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 .

Jason O'Rawe

Yiyang Wu

Han Fang

Cold Spring Harbor Laboratory

Uncovering genetic components of a previously un-described syndrome

UFBR UTAH FOUNDATION FOR BIOMEDICAL RESEARCH

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Cold Spring Harbor Laboratory

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

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Omicia

Martin Reese
Edward Kiruluta

UFBR
UTAH FOUNDATION FOR BIOMEDICAL RESEARCH

Reid Robison

VBI VIRGINIA BIOINFORMATICS INSTITUTE AT VIRGINIA TECH

David Mittelman
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THE UNIVERSITY OF UTAH

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CSH STANLEY INSTITUTE FOR COGNITIVE GENOMICS
COLD SPRING HARBOR LABORATORY

Jason O'Rawe
Yiyang Wu
Han Fang
Michael Schatz
Giuseppe Narzisi

USC TROJANS

Kai Wang

illumina®

Tina Hambuch
Erica Davis
Dawn Barry

our study families

Severe Mental Illness (and other severe illness) in current system

<u>Current Standard of Care in America</u>

Hospitalization
Therapy- counseling
Medication

Disruptive developments in Medicine

Prevention efforts, genomics-guided

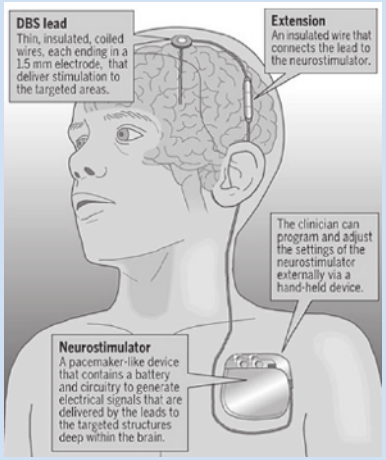
PatientsLikeMe

23andMe

ancestry.com

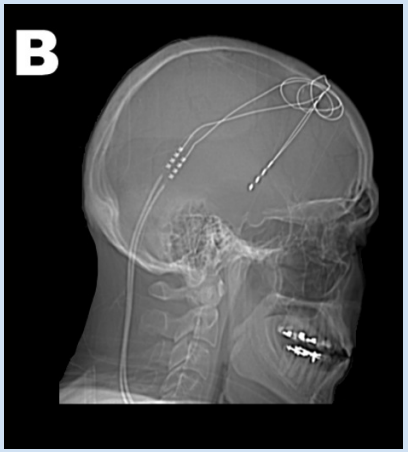
Google

More direct action on the brain itself



Medtronic

When Life Depends on Medical Technology



PeerJ

Integrating precision medicine in the study and clinical treatment of a severely mentally ill person

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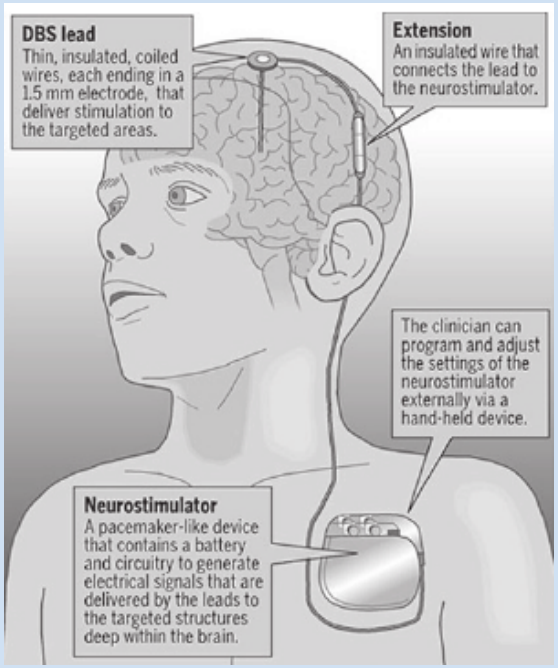

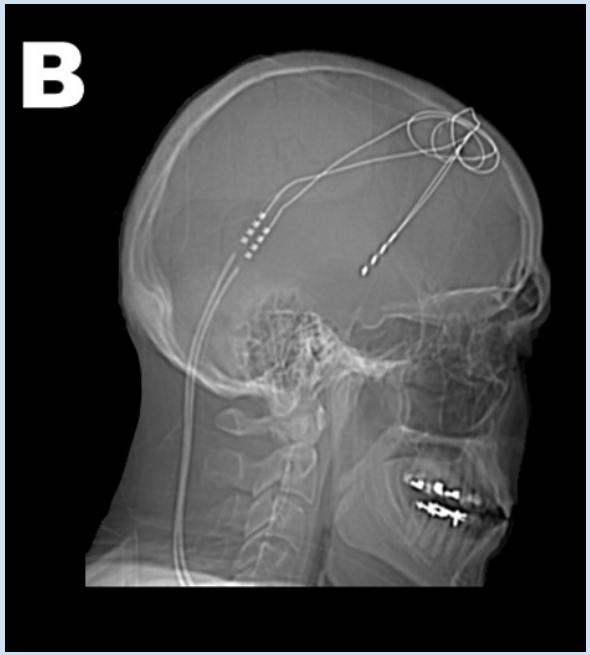

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Additional Information and Declarations can be found on page 18

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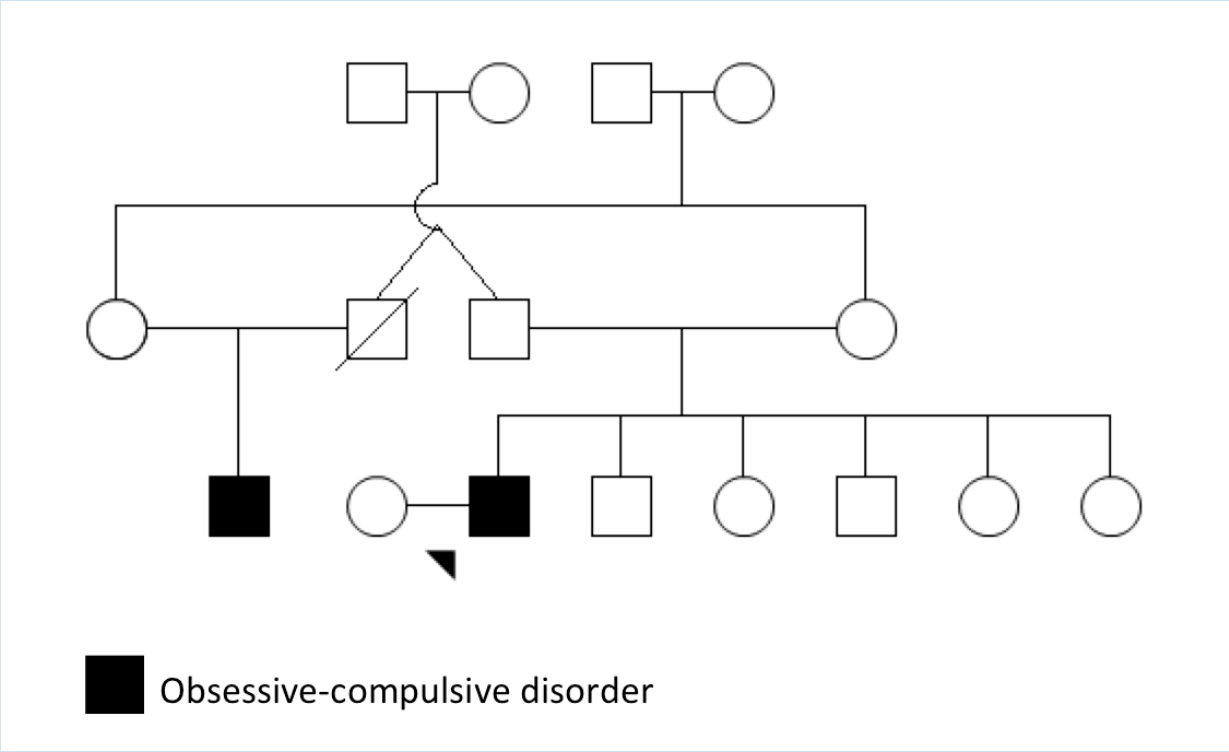
A family in Utah, with a 40 year old Caucasian man with
very severe obsessive compulsive disorder, severe depression and intermittent paranoia, with symptoms that started around age 5.

