritated by her children nowadays. She hardly sleeps and eats only for survival. She has often contemplated suicide, but thoughts of her children prevent her.



- Clinical Diagnosis?

- How will you manage her?

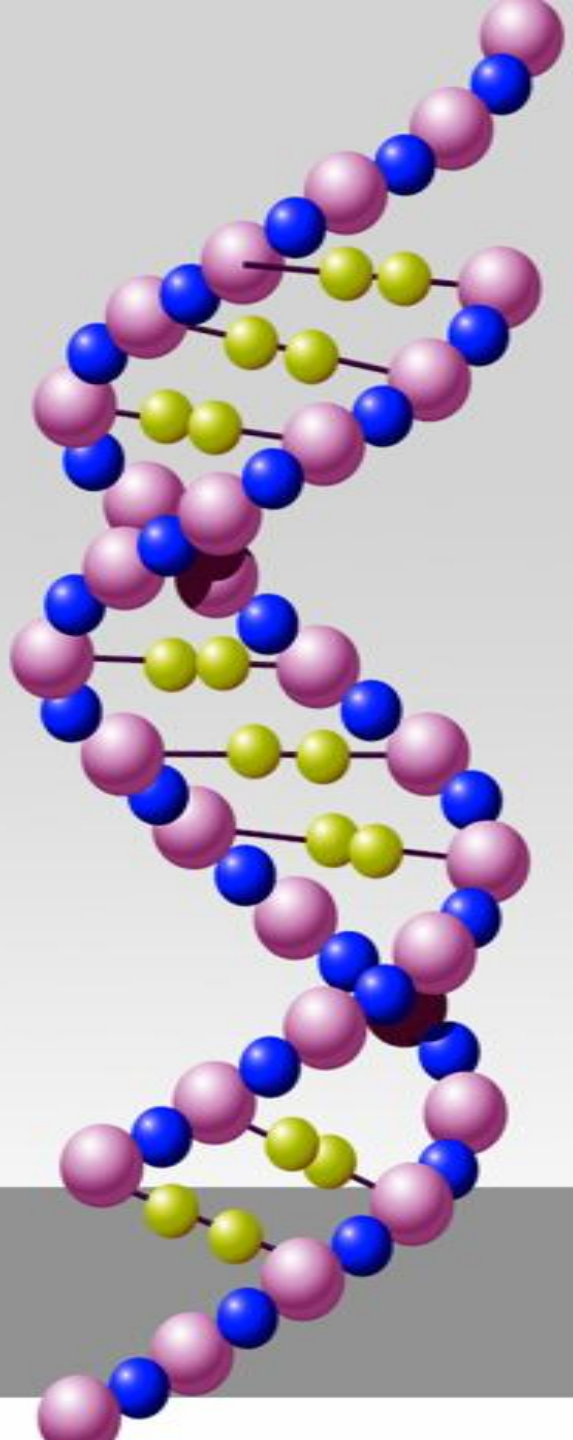


Neurotrophic Hypothesis of Depression

Loss of Brain-Derived Neurotrophic Factor (BDNF) contributes to hippocampal atrophy that underlie aspects of depression.

Antidepressants mediate therapeutic effects by increasing expression of neurotrophic factors (BDNF) in this region.

DNA methyltransferase (DNMT) 3b expression, an enzyme that *de novo* methylates CpG islands, is increased in suicide completers compared to controls in frontopolar cortex

