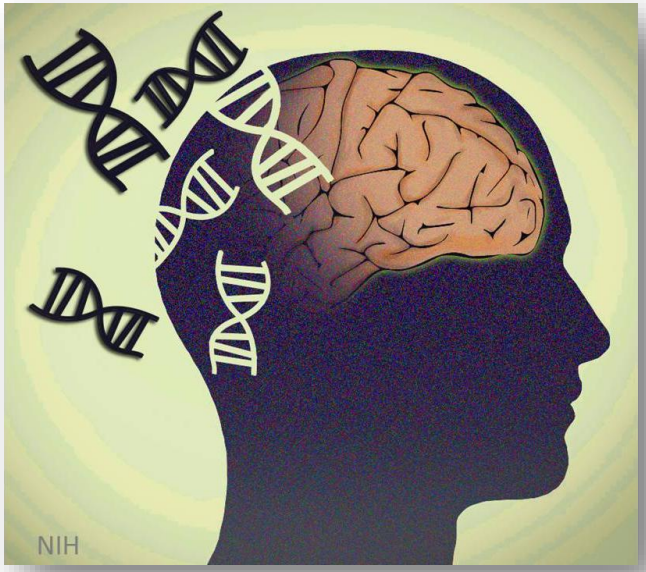
Make waves

COMMUNITY EDUCATION DAY

BREAK
THE SILENCE.

Lindner Center of HOPE | UC Health

Mental Health and Genetics: An Overview of What We Know



Jen Milau, APRN, PMHNP-BC

Psychiatric Mental Health Nurse Practitioner

Objectives

- Address link between genetics and psychiatric diagnoses
- Review psychiatric pharmacogenomic panels available
- Discuss advantages of obtaining pharmacogenetic results and clarify misconceptions about clinical utility / relevance
- Open panel for questions

The Link Between Genetics and Mental Illness

A Review of Current Research and Theories

Mental Illness and Heritability

Theory that a link exists has been supported by:

- Clustering of illness in families
- Higher concordance rates between monozygotic than dizygotic twins
- Similarity of adoptee to their biological rather than adoptive relatives

(Uher, 2009)

Diagnoses with Suspected Genetic Link

- Schizophrenia
- Obsesive-compulsive Disorder
- Bipolar Spectrum Disorders
- Anxiety Disorders
- Major Depressive Disorder
- Autism Spectrum Disorder
- Attention-deficit Hyperactivity Disorder
- Eating Disorders (Anorexia Nervosa, Bulimia Nervosa)

Current Research

- Research Domain Criteria (RDoC) – NIMH
  - Research framework for new approaches to investigating mental disorders
  - Genetics is major area of interest under study
    - Limitations due to access/availability for genome-wide association studies
- 2013: NIH-funded team conducted largest genome-wide study of its kind
  - Discovered that people with disorders traditionally thought to be distinct – autism, ADHD, bipolar disorder, major depression and schizophrenia – were more likely to have suspect genetic variation at the same four chromosomal sites.

(The Lancet, 2013)

Limitations to Current Technology

- At this point there are no identified alterations to genes which consistently predict development of specific mental illness (NIMH, 2017)

- No genetic tests available which accurately predict risk of mental illness based upon genome scans or karyotyping

“Causes” of Mental Illness

- Multi-factorial
  - Genetic
  - Neurobiological
  - Environmental Exposures
  - Life experiences
    - Trauma
    - Attachment / Neglect
  - Culture
  - Relationships

Epigenetics

- Genetic control by factors other than an individual's DNA sequence (**genotype**) which can alter an individual's gene function (**phenotype**)
- Can switch genes on or off and determine which proteins are transcribed – "Gene silencing"
  - Methylation / Demethylation
    - Adding or Removal of Methyl group to DNA to modify the function and expression of a gene
  - Histone Changes
    - Modifications to arrangement of chromatin (area in cell nucleus that makes up complex of DNA and proteins)
  - RNA-Associated Silencing

(Simmons, 2008)

Epigenetics and Mental Illness

- Genetic susceptibility coupled with environmental factors – turn genes “on” or “off” leading to changes in gene expression (**phenotype**)
  - Diet / Nutrition
  - Stress
  - Exposure to Toxins or Substances
    - In-utero
    - Childhood
    - Adulthood
  - Early Adverse Life Events
  - Neglect / Lack of Attachment

(Klengel & Binder, 2015)

Pharmacogenomic Testing

Implications and Limitations

What is Pharmacogenomic Testing?

