Pharmacogenetics and Personalized Medicine

A Game Changer

Disclosure

Information related to Genetic Markers and Genetic Assay was adapted

For this presentation with permission from

http://genomind.com

Variability among individuals

- Sir William Osler, 1892

- "If it were not for the great variability among individuals, medicine might as well be a science and not an art.

How do we know how a patient will respond to a medication?

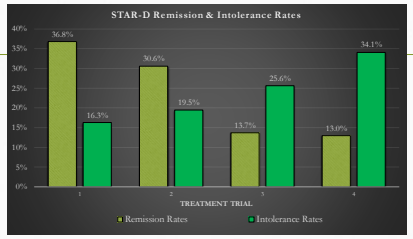
- DUH - We don't.
- Factors that affect response –many variabilities
- Result: clinicians use an educated trial and error method
- How will a patient respond to a particular medication?
- Will they experience an adverse response?
- Some patients take months to respond to the right medication cocktail

Treatment Resistance in Psychiatry

Diagnosis	Initial Remission Rate	Treatment Resistant/Relapse
Depression (MDD)[1]	30-37% (STAR-D)	30% treatment resistant following 4 treatments
Bipolar Disorder (BD)[2]	24-77% (STEP-BD)	50-70% relapse rates
Schizophrenia[3,4]	16-44% (CATIE)	Up to 74% discontinue medications due to lack of efficacy or poor side effects after 18 months
Anxiety (GAD)[5,6]	12-60%	Recurrence in up to 50%
Obsessive Compulsive Disorder (OCD)[7,8]	25-71%	Up to 80% in 10 year follow-up

30-80% of psychiatric patients have unresolved symptoms. Many have abandoned drug therapies due to inefficacy or side effects

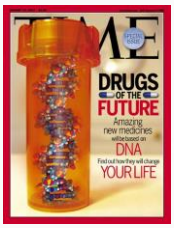
1) STARD NIMH
2) Sachs et al. NEJM 2007
3) Frey et al. Randomized controlled trial of efficacy of ziprasidone versus haloperidol for identifying early symptoms of relapse and clinical recurrence. BMJ 1999;318:1445
4) Alexander et al. Clin Neurosci Res 2006;6:277-285
5) Stein et al. Pharmacotherapy and recovery in generalized anxiety disorder. JCLP/Clin Trials 2009;65:1-12
6) Allgulander et al. Relapse versus continuation of citalopram and placebo in patients with generalized anxiety disorder. J Clin Psychiatry 2004;65:444-451
7) Stein et al. Pharmacotherapy and recovery in generalized anxiety disorder. JCLP/Clin Trials 2009;65:1-12
8) Ohland Grady, MD. Long-Term Outcomes, the Path to Obsessive-Compulsive Disorder screening. Mar 2011 Grad. Digest. Anxiety 2011 Mar 24



Rush et al 2006.

Why Should We Test?

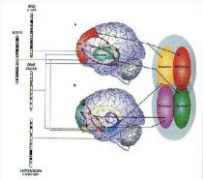
- Improve chances of selecting the right drug the first time
- Reduce medication choices using trial and error method
- Genetic markers "validate" psychiatric disorders as "medical" in origin.
- Understanding genetic markers may
  - Assist management
  - Improve outcomes in a more time efficient manner
  - Reduce stigma



Pharmacogenetics & Implications for Practice

Advantages

- Reducing adverse responses will improve patient safety and compliance
- Reduced experimentation will mean a more rapid therapeutic response
- Reduce unresponsiveness to medications – will better determine what medications to use and which ones to avoid
- Cost effective



"Over 25% of ALL common medications have genetic Information that can be tested And used to personalize medical treatment"
(Frueh et al, 2008)

What Are Biomarkers?

- Gene Based: Single Nucleotide Polymorphisms (SNPs)
- Epigenetics: Methylation Acetylation
- Gene Expression and Proteins
- Brain Imaging

Strimbu and Tavel 2010.

Genetics 101

Nature vs. Nurture

GENES + Environment = Phenotype

- In psychiatry we do a good job of determining what environmental factors have contributed to a particular disorder
- Until now, we have not had access to a large component of our phenotype…..genetic factors

GENECEPT ASSAY + Patient History = Personalized Treatment

Bay et al 2011

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Gene/Environment Interaction

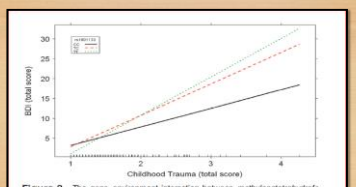

Figure 2 The gene–environment interaction between *methylenetetrahydrofolate reductase* (*MTHFR*) genotype and traumatic childhood events (TCEs) on depressive symptoms in 665 individuals from the general population ($P = 0.0027$). 0, T/T genotype; 1, C/T genotype; and 2, C/C genotype.

Transl Psychiatry (2013) 3, e288; doi:10.1038/tp.2013.60

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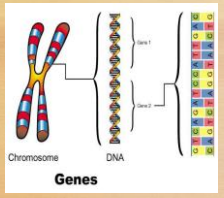
Definitions

Let's start with some basics.

What is DNA?