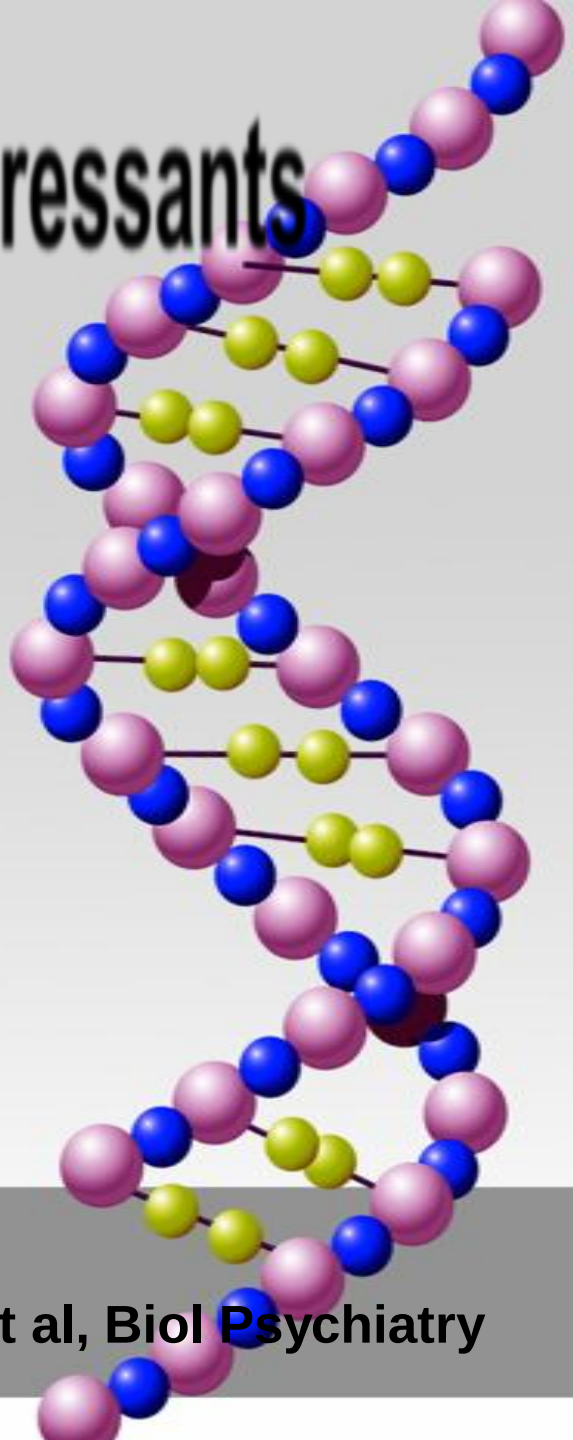


Neurotrophic Response to Antidepressants

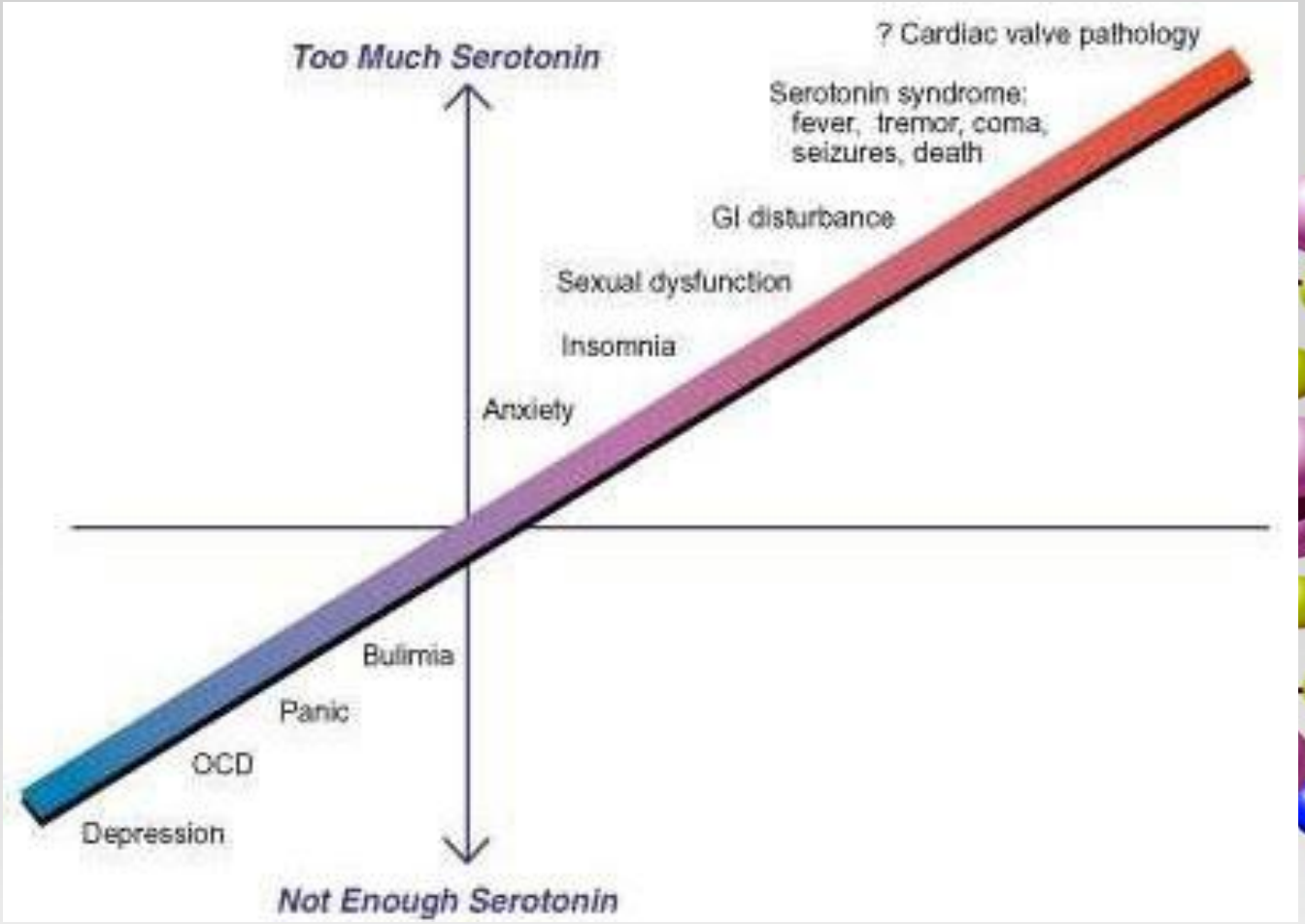
Increased BDNF in the DG

Increased survival and maturation

Enhanced synaptic plasticity of newborn granule cells



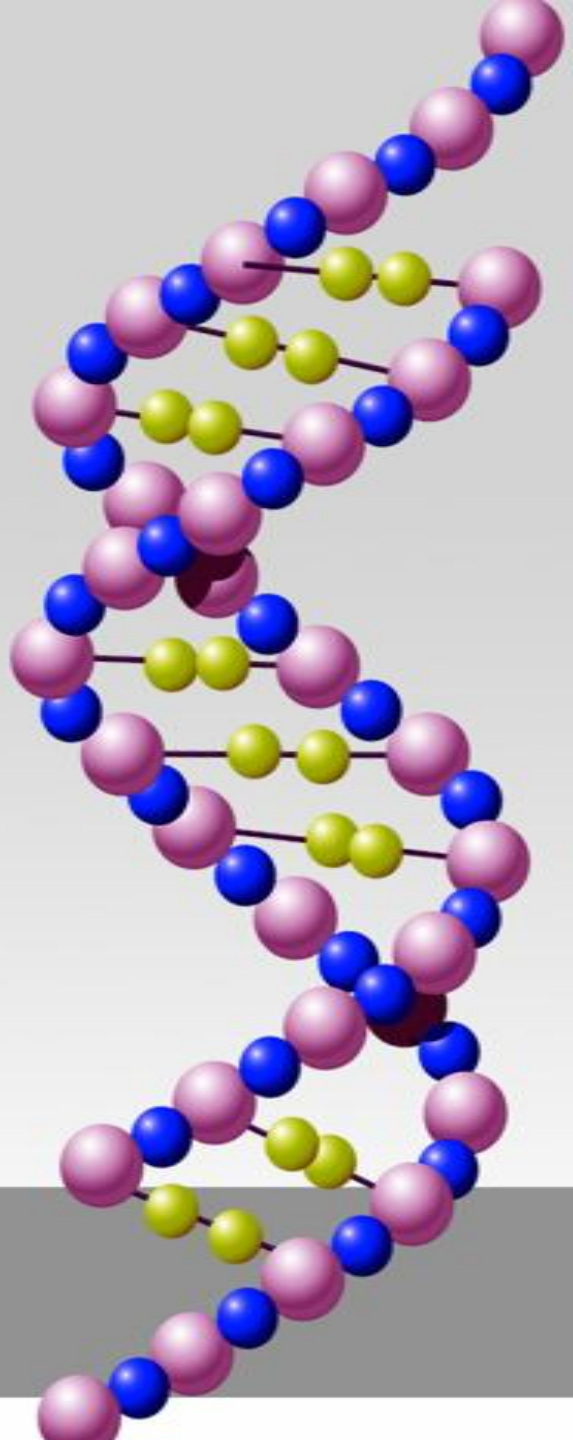
Adachi et al, Biol Psychiatry 2008



Stahl SM. Mechanism of action of serotonin selective reuptake inhibitors: serotonin receptors and pathways mediate therapeutic effects and side effects. J Affect Disord. 1998;51:215-235

Low Serotonin Activity
Nutrient Therapy Approach

- Enhance methylation and suppress acetylation of DNA and histones,
- SAMe and methionine act as serotonin reuptake inhibitors – reduced gene expression of SERT,
- Avoidance of folate supplements,
- Augmenting nutrients – zinc, serine, inositol, TMG, Cal/Mag, Vitamins A, B-6, C, D, E.



Treatment Example (160 lb adult)
Undermethylated Depression

SAMe, 400 mg/day (reduce SERT expression and inhibit serotonin reuptake)

- B-6, 200 mg/day and P5P, 50 mg/day (enhance synthesis of serotonin and glutathione)

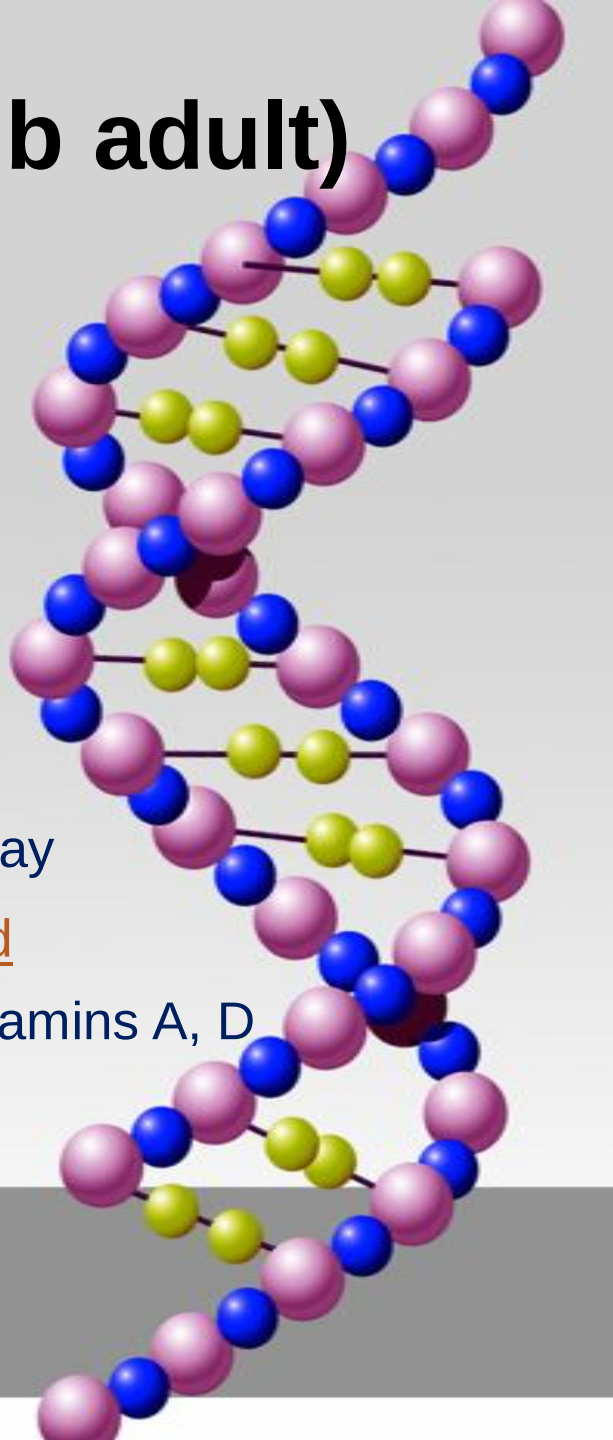
Antioxidant Support Vitamin C, 2000 mg/day

Vitamin E, 400 mg/day

Zinc (chelated form), 50 mg/day Selenium, 100 mcg/day

Augmenting Nutrients as indicated

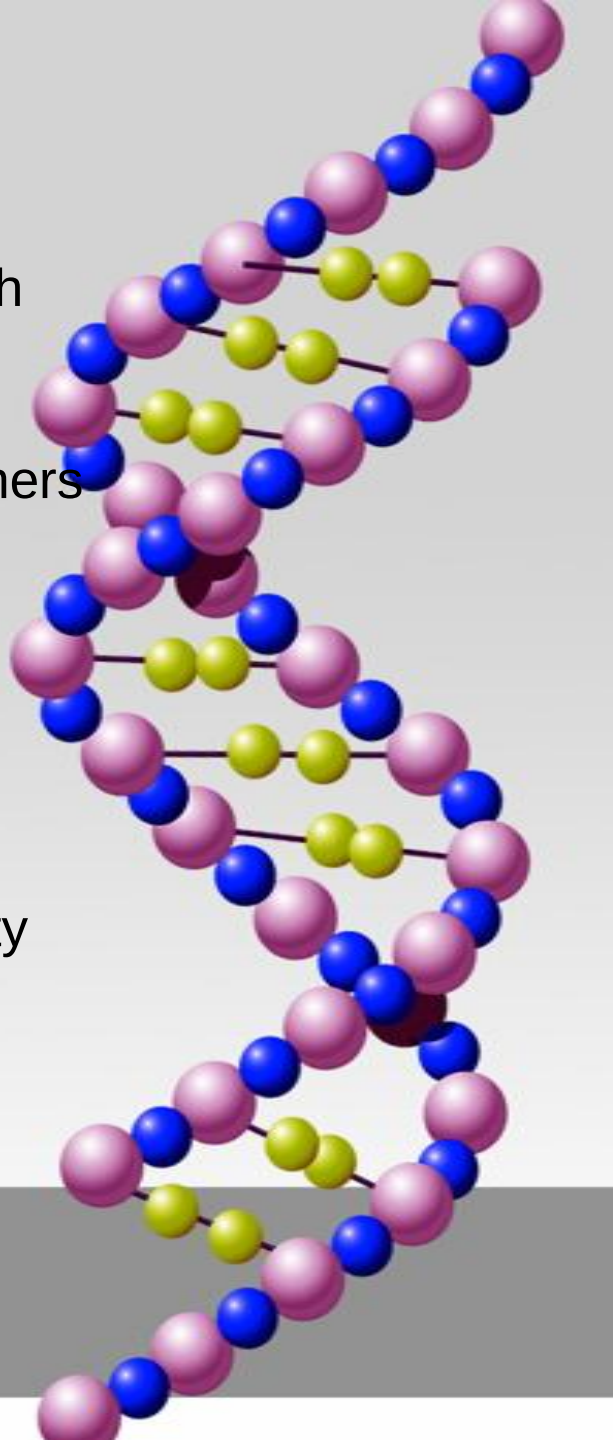
Biotin, Ca, Mg, Cr, TMG, Inositol, Serine, Vitamins A, D



Paroxetine—DNA Methylation—enzyme FKBP51-which is known to regulate the glucocorticoid receptor implicated in stress responses—is necessary for the efficacy of the antidepressant paroxetine. The researchers have now provided evidence that this drug can reduce the activity of DNMT1, a DNA methyltransferase that globally adds methyl groups throughout the genome

.

