

NeuroGenomics: Prevention and Treatment of Cognitive and Mood Disorders

Joe Veltmann PhD FAAIM DCCN
Institute for Individualized Medicine
GENESIS Center for Integrative Medicine
2713 Nublado Court
Santa Fe, NM 87505

Learning Objectives

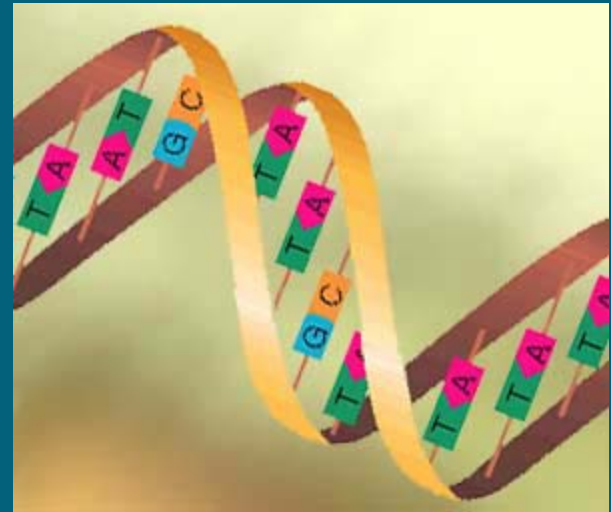
- Achieving Personalized Medicine
- Genomic Testing and Nutrigenomics
- NeuroGenomics: Cognitive/ Mood Disorders
 - Cognitive Impairment and Alzheimer's Disease
 - Depression
- Pharmacogenomics

Goal of Healthcare Professional

- Personalize, customize and individualize healing modalities, therapies and treatments based on the phenotypic and genotypic uniqueness of a particular patient.

Genotype and Chronic Disease

- Family Disease History
- Blood Type
- Human Genome Project
 - Nucleotides (A, C, T, G)
 - mRNA
 - Transcription
 - Translation

