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.

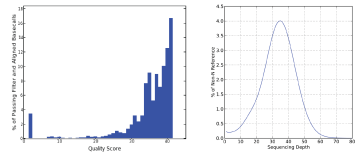
Methods
Detailed phenotyping and clinical evaluations were conducted over a four-year period for a single individual with severe mental illness. His genome was sequenced in the Illumina Whole Genome Sequencing Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory. This person was implanted 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



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

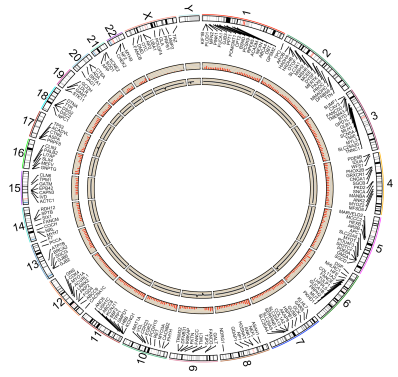


Figure 1. Illumina CLIA Whole genome sequencing data summarized in the form of a Circos plot. We show here a summary of the genomic coordinates corresponding to the 344 genes that were clinically evaluated by the Illumina CLIA WGS pipeline, the frequency of IGN validated SNVs across the genome (plotted in red) and a summary of highly confident copy number variations (CNVs) that were simultaneously detected by the Estimation by Read Depth with SNVs (ERDS) and Copy Number Analysis Method (CNAM) detection methods (plotted in black). Duplications and deletions are depicted as elevations and declinations, respectively. None of the identified CNVs have any published association with mental illness.

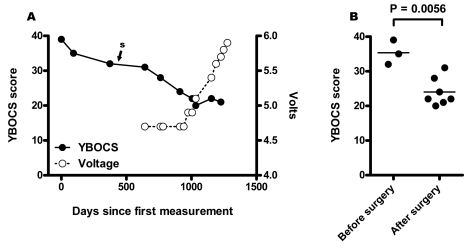


Figure 2. Yale Brown Obsessive Compulsive Scale (YBOCS) scores were measured for M.A over a three year and seven months period of time. A time series plot (**A**) shows a steady decline in YBOCS scores over the period of time spanning his DBS surgery (**s**) and treatment. Incremental adjustments to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

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.

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.

Questions? Email: GholsonJLyon@gmail.com