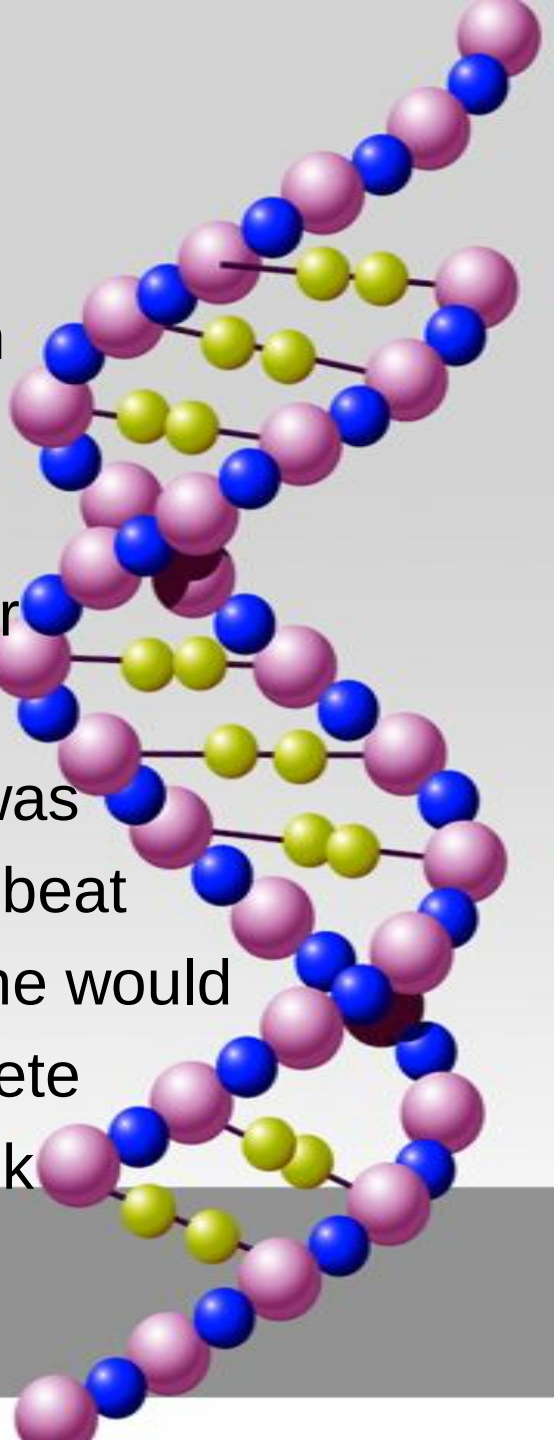
Adding paroxetine to mouse fibroblasts and primary astrocytes, the researchers observed decreased activity of DNMT1 that was FKBP51 dependent and increased expression of a gene, *BDNF*, that plays a role in the brain's ability to cope with stress.



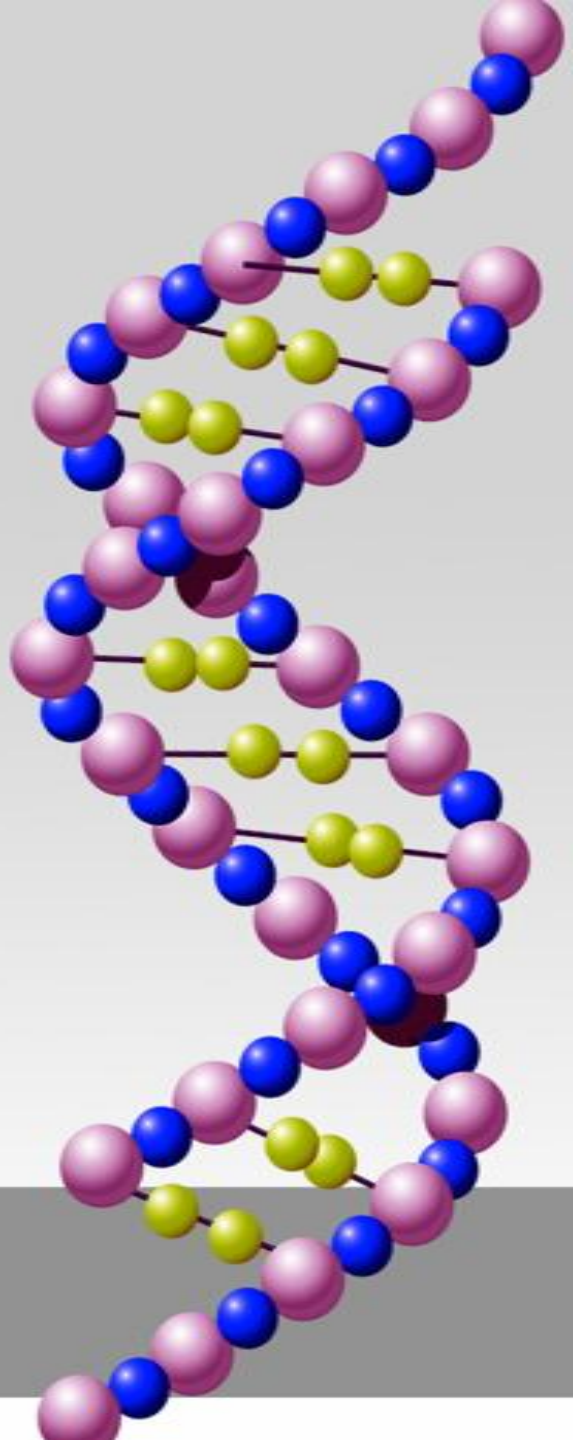
CASE # 5

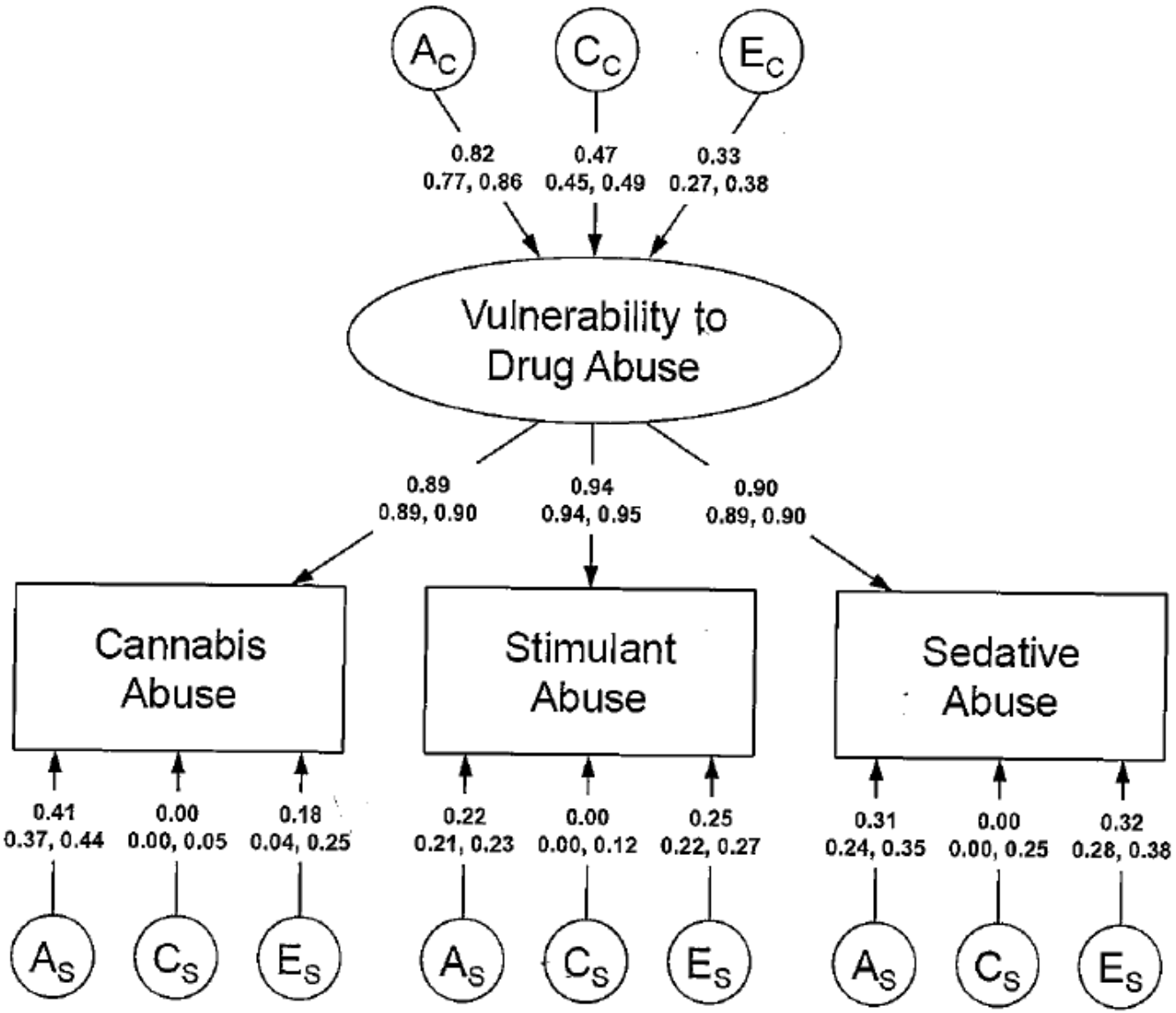
Master E , a 17 year old was brought by his mother for deaddiction. She had ‘caught’ him with his friends snorting coke and drinking. She was petrified, as she had divorced her husband because he was a drunk. She never allowed father and son to meet.

She was very busy earning for him, and he was thus at home with a punitive aunt, who often beat him black and blue. When he was younger, he would often cry himself to sleep. He only got complete relief, and felt calm when he had his first drink



What would you do for him?

