Advances in Diagnosis, Neurobiology, and Treatment of Mood Disorders

June 13 - 14, 2016

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CME Outfitters

Personalized Medicine in Psychiatry: From Genetics and Epigenetics to Brain Imaging

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CME Outfitters

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Disclosures

- ***Research/Grants:*** National Institutes of Health (NIH)
- ***Consultant:*** Bracket (Clintara); Fortress Biotech; Gerson Lehrman Group, Inc. (GLG) Healthcare & Biomedical Council; Lundbeck; Mitsubishi Tanabe Pharma Development America; Prismic Pharmaceuticals, Inc.; Sunovion Pharmaceuticals Inc.; Taisho Pharmaceutical Inc.; Takeda Pharmaceuticals North America, Inc.; Total Pain Solutions (TPS); Xhale, Inc..
- ***Stockholder***AbbVie Inc.; Bracket; Celgene Corporation; Intermediate Holding Corp.; Network Life Sciences Inc.; OPKO Health, Inc.; Seattle Genetics, Inc.; Titan Pharmaceuticals, Inc.; Xhale, Inc.
- ***Income Sources or Equity of $10,000 or More:*** American Psychiatric Publishing; Bracket (Clintara); CME Outfitters, LLC; Takeda Pharmaceuticals North America, Inc.; Xhale, Inc.
- ***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); Anxiety Disorders Association of America (ADAA); Bracket (Clintara); Brain & Behavior Research Foundation (BBRF) (formerly National Alliance for Research on Schizophrenia and Depression [NARSAD]); Laureate Institute for Brain Research, Inc. RiverMend Health, LLC; Skyland Trail; Xhale, Inc.
- ***Board of Directors:*** American Foundation for Suicide Prevention (AFSP); Anxiety Disorders Association of America (ADAA); GratitudeAmerica, Inc.

Learning Objectives

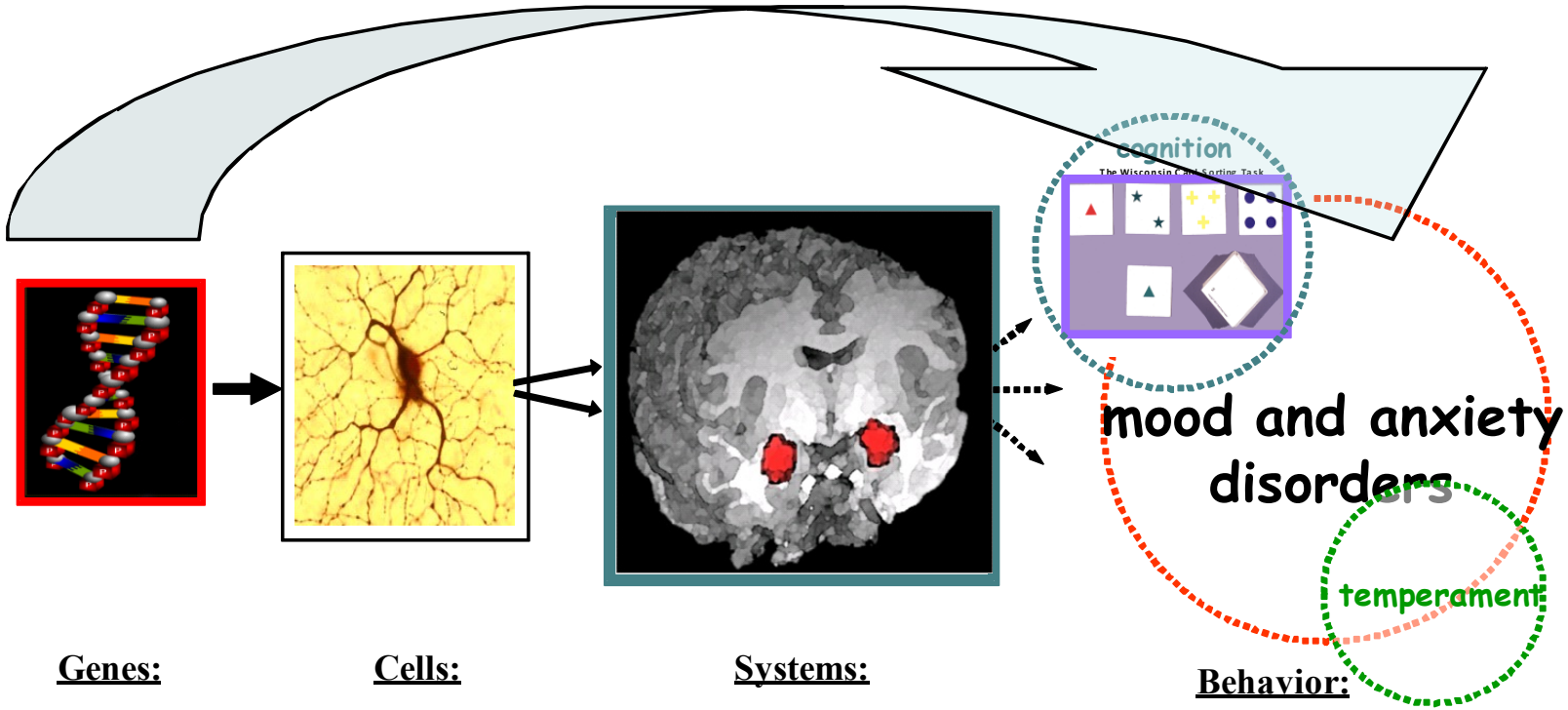
- Identify ways that clinical practice has been impacted by a personalized approach to medicine.
- Translate the latest evidence from genetics and brain imaging to improved care of patients with mood disorders.

Audience Response

Which of the following is true of NE dysfunction linked to depression?

A. Decreased density of B-adrenergic receptors is found postmortem
B. NE reuptake inhibitors are not effective antidepressants
C. High levels of NE metabolites are found in the urine
D. Low levels of NE metabolites are found in the urine

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



Genes:

sequence variants and variable gene processing

Cells:

molecular pathways

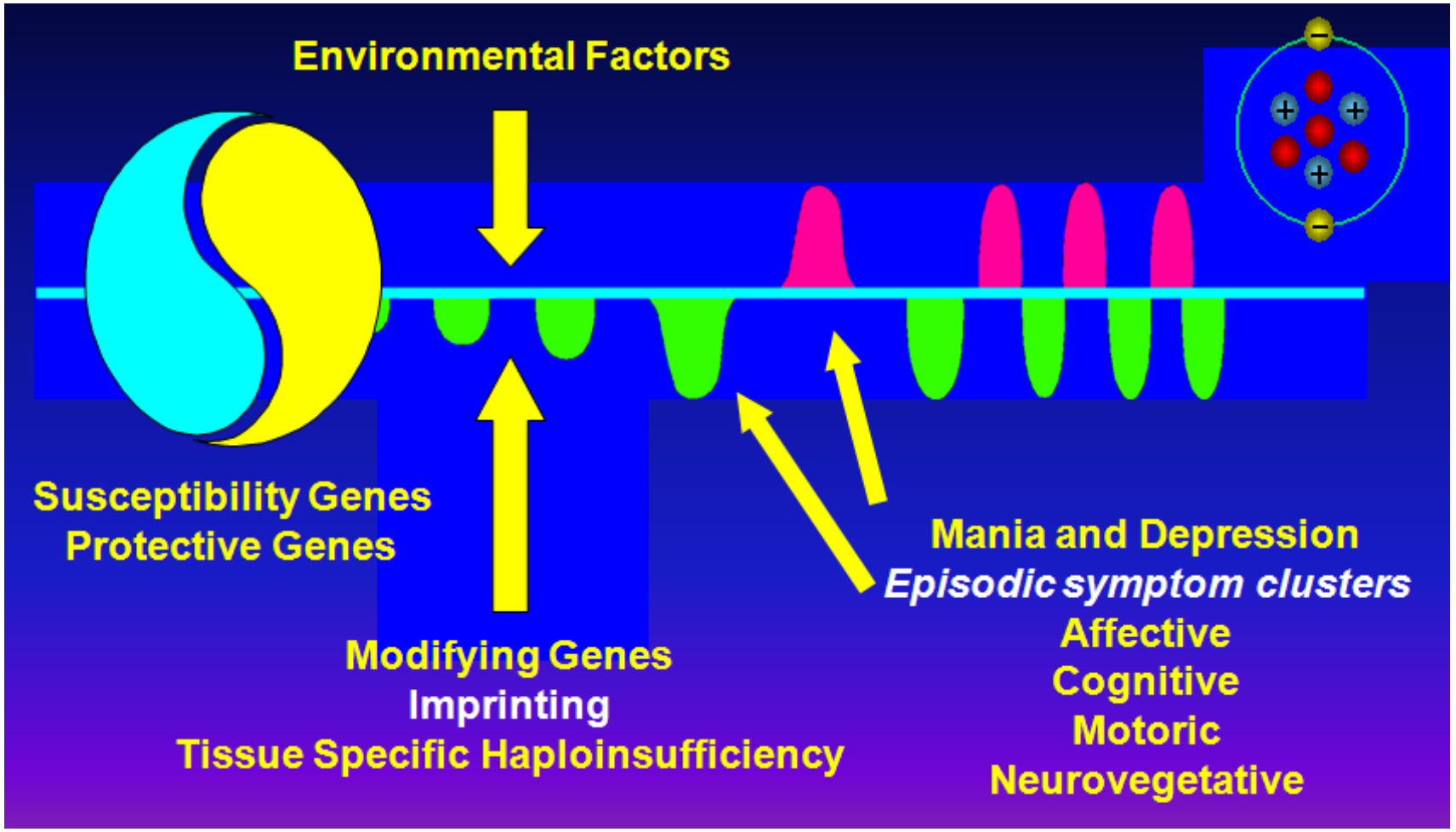
Systems:

activity in emotion processing circuitry

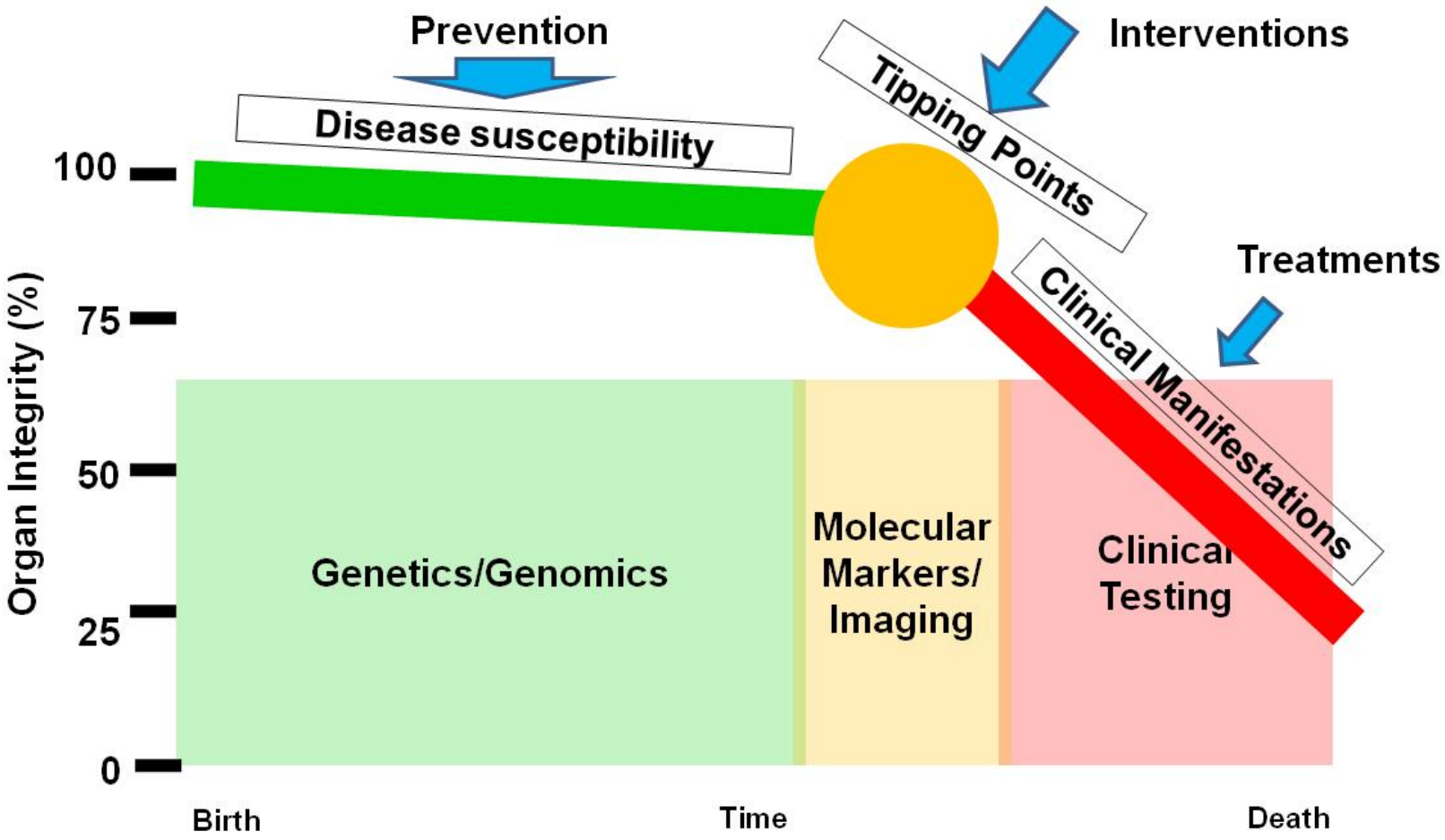
Behavior:

Clinical phenotype

The Neurobiology of Bipolar Disorder: Theoretical Considerations

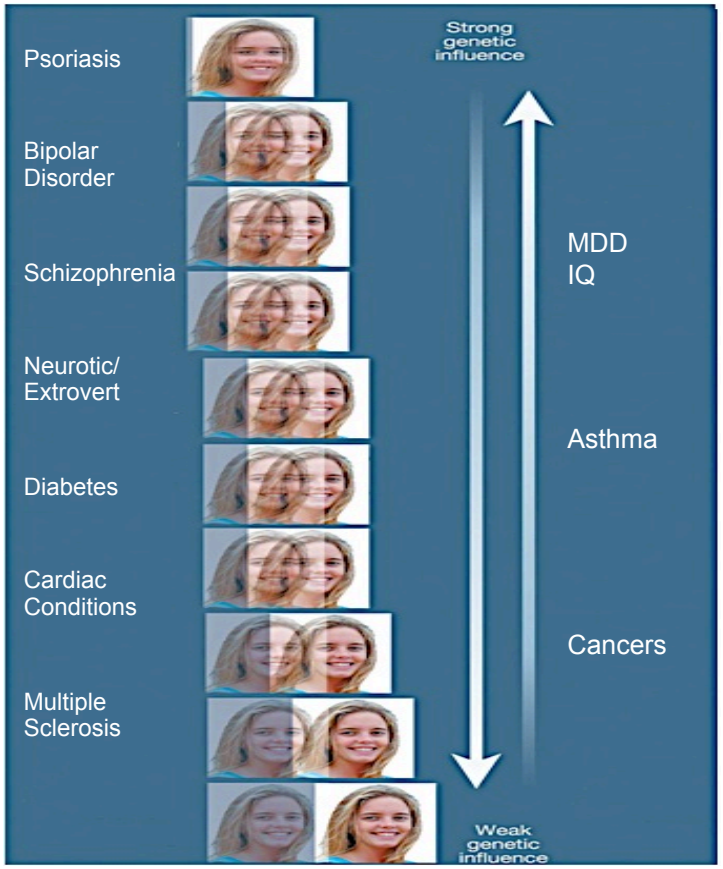


21st Century Medicine



Implications for Public Understanding

Nature, Nurture, and Human Disease



"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.

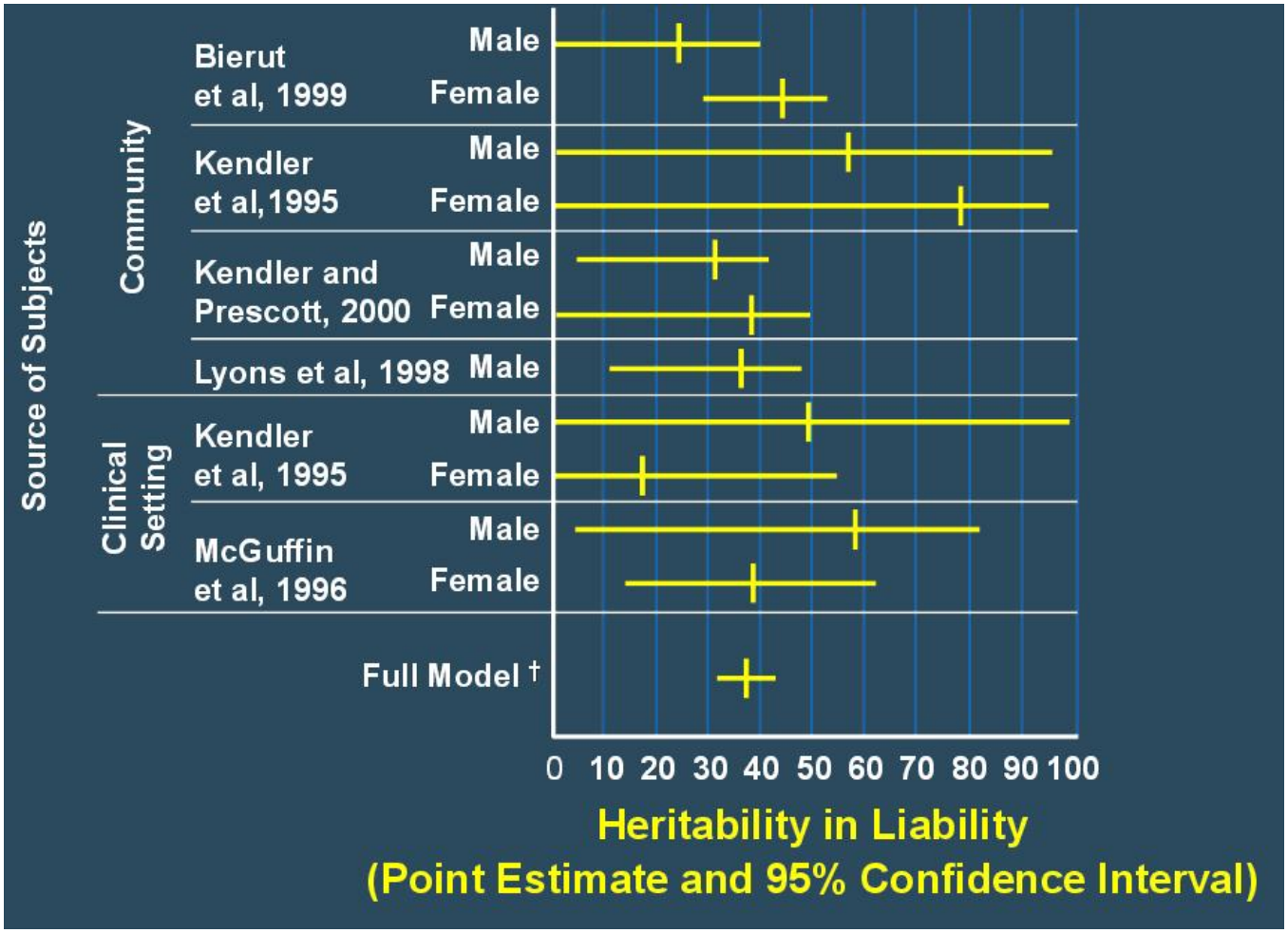
Chakravarti A, et al. *Nature*. 2003;421:412-414. PMID 12540911.

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

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. 1988 Sep;(3):16-25.

