Advancing Precision Medicine through clinical grade whole genome sequencing, return of results 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.
Uncovering genetic components of a previously un-described syndrome

Jason O’Rawe1, Yiyang Wu1, David Mittelman2, Han Fang3, Gholson J. Lyon1,3

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Whole genome sequencing analysis of a family with familial dysautonomia and neuropsychiatric symptoms

Han Fang1,2, Yiyang Wu1,2, Jason A. O’Rawe1,2, David Mittelman4,5, Gholson J. Lyon1,2,3*
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.
Severe Mental Illness (and other severe illness) in current system

Current Standard of Care in America

Hospitalization
Therapy- counseling
Medication
Disruptive developments in Medicine

Prevention efforts, genomics-guided

More direct action on the brain itself

PatientsLikeMe

Figure 1

Sagittal and transverse computed tomography (CT) images of the brain and skull of MA.

We show here sagittal and transverse sections taken from CT scans. Imaging was performed before (A) and after (B) MA received deep brain stimulation surgery for his treatment refractory OCD. Two deep brain stimulator probes can be seen to be in place from a bifrontal approach (B), with tips of the probes located in the region of the hypothalamus. Leads traverse through the left scalp soft tissues. Streak artifact from the leads somewhat obscures visualization of the adjacent bifrontal and left parietal parenchyma. We did not observe any intracranial hemorrhage, mass effect or midline shift or extra-axial fluid collection. Brain parenchyma was normal in volume and contour.

DBS implant has contributed to any of these issues. Attempts to add fluoxetine at 80 mg by mouth daily for two months to augment any efficacy from the DBS and ERP were unsuccessful, mainly due to no discernible benefit and prominent sexual side effects. MA still receives an injection of 37.5 mg risperidone every two weeks for his past history of OCD.
Integrating precision medicine in the study and clinical treatment of a severely mentally ill person

Jason A. O’Rawe¹,², Han Fang¹,², Shawn Rynearson³, Reid Robison⁴, Edward S. Kiruluta⁵, Gerald Higgins⁶, Karen Eilbeck³, Martin G. Reese³ and Gholson J. Lyon¹,²,⁴

¹ Stanley Institute for Cognitive Genomics, Cold Spring Harbor Laboratory, NY, USA
² Stony Brook University, Stony Brook, NY, USA
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⁴ Utah Foundation for Biomedical Research, Salt Lake City, UT, USA
⁵ Omicia Inc., Emeryville, CA, USA
⁶ AssureRx Health, Inc., Mason, OH, USA

In recent years, there has been an explosion in the number of technical platforms being developed. This has greatly improved our ability to more accurately, and more comprehensively, explore and characterize activities, but there exists a paucity of studies that integrate the areas of clinical neuropsychiatry, personal genomics and brain-machine interfaces.

data are now being generated and archived in many separate research and clinical laboratories. We report here the detailed phenotypic characterization, clinical-grade assessment, and which has been found to predispose carriers to various psychiatric illnesses.

The clinician can program and adjust the settings of the neurostimulator externally via a hand-held device. A rechargeable Activa RC neurostimulator. Thin, insulated, coiled wires, each ending in a 1.5 mm electrode, that deliver stimulation to the targeted areas.

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Additional Information and Declarations can be found on page 18

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OPEN ACCESS
A family in Utah, with a 40 year old Caucasian man with very severe obsessive compulsive disorder, severe depression and intermittent paranoia, with symptoms that started around age 5.

Some people had diagnosed him with bipolar and/or schizophrenia due to his mood states and possible paranoia.

Multiple medication trials failed over many years. Considered treatment refractory.
Pedigree structure

- Obsessive-compulsive disorder
Humanitarian Device Exemption (HDE) for OCD granted by FDA in 2009
Effects of DBS have been regulated its use specifically to treat psychiatric disorders. OCD, which, like dystonia, has been associated with relief of depressive symptoms in a patient with dyskinesia. DBS electrode. Medtronic DBS lead and microelectrode. (Courtesy of Medtronic Inc.)