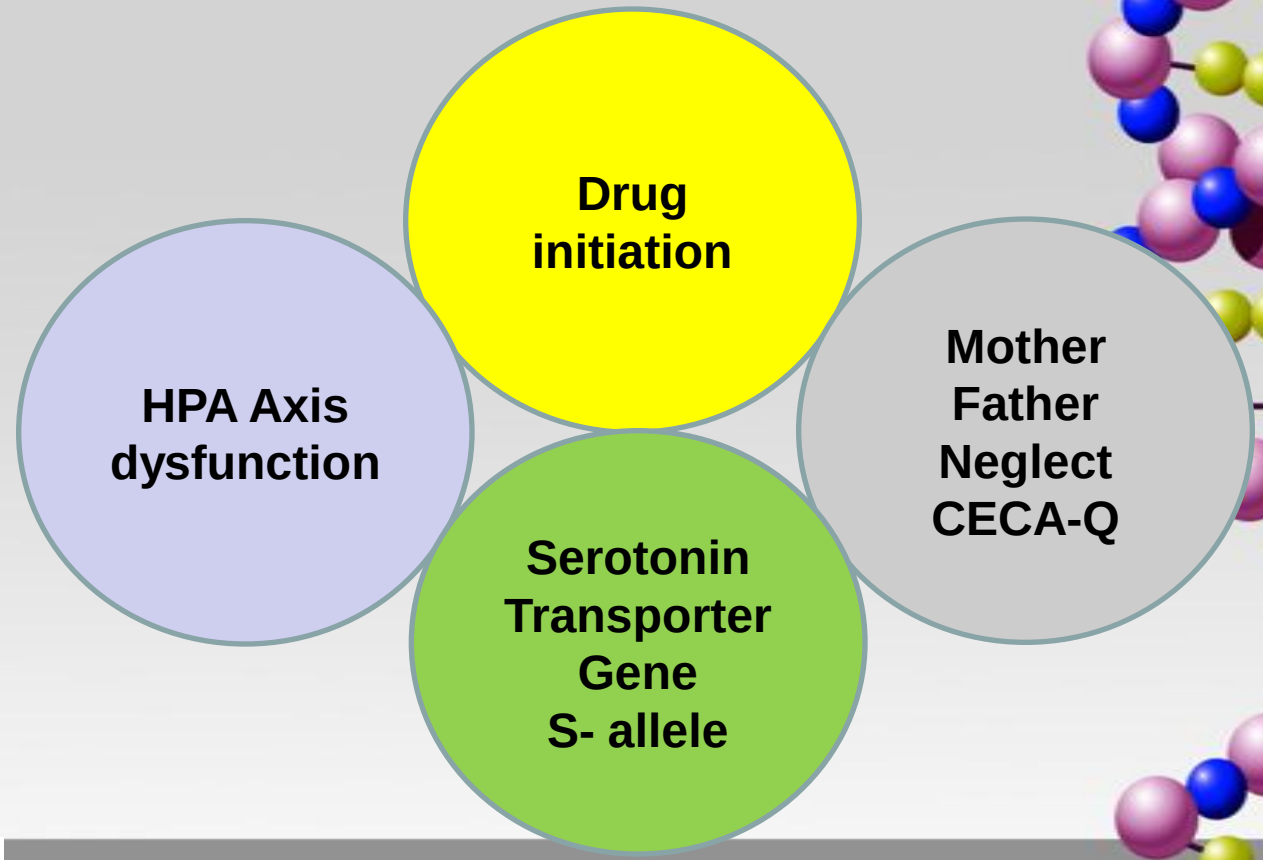




Am J Med Genet B Neuropsychiatr Genet.

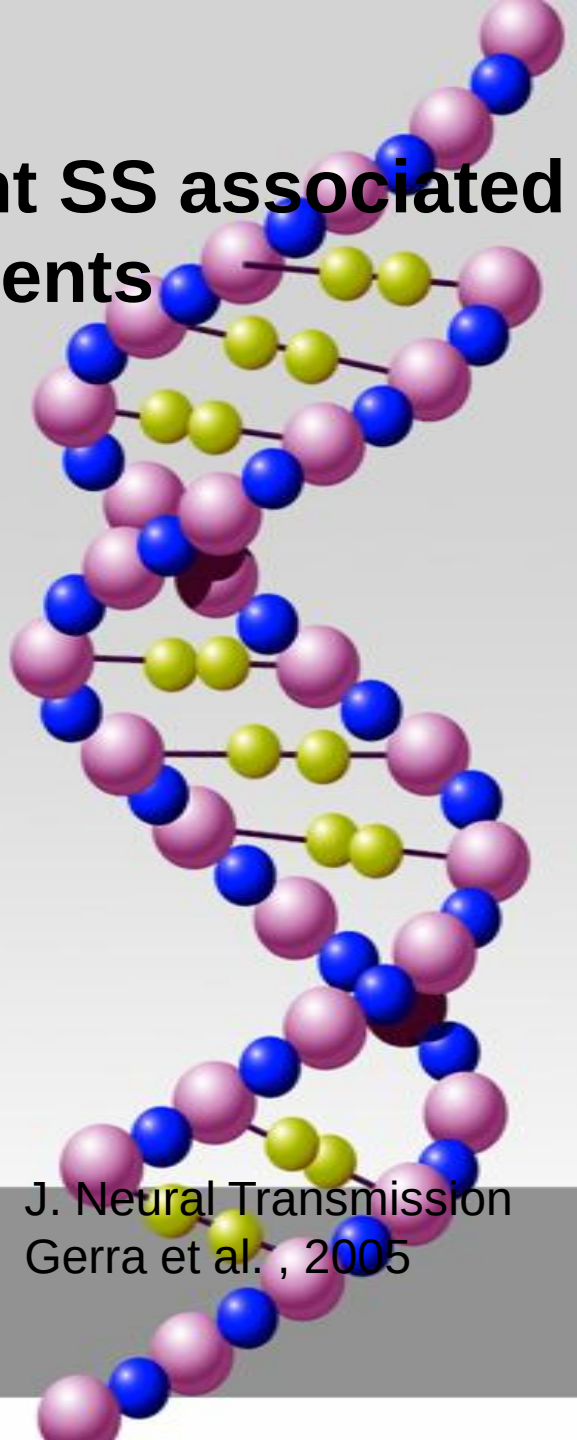
Relevance of perceived childhood neglect, 5-HTT gene variants and hypothalamus-pituitary-adrenal axis dysregulation to substance abuse susce

Gerra et al., 2010



Serotonin transporter Gene variant SS associated with temperament among adolescents

	LL	SL	SS
NOVELTY SEEKING	15,72	19,41	**21,75 ***
BDHI DIRECT AGGRESSION	51,03	55,70	**59,58 ***



J. Neural Transmission
Gerra et al. , 2005

Male participants of a classroom management programme in grade 1 have a decreased probability to have developed a drug-related disorder at age 21, especially if they were rated aggressive by their teachers at that time

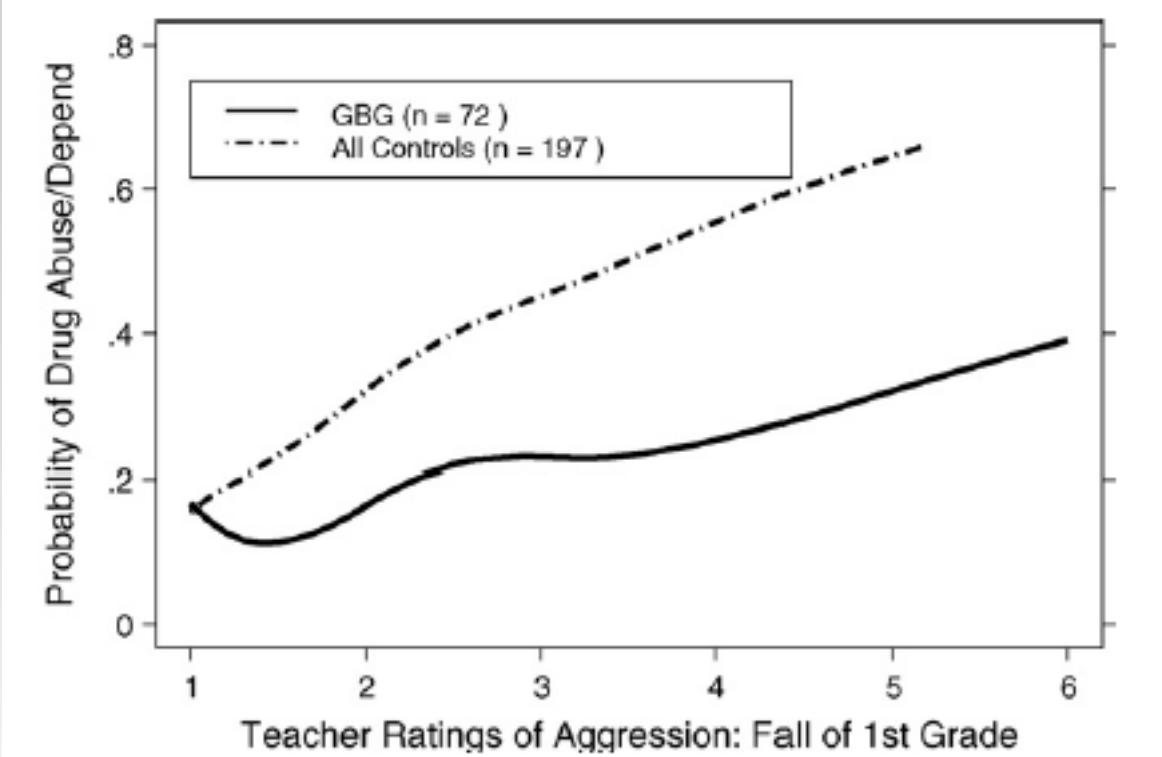


Fig. 2. Impact of GBG vs. all three controls combined on lifetime drug abuse/dependence disorders by baseline aggressive, disruptive behavior among Cohort 1 males.

Methylphenidate

Narcolepsy

ADHD

Obesity

Methylphenidate ?

