N=1 Human Study in Clinical Neurosciences: Genomics Guided Medicine and Deep Brain Stimulation

Gholson Lyon, M.D. Ph.D.
Conflicts of Interest

• I do not receive salary compensation, donations or “gifts” from anyone other than my current employer, CSHL.

• Any revenue that I earn from providing medical care in Utah is donated to UFBR for genetics research.
Figure 4. NAT activity of recombinant hNaa10p WT or p.Ser37Pro towards synthetic N-terminal peptides. A) and B) Purified MBP-hNaa10p WT or p.Ser37Pro were mixed with the indicated oligopeptide substrates (200 µM for SESSS and 250 µM for DDDIA) and saturated levels of acetyl-CoA (400 µM). Aliquots were collected at indicated time points and the acetylation reactions were quantified using reverse phase HPLC peptide separation. Error bars indicate the standard deviation based on three independent experiments. The five first amino acids in the peptides are indicated, for further details see materials and methods. Time dependent acetylation reactions were performed to determine initial velocity conditions when comparing the WT and Ser37Pro NAT-activities towards different oligopeptides.

C) Purified MBP-hNaa10p WT or p.Ser37Pro were mixed with the indicated oligopeptide substrates (200 µM for SESSS and AVFAD, and 250 µM for DDDIA and EEEIA) and saturated levels of acetyl-CoA (400 µM) and incubated for 15 minutes (DDDIA and EEEIA) or 20 minutes (SESSS and AVFAD), at 37°C in acetylation buffer. The acetylation activity was determined as above. Error bars indicate the standard deviation based on three independent experiments. Black bars indicate the acetylation capacity of the MBP-hNaa10p wild type (WT), while white bars indicate the acetylation capacity of the MBP-hNaa10p mutant p.Ser37Pro. The five first amino acids in the peptides are indicated.
Take Home Message

Genotype ≠ Phenotype

Environment matters!
Ancestry matters!
Genomic background matters!
Longitudinal course matters!

We can only begin to really understand this if we utilize the power of intense networking via internet-enabled archiving and distribution of consumer owned and managed data.
Categorical Thinking Misses Complexity
A conceptual model of canalization. The $y$ plane represents a phenotypic spectrum, the $x$ plane represents the canalized progression of development through time, and the $z$ plane represents environmental fluctuations.
Expression Issues

• We do not really know the expression of pretty much ALL mutations in humans, as we have not systematically sequenced or karyotyped any genetic alteration in Thousands to Millions of randomly selected people, nor categorized into ethnic classes, i.e. clans.
Complexity

- There are ~25-100 TRILLION cells in each human body, with ~6 billion nucleotides per cell.
- There is extensive modification of DNA, RNA and proteins both spatially and temporally.
- There are higher level mechanisms of somatic mosaicism, heterosis, and likely ancestral inheritance.
A family in Utah, with a 40 year old Caucasian man with very severe obsessive compulsive disorder, severe depression and intermittent psychoses, with symptoms that started around age 5.

Multiple medication trials failed over many years. Considered treatment refractory.
Humanitarian Device Exemption (HDE) for OCD
Nucleus accumbens
Fig. 1. Coronal section of the brain near the nucleus accumbens with the track of the electrodes on the left and right side.
2.5 year follow-up

Figure 2. Yale Brown Obsessive Compulsive Scale (YBOCS) scores were measured for M.A over a three year and seven months period of time. A time series plot (A) shows a steady decline in YBOCS scores over the period of time spanning his DBS surgery and treatment. Incremental adjustments to neurostimulator voltage are plotted over a period of time following DBS surgery (A). Mean YBOCS scores are plotted for sets of measurements taken before and after his Deep Brain Stimulation (DBS) surgery (B). A one-tailed unpaired t test with Welch's correction results in a p value of 0.0056, demonstrating a significant difference between YBOCS scores measured before and after the time of surgery.

Pulse width = 210, Frequency 130 Hz
Global Assessment of Functioning (GAF) 0 to 100 scale

From 5 to 15 in 2008-2009

To

45 to 55 in 2013

*Private Photograph – do not copy or further distribute*
Depletable nature of battery

- Battery replaced with a rechargeable battery in January 2012.

