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

Gholson J. Lyon[1,2,3*], Jason O'Rawe[1,2], Reid Robison[3], Edward S. Kiruluta[4], Gerald Higgins[5], Martin G. Reese[4]

Abstract

Background: There is an extraordinarily rich literature in clinical psychology, psychiatry and neurology of N=1 studies. Until now, however, such studies have included the exciting but mostly parallel areas of clinical neuropsychiatry, personal genomics and brain-machine interfaces. As medical care moves toward more individual-focused and personalized treatment, a more integrative approach is needed.

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, with follow-up genomic annotations being assigned by the Omicia Opal® system. This person was implanted with the Medtronic Reclaim® Deep Brain Stimulation (DBS) Therapy device for Obsessive Compulsive Disorder (OCD). The device is approved under a Humanitarian Device Exemption (HDE) for people with chronic, severe, treatment-resistant 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 one 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 protein that is 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, which synthesizes the neurotransmitter acetylcholine, with both alleles having been shown to confer an elevated susceptibility to psychoses. We have discovered many 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.

Conclusions: To our knowledge, this is the first N=1 human study in the clinical neurosciences including 1) clinical-grade WGS with management 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.

[1]Stanley Institute for Cognitive Genomics, One Bungtown Road, Cold Spring Harbor Laboratory, NY, USA, 11724; [2]Stony Brook University, 100 Nicolls Rd, Stony Brook, NY, USA, 11794; [3]Utah Foundation for Biomedical Research, E 3300 S, Salt Lake City, Salt Lake City, UT, USA, 84106; [4]Omicia Inc., 2200 Powell St., Emeryville, CA, USA, 94608; [5]AssureRx Health, Inc., 6030 S. Mason-Montgomery Road, Mason, Ohio 45040

* Correspondence: Gholson J. Lyon
Email: GholsonJLyon@gmail.com

Introduction

There is a substantial body of literature spanning hundreds of years that highlights the breadth of human phenotypic diversity[1-12]. And yet, despite a body of scientific work demonstrating significant contributions from extreme genetic and environmental heterogeneity to this diversity, many have resorted to overly coarse categorizations in psychiatry that bear little resemblance to reality[13-17]. Over the past 50 years, psychiatry, and medicine in general, has shifted its focus toward providing pre-market proof of the overall efficacy and safety of drugs in randomized clinical trials involving hundreds (and sometimes thousands) of people, despite the existence of extreme phenotypic heterogeneity and variable expressivity in nearly every person and every disease over time[6, 8, 9, 18]. This course of affairs was brought about by a large confluence of societal factors, including safety concerns stemming from numerous biomedical transgressions over the years [19], including the indiscriminate use of lobotomy in the field of psychiatry[20, 21]. Unfortunately and perversely, the intense monetary incentives inherent in achieving "successful" clinical trials has now led to controversies regarding trial design, data collection, data quality, and reporting[22, 23]. However, there is some evidence suggesting that we might be undergoing a transformation of the medical world[24, 25], with a return to individual-focused medical care and to the realization that each individual is truly unique, influenced by their own genetic and environmental factors[3, 5, 26-28]. Accordingly, some are beginning to embrace the notion of individualized, participatory medicine[29], including the "quantified self movement"[30] and the "networking of science" model[27, 31, 32]. We report here our attempt to integrate, in our study of one individual, the areas of clinical neuropsychiatry, personal genomics and brain-machine interfaces.

Methods

Ethics compliance

Research was carried out in compliance with the Helsinki Declaration. The corresponding author (GJL) conducted all clinical evaluations and he is an adult psychiatry and child/adolescent psychiatry diplomate of the American Board of Psychiatry and Neurology. GJL received training regarding DBS for OCD at a meeting hosted by Medtronic in Minneapolis, Minnesota, in September 2009. The same author attended a Tourette Syndrome Association meeting on DBS for Tourette Syndrome, Miami, Florida, in December 2009. GJL obtained IRB approval at the University of Utah in 2009-2010 to evaluate candidates for surgical implantation of the Medtronic Reclaim® DBS Therapy for OCD, approved under a Humanitarian Device Exemption (HDE) for people with chronic, severe, treatment-resistant OCD[33]. The interdisciplinary treatment team consisted of one psychiatrist (GJL), one neurologist and one neurosurgeon.