Energy for dancing

Stay awake all the night

Being rewarded/excited

Methylphenidate

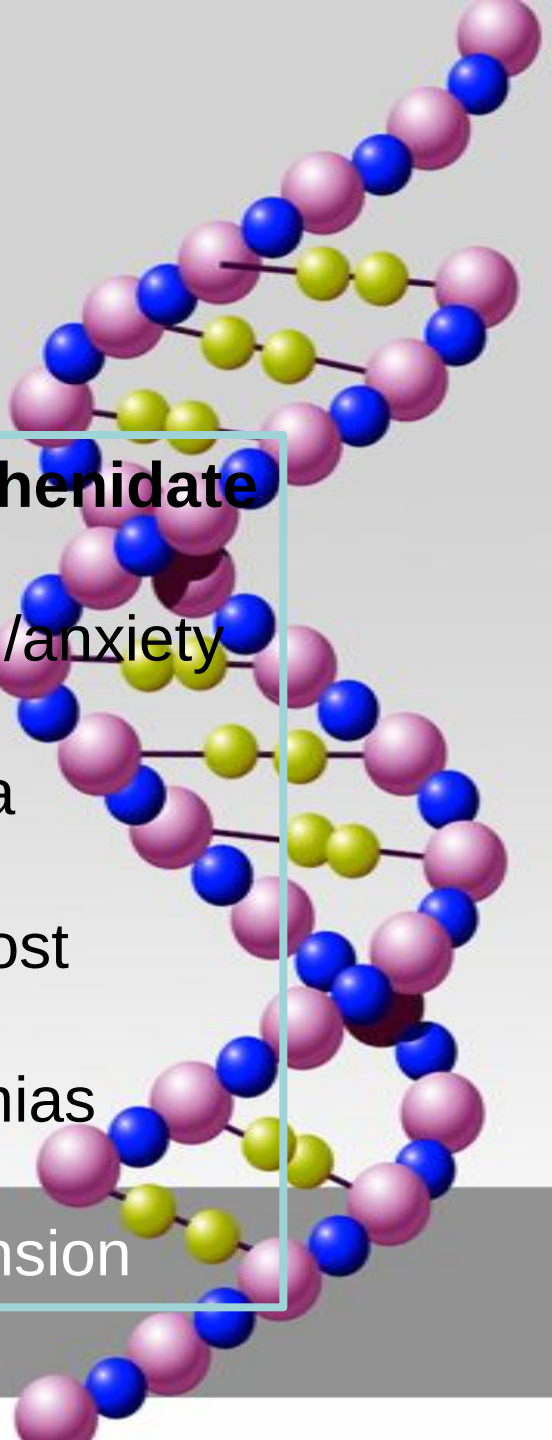
Agitation/anxiety

Insomnia

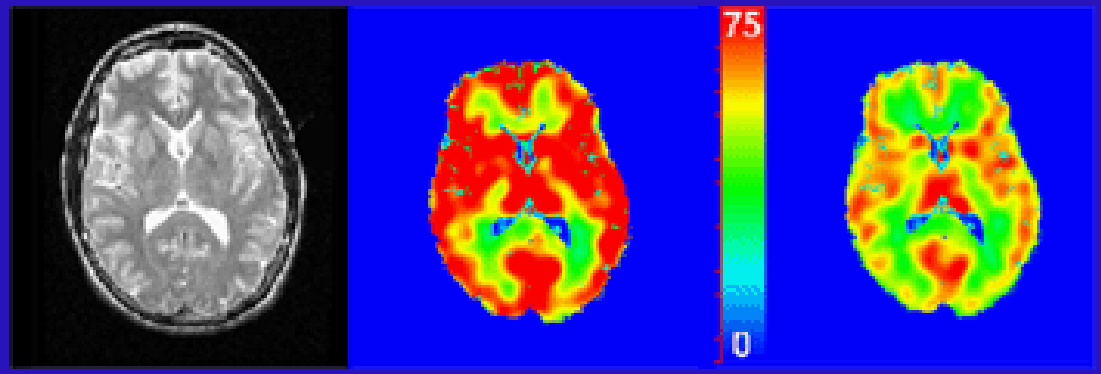
Weight lost

Arrhythmias

Hypertension



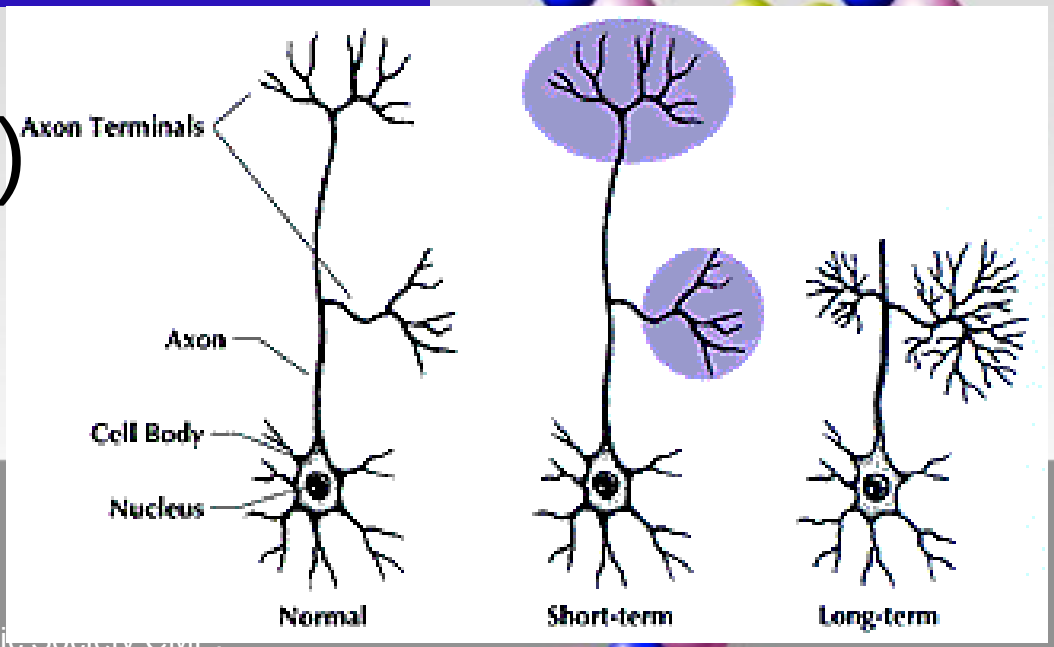
Effect of MDMA Administration on rCBF



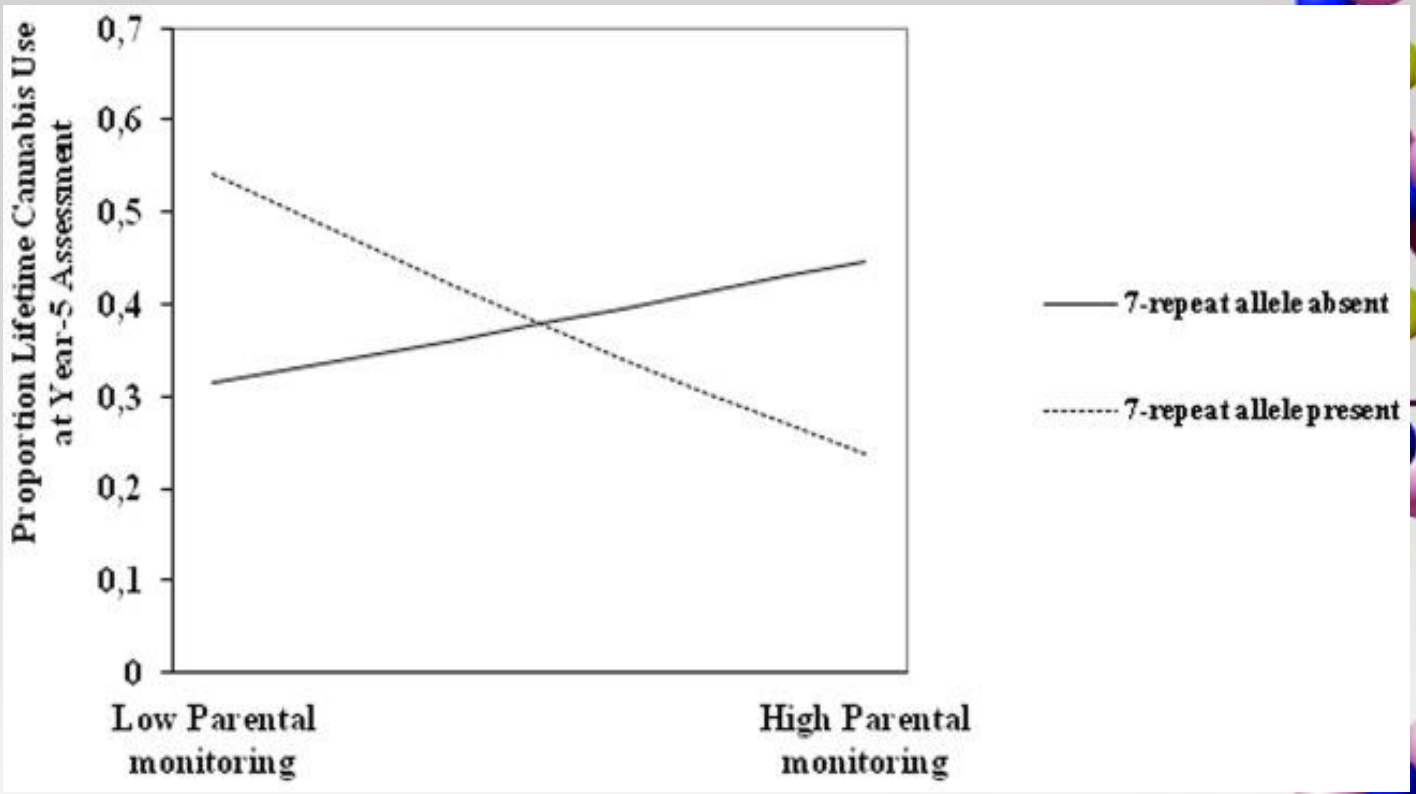
Subject (age 21 yr) | Baseline | 2 weeks post-MDMA

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Ecstasy (MDMA) effects on synapsis terminations



The interplay between parental monitoring and the dopamine D4 receptor gene in adolescent cannabis use.



