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 Fang2, Gholson J. Lyon1,3

1Cold Spring Harbor Laboratory, Human Genetics, Cold Spring Harbor, NY, 11724, 2Virginia Tech, Department of Biological Sciences, Blacksburg, VA, 24061, 3Utah Foundation for Biomedical Research, UFBR, Salt Lake City, UT, 84106

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

1Cold Spring Harbor Laboratory, Human Genetics, Cold Spring Harbor, NY, 11724, 2Virginia Tech, Department of Biological Sciences, Blacksburg, VA, 24061, 3Utah Foundation for Biomedical Research, UFBR, Salt Lake City, UT, 84106, 4HiSeq2000 platform, with four (the two affected boys: CG WGS covered >85% of the genome and >90% of the genome in the two affected boys, and variants were found to conform to an X-linked disease model, in TAF1, ZNF41 and ASB12 respectively. However, the study design reliably identified three putative variants that followed an X-linked disease model. TAF1 encodes a member of the POU-IV class of neural transcription factors. The POU-IV domain is predicted to have DNA-binding properties and is conserved in a number of species, including humans. The other two genes, ZNF41 and ASB12, are involved in various biological processes, but their specific functions are not well understood.

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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. Reese⁴ 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
³ Department of Biomedical Informatics, University of Utah, Salt Lake City, UT, USA
⁴ Utah Foundation for Biomedical Research, Salt Lake City, UT, USA
⁵ Omicia Inc., Emeryville, CA, USA
⁶ AssureRx Health, Inc., Mason, OH, USA

ABSTRACT

In recent years, there has been an explosion in the number of technical, genetic, and medical diagnostic platforms being developed. This has greatly improved our understanding of the human biological systems on the individual level. Large quantities of biomedical data are now being generated and archived in many separate research and clinical laboratories. These data are then used to aid in the diagnosis, treatment, and prevention of a wide variety of illnesses. However, challenges still remain regarding how to effectively use this data for the betterment of the patient. Here, we report the results of integrating precision medicine in the study and clinical treatment of a severely mentally ill person.

RESULTS.

Improvement Amendments (CLIA)-certified laboratory.

The patient, MA, was a 25 year old man with a history of treatment resistant Obsessive Compulsive Disorder (OCD), targeting his nucleus accumbens/anterior limb of the internal capsule. Programming of the device and psychiatric assessments occurred at regular intervals.

Figure 1

Sagittal and transverse computed tomography (CT) images of the brain and skull of MA. A single person with severe mental illness was implanted with the Deep Brain Stimulation (DBS) Therapy device for Obsessive Compulsive Disorder by Medtronic®. The DBS lead has been placed such that it is optimized for the delivery of electrical stimulation to the targeted structures deep within the brain.

The clinician can program and adjust the settings of the neurostimulator externally via a hand-held device. The extension is an insulated wire that connects the lead to the neurostimulator. Thin, insulated, coiled wires, each ending in a 1.5 mm electrode, that deliver stimulation to the targeted areas.

How to cite this article

O’Rawe et al. (2013), Integrating precision medicine in the study and clinical treatment of a severely mentally ill person.
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

[Diagram of a pedigree chart showing family relationships and the presence of Obsessive-compulsive disorder.]
Humanitarian Device Exemption (HDE) for OCD granted by FDA in 2009
disorders. In this discussion, one of the main concerns for psychiatric disorders is OCD, which, like dystonia, has been granted a humanitarian device exemption status. OCD, like dystonia, is a movement disorder that is characterized by compulsive behaviors and rituals. Effects of DBS have been reported in approximately 100 OCD patients. The limited data for DBS in psychiatric disorders is also reflected by its regulatory status; thalamic DBS for essential tremor received Food and Drug Administration (FDA) approval in 2003. Currently, the only psychiatric disorder with FDA approval for DBS is Tourette syndrome, which was approved in 2002 followed by globus pallidus interna DBS for Parkinson syndrome in 2004. DBS of the globus pallidus interna has demonstrated anxiolytic effects (114, 115, 126) and few cases for each site preclude full discussion here. The limited data for DBS in psychiatric disorders, fewer studies have investigated its use specifically to treat psychiatric disorders, and nonresponse in one patient may be related to a comorbid somatoform disorder. When stimulation was turned off, all three of these responders experienced significant worsening of mood and OCD symptoms. The enhancing of mood and OCD symptoms. The improvement in three of four patients with reduction in Y-BOCS; the authors suggest that the patients all had severe symptoms at baseline, and the best clinical response was reported as 3.5 global assessment of function scores 45.

Implantable Components

Figure 10. DBS electrode. Medtronic DBS lead and microelectrode. (Courtesy of Medtronic Inc.)

Electrode End

Indicated for OCD only

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

8840 N’Vision® Clinician Programmer

Review Patient Access

Controller (Soletra)

Clincian Programmer (Kinetra)
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
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
Depletable 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>

<table>
<thead>
<tr>
<th>Analytic system</th>
</tr>
</thead>
<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>
</tr>
<tr>
<td>3) Establishment and verification of performance specifications</td>
</tr>
<tr>
<td>4) Maintenance and function checks</td>
</tr>
<tr>
<td>5) Calibration and calibration verification procedures</td>
</tr>
<tr>
<td>6) Control procedures, test records, and corrective actions</td>
</tr>
<tr>
<td>7) Analytic systems assessment</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Post-analytic system</th>
</tr>
</thead>
<tbody>
<tr>
<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>
</tr>
<tr>
<td>2) Post-analytic systems assessment</td>
</tr>
</tbody>
</table>

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

Individual Genome Sequence Results

Clinical Report

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 encrypting the 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.