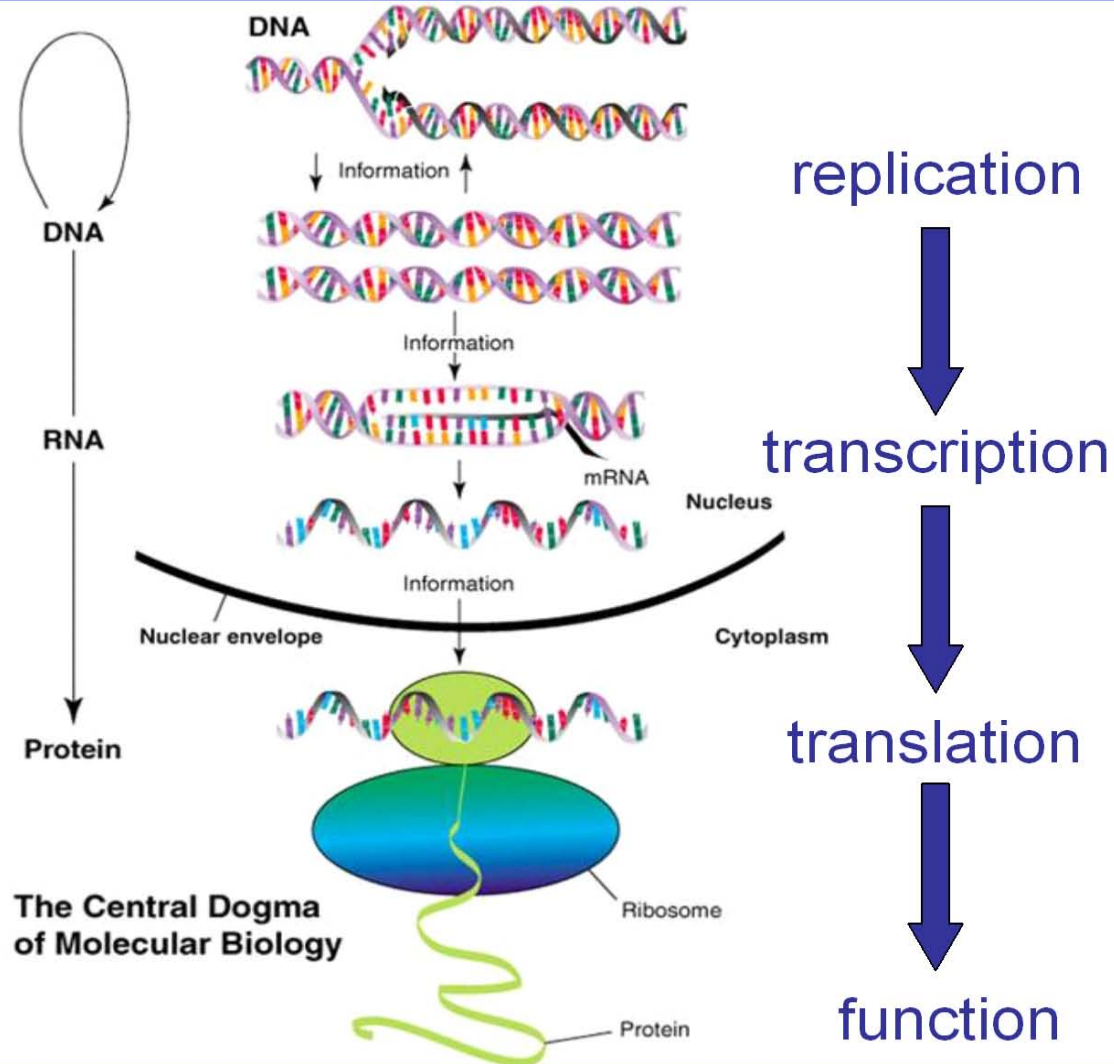


Autobiography of a Species

- The Human Genome is a book:
- Within this book, there are 23 chapters which we can call **CHROMOSOMES**;
- Each chapter (chromosome) contains several stories called **GENES**;
- Each story contains paragraphs or **EXONS**
- Words within each paragraph are called **CODONS**
- Words making up each paragraph are written in four letters (A, C, G, T)
- These four letters code for every protein and enzyme made by the body

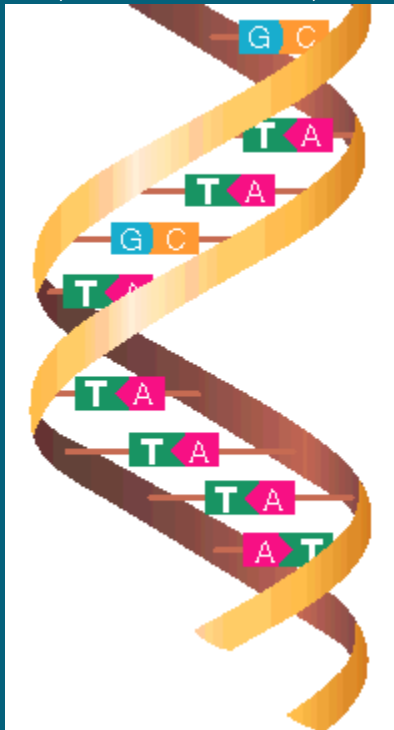
Matt Riley 2000. Autobiography of a Species in 23 Chapters

Information

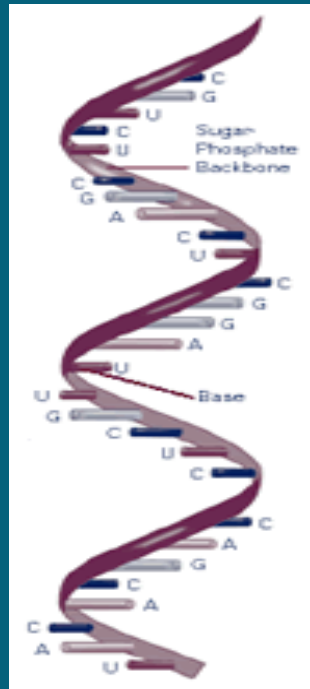


Genomics to Cellular Function

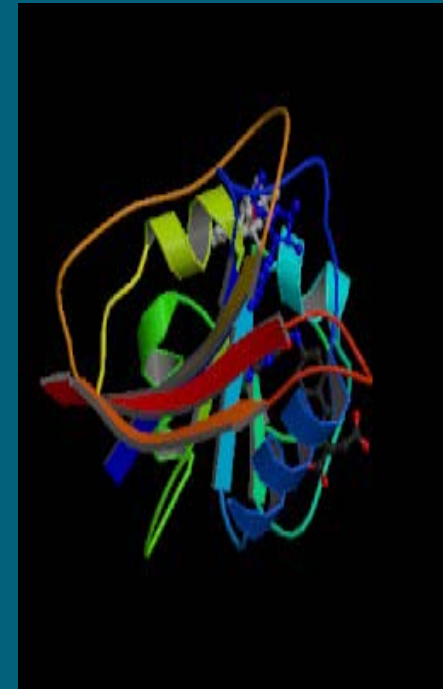
Genomics
(Nucleus)