- Pharmacogenomics: Study of how a person's genes affect their response to medications
  - Pharmacology: Study of use / effects of drugs
  - Genomics: Study of genes and their functions

- Information available to help personalize treatment
  - Efficacy
  - Side Effects
  - Dosing and Titration
- Asthma, HIV, Pain medications/anesthesia, Cancer, Heart Disease, Psychiatric Disorders

Pharmacogenomics is in its infancy!

Terminology

- Pharmacokinetics (What the body does to a drug)
  - Absorption, distribution, metabolism, and excretion.
  - Helps with understanding of dose and associated response
- Pharmacodynamics (What the drug does to the body)
  - Biochemical, physiologic, and molecular effects of drugs on the body
  - Involves receptor binding (including receptor sensitivity), post-receptor effects, and chemical interactions.

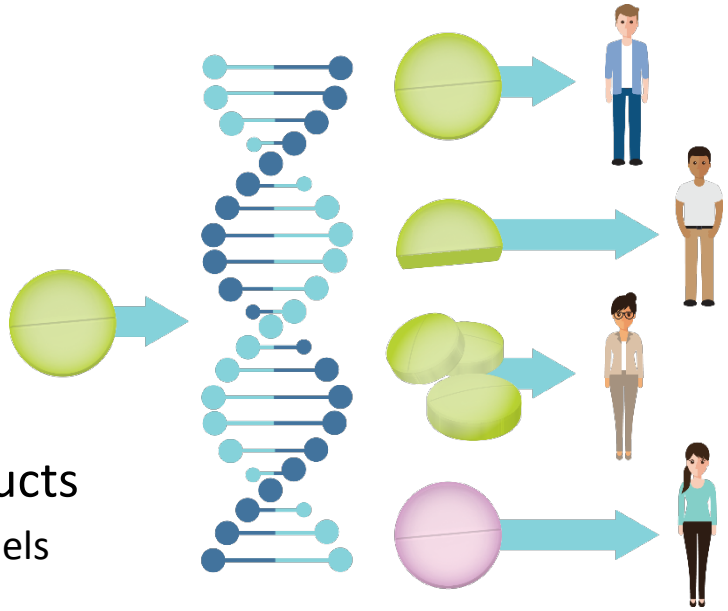
Research Backing

- **Clinical Pharmacogenetics Implementation Consortium (CPIC)**
  - Started as shared project between PharmGKB and Pharmacogenomics Research Network (PGRN) in 2009. CPIC guidelines are indexed in PubMed as clinical guidelines, endorsed by ASHP and ASCPT, and referenced in ClinGen and PharmGKB
  - Goal = Address barrier to clinical implementation of pharmacogenomic tests
    - Freely available
    - Peer-reviewed
    - Evidence-based
    - Detailed gene/drug clinical practice guidelines
- **Pharmacogenetic Working Group (PWG)**
  - 85 genotype and phenotype drug combinations for 25 medications (this number is likely higher at this point in time)
  - Available on the PharmGKB site
  - Translate phenotype and genotype information into therapeutic dose recommendations.
  - Information re: clinical relevance provided with clearly stated level of the evidence (strong, moderate, and optional). (CPIC, 2019; Drozda et al., 2014)

How is the Information Used?