- After the battery was turned off the first time, M.A. was not immediately under any pain. However, after 3 days, M.A. almost attempted suicide because of the increase in depression, anxiety, and physical pain. Even worse, M.A. had little to no insight into his disease, and had an increase in memory and cognitive deficit and had thus forgotten the benefits that had been his just a few days prior.

- M.A. decided to kill himself since he was unable to connect the renewal of traumatic symptoms with the battery’s termination. Before getting in his car to end his life in another planned car wreck, M.A. saw his battery modulator on the front seat of his car. The modulator could turn his pacemaker on and off. When M.A. saw it, he had a brief moment of clarity about feeling better in the past.

- Unsure if he was delusional or not, M.A. put the device up to his shoulder and turned the battery on. The change was instantaneous.
Practical, ethical and regulatory considerations for the evolving medical and research genomics landscape

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c New York Genome Center, New York City, NY, United States

Table 1

Processes involved in a CLIA-certified genetic test.

<table>
<thead>
<tr>
<th>Preanalytic system</th>
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<tbody>
<tr>
<td>1) Test request and specimen collection criteria</td>
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<tr>
<td>2) Specimen submission, handling and referral procedures</td>
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<tr>
<td>3) Preanalytic systems assessment</td>
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<table>
<thead>
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<th>Analytic system</th>
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<tbody>
<tr>
<td>1) A detailed step-by-step procedure manual</td>
</tr>
<tr>
<td>2) Test systems, equipment, instruments, reagents, materials and supplies</td>
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<tr>
<td>3) Establishment and verification of performance specifications</td>
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<td>4) Maintenance and function checks</td>
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<td>5) Calibration and calibration verification procedures</td>
</tr>
<tr>
<td>6) Control procedures, test records, and corrective actions</td>
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<tr>
<td>7) Analytic systems assessment</td>
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<table>
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<td>1) Test report, including (among other things):</td>
</tr>
<tr>
<td>a) interpretation</td>
</tr>
<tr>
<td>b) reference ranges and normal values</td>
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<tr>
<td>2) Post-analytic systems assessment</td>
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1. Sample Collection and handling
2. Sequencing/Analytics
3. Interpretation
“This laboratory test was developed, and its performance characteristics were determined by the Illumina Clinical Services Laboratory (CLIA-certified, CAP-accredited). Consistent with laboratory-developed tests, it has not been cleared or approved by the U.S. Food and Drug Administration. If you have any questions or concerns about what you might learn through your genome sequence information, you should contact your doctor or a genetic counselor. Please note that Illumina does not accept orders for Individual Genome Sequencing services from Florida and New York.”
Understand Your Genome Symposium

During this two-day educational event, industry experts will discuss the clinical implementation of whole-genome next-generation sequencing (NGS) technology.

Individual Genome Sequence Results

Clinical Report

Ordering Physician:
Gholson Lyon, MD
Steinmann Institute
10 West Broadway, Suite #820
Salt Lake City, UT 84101

www.everygenome.com
CLIA#: 05D1092911
Sample Collection and Handling

The Sample Collection kit includes barcoded collection tubes, a Test Requisition form, an Informed Patient Consent form, and a pre-paid shipping envelope. All paperwork must be completed and returned for sample processing. Requests for Sample Collection kits must be submitted by a physician.

http://www.illumina.com/clinical/illumina_clinical_laboratory/igs_for_doctors/how_to_order.ilmn
Sequencing and Analytics

From the Illumina Understand Your Genome Symposium October 2012
Evaluation of 344 genes by Illumina

A total of 1247 variants were detected in the subset of genes for this patient. Each variant was evaluated for clinical significance and placed into one of five possible categories for classification, based on the American College of Medical Genetics and Genomics interpretation guidelines as outlined below and described at the end of this report.

