

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

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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

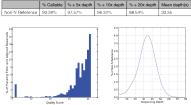
(DBS) Therapy device for Obsessive Compulsive Disorder (OCD). Programming of the device and psychiatric assessments occurred in an outpatient setting for over two years.

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. ValfoMet 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.





SNP Assessment									
Total	Het/Hom	% in dbSNP	% in Genes	% in Coding					
2.220.240	1.01	00.120	45 47W	A con-					

Variant Statistics

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

 Gene Symbol 0 	Variant Min	er			4 Report Fil	ters He	nace Filters	O Rolet	on Hiner	O Deport	Report O Report Versions
р.	Overview Genome: PG	0000644-EK.D genor	ne. block anna vot g								
O Omicia Category ()	Current Versi Pipeline Vers	ion: 0.0									
Cardiovascular Drugs and Pharmacology	Gene	Fosition 66NP	Change	Zygosty	Effect	Quality Coverage	Prequency	Onicia Score	Polyphen Mrt-Taster		Evidence
Endocrinalogical and Metabalic Gastrointectinal Blood and Lymphatic	MODI	6916 8916166 rs1500566	G-AA c.569C-T p.Pro1875er	hom	non-synon	32.0.33	0.72% A:28%	0.836	benign	0.11 5.06	MAN MAN PARK
Immuse and Joints Infectious Disease Ridney and Urinary Tract	DEVD	98348886 rs1901265	G-AA e.86C+F p.Arg29Cys	hom	non-synon	300.00	G:23% A:77%	0.708		2.55	1000 FOR
Neurological Nutrition Cancer	ABON	099 107903804 192230808	10.0 c.4760ArG p.Lys1587Arg	hom	non-synon	535 38 0 38	T-81% C-88%		benign benign	de	MAN .
Other Psychiatric Reservatory	1072	0000000 10000100 151799900	G-A,G c.590G+A p.Arg197GH	hel	non-syron	220 37.16(21	C768 A268	0.663	denaging bengn	0.08 3.11	DAME MORE FORE
Sight Hearing, Smell and Teste	ABCAI	CN9 107589355 H2096718	0-0.T 0.2311GPA p.Vel771Met	het	non-synon	195 40.19:21	TIEN	0.962	benign deneging	å	2000
Disease Set 0 Drug Set 0	CHTHF2	6919 16860131 192108522	C-CT c.1297374 p.VeR33Met	het	non-synon	183 30:12:15	C.78% T.22%	0.473	denaging benign	0.01 2.31	200 200 OM
Pathway Set 0	1972	18267664 18267664 191501260	TC,T e.3411HC e.8e114Thr	het	non-synon	191 99:20:19	T:70% C:30%	0.467	benign benign	0.08 0.74	2000, 2000, 2000,
Hy Set 0 Exclude Set 0	DEVD	chr1 87501396 01901398	TC.T c.1627A+G c.86642Vol	het	non-synon	153 24.11:13	T.80% C:20%	0.396	benign benign	0.86	2000 FREE
Chromosome 0	0001	chr3 9798773 rs1392133	C-CG c.2940-G	Net	non-synon	140 30.16:14	0.79% G:30%	0.258		0.01	2000
Pilter By 0 Require 0	0001	CN/3 SPS0773 IN1052133	C-CG c 9HO-G a PH333Na	hel	non-syron	149 30:16:14	C79% G30%	0.258		0.01 -0.25	2000
Genotype Hotercoygous	0001	6998773 9198773	0-00 6.977050 8.5er3350re	het	non-synon	169 30:16:14	C79% G36%	0.258		0.01 -0.25	2000
Protein Impact All Stap Gained/Lost	CYPEGE	69410 96741063 191257910	A C.C s.1076A-C p.Fe309Leu	hom	non-synon	496 30.0:30	A985 C45	0.109	benign danaging	0.11	2000, 2000, 2000,
Indel/Frameshift Spice Site Non-synonymous	ABON	04/3 10/620867 102220808	C-CT e.696G-A p.Ars216.vs	het	non-synon	131 20:16:12	C:58% T:42%	0.197	benign benign	0.32 0.18	2005 AND 2005
Supporting Evidence W Any OHDM	CYF296	0919 41515253 H29299187	A-A.G c.765A-O c.Lvs265A-0	het	non-synon	54 17.83		0.178	benign benign	0.84	MAG.
Gone Models CCDS RefSeq	MBN	CMS 90900179 91909794	CC.G c.555G+C e.Gu186GH	Net	non-synon	193 30,12,18	C67% G39%	0.172	benign benign	0.6	1000
Polyphen Prediction Probably Demaging Possibly Demaging	CHTHP12	07/19 15/19/140 19/09/290	A0,0 c.397+1A-0	hom	spice site	579 44.0.44	A9% G94%	0.172		0.6	2000
O Exclude 0	CYPSAT	697	0-40,0 6.1229GHZ	hom	non-synon	391 22:0:22	0.27% G:73%	0.163	benign benign	0.16	PROS.
O Sort By O	CYF4F12	rs2257401 ehr19	p.Arg409Thr AG.G	hom	non-synon	678	A4%	0.126		0.7	anno.
Position Gene Symbol		19769140 rx609290	e.269AHG p.Re90Val			44244	G:94%		benign	-0.6	
© Omicie Score	(100 t)	H 4 Page 1	0-A.G	MI G E	non-synon teclaring 1 to 24	203 of 24 terms	0.45%	0.068	benign		HAS FOR
Change		1000			3.00						

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.

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 MTHER, BDNF, and ClAT 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 Urba genotyped on Illumina 2.5M arrays, only 2 of them carried all three of these variants, which is consistent with the noted minor allelle frequencies on these 3 separate autosomes.

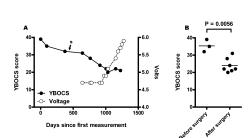


Figure 2. Yale Brown Obsessive Compulsive Scale (YBOCS) scores were measured for M.A over a three year and seven months period of time. A time series plot (A) shows a steady decline in YBOCS scores over the period of time spanning his DBS surgery (s) and treatment. Incremental adjustments to neurostimulator 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 neurosciences including 1) clinical-grade WGS with 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 clinical-grade 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.