

# Whole genome sequencing, clinical interpretation, and deep brain stimulation in a severely mentally ill person

INSTITUTE FOR GENOMIC MEDICINE **BIOMEDICAL** RESEARCH Your genome, your medicine.

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### **Background**

There is a rich literature in clinical psychology, psychiatry and neurology of single patient studies. Until now, however, such studies have focused on the parallel areas of clinical neuropsychiatry, personal genomics and brain-machine interfaces.

#### Methods

Detailed phenotyping and clinical evaluations were conducted over a four-year period for a single United States Veteran male with severe mental illness. His genome was sequenced in the Illumina Whole Genome Sequencing Clinical Laboratory Improvement Amendments (CLIA)certified laboratory. This person was implanted with the Medtronic Reclaim® Deep Brain Stimulation

DBS) Therapy device for Obsessive Compulsive Disorder (OCD). Programming of the device and psychiatric assessments occurred in an outpatient setting for over two years.

### Results

We report here the detailed phenotypic characterization, clinical-grade whole genome sequencing (WGS), and two year outcome of a man with severe obsessive compulsive disorder treated with deep brain stimulation (DBS) targeting the nucleus accumbens / anterior limb of the internal capsule (ALIC). Since implantation, this man has reported steady improvement, highlighted by a steady decline in his Yale-Brown Obsessive Compulsive Scale (YBOCS) score from ~38 to a score of ~25. A rechargeable Activa RC neurostimulator battery has been of major benefit in terms of facilitating a degree of stability and control over the stimulation. His psychiatric symptoms reliably worsen within

hours of the battery becoming depleted, thus providing confirmatory evidence for the efficacy of DBS for OCD in this person. Whole genome sequencing revealed that he is a heterozygote for the p.Val66Met variant in BDNF, encoding a member of the nerve growth factor family, and which has been found to predispose carriers to various psychiatric illnesses. He carries the p.Glu429Ala allele in methylenetetrahydrofolate reductase (MTHFR) and the p.Asp7Asn allele in ChAT, encoding choline O-acetyltransferase, with both alleles having been shown to confer an elevated susceptibility to psychoses. We have found thousands of other variants in his genome, including pharmacogenetic variants, and have archived and offered the clinical sequencing data to him, so that he and others can re-analyze his genome for years to come. As this individual is a U.S. Veteran, we are working with the VA to incorporate his genomic data into the electronic medical record, VistA, which is of relevance to the One Million Veteran Program.

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	
Non-N Reference  18- 14- 19- 10- 8- 4- 4- 2- 10- 8- 10- 8- 10- 8- 10- 10- 10- 10- 10- 10- 10- 10- 10- 10	93.28%	97.57%	96.22%  - 4.5 - 4.0 - 3.5 - 3.0 - Non-N Reference - 2.0 - 1.5 - 1.0	88.54%	33.35	
\$ 2 0 10	20	30 40	0.5		50 60 70 80	
	Quality Score			Sequencing De	epth	

