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

Presented by:

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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)

Speakers Bureau:
None

Honoraria
Various

Royalties
Various

Expert Witness
Various
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
- mood and anxiety disorders
- temperament

Behavior:
- Clinical phenotype

The Wisconsin Card Sorting Task
The Neurobiology of Bipolar Disorder: Theoretical Considerations

Susceptibility Genes
Protective Genes

Modifying Genes
Imprinting
Tissue Specific Haploinsufficiency

Environmental Factors

Mania and Depression
*Episodic symptom clusters*
Affective
Cognitive
Motoric
Neurovegetative
Implications for Public Understanding
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.

“*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

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

<table>
<thead>
<tr>
<th>Study</th>
<th>MZ</th>
<th>DZ</th>
</tr>
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<tbody>
<tr>
<td>Rosanoff et al, 1934</td>
<td>69.9</td>
<td>16.4</td>
</tr>
<tr>
<td>Kallmann, 1954</td>
<td>92.6</td>
<td>23.6</td>
</tr>
<tr>
<td>Da Fonseca, 1959</td>
<td>71.4</td>
<td>38.5</td>
</tr>
<tr>
<td>Harvald, Hauge, 1965</td>
<td>50.0</td>
<td>2.6</td>
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<tr>
<td>Kringlen, 1967</td>
<td>33.3</td>
<td>0.0</td>
</tr>
<tr>
<td>Bertelsen, 1977</td>
<td>58.0</td>
<td>17.0</td>
</tr>
<tr>
<td>Torgersen, 1986</td>
<td>75.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

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

Mood Disorders Across the Life Cycle

- Early Onset Depression
- Bipolar Disorders
- Premenstrual Dysphoric Disorder
- Depression During Pregnancy
- Depression Associated With Infertility, Miscarriage, or Perinatal Loss
- Depression During the Perimenopausal Period
- Depression During the Postpartum Period
- Depression Comorbid Medical Disease: Heart Disease, Stroke, Diabetes, Cancer
- Depression During the Menopausal Period
- Late Onset Depression

Orange = Women
Green = Men
## Confirmed Linkages in Bipolar Disorder

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

*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
Regulation of Behavioral Circuits by Neuromodulatory Systems

- **Prefrontal Cortex**
  - Cognition
  - Working memory
  - Modulation of affect

- **Thalamus**
  - Arousal/sleep, sensorimotor gating

- **Hypothalamus**
  - Stress response, sleep/wake/appetite regulation

- **Nucleus Accumbens**
  - Reward/pleasure

- **Amygdala/BNST/ Hippocampus**
  - Fear/stress response, anxiety symptoms, memory

**Abbreviations:**
- LC=locus coeruleus;
- NE=norepinephrine;
- CRH=corticotropin-releasing hormone;
- 5HT=5-hydroxytryptamine.
Reduced Brainstem $[^{123}\text{I}]\beta$-CIT Binding in Depression


Drug Free
Drug Naive
*p=0.03
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
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: $F_{1,29} = 7.1$, $P = 0.01$).
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)
TH and NSE Levels in Sections of LC from Control and Suicide Victims

Our DNA is our instruction manual!

We can now read the whole manual!!
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.
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.

Regulation of Stress Response by CRH and HPA Axis

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

*P<0.01; mean ± SEM.
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

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>194</td>
<td>39%</td>
</tr>
<tr>
<td>Female</td>
<td>303</td>
<td>61%</td>
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<tr>
<td><strong>Self-Identified Race/Ethnicity</strong></td>
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<td></td>
</tr>
<tr>
<td>African American or Black</td>
<td>484</td>
<td>97%</td>
</tr>
<tr>
<td>Caucasian or White</td>
<td>4</td>
<td>.8%</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>2</td>
<td>.4%</td>
</tr>
<tr>
<td>Asian</td>
<td>1</td>
<td>.2%</td>
</tr>
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<td>Mixed</td>
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<tr>
<td>Other</td>
<td>3</td>
<td>.6%</td>
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<tr>
<td><strong>Education</strong></td>
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<tr>
<td>&lt; 12th Grade</td>
<td>153</td>
<td>31%</td>
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<tr>
<td>High School Graduate or GED</td>
<td>217</td>
<td>44%</td>
</tr>
<tr>
<td>Some College or Technical School</td>
<td>78</td>
<td>15%</td>
</tr>
<tr>
<td>Technical School Graduate</td>
<td>21</td>
<td>4%</td>
</tr>
<tr>
<td>College Graduate</td>
<td>21</td>
<td>4%</td>
</tr>
<tr>
<td>Some Graduate School</td>
<td>9</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Employment Status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Currently Unemployed</td>
<td>338</td>
<td>68%</td>
</tr>
<tr>
<td>Currently Employed</td>
<td>162</td>
<td>32%</td>
</tr>
<tr>
<td><strong>Disability Status</strong></td>
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<td></td>
</tr>
<tr>
<td>Not Currently Receiving Disability</td>
<td>394</td>
<td>79%</td>
</tr>
<tr>
<td>Currently Receiving Disability</td>
<td>103</td>
<td>21%</td>
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<tr>
<td><strong>Household Monthly Income</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$0 – $249</td>
<td>158</td>
<td>32%</td>
</tr>
<tr>
<td>$250 – $499</td>
<td>51</td>
<td>10%</td>
</tr>
<tr>
<td>$500 - $999</td>
<td>136</td>
<td>28%</td>
</tr>
<tr>
<td>$1000 - $1999</td>
<td>106</td>
<td>21%</td>
</tr>
<tr>
<td>$2000 or more</td>
<td>158</td>
<td>30%</td>
</tr>
</tbody>
</table>