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<th>Interpretation</th>
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**Refsum Disease**
Refsum disease is an inherited condition that causes vision loss, anosmia, and a variety of other signs and symptoms. The vision loss is caused by retinitis pigmentosa. The first sign of retinitis pigmentosa is usually a loss of night vision, which often becomes apparent in childhood. Over a period of years, the disease disrupts peripheral vision and may eventually lead to blindness. Vision loss and anosmia are seen in almost everyone with Refsum disease, but other signs and symptoms vary. About one-third of affected individuals are born with bone abnormalities of the hands and feet. Features that appear later in life can include progressive myopathy; ataxia; hearing loss; and ichthyosis. Additionally, some people with Refsum disease develop arrhythmia and cardiomyopathies that can be life-threatening.
Refsum Disease?

- Referred to optometry for further evaluation of this.
- Found to have bilateral cataracts, large pupils, and loss of night vision.
- His mother and grandmother both have large pupils and loss of night vision. No cataracts known.
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<th>Gene</th>
<th>Position</th>
<th>Change</th>
<th>Zygosity</th>
<th>Effect</th>
<th>Quality</th>
<th>Coverage</th>
<th>Frequency</th>
<th>GeneArt</th>
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<td>splice site</td>
<td>578</td>
<td>38%</td>
<td>1.668e+03</td>
<td>damaging</td>
<td>0.28</td>
<td>6.29</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CETP</td>
<td>chr18</td>
<td>G&gt;A</td>
<td>hom</td>
<td>non-syn</td>
<td>203</td>
<td>45%</td>
<td>1.668e+03</td>
<td>damaging</td>
<td>0.55</td>
<td>6.29</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**Legend:**
- **Aging**
- **Cardiovascular**
- **Drug and Pharmacology**
- **Endocrinological and Metabolic**
- **Gastrointestinal**
- **Blood and Lymphatic**
- **Immunological and Infectious Diseases**
- **Kidney and Urinary Tract**
- **Neural**
- **Psychiatric**
- **Respiratory**
- **Sensory**
- **Hearing, Small and Taste**

---

**Filter By:**
- **Genotype:** Homozygous, Heterozygous
- **Homozygous**
- **Protein Impact:** Missense, Nonsense, Frameshift, Inframe, Splice Site, NON-synonymous, STOP, Splice Site, NON-synonymous, Supporting Evidence
- **OMIM:**
- **Gene Model:** CCDS, RefSeq
- **Polyphen Prediction:** POLYPHEN, probably damaging, probably tolerated

---

**Exclude:**
- **Position**
- **Gene Symbol**
- **Omics Score**
- **Effect**
- **Zygosity**
No rare variants or CNVs with high biological effect as related to mental illness.

3 common SNVs in this person that have been implicated in the literature as predisposing to mental illness.

<table>
<thead>
<tr>
<th>Gene name</th>
<th>Genomic coordinates</th>
<th>Amino acid change</th>
<th>Zygosity</th>
<th>Mutation type</th>
<th>Population Frequency</th>
<th>Clinical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTHFR</td>
<td>chr1: 11854476</td>
<td>Glu&gt;Ala</td>
<td>heterozygous</td>
<td>non-synon</td>
<td>T:77% G:23%</td>
<td>Susceptibility to psychoses, schizophrenia, occlusive vascular disease, neural tube defects, colon cancer, acute leukemia, and methylenetetra-hydrofolate reductase deficiency</td>
</tr>
<tr>
<td>BDNF</td>
<td>chr11: 27679916</td>
<td>Val&gt;Met</td>
<td>heterozygous</td>
<td>non-synon</td>
<td>C:77% T:23%</td>
<td>Susceptibility to OCD, psychosis, and diminished response to exposure therapy</td>
</tr>
<tr>
<td>CHAT</td>
<td>chr10: 50824117</td>
<td>Asp&gt;Asn</td>
<td>heterozygous</td>
<td>non-synon</td>
<td>G:85% A:15%</td>
<td>Susceptibility to schizophrenia and other psychopathological disorders</td>
</tr>
</tbody>
</table>
Gene Summary for CHAT