7-repeat allele were more likely to show lifetime cannabis use

Otten et al., 2012

Prevention of drug use disorders

Parental monitoring

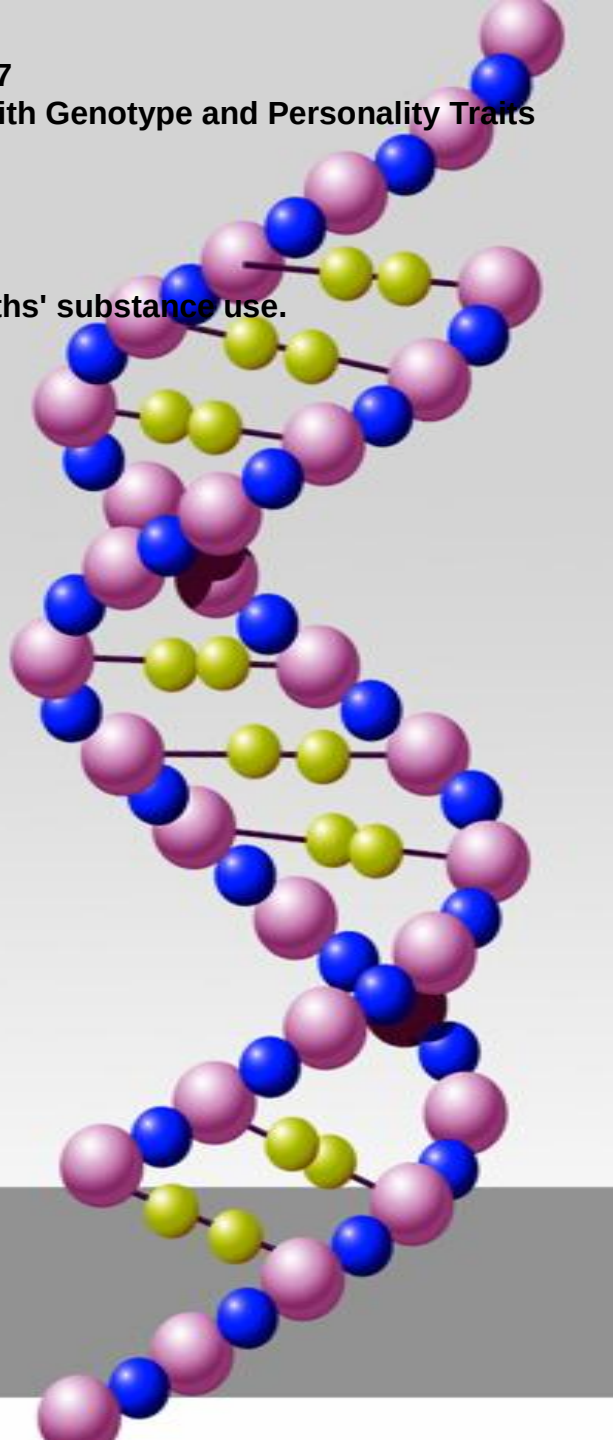
Undivided time for children

Warm/supportive style

Clear rules in family life

American Journal of Medical Genetics Part B (Neuropsychiatric Genetics) 141B:1–7
Perceived Parenting Behaviour in the Childhood of Cocaine Users: Relationship With Genotype and Personality Traits
Gerra et al., 2007

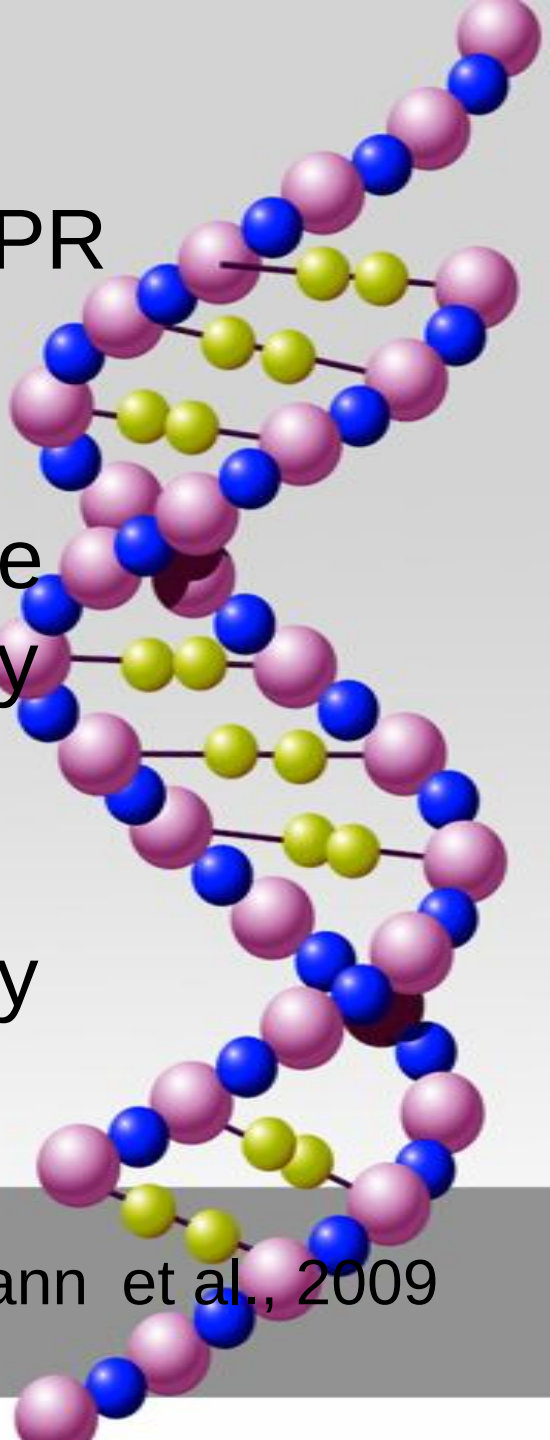
J Consult Clin Psychol. 77(1):1-11.
Parenting moderates a genetic vulnerability factor in longitudinal increases in youths' substance use.
Brody et al., 2009



5-HTTLPR status SS linked with increases in substance use over time

the association was greatly reduced by **involved-supportive parenting**

Short version (S) of the 5-HTTLPR



secure attachment → agreeable autonomy

insecure attachment → hostile autonomy

Zimmermann et al., 2009

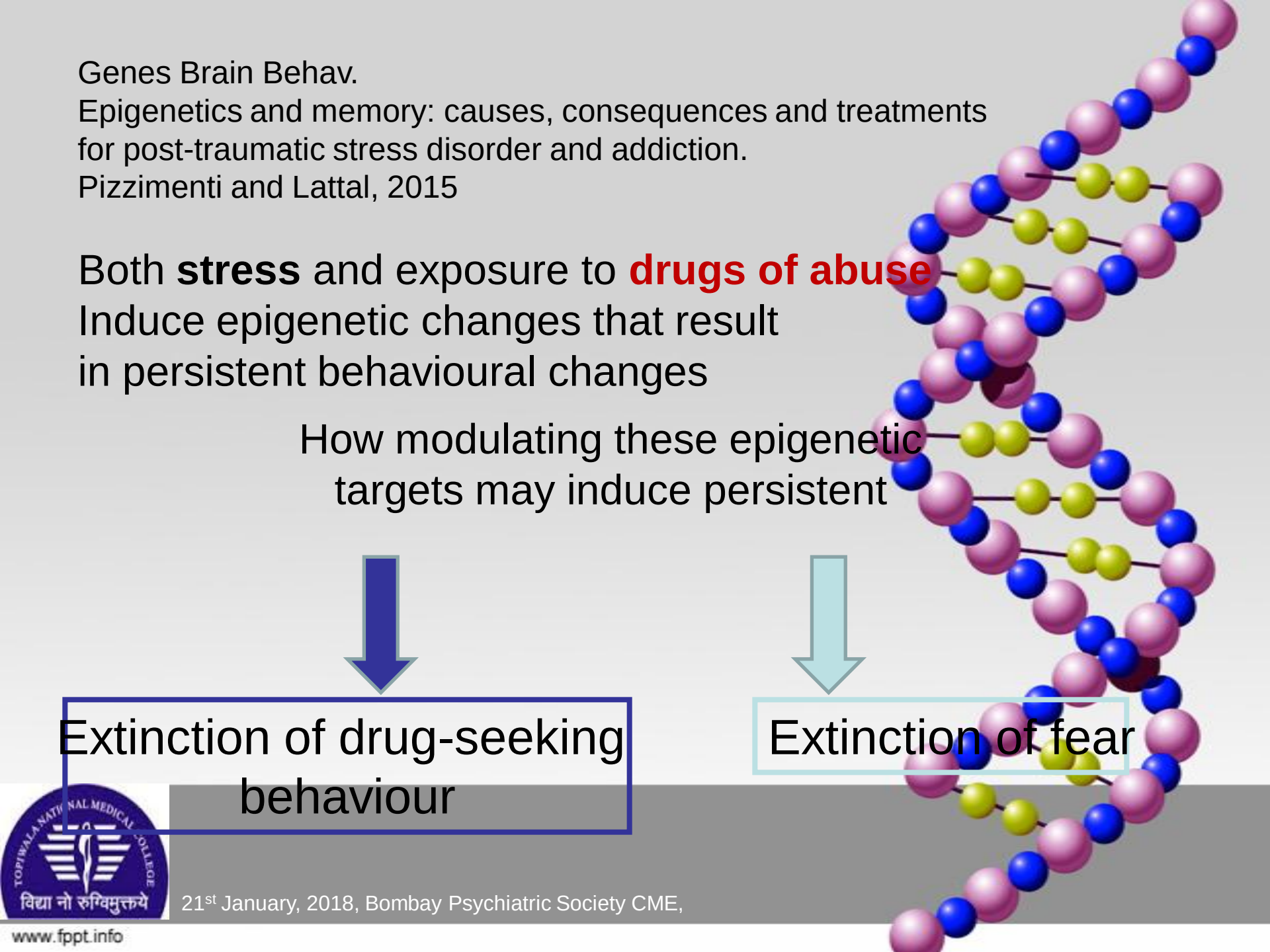
Genes Brain Behav.
Epigenetics and memory: causes, consequences and treatments for post-traumatic stress disorder and addiction.
Pizzimenti and Lattal, 2015

Both **stress** and exposure to **drugs of abuse**
Induce epigenetic changes that result
in persistent behavioural changes