Proteomics
(Cytoplasm)



Metabolomics
(Cell Function)



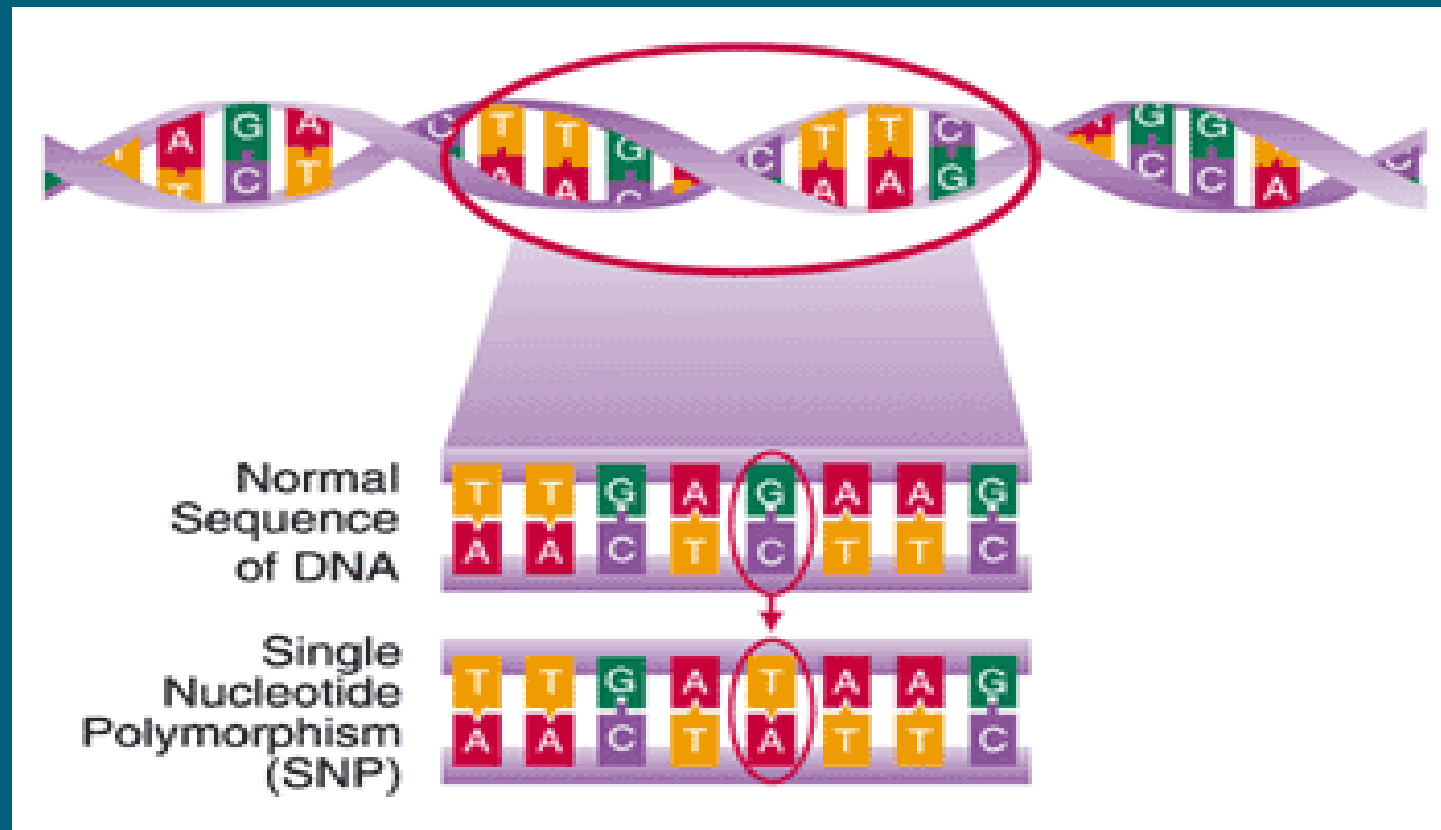
Mendelian Genetics

- Dominant versus Recessive
- Heterozygous versus Homozygous
- Allele versus Crossover
 - Leads to medical determinism
 - One bad gene leads to a disease
 - A genetic mutation confers a inborn error of metabolism