The 0.1% variance can help clinicians understand how a patient will respond to treatment

- **Chromosomes** are long strands of DNA (23 pairs)
- **DNA** (deoxyribonucleic acid) is composed of four nucleotide base pairs: adenine (A), thymine (T), guanine (G), and cytosine (C)
- **Genes** are sections of DNA that code for protein
- Each person has approximately 23,000 different genes, which are 99.9% identical between all individuals

http://ghr.nlm.nih.gov/handbook/basics/dna

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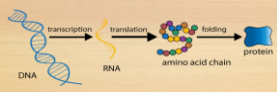
Genes Code for Proteins – "Recipe"

- DNA synthesis = specific sequences of nucleotides
  - DNA → Protein synthesis
- Protein synthesis → Directs metabolism



Definitions – 2 Significant Players

➢ **Allele**

- One member of a pair of genes, at a specific location on a specific chromosome.
- One allele from each parent

➢ **Substrate**

- Drug that binds to and is metabolized by an enzyme

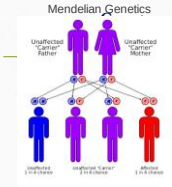
Genotype – Genetic Identity

- A combination of alleles located on chromosome pairs which determine a specific trait.
- Homozygous or heterozygous

- Genotype is an individual's Genetic identity

Phenotype

- The observable physical or biochemical characteristics of an organism
- determined by both genetic and environmental factors.
- Physical and biochemical characteristics
- Height, weight, skin color - examples



Contributes to Phenotype

MTHFR: C/T
DRD2: C/DEL
SLC6A4: L/S
COMT: VAL/VAL

Heterozygous

Homozygous

Alleles are different variants of a gene. Humans are diploid organisms and receive one allele from each parent

https://en.wikibooks.org/wiki/Human_Physiology/Genetics_and_Inheritance/ https://ccpro.zotec.org/genetic-education/genetic-and-non-genetic-risk

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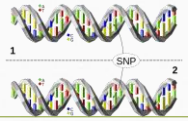
Recipe Errors - Oops

- As DNA is transcribed and translated, errors occur that can:
- Alter the proper structure and function of protein!

- Affect response to medications which target these proteins or associated pathways.

Single Nucleotide Polymorphism(SNPs)

- Most common variant among people
- Each SNP represents a difference in a single nucleotide building block
- Example: SNP may replace the nucleotide cytosine (C) with the nucleotide thymine (T) in a certain stretch of DNA.
- AATTCC
- AATTTC



The Genecept Assay

- The Genecept Assay was introduced commercially in 2010:
  - Patented gene-based assay informs treatment decisions for patients with mental health conditions, such as;
  - depression, anxiety, obsessive-compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), bipolar disorder, post traumatic stress disorder (PTSD), autism, schizophrenia, chronic pain and substance abuse
  - There are other companies: GeneSight

Data on file. Genomind 2016.

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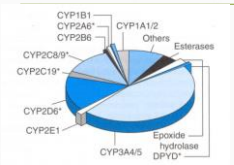
Why Pharmacogenetics?

- Individual genotype is invariable from birth to death.
- Based on our raw DNA
- Genotype is NOT affected by treatments/drugs
- Importance - CYP450 enzymes are essential for drug metabolism
- Approximately 35% of psychotropics are metabolized by
- CYP2D6 or CYP2C19
- Influences both therapeutic and adverse responses to medications

CYP450's Important to Drug Metabolism



- CYP3A4/5
  - Most important (50%)
  - Inducible
- CY2D6
  - Next in line (20%)
  - Not inducible
- CYP 2C9 and 2C19
  - 15%
  - Inducible

Pharmacogenetics

1. Study of how genetic variations influence pharmacokinetics and pharmacodynamics of drug action.
2. Study of how genetic variations influence response to medication.

Pharmacodynamics/Pharmacokinetics?

- Pharmacodynamics – What the drug does to the body
  - Interactions with receptors, transporters, & neurotransmitters
- Pharmacokinetics - What the body does to the drug
  - Including absorption, metabolism, elimination

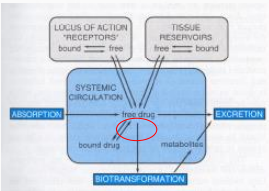
A patient's response to a drug may depend on factors that can vary according to the alleles that an individual carries, including

Pharmacokinetic factors

- Absorption
- Distribution
- Metabolism
- Elimination

Pharmacodynamic factors

- target proteins
- downstream messengers



Genetic Testing

- Variations in DNA can alter
  - gene functions
  - individual responses to psychotropic medications
  - These differences can be partially explained by analyzing genetic functioning
  - Help the clinician develop informed and personalized therapeutic decisions

Genecept Assay Genes in Detail:

Kinetic Variants

CYP450 Variations Mediate Drug Response

- 4 Gene variants associated with altered liver enzyme **metabolism** activity may lead to ***side effects and toxicity***

PM	**Poor metabolizers or inhibitors** of P450 may have increased drug serum levels and adverse events.
IM	**Intermediate metabolizers or inhibitors** of P450 may have increased drug serum levels and adverse events.
EM	**Extensive metabolizers** metabolize substrates normally.
UM	**Ultra-rapid metabolizers or inducers** of P450 may have reduced drug serum levels and poor efficacy.

FDA warning (Aug 2011): Citalopram maximum dose of 20mg in CYP2C19 poor metabolizers and those receiving CYP2C19 inhibitors

Swen et al 2011; http://www.fda.gov/

Specific Genes

What are they and what are the implications of genetic variations?