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.

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

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

**A**

**Block 1 Haplotypes**

<table>
<thead>
<tr>
<th>rs7209436</th>
<th>rs4792887</th>
<th>rs110402</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>T</td>
<td>G</td>
<td>34.1</td>
</tr>
<tr>
<td>C</td>
<td>C</td>
<td>G</td>
<td>34.0</td>
</tr>
<tr>
<td>T</td>
<td>C</td>
<td>A</td>
<td>30.4</td>
</tr>
</tbody>
</table>

**B**

**TCA Haplotype Block 1**

- None to Mild Child Abuse
- Moderate to Severe Child Abuse

P < 0.001

**C**

**Most Significant SNP Haplotypes**

<table>
<thead>
<tr>
<th>rs7209436</th>
<th>rs110402</th>
<th>rs242924</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>G</td>
<td>G</td>
<td>66.5</td>
</tr>
<tr>
<td>T</td>
<td>A</td>
<td>T</td>
<td>28.8</td>
</tr>
</tbody>
</table>

**D**

**Protective Haplotype: TAT**

- None to Mild Child Abuse
- Moderate to Severe Child Abuse

P < 0.005

Adult Trauma and Child Abuse predict PTSD

Increasing levels of adult trauma are associated with increasing levels of adult PTSD

Child abuse is associated with higher levels of adult PTSD symptoms

Child abuse and adult trauma have additive effects on adult PTSD symptom

FKBP5 SNPs and main genetic effect on PTSD symptoms and interaction effects with adult trauma levels and child abuse

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.

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**

Epigenetic mechanisms are affected by these factors and processes:
- Development (in utero, childhood)
- Environmental chemicals
- Drugs/Pharmaceuticals
- Aging
- Diet

**DNA methylation**

Methyl group (an epigenetic factor found in some dietary sources) can tag DNA and activate or repress genes.

**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.

**Health Endpoints**

- Cancer
- Autoimmune disease
- Mental disorders
- Diabetes
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.
Post-traumatic stress disorder is associated with PACAP and the PAC1 receptor

Kerry J. Ressler1,2,4, Kristina B. Mercer1, Bekh Bradley2,3, Tanja Jovanovic2, Amy Mahan4, Kimberly Kerley1, Seth D. Norrholm2,3, Varun Kilaru2, Alicia K. Smith2, Amanda J. Myers5, Manuel Ramirez5, Anzhelika Engel5, Sayarnwong E. Hammack6, Donna Toufexis4,6, Karen M. Braas7, Elisabeth B. Binder2,8 & Victor May7

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 ADCYAPI) and PAC1 (encoded by ADCYAPI1) genes, demonstrating a sex-specific association with PTSD. A single SNP in a putative oestrogen response element within ADCYAPI1, rs2267735, predicts PTSD diagnosis and symptoms in females only. This SNP also associates with fear discrimination and with ADCYAPI1 messenger RNA expression in human brain. Methylation of ADCYAPI1 in peripheral blood is also associated with PTSD. Complementing these human data, ADCYAPI1 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 ADCYAPI1. PACAP levels and ADCYAPI1 SNPs may serve as useful biomarkers to further our mechanistic understanding of PTSD.
### Table: rs2267735-PTSD