Evaluation and recruitment for DBS for treatment-refractory OCD

Approximately ten candidates were evaluated over a one-year period in 2010. The individual discussed herein received deep brain stimulation surgery at another site, and then returned for follow-up with GJL. Another psychiatrist, author RR, provided ongoing consultation throughout the course of this study. Although other candidates have since returned for follow-up (with GJL), no others have been surgically treated.

A 37-year old man and U.S. veteran (here named with pseudonymous initials M.A.) was evaluated by GJL in 2010 for severe, treatment-refractory obsessive compulsive disorder (OCD), which is an illness that can be quite debilitating[34]. M.A. had a lifelong history of severe obsessions and compulsions, including contamination fears, scrupulosity, and the fear of harming others, with much milder symptoms in childhood that got much worse in his early 20's. His Yale-Brown Obsessive Compulsive Scale (YBOCS)[35, 36] ranged from 32-40, indicating extremely severe OCD. Perhaps the worst period of OCD included a 5-day, near continuous, period of tapping on his computer keyboard as a compulsion to prevent harm from occurring to his family members. M.A. had suffered throughout his life from significant periods of depression with suicidal ideation, and he had attempted suicide at least three times. His prior psychiatric history also includes episodes of paranoia relating to anxieties from his OCD, and he continues to be treated with biweekly injections of risperidone.

His treatment history included over 15 years of multiple medication trials, including clomipramine and multiple SSRIs at high doses, including fluoxetine at 80 mg by mouth daily, along with several attempts with outpatient exposure and ritual prevention (ERP) therapy[37]. M.A. inquired

and was evaluated by GJL at the University of Utah and then at two other centers independently offering deep brain stimulation for OCD. One of these centers required (as a condition for eligibility for an ongoing clinical trial) a two-week inpatient hospitalization with intensive ERP, which was documented as improving his YBOCS score to 24 at discharge. He maintains that he actually experienced no improvement during that hospitalization, but rather told the therapists what they wanted to hear, as they were "trying so hard". See the Additional File 15: Supplementary Information for other clinical details.

The teams at the University of Utah and two other centers declined to perform surgery due to his prior history of severe depression, suicide attempts and possible psychoses with paranoia. Through substantial persistence of M.A. and his family members, a psychiatrist and neurosurgeon at a fourth center decided that he was an appropriate candidate for surgical implantation of the Medtronic Reclaim® DBS Therapy device for OCD, approved under a Humanitarian Device Exemption (HDE) for people with chronic, severe, treatment-resistant OCD[33], and he was implanted in January of 2011. The device targets the nucleus accumbens / anterior limb of the internal capsule (ALIC).

CLIA Whole Genome Sequencing and the Management of Results from Sequencing data

Whole genome sequencing was ordered on this individual in order to glean clinically relevant genetic information that might shed light on the etiology of his psychiatric condition. His genome was sequenced in the Illumina Clinical Services Laboratory (CLIA-certified, CAP-accredited) as part of the TruSight Individual Genome Sequencing (IGS) test, a whole-genome sequencing service using Illumina's next-generation sequencing (NGS) technology[38]. Although clinical genome sequencing was ordered by GJL on a clinical basis (thus not requiring IRB approval), the clinical phenotyping and collection of blood and saliva for other research purposes was approved by the Institutional Review Board (iIRB) (Plantation, Florida) as part of a study protocol at the Utah Foundation for Biomedical Research (UFBR). Consistent with laboratory-developed tests, WGS has not been cleared or approved by the U.S. Food and Drug Administration[39]. The entire procedure included barcoded sample tracking of the blood collected by GJL from this person**,** followed by DNA isolation and sequencing in the Illumina CLIA lab. Data statistics are summarized in Additional File 11: Figure S1. For the bioinformatics analyses, Illumina utilized the internal assembler and variant caller CASAVA (short for Consensus Assessment of Sequence And VAriation). Data for sequenced and assembled genomes was provided on one hard drive, formatted with the NTFS file system and encrypted using the open source cross platform TrueCrypt software (http://www.truecrypt.org) and the Advanced Encryption Standard (AES) algorithm (Federal Information Processing Standards Publication 197).