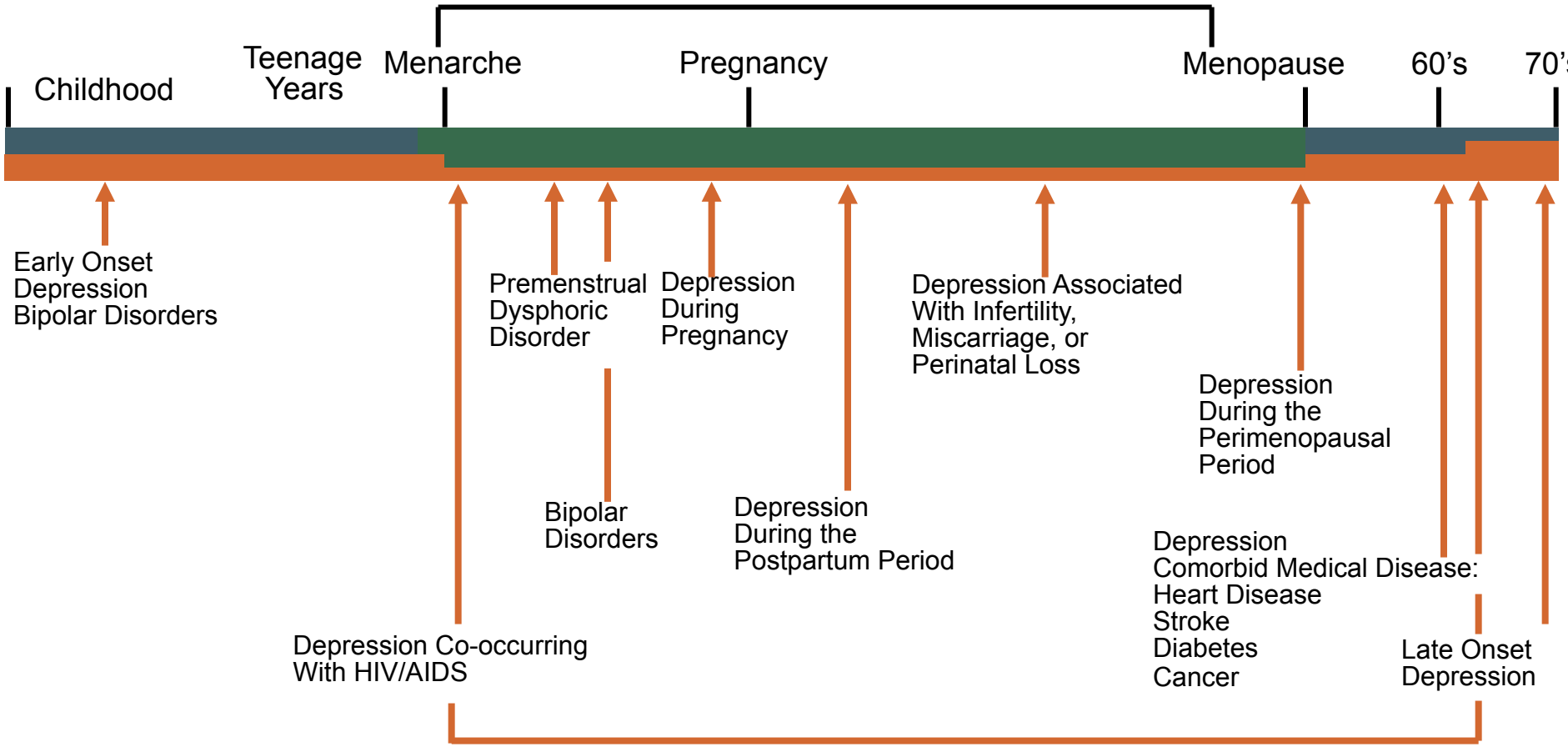
Genetics of MDD



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

Sullivan PF, et al. *Am J Psychiatry*. 2000;157(10):1552-1562.

Mood Disorders Across the Life Cycle



Orange = Women; Blue = Men

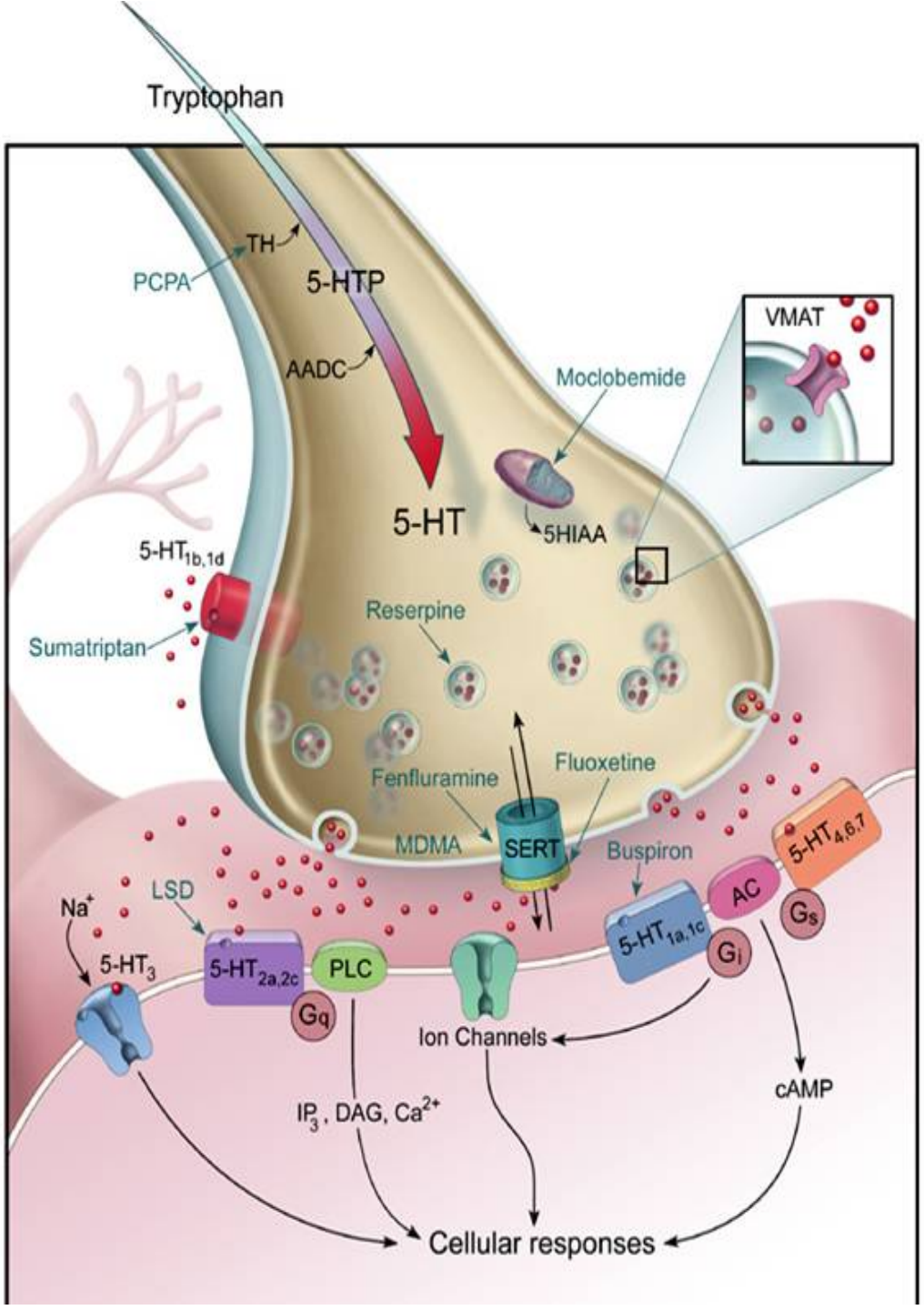
Confirmed Linkages in Bipolar Disorder

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

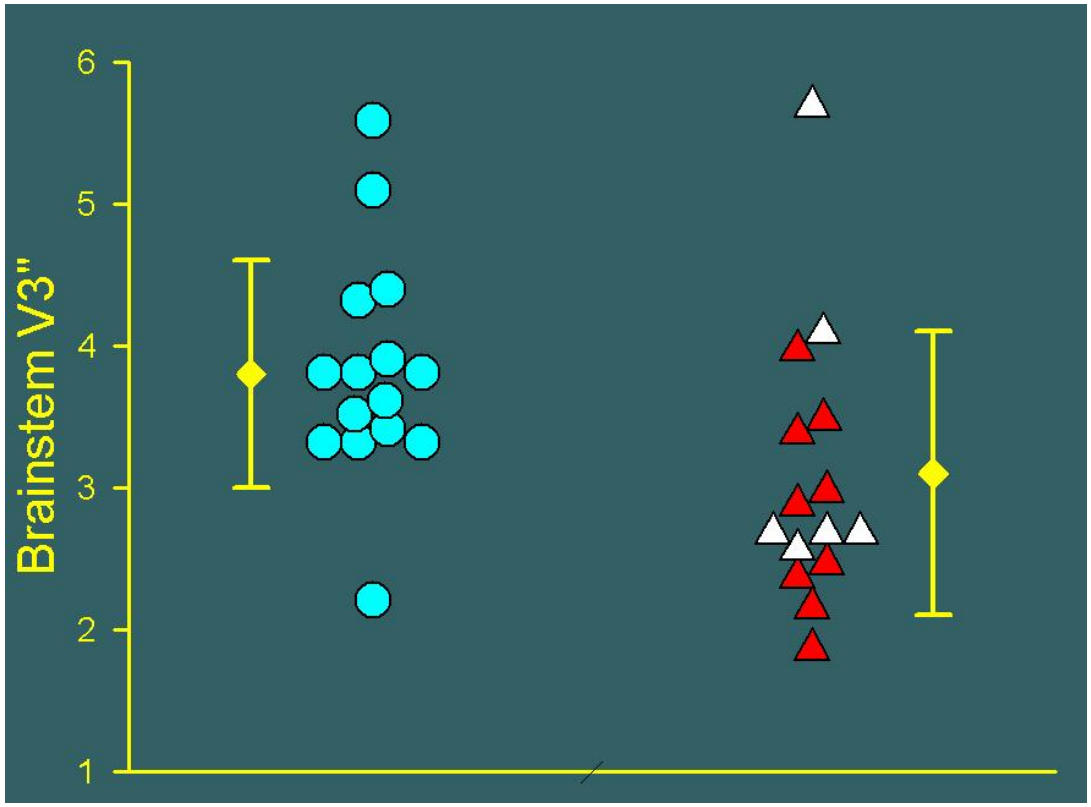
Berrettini. In *Neuropsychopharmacology; The Fifth Generation of Progress* (Davis et al editors) 2002; p1031.

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


Tryptophan
TH
PCPA
5-HTP
AADC
VMAT
Moclobemide
5-HT
5HIAA
5-HT1b,1d
Sumatriptan
Reserpine
Fenfluramine
Fluoxetine
MDMA
SERT
Buspiron
5-HT4,6,7
AC
Gs
LSD
Na+
5-HT3
5-HT2a,2c
PLC
Gq
5-HT1a,1c
Gi
Ion Channels
cAMP
IP3, DAG, Ca2+
Cellular responses

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



*p = 0.03

Malison RT, et al. *Biol Psychiatry* 1998;44(11):1090-1098.

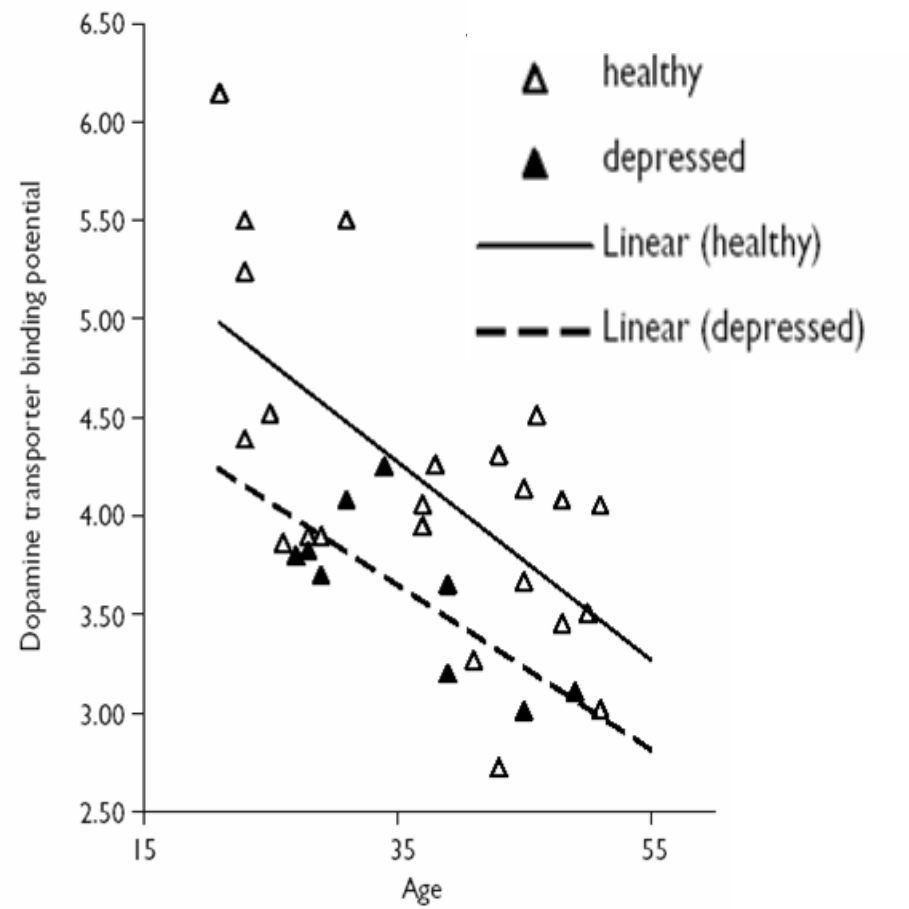
Dopamine and Depression

- 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 Biological Fluids Studies

- Role of DA circuits in the actions of antidepressants
  - MAOIs
  - Effects on the DA transporter

Lower Dopamine Tranporter Binding Potential in Striatum During Depression



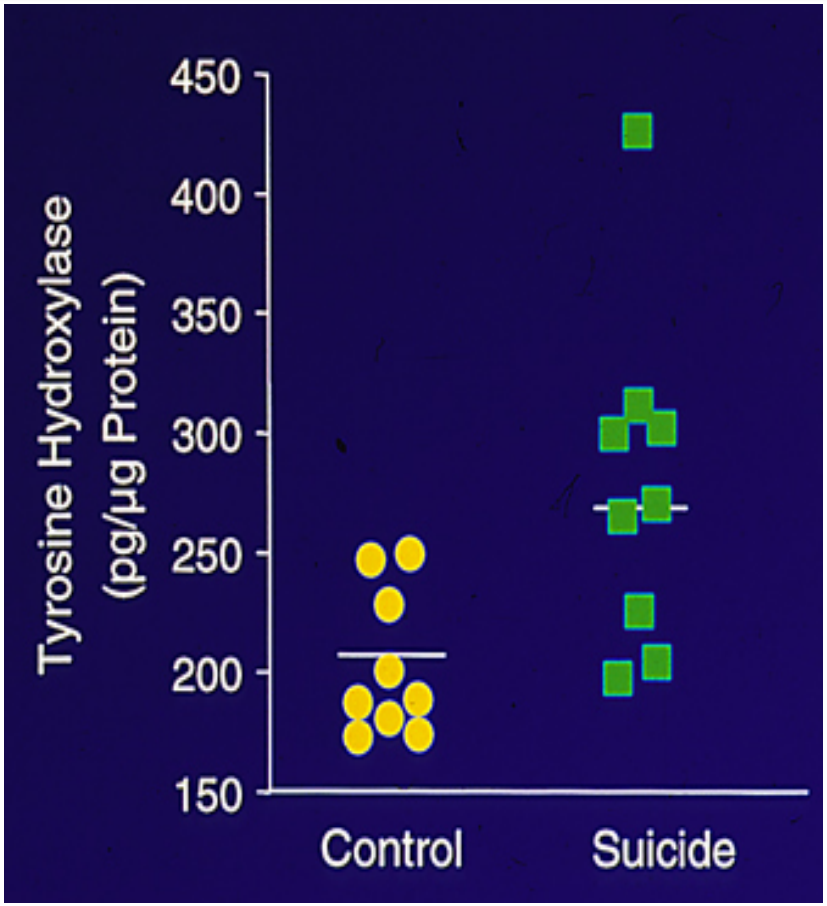
Dopamine transporter binding potential in bilateral striatum is lower in depressed patients. Data was analyzed using analysis of covariance with age as a covariate, examining effect of diagnosis (effect of diagnosis: $F_{1,29} = 7.1$, $p = 0.01$).

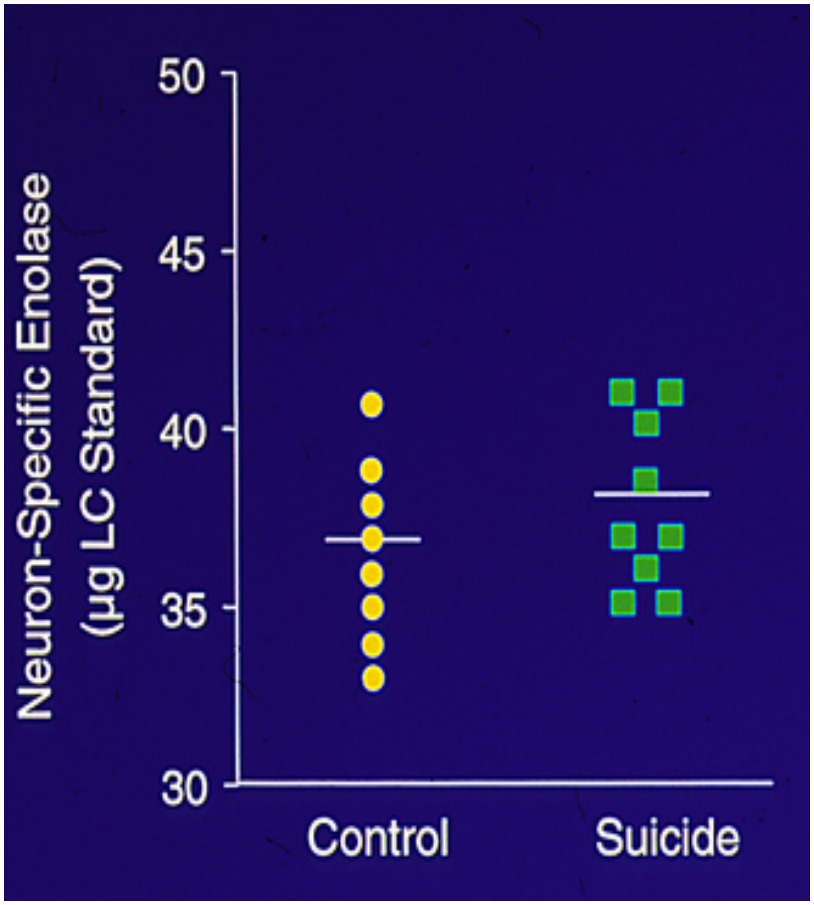
Meyer JH, et al. *Neuroreport.* 2001;12(18):4121-4125.

Norepinephrine Alterations

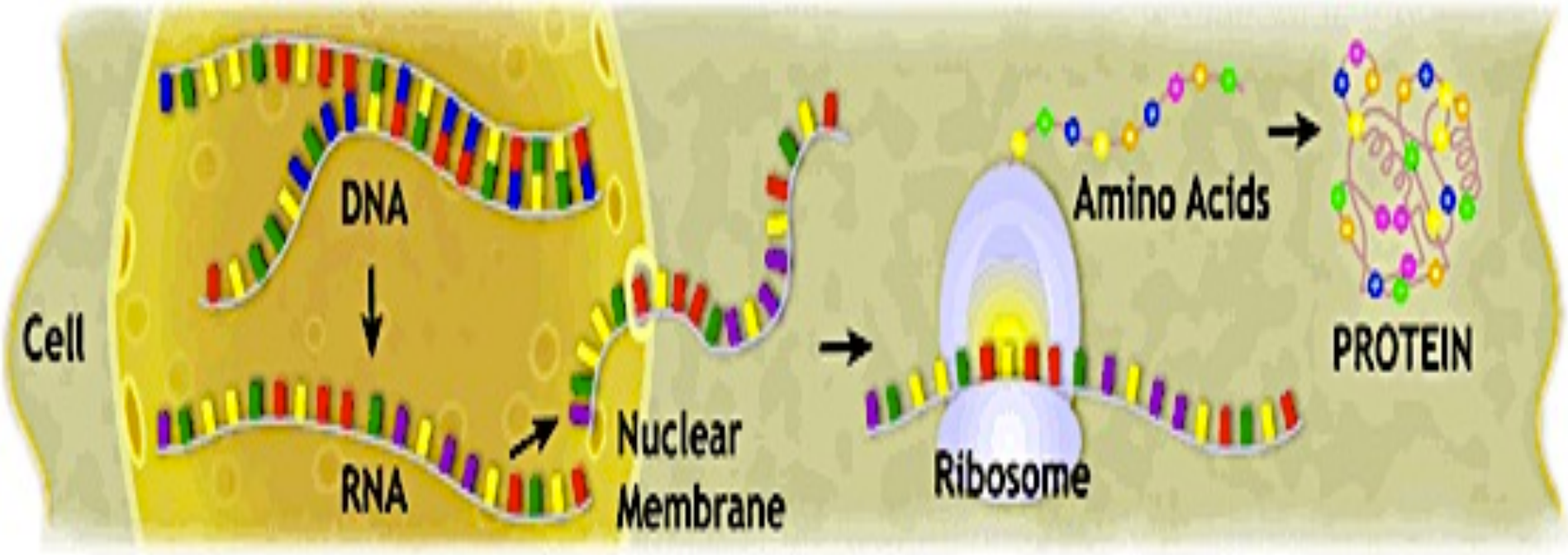
- NE dysfunction is linked to depression
  - Low levels of NE metabolites are found in the urine and CSF of depressed patient
  - Increased density of B-adrenergic receptors is found at postmortem in the cortex of depressed suicide victims
  - NE reuptake inhibitors are effective antidepressants (desipramine,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

