Personalized Mental Health

DNA-Guided Psychotropic Management

Gualberto Ruaño, M.D., Ph.D.
President and Chief Executive Officer, Genomas
Director of Genetics Research, Hartford Hospital
Institute of Living, Hartford Hospital
Genomas Partners for DNA-Guided Medicine

Pharmaceutical Genomics

DNA-Guided Medicine

Discovery Development Diagnostic Treatment

Technology Databases Biologicals Drugs Assays Devices Healthcare Delivery

HARTFORD HOSPITAL
GENOMAS

The Hospital of Central Connecticut
Clinical Laboratory Partners LLC
THE INSTITUTE OF LIVING
Each person’s DNA is unique. The DNA is inherited from ancestors who adapted best to the challenges posed by their environments. The Legacy of the Genome is the repertoire of these adaptive traits. The optimal use of these traits is the basis of personalized health.
A genetically encoded characteristic may be adaptive in one environment but maladaptive in another. A common pattern is that a genetically encoded characteristic adaptive in an ancestral environment, may become maladaptive in a modern one.
The Legacy of the Genome

Detoxification

**Cytochrome P450 Enzymes**
- 57 genes known
- Each with multiple alleles

**ANCESTRAL**
Process plant and environmental toxins

**MODERN**
Metabolism of 90% current drugs
LPH Laboratory of Personalized Health
Clinical Lab, High Complexity DNA Typing

• Licensed by CT Dept of Public Health (CL-0644)

• CLIA registered (ID # 07D1036625 Clinical Laboratory Improvement Amendments)
Centers Medicare and Medicaid (CMS)

• One of the pioneering DNA typing centers

In operation since October 2005
Cytochrome P450 DNA Typing
HILomet CYP 2D6, 2C9, 2C19

50 doctors served
300 patients referred
900 DNA Typing tests
Somatic Complications of Psychotropic Medications in a Patient with Multiple CYP2 Drug Metabolism Deficiencies

C. Lee Blair, M.D.
Godfrey Pearlson, M.D.
John W. Goethe, M.D.
Harold I. Schwartz, M.D.
A 54-year Caucasian woman with a history of:
- persistent malaise
- headache
- muscle tension
- jaw clenching
- hypervigilance
- severe anxiety

The patient’s difficulties had developed six years ago:
- improper installation, heating system leaked volatile fuels
- escalating fear, frustration, increasingly symptomatic

She had become:
- increasingly preoccupied with her somatic condition
- had stopped working as a well paid professional
- had withdrawn from many of her usual activities
- had spent a large amount of time and effort on medical care
Case History: 18 Psychotropic Drugs
Adverse Drug Reactions and Side Effects

**ANTI-DEPRESSANTS**
- Sertraline (Zoloft®)
- Paroxetine (Paxil®)
- Escitalopram (Lexapro®)
- Venlafaxine (Effexor® XR)
- Citalopram (Celexa®)
- Mirtazapine (Remeron®)
- Nortriptyline (Pamelor®)

**ANTI-PSYCHOTICS**
- Olanzapine (Zyprexa®)
- Quetiapine (Seroquel®)
- Risperidone (Risperdal®)

**ANTI-CONVULSANTS**
- Gabapentin (Neurontin®)
- Oxcarbazepine (Trileptal®)
- Topiramate (Topamax®)

**ANTI-CONVULSANTS**
metallic taste
dry mouth
nausea
vomiting
diarrhea
flatulence
sweating
“crawling” feel
insomnia
akathisia
twitching
parasthesias
“fogginess”

**WEIGHT GAIN**

**ANXIO-LYTICS**
- Buspirone (Buspar®)
- Clonazepam (Klonopin®)
- Clonazepam (Valium®)
- Lorazepam (Ativan®)
- Flurazepam (Dalmane®)
DNA-Guided Drug Therapy

HIL Omot CYP: Traffic Light for Drugs

Lipophilic Drug → Oxidative Reactions: Hydroxylation, Demethylation → Hydrophilic Drug Metabolite → Excretion

