Prediction of Disease Vulnerability and Treatment Response in Mood Disorders: Personalized Medicine in Psychiatry

Presented by:
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DISCLOSURES

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- ***Speakers Bureau:*** None
- ***Consultant:*** Xhale, Takeda, SK Pharma, Shire, Roche, Lilly, Allergan
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- ***Other Financial Interest:*** CeNeRx BioPharma, PharmaNeuroBoost
- ***Patents:*** Method and devices for transdermal delivery of lithium (US 6,375,990B1), Method of assessing antidepressant drug therapy via transport inhibition of monoamine neurotransmitters by ex vivo assay (US 7,148,027B2)
- ***Scientific Advisory Board:*** American Foundation for Suicide Prevention (AFSP), CeNeRx BioPharma, National Alliance for Research on Schizophrenia and Depression (NARSAD), PharmaNeuroBoost, Anxiety Disorders Association of America (ADAA), Skyland Trail
- ***Board of Directors:*** AFSP, Gratitude America, Skyland Trail, ADAA

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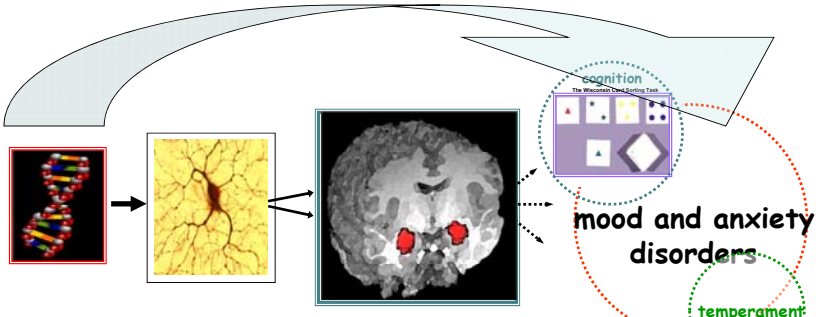
Depression and Anxiety are Ultimately About How the Brain Responds to the Environment



Genes: *sequence variants and variable gene processing*

Cells: *molecular pathways*

Systems: *activity in emotion processing circuitry*

Behavior: *Clinical phenotype*

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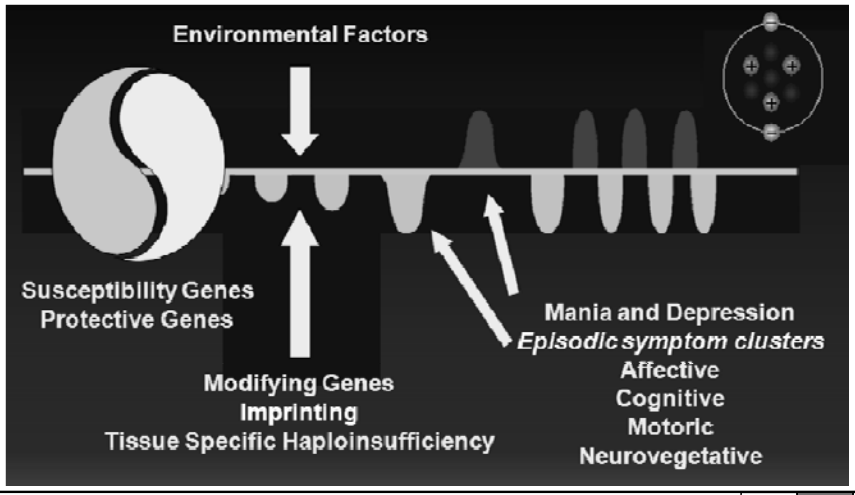
The Neurobiology of Bipolar Disorder: Theoretical Considerations



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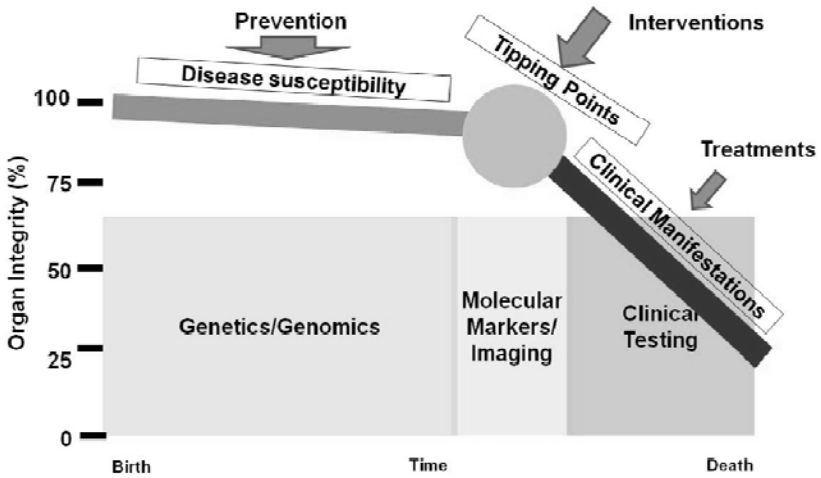
5

21st Century Medicine



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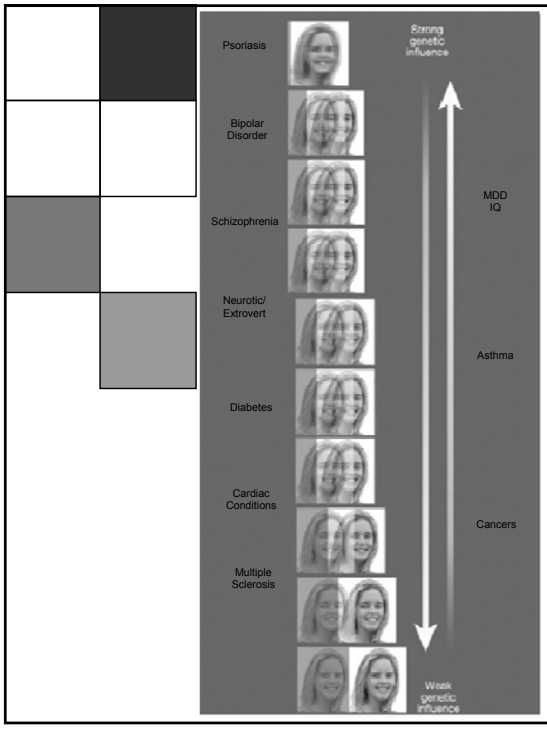
6

Implications for Public Understanding



"We used to think our fate was in our stars. Now we know, in large measure, our fate is in our genes." J. D. Watson

Studies of identical twins have revealed that some conditions, such as psoriasis, have a strong genetic component and are less influenced by environmental and lifestyle factors — identical twins are more likely to share these diseases. But other conditions, such as multiple sclerosis, are only weakly influenced by genetic makeup and therefore twins may show differences depending on their exposure to various environmental factors.

*Chakravarti & Little, Nature **421**: 412 – 414, 2003*

Concordance Rates for Manic-Depressive Illness in Monozygotic (MZ) and Dizygotic (DZ) Twins

	Concordance Rate (%)	
Study	**MZ**	**DZ**
Rosanoff et al, 1934	69.9	16.4
Kallmann, 1954	92.6	23.6
Da Fonseca, 1959	71.4	38.5
Harvald, Hauge, 1965	50.0	2.6
Kringlen, 1967	33.3	0.0
Bertelsen, 1977	58.0	17.0
Torgersen, 1986	75.0	0.0

Mendlewicz J. Br J Psychiatry Suppl. September 1988:16-25.