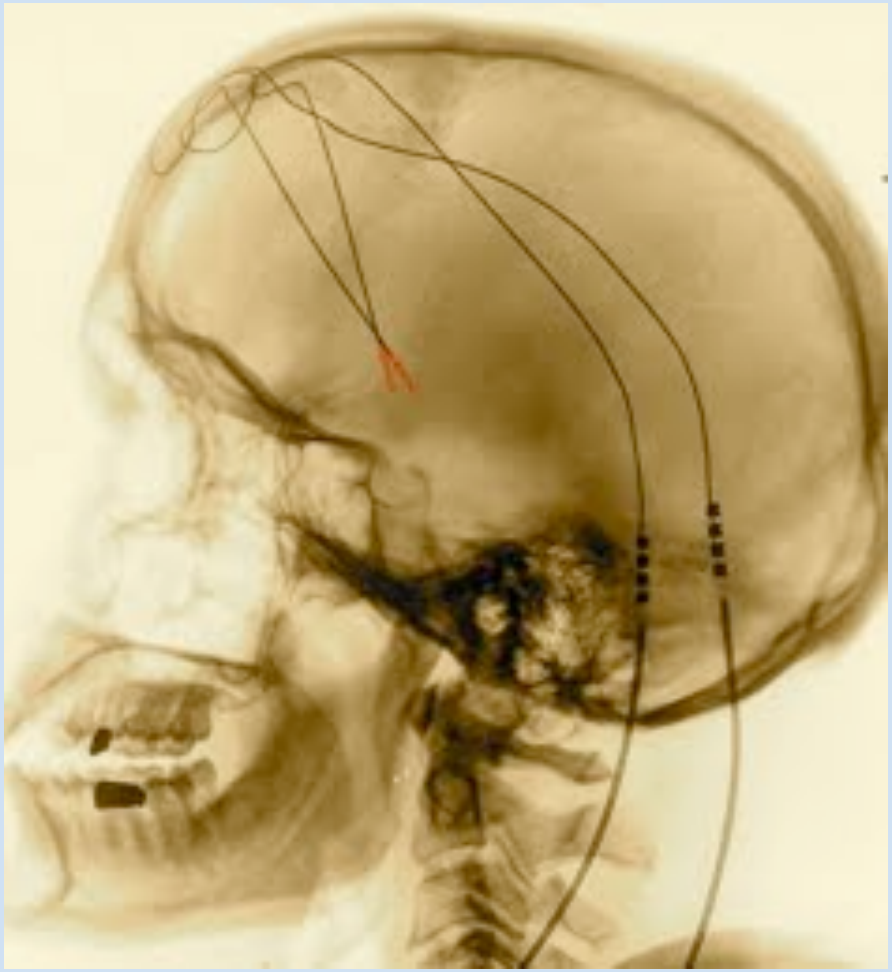
Some people had diagnosed him with bipolar and/or schizophrenia due to his mood states and possible paranoia.

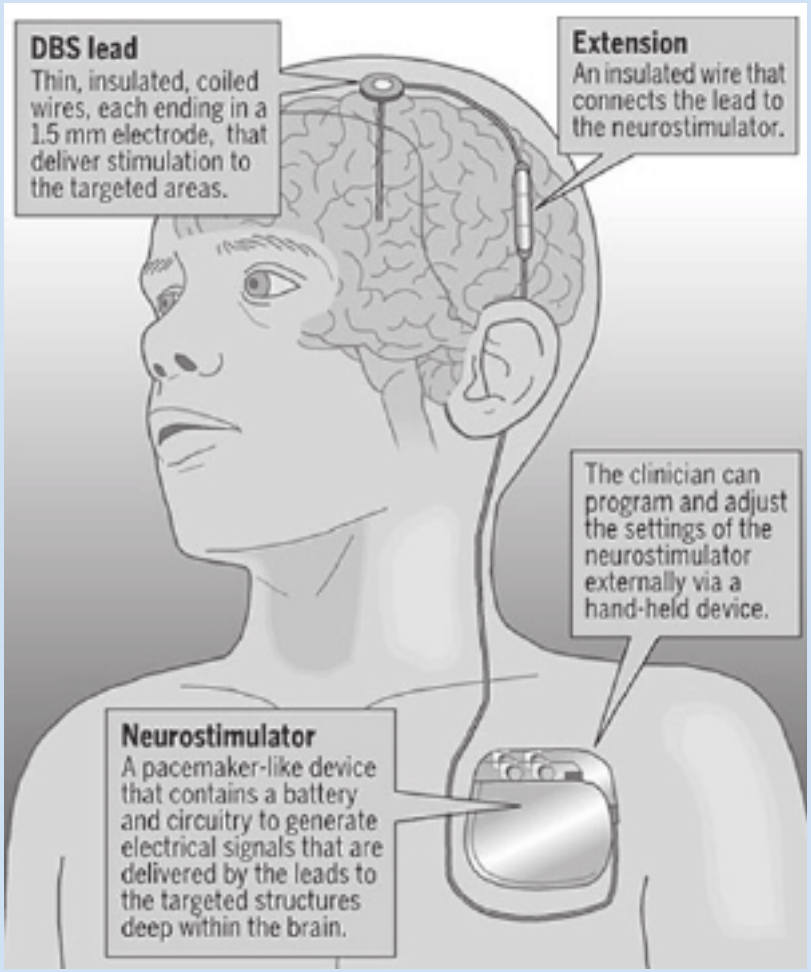
Multiple medication trials failed over many years. Considered treatment refractory.