18 Genes Analyzed

Gene	Physiological Role	Impact of Mutation	Treatment Impact
Serotonin Transporter (SLC6A4)	Protein responsible for reuptake of serotonin from the synapse	Inhibition of the protein by SSRIs, which may lead to increased risk for non-response/side effects	Use caution with SSRIs, atypical antipsychotics or SSRIs may be used if clinically indicated
Calcium Channel (CACNA1C)	A subunit of the calcium channel which mediates excitatory signaling	Associated with conditions characterized by mood instability/lability	Atypical antipsychotics, mood stabilizers, and/or omega-3 fatty acids, which may help to reduce excitatory signaling, may be used if clinically indicated
Sodium Channel (AVKS)	Protein that plays a role in sodium channel function and regulation of excitatory signaling	Associated with conditions characterized by mood instability/lability	Mood stabilizers and/or omega-3 fatty acids, which may help to reduce excitatory signaling, may be used if clinically indicated
Serotonin Receptor 2C (HTR2C)	Receptor involved in regulation of satiety	Mixed by atypical antipsychotics, resulting in metabolic side effects	Use caution with atypical antipsychotics; mirtaz may be used to mitigate risk for weight gain if clinically indicated
Melanocortin 4 Receptor (MC4R)	Receptor that plays a role in the control of food intake	Increased risk for weight gain and higher BMI, which is associated by atypical antipsychotics	Use caution with atypical antipsychotics
Dopamine 2 Receptor (DRD2)	Receptor affected by dopamine in the brain	Blocked by antipsychotic medications and is associated with risk for non-response/side effects	Use caution with antipsychotics
Catechol-O-Methyltransferase (COMT)	Enzyme primarily responsible for the degradation of dopamine in the frontal lobes of the brain	Altered dopamine states can have emotional/cognitive effects and impact response to dopaminergic agents	Dopaminergic agents or TMS may be used if clinically indicated for **Met/Met patients**
			Use caution with dopaminergic agents in **Met/Met patients**
Alpha-2A Adrenergic Receptor (ADRA2A)	Receptor involved in neurotransmitter release	Associated with improved response to stimulant agents	Stimulant agents may be used if clinically indicated
Methylenetetrahydrofolate Reductase (MTHFR)	Predominant enzyme that converts folic acid/folate to its active form (methylfolate) needed for synthesis of serotonin, dopamine, and norepinephrine	Associated with varied activity and conversion of folic acid/folate to methylfolate	Supplementation with L-methylfolate may be used if clinically indicated
+ AC6BG			
+ CBT7T			
Brain-derived Neurotrophic Factor (BDNF)	Important for proper neuronal development and neural plasticity	Impaired BDNF secretion, which may be associated with altered SSRI response in Caucasians	Increased physical activity/exercise may be beneficial for **Met carriers** if clinically indicated
μ-Opioid Receptor (OPRM1)	Opioid receptor affected by natural and synthetic components	Activated by opioids and associated with varied analgesic response, dosage, and abuse/addiction risk	Use caution with opioids; non-opioid analgesics may be used if clinically indicated
Glutamate Receptor (GRIK1)	An excitatory neurotransmitter receptor in the brain	Associated with response to topiramate for alcohol abuse	Topiramate may be used for treatment of alcohol abuse if clinically indicated
CYP1A2, CYP2B6, CYP2C9	Enzymes that metabolize medications in the liver	Large number of psychiatric medications are metabolized by CYP450s	Dose adjustment (or) increase or decreased may be required
CYP2C19, CYP2A6/5			

= newly added to the Genecept Assay, January 2016

Data on file. Genomind 2016.

CYP1A2 Environmental Inducers

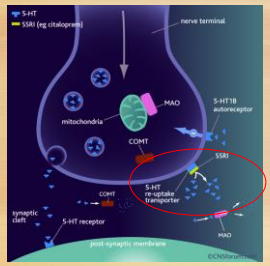
- CYP1A2 is highly induced by certain environmental factors
  - Tobacco smoke: CYP1A2 levels will be increased with smokers
  - Cruciferous vegetables: broccoli, cauliflower, cabbage consumption will increase CYP1A2 levels
  - Char-grilled meats: consumption of char-grilled meats will increase CYP1A2 levels

Zhou SF et al 2009; Browning SL et al 2010; 137. Gunes A and Dahl ML 2008

Genecept Assay Genes in Detail:

Dynamic Variants

Serotonin Transporter (SLC6A4)



- SLC6A4 is reported as L(A) (normal) or L(G) or S (risk)
- Patients carrying the S or L(G) allele are at *higher risk for side effects and lack of response to SSRIs*

Clinical Impact:

- Caution with SSRIs
- Therapeutic Options: SNRIs and Atypical Antidepressants

www.pharmgkb.org/pathway/PA161749006; Kato M and Serretti A 2010; Porcelli 2012

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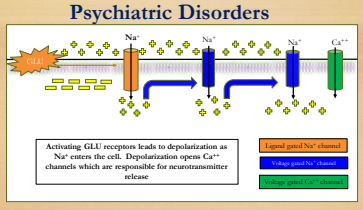
Serotonin Transporter Gene
SLC6A4