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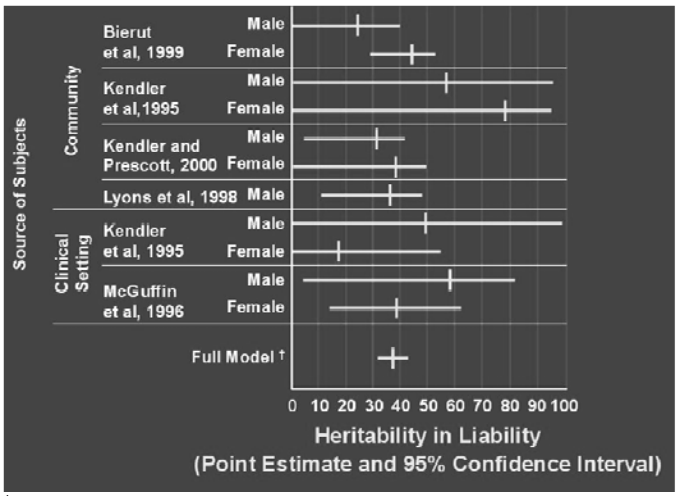
9

Genetics of MDD



† Aggregate values across studies of heritability in liability to major depression.

Sullivan PF et al. Am J Psychiatry. 2000;157:1552-1562.

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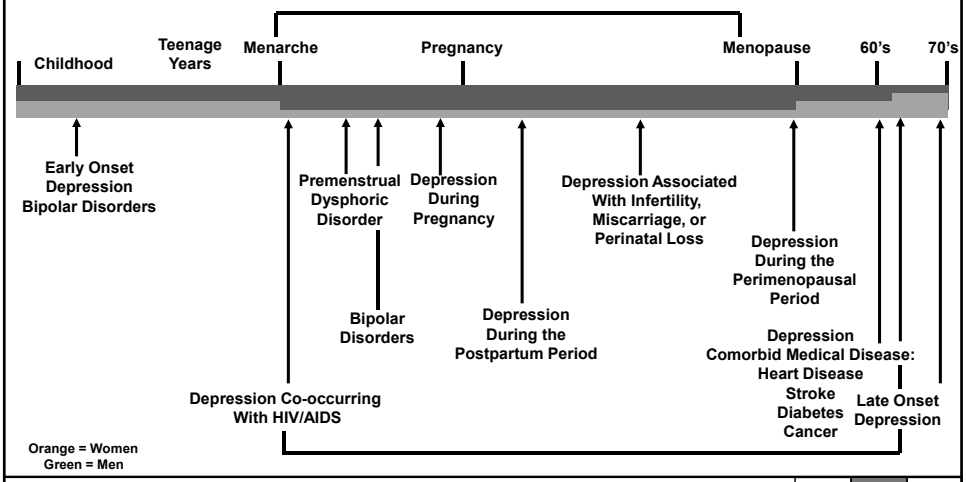
10

Mood Disorders Across the Life Cycle



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11

Confirmed Linkages in Bipolar Disorder

Genomic Location	Principle Report	Independent Confirmations	Comments
18p11.2	Berrettini et al., 1994 and 1997	Stine et al., 1995; Nothen et al., 1999; Turecki et al., 1999	Paternal parent-of-origin effect; see Schwab et al., 1998
21q22	Straub et al., 1994	Detera-Wadleigh et al., 1996, Smyth et al.,1996, Kwok et al.,1999; Morissette et al.,1999	
22q11-13	Kelsoe et al., 2001	Detera-Wadleigh et al., 1997 and 1999	Velocardiofacial syndrome region; possible overlap with a schizophrenia locus
18q22	Stine et al., 1995	McInnes et al., 1996; McMahon et al., 1997; De Bruyn et al., 1996	See Freimer et al., 1996
12q24	Morissette et al., 1999	Ewald et al., 1998; Detera-Wadleigh et al., 1999	Principal report in a Canadian isolate
4p15	Blackwood et al.,1996	Ewald et al., 1998; Nothen et al., 1997; Detera-Wadleigh et al., 1999	See Ginns et al., 1998

Berrettini. In Neuropsychopharmacology; The Fifth Generation of Progress (Davis et al editors) 2002; p1031

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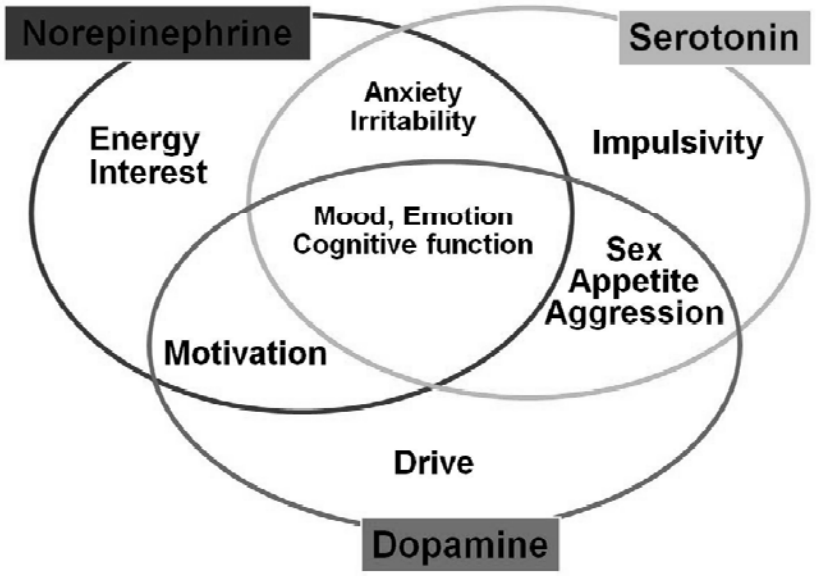
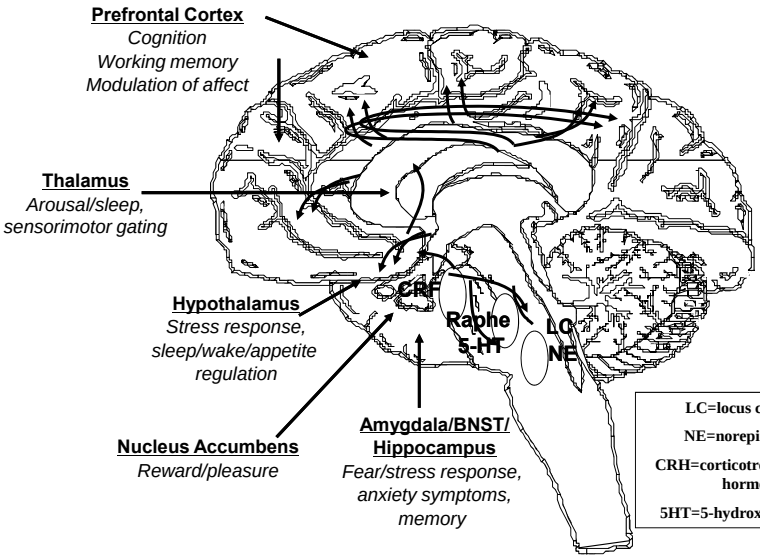
12