- Language now being included on FDA product labeling for certain psychotropic medications!
  - Table of Pharmacogenomic Biomarkers in Drug Labeling available on FDA website:

https://www.fda.gov/drugs/scienceresearch/ucm572698.htm



- Pharmacogenetic / Pharmacogenomic Test Products
  - Many available – Over 20 companies with different panels
    - FDA currently increasing scrutiny
  - Algorithm-Based – Varying Evidence
  - GeneSight (AssureRx Health) has most substantial evidence base in regards to clinical trials and outcomes

(Zeier, et al., 2018)

Antidepressants

Use as directed	Use with caution	Use with increased caution and with more frequent monitoring
Desvenlafaxine (Pristiq®)	Amitriptyline (Elavil®)[3,8]	Bupropion (Wellbutrin®)[1,6]
Vilazodone (Viibryd®)	Citalopram (Celexa®)[3,4]	Clomipramine (Anafranil®)[3,7,8]
	Doxepin (Sinequan®)[3,8]	Desipramine (Norpramin®)[1,6,8]
	Escitalopram (Lexapro®)[3,4]	Duloxetine (Cymbalta®)[3,7,8]
	Fluvoxamine (Luvox®)[3,7,8]	Fluoxetine (Prozac®)[1,6]
	Sertraline (Zoloft®)[4]	Imipramine (Tofranil®)[1,6,8]
	Trazodone (Desyrel®)[1]	Mirtazapine (Remeron®)[3,7]
	Venlafaxine (Effexor®)[3]	Nortriptyline (Pamelor®)[1,6,8]
		Paroxetine (Paxil®)[1,4,6,8]
		Selegiline (Emsam®)[2,7]

Antipsychotics

Use as directed	Use with caution	Use with increased caution and with more frequent monitoring
Asenapine (Saphris®)	Chlorpromazine (Thorazine®)[3,7]	Aripiprazole (Abilify®)[1,6,8]
Lurasidone (Latuda®)	Clozapine (Clozaril®)[3,7,8]	Haloperidol (Haldol®)[1,6]
Paliperidone (Invega®)	Fluphenazine (Prolixin®)[1]	Iloperidone (Fanapt®)[1,6,8]
Ziprasidone (Geodon®)	Olanzapine (Zyprexa®)[3,7]	Thioridazine (Mellaril®)[3,6,7,9]
	Perphenazine (Trilafon®)[3,7,8]	
	Quetiapine (Seroquel®)[1]	
	Risperidone (Risperdal®)[1,8]	
	Thiothixene (Navane®)[2,7]	

[1]: Serum level may be too high, lower doses may be required.

[2]: Serum level may be too low, higher doses may be required.

[3]: Difficult to predict dose adjustments due to conflicting variations in metabolism.

[4]: Genotype may impact drug mechanism of action and result in reduced efficacy.

[6]: Use of this drug may increase risk of side effects.

[7]: Serum level may be too low in smokers.

[8]: FDA label identifies a potential gene-drug interaction for this medication.

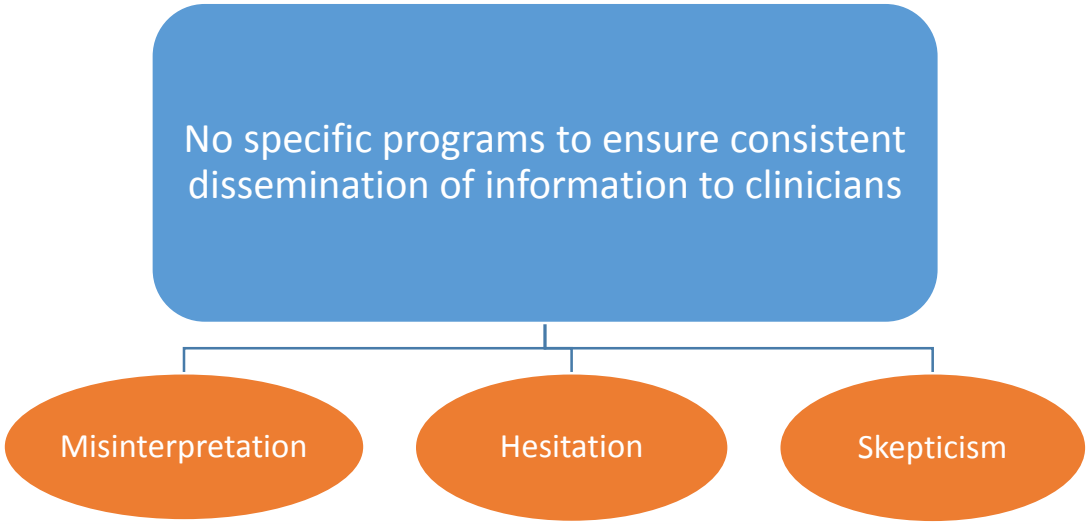
[9]: Per FDA label, this medication is contraindicated for this genotype.