<table>
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<tr>
<th>rs2267735-PTSD</th>
<th>N</th>
<th>Wald χ²</th>
<th>OR (CI)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Male original</td>
<td>295</td>
<td>0.036</td>
<td>1.03 (0.71–1.49)</td>
<td>0.85</td>
</tr>
<tr>
<td>Male replication</td>
<td>179</td>
<td>0.57</td>
<td>0.83 (0.52–1.33)</td>
<td>0.45</td>
</tr>
<tr>
<td>Male combined</td>
<td>474</td>
<td>0.123</td>
<td>0.95 (0.71–1.27)</td>
<td>0.73</td>
</tr>
<tr>
<td>Female original</td>
<td>503</td>
<td>13.7</td>
<td>1.72 (1.29–2.28)</td>
<td>0.00021</td>
</tr>
<tr>
<td>Female replication</td>
<td>260</td>
<td>4.8</td>
<td>1.54 (1.04–2.29)</td>
<td>0.029</td>
</tr>
<tr>
<td>Female combined</td>
<td>763</td>
<td>18.4</td>
<td>1.66 (1.32–2.09)</td>
<td>0.000018</td>
</tr>
</tbody>
</table>

### Graph: PTSD symptoms (total)

- CC: 309
- CG: 353
- GG: 101

**Significant difference: **

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

Raül Andero,1,2 Shaun P. Brothers,3,4 Tanja Jovanovic,5 Yen T. Chen,6,* Hasib Salah-Uddin,1 Michael Cameron,1,2 Thomas D. Bannister,3,4 Lynn Almli,2 Jennifer S. Stevens,2 Bekh Bradley,2 Elisabeth B. Binder,1,6 Claes Wahlestedt,1 Kerry J. Ressler,1,2,7

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.

Science Translational Medicine 5 June 2013 Vol 5 Issue 188 188ra73
Genome-wide association study reveals two new risk loci for bipolar disorder

Thomas W. Mühleisen1,2,3,*, Markus Leber4,5,*, Thomas G. Schulze6,*, Jana Strohmaier7, Franziska Degenhardt1,2, Jens Treutlein7, Manuel Mattheisen8,9, Andreas J. Forstner1,2, Johannes Schumacher1,2, René Breuer7, Sandra Meier7,10, Stefan Herms1,2,11, Per Hoffmann1,2,3,11, André Lacour5, Stephanie H. Witt7, Andreas Reif12, Bertram Müller-Myhsok13,14,15, Susanne Lucae13, Wolfgang Maier16, Markus Schwarz17, Helmut Vedder17, Jutta Kammerer-Ciernioch17, Andrea Pfennig18, Michael Bauer18, Martin Hautzinger19, Susanne Moebus20, Lutz Priebe12, Piotr M. Czerski21, Joanna Hauser21, Jolanta Lissowska22, Neonila Szeszenia-Dabrowska23, Paul Brennan24, James D. McKay25, Adam Wright26,27, Philip B. Mitchell26,27, Janice M. Fullerton28,29, Peter R. Schofield28,29, Grant W. Montgomery30, Sarah E. Medland30, Scott D. Gordon30, Nicholas G. Martin30, Valery Krasnow31, Alexander Chuchalin32, Gulja Babadjanova32, Galina Pantelejeva33, Lilia I. Abramova33, Alexander S. Tiganov33, Alexey Polonikov34, Elza Khusnutdinova35, Martin Alda36,37, Paul Grof38,39, Guy A. Rouleau40, Gustavo Turecki41, Catherine Laprise42, Fabio Rivas43, Fermin Mayoral43, Manolis Kogevinas44, Maria Grigoroiu-Serbanescu45, Peter Propping1, Tim Becker5,4, Marcella Rietschel7,*, Markus M. Nöthen1,2,*, & Sven Cichon1,2,3,11,*
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.

Figure 2 | Association results for the Mood-PGC GWAS and the two new risk loci for BD. (a) Manhattan plot for all analysed SNPs, (b,c) regional association plots for the SNPs analysed at ADCY2 (5p15.31) and MIR2113-POU5F2 (6q16.1). Regional association plots were drawn using SNAP54 and data for LD (red) and recombination frequency (blue line) from the 1000 Genomes Project.

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\textsuperscript{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.
PGC 2 – 150,000 subjects, 108 “GWAS significant” loci

Polygene risk score based on all independent SNPs \(p<.05\), explains \(\approx 7\%\) of trait liability

PGC Nature 2014
The schizophrenia GWAS “success story”: strong statistics, *(weak effects)*

doi:10.1038/nature13595

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

<table>
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<tr>
<th>Rank</th>
<th>Index SNP</th>
<th>A12</th>
<th>Frq_case</th>
<th>Frq_control</th>
<th>Chr</th>
<th>Position</th>
<th>Combined OR (95% CI)</th>
<th>P</th>
<th>Discovery OR</th>
<th>P</th>
<th>Replication OR</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>54</td>
<td>rs4538345</td>
<td>TC</td>
<td>0.533</td>
<td>0.527</td>
<td>1</td>
<td>2,372,401-2,402,501</td>
<td>1.072 (1.049-1.097)</td>
<td>8.7e-10</td>
<td>1.071</td>
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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
Modified “Central Dogma”