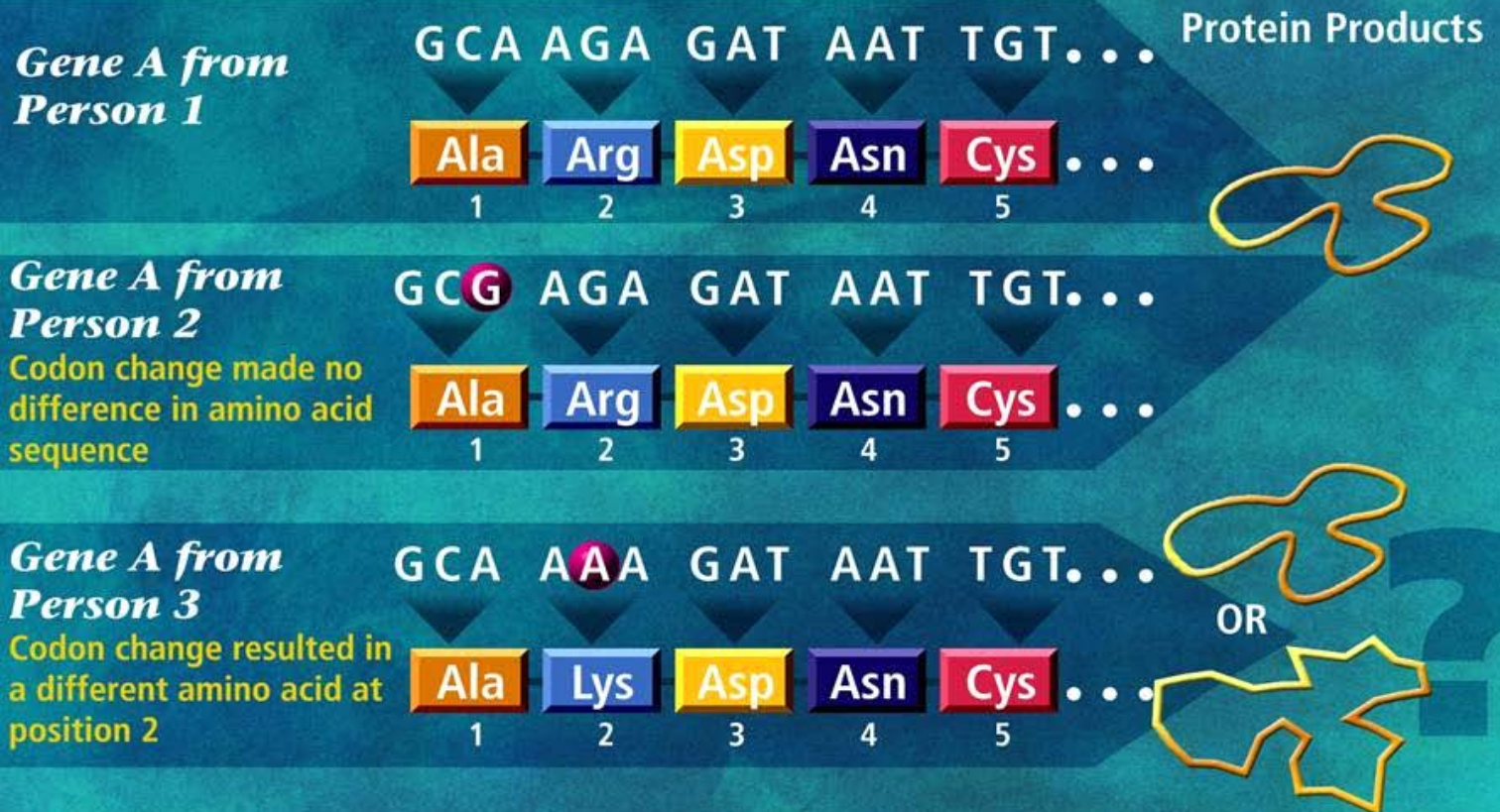
Key Points about Human Diseases

- All human diseases occur from the interaction between a genetic predisposition and modifiable environmental, nutritional and/or lifestyle factors.
- Slight variations in DNA called SNPs are associated with almost all chronic diseases.