(Assurex Health, 2019)

Not as Easy as It Looks!

- "Stoplight" analogy greatly over-simplifies the content of results

Does NOT indicate which medication will be the best or most effective choice for a particular person!



Advantages

- Adjustments to dosing and titration rates
  - Decreased risk for intolerable side effects
  - Reasonable expectations for duration of action / efficacy
- Patient Buy-In
  - Validation for past negative responses to medications
  - More likely to adhere to regimen
- Possible cost reduction long-term
  - Avoiding less ideal medication trials
  - Decreased risk of adverse reactions leading to hospitalization

GeneSight® Psychotropic
COMBINATORIAL PHARMACOGENOMIC TEST

genesight

Patient, Sample
DOB: 7/22/1984
Order Number: 9904
Report Date: 6/22/2016
Clinician: Sample Clinician
Reference: 1456CIP

Questions? Call 855.891.9415 or email medinfo@assurexhealth.com

PATIENT GENOTYPES AND PHENOTYPES

PHARMACODYNAMIC GENES (PD)

SLC6A4 — **Reduced Response**
S/S

This patient is homozygous for the short promoter polymorphism of the serotonin transporter gene. The short promoter allele is reported to decrease expression of the serotonin transporter compared to the homozygous long promoter allele. The patient may have a decreased likelihood of response to selective serotonin reuptake inhibitors due to the presence of the short form of the gene and may benefit from medications with an alternative mechanism of action.

HTR2A — **Increased Sensitivity**
G/G

This individual is homozygous variant for the G allele of the -1438G>A polymorphism for the Serotonin Receptor Type 2A. They carry two copies of the G allele. This genotype has been associated with an increased risk of adverse drug reactions with certain selective serotonin reuptake inhibitors.

HLA-B*1502 — **Higher Risk**
Present

This patient carries either the HLA-B*1502 allele or a closely related *15 allele. Presence of HLA-B*1502 or some of the closely related *15 alleles suggests higher risk of serious dermatologic reactions including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) when taking certain mood stabilizers.

HLA-A*3101 — **Higher Risk**
A/T

This patient is heterozygous for the A allele and the T allele of the rs1061235 A>T polymorphism indicating presence of the HLA-A*3101 allele or certain HLA-A*33 alleles. This genotype suggests a higher risk of serious hypersensitivity reactions, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), maculopapular eruptions, and Drug Reaction with Eosinophilia and Systemic Symptoms when taking certain mood stabilizers.

(Assurex Health, 2019)

GeneSight® Psychotropic
COMBINATORIAL PHARMACOGENOMIC TEST

genesight

Patient, Sample
DOB: 7/22/1984
Order Number: 9904
Report Date: 6/22/2016
Clinician: Sample Clinician
Reference: 1456CIP

Questions? Call 855.891.9415 or email medinfo@assurexhealth.com

PATIENT GENOTYPES AND PHENOTYPES

PHARMACOKINETIC GENES (PK)

CYP1A2 — **Extensive (Normal) Metabolizer**
*1/*1

This genotype is most consistent with the extensive (normal) metabolizer phenotype.