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

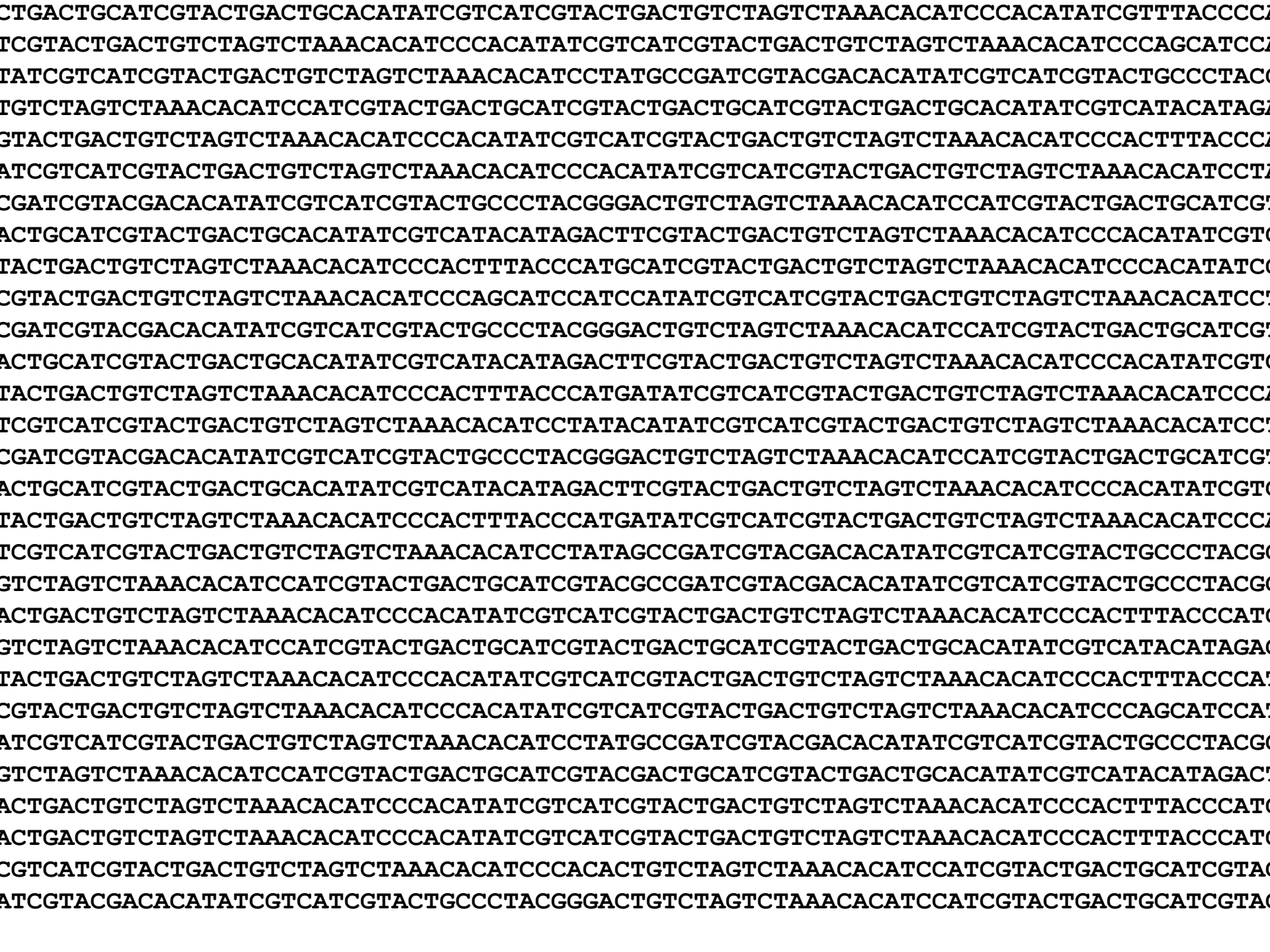




Ordway GA, et al. *J Neurochem*. 1994;62(2):680-685.



Our DNA is our instruction manual!
We can now read the whole manual!!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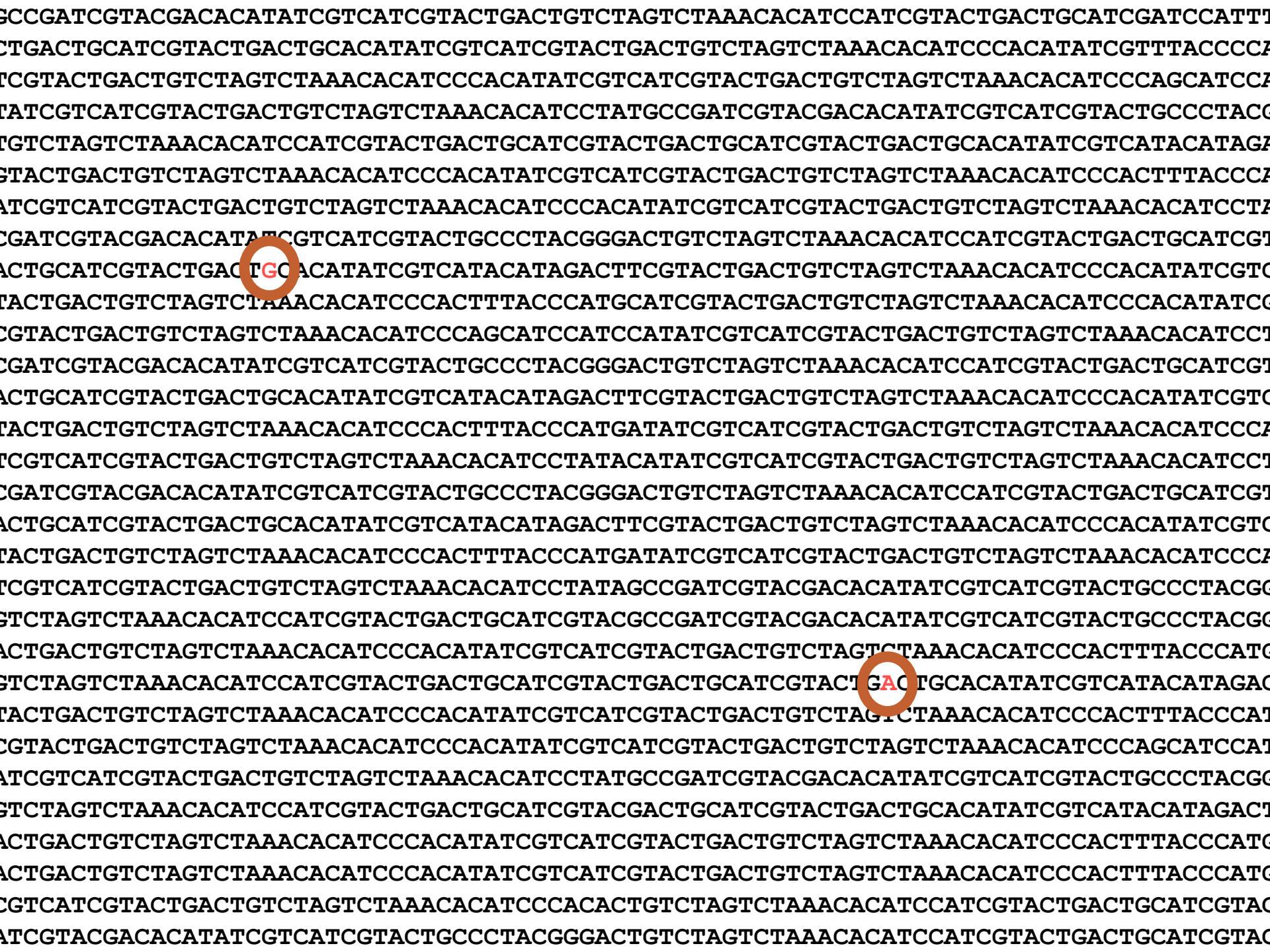
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CGATCGTACGACACATATCGTCATCGTACTGCCCTACGGGACTGTCTAGTCTAAACACATCCATCGTACTGACTGCATCGT
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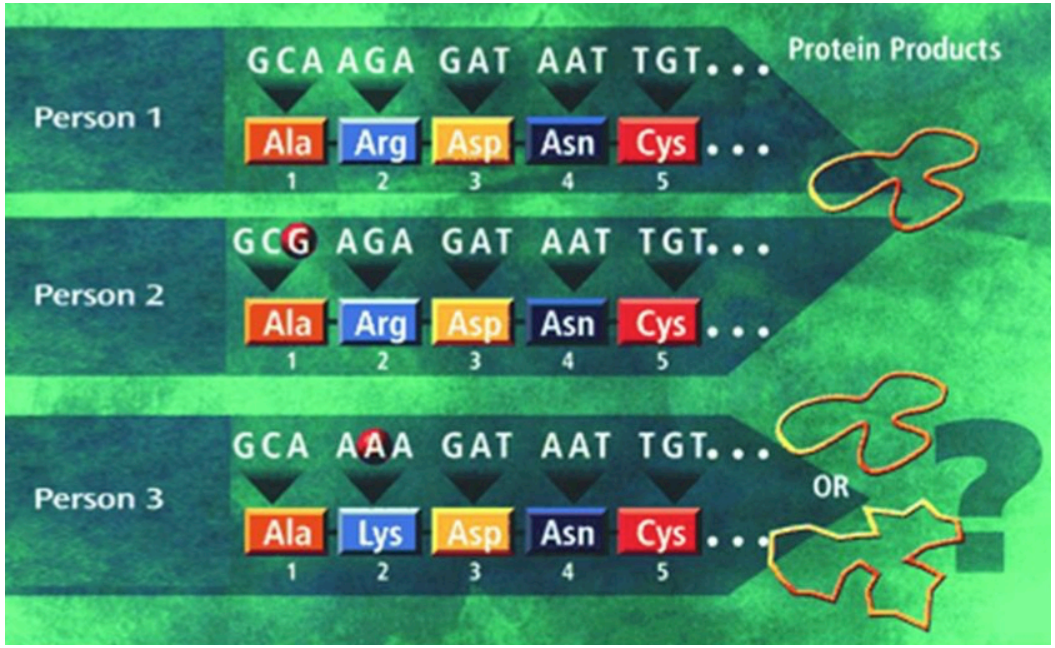
ATCGTACGACACATATCGTCATCGTACTGCCCTACGGGACTGTCTAGTCTAAACACATCCATCGTACTGACTGCATCGTAC

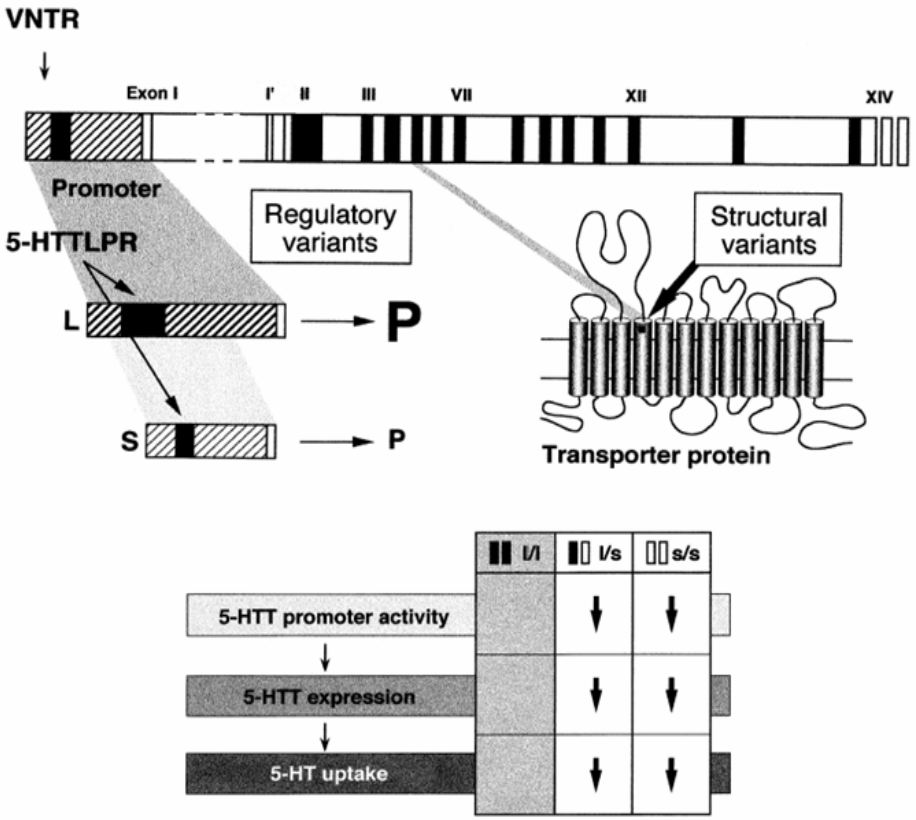
DNA Sequence Variation Can Change the Protein Produced by the Genetic Code



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.

Tamminga, CA. *Am J Psychiatry*. 2001;158:691.

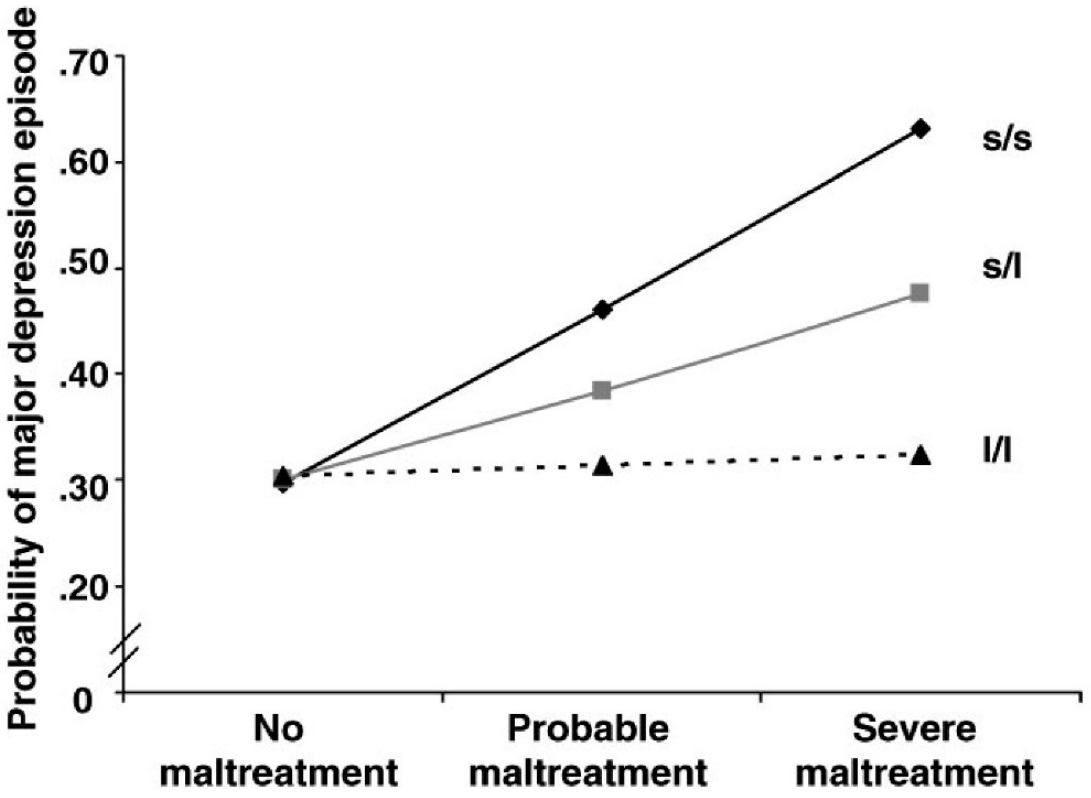
5’-HT Transporter Promoter Polymorphism (SLC6A4, 17q11)



Adapted from Lesch KP, Mossner R. *Biol Psychiatry.* 1998;44(3):179-192.

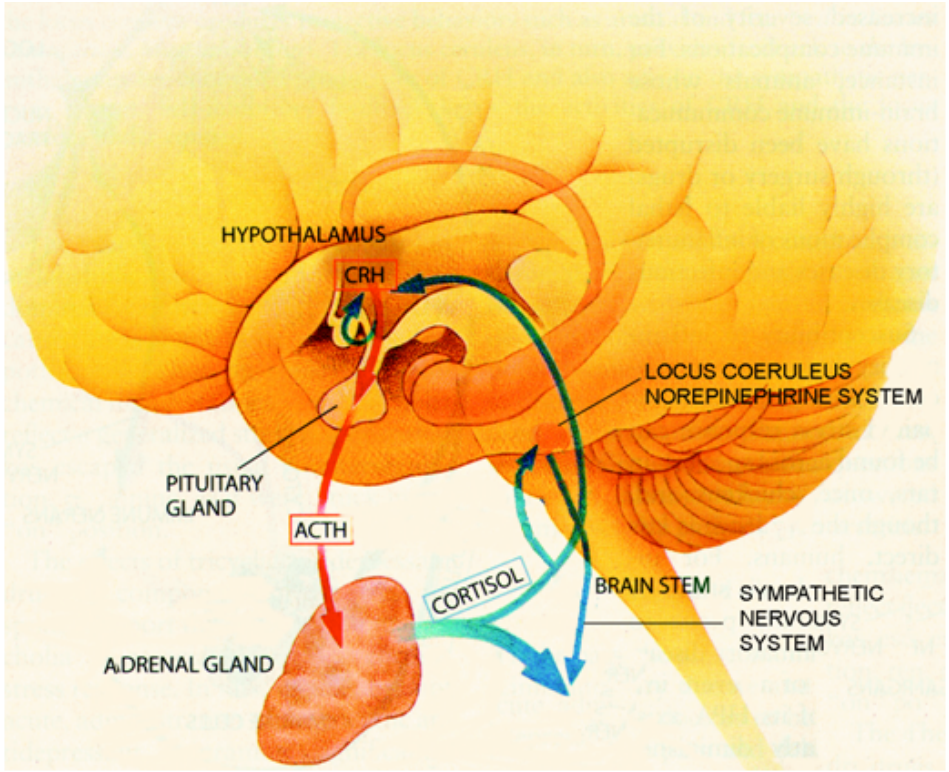
Results of Regression Analysis

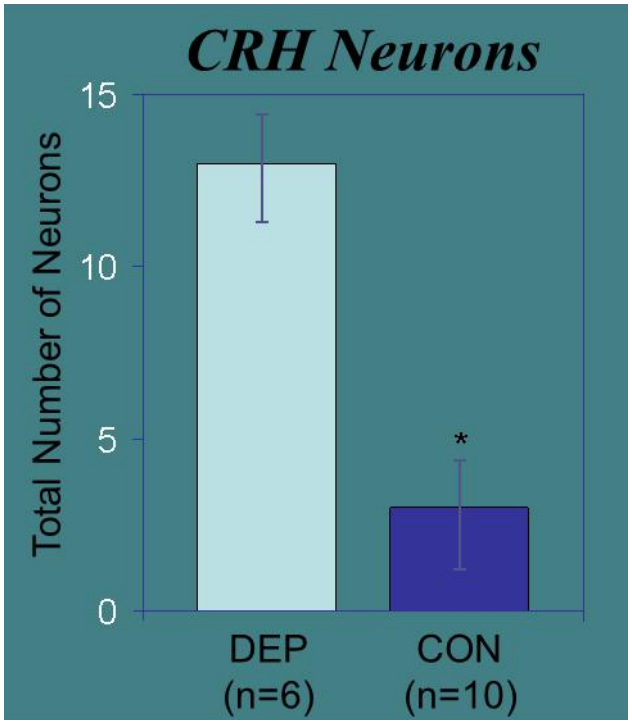
Estimating the Association Between Childhood Maltreatment (Between the Ages of 3 and 11 Years) and Adult Depression (Ages 18 to 26), as a Function of 5-HTT Genotype



Caspi A, et al. *Science*. 2003;301(5631):386-389. PMID: 12869766.

Regulation of Stress Response by CRH and HPA Axis





*p < .01; mean ± SEM

HPA = hypothalamic-pituitary-adrenal; ACTH = adrenocorticotropic hormone;
DEP = depressed patients; CON = control patients

Purba JS, et al. *Neuroendocrinology.* 1995;62(1):62-70. PMID: 7566440.
Raadsheer FC, et al. *Neuroendocrinology.* 1994;60:436-444.

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

Sample Demographics

	N	Percentage
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%
Mixed	5	1%
Other	3	.6%
Education		
< 12th Grade	153	315
High School Graduate or GED	217	44%
Some College or Technical School	78	15%
College Graduate	21	45
Some Graduate School	9	25

Bradley RG, et al. *Arch Gen Psychiatry.* 2008; 65(2):190-200.