Pedigree structure



Humanitarian Device Exemption (HDE) for OCD granted by FDA in 2009





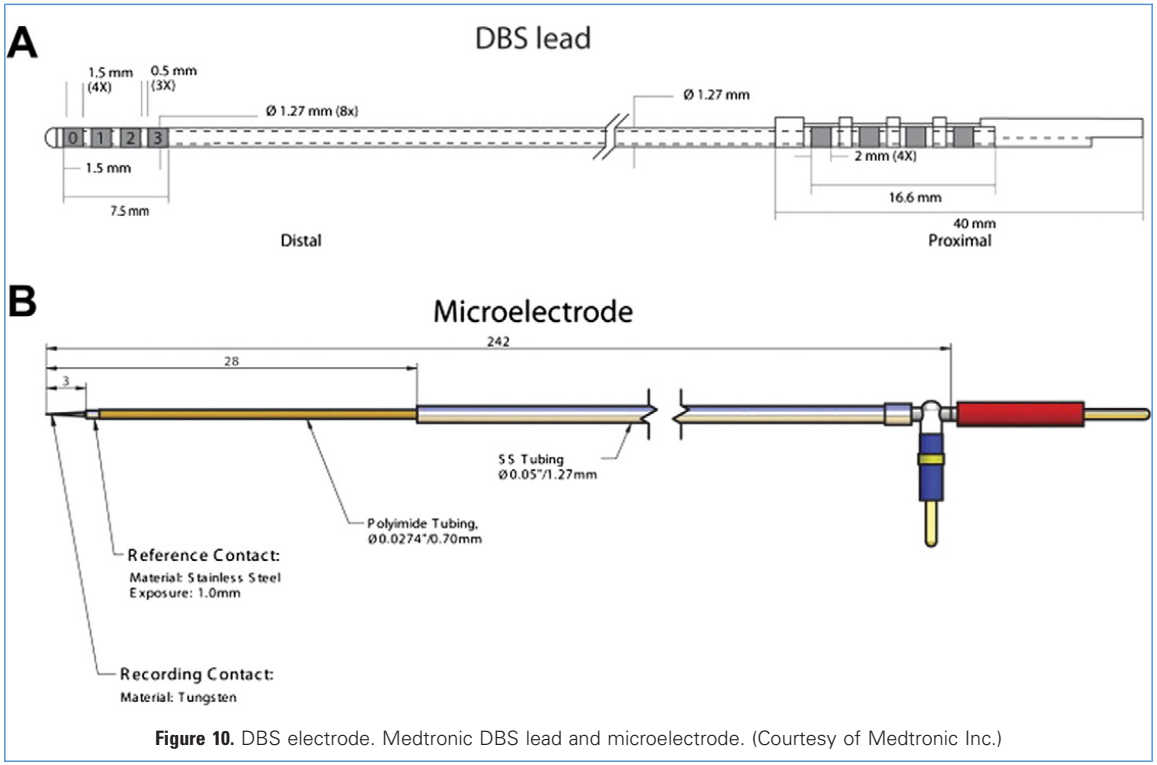
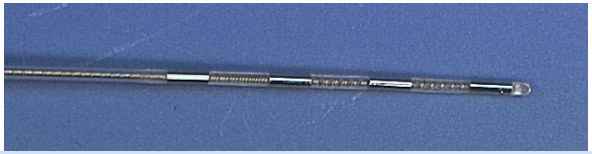


Figure 10. DBS electrode. Medtronic DBS lead and microelectrode. (Courtesy of Medtronic Inc.)

8840 N'Vision® Clinician Programmer

Electrode End

Indicated for OCD only



3391S

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

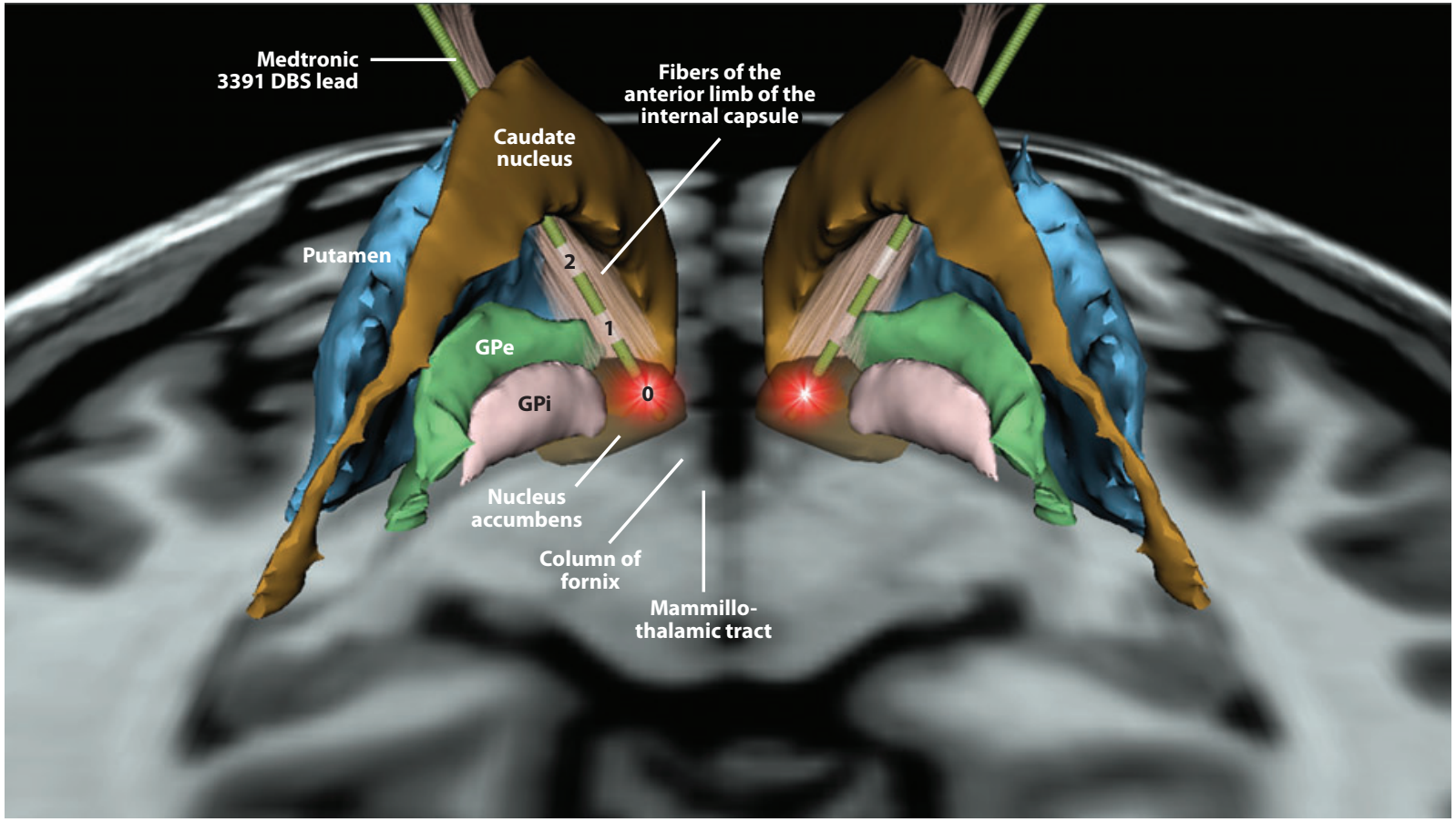


Figure 1

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).