Neurotransmitters and Depression

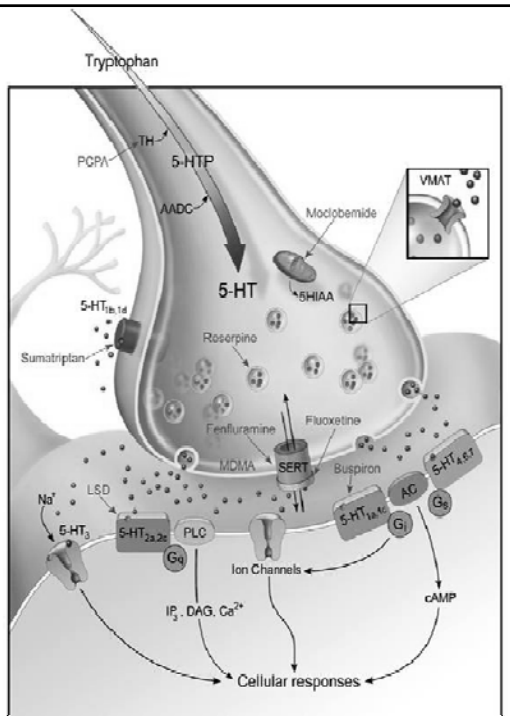
- There are disturbances in the monoamine systems
  - serotonin (5-hydroxytryptamine, 5-HT)
  - norepinephrine (NE)
  - dopamine (DA)??
- There are also disturbances in other neurotransmitter systems (e.g., corticotropin-releasing factor [CRF] and substance P)
- Serotonin and norepinephrine have been the most extensively studied in the clinical setting



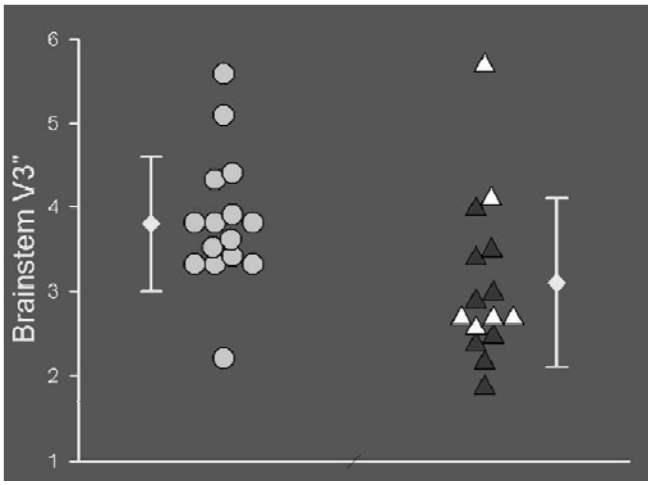
Regulation of Behavioral Circuits by Neuromodulatory Systems



LC=locus coeruleus;
NE=norepinephrine;
CRH=corticotropin-releasing hormone;
5HT=5-hydroxytryptamine.



Reduced Brainstem [^{123}I]β-CIT Binding in Depression



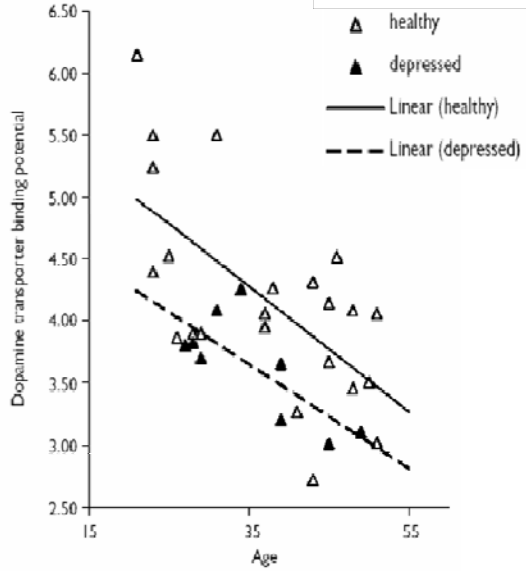
Malison et al. Biol Psychiatry 44: 1090-1098, 1998

Dopamine and Depression

- Role of Dopamine neurons in behavioral and physiological areas altered in depression
- High rate of Comorbidity of Parkinson's Disease and Depression
- Pathophysiological involvement of DA systems in Depression

Imaging Studies | Postmortem Studies Fluids Studies | Biological

- Role of DA circuits in the Actions of Antidepressants
  - MAOIs
  - effects on the DA transporter



Dopamine transporter binding potential in bilateral striatum is lower in depressed patients. Data was analyzed using analysis of covariance with age as a covariate, examining effect of diagnosis (effect of diagnosis: $F_{1,29} = 7.1$, $P = 0.01$).

NeuroReport 2001; 12:4121-4125

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Norepinephrine Alterations

- NE dysfunction is linked to depression
  - low levels of NE metabolites are found in the urine and CSF of depressed patients
  - increased density of B-adrenergic receptors is found at postmortem in the cortex of depressed suicide victims
  - NE reuptake inhibitors are effective antidepressants (desipramine, reboxetine, maprotiline)

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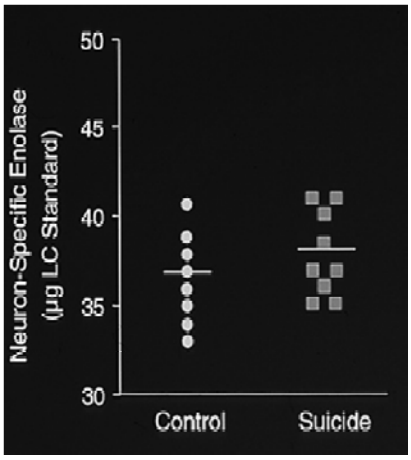
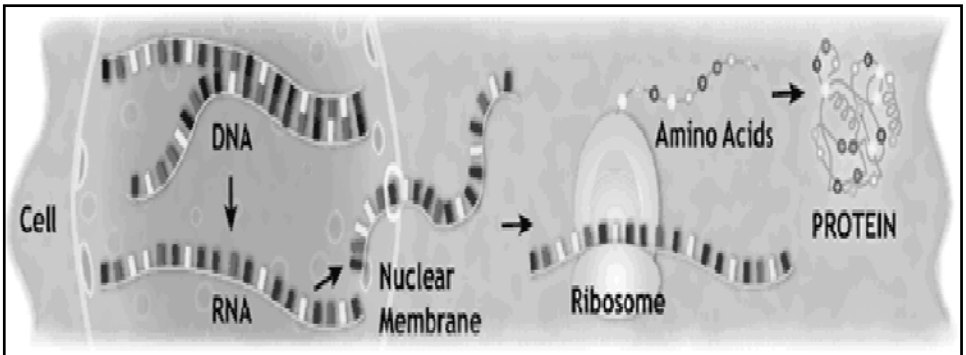
20