Example of Single Nucleotide Polymorphism



DNA Sequence Variation in a Gene Can Change the Protein Produced by the Genetic Code



Genomic Tests

- CardioGenomic
 - Cholesterol regulation, methylation, blood pressure, coagulation, oxidation/reduction
- ImmunoGenomic
 - Chronic inflammation, Cytokines, Interleukins
- OsteoGenomic
 - Collagen, Calcitonin, Vit D receptor, Inflammation
- DetoxGenomic
 - Phase I (Cytochrome P₄₅₀ enzymes)
 - Phase II (Acetylation, Methylation, Glutathione Conjugation, Superoxide Dismutase)

NeuroGenomics

- The study of genetic variability between individuals and its relationship to an individual's response to a pain, neurological conditions including cognitive impairment, Alzheimer's disease, Parkinson's, depression, anxiety, and bipolar disorder.

NeuroGenomic Profile

Methylenetetrahydrofolate Reductase

Catechol-O-methyltransferase

Glutathione-S-transferase

Superoxide Dismutase

Interleukin 1-Beta

Tumor Necrosis Factor Alpha

Interleukin 1

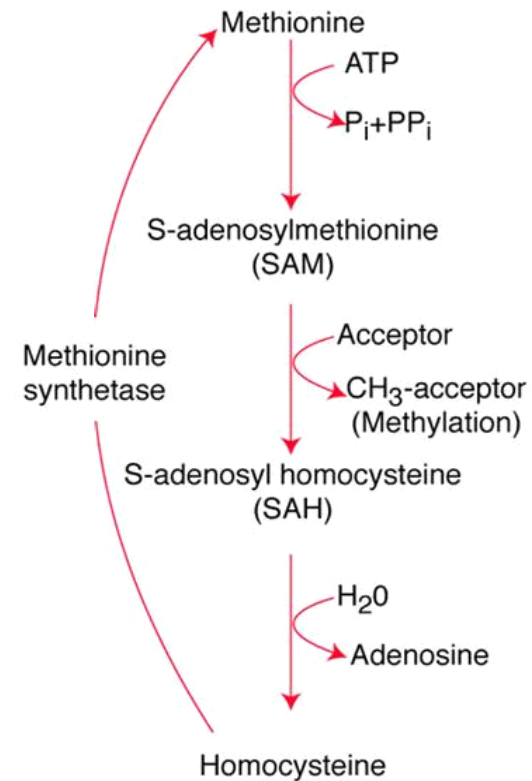
Interleukin 6

Methylenetetrahydrofolate Reductase

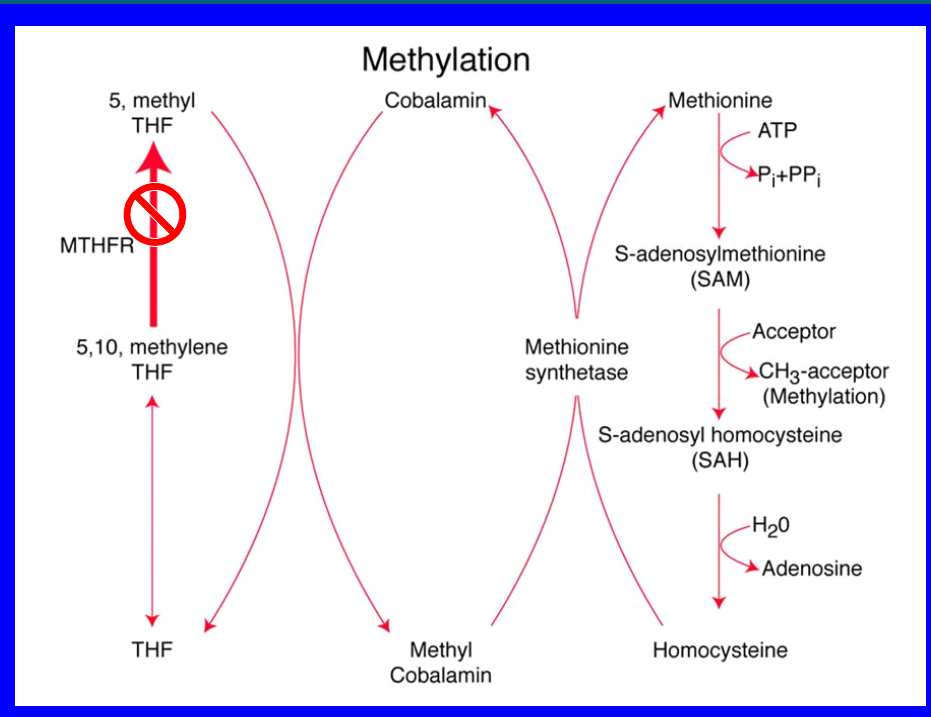
- Critical enzyme under genetic control in folate metabolism
 - SNPs lead to elevated homocysteine levels and defective methylation capacity
 - Atherosclerosis
 - Stroke
 - Cervical Dysplasia
 - Cognitive Impairment
 - Senility
- Coronary Heart Disease
Deep Vein Thrombosis
Cervical Cancer
ALZ Disease
Neural Tube Defect

Methylation (Step 1)

Methylation



Methylation (Step 3)



Prevalence of MTHFR 677C-T Single Nucleotide Polymorphism

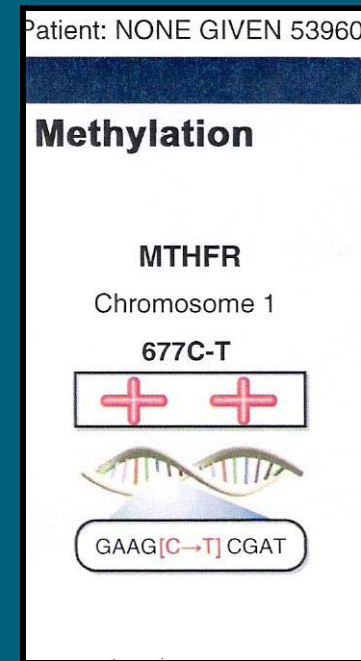
- Approximately 50 % of all Caucasians and Asians are heterozygous for the 677C-T