DNA

transcription

mRNAs

transcription

Non-coding RNAs

translation

regulation

Proteins

F. Crick
The Proportion of Noncoding 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.

From New York Times, 2009
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
Lithium  Valproate  Atypical Antipsychotics

Lamotrigine  Carbamazepine  Anti-Depressants  CBT
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)
Montgomery-Åsberg Depression scores during 6 week treatment in relation to the NET T-128C polymorphism

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

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


Polymorphisms in FKBP5 are associated with rapid response to antidepressant treatment

a. All Individuals

b. SSRIs

c. Tricyclic antidepressants
d. Mirtazapine

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 peripheral blood and csf innate immune cytokines (IL-6 and TNF-alpha 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 (CRP>3mg/L) - ~5 million depressed individuals in US and 1/3 with CRP>5mg/L ~3 million depressed individuals in US].
Does Blockade of Inflammatory Cytokines Reverse Depression in Patients with TRD?

Testing the Cytokine Hypothesis of Depression

Raison et al., Arch Gen Psychiatry 2012, on line
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
Goal: To test the cytokine hypothesis of depression in patients with TRD

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
Double-Blind, Parallel-Group, Randomized Design

TRD Pts (N=60)

Stratification
Male vs Female
CRP >2 vs CRP ≤2

Randomization

INFLIX (5mg/kg)

N =30

PLACEBO

N =30

Clinician-Administered Psychiatric Assessments (HAM-D, CGI)
Adverse Events Evaluation
Blood Draw for Inflammatory Markers and Safety Labs

Raison et al., Arch Gen Psychiatry 2012, on line
Inclusion/Exclusion Criteria

- Males/Females age 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 et al., Arch Gen Psychiatry 2012, on line
## Demographic Characteristics of Study Sample

<table>
<thead>
<tr>
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<th>Infliximab (n=30)</th>
<th>Placebo (n=30)</th>
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<tbody>
<tr>
<td><strong>Age (yrs.) – mean (SD)</strong></td>
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<td>44.3 (9.4)</td>
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<tr>
<td><strong>Sex (female) – no. (%)</strong></td>
<td>20 (66%)</td>
<td>20 (66%)</td>
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<tr>
<td><strong>Ethnic Origin - no. (%)</strong></td>
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<tr>
<td>Caucasian</td>
<td>23 (77%)</td>
<td>23 (77%)</td>
</tr>
<tr>
<td>Black</td>
<td>6 (20%)</td>
<td>5 (17%)</td>
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<tr>
<td>Other</td>
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<td>2 (6%)</td>
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<tr>
<td><strong>Education (Highest Degree) – no. (%)</strong></td>
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<td>Graduate Degree</td>
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<td>College Graduate</td>
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<td>13 (43%)</td>
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<tr>
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<td>9 (30%)</td>
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<tr>
<td>High School Graduate</td>
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<tr>
<td><strong>Unemployed – no. (%)</strong></td>
<td>12 (40%)</td>
<td>12 (40%)</td>
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Change in HAM-D-17 in Infliximab- versus Placebo-Treated TRD Patients

Significant interaction among treatment, time and log hs-CRP (t=2.65, df=302, p=0.01)

Raison et al., Arch Gen Psychiatry 2012, on line
Change in HAM-D-17 Score from Baseline to Week 12 (Infliximab-Placebo) in TRD Patients Subgrouped By Baseline Plasma hs-CRP

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

Raison et al., Arch Gen Psychiatry 2012, on line
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 versus ≤5mg/L

A. CRP >5mg/L

B. CRP ≤5mg/L

Raison et al., Arch Gen Psychiatry 2012, on line
Percent Treatment Responders in Infliximab- Versus Placebo-Treated TRD Patients with a Baseline hs-CRP ≤5mg/L or >5mg/L

Treatment Response (≥50 reduction in HAM-D-17 at any point during treatment)

Raison et al., Arch Gen Psychiatry 2012, on line
Symptoms Responsive to Infliximab and Placebo in TRD subjects with Baseline hs-CRP>5

Raison et al., Arch Gen Psychiatry 2012, on line
Hitting the Sweet Spot

Diagram showing the relationship between inflammatory cytokines and learning/memory, neural plasticity, immune-targeted intervention point, monoamine disruption, impaired neurogenesis, and glutamergic excitotoxicity.
“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