- Reported as L (A)(normal), L(G), or S (risk)
- Patients with L/G or S are at higher risk for poor response or side effects
- Clinical Impact
  - Use caution with SSRIs
  - Therapeutic Options: May substitute SNRIs or atypical antidepressants, if clinically indicated

2 Ion Channels in the Brain and Psychiatric Disorders

ANK3
Na channel

CACNA1C
Ca channel



- Homozygotes of the ANK3 'T' allele or CACNA1C 'A' allele are at higher risk of altered neuronal signaling. Mediate excitatory signaling.. Mood instability.
- Clinical Impact: therapeutic options include agents that reduce neuronal signaling such as mood stabilizers, atypical antipsychotics, omega 3 fatty acids

Ferreira et al., 2008

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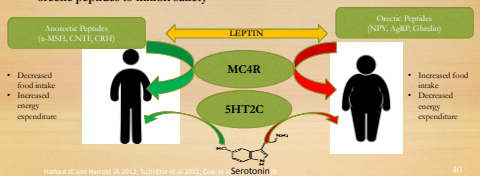
Genetics of Atypical Antipsychotic Metabolic Effects

- Satiety signaling: regulation of feeding behavior and energy balance is highly complex and controlled mainly in the hypothalamus
  - Serotonin signaling regulates satiety through activation of 5HT2C receptors
  - MC4R is activated by anorectic peptides to induce satiety and inhibited by orectic peptides to inhibit satiety



Halford JC and Harrold JA 2012; Tschöp et al 2011; Cole et al

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5HT2C and MC4R
Genetic Variations Affect Metabolic Risk

Serotonin Receptor 2C (5HT2C)

- Receptor site on which various neuroleptic medications act
- Regulates appetite and feeling of satiety
- Blocking this pathway (through mutation) leads to increased appetite/food intake
- The C allele – risk for weight gain (80 % of Caucasians)
- The T allele – protective effect against weight gain
- Inositol – helps some people control appetite

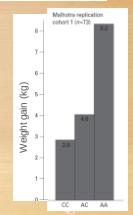
Melanocortin 4 Receptor (MC4R)

- Regulates satiety, body weight, and energy balance

Mutation

- Melanocortin 4 Receptors (MC4R) A allele may increase risk for weight gain and higher BMI

Impact of MC4R Genotype on Weight Gain with Atypical Antipsychotics



Clinical Impact

- Atypical antipsychotics exacerbate the risk for weight gain for A allele carriers
- Use caution with atypical antipsychotics
  - High risk medications: clozapine and olanzapine
  - Medium risk medications: aripiprazole; iloperidone; paliperidone; quetiapine; risperidone
  - Low risk medications: asenapine; cariprazine; brexpiprazole; lurasidone; ziprasidone

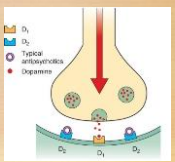
Sicard et al 2012; Giordano et al 2011; Gerfi et al 2007; Capasso et al 2013; Malhotra et al 2012; Corell et al 2011.

Dopamine Receptor (DRD2)

- Antipsychotic clinical efficacy is highly correlated with the blockade of *Dopamine 2 Receptor*
- Deletions (DEL) in the dopamine receptor gene can inhibit dopamine signaling
- Indicates that antipsychotics are
  - less likely to be effective and
  - more likely to cause side effects.

C/C | C/Del | Del/Del

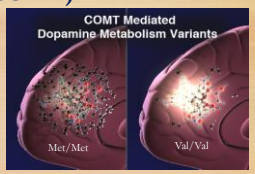
- Clinical Impact Use antipsychotics with caution or use an alternative agent



Zang et al 2010

Catechol-o-methyltransferase (COMT)

- COMT, is an enzyme found in the prefrontal cortex(PFC)
- responsible for dopamine degradation
- Normal: Val/Met



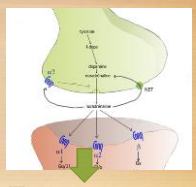
COMT Activity	DA Levels	Clinical Impact
High (Val/Val)	Low ↓	• Impaired Executive Function • Superior response with Stimulants
Low (Met/Met)	High ↑	• Superior Executive Function • Caution with Stimulants

Barnett et al 2007; Palmiro, Stewart Ryan and Akbar, Oxford 2011; ; genetic.www.healthcare-ehr2.com ; Henderson et al 2016

Adrenergic α2A-receptor (ADRA2A)

Major subtype of adrenergic receptor found in prefrontal cortex (PFC)

- Job is neurotransmitter release, Norepinephrine (NE)
- NE signaling in the PFC is critical for working memory and executive function;
- ADRA2A dysfunction is associated with impaired PFC function and ADHD



Working memory and cognitive function

Kim et al 2010; Arnsten AF and Dudley AG 2005; www.ncbi.nlm.nih.gov/pubmed/20925474

Adrenergic α2A-receptor (ADRA2A)

- ADRA2A
- Receptor involved with neurotransmitter release
- Associated with improved response to stimulant agents
- Stimulant agents may be use if clinically indicated

Adrenergic α2A-receptor (ADRA2A)

Published research

- Naturalistic pharmacogenetic study - demonstrated that G allele carriers had greater improvement of inattentive symptoms with methylphenidate treatment in the first month (da Silva, 2008)
- Clinical study - GG + CG genotypes are associated with response to MPH (Kim, 2013)
- G allele linked to improvement in inattention symptoms with MPH in children with ADHD (Polanczyk, 2007)

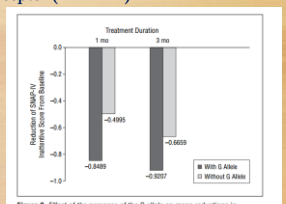


Figure 2. Effect of the presence of the G allele on mean reductions in Swanson, Nolan, and Pelham Scale version IV (SNAP-IV) inattentive scores from baseline in a mixed-effects model (n=106). Presence of the G allele: $F_{1,93}$ =6.6; P = .01.