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

O’Rawe et al. (2013), PeerJ, DOI 10.7717/peerj.177
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</td>
</tr>
<tr>
<td></td>
<td></td>
<td>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>

**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

Golden Helix Product Offerings

Identify causal variants from human sequencing data in just hours

Opal adds clinical context for genomic data

Omicia Opal

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

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. Aphasia, Primary Progressive, Susceptibility To, Included
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.

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>
<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 3: Description of the 22 genome-wide significant loci in the combined analysis

<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, CNMN2, CYP17A1, INA, MIR1307, NT5C2, PC8F6, PDCD11, SF3N2, ST13P13, TAF5, USMG5, WBPI1</td>
<td>Many</td>
<td>ACTR1A, ARL3, AS3MT, C10orf32, C10orf78, NT5C2, TMEM180, TRIM8, WBPI1</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>FTSJ2, NUDT1, SNX8</td>
<td></td>
<td></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>DYPD, lincRNA, SNX8</td>
<td></td>
<td></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></td>
<td></td>
</tr>
<tr>
<td>Chr. 10: 18601,928-18,934,390</td>
<td>$1.27 \times 10^{-10}$</td>
<td>5 disorders</td>
<td>CACNB2</td>
<td>NSUN6</td>
<td></td>
<td></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></td>
<td></td>
</tr>
<tr>
<td>Chr. 1: 73,275,828-74,099,273</td>
<td>$3.64 \times 10^{-10}$</td>
<td>No</td>
<td>(x1ONST00000415686.1, lincRNA 4 kb)</td>
<td>–</td>
<td></td>
<td></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 (GRIA1)</td>
<td></td>
<td></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></td>
<td></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></td>
<td></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>CLIP2, GATAD2A, GMIP, HAPLN4, LPAR2, MIR640, NCRN, NDUFA13, PBX4, SUGP1, TM6SF2, TSSK6, YIEFN3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*aRegions reported to meet genome-wide significance thresholds of association for schizophrenia (SCZ) or bipolar disorder (BPD). bThe 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. cSNP-transcript associations with $q < 0.05$ in peripheral blood. dQTLs with the SNP with the strongest association are shown in bold. eData from the NHGRI GWAS catalog24, OMIM25 and a compilation of genes related to autism73 and mental retardation97,84. No data means no Affymetrix U219 probe sets or low expression in peripheral blood. The CACNB2 association emerged when considering attention deficit/hyperactivity disorder (ADHD), autism, bipolar disorder, major depressive disorder and schizophrenia as affected59. 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

Ripke et.al (2013) Nature Genetics
<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Start/End</th>
<th>P-value</th>
<th>Allele</th>
<th>Gene(s)</th>
<th>eQTL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chr. 2:</td>
<td>37,422,072–37,592,628</td>
<td>$6.78 \times 10^{-9}$</td>
<td>No</td>
<td>QPCT, C2orf56, CEBPZ, PRKD3, SULT6B1 lincRNA</td>
<td>No eQTL</td>
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<tr>
<td>Chr. 5:</td>
<td>101,581,848–101,870,822</td>
<td>$9.03 \times 10^{-9}$</td>
<td>No</td>
<td>SLC06A1 lincRNA</td>
<td>No data</td>
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<td>Chr. 3:</td>
<td>52,215,002–53,175,017</td>
<td>$1.16 \times 10^{-8}$</td>
<td>SCZ, BPD</td>
<td>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, TNRC1, TWF2, WDR82, lincRNA</td>
<td>No data (ITIH1-ITIH3-ITIH4): Glyceric aciduria, mental retardation; RTF1: mental retardation; GWAS: adiponectin, height, waist-hip ratio</td>
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<td>Chr. 2:</td>
<td>145,139,727–145,214,607</td>
<td>$1.19 \times 10^{-8}$</td>
<td>No</td>
<td>ZEB2</td>
<td>No eQTL</td>
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<tbody>
<tr>
<td>Chr. 1:</td>
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<td>No</td>
<td>AKT3, CEP170</td>
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<tbody>
<tr>
<td>Chr. 1:</td>
<td>243,418,063–243,627,135</td>
<td>$2.53 \times 10^{-8}$</td>
<td>Yes</td>
<td>SDCCAG8</td>
<td>SDCCAG8</td>
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<tbody>
<tr>
<td>Chr. 12:</td>
<td>123,447,928–123,913,433</td>
<td>$2.28 \times 10^{-8}$</td>
<td>No</td>
<td>C12orf65, ABCB9, ARL6IP4, CDK2AP1, C2orf69, ENST00000565991.1 (21 kb), lincRNA</td>
<td>No eQTL</td>
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<tbody>
<tr>
<td>Chr. 8:</td>
<td>89,188,454–89,761,163</td>
<td>$3.33 \times 10^{-8}$</td>
<td>SCZ</td>
<td>Intergenic, MMP16, lincRNA</td>
<td>MMP16</td>
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</tbody>
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<tbody>
<tr>
<td>Chr. 5:</td>
<td>60,484,179–60,843,706</td>
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<td>No</td>
<td>ENST00000506902.1, ZSWIM6, C5orf43, lincRNA</td>
<td>C5orf43, ZSWIM6</td>
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</table>

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

PatientsLikeMe

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.”