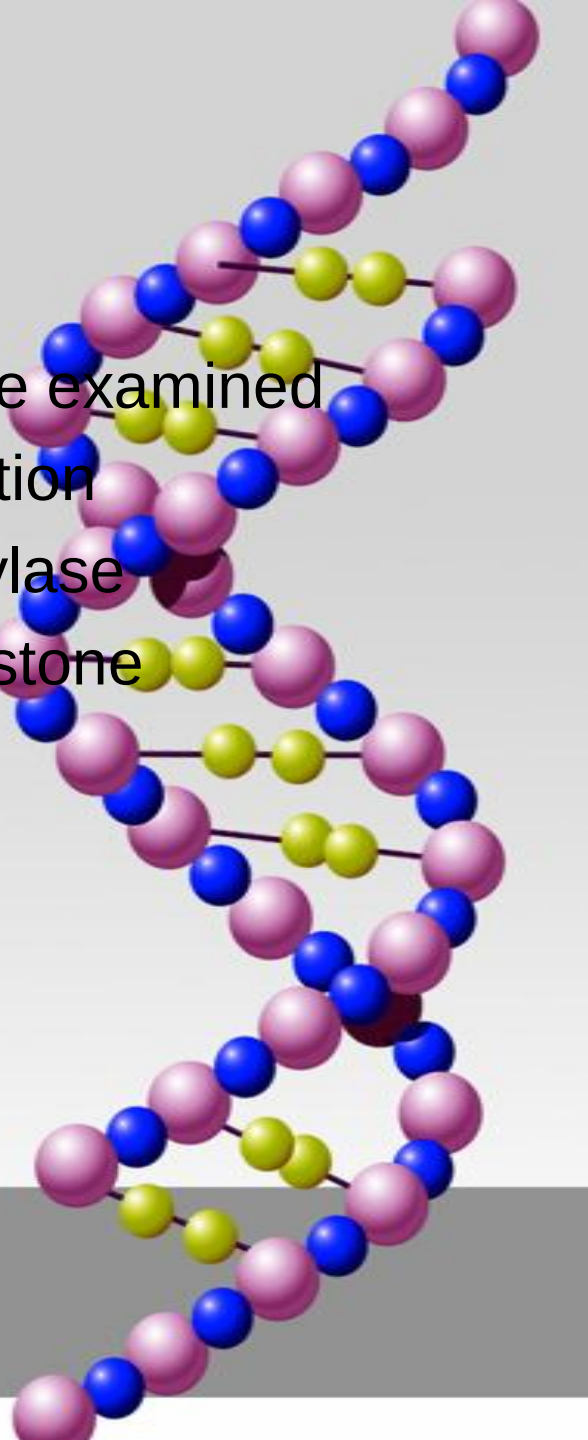
How modulating these epigenetic targets may induce persistent

Extinction of drug-seeking behaviour

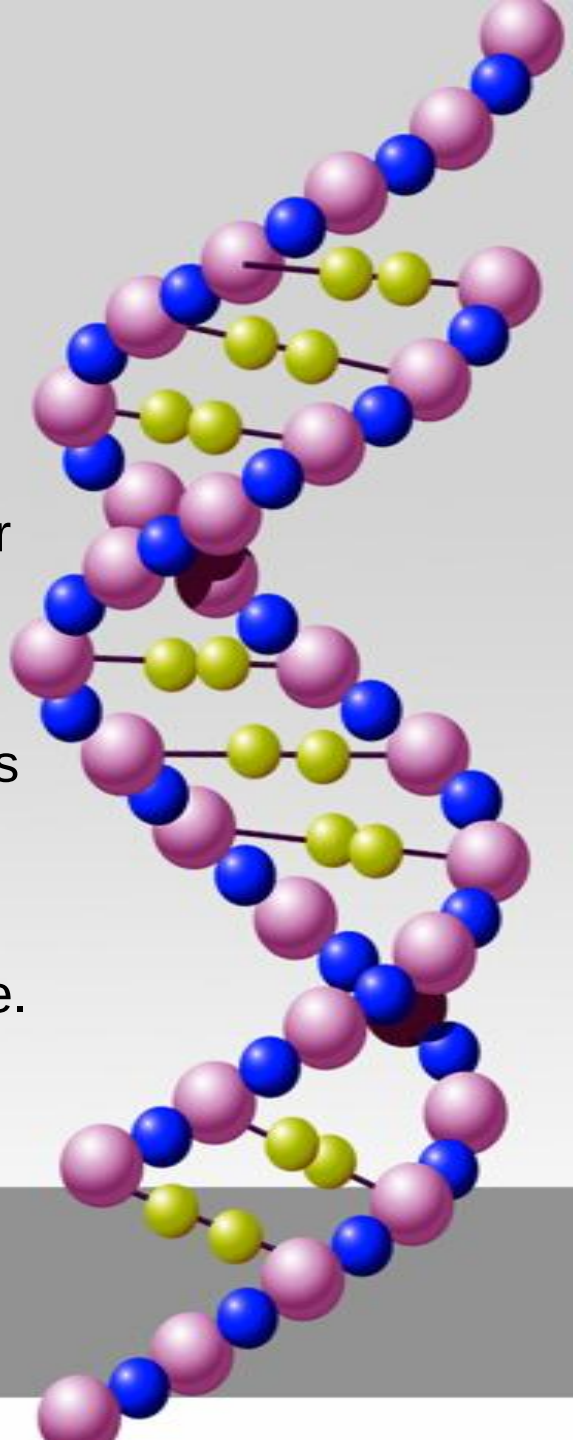
Extinction of fear



- Several pharmacological agents might be examined for addictions, such as the DNA methylation inhibitor azacitidine, the histone deacetylase inhibitor, valproic acid or the selective histone deacetylase inhibitor, SAHA.

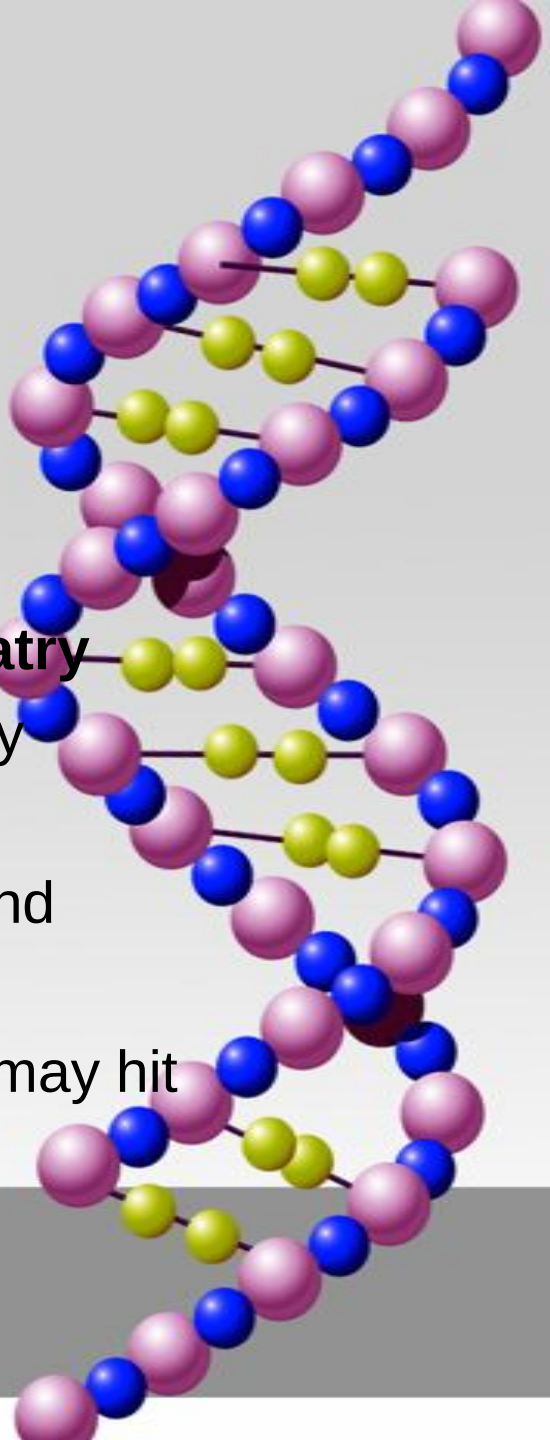


- Furthermore, the histone deacetylase inhibitor suberoylanilide hydroxamine acid (SAHA) enhanced cocaine response in a similar manner to that of nicotine. Many cocaine addicts had initiated smoking prior to developing cocaine addiction. It may be that these epigenetic effects of nicotine may increase the vulnerability of nicotine users to become addicted to cocaine, I n part, by heightening their sensitivity to cocaine.