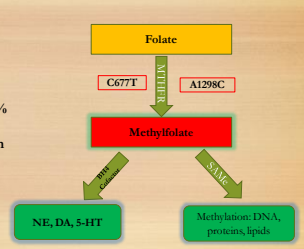
Clinical Impact

- The G allele is associated with better response to stimulants for ADHD

da Silva et al 2008; Polanczyk et al 2007;

MTHFR and Folate Metabolism

- Depending on the different combinations of C677T and A1298C alleles
- total conversion rates of folic acid range from 100% to <30%
  - C677T; T = 35% reduction in conversion rates
  - A1298C; C = 20% reduction in conversion rates



Frazzetta, 2005; Ariyoshi 1997; Bellard et al 2003; Kelly B 2004; SGM 2006; Robinson 2009; Wu YL et al 2011; Gilbody S et al 2007; Pardiñero DD, et al 2005.

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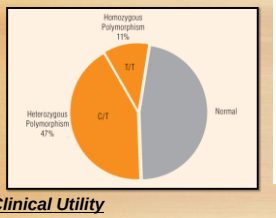
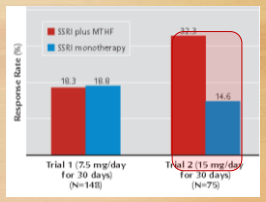
Methylenetetrahydrofolate Reductase

- MTHFR
- Predominant enzyme responsible for converting folic acid to L methylfolate, active form of folic acid- needed for synthesis of dopamine, neuroepinephrine, dopamine
- Supplementation with L-methylfolate – if clinically indicated
- Deplin

MTHFR Polymorphism





Clinical Utility

- **L-methylfolate supplementation may be relevant in patients with the T allele**

Papakostas et al 2012; Ginsberg et al 2011; Wade et al 2014; Papakostas et al 2014

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Brain Derived Neurotrophic Factor

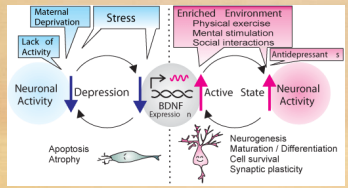
- BDNF -Needed for proper neuronal development and neural plasticity
- Impaired ↓ BDNF secretion associated with altered SSRI response – Caucasians
- Met/Met and Val/Met carriers – have poorer response to SSRIs. Impaired cognition and may benefit from increased activity/EXERCISE
- Val/Val carriers may have better response to SSRIs

Brain-derived Neurotrophic Factor (BDNF)

Mutation

- **(Val/Met) and Met/Met linked to impaired cellular secretion; At risk for depression, impaired memory, & altered stress response**

Val/Met
Met/Met
Not good



Val/Val
Good

Martínez-Levy GA, Cruz-Fuentes CS 2014; Hosang et al 2014

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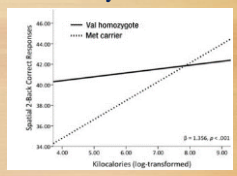
BDNF and Physical Activity

Clinical Impact:

- Greater levels of physical activity can offset the deleterious effect of Met allele on working memory (Erickson, 2013)
- Exercise has been linked to improved cognition, working memory, and higher BDNF levels



Erickson et al 2013; Colle et al 2015

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μ-Opioid Receptor (OPRM1)

Mutation

- **The G allele is associated with decreased response to opioids and increased risk for addiction. Decreased sensitization to opioids**

Clinical Impact

- **Clinicians may increase dose for G allele carriers, however these patients are at risk for substance abuse**
- **Non-opioid analgesics may be recommended for G allele carriers**

Table 2

Genotype frequency, demand and consumed morphine dose in milligrams for the patients who received patient-controlled analgesia alone.

	Genotype frequency (%)	Demand in first 24 h	Demand in second 24 h	Demand in first 48 h	Dose in first 24 h	Dose in first 48 h
AA	62	24.3 (15.4)	9.5 (9.4)	39.0 (24.7)	16.0 (8.0)	25.3 (15.5)
GG	11	36.1 (15.2)	18.3 (14.9)	57.8 (24.7)	22.3 (10.0)	40.4 (22.1)

Crist RC et al 2014; Ren ZY et al 2015; Haji et al 2015; Hairian BS et al 2013; Chou et al. 2006

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U-Opioid Receptor*

- Opioid receptor activated by natural and synthetic compounds
- Varied analgesic response, dosage, and abuse/addiction risk
- Use caution with opioids
- Use non opioids if clinically indicated

Glutamate Receptor Kainate 1 (GRIK1)

- An predominant excitatory neurotransmitter receptor in brain
- C allele may be associated with alcohol dependence
  - Polymorphism associated with increased response to topiramate for alcohol abuse