Gene Overview
Symbol: CHAT
Name: choline O-acetyltransferase
Location: 10e11.2
Summary: This gene encodes an enzyme which catalyzes the biosynthesis of the neurotransmitter acetylcholine. This gene product is a characteristic feature of cholinergic neurons, and changes in these neurons may explain some of the symptoms of Alzheimer's disease. Polymorphisms in this gene have been associated with Alzheimer's disease and mild cognitive impairment. Mutations in this gene are associated with congenital myasthenic syndrome associated with episodic apnea. Multiple transcript variants encoding different isoforms have been found for this gene, and some of these variants have been shown to encode more than one isoform. (provided by RefSeq, May 2010)

Relevant Reference Resources
Ensembl: http://www.ensembl.org/human/Gene/Summary?g=ENSG00000070748
UCSC Gene Browser: http://genome.ucsc.edu/cgi-bin/hgTracks?org=human&db=hg19&position=knownCanonical&position=CHAT

Associated Disease Categories
Category: DRUGS, CLINICAL PHARMACOLOGY AND ENVIRONMENT
Disease: Drug toxicity
Citation: Rodan et al., 2002

Associated Knowledge Sets
Name: Omicia Disease Genes (ODG) Top 10 Neurological - Alzheimer's
Type: disease
Description: Illumina's targeted rare genetic conditions exome test containing 2,761 genes covered in the HGMD database.

Name: Mit2GO
Type: myset
Description: A list of genes from phenomizer build from Patient Features MP:0004359. Long List ~3000 genes

Personal Variants in this Gene
<table>
<thead>
<tr>
<th>Position</th>
<th>Transcript</th>
<th>Transcript HGVS</th>
<th>Protein</th>
<th>Protein HGVS</th>
<th>Zyg</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>50624617</td>
<td>NM_001142933.1</td>
<td>c.195G&gt;A</td>
<td>NP_001136405</td>
<td>p.Asp74Ser</td>
<td>het</td>
<td>non-synon</td>
</tr>
<tr>
<td>50624619</td>
<td>NM_001142933.1</td>
<td>c.112G&gt;A</td>
<td>NP_001136405</td>
<td>p.Ala37Thr</td>
<td>het</td>
<td>non-synon</td>
</tr>
<tr>
<td>50634532</td>
<td>NM_020549</td>
<td>c.138C&gt;A</td>
<td>NP_056574</td>
<td>p.Val461Met</td>
<td>hom</td>
<td>non-synon</td>
</tr>
<tr>
<td>50863147</td>
<td>NM_020549</td>
<td>c.1842T&gt;C</td>
<td>NP_056574</td>
<td>p.His548His</td>
<td>hom</td>
<td>synonymous</td>
</tr>
</tbody>
</table>
Pharmacogenetics

◆ MA is homozygous for a p.Ile359Leu change in CYP2C9, and this variant has been linked to a reduction in the enzymatic activity of CYP2C9, a member of the cytochrome P450 superfamily of enzymes.

◆ Cytochrome P450 proteins are mono-oxygenases, which catalyze many reactions associated with drug metabolism as well as reactions associated with the synthesis of cholesterol, steroids and other lipids.

◆ Fluoxetine is commonly used in the treatment of OCD; it has been shown to be as effective as clomipramine and causes less side effects.

◆ CYP2C9 acts to convert fluoxetine to R-norfluoxetine, and so MA may not be able to adequately biotransform fluoxetine.

◆ It is notable that MA had no response to an 80 mg daily dose of fluoxetine.

◆ However, CYP2C9 does not play a rate-limiting role for other SSRIs or clomipramine.
Utah, New York and Faroe Islands
Will results from my blood tests be forwarded to me?