TRAFFIC LIGHT FOR DRUGS

CYP

OXIDATION

Pharmacokinetics

Lipophilic Drug

Hydrophilic Drug Metabolite

Kidney

Excretion

CYP CYP CYP CYP

CYP2C9 CYP2C19 CYP2D6

CYTOCHROME P450

Oxidative Reactions

Hydroxylation
Demethylation

Drug Contraindicated
Low Metabolic capacity

Drug Interactions

Med Metabolic Capacity

Drug Indicated
High Metabolic Capacity

CAUTION

GO

STOP

Drug Contraindicated
Low Metabolic capacity

Drug Interactions

Med Metabolic Capacity

Drug Indicated
High Metabolic Capacity

CAUTION

GO

STOP
**Representative Alleles (from a total of 14 genotyped at LPH)**

<table>
<thead>
<tr>
<th>Alleles</th>
<th>Amino Acid Change</th>
<th>Nucleotide Change</th>
<th>Metabolizer Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1</td>
<td>Reference</td>
<td>Reference</td>
<td>WILD-TYPE</td>
</tr>
<tr>
<td>*3</td>
<td>Frameshift</td>
<td>2549-A Del</td>
<td>NULL</td>
</tr>
<tr>
<td>*4</td>
<td>Splicing defect</td>
<td>G-1846-A SNP</td>
<td>NULL</td>
</tr>
<tr>
<td>*5</td>
<td>No protein</td>
<td>Deletion of gene</td>
<td>NULL</td>
</tr>
<tr>
<td>*9</td>
<td>Lys 281del</td>
<td>2613-15 AGA Del</td>
<td>DEFICIENT</td>
</tr>
<tr>
<td>*10</td>
<td>Pro-34-Ser</td>
<td>C-100-T SNP</td>
<td>DEFICIENT</td>
</tr>
<tr>
<td>*17</td>
<td>Thr-107-Ile</td>
<td>C-1023-T SNP</td>
<td>DEFICIENT</td>
</tr>
<tr>
<td>Duplication</td>
<td>Reference</td>
<td>Tandem genes</td>
<td>ULTRA</td>
</tr>
</tbody>
</table>
# Case History: DNA Typing Results

**Multi-gene drug metabolism deficiencies**

<table>
<thead>
<tr>
<th></th>
<th>2D6</th>
<th>2C9</th>
<th>2C19</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient</strong></td>
<td><img src="2D6.png" alt="Image" /></td>
<td><img src="2C9.png" alt="Image" /></td>
<td><img src="2C19.png" alt="Image" /></td>
</tr>
<tr>
<td><strong>Mother</strong></td>
<td><img src="2D6.png" alt="Image" /></td>
<td><img src="2C9.png" alt="Image" /></td>
<td><img src="2C19.png" alt="Image" /></td>
</tr>
<tr>
<td><strong>Father</strong></td>
<td><img src="2D6.png" alt="Image" /></td>
<td><img src="2C9.png" alt="Image" /></td>
<td><img src="2C19.png" alt="Image" /></td>
</tr>
</tbody>
</table>

Case History: DNA Typing Results
Pedigree Analysis: Inherited DNA Types

**2D6**

- **Mother**
  - *1
  - *6
  - *6
- **Father**
  - *4
  - *6
  - *4
  - *6
- **LPH1**
  - *6
  - *6
- **Brother**
  - *6
  - *6
  - *4
  - *6

Key:
- Red: NULL
- Green: Functional
- Yellow: Deficient
Case History: 18 Psychotropic Drugs
DNA-Guided Drug Selection

ANTI-DEPRESSANTS
Sertraline (Zoloft®)
Paroxetine (Paxil®)
Escitalopram (Lexapro®)
Venlafaxine (Effexor® XR)
Citalopram (Celexa®)
Mirtazapine (Remeron®)
Nortriptyline (Pamelor®)

ANTI-CONVULSANTS
Gabapentin (Neurontin®)
Oxcarbazepine (Trileptal®)
Topiramate (Topamax®)

ANTI-PSYCHOTICS
Olanzapine (Zyprexa®)
Quetiapine (Seroquel®)
Risperidone (Risperdal®)

ANXIO-LYTICS
Buspirone (Buspar®)
Clonazepam (Klonopin®)
Diazepam (Valium®)
Lorazepam (Ativan®)
Flurazepam (Dalmane®)
Case History: 18 Psychotropic Drugs

DNA-Guided Drug Selection

ANTI-DEPRESSANTS
- Sertraline *(Zoloft®)*
- Paroxetine *(Paxil®)*
- Escitalopram *(Lexapro®)*
- Venlafaxine *(Effexor® XR)*
- Citalopram *(Celexa®)*
- Mirtazapine *(Remeron®)*
- Nortriptyline *(Pamelor®)*