Clinical Impact – Topiramate (Topomax)

- **Topiramate blocks glutamate receptors, notably ones with GRIK1**
- **Topiramate is more likely to cause side effects in A allele carriers**
- **The C/C genotype is associated with better response to topiramate in the treatment of alcohol abuse/alcoholism**

Kranzler et al Apr 2014

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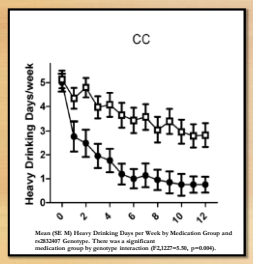
Glutamate Receptor Kainate 1 (GRIK1)



Mean (SE M) Heavy Drinking Days per Week by Medication Group and rs2832407 Genotype. There was a significant medication group by genotype interaction ($F_{2,1227}$=5.30, p=0.004).

- **GRIK1 CC genotype (rs2832407) resulted in significantly fewer heavy drinking days compared to placebo**
- **The difference in heavy drinking days with A allele carriers was not significant**

Kranzler et al Apr 2014; Oct 2014; Dec 2014

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Evidence Base of the Genecept Assay

- Inclusion of genes in the panel is supported by strong peer reviewed literature
  - Genomind's clinical team, working closely with our SAB, assesses the strength of the data
  - Genes were selected based on the critical examination of hundreds of studies showing that variations in these genes can inform treatment decisions
- Report content is fully cited, with 200 references to date
- Genomind has developed a full Literature Summary, summarizing each citation related to the genetic variations analyzed

Data on file. Genomind 2016.

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Results of the test, combined with expert clinical consultations, enable better patient responses to treatment.

The Genecept Assay – How it Works

1. Patients provide cheek swab via a collection kit supplied by Genomind
2. Prepaid overnight shipping packet and barcoded requisition form provided so patient sample can be sent securely to Genomind's lab
3. Genomind's CLIA-certified lab performs test with 3-5 day turnaround time
4. A patented algorithm results in online analytical report delivered to clinician to inform treatment decisions
5. Genomind-certified physicians and PharmD's available to discuss results with treating clinicians via telephonic consult

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The Value of Genomind's Clinical Consultation

- *Personalized access to consultations with Genomind certified physicians, Ph.D.'s and Pharm.D.'s, in conjunction with every patient report in a timely manner*
- *Creates a significant connection between the patient, their clinical history, their genetic results, and the treating clinician*
- *Enhances education of biomarkers and translation of genetic results into potential treatment strategies*
- *Can be leveraged for the clinician's family consultations and program discharge planning*

Data on file. Genomind 2016.

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Case Study

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Case Study

- 32 y/o mom, married, stay at home mom, has two children and had Baby #3 five days ago. SVD, uncomplicated.
- Chronic diagnosis of Anxiety Disorder since her early teen years. Brother committed suicide at age 21.
- Her OB doctor prescribed Sertraline 25 mg yesterday and today she feels much worse. Mother was with her
- Presents with severe anxiety, agitation, and afraid she is going to lose control. Does feel attached to her infant.

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Case Study

- *What would your treatment choice be?*
  - Different SSRI
  - Tricyclic
  - Duloxetine
  - Bupropion
  - Mood stabilizer
  - Methylfolate

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RESULTS REPORT: Pharmacodynamic Gene Variations; Drug Target Sites

Use caution with related therapies | Therapeutic options | No known gene-drug interaction

GENE RESULT	THERAPEUTIC IMPLICATIONS	INTERACTION	CLINICAL IMPACT
Serotonin Transporter (SLC6A4) CC (High risk vs non-reference)	*SLC6A4 is a presynaptic transmembrane protein responsible for serotonin reuptake* • SSRIs act by blocking this transporter to produce a therapeutic response • Higher risk of poor response, slow response or intolerance to SSRIs, potential increased risk for PTSD and reduced stress resilience • Therapeutic options such as atypical antidepressants or SNRIs may be used as clinically appropriate		**Use caution** with SSRIs **Therapeutic options: atypical antidepressants** or **SNRIs** may be used as clinically indicated
Calcium Channel (CACNA1C) AG (Hybrid risk of altered neuronal signaling)	*CACNA1C is a subunit of L-type voltage gated calcium channels which is involved in excitatory signaling in the brain* • Abnormal calcium signaling may be clinically associated with conditions characterized by mood instability or lability		**Therapeutic options: atypical antipsychotics, mood stabilizers, calcium channel blocker, fatty acids** may be used if clinically indicated
Melanocortin-4 Receptor (MC4R) AA (High weight gain risk)	*MC4R is a receptor that plays a central role in the control of food intake* • Risk of increased weight gain and BMI in healthy individuals and this risk may be further exacerbated with atypical antipsychotics **High risk**: Clozapine, Olanzapine **Moderate risk**: Aripiprazole, Asenapine, Paliperidone, Quetiapine, Risperidone **Lower risk**: Iloperidone, Ziprasidone, Lurasidone, Quetiapine		**Use caution** with atypical antipsychotics
Methylenetetrahydro-folate Reductase (MTHFR) CTTT CT AT/GNRC AC (Low activity)	*MTHFR is an enzyme responsible for the conversion of folic acid to methylfolate which is a precursor needed for serotonin, norepinephrine and dopamine synthesis* • Risk for reduced MTHFR enzyme activity and reduced methylfolate production • Folic acid-based supplementation of SSRIs and SNRIs show superior symptom reduction and medication adherence compared to SSRIs/SNRIs alone in Major Depressive Disorder		Higher intake of folic acid based elementaries may be required **Therapeutic options: L-methylfolate** may be used if clinically indicated
Brain-derived Neurotrophic Factor (BDNF) Met/Met	*BDNF is a protein involved in neuronal development and neural plasticity* • Potential risk for increased depressive symptoms, impaired working memory and reduced neuroplasticity • Studies have shown that Met carriers may have less satisfactory response to SSRIs in Caucasians, but not Asians; however larger studies need to be conducted to confirm these findings • Exercise has been linked to improvements in cognition, and recent studies show that Met allele carriers may demonstrate enhanced effects of exercise on working memory compared to Val/Val patients		**Therapeutic options:** increased levels of **physical activity/exercise** if clinically appropriate