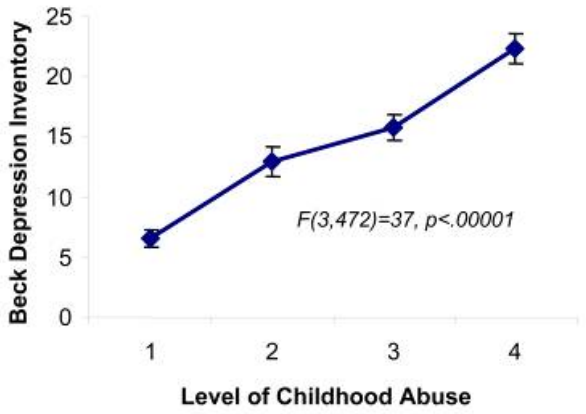
Sample Demographics

	N	Percentage
Employment Status		
Currently Unemployed	338	68%
Currently Employed	162	38%
Caucasian or White	4	.8%
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

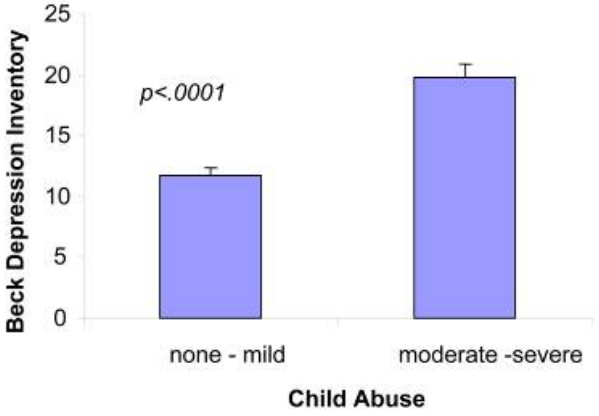
Bradley RG, et al. *Arch Gen Psychiatry.* 2008; 65(2):190-200.

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 RG, et al. *Arch Gen Psychiatry.* 2008; 65(2):190-200.

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

Bradley RG, et al. *Arch Gen Psychiatry.* 2008; 65(2):190-200.

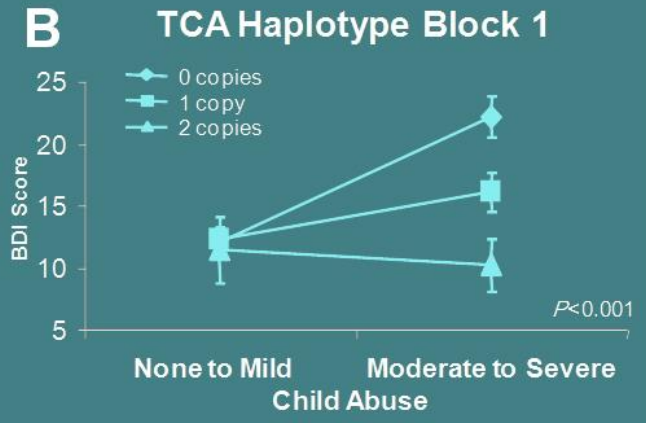
CRHR1 Polymorphism Haplotypes Interact With Level of Childhood Abuse in the Prediction of Adult Depression

A

Block 1 Haplotypes

rs7209436	rs4792887	rs110402	Frequency (%)
C	T	G	34.1
C	C	G	34.0
T	C	A	30.4

B



C

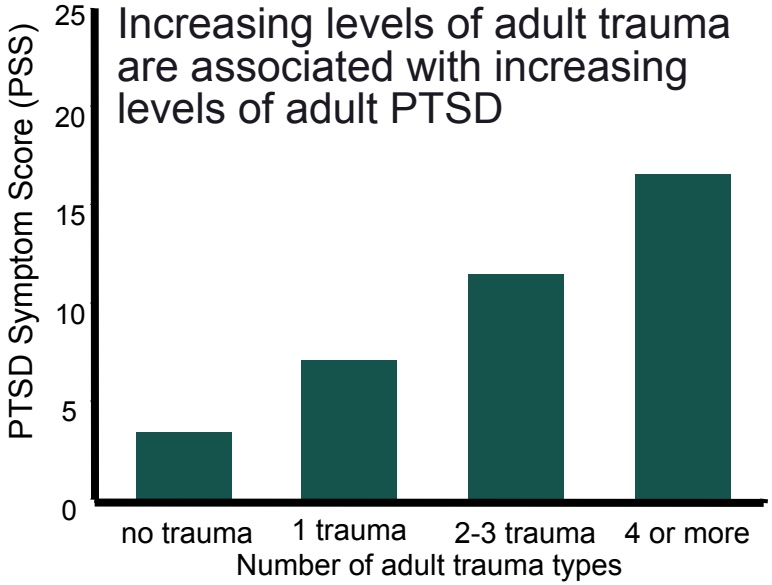
Most Significant SNP Haplotypes

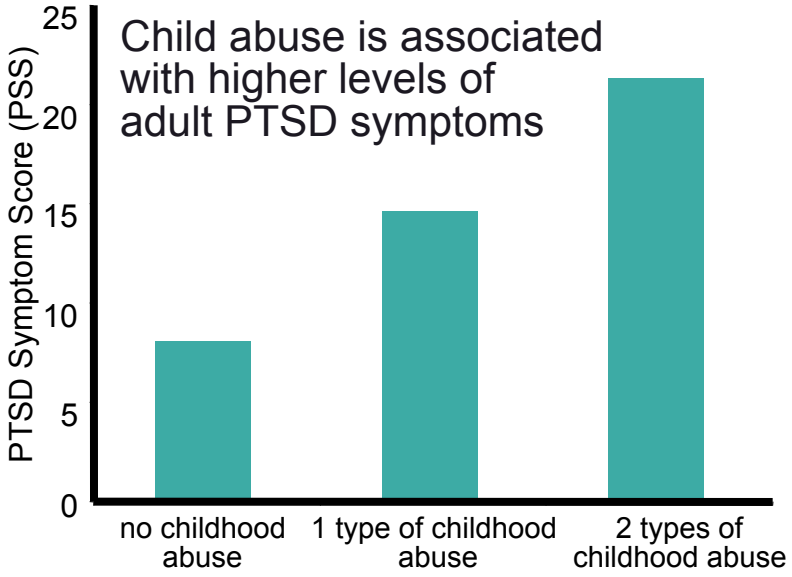
rs7209436	rs110402	rs242924	Frequency (%)
C	G	G	66.5
T	A	T	28.8

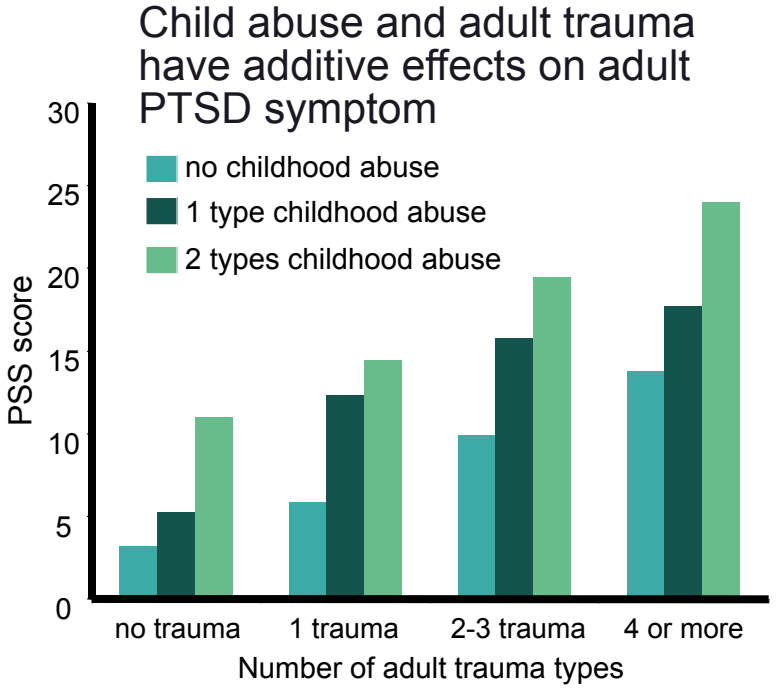
D

Bradley RG, et al. *Arch Gen Psychiatry.* 2008;65:190-200.

Adult Trauma and Child Abuse Predict PTSD

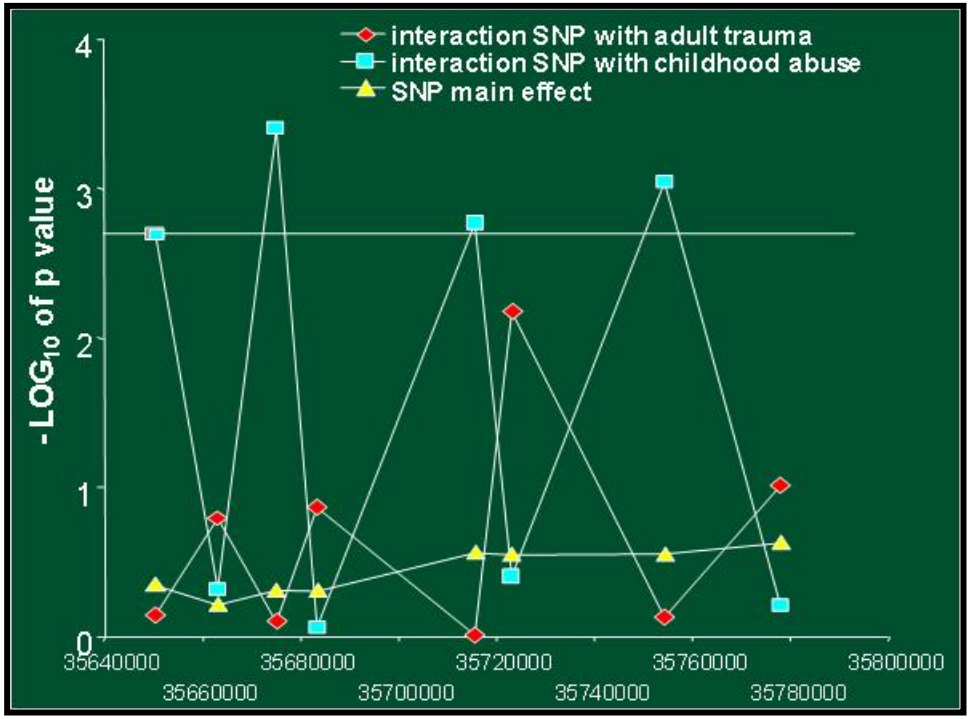


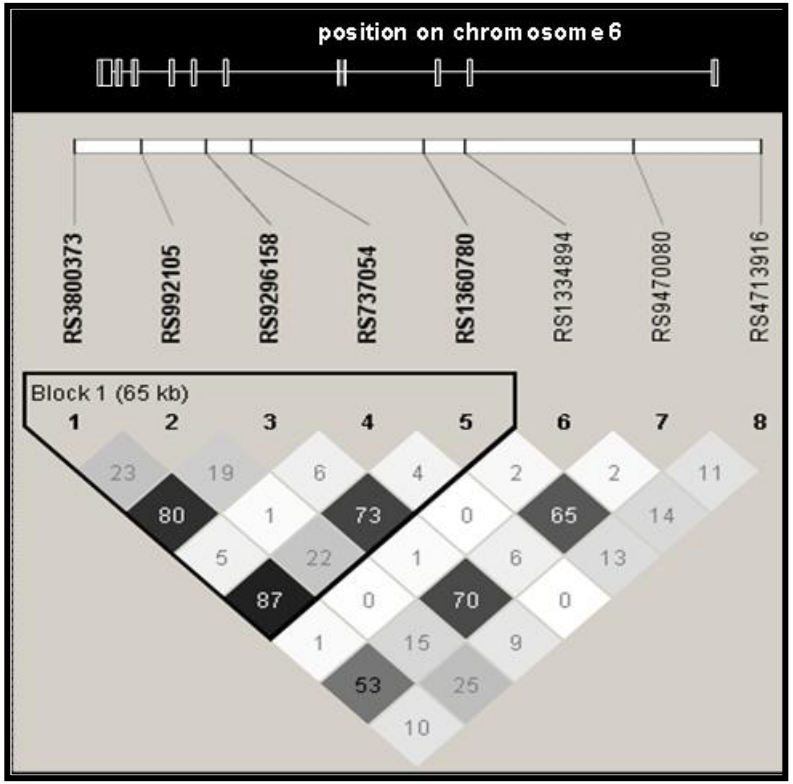




Binder EB, et al. *JAMA*. 2008;299:1291-1305.

FKBP5 SNPs and Main Genetic Effect on PTSD Symptoms and Interaction Effects with Adult Trauma Levels and Child Abuse

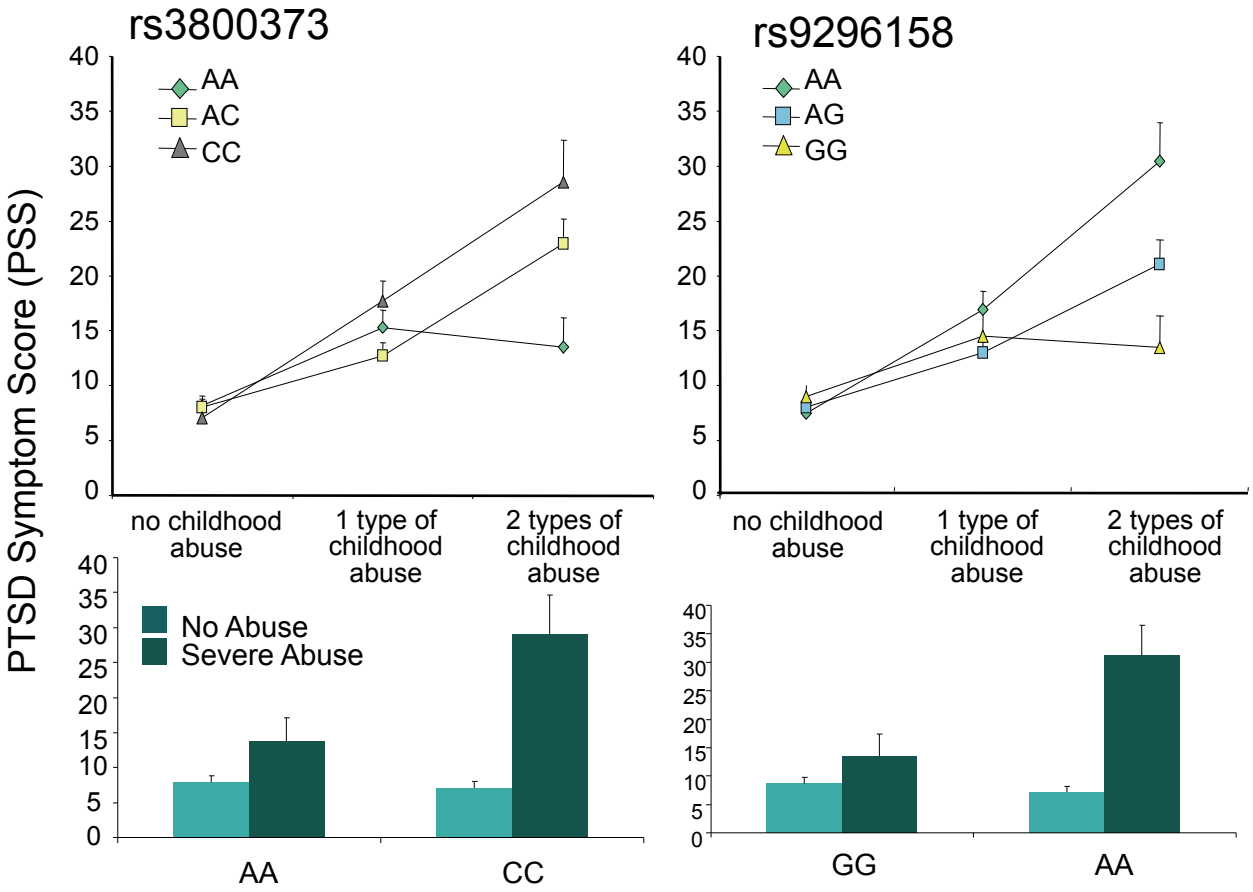




Binder EB, et al. *JAMA*. 2008;299(11):1291-1305.

PTSD Severity, *FKBP5* SNP Genotypes and Child Abuse

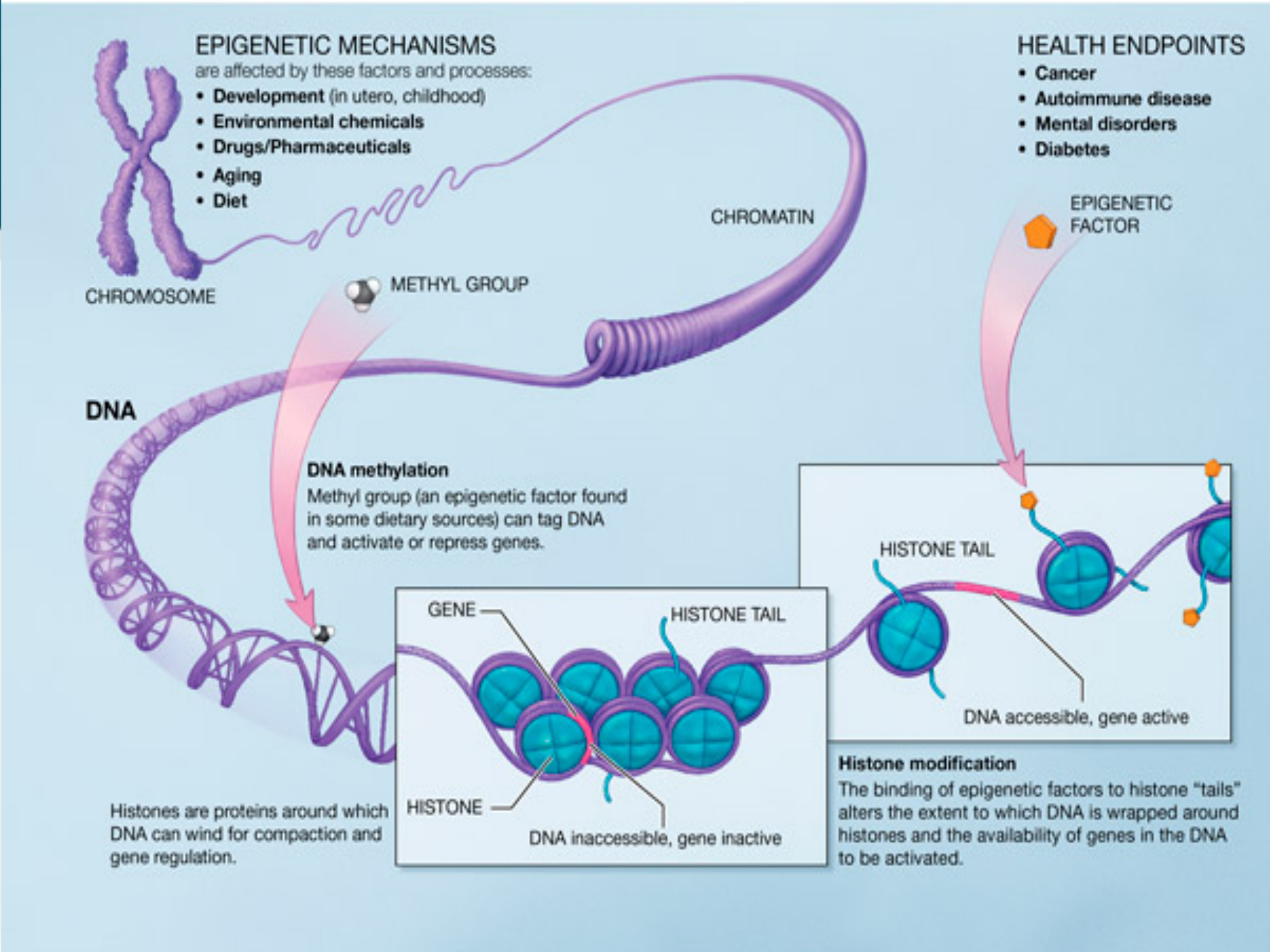
For all 4 SNPs *(rs1360780 and rs9470080 not shown)* an additive interaction effect with child abuse on PSS score is observed



Binder EB, et al. *JAMA.* 2008:299:1291-1305.

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.