Medtronic Kinetra® Neurostimulator Model 7428
- Dual channel
- Accommodates two extensions/leads
- Kinetra takes the place of two Soletras
- For OCD, two Kinetras may be used for bilateral leads
Figure 1

Three-dimensional (3D) illustration of bilaterally implanted deep brain stimulation (DBS) electrodes in the ventral capsule/ventral striatum. The 3D objects (leads and brain structures) are sitting on the axial plane 5 mm below the AC–PC plane as viewed posterior to anterior. The trajectory of the leads is down the barrel of the anterior limb of the internal capsule. Each lead has four contacts, but only three are shown (contacts #0, #1, and #2); contact #3 is hidden by the caudate nucleus. The most ventral #0 contact is active, as represented by red radiating stimulation fields. Abbreviations: AC–PC, anterior commissure–posterior commissure; GPe, globus pallidus externus; GPi, globus pallidus internus. Image courtesy of Kirk Finnis, PhD (Medtronic Inc., USA).
Figure 1  Sagittal and transverse computed tomography (CT) images of the brain and skull of MA. We show here sagittal and transverse sections taken from CT scans. Imaging was performed before (A) and after (B) MA received deep brain stimulation surgery for his treatment refractory OCD. Two deep brain stimulator probes can be seen to be in place from a bifrontal approach (B), with tips of the probes located in the region of the hypothalamus. Leads traverse through the left scalp soft tissues. Streak artifact from the leads somewhat obscures visualization of the adjacent bifrontal and left parietal parenchyma. We did not observe any intracranial hemorrhage, mass effect or midline shift or extra-axial fluid collection. Brain parenchyma was normal in volume and contour.
2.5 year follow-up

Global Assessment of Functioning (GAF) 0 to 100 scale

From 5-15 in 2008-2009 to 45-55 in 2013

Pulse width = 210, Frequency 130 Hz
Depleteable nature of battery

• Battery replaced with a rechargeable battery in January 2012.

• Numerous episodes of forgetting to recharge battery, with relapse to baseline condition.
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

Table 1
Processes involved in a CLIA-certified genetic test.

<table>
<thead>
<tr>
<th>Preanalytic system</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Test request and specimen collection criteria</td>
</tr>
<tr>
<td>2) Specimen submission, handling and referral procedures</td>
</tr>
<tr>
<td>3) Preanalytic systems assessment</td>
</tr>
</tbody>
</table>

Analytic system

1) A detailed step-by-step procedure manual
2) Test systems, equipment, instruments, reagents, materials and supplies
3) Establishment and verification of performance specifications
4) Maintenance and function checks
5) Calibration and calibration verification procedures
6) Control procedures, test records, and corrective actions
7) Analytic systems assessment

Post-analytic system

1) Test report, including (among other things):
   a) interpretation
   b) reference ranges and normal values
2) Post-analytic systems assessment

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.

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
We have implemented the analytic-interpretive split model here with MA, with WGS being performed in a CLIA certified and CAP accredited lab at Illumina as part of the Individual Genome Sequencing test developed by them. The WGS acts as a discrete deliverable clinical unit from which multiple downstream interpretive analyses were performed. We used the ERDS CNV caller, the Golden Helix SVS CNAM for CNV calling, and the Omicial Opal and the AssureRx Health Inc. pipelines for variant annotation and clinical interpretation of genomic variants. By archiving and returning to him the encrypted hard drive containing his “raw” sequencing data, any number of people, including the individual and/or his/her health care providers can analyze his genome for years to come.

Abbreviations: CLIA, Clinical Laboratory Improvement Amendments; CAP, College of American Pathologists; CASAVA, Consensus Assessment of Sequence and Variation; ERDS, Estimation by Read Depth with SNVs; CNAM, Copy Number Analysis Method; WGS, Whole Genome Sequencing.

After consultation with a genetic counselor, the genetic findings were returned to M.A. with the option given to him to keep the raw data (which he declined). SNVs and Indels that were detected by the CASAVA pipeline were also converted to the GVFClin file format so that his WGS data could be, in the future, incorporated into his electronic medical record.
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.

<table>
<thead>
<tr>
<th>Category</th>
<th>Number of Variants</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically Significant in Patient</td>
<td>Pathogenic</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Likely Pathogenic</td>
<td>0</td>
</tr>
<tr>
<td>Carrier Status for Patient</td>
<td>Pathogenic</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Likely Pathogenic</td>
<td>1 Refsum Disease</td>
</tr>
<tr>
<td>Variants of Unknown Significance</td>
<td></td>
<td>284</td>
</tr>
<tr>
<td>Likely Benign Variants</td>
<td></td>
<td>349</td>
</tr>
<tr>
<td>Benign Variants</td>
<td></td>
<td>613</td>
</tr>
</tbody>
</table>

**Gene** | **Call** | **Amino Acid** | **Interpretation** | **Associated Condition** | **Mode of Inheritance**
--- | --- | --- | --- | --- | ---
PHYH | c.734G>A | p.Arg245Gln | Likely Pathogenic | Refsum Disease | Autosomal Recessive

**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 grandfather both have large pupils and loss of night vision. No cataracts known.