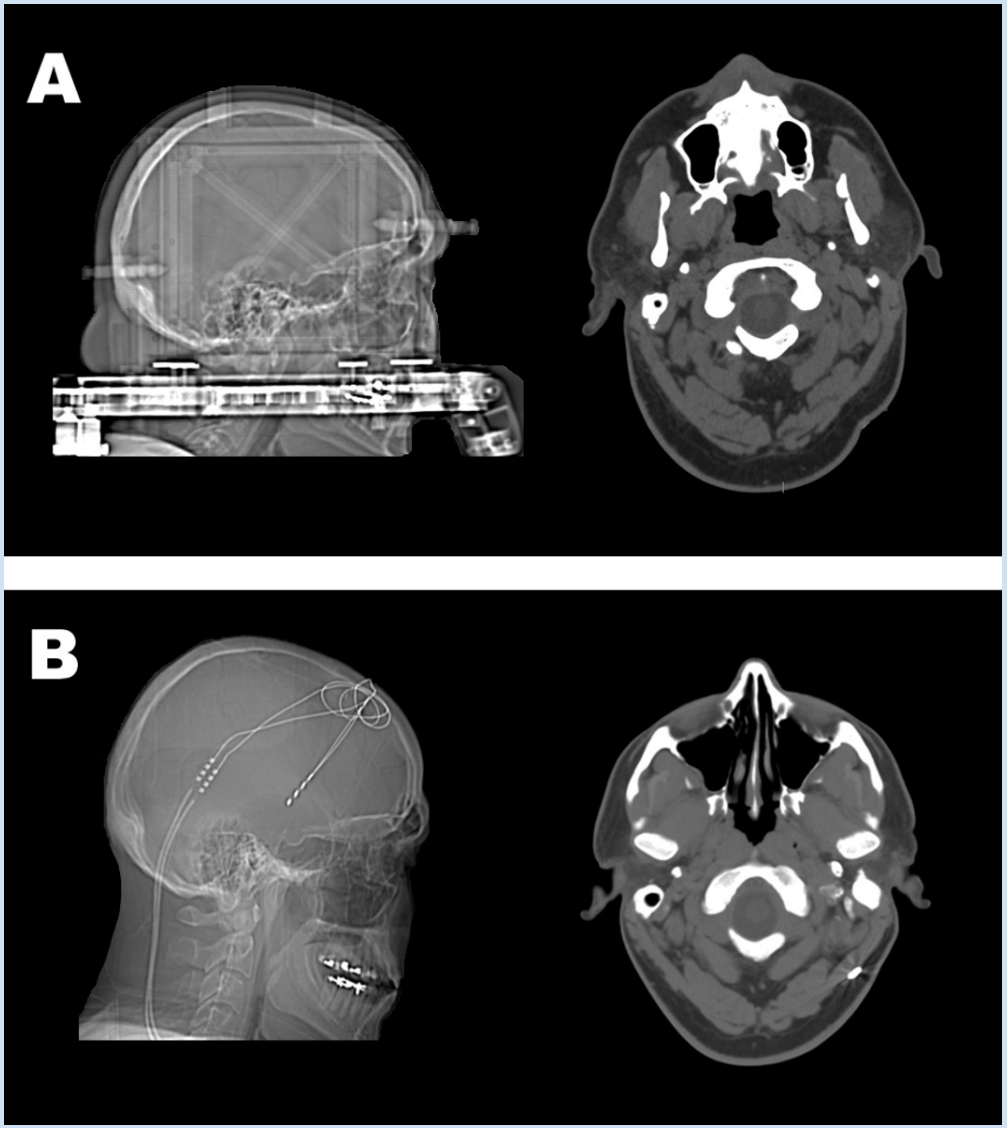
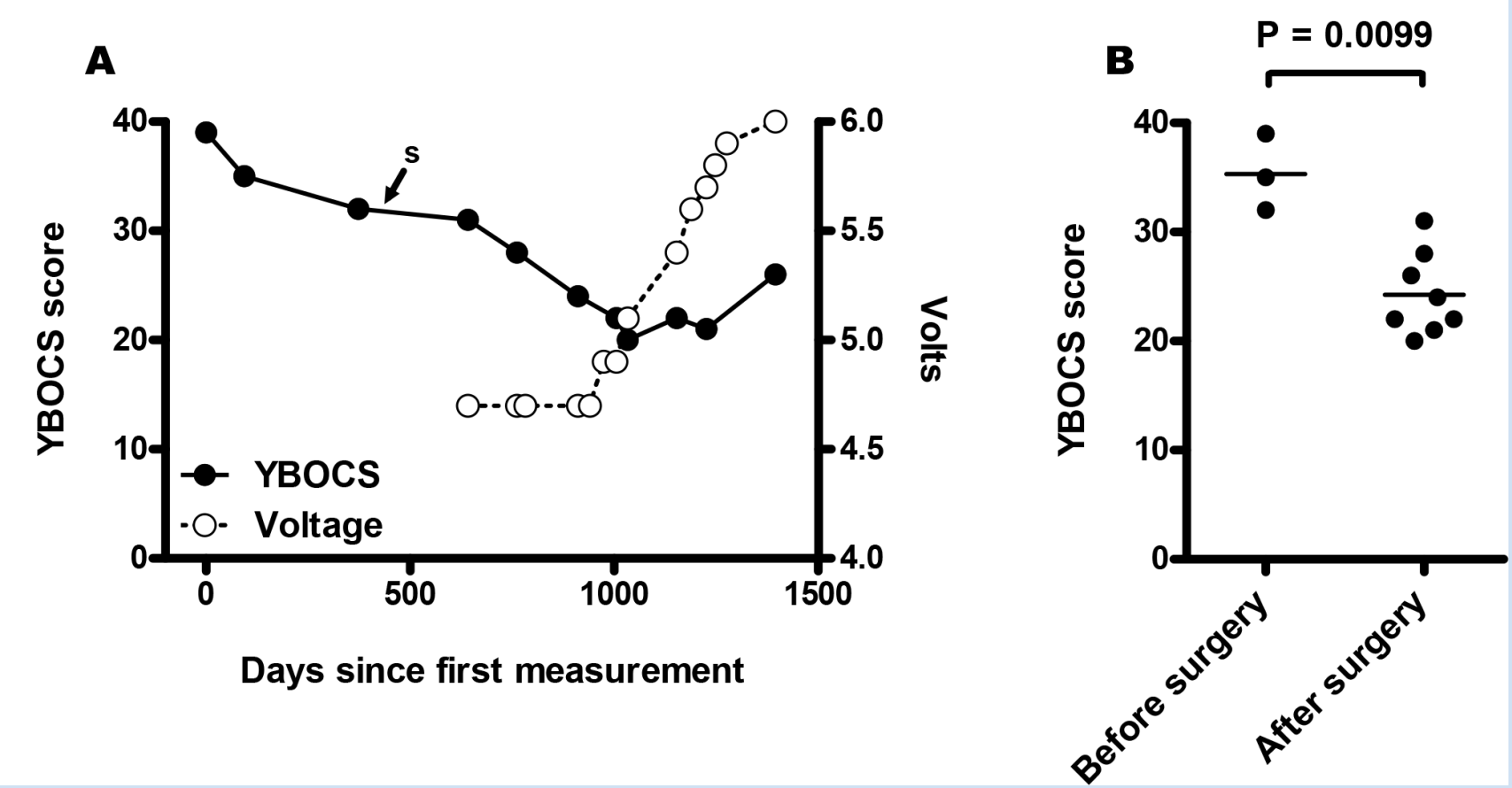


Figure 1 Sagittal and transverse computed tomography (CT) images of the brain and skull of MA. We show here sagittal and transverse sections taken from CT scans. Imaging was performed before (A) and after (B) MA received deep brain stimulation surgery for his treatment refractory OCD. Two deep brain 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.

Contents lists available at SciVerse ScienceDirect

Applied & Translational Genomics

journal homepage: www.elsevier.com/locate/atg

Practical, ethical and regulatory considerations for the evolving medical and research genomics landscape

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

Preanalytic system
1) Test request and specimen collection criteria
2) Specimen submission, handling and referral procedures
3) Preanalytic systems assessment
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

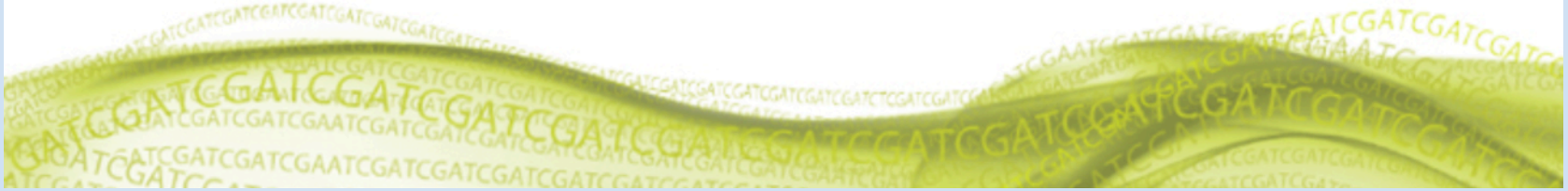
Individual Genome Sequencing Service

Available from Illumina's CLIA-certified laboratory.

"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.



illumina®

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.