- Approximately 12 % are homozygous with severely impaired methylation capacity
- Approximately 28 % of patients with elevated homocysteine levels and 677C-T SNP did not respond to folic acid, B-6 and B-12 supplementation
 - Am. J. Human Genetics 56: 142-150 (1995)

Riboflavin (B-2) and Homocysteine

- High plasma homocysteine correlates with low riboflavin
- Riboflavin is precursor molecule
 - Flavin mononucleotide (FMN) acts as a coenzyme for the conversion of B-6 to its active form pyridoxal-5-phosphate
 - Flavin dinucleotide (FADH₂) is a coenzyme for Methylenetetrahydrofolate reductase
- The 677C-T SNP alters the enzyme's shape at the FADH₂ binding site

Treatment for MTHFR Defect

- Folic Acid
- 5-methyl and 5-formyl THF
- Betaine/ Trimethylglycine
- Methylcobalamin (B-12)
- Pyridoxal-5-phosphate
- Riboflavin (B-2)



Nutrigenomics

- Nutrigenomics is the understanding that micronutrients and macronutrients can be potent dietary signals that influence the metabolic programming of cells and have an important role in the control of homeostasis
 - Muller and Kersten, Nutrigenomics goals and strategies, Nature Review 4: 315-322 (2003)

Depression

- Depression is a common mental disorder characterized:
 - depressed mood
 - loss of interest or pleasure,
 - feelings of guilt or low self-worth,
 - disturbed sleep or appetite,
 - low energy,
 - poor concentration.

Depressing Statistics

- Depression is common, affecting about 121 million people worldwide.
- Depression is among the leading causes of disability worldwide.
- Depression can be reliably diagnosed and treated in primary care.
- Fewer than 25 % of those affected have access to effective treatments.