• Preventive measures implemented
Figure 2. Flow chart of our variant analysis pipeline.
* Both Scalpel and CADD are still in press. For CADD, see http://cadd.gs.washington.edu/
Some genomic analysis online platforms and analysis suites

**Identify causal variants** from human sequencing data in just hours

**Golden Helix Product Offerings**

SNP & VARIATION SUITE 7

SNP & Variation Suite 7 is an integrated collection of user-friendly, yet powerful analytic tools for managing, analyzing, and visualizing multifaceted genomic and phenotypic data. SVS was created specifically to empower biologists and other researchers to easily perform complex analyses and visualizations, eliminating the need to rely exclusively on bioinformatics experts or cobble together difficult-to-use, incompatible freeware. With SVS you can focus on your research instead of learning to be a programmer or waiting in line for bioinformaticians.

**Golden Helix GenomeBrowse**

Visualization tool raises the bar on the experience of exploring and finding key insights into your genomic data. Every component has been designed and optimized to give you a user-experience beyond imagination.

Find out more information about GenomeBrowse »
Easily select variants with prior evidence

<table>
<thead>
<tr>
<th>Variant Class</th>
<th>Gene</th>
<th>Position dbSNP</th>
<th>Change</th>
<th>Zygosity</th>
<th>Quality Coverage</th>
<th>Frequency</th>
<th>Omicia Score</th>
<th>Polyphen Mut-Taster</th>
<th>SIFT PhyLOP</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>VUS (dg)</td>
<td>FCGR3A</td>
<td>chr1 161516333 rs10127939</td>
<td>A→A,G</td>
<td>non-synon</td>
<td>6342.21</td>
<td>0.019</td>
<td>damaging</td>
<td>damaging</td>
<td>0.09</td>
<td>LDB</td>
</tr>
<tr>
<td>VUS (dg)</td>
<td>AGT</td>
<td>chr1 230845794 rs699</td>
<td>A→G,G</td>
<td>hom-synon</td>
<td>3430.34</td>
<td>0.086</td>
<td>benign</td>
<td>benign</td>
<td>0.68</td>
<td>LDB</td>
</tr>
<tr>
<td>VUS (other)</td>
<td>SLC22A1</td>
<td>chr6 160560881 rs35167514</td>
<td>ATG→ATG</td>
<td>non-synon</td>
<td>30515.15</td>
<td>0.424</td>
<td>-</td>
<td>-</td>
<td>0.97</td>
<td>LGB</td>
</tr>
<tr>
<td>VUS (other)</td>
<td>OR52B4</td>
<td>chr11 4389405 c.121_121del</td>
<td>G→G</td>
<td>non-synon</td>
<td>2139.12</td>
<td>0.321</td>
<td>-</td>
<td>-</td>
<td>0.88</td>
<td>HGMD</td>
</tr>
<tr>
<td>VUS (other)</td>
<td>CHRFMAM7A</td>
<td>chr15 30665281</td>
<td>C→A</td>
<td>non-synon</td>
<td>21.19</td>
<td>0.187</td>
<td>benign</td>
<td>benign</td>
<td>0.41</td>
<td>OMIM</td>
</tr>
<tr>
<td>VUS (other)</td>
<td>XYLT1</td>
<td>chr16 17564311 rs1758386</td>
<td>G→G</td>
<td>non-synon</td>
<td>2139.12</td>
<td>0.321</td>
<td>-</td>
<td>-</td>
<td>0.88</td>
<td>HGMD</td>
</tr>
<tr>
<td>VUS (other)</td>
<td>P2RX5</td>
<td>chr17 3592477 rs11681907</td>
<td>hom</td>
<td>non-synon</td>
<td>333.33</td>
<td>0.247</td>
<td>-</td>
<td>-</td>
<td>0.54</td>
<td>HGMD</td>
</tr>
<tr>
<td>VUS (dg)</td>
<td>MAPT</td>
<td>chr1 44067382 rs11275718</td>
<td>T→C,C</td>
<td>hom-synon</td>
<td>17.17</td>
<td>0.266</td>
<td>-</td>
<td>-</td>
<td>0.26</td>
<td>OMIM</td>
</tr>
<tr>
<td>VUS (other)</td>
<td>C17orf57</td>
<td>chr17 453606730 rs6918</td>
<td>hom</td>
<td>non-synon</td>
<td>4832.35</td>
<td>0.089</td>
<td>benign</td>
<td>benign</td>
<td>0.43</td>
<td>HGMD</td>
</tr>
<tr>
<td>VUS (other)</td>
<td>SLC14A2</td>
<td>chr18 43262359 rs3745009</td>
<td>hom</td>
<td>non-synon</td>
<td>21.02</td>
<td>0.546</td>
<td>benign</td>
<td>benign</td>
<td>0.36</td>
<td>OMIM</td>
</tr>
<tr>
<td>VUS (dg)</td>
<td>TYK2</td>
<td>chr19 10463118 rs34638443</td>
<td>hom</td>
<td>non-synon</td>
<td>4523.22</td>
<td>0.816</td>
<td>damaging</td>
<td>damaging</td>
<td>3.89</td>
<td>OMIM</td>
</tr>
<tr>
<td>VUS (dg)</td>
<td>PRNP</td>
<td>chr20 4680251 rs1799990</td>
<td>hom</td>
<td>non-synon</td>
<td>37.03</td>
<td>0.302</td>
<td>damaging</td>
<td>benign</td>
<td>0.66</td>
<td>HGMD</td>
</tr>
</tbody>
</table>