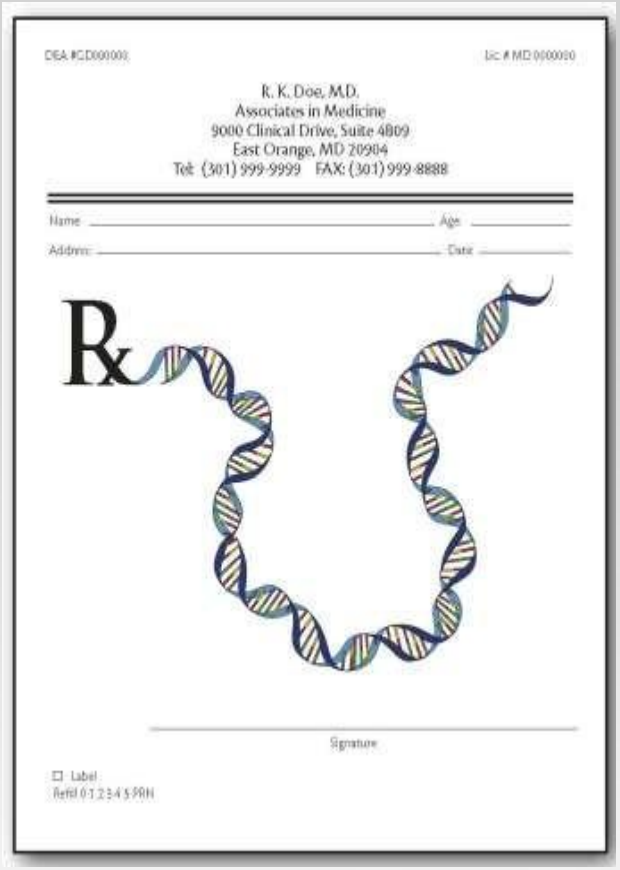


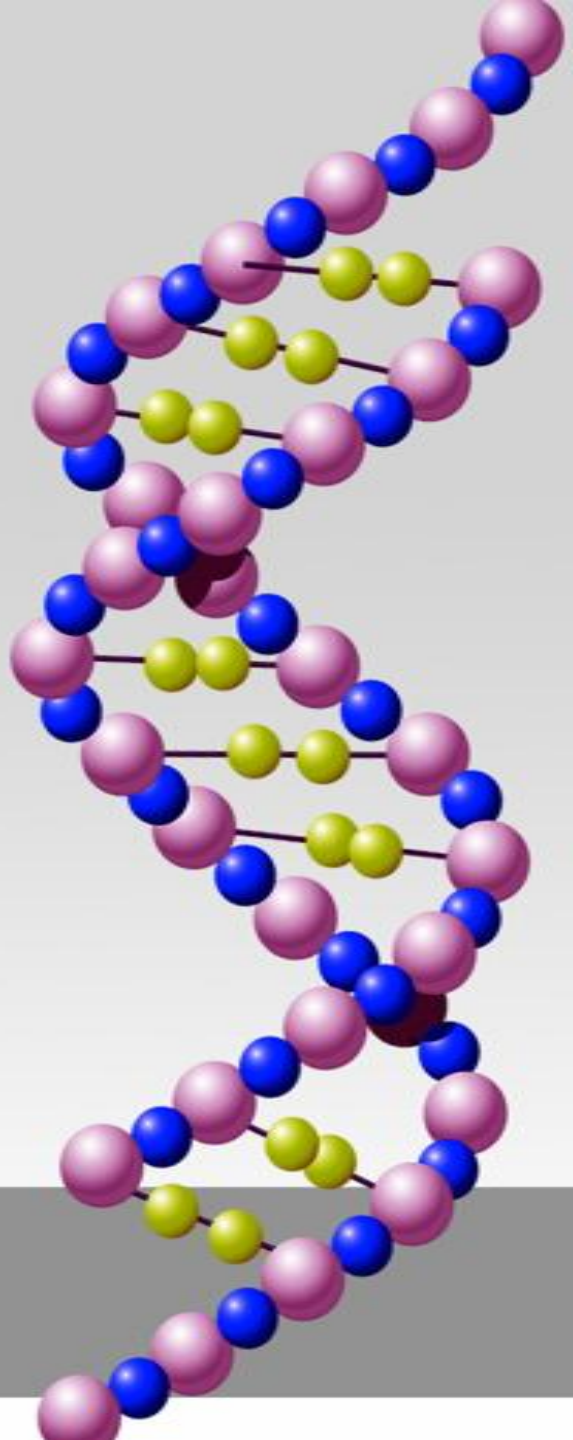
QUICK RECAP

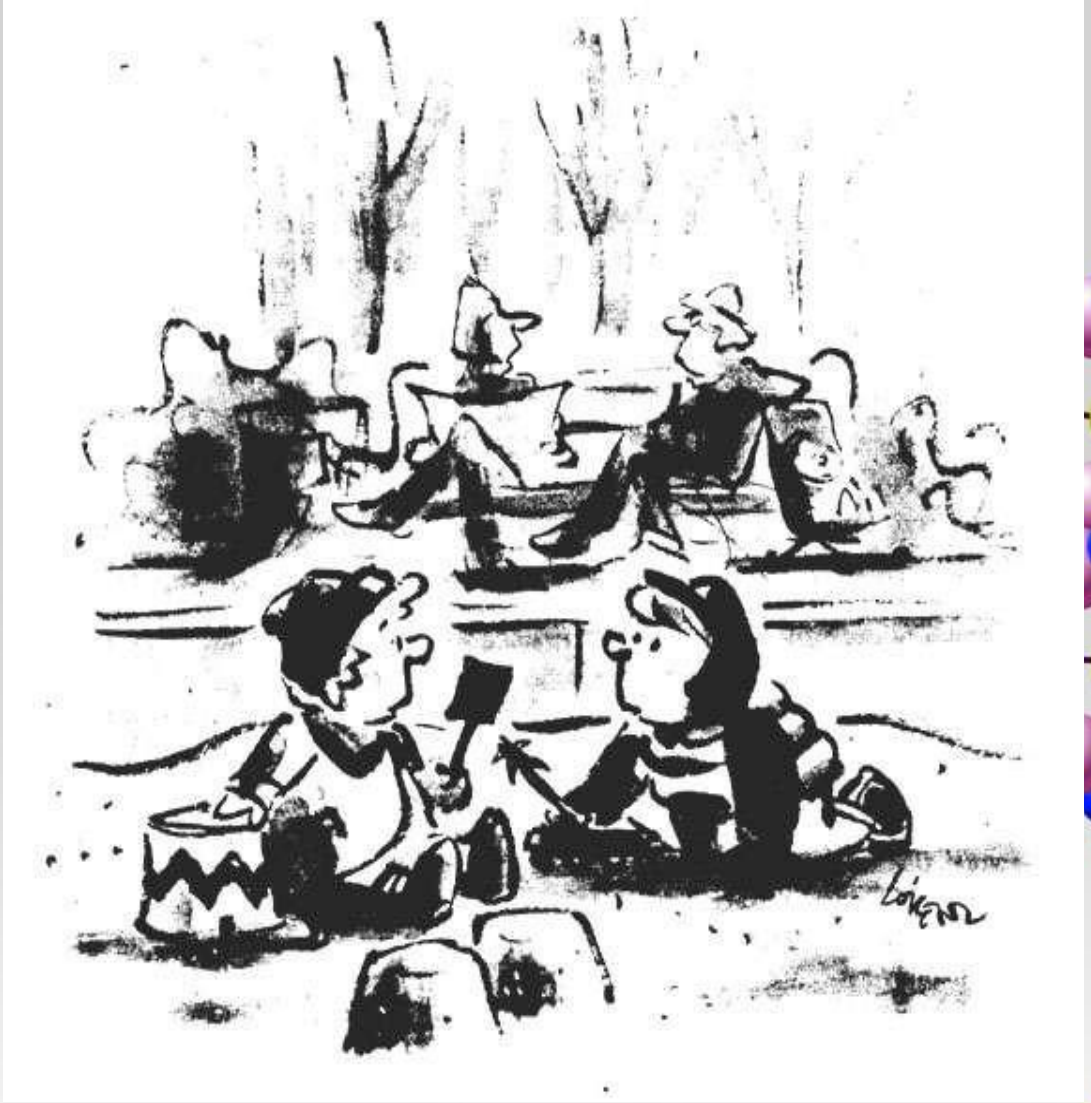
- Therapeutics will involve biomarkers for diagnostic therapy as well as targeted drug therapy.
- At present Valproic acid and folate are best studied
- **Perinatal psychiatry and preventive psychiatry** are probably what we will see emerging as very strong upcoming fields.
- **Predictive therapuetics**—both drug related and therapy related will also play an important role.
- Epigenetic mediated high dose nutraceuticals may hit jackpot or may totally flop.



Personalized Medicine

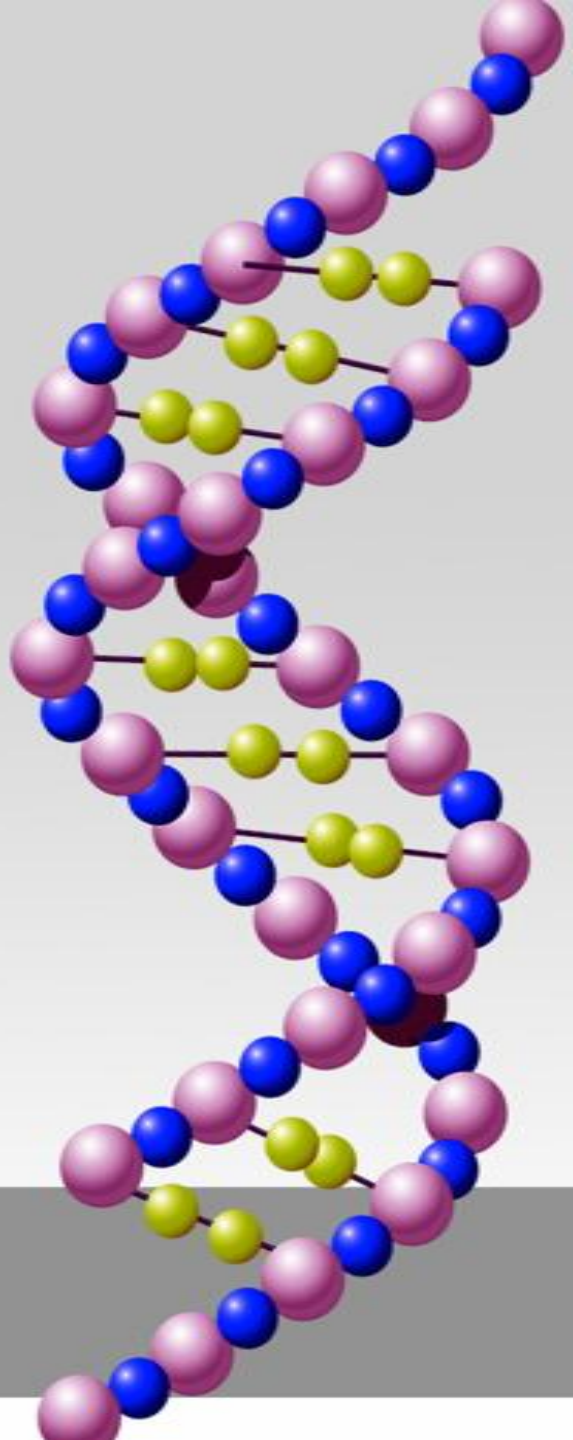






"I still don't have the answers, but I'm beginning to ask the right questions."

THANK YOU



Title

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