TH and NSE Levels in Sections of LC from Control and Suicide Victims

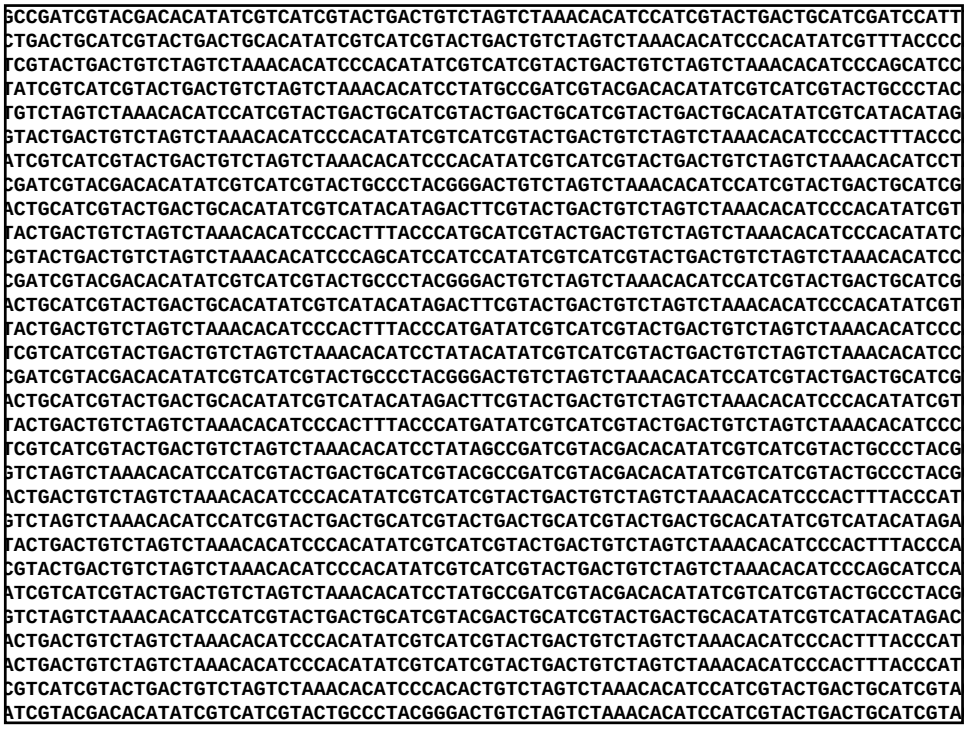


Ordway et al. J Neurochem 1994; 62:680-685.



Our DNA is our instruction manual !

We can now read the whole manual !!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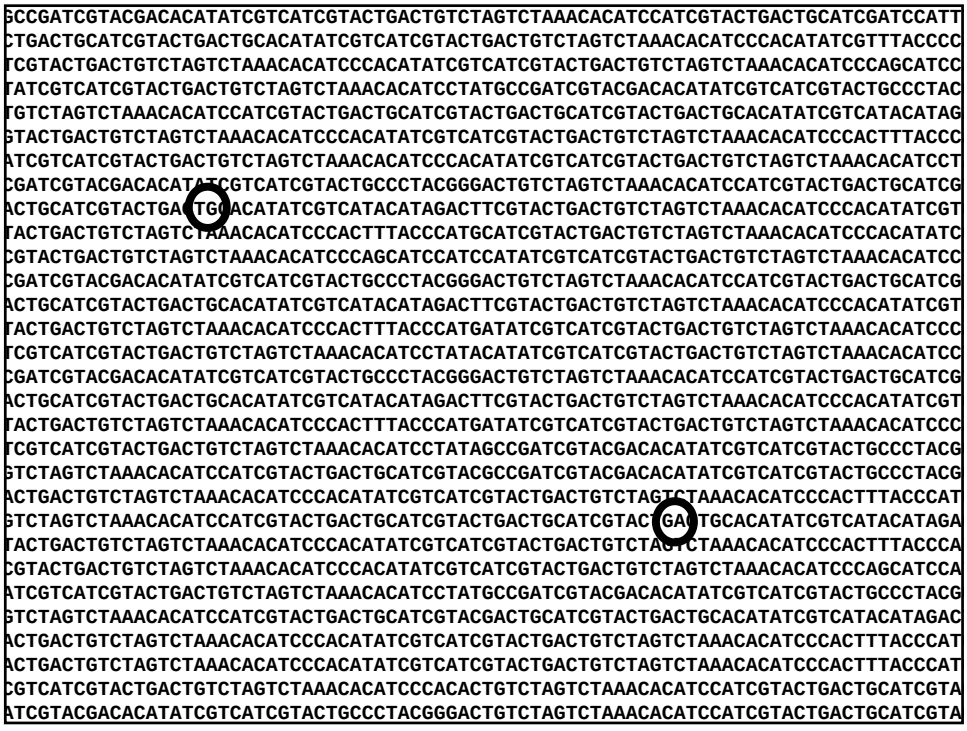
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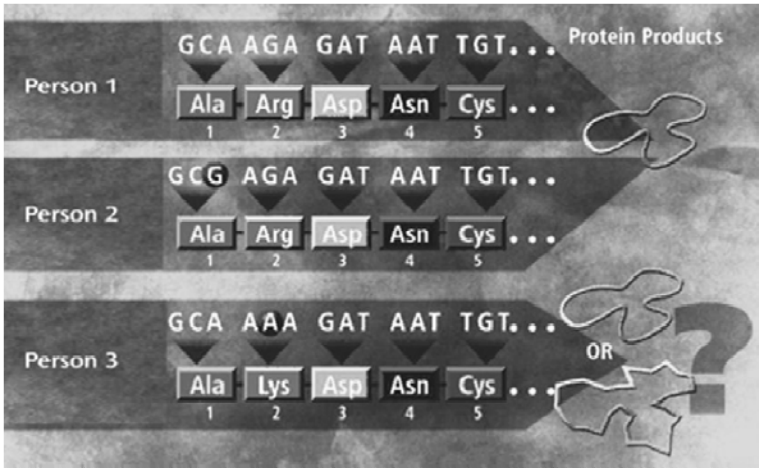
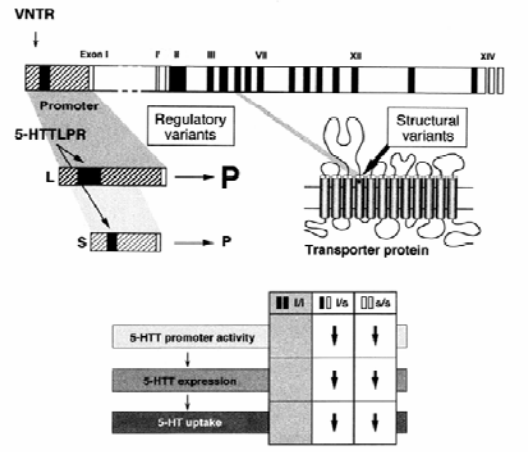


The image shows how DNA sequence variation in a gene can change the protein produced by the genetic code. The nucleotide triplet codon at position 1 in the gene depicted is different in person 1 and person 2, but the codon difference does not change the amino acid sequence. In person 3, the nucleotide triplet codon at position 2 is different from that in person 1 and person 2, and the codon change results in production of a different amino acid at position 2 in person 3.