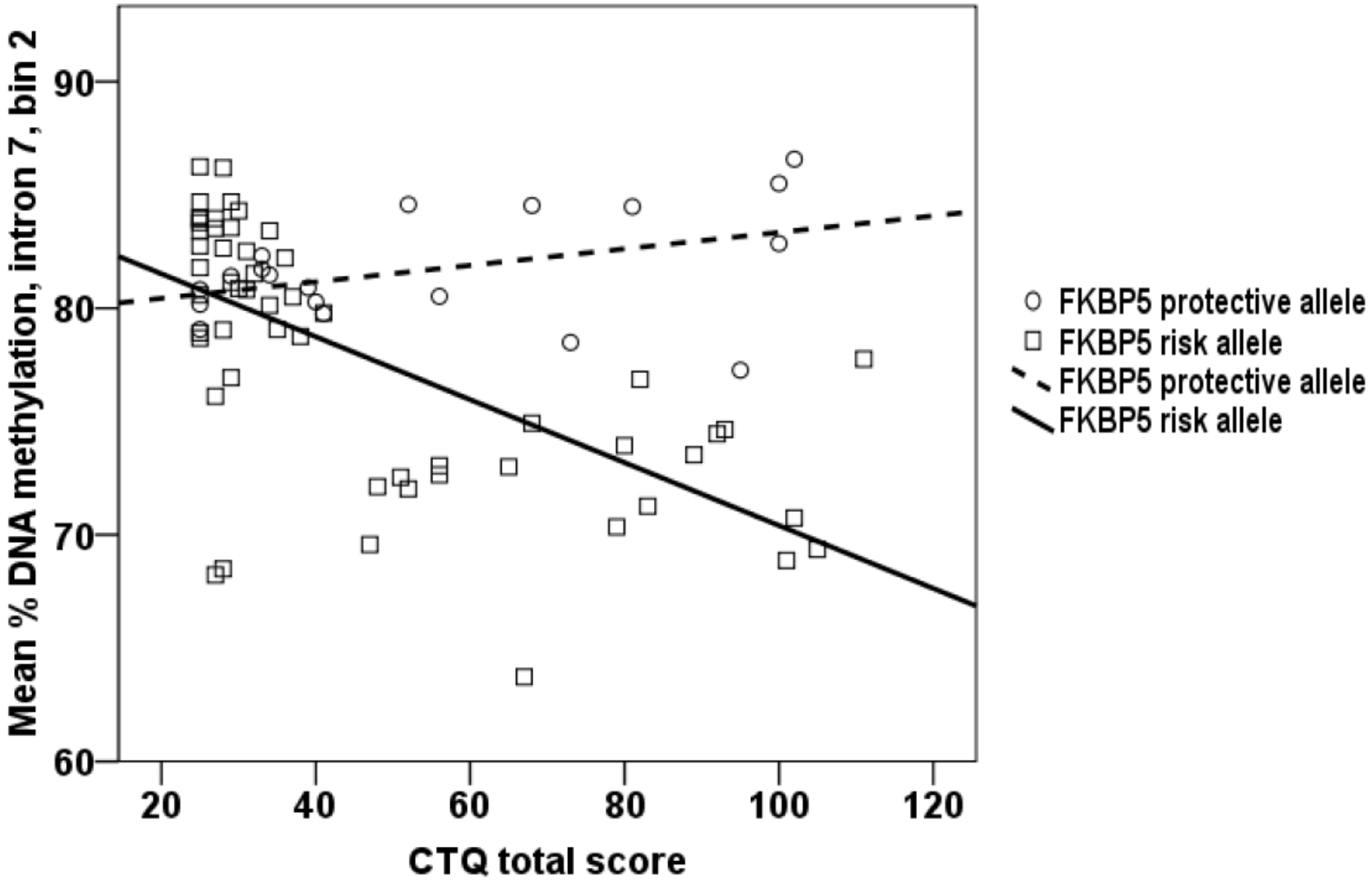

EPIGENETIC MECHANISMS
are affected by these factors and processes:
• Development (in utero, childhood)
• Environmental chemicals
• Drugs/Pharmaceuticals
• Aging
• Diet
HEALTH ENDPOINTS
• Cancer
• Autoimmune disease
• Mental disorders
• Diabetes
CHROMOSOME
CHROMATIN
METHYL GROUP
EPIGENETIC FACTOR
DNA
DNA methylation
Methyl group (an epigenetic factor found in some dietary sources) can tag DNA and activate or repress genes.
GENE
HISTONE TAIL
HISTONE
DNA inaccessible, gene inactive
HISTONE TAIL
DNA accessible, gene active
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.

Allele-Specific DNA Demethylation in *FKBP5*: A Molecular Mediator of Gene X Childhood Trauma Interactions

Torsten Klengel, Divya Mehta, Christoph Anacker, Jens C. Pruessner, Carmine M. Pariante, Thaddeus W.W. Pace, Kristina B. Mercer, Helen S. Mayberg, Bekh Bradley, Charles B. Nemeroff, Florian Holsboer, Christine M. Heim, Kerry J. Ressler, Theo Rein, and Elisabeth B. Binder

A polymorphism in the FK506 binding protein 5 (*FKBP5*) gene, an important regulator of the stress hormone system, increase the risk of developing stress-related psychiatric disorders in adulthood by allele-specific, childhood trauma-dependent DNA demethylation in functional glucocorticoid response elements (GREs) of *FKBP5*. This demethylation is linked to increased stress-dependent gene transcription followed by a long-term dysregulation of the stress hormone system and a global impact on the function of immune cells and brain areas associated with stress regulation.

Klengel T, et al. *Nat Neurosci.* 2013;16(1):33-41. PMID: 23201972.



Klengel T, et al. *Nat Neuroci.* 2013;16(1):33-41.

ARTICLE

doi:10.1038/nature09856

Post-traumatic stress disorder is associated with PACAP and the PAC1 receptor

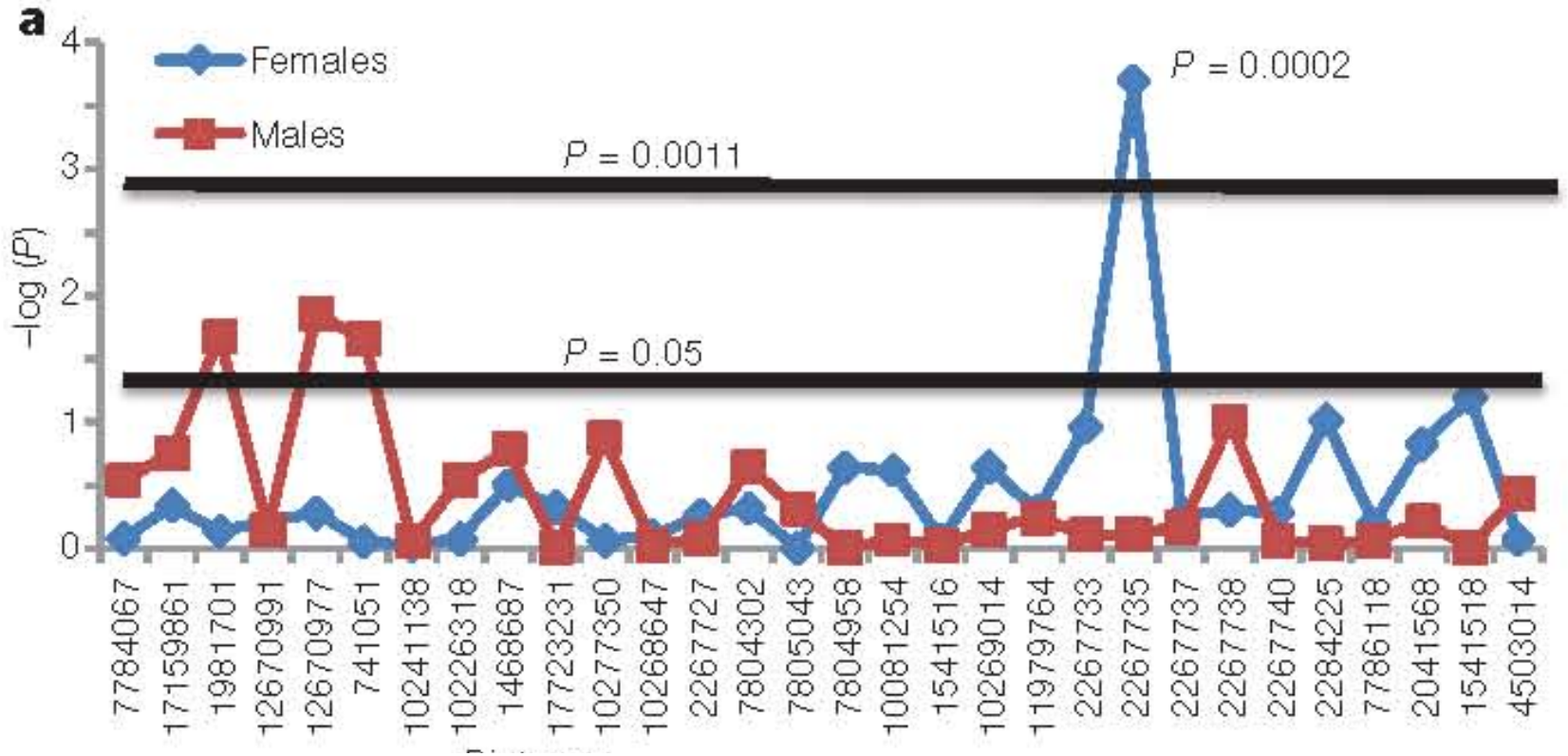
Kerry J. Ressler[1,2,4], Kristina B. Mercer[1], Bekh Bradley[2,3], Tanja Jovanovic[2], Amy Mahan[4], Kimberly Kerley[1], Seth D. Norrholm[2,3], Varun Kilaru[2], Alicia K. Smith[2], Amanda J. Myers[5], Manuel Ramirez[5], Anzhelika Engel[5], Sayamwong E. Hammack[6], Donna Toufexis[4,6], Karen M. Braas[7], Elisabeth B. Binder[2,8] & Victor May[7]

Pituitary adenylate cyclase-activating polypeptide (PACAP) is known to broadly regulate the cellular stress response. In contrast, it is unclear if the PACAP–PAC1 receptor pathway has a role in human psychological stress responses, such as post-traumatic stress disorder (PTSD). Here we find, in heavily traumatized subjects, a sex-specific association of PACAP blood levels with fear physiology, PTSD diagnosis and symptoms in females. We examined 44 single nucleotide polymorphisms (SNPs) spanning the PACAP (encoded by *ADCYAP1*) and PAC1 (encoded by *ADCYAP1R1*) genes, demonstrating a sex-specific association with PTSD. A single SNP in a putative oestrogen response element within *ADCYAP1R1*, rs2267735, predicts PTSD diagnosis and symptoms in females only. This SNP also associates with fear discrimination and with *ADCYAP1R1* messenger RNA expression in human brain. Methylation of *ADCYAP1R1* in peripheral blood is also associated with PTSD. Complementing these human data, *ADCYAP1R1* mRNA is induced with fear conditioning or oestrogen replacement in rodent models. These data suggest that perturbations in the PACAP–PAC1 pathway are involved in abnormal stress responses underlying PTSD. These sex-specific effects may occur via oestrogen regulation of *ADCYAP1R1*. PACAP levels and *ADCYAP1R1* SNPs may serve as useful biomarkers to further our mechanistic understanding of PTSD.

Ressler KJ, et al. *Nature*. 2011;470(7335):492-497.

ADCYAP1R1 Associated with PTSD in Females

Only the *ADCYAP1R1* receptor SNP rs2267735 remained significant after experiment correction for sex and 44 independent tests



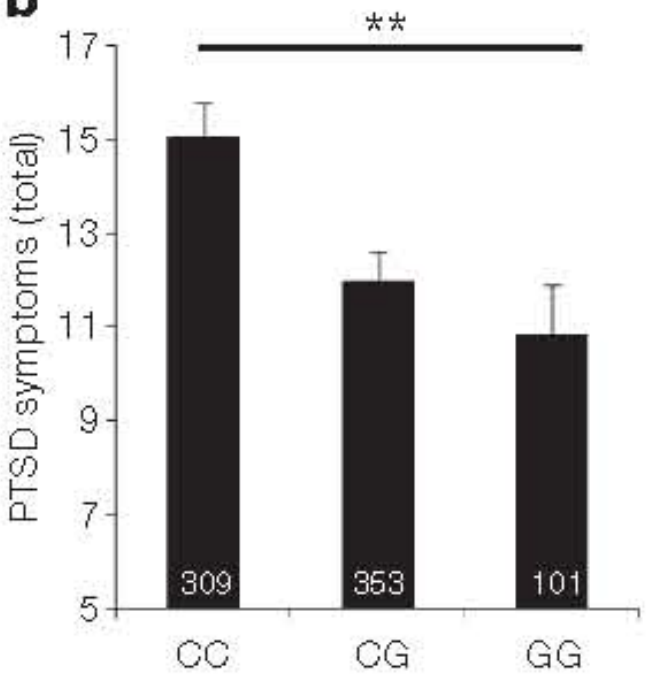
Ressler KJ, et al. *Nature*. 2011;470(7335):492-497.

Association of *ADCYAP$_1$R$_1$* with PTSD Symptoms and Physiological Fear Response

a

rs2267735–PTSD	*N* (1,237)	*Wald* χ^2	OR (CI)	*P*-value
Male original	295	0.036	1.03 (0.71–1.49)	0.85
Male replication	179	0.57	0.83 (0.52–1.33)	0.45
Male combined	474	0.123	0.95 (0.71–1.27)	0.73
Female original	503	13.7	1.72 (1.29–2.28)	**0.00021**
Female replication	260	4.8	1.54 (1.04–2.29)	**0.029**
Female combined	763	18.4	1.66 (1.32–2.09)	**0.000018**

b



Ressler KJ, et al. *Nature*. 2011;470(7335):492-497.

Amygdala-Dependent Fear Is Regulated by *Oprl1* in Mice and Humans with PTSD

Raül Andero, Shaun P. Brothers, Tanja Jovanovic, Yen T. Chen, Hasib Salah-Uddin, Michael Cameron, Thomas D. Bannister, Lynn Almli, Jennifer S. Stevens, Bekh Bradley, Elisabeth B. Binder, Claes Wahlestedt, Kerry J. Ressler

The amygdala-dependent molecular mechanisms driving the onset and persistence of posttraumatic stress disorder (PTSD) are poorly understood. Recent observational studies have suggested that opioid analgesia in the aftermath of trauma may decrease the development of PTSD. Using a mouse model of dysregulated fear, we found altered expression within the amygdala of the Oprl1 gene (opioid receptor–like 1), which encodes the amygdala nociceptin (NOP)/orphanin FQ receptor (NOP-R). Systemic and central amygdala infusion of SR-8993, a new highly selective NOP-R agonist, impaired fear memory consolidation. In humans, a single-nucleotide polymorphism (SNP) within OPRL1 is associated with a self-reported history of childhood trauma and PTSD symptoms (n = 1847) after a traumatic event. This SNP is also associated with physiological startle measures of fear discrimination and magnetic resonance imaging analysis of amygdala-insula functional connectivity. Together, these data suggest that Oprl1 is associated with amygdala function, fear processing, and PTSD symptoms. Further, our data suggest that activation of the Oprl1/NOP receptor may interfere with fear memory consolidation, with implications for prevention of PTSD after a traumatic event.

Andero R, et al. *Sci Transl Med.* 2013;5(188): 188ra73.

ARTICLE

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DOI: 10.1038/ncomms4339

Genome-wide association study reveals two new risk loci for bipolar disorder

Thomas W. Mühleisen[1,2,3,*], Markus Leber[4,5,*], Thomas G. Schulze[6,*], Jana Strohmaier[7], Franziska Degenhardt[1,2], Jens Treutlein[7], Manuel Mattheisen[8,9], Andreas J. Forstner[1,2], Johannes Schumacher[1,2], René Breuer[7], Sandra Meier[7,10], Stefan Herms[1,2,11], Per Hoffmann[1,2,3,11], André Lacour[5], Stephanie H. Witt[7], Andreas Reif[12], Bertram Müller-Myhsok[13,14,15], Susanne Lucae[13], Wolfgang Maier[16], Markus Schwarz[17], Helmut Vedder[17], Jutta Kammerer-Ciernioch[17], Andrea Pfennig[18], Michael Bauer[18], Martin Hautzinger[19], Susanne Moebus[20], Lutz Priebe[1,2], Piotr M. Czerski[21], Joanna Hauser[21], Jolanta Lissowska[22], Neonila Szeszenia-Dabrowska[23], Paul Brennan[24], James D. McKay[25], Adam Wright[26,27], Philip B. Mitchell[26,27], Janice M. Fullerton[28,29], Peter R. Schofield[28,29], Grant W. Montgomery[30], Sarah E. Medland[30], Scott D. Gordon[30], Nicholas G. Martin[30], Valery Krasnow[31], Alexander Chuchalin[32], Gulja Babadjanova[32], Galina Pantelejeva[33], Lilia I. Abramova[33], Alexander S. Tiganov[33], Alexey Polonikov[34], Elza Khusnutdinova[35], Martin Alda[36,37], Paul Grof[37,38,39], Guy A. Rouleau[40], Gustavo Turecki[41], Catherine Laprise[42], Fabio Rivas[43], Fermin Mayoral[43], Manolis Kogevinas[44], Maria Grigoroiu-Serbanescu[45], Peter Propping[1], Tim Becker[5,4], Marcella Rietschel[7,*], Markus M. Nöthen[1,2,*] & Sven Cichon[1,2,3,11,*]

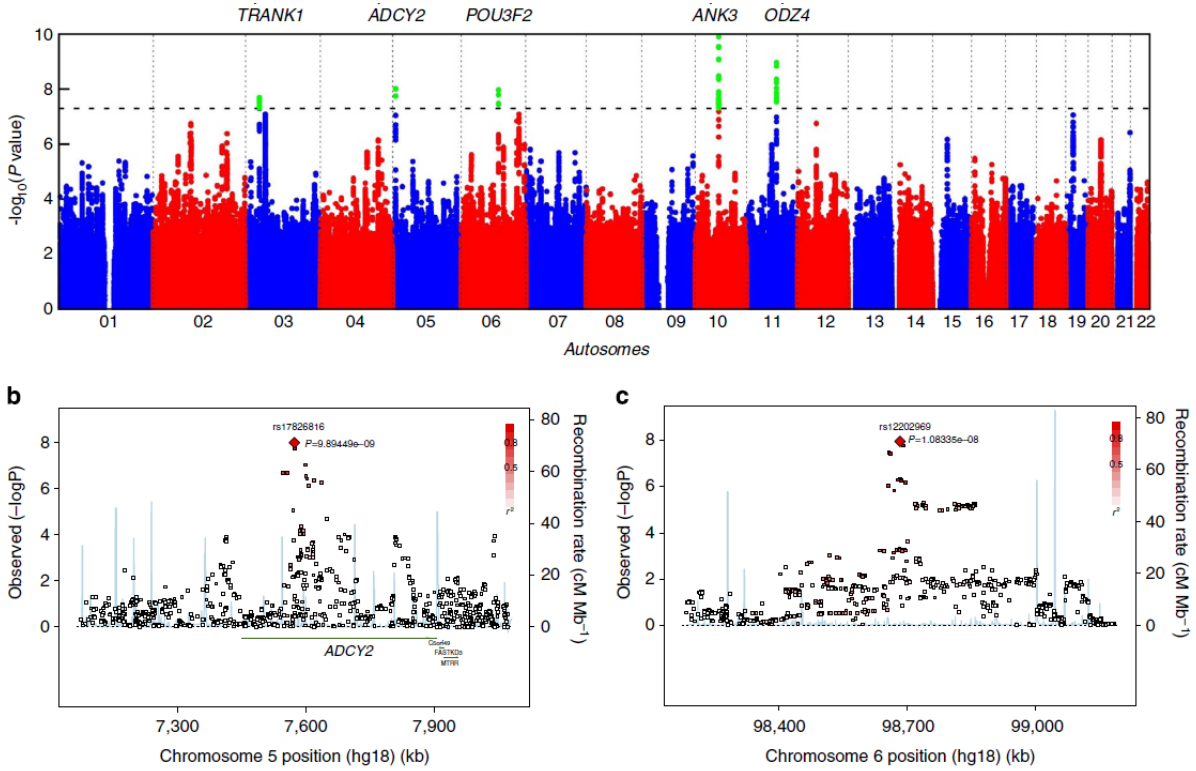
Mühleisen TW, et al. *Nat. Commun.* 2014;5:3339.

Abstract

Bipolar disorder (BD) is a common and highly heritable mental illness and genome-wide association studies (GWAS) have robustly identified the first common genetic variants involved in disease aetiology. The data also provide strong evidence for the presence of multiple additional risk loci, each contributing a relatively small effect to BD susceptibility. Large samples are necessary to detect these risk loci. Here we present results from the largest BD GWAS to date by investigating 2.3 million single-nucleotide polymorphisms (SNPs) in a sample of 24,025 patients and controls. We detect 56 genome-wide significant SNPs in five chromosomal regions including previously reported risk loci *ANK3*, *ODZ4* and *TRANK1*, as well as the risk locus *ADCY2* (5p15.31) and a region between *MIR2113* and *POU3F2* (6q16.1). *ADCY2* is a key enzyme in cAMP signalling and our finding provides new insights into the biological mechanisms involved in the development of BD.

Mühleisen TW, et al. *Nat. Commun.* 2014;5:3339.

Association Results for the MooDS-PGC GWAS and 2 New Risk Loci for Bipolar Disorder



a) Manhattan plot for all analyzed SNPs

b,c) Regional association plots for the SNPs analysed at *ADCY2* (5p15.31) and *MIR2113-POU3F2* (6q16.1)

Red = Data for LD

Blue = Recombination frequency

Mühleisen TW, et al. *Nat. Commun.* 2014;5:3339.