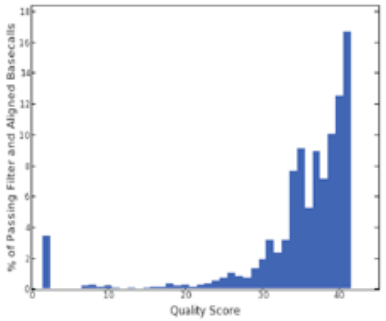
http://www.illumina.com/clinical/illumina_clinical_laboratory/igs_for_doctors/how_to_order.ilmn

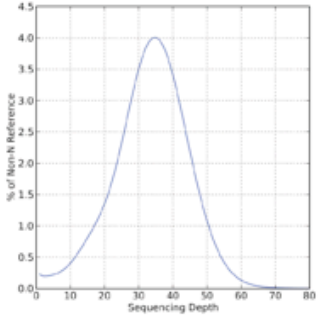
Sequencing and Analytics

Data Volume and Quality

	Yield (Gigabases)	% Bases ≥ Q30	% Bases Aligned
Passing Filter	113.10	87.10%	87.80%

	% Callable	% ≥ 5x depth	% ≥ 10x depth	% ≥ 20x depth	Mean depth(x)
Non-N Reference	93.28%	97.57%	96.22%	88.54%	33.35





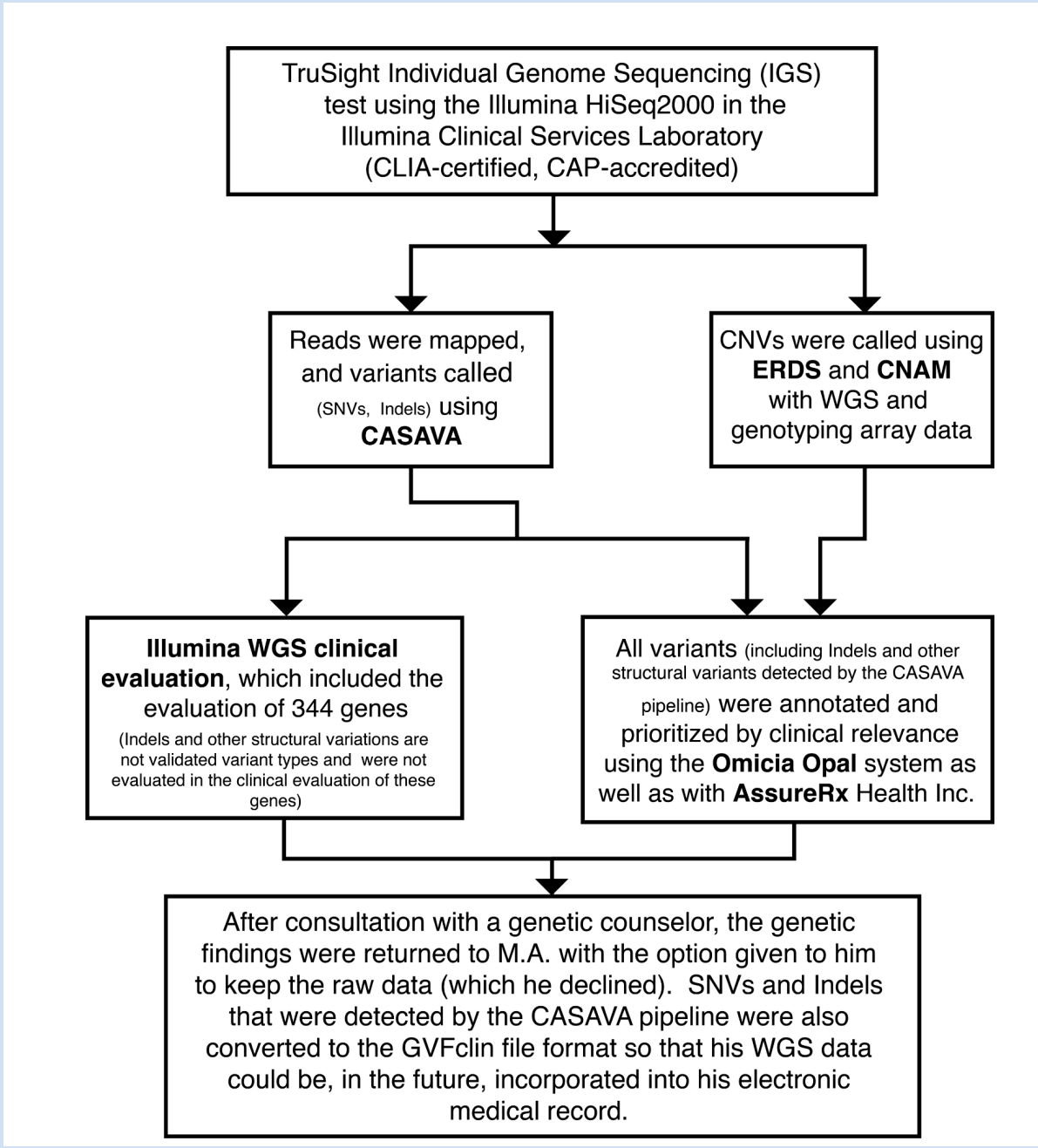
SNP Assessment

Total	Het/Hom	% in dbSNP	% in Genes	% in Coding
3,308,246	1.61	98.13%	45.47%	0.63%

Variant Statistics

	SNVs
Total Number	3,308,246
Number in Genes	1,504,121
Number in Coding Regions	20,879
Number in UTRs	24,946
Splice Site Region	2,917
Stop Gained	72
Stop Lost	16
Non-synonymous	9,884
Synonymous	10,907
Mature miRNA	36

From the Illumina Understand Your Genome Symposium October 2012


TruSight Individual Genome Sequencing (IGS) test using the Illumina HiSeq2000 in the Illumina Clinical Services Laboratory (CLIA-certified, CAP-accredited)
Reads were mapped, and variants called (SNVs, Indels) using **CASAVA**
CNVs were called using **ERDS** and **CNAM** with WGS and genotyping array data
Illumina WGS clinical evaluation, which included the evaluation of 344 genes (Indels and other structural variations are not validated variant types and were not evaluated in the clinical evaluation of these genes)
All variants (including Indels and other structural variants detected by the CASAVA pipeline) were annotated and prioritized by clinical relevance using the **Omicia Opal** system as well as with **AssureRx** Health Inc.
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.

Category		Number of Variants	Condition
Clinically Significant in Patient	Pathogenic	0	
	Likely Pathogenic	0	
Carrier Status for Patient	Pathogenic	0	
	Likely Pathogenic	1	Refsum Disease
Variants of Unknown Significance		284	
Likely Benign Variants		349	
Benign Variants		613	