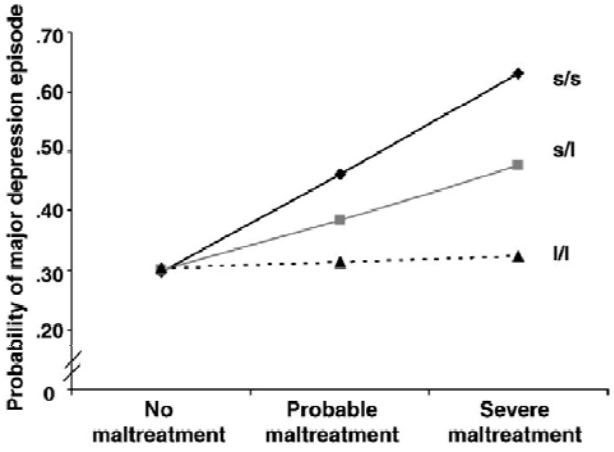
AJP 158:791, 2001

5'-HT transporter promoter polymorphism (SLC6A4, 17q11)



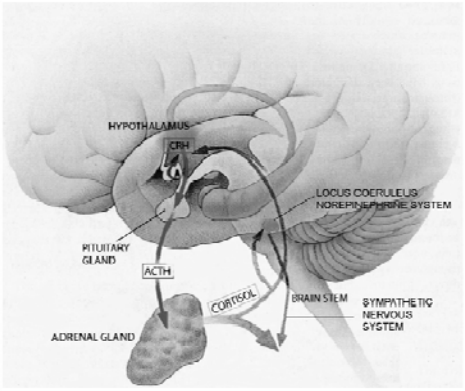
Adapted from Lesch & Mossner (1998) *Biol Psychiatry* 44 .

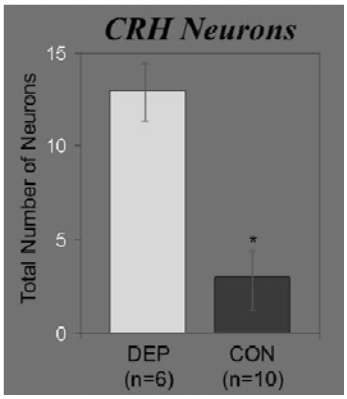
Results of regression analysis estimating the association between childhood maltreatment (between the ages of 3 and 11 years) and adult depression (ages 18 to 26), as a function of 5-HTT genotype.



Caspi et al (2003) *Science* 301:386-389.

Regulation of Stress Response by CRH and HPA Axis





HPA=hypothalamic-pituitary-adrenal; ACTH=adrenocorticotropic hormone.

*P<0.01; mean ± SEM.

Purba JS, et al. *Neuroendocrinology.* 1995;62:62-70; Raadsheer FC, et al. *Neuroendocrinology.* 1994;60:436-444.

DEP=depressed patients; CON=control patients.

Central CRH: A Mediator of Stress and Depression

- CRH CSF concentrations are elevated in depression
- CRH stimulation test shows blunted ACTH response in depression
- Combined dexamethasone/CRH stimulation test is dysregulated in depression
- Increased pituitary/adrenal gland size in depression
- In animals, CRF injections into brain mimic anxiety and chronic depression
- These effects can be blocked by CRHR1 antagonists and a neurokinin-2 (NK2) receptor antagonist
- A principle source of brain CRH is the central nucleus of the amygdala, known to be involved in stress response and depression

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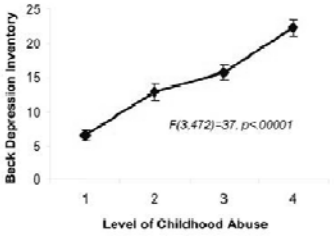
Sample Demographics

	N	Percentage
Gender		
Male	194	39%
Female	303	61%
Self-Identified Race/Ethnicity		
African American or Black	484	97%
Caucasian or White	4	.8%
Hispanic or Latino	2	.4%
Asian	1	.2%
Mixed	5	1%
Other	3	.6%
Education		
< 12th Grade	153	31%
High School Graduate or GED	217	44%
Some College or Technical School	78	15%
Technical School Graduate	21	4%
College Graduate	21	4%
Some Graduate School	9	2%
Employment Status		
Currently Unemployed	338	68%
Currently Employed	162	32%
Disability Status		
Not Currently Receiving Disability	394	79%
Currently Receiving Disability	103	21%
Household Monthly Income		
$0 – $249	158	32%
$250 – $499	51	10%
$500 - $999	136	28%
$1000 - $1999	106	21%
$2000 or more	158	9%

Bradley, Binder et al (2008) Arch Gen Psychiatry 65:190-200.

Early Life Stress Significantly Enhances Risk for Depression in Adults

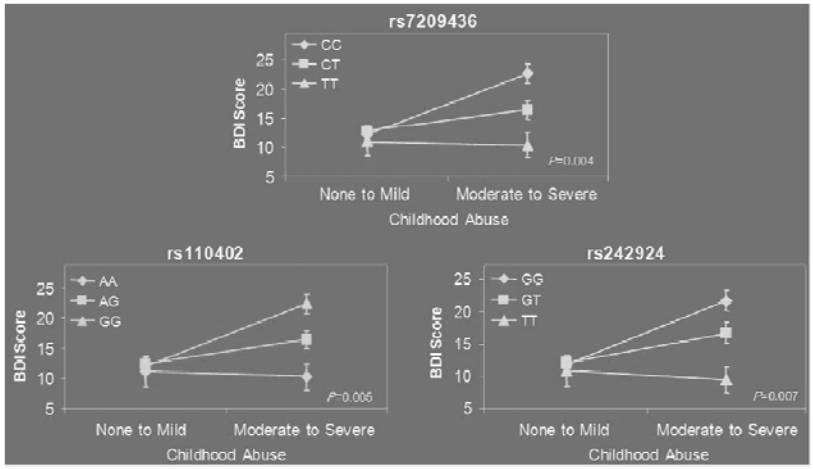
Beck Depression Inventory (BDI) scores are predicted by continuous scores on the childhood trauma questionnaire.



Depression is predicted by presence/absence of childhood trauma.

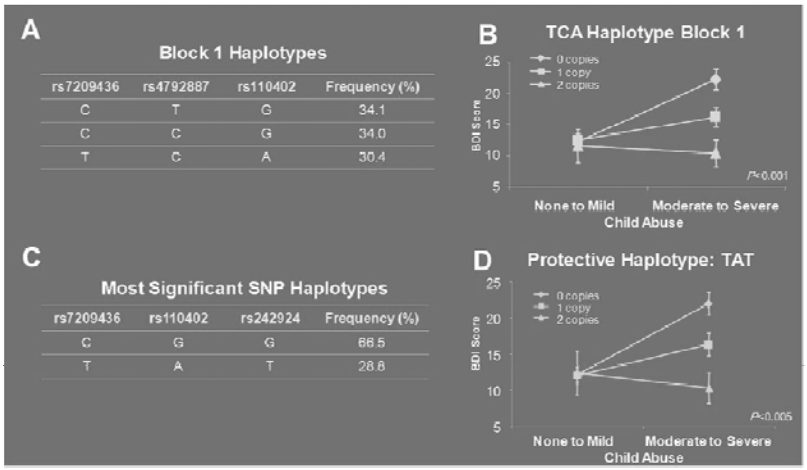
Bradley, Binder et al (2008) Arch Gen Psychiatry 65:190-200.

CRHR1 Polymorphisms Strongly Interact With Level of Childhood Abuse in the Prediction of Adult Depression



Bradley, Binder et al (2008) Arch Gen Psychiatry 65:190-200.