Genetic Effect Sizes for the New Loci Identified Through the MooDS-PGC GWAS of Bipolar Disorder

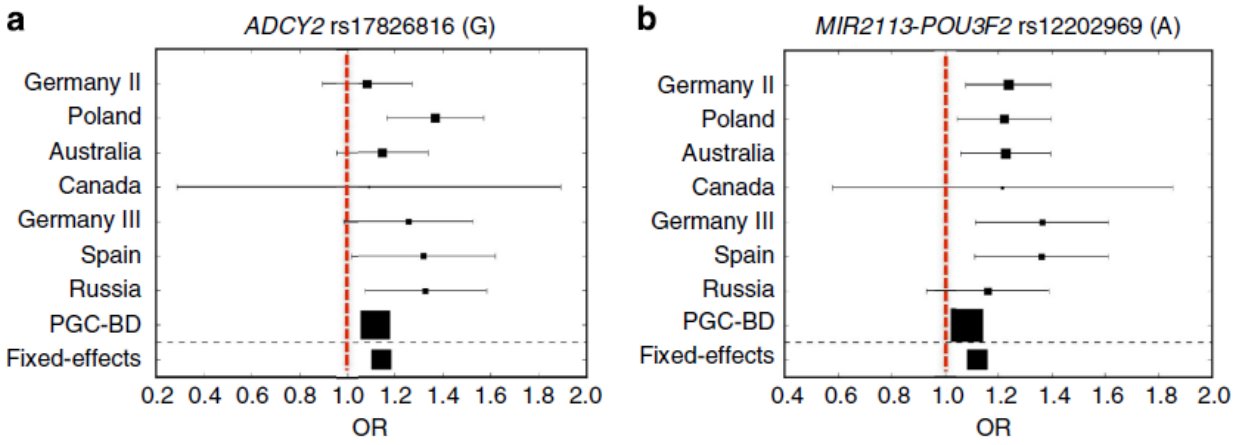
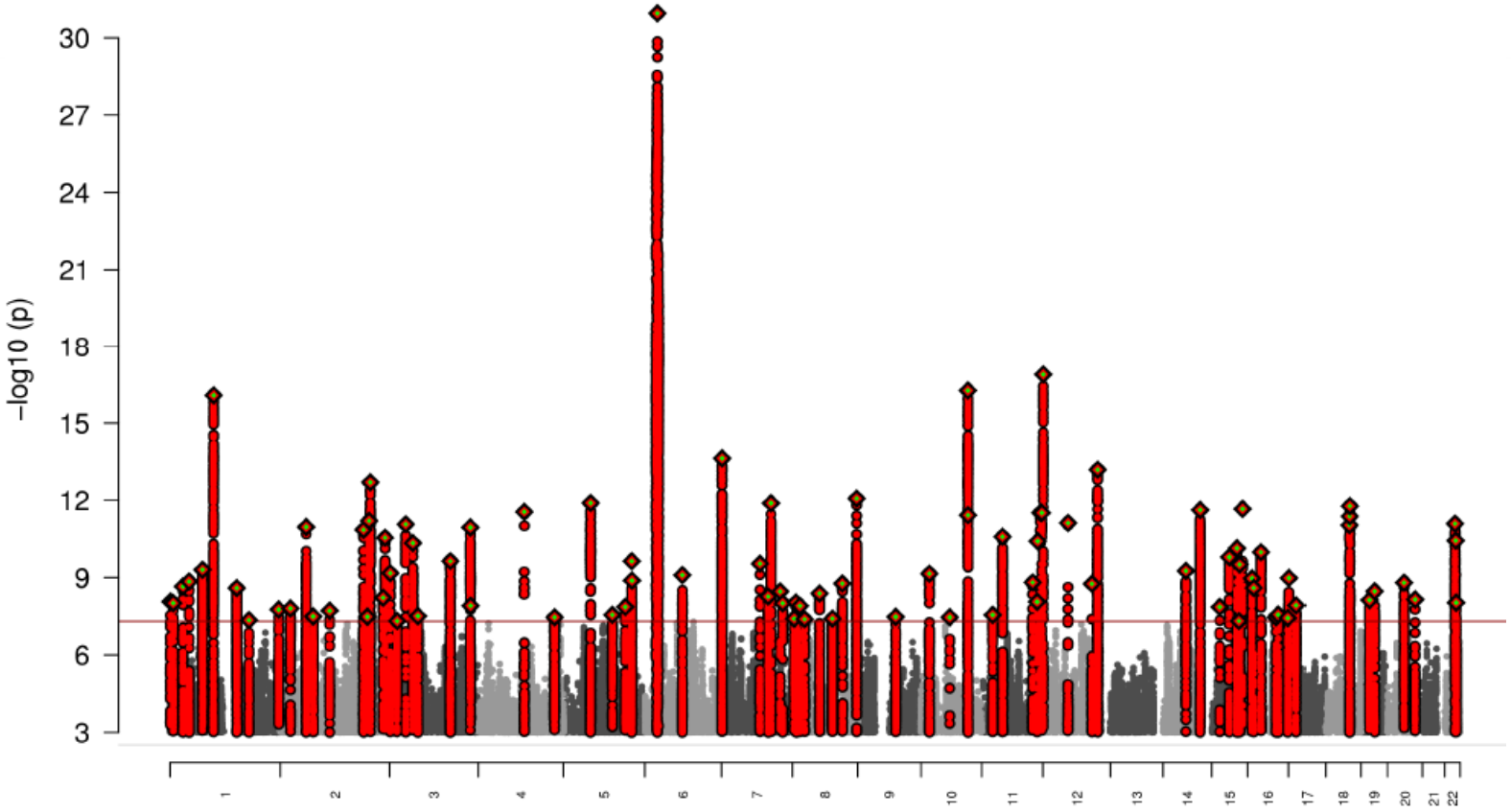


Figure 3 | Genetic effect sizes for the two new risk loci identified through the MooDS-PGC GWAS of BD. (**a**,**b**) Forest plots displaying the most significant SNP's odds ratio (OR, full square) and their 95% confidence interval (horizontal continuous lines) for the gene *ADCY2* (5p15.31) as well as the region between the genes *MIR2113* and *POU3F2* (6q16.1). The overall OR was calculated using a fixed-effects meta-analysis based on the weighted *z*-score method[51]. The effect allele of each SNP is given in brackets. The area of a square reflects the statistical power of the respective study sample. Areas were calculated by the reciprocal value of the standard deviations.

Mühleisen TW, et al. *Nat. Commun*. 2014;5:3339.

PGC 2 –150,000 subjects, 108 "GWAS significant" loci



Polygene risk score based on all independent SNPs p<.05, explains ≈ 7% of trait liability

Schizophrenia Working Group of the Psychiatric Genomics Consortium. *Nature*. 2014;511(7510):421-427.

The Schizophrenia GWAS "Success Story": Strong Statistics, *(Weak Effects)*

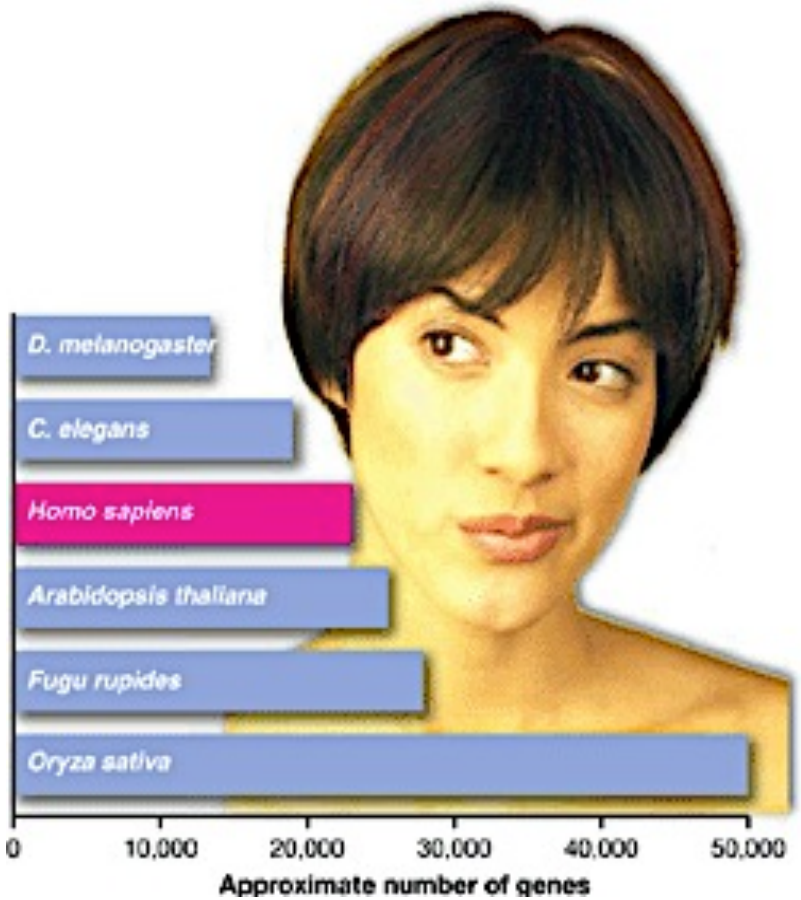
doi:10.1038/nature13595

Supplementary Table 2: 128 genome-wide significant associations for schizophrenia

Rank	Index SNP	A12	Frq_{case}	$Frq_{control}$	Chr	Position	Combined		Discovery		Replication	
							OR (95% CI)	P	OR	P	OR	P
54	rs4648845	TC	0.533	0.527	1	2,372,401-2,402,501	1.072 (1.049-1.097)	8.7e-10	1.071	4.03e-9	1.088	8.85e-2
57	chr1_8424984_D	I2D	0.319	0.301	1	8,411,184-8,638,984	1.071 (1.048-1.095)	1.17e-9	1.071	2.03e-9	1.057	2.96e-1
65	rs1498232	TC	0.311	0.296	1	30,412,551-30,437,271	1.069 (1.046-1.093)	2.86e-9	1.072	1.28e-9	0.999	9.88e-1
50	rs11210892	AG	0.659	0.677	1	44,029,384-44,128,084	0.934 (0.914-0.954)	3.39e-10	0.933	4.97e-10	0.949	3.08e-1
22	rs12129573	AC	0.377	0.358	1	73,766,426-73,991,366	1.078 (1.056-1.101)	2.03e-12	1.072	2.35e-10	1.217	6.25e-5
107	rs76869799	CG	0.959	0.964	1	97,792,625-97,834,525	0.846 (0.798-0.897)	2.64e-8	0.850	1.44e-7	0.779	5.34e-2
2	rs1702294	TC	0.175	0.191	1	98,374,984-98,559,084	0.887 (0.865-0.911)	3.36e-19	0.891	2.79e-17	0.831	1.35e-3
52	rs140505938	TC	0.151	0.164	1	149,998,890-150,242,490	0.914 (0.888-0.940)	4.49e-10	0.913	9.34e-10	0.928	2.53e-1
120	rs6670165	TC	0.196	0.184	1	177,247,821-177,300,821	1.075 (1.047-1.103)	4.45e-8	1.074	1.16e-7	1.090	1.46e-1
121	rs7523273	AG	0.695	0.685	1	207,912,183-208,024,083	1.063 (1.040-1.087)	4.47e-8	1.062	1.61e-7	1.092	8.85e-2
101	rs10803138	AG	0.232	0.238	1	243,503,719-243,612,019	0.933 (0.911-0.956)	2.03e-8	0.932	1.79e-8	0.968	5.56e-1
68	rs77149735	AG	0.0225	0.0191	1	243,555,105-243,555,105	1.317 (1.202-1.444)	3.73e-9	1.329	4.4e-9	1.173	3.66e-1
119	rs14403	TC	0.207	0.222	1	243,639,893-243,664,923	0.934 (0.911-0.957)	4.42e-8	0.935	1.31e-7	0.920	1.53e-1
78	chr1_243881945_I	I2D	0.638	0.619	1	243,690,945-244,002,945	1.068 (1.045-1.092)	6.53e-9	1.066	3.11e-8	1.107	6.17e-2

Schizophrenia Working Group of the Psychiatric Genomics Consortium. *Nature*. 2014;511(7510):421-427.

Biggest Surprise From the Genome Projects: Number of Conventional Genes Do Not Scale with Complexity



Daiger, SP. *Science*. 2005;362-364.

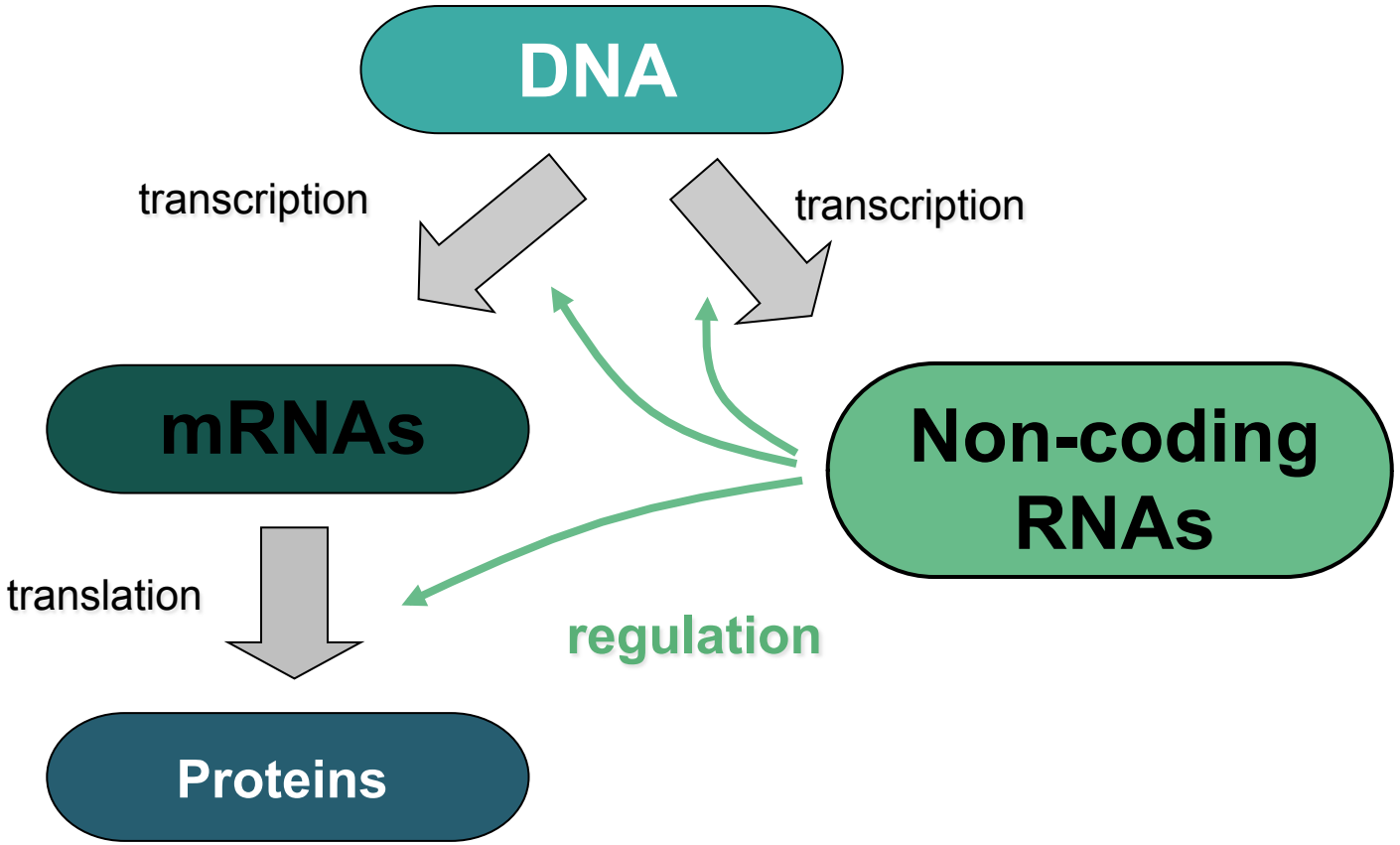
Where is the Information That Programs Our Complexity?

Answer?

- Additional regulatory components in our genome: RNAs

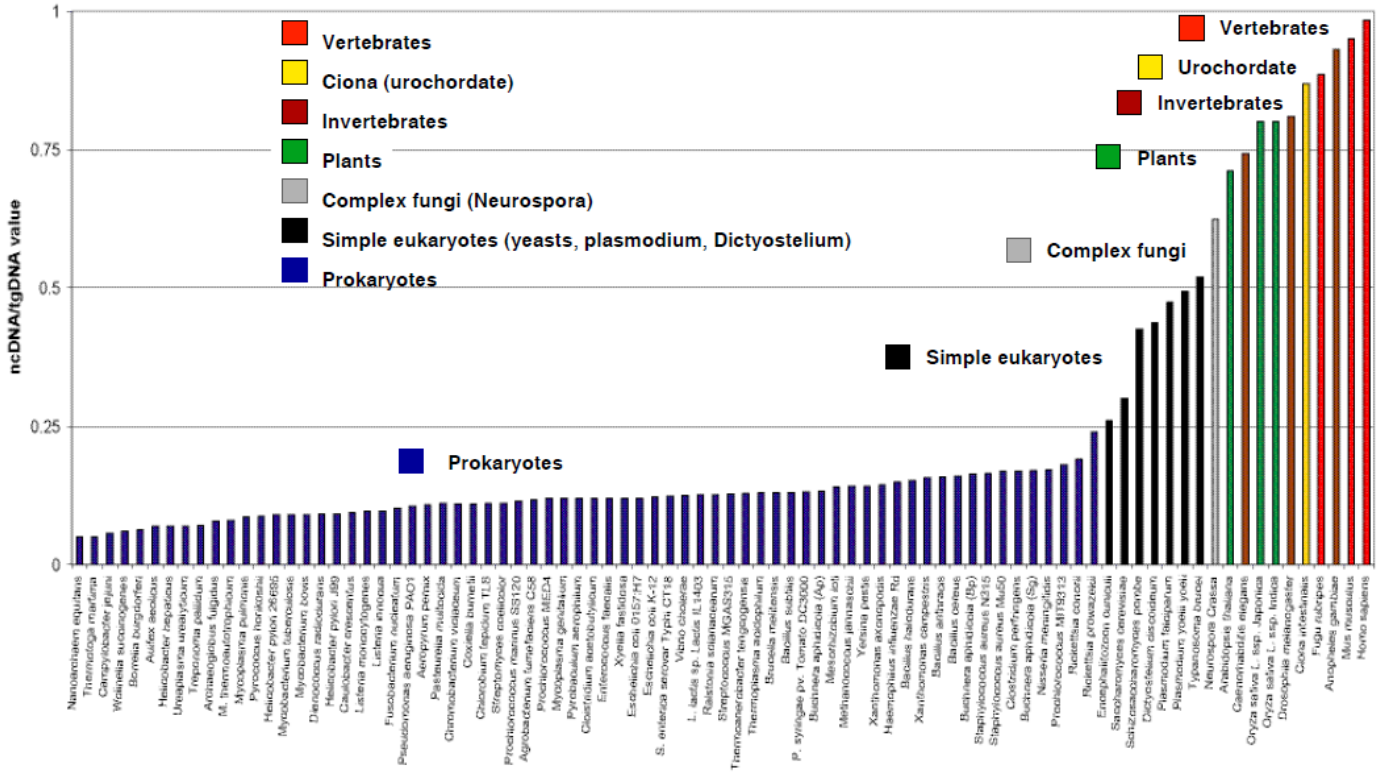
Modified “Central Dogma”

F. Crick

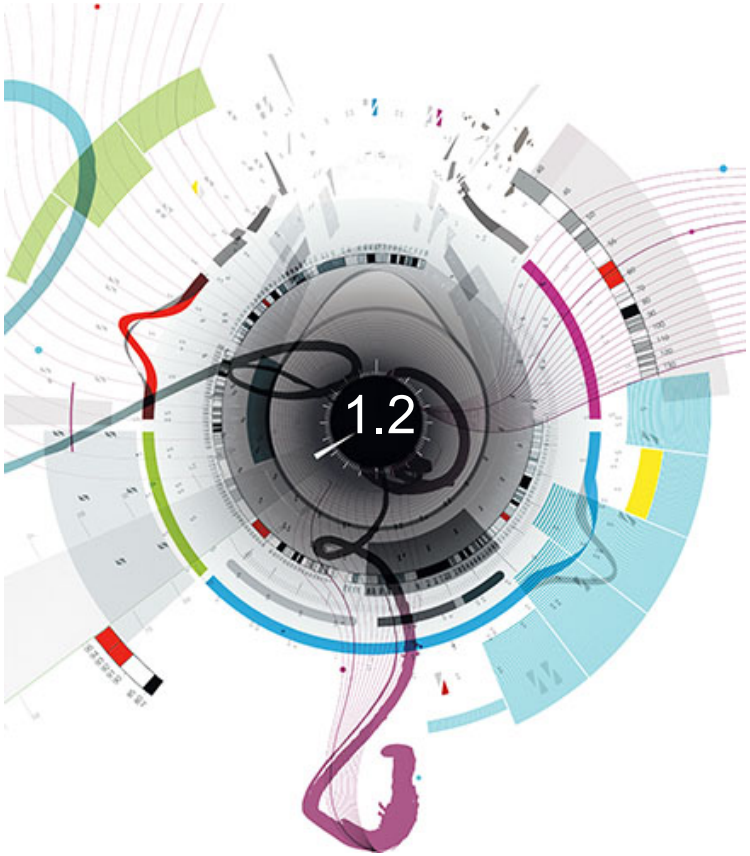


The Proportion of Nancoding DNA Broadly Increases with Developmental Complexity

J. Mattick



Only 1.2% of the Genome is Made Up of Conventional Genes…



…but most of the genome is transcribed.

Zimmer C. *New York Times*, November 10, 2008. http://www.nytimes.com/2008/11/11/science/11gene.html?_r=0. Accessed May 8, 2016.