The encrypted hard drive contains several files, including a "genotyping folder" within which there is a genotyping report (see Additional File 1) in a text-based tab-delimited format and including a header with a minimum of the following columns:

SNP Name: The snp identifier. An rsID for dbSNP content, Illumina labels otherwise.

GC Score: This score is a quality metric that generally indicates reliability of the genotypes called. The GenCall score is a value with a maximum of 1 assigned to every genotype called. GenCall scores are calculated using information from the clustering of the samples. Each SNP is evaluated based on the angle of the clusters, dispersion of the clusters, overlap between clusters, and intensity. Genotypes with lower GenCall scores are located furthest from the center of a cluster and have a lower reliability.

Allele A – Forward: A allele call relative to the Forward sequence as defined by the SNP source database (dbSNP, 1000Genomes, etc.)

Allele B – Forward: B allele call relative to the Forward sequence as defined by the SNP source database (dbSNP, 1000Genomes, etc.)

Allele A – Design: A allele call relative to the probe used.

Allele B – Design: B allele call relative to the probe used.

Insertions, deletions and structural alterations are not validated variant types in the Illumina Clinical Services Laboratory. Insertions and deletions provided in the gVCF file are for investigative or research purposes only. A medical report and the raw genomic data were provided

back to the ordering physician (GJL) on an encyrypted hard drive as part of the Illumina Understand your Genome Symposium, held in October 2012, which included the clinical evaluation of 344 genes (see Additional File 2 and 3)[40].

To perform more comprehensive downstream analyses using a greater portion of the genomic data, all of the variants that were detected by the Illumina CLIA WGS pipeline were imported and analyzed within the Omicia Opal web-based clinical genome interpretation platform, version 1.5.0[41]. The Omicia system annotates variants and allows for the identification and prioritization of potentially deleterious alleles. Omicia Scores, which are a computationally derived measure of deleteriousness, were calculated by using a decision-tree based algorithm, which takes as input the Polyphen, SIFT, MutationTaster and PhyloP score(s), and derives an integrative score between 0 and 1. Receiver operating characteristic (ROC) curves are plotted for that score based on annotations from HGMD. For an Omicia Score of 0.85, this analyses results in a 1% false positive rate. For further details on the method and the program see the Supplementary Information and www.omicia.com. The AssureRx Health, Inc. annotation and analysis pipeline was used to further annotate variants (see Supplementary Information for more detailed methods).

We also applied a recently published method, ERDS (Estimation by Read Depth with SNVs) version 1.06.04[42], in combination with genotyping array data, to generate a set of CNV calls. ERDS starts from read depth information inferred from BAM files, but also integrates other information including paired end mapping and soft-clip signature, to call CNVs sensitively and accurately. We collected deletions and duplications that were >200 kb in length, with confidence scores of >300. CNVs that were detected by the ERDS method were visually inspected by importing and visualizing the read alignment data in the Golden Helix Genome Browser, version 1.1.1. CNVs were also independently called from Illumina HumanOmni2.5-8v1 genotyping array data. Array intensities were imported and analyzed within the Illumina GenomeStudio software suite, version 1.9.4. LogR values were exported from GenomeStudio and imported into Golden Helix SVS, version 7.7.5. A Copy Number Analysis Method (CNAM) optimal segmentation algorithm was used to generate a list of putative CNVs, which was then restricted to include only CNVs that were >200kb in length with average segment LogR values of > 0.15 and < -0.15 for duplications and deletions, respectively. LogR and covariate values were plotted and visually inspected at all genomic locations where the CNAM method detected a CNV. CNVs that were simultaneously detected by both methods (ERDS and CNAM) were considered to be highly confident CNVs. Highly confident CNVs were, again, visually inspected within Golden Helix Genome Browser to further eliminate any artefactual CNV calls.