Medications for Depression

Antidepressants

Wellbutrin

Cymbalta

Remeron

Effexor

SSRI

Celexa

Lexapro

Prozac

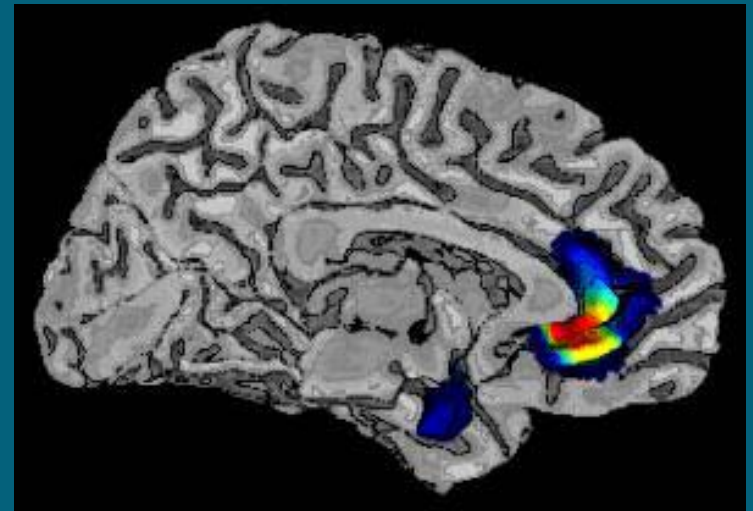
Luvox

Paxil

Zoloft

Causes of Depression

- Genes
- Life Events
 - Divorce
 - Death of a Loved One
 - Financial Problems
- Chronic Diseases
- Medications



Genes and Depression

Mind Matters

Researchers are now decoding depression at the molecular level. Some new tools:

G1463A

A variation at this point in your DNA sequence causes low levels of serotonin, making you less responsive to drugs like Prozac.

The Stress Gene

People with a particular mutation in the serotonin transporter gene are more likely to become depressed in response to stress.

Beta-Arrestin-1

Depressed patients have unusually low levels of this protein. Measuring it may enable doctors to monitor the effects of treatment.

Tryptophan Hydroxylase-2 Gene

- G1463A encodes for tryptophan hydroxylase, rate limiting enzyme of neuronal serotonin synthesis
- SNPs associated with G1463A linked to:
 - Unipolar major depression
 - Resistance to SSRIs (Prozac, Zoloft)
 - Alcohol abuse
 - Anxiety disorders

Serotonin Transporter Gene

- SLC6A4 : gene encodes for the serotonin transporter protein, allowing neurons, platelets and other cells to accumulate serotonin, thereby affecting emotions and motivation.
- Polymorphism linked to alcoholism, depression, OCD, and bipolar disorder.

COMT and Depression

- Catechol-O-methyltransferase (COMT)
 - Enzyme primarily responsible for breaking down the neurotransmitters dopamine, epinephrine and norepinephrine
 - Fight or Flight Response
 - Polymorphism reduces COMT activity, resulting in decreased degradation of neurotransmitters.

COMT Polymorphism & Treatment Options

<i>Methylation</i>				
		SNP		
Result	Gene	Location	Internet Information	Affects
++	COMT	V158M	www.genovations.com/gdv158m	Liver/Gut

- SamE:
 - Cofactor for Catechol-O-methyltransferase
- GABA:
 - Inhibitory neurotransmitter

Pharmacogenomics

- The study of genetic variability and its relationship to an individual's response to pharmaceutical drugs, non-prescription drugs and OTC medications.

Pharmacogenomics and Drug Dosage

Getting Exactly What You Need

A gene variant can influence tolerance for a drug commonly used to treat acute lymphoblastic leukemia in children:

90 percent of kids have two normal copies of the gene and can tolerate a full dose of mercaptopurine

10 percent have only one normal copy of the gene and should receive only 50 percent of the standard dose

.03 percent have two defective copies and should receive just 5 to 10 percent of a normal dose

Summary

- NeuroGenomics will differentiate subpopulations of people who will benefit from “boutique” medications/ botanicals to treat neurological disorders.
- NeuroGenomics will identify those people genetically susceptible to anxiety, OCD, bipolar disorders, attention deficit and addictions and provide practitioners with successful prevention or treatment strategies.