Viral infections, recurrent, susceptibility to
Condition: Hypertension, essential, susceptibility to
Description: Reduced metformin uptake in transfected cells

Pseudoxanthoma elasticum

associated with shorter bleeding time and less response to aspirin.
a higher risk of secondary coronary events which was reduced by
pravastatin
associated with blood pressure response to nifedipine treatment.
cancer-associated

Description: Prion Disease, Susceptibility To Alzheimer Disease, Early-onset, Susceptibility To, Included, Aphasía, Primary Progressive, Susceptibility To, Included
Assurex / Mayo Clinic Pharmacogenomics Pipeline

1. Check coding single nucleotide variants and structural variants in exons of candidate genes;
2. Check genome variants within intergenic, intronic, 5’UTR and 3’ UTRs;
3. Check pharmacoepigenomic variants, emphasizing TF binding motifs;
4. Check epistasis and LD;
5. Determine allele frequency.

Manual Curation of Output

Gerry Higgins, MD, PhD
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.

◆ 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.
No rare variants or CNVs with high biological effect as related to mental illness.

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

**Table 1** A summary of three clinically relevant alleles found in the sequencing results of MA. Variations in MTHFR, BDNF, and ChAT were found to be of potential clinical relevance for this person as they are all implicated in contributing to the susceptibility and development of many neuropsychiatric disorders that resemble those present within MA. A brief summary of the characteristics of each variation is shown, including the gene name, genomic coordinates, amino acid change, zygosity, variation type, estimated population frequency and putative clinical significance.

<table>
<thead>
<tr>
<th>Gene name</th>
<th>Genomic coordinates</th>
<th>Amino acid change</th>
<th>Zygosity</th>
<th>Variation 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 methylenetetrahydrofolate 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>
Q: How frequent can we observe people with all three SNPs?