A board-certified genetic counselor was consulted by GJL prior to returning results, and all therapy and counseling was provided by GJL.

Results

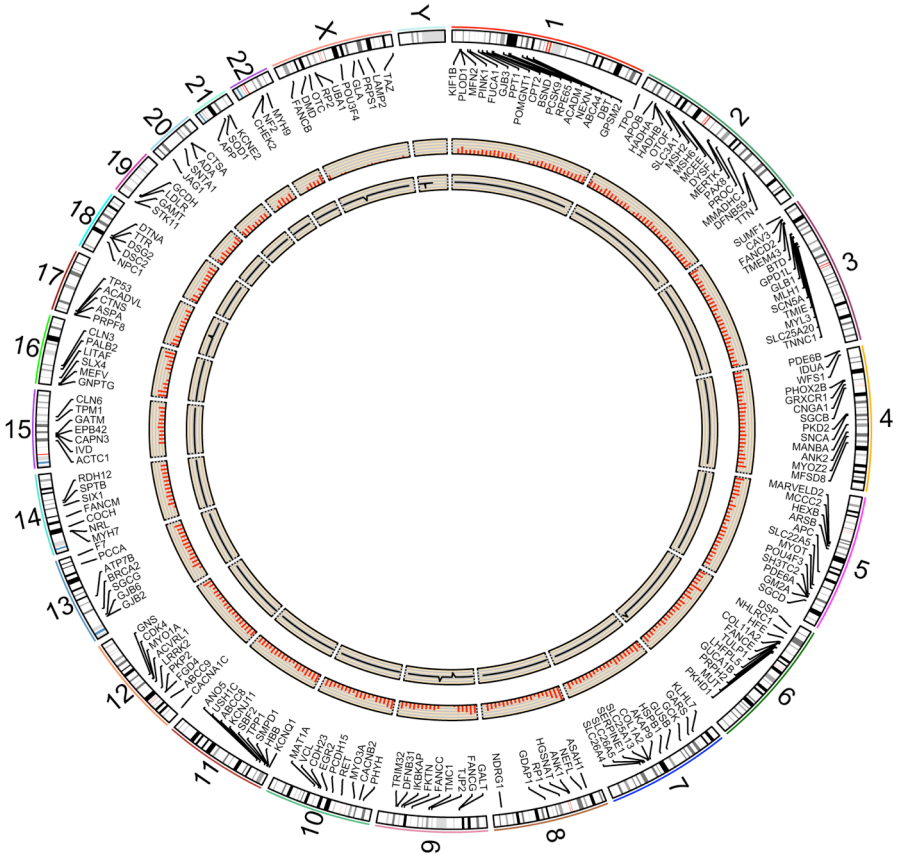
This is a report on the efforts of one of us (GJL) to provide individualized treatment in neuropsychiatry including both whole genome sequencing and deep brain stimulation in one person.

CLIA certified Whole Genome Sequencing results

The Illumina WGS clinical evaluation included manual annotation of 344 genes (see Figure 1, Additional File 2 and 3), which led to the following conclusion:

> "*No pathogenic or likely pathogenic variants were found in the 344 genes evaluated that are expected to be clinically significant for the patient. The coverage for these 344 genes is at least 99%. Therefore, significant variants could exist that are not detected with this test.*"

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.

The clinical evaluation did, however, identify M.A. as a carrier for a mutation (c.734G>A ,p.Arg245Gln) in *PHYH*, which has been associated in the autosomal recessive or compound heterozygote states with Refsum disease, which is an inherited condition that can lead to vision loss, anosmia, and a variety of other signs and symptoms[43]. In silico prediction programs suggest little impact; however, the variant is rare with a 1000 Genomes frequency of ~0.18%. The frequency with which the variant was seen in cases compared to both controls and the 1000 Genomes population frequency is suggestive that it might contribute to disease development. In this regard, it is worth noting that M.A. has always had poor night vision and that he was recently diagnosed with small bilateral cataracts, affecting his vision. We have referred M.A. back to his optometrist for further evaluation of his visual problems, along with the question of whether this might be related in any way to this particular mutation in his genome.