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

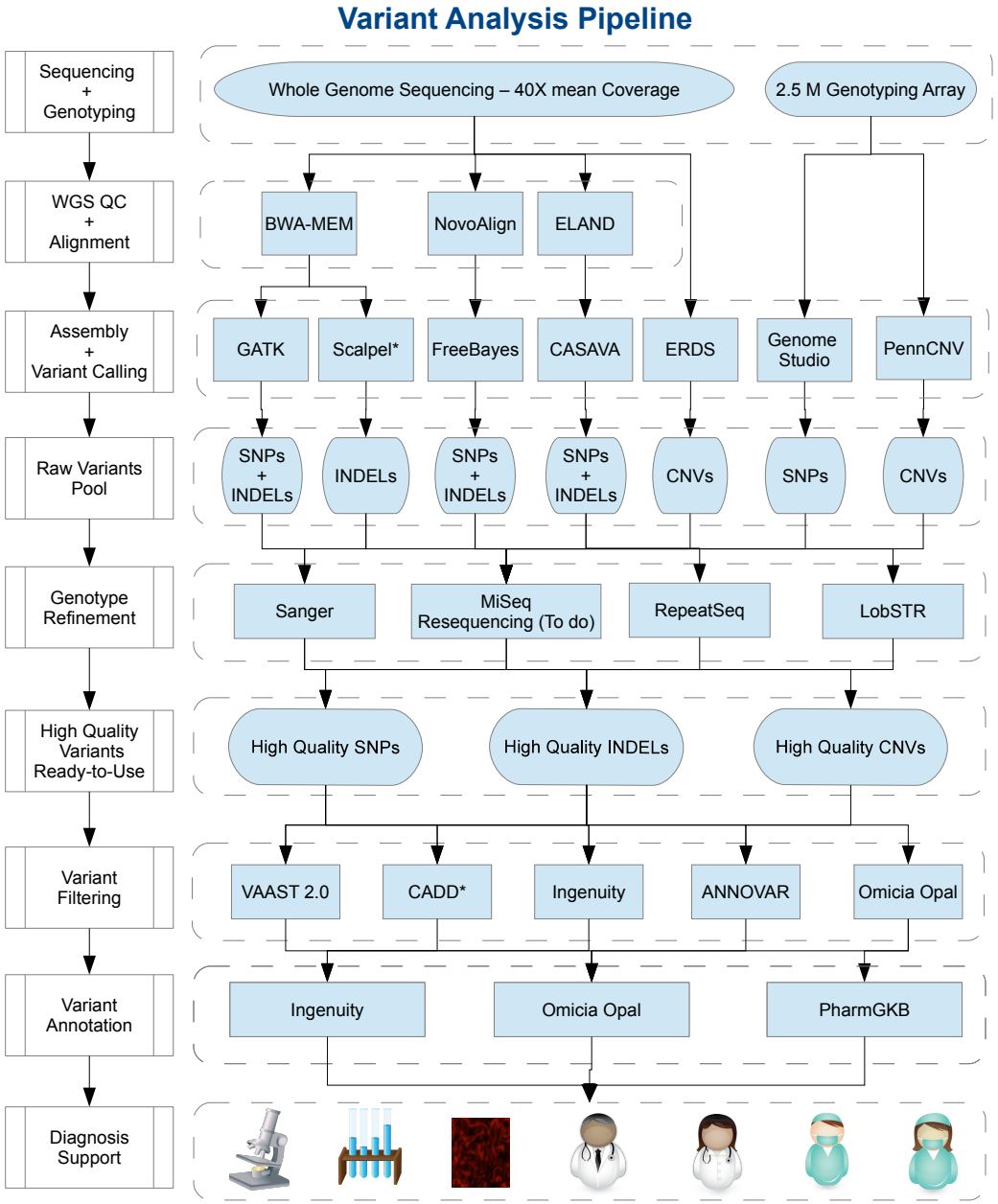
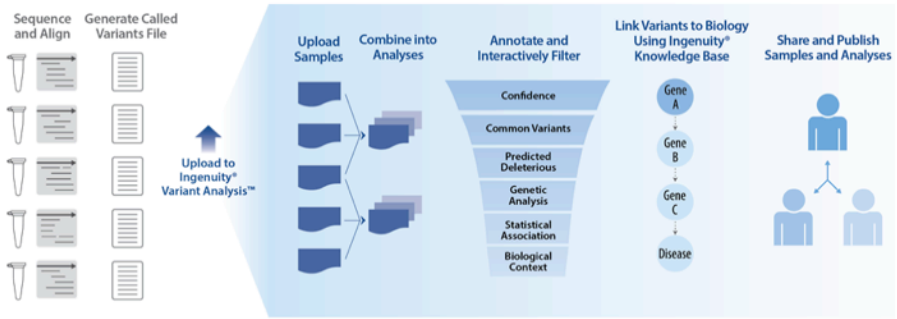


Figure 2. Flow chart of our variant analysis pipeline.
* Both Scalpel and CADD are still inpress. For CADD, see http://cadd.gs.washington.edu/

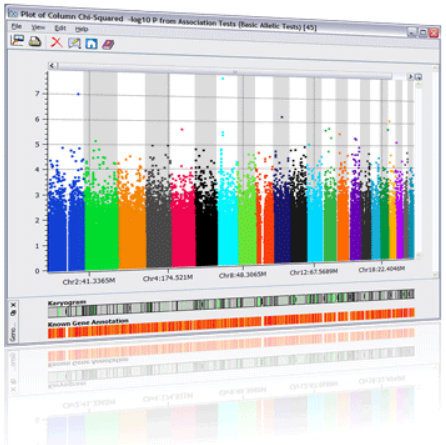
Some genomic analysis online platforms and analysis suites

Identify causal variants from human sequencing data in just hours



BIOLOGICAL INTERPRETATION OF HUMAN WHOLE GENOME, EXOME, AND TARGETED PANEL SAMPLES

Golden Helix Product Offerings

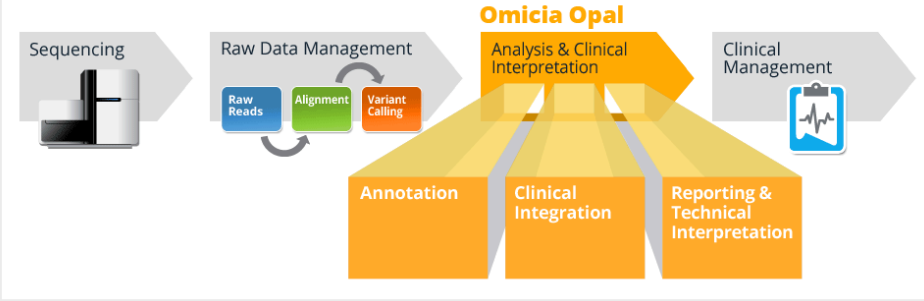


SNP & VARIATION SUITE 7

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.

Opal adds clinical context for genomic data

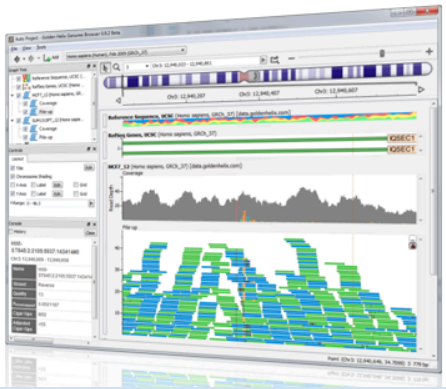
Omicia is unlocking individualized medicine by translating data derived from whole-genome sequencing into actionable information for researchers and clinicians.