CYP2B6 — **Intermediate Metabolizer**
*1/*6

CYP2B6*1 allele enzyme activity: Normal
CYP2B6*6 allele enzyme activity: Reduced

This genotype is most consistent with the intermediate metabolizer phenotype. This patient may have reduced enzyme activity as compared to individuals with the normal phenotype.

CYP2C19 — **Ultrarapid Metabolizer**
*17/*17

CYP2C19*17 allele enzyme activity: Increased
CYP2C19*17 allele enzyme activity: Increased

This genotype is most consistent with the ultrarapid metabolizer phenotype. This patient may have increased enzyme activity as compared to individuals with the normal phenotype.

CYP2C9 — **Intermediate Metabolizer**
*1/*2

CYP2C9*1 allele enzyme activity: Normal
CYP2C9*2 allele enzyme activity: Reduced

This genotype is most consistent with the intermediate metabolizer phenotype. This patient may have reduced enzyme activity as compared to individuals with the normal phenotype.

CYP3A4 — **Extensive (Normal) Metabolizer**
*1/*1

CYP3A4*1 allele enzyme activity: Normal
CYP3A4*1 allele enzyme activity: Normal

This genotype is most consistent with the extensive (normal) metabolizer phenotype.

CYP2D6 — **Poor Metabolizer**
*4/*4 (Duplication)

CYP2D6*4 allele enzyme activity: None
CYP2D6*4 allele enzyme activity: None

This genotype is most consistent with the poor metabolizer phenotype. This patient may have reduced enzyme activity as compared to individuals with the normal phenotype.

A duplication of the gene CYP2D6 has been detected in this patient. While current genotyping techniques allow for the detection of this duplication, in the case of heterozygosity, such techniques do not allow for the identification of the allele that has been duplicated. This duplication, depending on the allele duplicated, can result in increased expression of CYP2D6.

UGT1A4 — **Extensive (Normal) Metabolizer**
*1/*1

UGT1A4*1 allele enzyme activity: Normal
UGT1A4*1 allele enzyme activity: Normal

This genotype is most consistent with the extensive (normal) metabolizer phenotype. The patient is expected to have normal enzyme activity.

UGT2B15 — **Intermediate Metabolizer**
*2/*2

UGT2B15*2 allele enzyme activity: Reduced
UGT2B15*2 allele enzyme activity: Reduced

This genotype is most consistent with the intermediate metabolizer phenotype. This patient may have reduced enzyme activity as compared to individuals with the normal phenotype.

(Assurex Health, 2019)

GeneSight® Psychotropic
COMBINATORIAL PHARMACOGENOMIC TEST

genesight

Patient, Sample
DOB: 7/22/1984
Order Number: 9904
Report Date: 6/22/2016
Clinician: Sample Clinician
Reference: 1456CIP

Questions? Call 855.891.9415 or email medinfo@assurexhealth.com

GENE-DRUG INTERACTIONS

USE AS DIRECTED

	CYP1A2	CYP2B6	CYP2C19	CYP2C9	CYP3A4	CYP2D6	UGT1A4	UGT2B15
ANTIDEPRESSANTS								
desvenlafaxine (Pristiq®)			●		○			
levomilnacipran (Fetzima®)			●		○	●		
vilazodone (Viibryd®)			●		○	●		
ANXIOLYTICS AND HYPNOTICS								
alprazolam (Xanax®)					○			
buspirone (BuSpar®)					○	●		
clonazepam (Klonopin®)					○			
eszopiclone (Lunesta®)				●	○			
temazepam (Restoril®)		●		●	○			●
zolpidem (Ambien®)	○		●	●	○	●		
ANTIPSYCHOTICS								
asenapine (Saphris®)	○				○	●	○	
lurasidone (Latuda®)					○			
paliperidone (Invega®)					○	●		
thiothixene (Navane®)	○							
ziprasidone (Geodon®)	○				○			
MOOD STABILIZERS								
lamotrigine (Lamictal®)							○	