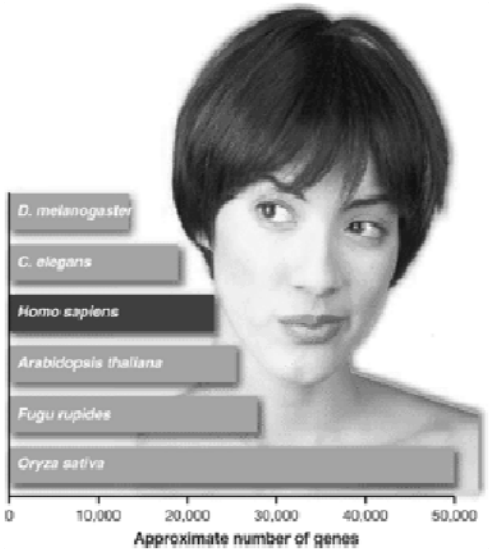
CRHR1 Polymorphism Haplotypes Interact With Level of Childhood Abuse in the Prediction of Adult Depression



Bradley, Binder et al (2008) Arch Gen Psychiatry 65:190-200.

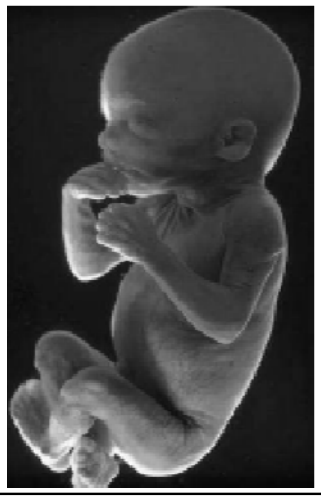
UHealth University of Miami Health System | University of Miami Miller School of Medicine

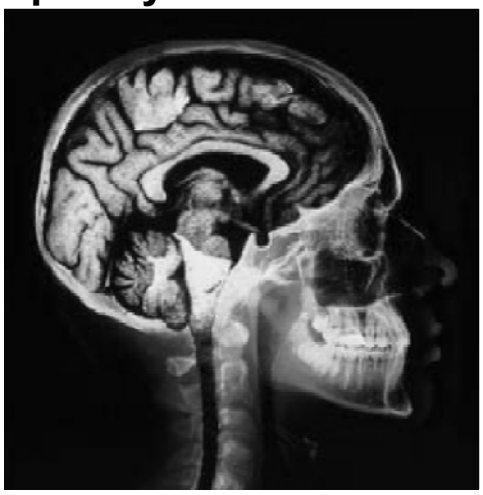
Biggest Surprise from the Genome Projects: Number of Conventional Genes do not Scale with Complexity



Science, 2005

Where is the information that programs our complexity?



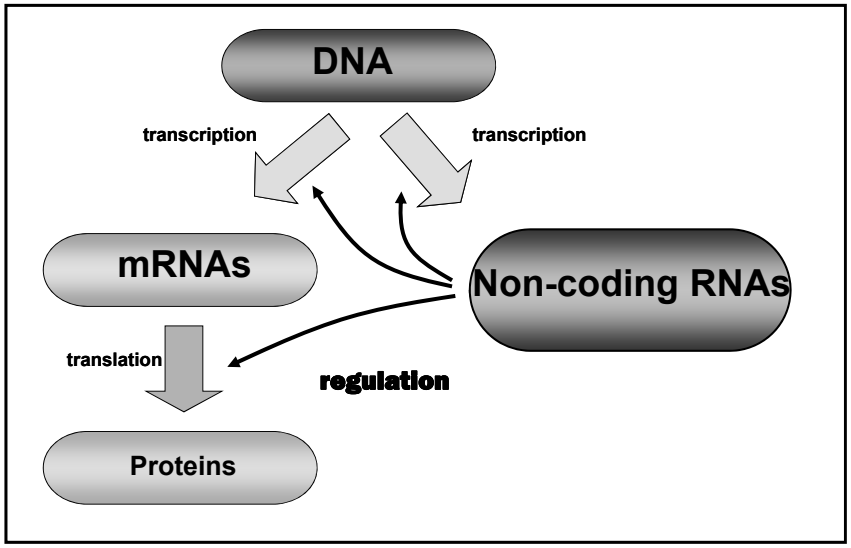


Answer?

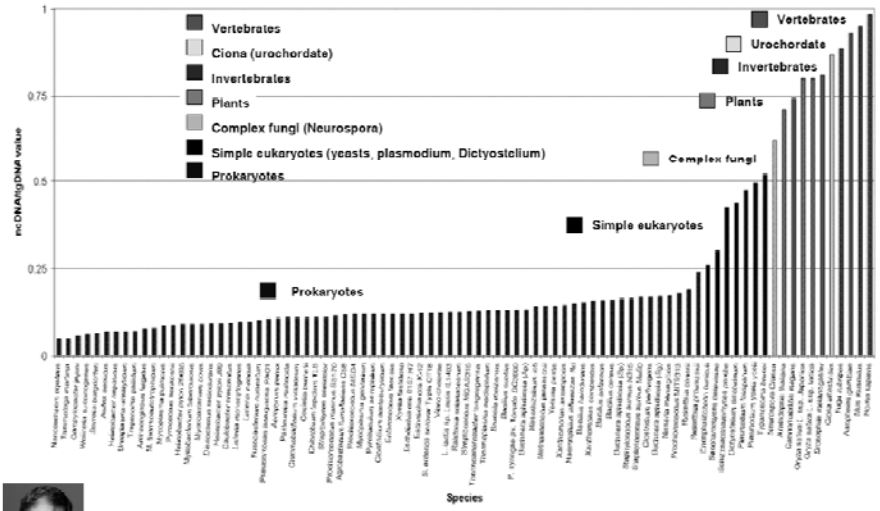
Additional regulatory components in our genome: RNAs

F. Crick

Modified "Central Dogma"

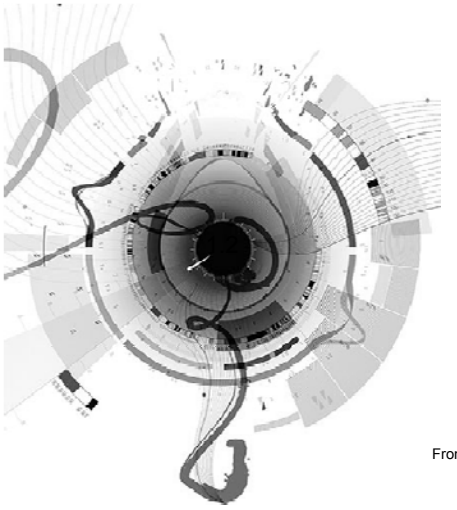


The Proportion of Nancoding DNA Broadly Increases with Developmental Complexity



J. Mattick

Only 1.2% of the genome is made up of conventional genes…



From *New York Times*, 2009

…but most of the genome is transcribed.