Golden Helix GenomeBrowse™

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

Variant Class	Gene	Position dbSNP	Change	Zygosity Effect	Quality Coverage	Frequency	Omicia Score	Polyphen Mut-Taster	SIFT PhyloP	Evidence
VUS (dg)	FCGR3A	chr1 161518333 rs10127939	A→A,C c.197T>G p.Leu66Arg	het non-synon	339.77 63:42:21	A:96% C:4%	0.109	damaging damaging	0.09 0.14	CV HGMD LSDB
VUS (dg)	AGT	chr1 230845794 rs699	A→G,G c.803T>C p.Met268Thr	hom non-synon	829.77 34:0:34	A:34% G:66%	0.086	benign benign	0.68 0.06	CV HGMD PGKB
VUS (other)	SLC22A1	chr6 160560881 rs35167514	ATG→-,ATG c.1258_1260del p.Ser420del	het nonframeshift deletion	693.76 30:15:15	-	0.424	- -	- 0.97	PGKB
VUS (other)	OR52B4	chr11 4389405 rs80193749	G→-,G c.121_121del p.Ser41del	het frameshift deletion	536.76 39:21:18	-	0.133	- -	- -0.77	HGMD
VUS (other)	CHRFAM7A	chr15 30665281	CA→-,CA c.227_228del p.Ser76del	het frameshift deletion	422.76 51:39:12	-	0.321	- -	- 0.88	HGMD
Known Pathogenic	XYLT1	chr16 17564311 rs61758388	C→A,C c.343G>T p.Ala115Ser	het non-synon	135.77 20:11:9	C:99% A:1%	0.187	benign benign	0.41 0.78	CV OMIM HGMD
VUS (other)	P2RX5	chr17 3594277 rs5818907	G→-,- c.333_333del p.Ser111del	hom frameshift deletion	1114.76 33:0:33	-	0.247	- -	- -0.54	HGMD
VUS (dg)	MAPT	chr17 44067382 rs112757188	T→C,C c.1321T>C p.Tyr441His	hom non-synon	531.77 17:0:17	T:68% C:32%	0.266	- -	0.26 0.43	LSDB
VUS (other)	C17orf57	chr17 45360730 rs5918	T→C,T c.176T>C p.Leu59Pro	het non-synon	588.77 48:23:25	T:91% C:9%	0.089	benign benign	0.43 -3.9	CV HGMD PGKB LSDB
VUS (other)	SLC14A2	chr18 43262359 rs3745009	G→A,A c.2638G>A p.Ala880Thr	hom non-synon	642.77 21:0:21	G:60% A:40%	0.546	benign benign	0.38 2.12	HGMD PGKB LSDB
VUS (dg)	TYK2	chr19 10463118 rs34536443	G→C,G c.3310C>G p.Pro1104Ala	het non-synon	435.77 45:23:22	G:99% C:1%	0.816	damaging damaging	- 3.89	HGMD
VUS (dg)	PRNP	chr20 4680251 rs1799990	A→G,G c.385A>G p.Met129Val	hom non-synon	742.77 37:0:37	A:74% G:26%	0.302	damaging benign	0.02 0.66	CV OMIM HGMD PGKB GWAS

Viral infections, recurrent, susceptibility to

Condition: Hypertension, essential, susceptibility to

Description: Reduced metformin uptake in transfected cells

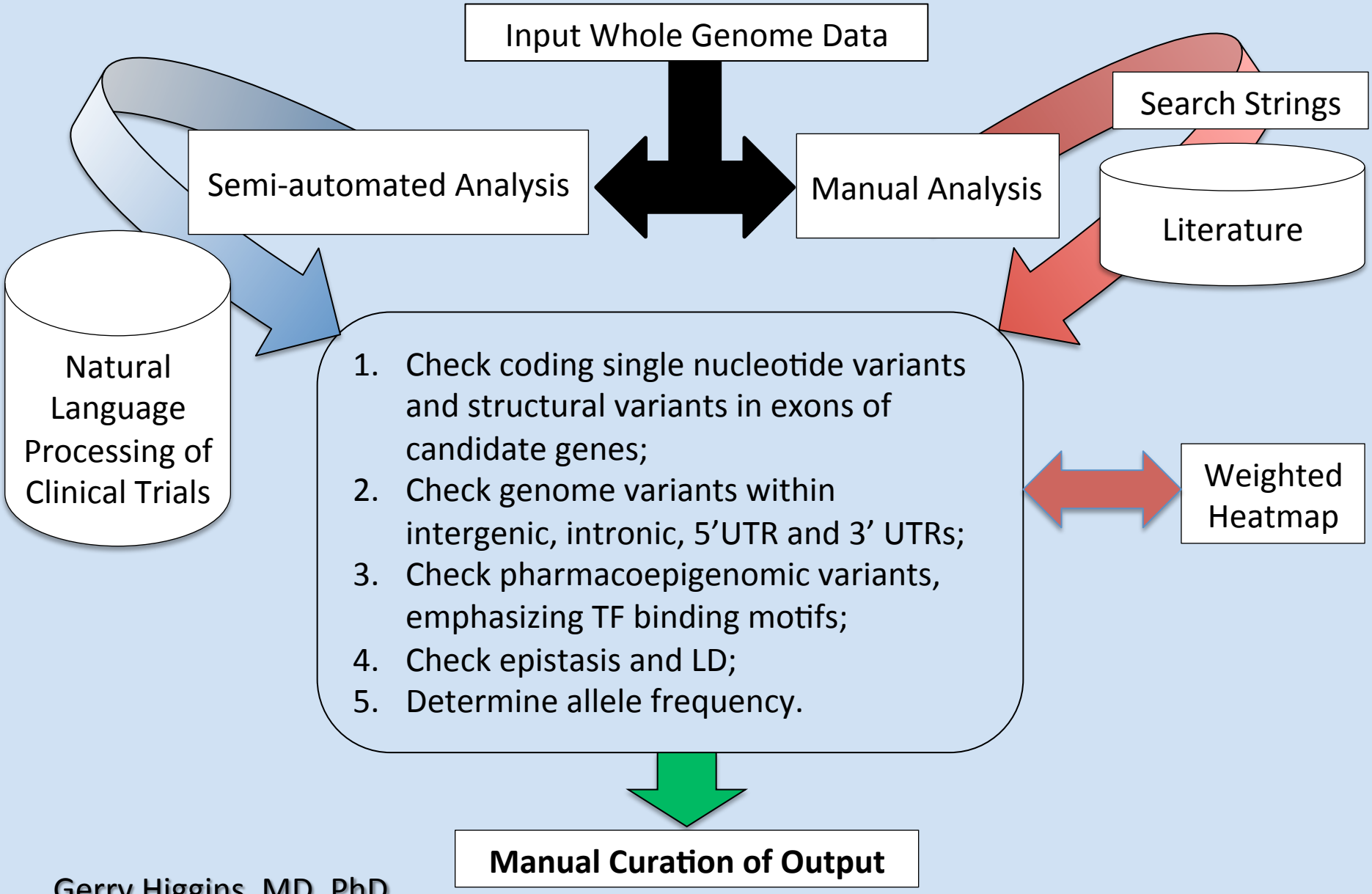
Pseudoxanthoma elasticum

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

Assurex / Mayo Clinic Pharmacogenomics Pipeline



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.

Gene name	Genomic coordinates	Amino acid change	Zygosity	Variation type	Population frequency	Clinical significance
MTHFR	chr1: 11854476	Glu > Ala	heterozygous	non-synon	T:77% G:23%	Susceptibility to psychoses, schizophrenia occlusive vascular disease, neural tube defects, colon cancer, acute leukemia, and methylenetetra-hydrofolate reductase deficiency
BDNF	chr11: 27679916	Val > Met	heterozygous	non-synon	C:77% T:23%	Susceptibility to OCD, psychosis, and diminished response to exposure therapy
CHAT	chr10: 50824117	Asp > Asn	heterozygous	non-synon	G:85% A:15%	Susceptibility to schizophrenia and other psy-chopathological disorders.