Further downstream analyses identified and prioritized a number of potentially clinically relevant variants. Variants that were imported into the Omicia Opal system were filtered to include those that had a high likelihood of being damaging (as defined by an Omicia score > 0.7) and those that have supporting Online Mendelian Inheritance in Man (OMIM; an online database of human genetics and genetic disorders) evidence. We chose to filter based on an Omicia Score of > 0.7 as this value derives a slightly more inclusive list of variants which still cannot be dismissed, but for which we have additional corroborating evidence (i.e., Illumina Genome Network (IGN) validation and annotation). These prioritized variants were further annotated and evaluated by the AssureRx Health, Inc. annotation and analysis pipeline. Prioritized variants are shown in Additional File 4 and Additional File 12: Figure S2. A longer list of variants, which were required only to have supporting evidence within the OMIM database, is

shown in Additional File 5. We highlight here some of the findings:

M.A. was found to be a heterozygote for a p.Val66Met change in *BDNF*, which encodes a protein that is a member of the nerve growth factor (NGF) family. The protein is induced by cortical neurons, and is deemed necessary for the survival of striatal neurons in the brain. In drug naïve patients, BDNF serum levels were found to be significantly decreased in OCD patients when compared to controls (36.90 ± 6.42 ng/ml versus 41.59 ± 7.82 ng/ml; p = 0.043)[44], suggesting a link between this protein and OCD. Moreover, a study including 164 proband-parent trios with obsessive-compulsive disorder[45] uncovered significant evidence of an association between OCD and all of the *BDNF* markers that were tested, including the exact variant found here in this person, p.Val66Met. This particular variant has been further studied in a sample of 94 nuclear families[46], which included 94 probands with schizophrenia-spectrum disorders and 282 family members. The results of this study suggest that the p.Val66Met polymorphism may play a role in the phenotype of psychosis. Similar anxiety-related behavioral phenotypes have also been observed among mice and humans having the p.Val66Met variant in BDNF[47]. In humans, the amygdala mediates conditioned fear[48], normally inhibited by 'executive centers' in medial prefrontal cortex[49]. Deep brain stimulation of the pathways between medial prefrontal cortex and the amygdala increased the extinction of conditioned fear in a rat model of OCD[50]. Studies using functional magnetic resonance imaging (fMRI) demonstrate that humans with the p.Val66Met variant exhibit exaggerated activation of the amygdala in response to an emotional stimulus in comparison to controls lacking the variant[51, 52]. It is thought that this variant may influence anxiety disorders by interfering with the learning of cues that signal safety rather than threat and may also lessen efficacy of treatments that rely on extinction mechanisms, such as exposure therapy[47]. In this regard, it is interesting to note that this person did indeed obtain very little benefit from exposure therapy prior to surgery.

M.A heterozygously carries the p.Glu429Ala allele in MTHFR, encoding a protein that catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, a co-substrate for homocysteine remethylation to methionine, and which has been shown to confer an elevated susceptibility to psychoses. Variants in *MTHFR* influence susceptibility to occlusive vascular disease, neural tube defects, colon cancer and acute leukemia. Mutations in this gene are associated with methylenetetra-hydrofolate reductase deficiency. In addition, a meta-analysis comparing 1,211 cases of schizophrenia with 1,729 controls found that the MTHFR p.Glu429Ala allele was associated with susceptibility to schizophrenia[53] (odds ratio, 1.19; 95% CI, 1.07- 1.34; p = 0.002). According to the Venice guidelines for the assessment of cumulative evidence in genetic association studies, the *MTHFR* association exhibited a strong degree of epidemiologic credibility[54]. Pharmacogenetic studies have found a consistent association between the MTHFR p.Glu429Ala allele and metabolic disorder in adult, adolescent and children taking atypical antipsychotic drugs[55, 56].