New View of the Human Genome

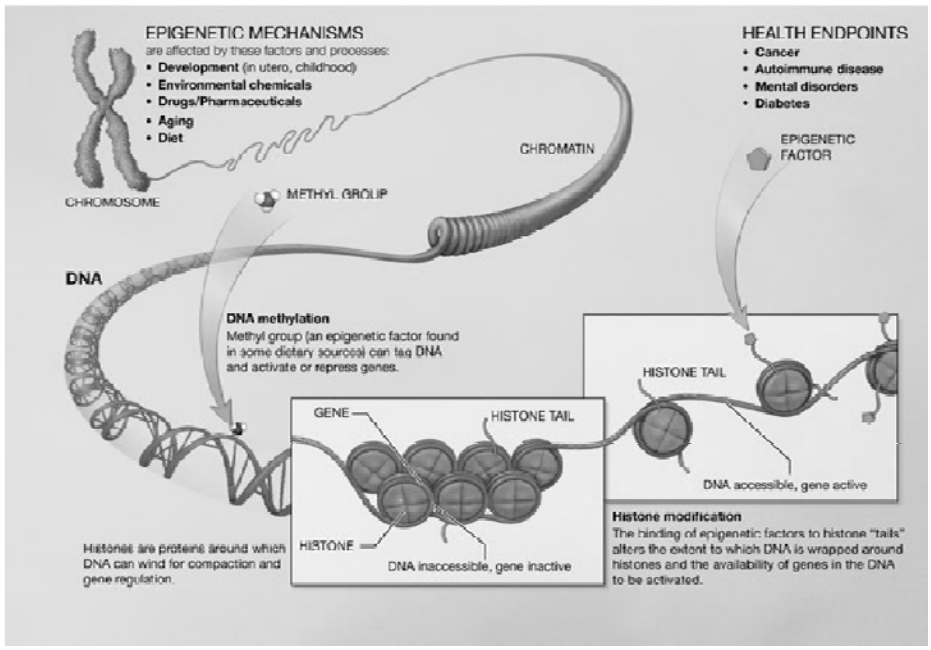
- Islands of (conventional) protein-coding genes in a sea of regulatory information.
- "Genes" are not discrete entities.
- Regulation is orchestrated by RNA as well as proteins.
- Theory: Complexity is achieved primarily by RNA.

Why Study microRNAs in Psychiatric Disease?

- MicroRNAs are predicted to regulate up to hundreds of genes each ('master regulators')
- At least half of protein-coding genes may be regulated by microRNAs
- Single microRNAs may target multiple genes within a biological pathway
- MicroRNAs evolve easily and their number increases with organismal complexity
- Major role in neurodevelopment and cell differentiation
- Regulatory layer that may account for missing genetic/epigenetic variability in the etiology of disease

Epigenetics

The phenomenon of heritable ('metastable') changes in gene regulation that are governed by non-Mendelian processes, primarily through biochemical modifications to chromatin structure that occur during life.


EPIGENETIC MECHANISMS
are affected by these factors and processes:
• Development (in utero, childhood)
• Environmental chemicals
• Drugs/Pharmaceuticals
• Aging
• Diet
HEALTH ENDPOINTS
• Cancer
• Autoimmune disease
• Mental disorders
• Diabetes
CHROMOSOME
CHROMATIN
METHYL GROUP
EPIGENETIC FACTOR
DNA
DNA methylation
Methyl group (an epigenetic factor found in some dietary sources) can tag DNA and activate or repress genes.
GENE
HISTONE TAIL
HISTONE TAIL
DNA accessible, gene active
HISTONE
DNA inaccessible, gene inactive
Histones are proteins around which DNA can wind for compaction and gene regulation.
Histone modification
The binding of epigenetic factors to histone "tails" alters the extent to which DNA is wrapped around histones and the availability of genes in the DNA to be activated.


CURRENTLY ON
EXIT 58A-B
95
I
9
Lithium
Valproate
Atypical
Antipsychotics
LAST EXIT BEFORE TOLL
Lamotrigine
Carbamazepine
Anti-Depressants
CBT

Article

Prediction of Antidepressant Response to Milnacipran by Norepinephrine Transporter Gene Polymorphisms

Keizo Yoshida, M.D., Ph.D.
Hitoshi Takahashi, M.D., Ph.D.
Hisashi Higuchi, M.D., Ph.D.
Mitsuhiro Kamata, M.D., Ph.D.
Ken-ichi Ito, M.D., Ph.D.
Kazuhiro Sato, M.D., Ph.D.
Shingo Naito, M.D.
Tetsuo Shimizu, M.D., Ph.D.
Kunihiko Itoh, Ph.D.
Kazuyuki Inoue, M.S.C.
Toshio Suzuki, Ph.D.
Charles B. Nemeroff, M.D., Ph.D.

Objective: With a multitude of antidepressants available, predictors of response to different classes of antidepressants are of considerable interest. The purpose of the present study was to determine whether norepinephrine transporter gene (NET) and serotonin transporter gene (5-HTT) polymorphisms are associated with the antidepressant response to milnacipran, a dual serotonin/norepinephrine reuptake inhibitor.

Method: Ninety-six Japanese patients with major depressive disorder were treated with milnacipran, 50–100 mg/day, for 6 weeks. Severity of depression was assessed with the Montgomery-Åsberg Depression Rating Scale. Assessments were carried out at baseline and at 1, 2, 4, and 6 weeks of treatment. The method of polymerase chain reaction was used to determine allelic variants.

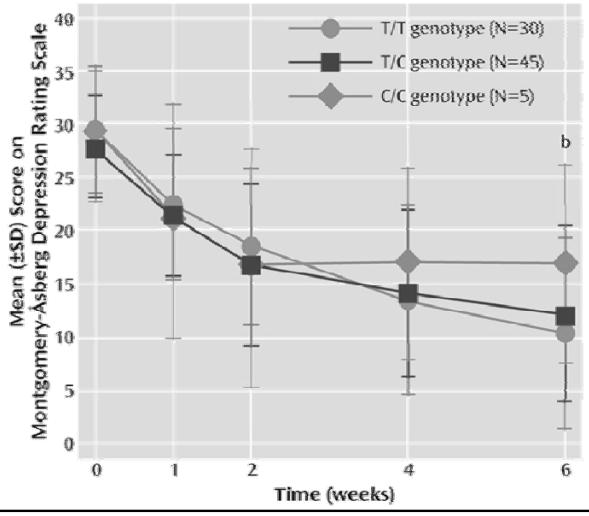
Results: Eighty patients completed the study. The presence of the T allele of the NET T-182C polymorphism was associated with a superior antidepressant response, whereas the A/A genotype of the NET G1287A polymorphism was associated with a slower onset of therapeutic response. In contrast, no influence of 5-HTT polymorphisms on the antidepressant response to milnacipran was detected.

Conclusions: The results suggest that NET but not 5-HTT polymorphisms in part determine the antidepressant response to milnacipran.

(Am J Psychiatry 2004; 161:1575–1580)

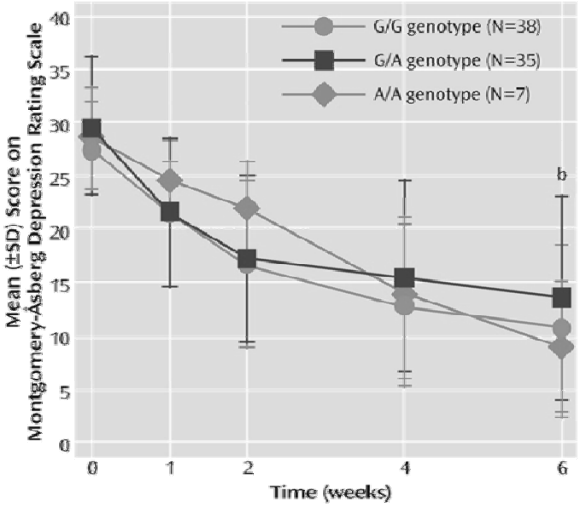
UHealth UNIVERSITY OF MIAMI HEALTH SYSTEM | UNIVERSITY OF MIAMI MILLER SCHOOL of MEDICINE

Montgomery-Åsberg Depression scores during 6 week treatment in relation to the NET T-128C polymorphism



Yoshida et al (2004) Am J Psychiatry 161:1575-1580.