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)

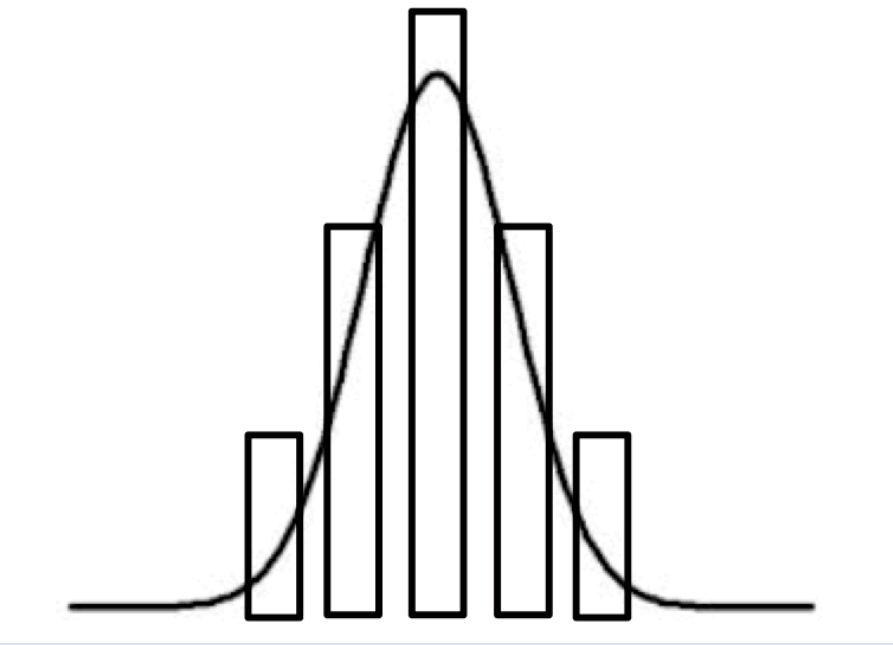


Table 3 Description of the 22 genome-wide significant loci in the combined analysis

Chromosomal region	*P* value	Previous association[a]	Candidate gene in relation to index SNP[b]	Other genes in genomic region defined by LD[c]	eQTL[d]	Disease associations[e]
Chr. 6: 31,596,138–32,813,768	9.14×10^{-14}	SCZ	*HLA-DRB9*	MHC class II, many other genes, lincRNA	Many	Many
Chr. 10: 104,487,871–105,245,420	3.68×10^{-13}	SCZ	*C10orf32-AS3MT*	*CALHM1*, *CALHM2*, *CALHM3*, *CNNM2*, *CYP17A1*, *INA*, *MIR1307*, *NT5C2*, *PCGF6*, *PDCD11*, *SFXN2*, *ST13P13*, *TAF5*, *USMG5*, *WBP1L*	*ACTR1A*, *ARL3*, *AS3MT*, *C10orf32*, *C10orf78*, *NT5C2*, *TMEM180*, *TRIM8*, *WBP1L*	GWAS: blood pressure, CAD, aneurysm
Chr. 7: 1,827,717–2,346,115	5.93×10^{-13}	No	*MAD1L1*	*FTSJ2*, *NUDT1*, *SNX8*	*C7orf27*, *FTSJ2*, *MAD1L1*, *NUDT1*	
Chr. 1: 98,141,112–98,664,991	1.72×10^{-12}	SCZ	(*MIR137*, 37 kb)	*DPYD*, lincRNA	***DPYD***	*DPYD*: mental retardation
Chr. 12: 2,285,731–2,440,464	5.22×10^{-12}	SCZ, BPD	*CACNA1C*	–	No data	*CACNA1C*: autism, Timothy syndrome, Brugada syndrome 3
Chr. 10: 18,601,928–18,934,390	1.27×10^{-10}	5 disorders	*CACNB2*	*NSUN6*	No data	*CACNB2*: Brugada syndrome 4; GWAS: blood pressure
Chr. 8: 143,297,312–143,410,423	2.19×10^{-10}	No	*TSNARE1*	–	No data	
Chr. 1: 73,275,828–74,099,273	3.64×10^{-10}	No	(x10NST00000415686.1, 4 kb)	lincRNA	No data	
Chr. 11: 130,706,918–130,894,976	1.83×10^{-9}	No	(*SNX19*, 31 kb)	lincRNA	***SNX19***	
Chr. 5: 151,888,959–152,835,304	2.65×10^{-9}	No	ENST00000503048.1	lincRNA (*GRIA1*)	No data	
Chr. 5: 152,505,453–152,707,306	4.12×10^{-8}	No				
Chr. 19: 19,354,937–19,744,079	3.44×10^{-9}	BPD	(*MAU2*, 4 kb)	*CILP2*, *GATAD2A*, *GMIP*, *HAPLN4*, *LPAR2*, *MIR640*, *NCAN*, *NDUFA13*, *PBX4*, *SUGP1*, *TM6SF2*, *TSSK6*, *YJEFN3*	No data	GWAS: lipid levels

[a]Regions reported to meet genome-wide significance thresholds of association for schizophrenia (SCZ) or bipolar disorder (BPD). [b]The gene within which an index SNP is located is given. For intergenic index SNPs, the nearest gene is given in parentheses. [c]Other named genes in the genomic interval. [d]SNP-transcript associations with $q < 0.05$ in peripheral blood. eQTLs with the SNP with the strongest association are shown in bold. [e]Data from the NHGRI GWAS catalog[24], OMIM[43] and a compilation of genes related to autism[73] and mental retardation[43,74,75]. 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 affected[30]. 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

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	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	*SLCO6A1*	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*, *TNNC1*, *TWF2*, *WDR82*, lincRNA	No data (*ITIH1-ITIH3-ITIH4*)	*GLYCTK*: D-glyceric aciduria, mental retardation; *RTF1*: mental retardation; GWAS: adiponectin, height, waist-hip ratio
	Chr. 2: 145,139,727–145,214,607	1.19×10^{-8}	No	*ZEB2*	–	No eQTL	*ZEB2*: Mowat-Wilson syndrome, mental retardation
	Chr. 2: 200,628,118–201,293,421	1.21×10^{-8}	No	*FONG*	*C2orf47*, *C2orf69*, *SPATS2L*, *TYW5*, lincRNA	No data	GWAS: osteoporosis
	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*		***SDCCAG8***	
	Chr. 12: 123,447,928–123,913,433	2.28×10^{-8}	No	*C12orf65*	*ABCB9*, *ARL6IP4*, *CDK2AP1*, *MIR4304*, *MPHOSPH9*, *OGFOD2*, *PITPNM2*, *RILPL2*, *SBNO1*, *SETD8*, lincRNA	*ARL6IP4*, *CDK2AP1*, *OGFOD2*, *SBNO1*	*C12orf65*: mental retardation; GWAS: HDL, height, head size
	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

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Disruptive developments

Prevention efforts, genomics-guided

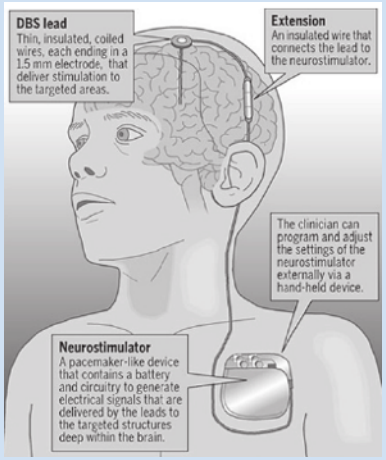
PatientsLikeMe

23andMe

ancestry.com

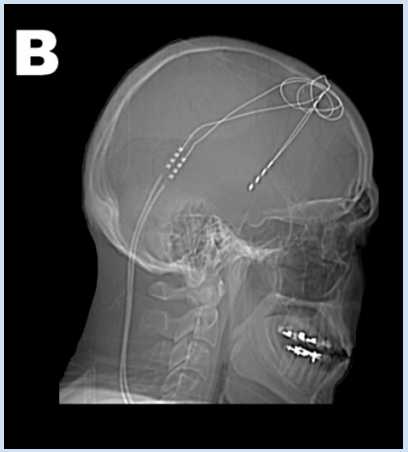
Google

More direct action on the brain itself



Medtronic

When Life Depends on Medical Technology



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".