Data on file. Genomind 2016.

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Use caution with related therapies | Therapeutic options | No known gene-drug interaction

GENE RESULT	THERAPEUTIC IMPLICATIONS	INTERACTION	CLINICAL IMPACT
Sodium Channel (SCN5A) [Normal]	*SCN5A is a protein that plays a role in sodium ion channel function and is involved in excitatory signaling in the brain* • This genotype confers normal activity	✓	There are no known gene-drug interactions for this genotype
Serotonin Receptor 2C (5HT2C) [Lowest weight gain risk]	*5HT2C is a receptor involved in the regulation of satiety* • The T allele confers a protective effect against risk of weight gain with atypical antipsychotics as compared to the C allele	✓	There are no known gene-drug interactions for this genotype
Dopamine 2 Receptor (DRD2) GC [Normal]	*DRD2 is a receptor affected by dopamine in the brain* • DRD2 is involved in response to antipsychotics • This genotype confers normal activity	✓	There are no known gene-drug interactions for this genotype
Catechol-O-Methyltransferase (COMT) Val/Met [Normal]	*COMT is an enzyme responsible for breakdown of dopamine in the frontal lobes of the brain* • COMT is involved in response to stimulants • This genotype confers normal activity	✓	There are no known gene-drug interactions for this genotype
Alpha-2A Adrenergic Receptor (ADRA2A) GG [Normal response]	*ADRA2A is a receptor which plays an important role in neurotransmitter release* • ADRA2A is involved in response to stimulants • This genotype confers normal activity	✓	There are no known gene-drug interactions for this genotype
μ-Opioid Receptor (OPRM1) AA [Normal response]	*OPRM1 is an opioid receptor which is affected by natural and synthetic compounds* • OPRM1 is involved in response to opioids • This genotype confers normal activity	✓	There are no known gene-drug interactions for this genotype
Glutamate Receptor Kainate 1 (GRIK1) AA [Normal response]	*GRIK1 is an excitatory neurotransmitter receptor* • GRIK1 is involved in response to topiramate for alcohol abuse • This genotype confers normal activity	✓	There are no known gene-drug interactions for this genotype

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Use caution with related therapies | Therapeutic options | No known gene-drug interaction

Patient Results

RESULTS REPORT: Pharmacokinetic Gene Variations; CYP450 Drug Metabolism

GENE RESULT	THERAPEUTIC IMPLICATIONS	INTERACTION	CLINICAL IMPACT
CYP2B6 IM *5/*6 [Intermediate activity]	*Intermediate metabolizer*: risk of elevated serum levels and drug interactions • A dose adjustment or alternate therapy may be necessary	⚠	**Use caution** with medications metabolized by CYP2B6 *See Drug Interaction Summary for details*
CYP2C19 PM *2/*2 [Low activity]	*Poor metabolizer*: risk of elevated serum levels and drug interactions • A dose adjustment or alternate therapy may be necessary	⚠	**Use caution** with medications metabolized by CYP2C19 *See Drug Interaction Summary for details*
CYP1A2 EM *1/*1F [Normal activity]	*Variations in the CYP1A2 liver enzyme can result in altered drug metabolism and unexpected drug serum levels* • This genotype confers normal activity	✓	There are no known gene-drug interactions for this genotype
CYP2C9 EM *1/*2 [Normal activity]	*Variations in the CYP2C9 liver enzyme can result in altered drug metabolism and unexpected drug serum levels* • This genotype confers normal activity	✓	There are no known gene-drug interactions for this genotype
CYP2D6 EM *2/*2 [Normal activity]	*Variations in the CYP2D6 liver enzyme can result in altered drug metabolism and unexpected drug serum levels* • This genotype confers normal activity	✓	There are no known gene-drug interactions for this genotype
CYP3A4 *1/*1 CYP3A5 *3/*3 [Normal activity]	*Variations in the CYP3A4/5 liver enzymes can result in altered drug metabolism and unexpected drug serum levels* • This genotype confers normal activity • CYP3A activity is determined by the sum activity of the CYP3A family of genes; in adults the most influential are CYP3A4 and 3A5	✓	There are no known gene-drug interactions for this genotype

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Interpretation

Drug Interaction Summary:

This summary provides a listing of implications for psychotropic and pain medications specific to your patient's genetic profile