CYP2D6

ANTI-CONVULSANTS
- Gabapentin *(Neurontin®)*
- Oxcarbazepine *(Trileptal®)*
- Topiramate *(Topamax®)*

High ADR Risk

ANTI-PSYCHOTICS
- Olanzapine *(Zyprexa®)*
- Quetiapine *(Seroquel®)*
- Risperidone *(Risperdal®)*

ANXIO-LYTICS
- Buspirone *(Buspar®)*
- Clonazepam *(Klonopin®)*
- Diazepam *(Valium®)*
- Lorazepam *(Ativan®)*
- Flurazepam *(Dalmame®)*

LPH1 is here
Case History: 18 Psychotropic Drugs
DNA-Guided Drug Selection

**ANTI-DEPRESSANTS**
- Sertraline (Zoloft®)
- Paroxetine (Paxil®)
- Escitalopram (Lexapro®)
- Venlafaxine (Effexor® XR)
- Citalopram (Celexa®)
- Escitalopram (Lexapro®)
- Mirtazapine (Remeron®)
- Nortriptyline (Pamelor®)

**CYP2C9 CYP2C19**

**ANXIOLYTICS**
- Buspirone (Buspar®)
- Clonazepam (Klonopin®)
- Diazepam (Valium®)
- Lorazepam (Ativan®)
- Flurazepam (Dalmame®)

**ANTI-CONVULSANTS**
- Gabapentin (Neurontin®)
- Oxcarbazepine (Trileptal®)
- Topiramate (Topamax®)

**Medium ADR Risk**

**ANTI-PSYCHOTICS**
- Olanzapine (Zyprexa®)
- Quetiapine (Seroquel®)
- Risperidone (Risperdal®)

CYP2C9

LPH1 is here

Medium ADR Risk

CYP2C19
HILomet CYP: CYP2D6, Survey at HH DNA-Guided Drug Treatment

Personalized Medicine 3: 131-137, 2006

High carrier prevalence of deficient and null alleles of CYP2 genes in a major USA hospital: implications for personalized drug safety

GualbertoRuaño†, GregMakowski II, AndreasWindennah, MohanKocherla †, John W Goethe †, Bruce Bower †, AlanHBWu †, PaulDThompson †.
Clinical DNA Typing at HH and IOL

Drug Metabolizer Status CYP2D6

Metabolizer Status from DNA Typing

<table>
<thead>
<tr>
<th>Metabolizer Status</th>
<th>Percentage of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional</td>
<td></td>
</tr>
<tr>
<td>Deficient</td>
<td></td>
</tr>
<tr>
<td>Null</td>
<td></td>
</tr>
<tr>
<td>Ultra</td>
<td></td>
</tr>
</tbody>
</table>

IOL patients

Cardiology patients
CYP2D6 DNA Typing Survey
Allele Carrier Frequencies

Antidepressants
- Amitriptyline (Elavil®)
- Mirtazapine (Remeron®)
- Fluvoxamine (Luvox®)
- Duloxetine (Cymbalta®)
- Venlaxafine (Effexor® XR)
- Paroxetine (Paxil®)

Antipsychotics
- Haloperidol (Haldol®)
- Aripiprazole (Abilify®)
- Risperidone (Risperdal®)

ADHD
- Atomoxetine (Strattera®)
- Dextroamphetamine (Adderall®)

Pain
- Codeine

Cancer
- Tamoxifen (Nolvadex®)

Beta Blockers
- Propranolol (Inderal®)
- Metoprolol (Lopressor®)
CYP2C9 DNA Typing Survey
Allele Carrier Frequencies

Antidepressants
Fluoxetine (Prozac®)
Sertraline (Zoloft®)

NSAIDs
Ibuprofen (Advil®)
Naproxen (Naprosyn®)

COX-2 Inhibitors
Celecoxib (Celebrex®)

Thromboembolism
Warfarin (Coumadin®)

Glitazones + Diabetes
Rosiglitazone (Avandia®)
Pioglitazone (Actos®)
Sulfonylureas
Glipizide (Glucotrol®)
Glimepiride (Amaryl®)