- Empirical genotype frequencies:
  - 1000G: 3.20% (35 out of 1092, phenotypes unknown)
  - UFBR: 4.58% (7 out of 153, including M.A. and M.A.’s father)
<table>
<thead>
<tr>
<th>Chromosomal region</th>
<th>$P$ value</th>
<th>Previous association</th>
<th>Candidate gene in relation to index SNP</th>
<th>Other genes in genomic region defined by LD</th>
<th>eQTL</th>
<th>Disease associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chr. 6: 31,596,138-32,813,768</td>
<td>$9.14 \times 10^{-14}$</td>
<td>SCZ</td>
<td>HLA-DRB9</td>
<td>MHC class II, many other genes, lincRNA</td>
<td>Many</td>
<td>Many</td>
</tr>
<tr>
<td>Chr. 10: 104,487,871-105,245,420</td>
<td>$3.68 \times 10^{-13}$</td>
<td>SCZ</td>
<td>C10orf32-AS3MT</td>
<td>CALHM1, CALHM2, CALHM3, CNNM2, CYP17A1, IRA, MIR1307, NTS2, PSF6, PDCD11, SFXN2, ST13P13, TAF5, USM9, WBP1L</td>
<td>ACTR1A, ACTR3, AS3MT, C10orf32, C10orf78, NTS2, TME180, TM8B, WBP1L</td>
<td>GWAS: blood pressure, CAD, aneurysm</td>
</tr>
<tr>
<td>Chr. 7: 1,827,717-2,346,115</td>
<td>$5.93 \times 10^{-13}$</td>
<td>No</td>
<td>MAD1L1</td>
<td>FTS2, NUDT1, SNX8</td>
<td>C7orf27, FTS2, MAD1L1, NUDT1</td>
<td>DPYD: mental retardation</td>
</tr>
<tr>
<td>Chr. 1: 98,141,112-98,664,991</td>
<td>$1.72 \times 10^{-12}$</td>
<td>SCZ</td>
<td>(MIR137, 37 kb)</td>
<td>DPYD, lincRNA</td>
<td>No data</td>
<td>CACNA1C: autism, Timothy syndrome, Brugada syndrome 3</td>
</tr>
<tr>
<td>Chr. 12: 2,285,731-2,440,464</td>
<td>$5.22 \times 10^{-12}$</td>
<td>SCZ, BPD</td>
<td>CACNA1C</td>
<td>–</td>
<td>No data</td>
<td>CACNB2: Brugada syndrome 4; GWAS: blood pressure</td>
</tr>
<tr>
<td>Chr. 10: 18,601,928-18,934,390</td>
<td>$1.27 \times 10^{-10}$</td>
<td>5 disorders</td>
<td>CACNB2</td>
<td>NSUN6</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Chr. 8: 143,297,312-143,410,423</td>
<td>$2.19 \times 10^{-10}$</td>
<td>No</td>
<td>TSNARE1</td>
<td>–</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Chr. 1: 73,275,828-74,099,273</td>
<td>$3.64 \times 10^{-10}$</td>
<td>No</td>
<td>(x10NST00000415686.1, lincRNA 4 kb)</td>
<td>–</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Chr. 11: 130,706,918-130,894,976</td>
<td>$1.83 \times 10^{-9}$</td>
<td>No</td>
<td>SNX19, 31 kb</td>
<td>lincRNA</td>
<td>SNX19</td>
<td>No data</td>
</tr>
<tr>
<td>Chr. 5: 151,888,959-152,835,304</td>
<td>$2.65 \times 10^{-9}$</td>
<td>No</td>
<td>ENST00000503048.1</td>
<td>lincRNA (GRIA1)</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Chr. 5: 152,505,453-152,707,306</td>
<td>$4.12 \times 10^{-8}$</td>
<td>No</td>
<td></td>
<td></td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Chr. 19: 19,354,937-19,744,079</td>
<td>$3.44 \times 10^{-9}$</td>
<td>BPD</td>
<td>MAU2, 4 kb</td>
<td>CILP2, GATA2A, GMIP, HAPLN4, LPAR2, MIR640, NCAK, NDUFA13, PBX4, SUGP1, TM6SF2, TSSK6, YJEFN3</td>
<td>No data</td>
<td>GWAS: lipid levels</td>
</tr>
</tbody>
</table>

*Regions reported to meet genome-wide significance thresholds of association for schizophrenia (SCZ) or bipolar disorder (BPD). The gene within which an index SNP is located is given. For intergenic index SNPs, the nearest gene is given in parentheses. Other named genes in the genomic interval. SNP-transcript associations with $q < 0.05$ in peripheral blood. eQTLs with the SNP with the strongest association are shown in bold. Data from the NHGRI GWAS catalog. A compilation of genes related to autism[23] and mental retardation[73,74]. No data means no Affymetrix U219 probe sets or low expression in peripheral blood. The CACNB2 association emerged when considering attention deficient/hyperactivity disorder (ADHD), autism, bipolar disorder, major depressive disorder and schizophrenia as affected[59]. CAD, coronary artery disease; HDL, high-density lipoprotein.