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


CURRENTLY ON
EXIT 58A-B
95
1
9
Lithium
Valproate
Atypical
Antipsychotics
LAST EXIT
BEFORE TOLL
Lamotrigine
Carbamazepine
Antidepressants
CBT


CURRENTLY ON
EXIT 58A-B
95
1
9
Sertraline
Fluoxetine
Paroxetine
LAST EXIT BEFORE TOLL
Buspirone
Bupropion
Citalopram
Alprazolam

Prediction of Antidepressant Response

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.

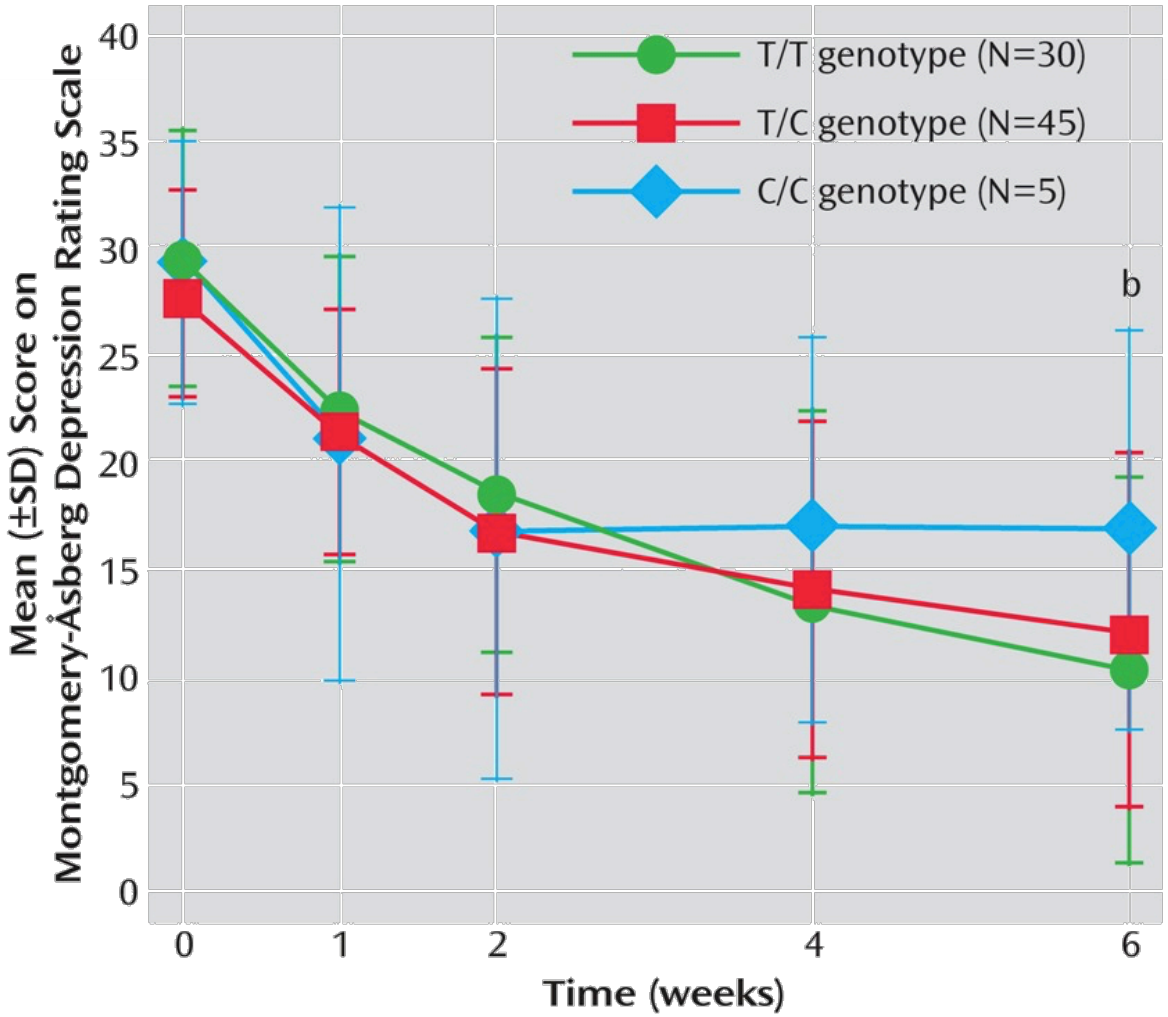
Method: Ninety-six Japanese patients with major depressive disorder were treated with milnacipran, 50–100 mg/day, for 6 weeks. Severity of depression was assessed with the Montgomery-Åsberg Depression Rating Scale. Assessments were carried out at baseline and at 1, 2, 4, and 6 weeks of treatment. The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

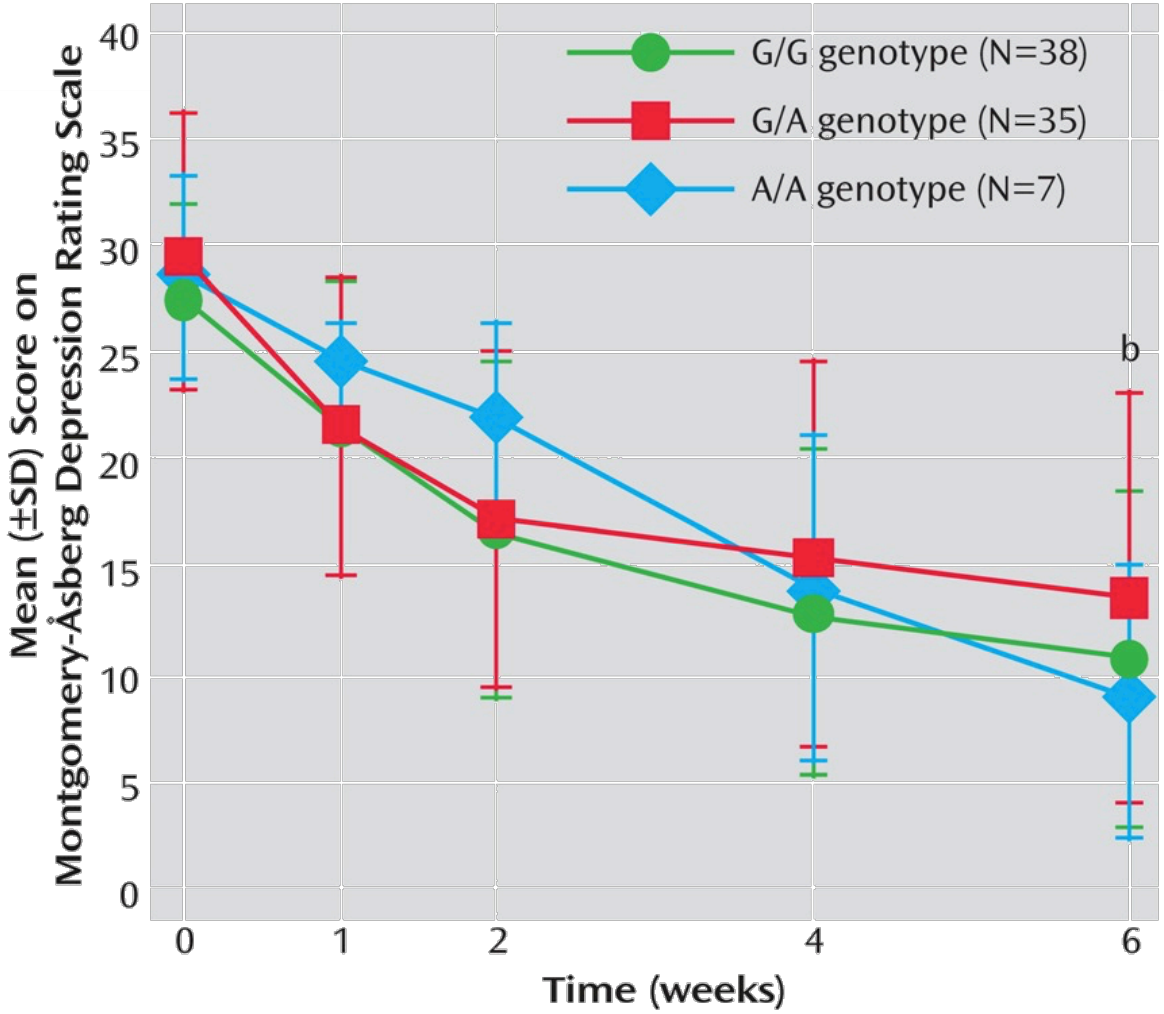
Yoshida K, et al. *Am J Psychiatry.* 2004:161:1575-1580.

Montgomery-Åsberg Depression Scores During 6 Week Treatment in Relation to the NET T-128C Polymorphism



Yoshida K, et al. *Am J Psychiatry*. 2004:161:1575-1580.

Montgomery-Åsberg Depression Scores During 6 Week Treatment in Relation to the Polymorphism



Yoshida K, et al. *Am J Psychiatry*. 2004:161:1575-1580.

Association of Polymorphisms in Genes

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

Binder EB, et al. *Arch Gen Psychiatry.* 2010;67(4):369-379.

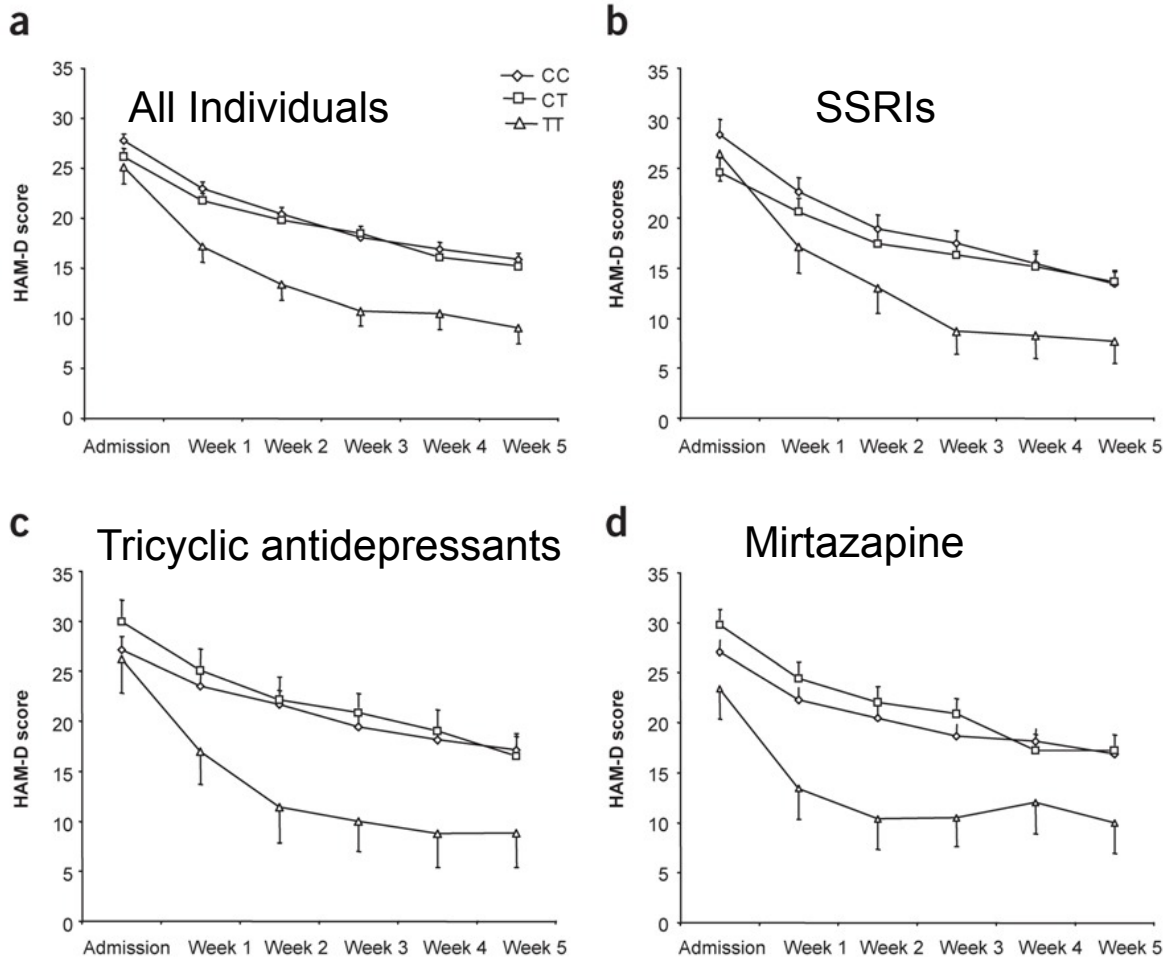
Polymorphisms in *FKBP5*

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

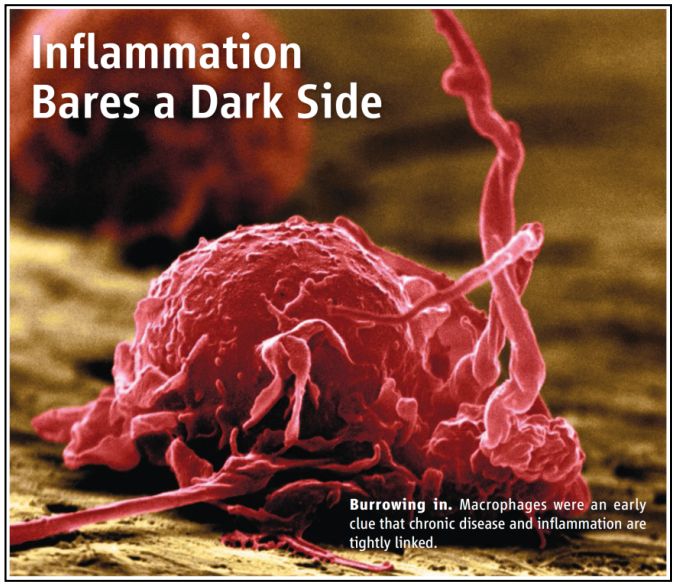
Elisabeth B Binder[1], Daria Salyakina[1], Peter Lichtner[2], Gabriele M Wochnik[1], Marcus Ising[1], Benno Pütz[1], Sergi Papiol[3], Shaun Seaman[1], Susanne Lucae[1], Martin A Kohli[1], Thomas Nickel[1], Heike E Künzel[1], Brigitte Fuchs[1], Matthias Majer[1], Andrea Pfennig[1], Nikola Kern[1], Jürgen 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]

Binder EB, et al. *Nat Genet.* 2004;36(12):1319-1325.

Polymorphisms in *FKBP5* are Associated with Rapid Response to Antidepressant Treatment



Binder EB, et al. *Nature Genetics*. 2004;36(12):1319-1325. PMID: 1556110.



Inflammation: A Common Mechanism of Disease - Insight of the Decade (Science, 2010)

Basis for the Hypothesis that Inflammation and an Activated Innate Immune Response May Play a Role in Depression

- Patients with depression (both medically ill and medically healthy) have been found to exhibit all the cardinal features of inflammation
  - Increased plasma and CSF concentrations of innate immune cytokines (IL-6 most reliable)
  - Increased acute phase reactants (CRP most reliable)
  - Increased chemokines
  - Increased cellular adhesion molecules
- In the majority of studies, inflammatory markers decrease with successful antidepressant therapy ("state marker")
- Depressed patients with increased inflammatory markers are more likely to be treatment resistant

  In our study,
  - 2/3 with "high" inflammation according to CDC/AHA guidelines with CRP > 3mg/L - ~5 million depressed individuals in US
  - 1/3 with CRP > 5mg/L ~3 million depressed individuals in US

Testing the Cytokine Hypothesis of Depression

- Does blockade of inflammatory cytokines reverse depression in patients with treatment-resistant depression (TRD)?

Raison CL, et al. *Arch Gen Psychiatry*. 2012;3:1-11.

Goal: To Test the Cytokine Hypothesis of Depression in Patients with TRD

TNF-alpha Antagonist

- Scientific Reasons
  - TNF-alpha reliably elevated in MDD
  - TNF-alpha and its soluble receptor correlates with IFN-alpha-induced depression
  - TNF-alpha antagonist improved depressed mood in patients with inflammatory disorders
  - TNF receptor KO mice exhibit antidepressant-like response and decreased anxiety following immune stimulation

Raison CL, et al. *Arch Gen Psychiatry*. 2012;3:1-11.

Goal: To Test the Cytokine Hypothesis of Depression in Patients with TRD (cont'd.)

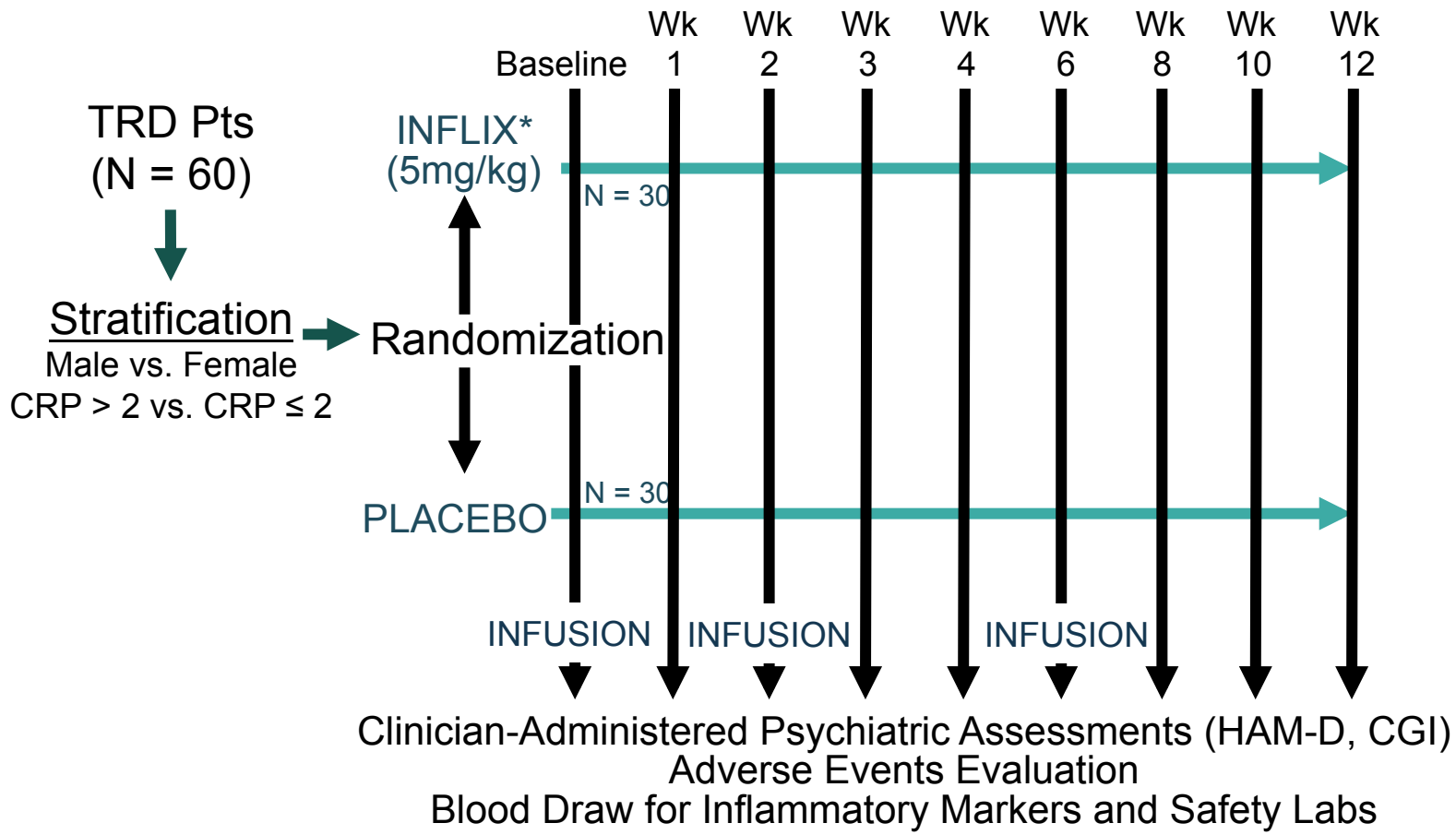
TNF-alpha Antagonist

- Infliximab* – monoclonal antibody directed at TNF-alpha
  - Used to treat autoimmune and inflammatory disorders
- Pharmacologic reasons
  - Biologics (monoclonal antibodies) have no off-target effects or drug-drug interactions (directly test the cytokine hypothesis of depression)
  - Limited brain penetrance (central vs. peripheral effects)
  - No compliance issues with infusions

*Off label use

Raison CL, et al. *Arch Gen Psychiatry*. 2012;3:1-11.

Double-Blind, Parallel-Group, Randomized Design



Raison CL, et al. *Arch Gen Psychiatry*. 2012;3:1-11..

*Off label use

Inclusion/Exclusion Criteria

- Males/Females ages 25-60
- Medically Healthy (Normal PE and labs)
- MDD or Bipolar depressed by SCID
- QIDS-16 score ≥14
- On stable antidepressant regimen or off meds for at least 4 weeks
- No psychotic symptoms or hx of psychosis
- No substance abuse X 6 months
- Not suicidal
- Non-pregnant on birth control

Raison CL, et al. *Arch Gen Psychiatry*. 2012;3:1-11.