	Medication	Primary metabolizing enzyme(s)	Use as Directed: No known gene-drug interactions	Therapeutic Options: Options which may be used if clinically indicated	Use with Caution: Serum levels may be (reduced dose may be required)	Serum levels may be (increased dose may be required)	Increased risk for adverse events or poor response
				CYP450			
	Antidepressants			SLC6A4			SLC6A4
SSRIs	Citalopram (Celexa®)	2C19, 3A4/5			✓		✓
	Escitalopram (Lexapro®)	2C19, 2D6					✓
	Fluoxetine (Prozac®)	2D6, 2C9					✓
	Fluvoxamine (Luvox®)	2D6, 1A2					✓
	Paroxetine (Paxil®)	2D6					✓
	Sertraline (Zoloft®)	–					✓
SNRIs	Desvenlafaxine (Pristiq®)	–	✓	✓			
	Duloxetine (Cymbalta®)	1A2, 2D6	✓	✓			
	Levomilnacipran (Fetzima®)	3A4/5	✓	✓			
	Venlafaxine (Effexor®)	2D6, 2C19, 3A4/5					
Bupropion	Bupropion (Wellbutrin®)	2B6	✓	✓			
Mirtazapine	Mirtazapine (Remeron®)	3A4/5	✓	✓			
Trazodone	Trazodone (Desyrel®)	2D6	✓	✓			

PV Prodrug - requiring activation by liver. 2D6 IMs/PMs may experience lower efficacy and increased side effects due to reduced conversion to the active Bupropion metabolite and higher levels of the inactive parent drug. 2D6 UMs may experience increased conversion of the parent drug, and higher levels of the active metabolite

DD Bidirectional - Gene-drug interaction may exist, however indeterminate due to varied impact of multiple CYP450 enzymes, unknown clinical significance of a metabolite, or genotype was unable to be determined.

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	Medication	Primary metabolizing enzyme(s)	Use as Directed: No known gene-drug interactions	Therapeutic Options: Options which may be used if clinically indicated	Use with Caution: Serum levels may be (reduced dose may be required)	Serum levels may be (increased dose may be required)	Increased risk for adverse events or poor response
				CYP450			
	Atypical Antipsychotic			CACNA1C			MC4R
	Aripiprazole (Abilify®) ⓓ	2D6, 3A4/5					✓ [3]
	Asenapine (Saphris®)	1A2	✓	✓			
	Brexpiprazole (Rexulti®) ⓓ	2D6, 3A4/5	✓	✓			
	Cariprazine (Vraylar®)	3A4/5	✓	✓			
	Clozapine (Clozaril®)	1A2, 2D6, 3A4/5					✓ [3]
	Iloperidone (Fanapt®)	2D6					✓ [3]
	Lurasidone (Latuda®)	3A4/5	✓	✓			
	Olanzapine (Zyprexa®)	1A2, 2D6					✓ [3]
	Paliperidone (Invega®)	–					✓ [3]
	Quetiapine (Seroquel®)	3A4/5					✓ [3]
	Ziprasidone (Geodon®)	–	✓	✓			✓ [3]

[3] This medication is listed to use with caution as there is a risk for weight gain because of a variation in 5HT2C, MC4R or both; these variations have not been shown to impact therapeutic efficacy and this medication may be used if clinically indicated

ⓓ Medication has manufacturer dose-administration FDA labeling; see the Genecept Assay Report Interpretation Guide

- **CACNA1C** variation in combination with clinical presentation, led clinician to try **lurasidone**.
- Careful monitoring of weight gain was warranted due to the **MC4R** variation. An **exercise regime was recommended** due the presence of this variant as well as the **BDNF** variation.

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- Lack of efficacy for SSRI's could be related to the **SLC6A4** or **2C19** variants
- SNRIs and atypical antidepressants are relevant for this patient; clinician decided to prescribe **duloxetine**
- Caution with any drugs metabolized by **2C19** or **2D6**

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	Medication	Primary metabolizing enzyme(s)	Use as Directed: No known gene-drug interactions	Therapeutic Options: Options which may be used if clinically indicated	Use with Caution: Serum levels may be (reduced dose may be required)	Serum levels may be (increased dose may be required)	Increased risk for adverse events or poor response
				CYP450			
	Alternative/Complementary			CACNA1C, MTHFR			
	Inositol	–	✓				
	L-methylfolate (Deplin®, Extr.ylfol®)	–	✓	✓			
	Omega-3 Fatty Acids	–	✓	✓			

- **L-methylfolate** and **Omega-3 fatty acids were also added to the patients regimen** due to the presence of variations in **MTHFR** and **CACNA1C**

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Follow-up

- Patient reported
  - Stable mood, with decreased anxiety
  - No sexual side effects
  - Reduction of HAM-A from 28 to 16
  - Reduction of anxiety, agitation, and headaches has allowed her to become more able to care for her children
  - Compliant with regimen and exercise plan

Prior Treatment	Genecept Assay Guided Treatment	Relevant Genes
Fluoxetine	Duloxetine	2D6, SLC6A4, BDNF
Escitalopram	Lurasidone	3A4, CACNA1C, MC4R
	Exercise	BDNF
	L-methylfolate	MTHFR
	Omega-3 fatty acids	CACNA1C

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https://www.mcmill.com/communities/modulations/wp-content/uploads/sites/2/2010/10/Questions-and-Answers.png

Conclusion

- Thank you for your interest and attention.