- Indicates that M.A. is homozygous for the exact variant of genome significance
- Indicates that M.A. is heterozygous for the exact variant of genome significance
| Chr. 2: 37,422,072–37,592,628 | 6.78 × 10⁻⁹ | No | QPCT | C2orf56, CEBPZ, PRKD3, SULT6B1 lincRNA | No eQTL |
| Chr. 5: 101,581,848–101,870,822 | 9.03 × 10⁻⁹ | No | SLC06A1 | lincRNA | No data |
| Chr. 3: 52,215,002–53,175,017 | 1.16 × 10⁻⁸ | SCZ, BPD | ITIH3 | ALAS1, ALDOAP1, BAP1, C3orf78, DNAH1, GLT8D1, GLYCTK, GNL3, ITIH1, ITIH4, MIR135A1, MIRLET7G, MUSTN1, NEK4, NISCH, NT5DC2, PBRM1, PHF7, PPM1M, RFT1, Sema3G, SFMBT1, SPCS1, STAB1, TLR9, TMEM110, TNCC1, TWF2, WDR82, lincRNA | No data |
| Chr. 2: 145,139,727–145,214,607 | 1.19 × 10⁻⁸ | No | ZEB2 | – | No eQTL |
| Chr. 2: 200,628,118–201,293,421 | 1.21 × 10⁻⁸ | No | FONG | C2orf47, C2orf69, SPATS2L, TYW5, lincRNA | No data |
| Chr. 18: 52,722,378–52,827,668 | 1.22 × 10⁻⁸ | No | (ENST00000565991.1, 21 kb) | lincRNA (TCF4) | No data |
| Chr. 2: 233,550,961–233,808,241 | 1.51 × 10⁻⁸ | No | C2orf82 | GIGYF2, KCNJ13, NGEF | No data |
| Chr. 1: 243,593,066–244,025,999 | 1.80 × 10⁻⁸ | No | AKT3 | CEP170 | AKT3 |
| Chr. 1: 243,418,063–243,627,135 | 2.53 × 10⁻⁸ | Yes | SDCCAG8 | – | No eQTL |
| Chr. 12: 123,447,928–123,913,433 | 2.28 × 10⁻⁸ | No | C12orf65 | ABCB9, ARL6IP4, CDK2AP1, MIR4304, MPHOSPH9, OGFOD2, PIP5NM2, RELPL2, SBNO1, SETD8, lincRNA | No data |
| Chr. 8: 89,188,454–89,761,163 | 3.33 × 10⁻⁸ | SCZ | Intergenic | MMP16, lincRNA | MMP16 |
| Chr. 5: 60,484,179–60,843,706 | 3.78 × 10⁻⁸ | No | ENST00000506902.1 | ZSWIM6, C5orf43, lincRNA | C5orf43, ZSWIM6 |

- Indicates that M.A. is homozygous for the exact variant of genome significance
- Indicates that M.A. is heterozygous for the exact variant of genome significance

Disruptive developments

Prevention efforts, genomics-guided

More direct action on the brain itself

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Figure 1

Sagittal and transverse computed tomography (CT) images of the brain and skull of MA. We show here sagittal and transverse sections taken from CT scans. Imaging was performed before (A) and after (B) MA received deep brain stimulation surgery for his treatment refractory OCD. Two deep brain stimulator probes can be seen to be in place from a bifrontal approach (B), with tips of the probes located in the region of the hypothalamus. Leads traverse through the left scalp soft tissues. Streak artifact from the leads somewhat obscures visualization of the adjacent bifrontal and left parietal parenchyma. We did not observe any intracranial hemorrhage, mass effect or midline shift or extra-axial fluid collection. Brain parenchyma was normal in volume and contour.

DBS implant has contributed to any of these issues. Attempts to add fluoxetine at 80 mg by mouth daily for two months to augment any efficacy from the DBS and ERP were unsuccessful, mainly due to no discernible benefit and prominent sexual side effects. MA still receives an injection of 37.5 mg risperidone every two weeks for his past history of OCD.

O’Rawe et al. (2013), PeerJ, DOI 10.7717/peerj.177
Feedback from M.A.’s mother

• “We are visiting Town X on the Island of X. Interestingly, I toured the "mental hospital " here yesterday. It was a sad reminder of how patients in America used to suffer and how they still do in most areas of the world. It made me even more grateful that M.A. had the very best in medical care and is now living a nearly normal life”.