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

## **Variant Statistics**

CVIVA

3,308,246
1,504,121
20,879
24,946
2,917
72
16
9,884
10,907
36

Gene Symbol ()					ै Reset F	incers Prior	nage Filters	₩ Relat	ion Miner	O Export	Report   Report Versions
Omicia Category ()	Overview Genome: PG0 Current Versio Pipeline Versio	n:	me.block.anno.vcf.g	z							
Aging Cardiovascular Drugs and Pharmacology	Gene	Position dbSNP	Change	Zygosity	Effect	Quality Coverage	Frequency	Omicia Score	Polyphen Mut-Taster	SIFT	Evidence
Endocrinological and Metabolic Gastrointestinal Blood and Lymphatic	NQO1	chr16 69745145 rs1800566	G→A,A c.559C>T p.Pro187Ser	hom	non-synon	458 33:0:33	G:72% A:28%	0.836	damaging benign	0.11 5.86	OMM HGMD PGKB
Immune and Joints Infectious Disease Kidney and Urinary Tract	DPYD	chr1 98348885 rs1801265	G→A,A c.85C>T p.Arg29Cys	hom	non-synon	317 20:0:20	G:23% A:77%	0.708	:	0.18 2.55	HGMD PGKB
Neonatal Neurological Nutrition Cancer	ABCA1	chr9 107562804 rs2230808	T→C,C c.4760A>G p.Lys1587Arg	hom	non-synon	536 38:0:38	T:41% C:59%	0.7	benign benign	1 4.87	НСМО
Other Psychiatric Respiratory	NAT2	chr8 18258103 rs1799930	G→A,G c.590G>A p.Arg197Gln	het	non-synon	220 37:16:21	G:76% A:24%	0.653	damaging benign	0.08 3.11	OMM HGMD PGKB
Sight Hearing, Smell and Taste	ABCA1	chr9 107589255 rs2066718	C→C,T c.2311G>A p.Val771Met	het	non-synon	195 40:19:21	C:94% T:6%	0.562	benign damaging	1.4	номо
Drug Set ()	CYP4F2	chr19 15990431 rs2108622	C→C,T c.1297G>A p.Val433Met	het	non-synon	183 30:12:18	C:78% T:22%	0.473	damaging benign	0.01 2.31	HGMD PGKB GWAS
Pathway Set (I)	NAT2	chr8 18257854 rs1801280	T→C,T c.341T>C p.lle114Thr	het	non-synon	191 39:20:19	T:70% C:30%	0.467	benign benign	0.08 0.74	OMM HGMD PGKB
My Set (I)  Exclude Set (I)	DPYD	chr1 97981395 rs1801159	T→C,T c.1627A>G p.Ile543Val	het	non-synon	153 24:11:13	T:80% C:20%	0.295	benign benign	1 0.86	HGMD PGKB
Chromosome (I)	OGG1	chr3 9798773 rs1052133	C→C,G c.294C>G p.Ile98Met	het	non-synon	146 30:16:14	C:70% G:30%	0.258	:	0.01 -0.25	намо
Require 0	OGG1	chr3 9798773 rs1052133	C→C,G c.994C>G p.Pro332Ala	het	non-synon	146 30:16:14	C:70% G:30%	0.258	-	0.01 -0.25	намо
Genotype  Heterozygous  Homozygous	OGG1	chr3 9798773 rs1052133	C→C,G c.977C>G p.Ser326Cys	het	non-synon	146 30:16:14	C:70% G:30%	0.258	-	0.01 -0.25	HGMD
Protein Impact  ✓ All  ✓ Stop Gained/Lost	CYP2C9	chr10 96741053 rs1057910	A→C,C c.1076A>C p.lle359Leu	hom	non-synon	496 36:0:36	A:96% C:4%	0.189	benign damaging	0.11	OMM HGMD PGKB
Indel/Frameshift Splice Site Non-synonymous	ABCA1	chr9 107620867 rs2230806	C→C,T c.656G>A p.Arg219Lys	het	non-synon	131 30:18:12	C:58% T:42%	0.187	benign benign	0.32 0.16	OMM HGMD PGKB
Supporting Evidence Any OMIM	CYP2B6	chr19 41515263 rs28399497	A→A,G c.785A>G p.Lys262Arg	het	non-synon	54 17:8:9	-	0.178	benign benign	1 0.84	номо
Gene Models  CCDS  RefSeq	NBN	chr8 90990479 rs1805794	C→C,G c.553G>C p.Glu185Gln	het	non-synon	193 30:12:18	C:67% G:33%	0.172	benign benign	1 0.5	HGMD
Polyphen Prediction Probably Damaging Possibly Damaging	CYP4F12	chr19 15789140 rs609290	A→G,G c.267+1A>G	hom	splice site	578 44:0:44	A:6% G:94%	0.172	-	-0.6	HGMD
Exclude ()	CYP3A7	chr7 99306685 rs2257401	C→G,G c.1226G>C p.Arg409Thr	hom	non-synon	331 22:0:22	C:27% G:73%	0.163	benign benign	0.16 0.35	PGKB
Sort By   Position Gene Symbol	CYP4F12	chr19 15789140 rs609290	A→G,G c.269A>G p.lle90Val	hom	non-synon	578 44:0:44	A:6% G:94%	0.126	- benign	0.7 -0.6	номо
Omicia Score Effect	CETP 100 \$	chr16	G→A,G	het	non-synon	203	G:45%	0.088	benign	1	HGMD PGKB

Figure 1. Variant prioritization was performed on all variants discovered by the Illumina CLIA WGS pipeline using the Omicia Opal platform. Variants were imported into the Omicia Opal cloud based clinical annotation and variant prioritization platform, and subsequently prioritized by requiring each variant to have prior evidence in OMIM and by additionally requiring each variant to be scored as having an Omicia Score of greater than 0.7.

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Gene name	Genomic coordinates	Amino acid change	Zygosity	Mutation 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 psychopathological disorders.

Table 1. A summary of three clinically relevant alleles found in the sequencing results of M.A. Mutations 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 M.A. A brief summary of the characteristics of each mutation is shown, including the gene name, genomic coordinates, amino acid change, zygosity, mutation type, estimated population frequency and putative clinical significance. Out of 91 other people in Utah genotyped on Illumina 2.5M arrays, only 2 of them carried all three of these variants, which is consistent with the noted minor allele frequencies on these 3 separate autosomes.