Angiotensin II Blockers
Losartan (Cozaar®)
Irbesartan (Avapro®)
CYP2C19 DNA Typing Survey
Allele Carrier Frequencies, 121 patients at HH

- **Antidepressants**
  - Escitalopram (Lexapro®)
  - Citalopram (Celexa®)

- **Anti-epileptics**
  - Phenytoin (Dilantin®)
  - Diazepam (Valium®)

- **Proton Pump Inhibitors**
  - Omeprazole (Prilosec®)
  - Lansoprazol (Prevacid®)
  - Esomeprazole (Nexium®)

27%
Psychototropic Adverse Drug Reactions

**DiMS: Diabetes + Metabolic Syndromes**

**Clinical Manifestations**
- Weight gain
- Increased waist size
- High Triglycerides
- Elevated blood glucose
- Diabetes

**Current Diagnostics**
- Body type changes
- Lipid+Glucose Profiles
- Confounders: mental status, appetite, poly-pharmacy, compliance

---

**ORIGINAL ARTICLE**

Physiogenomic comparison of weight profiles of olanzapine- and risperidone-treated patients

G Ruaño¹, JW Goethe², C Caley², S Woolley², TR Holford³, M Kocherla¹, A Windemuth¹ and J de Leon⁴

¹Genomas, Inc., Hartford, CT, USA; ²Institute of Living, Hartford Hospital, Hartford, CT, USA; ³Department of Epidemiology
The Legacy of the Genome

Energy and Nutrition

Multiple Pathways

- Hundreds of genes
- <1% variability

ANCESTRAL
Thrifty genes, extract and conserve energy from food sources

MODERN
Food- and Drug-induced obesity and diabetes
WARNINGS:
Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events...
PhyzioType Systems: Psychotropics

DIMS: Diabetes and Metabolic Syndromes

DNA
1 nm

SNPs (n = 384)

Body
1,000,000,000 nm
Phyziotype Systems
Next Generation DNA-Guided Medicine

Genotype gene A
Genotype gene B
Genotype gene C
Genotype gene D
Genotype gene E
Genotype gene F

α β γ δ ε ζ

ADR Risk DNA Markers
Protective DNA Markers

SNP Ensemble, Assays, Algorithms, Portal
Patient LPH1 on Zyprexa®

- Clinical Symptoms: 8 kg weight gain and abnormal lipids
- Referred to LPH and IOL for DNA typing of drug metabolism status
- PhyzioType Diagnosis: Psychotropic DiMS

*Risperdal®* is predicted to have the least weight gain for this patient and *Zyprexa®* the most.
PhyzioType Systems for Drug Safety

Enabling DNA-guided Medicine in Practice

**ADR diagnosis**
- Patient has taken a prescribed drug and manifested ADRs
- PhyzioType System used to diagnose likely cause of ADR based on individualized ADR risk
- Allows doctor to clarify etiology of symptoms versus confounding factors (mental status, physical activity, polypharmacy)

**ADR prevention**
- PhyzioType System allows doctor to prescribe drugs according to patient’s individualized ADR risk
- **IF ADR RISK IS LOW:**
  - Prescribe drug w. safeguard
- **IF ADR RISK IS HIGH:**
  - Reduce drug dose
  - Switch to other drugs
  - Proactively monitor/treat ADRs
Infrastructure for DNA-Guided Medicine

FDA, Medicare, Insurance, Distribution, Costs

Distribution
Reimbursement

DNA Typing
Report to Doctor

Products on the Market for DNA-Guided Medicine

CYP
OXIDATION

HILOmety

Vitamin K Reductase
Oxidized Vitamin K
ω-Carboxylation

Reduced Vitamin K
γ-glutamyl carboxylase

Hypofunctional
F. II, VII, IX, X
Protein C, S, Z

Functional
F. II, VII, IX, X
Proteins C, S, Z
What Are the Implications for Clinical Neuroscience?

2007

- Drug metabolism DNA Typing is first: assays available now
- FDA spearheading new guidelines for prescription of safest drugs

2008

- Diagnostics for drug-induced metabolic syndromes to prevent ADRs
- DNA-guided drug selection to minimize risk of ADRs

New paradigm for medicine

DNA-guided diagnosis, prevention and treatment

Personalized health will be expected by patients and their families
Thank you!

g.ruano@genomas.net

860-545-3773

www.genomas.net

Health Personalized

www.genomas.net