MODERATE GENE-DRUG INTERACTION

	CYP1A2	CYP2B6	CYP2C19	CYP2C9	CYP3A4	CYP2D6	UGT1A4	UGT2B15
ANTIDEPRESSANTS								
citalopram (Celexa®)			●		○	●		
escitalopram (Lexapro®)			●		○	●		
fluoxetine (Prozac®)			●	●	○	●		
selegiline (Emsam®)	○	●	●		○			
sertraline (Zoloft®)		●	●	●	○	●		
trazodone (Desyrel®)	○				○	●		
venlafaxine (Effexor®)			●	●	○	●		
ANXIOLYTICS AND HYPNOTICS								
chlordiazepoxide (Librium®)	○				○			●
clorazepate (Tranxene®)	○				○			●
diazepam (Valium®)	○	●	●	●	○			●
lorazepam (Ativan®)								●
oxazepam (Serax®)								●

● - Variation was found in patient genotype that may impact medication response.

○ - This gene is associated with medication response, but patient genotype is normal.

(Assurex Health, 2019)

Today's Takeaways

- Psychiatric Conditions are multifactorial in origin, with current theories supporting suspicion for major role of epigenetics
- Pharmacogenomics is an area of interest for current and future research with the ultimate goal of "individualizing" treatment based on a person's genetic code
- While pharmacogenomic testing can be helpful for making clinical decisions, the technology does not yet exist that would allow a clinician to determine the "best" treatment for a specific client.

Lindner Center of HOPE | UC Health

References

- Binder, E.B. and Klengel, T. (2015). Epigenetics of stress-related psychiatric disorders and gene x environment interactions. *Neuron,* 86(6), 1343-1357.
- CPIC Guidelines. (2019). Retrieved from https://cpicpgx.org/
- Cross-Disorder Group of the Psychiatric Genomics Consortium. (2013). Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. *The Lancet*.
- Drozda, K., Müller, D. J., & Bishop, J. R. (2014). Pharmacogenomic testing for neuropsychiatric drugs: current status of drug labeling, guidelines for using genetic information, and test options. *Pharmacotherapy*, *34*(2), 166–184. doi:10.1002/phar.1398
- Genesight: What does the report show? (2019). Retrieved from Assurex website: https://genesight.com/product/psychotropic-report-details/
- Genetics Home Reference. (2019). Retrieved from U.S. National Library of Medicine Website: https://ghr.nlm.nih.gov/
- Gross, T., & Daniel, J. (2018). Overview of pharmacogenomic testing in clinical practice. *The mental health clinician*, *8*(5), 235–241. doi:10.9740/mhc.2018.09.235
- Looking at my genes: What can they tell me about my mental health? (2017). *NIMH*. Retrieved from: https://www.nimh.nih.gov/health/publications/looking-at-my-genes/lookingatmygenes_508_02082017_154289.pdf
- Nestler, E. J., Peña, C. J., Kundakovic, M., Mitchell, A., & Akbarian, S. (2015). Epigenetic Basis of Mental Illness. *The Neuroscientist : a review journal bringing neurobiology, neurology and psychiatry*, *22*(5), 447–463. doi:10.1177/1073858415608147 Simmons, D. (2008). Epigenetic influence and disease. Nature Education 1(1):6.
- Uher, R. (2009). The role of genetic variation in the causation of mental illness: an evolution-informed framework. *Molecular Psychiatry, 14,* 1072-1082.
- Zeier, et al. (2018). Clinical implementation of pharmacogenomics decision support tools for antidepressant drug prescribing. *American Journal of Psychiatry, 175*(9), 873-886.

Pictures

In order of appearance:

- https://www.healthyplace.com/other-info/mental-illness-overview/coming-to-terms-with-a-family-members-mental-illness
- http://www.mentalhealthamerica.net/b4stage4-get-informed
- https://geneticliteracyproject.org/2017/04/27/can-epigenetics-help-fuel-personalized-medicine-revolution-cancer-treatment/
- https://carrington.edu/blog/student-tips/education/historical-overview-of-pharmacology/
- http://personalizedhealthsolutions.com/patients/medications/