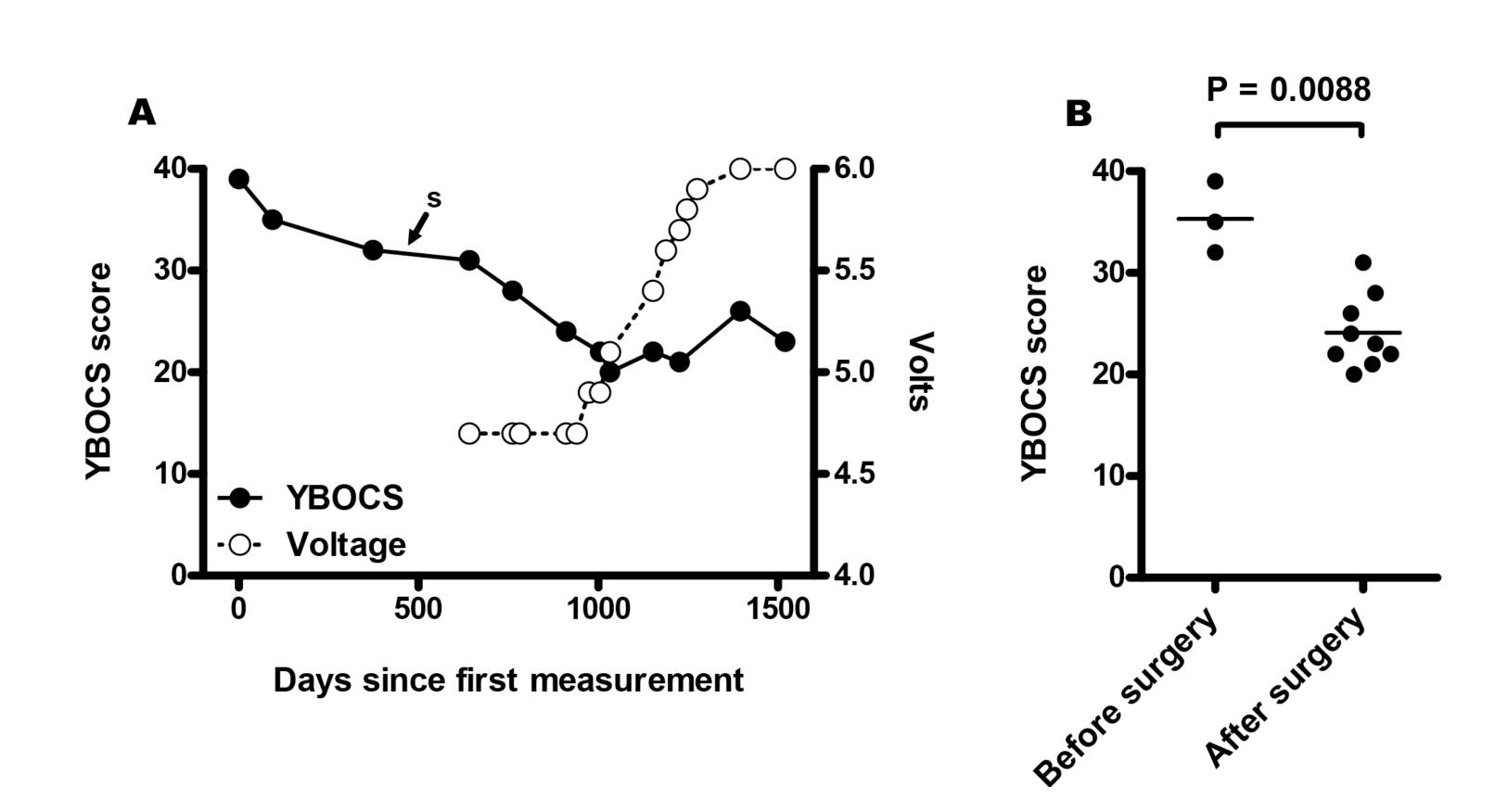


Figure 2. Yale Brown Obsessive Compulsive Scale (YBOCS) scores were measured for M.A over a three year and seven months period of time. A time series plot (A) shows a steady decline in YBOCS scores over the period of time spanning his DBS surgery (s) and treatment. Incremental adjustments to neurostimulator 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.

## **Conclusions**

To our knowledge, this is the first study in the clinical clinical-grade management and return of genetic results for a person with severe mental illness and 2) detailed neuropsychiatric phenotyping and individualized treatment with deep brain stimulation for his OCD. His WGS results and positive outcome with DBS for OCD is one example of individualized medicine in neuropsychiatry, including genomics-guided preventive efforts and brain-implantable devices. This is also an example of the split model for clinical genomics involving separate clinicalgrade processes for sample collection, sequencing, analysis, and clinical interpretation. This serves as a model for the One Million Veteran Program, as this is the first genome sequenced and data returned for a U.S. Veteran, to our knowledge.