It will not be possible to give participants results of the blood tests. Due to regulations under the Clinical Laboratory Improvement Amendments (CLIA), we are legally unable to return research results to participants. Results from the blood tests will not be placed in participants' electronic health record. Participants should discuss any health concerns with their doctor or other health care provider, who can arrange any necessary and appropriate tests.

http://www.research.va.gov/mvp/veterans.cfm
accessed March 6, 2013

“A partnership is an arrangement where parties agree to cooperate to advance their mutual interests.” - *Wikipedia*
Dealing with the unexpected: consumer responses to direct-access BRCA mutation testing

Uta Francke¹,², Cheri Dijamco¹, Amy K. Kiefer¹, Nicholas Eriksson¹, Bianca Moiseff¹, Joyce Y. Tung¹, and Joanna L. Mountain¹

¹ 23andMe, Inc., Mountain View, CA, USA
² Department of Genetics, Stanford University School of Medicine, Stanford, CA, USA

204 BRCA1 (185delAG or 5382insC) or BRCA2 6174delT mutation carriers (130 males and 74 females) in the 23andMe database of 114,627 customers who were at least 18 years of age and had consented to participate in research.
Clinical Validity with “Worldwide Human Genetic Variation Database” and/or “Medical Donor Information Network”?
The Empowered Genome Cohort

- Gives PGP/UYG sequencees full access to secure platform for exploring and *sharing* genomes, with each other *and with full-time researchers*, via Ingenuity Variant Analysis.

- Helps citizen-scientists make their whole genomes at least modestly useful. Today’s q not what my genome can do for me, but *what our genomes can do for everyone.*

- Leverages deep functional knowledge base & sensible comparison methods (e.g., rare variant tests) to give current data silos (PGP/hard drives) a working bakery for collaborative insight.

- Sequencees retain full control & rights to their private data.

- Upcoming talk @ ASHG (24 October, 9:15 Grand Ballroom East)
  Teaser: Includes preliminary collaborative findings on myopia in 111 whole genomes...

- Contact Nathan Pearson (npearson@ingenuity.com) for details
Take Home Message

Genotype ≠ Phenotype

Environment matters!
Ancestry matters!
Genomic background matters!
Longitudinal course matters!

We can only begin to really understand this if we utilize the power of intense networking via internet-enabled archiving and distribution of consumer owned and managed data.
The End
Practical, ethical and regulatory considerations for the evolving medical and research genomics landscape

Gholson J. Lyon a,b,*, Jeremy P. Segal c,***

a Stanley Institute for Cognitive Genomics, Cold Spring Harbor Laboratory, NY, United States
b Utah Foundation for Biomedical Research, Salt Lake City, UT, United States
c New York Genome Center, New York City, NY, United States

O’Rawe et al. Genome Medicine 2013, 5:28
http://genomemedicine.com/content/5/3/28

Low concordance of multiple variant-calling pipelines: practical implications for exome and genome sequencing

Jason O’Rawe1,2, Tao Jiang3, Guangqing Sun3, Yiyang Wu1,2, Wei Wang4, Jingchu Hu3, Paul Bodily5, Lifeng Tian6, Hakon Hakonarson6, W Evan Johnson7, Zhi Wei4, Kai Wang8,9* and Gholson J Lyon1,2,9*
Circular RNAs Are the Predominant Transcript Isoform from Hundreds of Human Genes in Diverse Cell Types

Julia Salzman¹, Charles Gawad¹,³*, Peter Lincoln Wang¹, Norman Lacayo³, Patrick O. Brown¹,²*

1 Department of Biochemistry, Stanford University School of Medicine, Stanford, California, United States of America, 2 Howard Hughes Medical Institute, Stanford University School of Medicine, Stanford, California, United States of America, 3 Department of Pediatric Hematology/Oncology, Stanford University School of Medicine, Stanford, California, United States of America

Abstract

Most human pre-mRNAs are spliced into linear molecules that retain the exon order defined by the genomic sequence. By deep sequencing of RNA from a variety of normal and malignant human cells, we found RNA transcripts from many human genes in which the exons were arranged in a non-canonical order. Statistical estimates and biochemical assays provided strong evidence that a substantial fraction of the spliced transcripts from hundreds of genes are circular RNAs. Our results suggest that a non-canonical mode of RNA splicing, resulting in a circular RNA isoform, is a general feature of the gene expression program in human cells.


Editor: Thomas Preiss, The John Curtin School of Medical Research, Australia

Received November 7, 2011; Accepted December 28, 2011; Published February 1, 2012