Montgomery-Åsberg Depression scores during 6 week treatment in relation to the NET G-1287A polymorphism



Yoshida et al (2004) Am J Psychiatry 161:1575-1580.

Association of Polymorphisms in Genes Regulating the Corticotropin-Releasing Factor System With Antidepressant Treatment Response

Elisabeth B. Binder, MD, PhD; Michael J. Owens, PhD; Wei Liu, PhD; Todd C. Deveau, BS; A. John Rush, MD; Madhukar H. Trivedi, MD; Maurizio Fava, MD; Bekh Bradley, PhD; Kerry J. Ressler, MD, PhD; Charles B. Nemeroff, MD, PhD

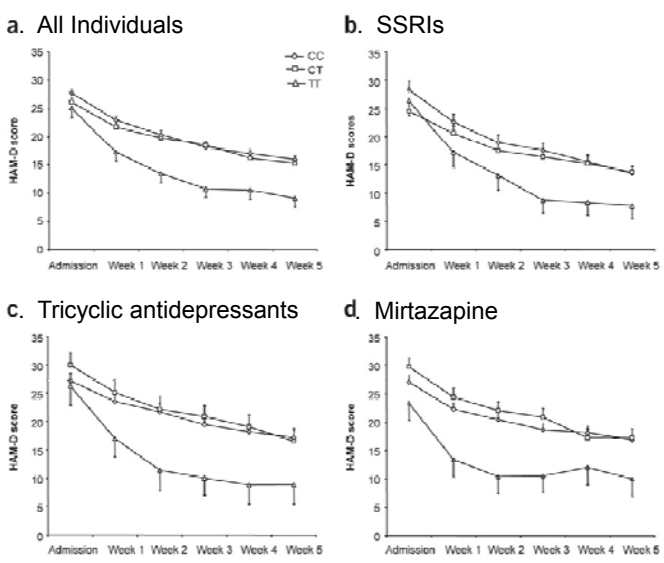
Arch Gen Psychiatry. 2010;67(4):369-379

Polymorphisms in *FKBP5* are associated with increased recurrence of depressive episodes and rapid response to antidepressant treatment

Elisabeth B Binder[1], Daria Salyakina[1], Peter Lichtner[2], Gabriele M Wochnik[1], Marcus Ising[1], Benno Pütz[1], Sergi Papiol[3], Shaun Seaman[1], Susanne Lucae[1], Martin A Kohli[1], Thomas Nickel[1], Heike E Künzel[1], Brigitte Fuchs[1], Matthias Majer[1], Andrea Pfennig[1], Nikola Kern[1], Jürgen Brunner[1], Sieglinde Modell[1], Thomas Baghai[4], Tobias Deiml[4], Peter Zill[4], Brigitta Bondy[4], Rainer Rupprecht[4], Thomas Messer[5], Oliver Köhnlein[5], Heike Dabitz[6], Tanja Brückl[1], Nina Müller[1], Hildegard Pfister[1], Roselind Lieb[1], Jakob C Mueller[2], Elin Lõhmussaar[2], Tim M Strom[2], Thomas Bettecken[2], Thomas Meitinger[2], Manfred Uhr[1], Theo Rein[1], Florian Holsboer[1] & Bertram Muller-Myhsok[1]

***Nature Genetics* (2004) 36 (12) 1319-1325.**

Polymorphisms in FKBP5 are associated with rapid response to antidepressant treatment



Binder et al (2004) Nature Genetics 36 (12) 1319-1325.

Epigenetic Drugs

- Drugs that target the proteins controlling chromatin modifications can modulate the expression of clusters of genes, presumably offering higher therapeutic efficacy than classical agents with single target pharmacologies that are susceptible to biochemical pathway degeneracy.

Valproic Acid has an Epigenetic Mode of Action (HDAC Inhibitor)

PSYCHOPHARMACOLOGY BULLETIN: Vol. 37 · Suppl. 2

Pharmacology of Divalproex

By Michael J. Owens, PhD, and Charles B. Nemeroff, MD, PhD

ORIGINAL ARTICLE

Efficacy of Valproate Maintenance in Patients With Bipolar Disorder and Alcoholism

A Double-blind Placebo-Controlled Study

Ihsan M. Salloum, MD, MPH; Jack R. Cornelius, MD, MPH; Dennis C. Daley, PhD; Levent Kirisci, PhD; Jonathan M. Himmelhoch, MD; Michael E. Thase, MD

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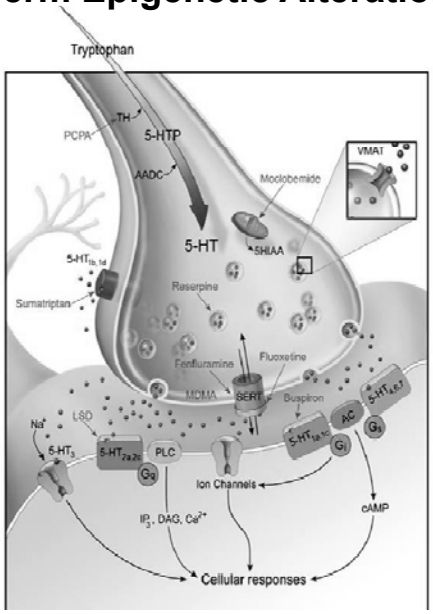
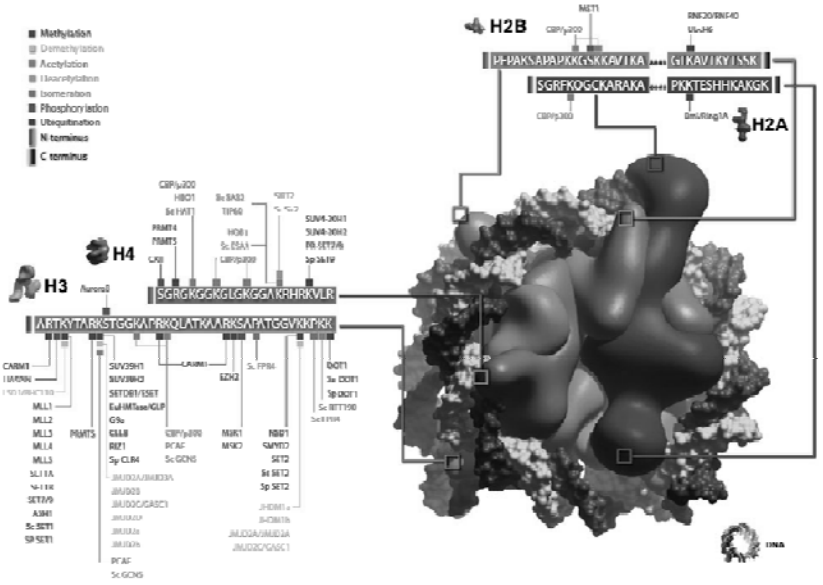
Antidepressants and ECT induce Long-Term Epigenetic Alterations



Hundreds of Histone / Chromatin Modifying Enzymes



"There's an old Wayne Gretzky quote that I love. 'I skate to where the puck is going to be, not where it has been.' And we've always tried to do that at Apple. Since the very very beginning. And we always will."

- Steve Jobs