Demographic Characteristics of Study Sample

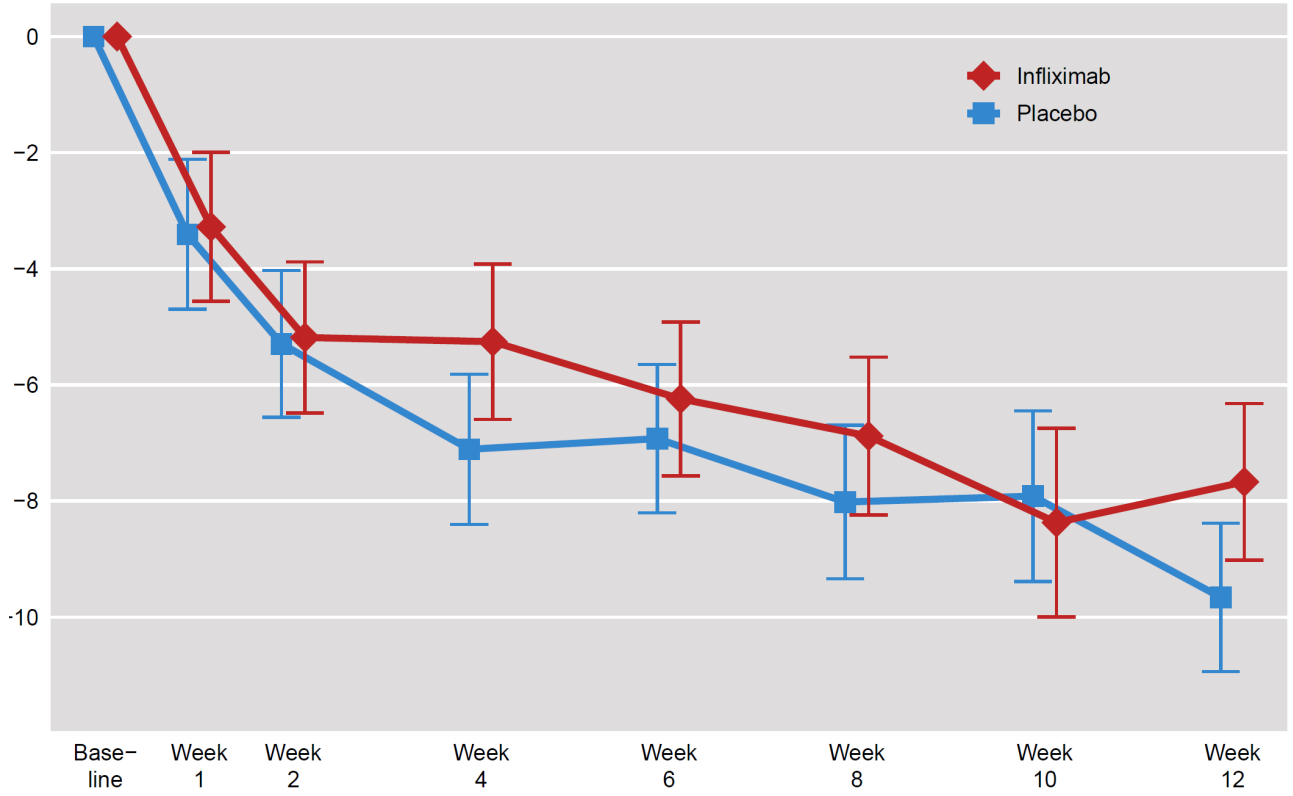
	Infliximab* (n = 30)	Placebo (n = 30)
Age (yrs.) – mean (SD)	42.5 (8.2)	44.3 (9.4)
Sex (female) – no. (%)	20 (66%)	20 (66%)
Ethnic Origin - no. (%) - Caucasian - Black - Other	 23 (77%) 6 (20%) 1 (3%)	 23 (77%) 5 (17%) 2 (6%)
Education (Highest Degree) – no. (%) - Graduate Degree - College Graduate - Partial College - High School Graduate	 8 (27%) 13 (43%) 8 (27%) 1 (3%)	 7 (23%) 13 (43%) 9 (30%) 1 (3%)
Unemployed – no. (%)	12 (40%)	12 (40%)

*Off label use

Raison CL, et al. *Arch Gen Psychiatry*. 2012;3:1-11.

Change in HAM-D-17 in Infliximab* vs. Placebo-Treated TRD Patients

LS Mean (SEM) Change in HAM-D-17 from Baseline

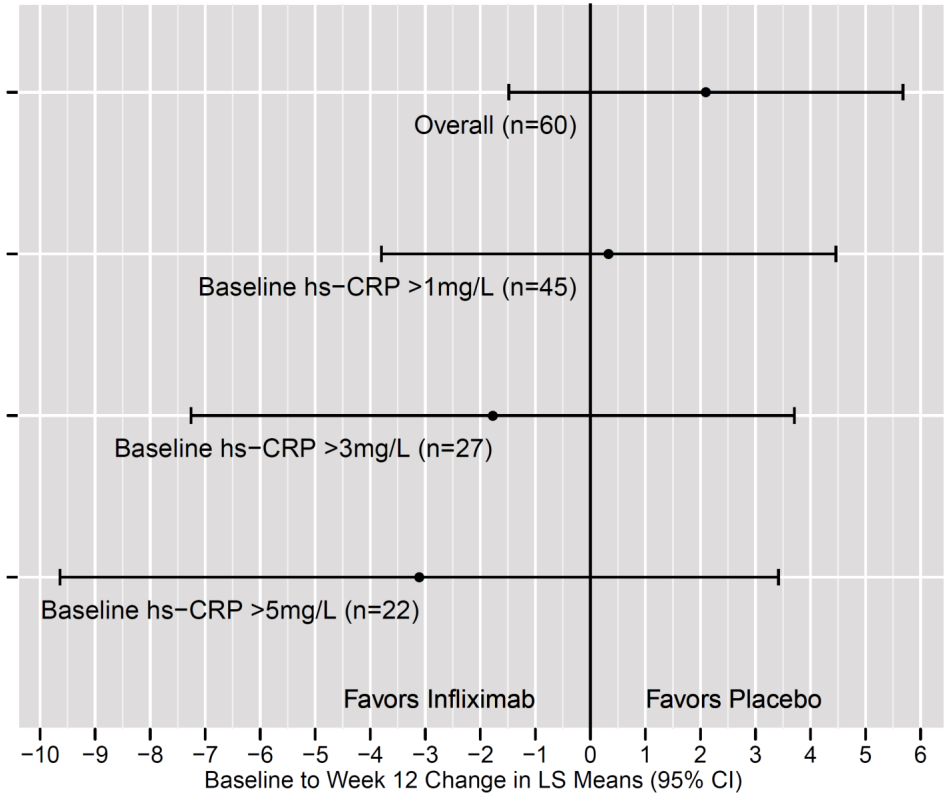


*Off label use

Significant interaction among treatment, time and log hs-CRP (t = 2.65, df = 302, *p* = .01)

Raison CL, et al. *Arch Gen Psychiatry*. 2012;3:1-11.

Change in HAM-D-17 Score from Baseline to Week 12 (Infliximab*-Placebo) in TRD Patients Subgrouped By Baseline Plasma hs-CRP



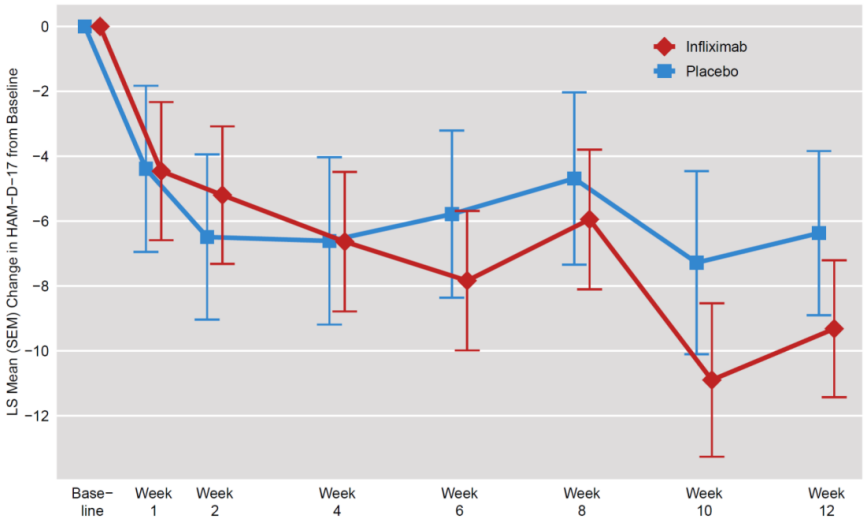
*Off label use

Standardized Effect Size = 0.41 favoring infliximab* at CRP > 5mg/L

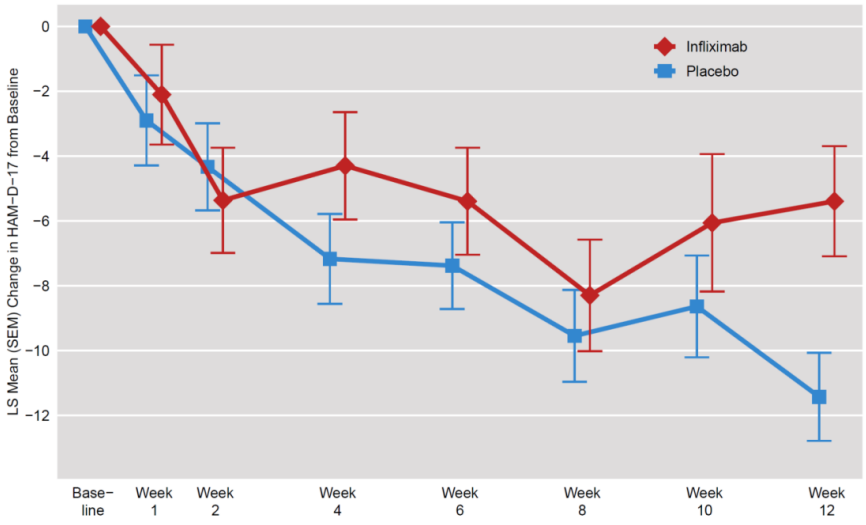
Raison CL, et al. *Arch Gen Psychiatry*. 2012;3:1-11. PMID: 22945416.

Change in HAM-D-17 Scores from Baseline to Week 12 in Infliximab*- or Placebo-Treated TRD Patients with a Baseline CRP > 5 mg/L vs. ≤ 5mg/L

A. CRP > 5mg/L



B. CRP ≤ 5mg/L



*Off label use

Raison CL, et al. *Arch Gen Psychiatry*. 2012;3:1-11.

REVIEW

Mesenchymal stem cells: environmentally responsive therapeutics for regenerative medicine

Matthew B Murphy[1], Kathryn Moncivais[1] and Arnold I Caplan[2]

Mesenchymal stem cells (MSCs) are partially defined by their ability to differentiate into tissues including bone, cartilage and adipose *in vitro*, but it is their trophic, paracrine and immunomodulatory functions that may have the greatest therapeutic impact *in vivo*. Unlike pharmaceutical treatments that deliver a single agent at a specific dose, MSCs are site regulated and secrete bioactive factors and signals at variable concentrations in response to local microenvironmental cues. Significant progress has been made in understanding the biochemical and metabolic mechanisms and feedback associated with MSC response. The anti-inflammatory and immunomodulatory capacity of MSC may be paramount in the restoration of localized or systemic conditions for normal healing and tissue regeneration. Allogeneic MSC treatments, categorized as a drug by regulatory agencies, have been widely pursued, but new studies demonstrate the efficacy of autologous MSC therapies, even for individuals affected by a disease state. Safety and regulatory concerns surrounding allogeneic cell preparations make autologous and minimally manipulated cell therapies an attractive option for many regenerative, anti-inflammatory and autoimmune applications.

Experimental & Molecular Medicine (2013) **45**, e54; doi:10.1038/emm.2013.94; published online 15 November 2013

A Randomized, Double-Blind, Placebo-Controlled, Dose-Escalation Study of Intravenous Adult Human Mesenchymal Stem Cells (Prochymal) After Acute Myocardial Infarction

Joshua M. Hare, MD,* Jay H. Traverse, MD,† Timothy D. Henry, MD,† Nabil Dib, MD,‡ Robert K. Strumpf, MD,‡ Steven P. Schulman, MD,§ Gary Gerstenblith, MD,§ Anthony N. DeMaria, MD,‖ Ali E. Denktas, MD,¶ Roger S. Gammon, MD,# James B. Hermiller, Jr, MD,** Mark A. Reisman, MD,†† Gary L. Schaer, MD,‡‡ Warren Sherman, MD§§

Conclusions Intravenous allogeneic hMSCs are safe in patients after acute MI. This trial provides pivotal safety and provisional efficacy data for an allogeneic bone marrow-derived stem cell in post-infarction patients. (Safety Study of Adult Mesenchymal Stem Cells [MSC] to Treat Acute Myocardial Infarction; NCT00114452) (J Am Coll Cardiol 2009;54:2277–86)

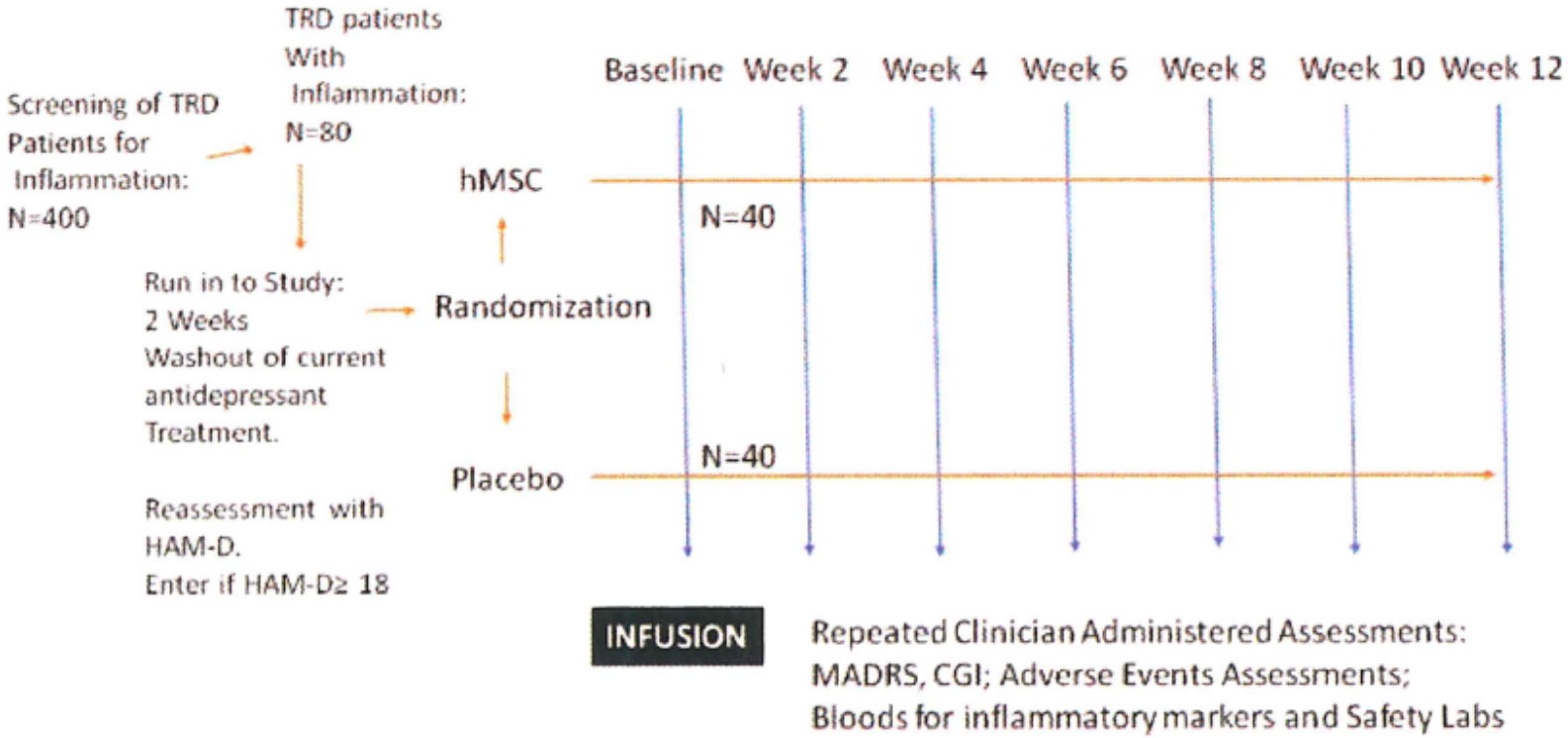
Journal of the American College of Cardiology. Volume 54, Issue 24, 8 December 2009, Pages 2277–2286

We propose the first study of mesenchymal stem cell therapy for the treatment of refractory depression.

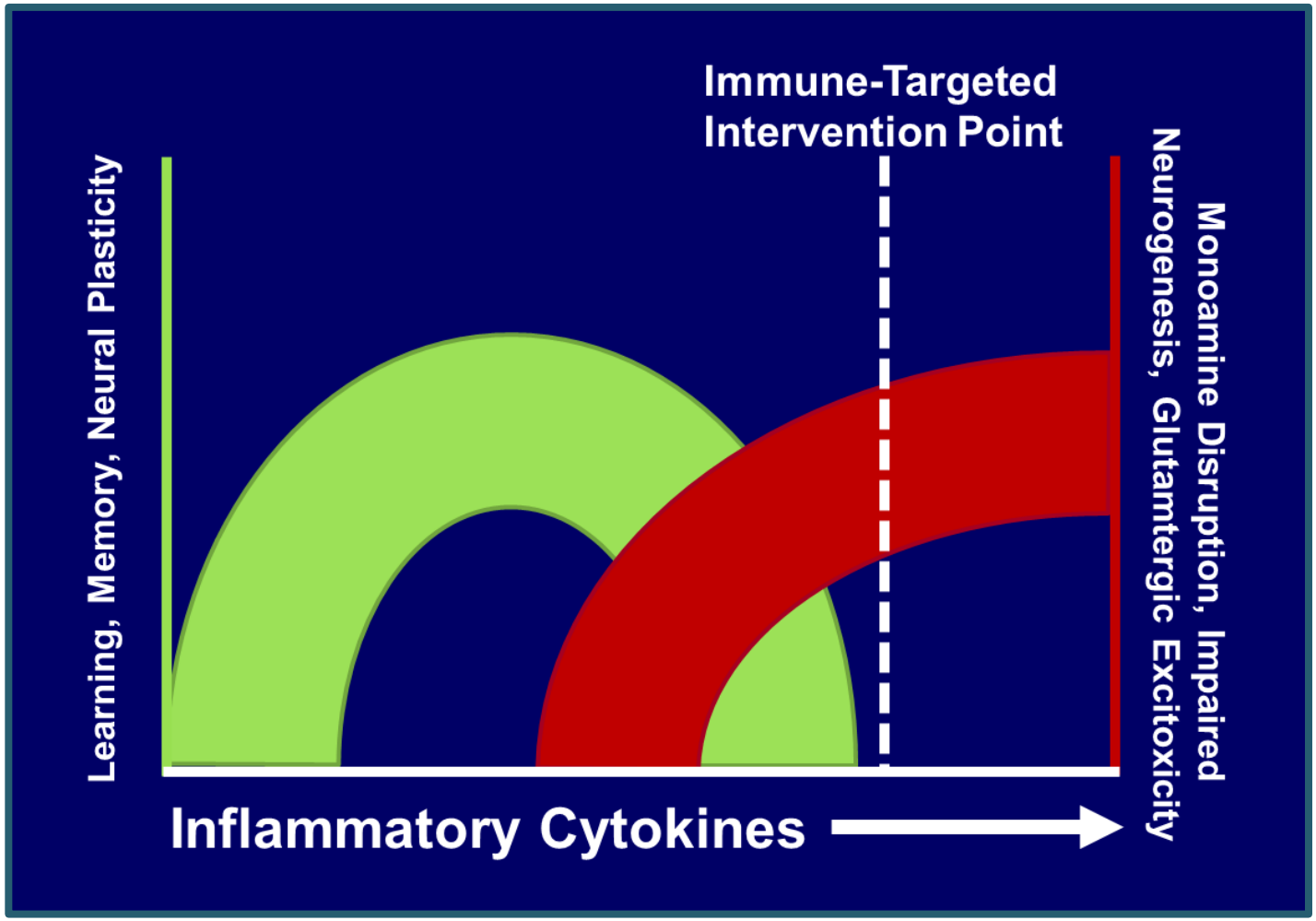
CME Outfitters

Screening of TRD Patients for Inflammation

Double-Blind Parallel Group Randomized Design



Hitting the Sweet Spot



“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

Audience Response

Which of the following is true of NE dysfunction linked to depression?

A. Decreased density of B-adrenergic receptors is found postmortem
B. NE reuptake inhibitors are not effective antidepressants
C. High levels of NE metabolites are found in the urine
D. Low levels of NE metabolites are found in the urine

Questions & Answers

CME Outfitters