M.A. is heterozygous for a c.19G>A p.Asp7Asn allele in ChAT, encoding choline O-acetyltransferase, which synthesizes the neuro-transmitter acetylcholine (see Additional File 13: Figure S3). This particular variant (rs1880676) is significantly associated with both risk for schizophrenia in Caucasians (P = 0.002), olanzapine response (P = 0.02) and for other psychopathology (P = 0.03)[57].

M.A. is also heterozygous for the p.Val108Met variation in catechol-O-methyltransferase(COMT), which catalyzes the transfer of a methyl group from S-adenosylmethionine to catecho- lamines, including the neurotransmitters dopamine, epinephrine, and norepinephrine. The minor allele A of this 472G>A variant produces a valine to methionine substitution, resulting in a less thermostable COMT enzyme that exhibits a 3-fold reduction in activity. A substantial body of literature implicates this variant as possibly elevating the risk for various neuropsychiatric disorders in some Caucasian populations but not necessarily in other genetic backgrounds[58-64]. There is some evidence that MTHFR x COMT genotype interactions might also be occurring in M.A. to influence his neuropsychiatric status[65], and the same is true for BDNF x COMT interactions[66].

Pharmacogenetic analyses were performed using the Omicia Opal platform. Pharmacogenetic variants were identified and prioritized by activating the "Drugs and Pharamcology" track within the Opal system and by requiring these variants to have prior evidence within a number of supporting databases (i.e., OMIM, HGMD, PharmGKB, LSDB and GWAS). Prioritized variants are shown in Additional File 6 and Additional File 14: Figure S4. A longer, more inclusive list is shown in Additional File 7;

Table 1. A summary of three clinically relevant alleles found in the sequencing results of M.A.

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.

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.

variants in this file are only required to be detected by the "Drugs and Pharmacology" track in Opal. Variants within Additional File 6/7 were further annotated and analyzed by the AssureRx Health, Inc. pipeline (see Additional File 8).

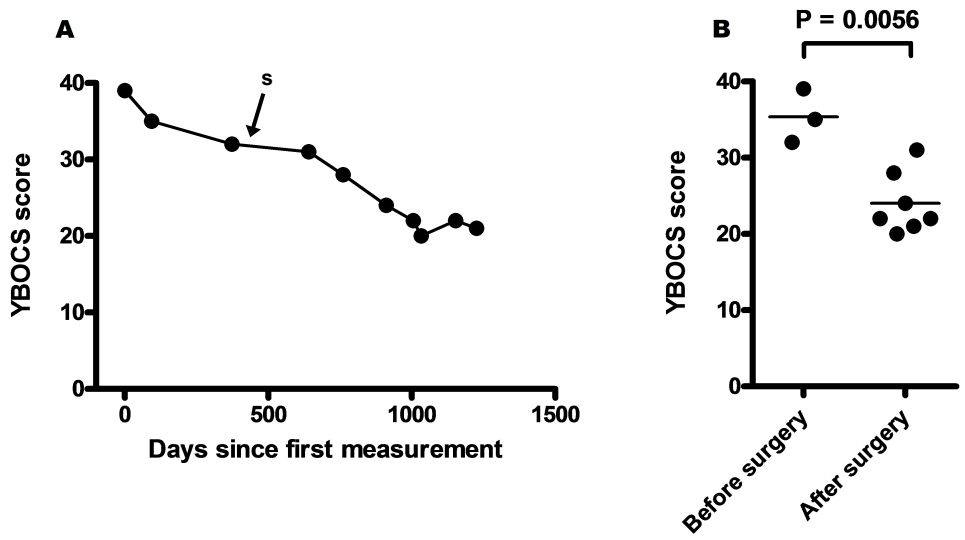
M.A. is homozygous for a p.Ile359Leu change in CYP2C9, and this mutation has been linked to a reduction in the enzymatic activity of CYP2C9[67]. *CYP2C9* encodes a member of the cytochrome P450 superfamily of enzymes. Cytochrome P450 proteins are mono-oxygenases, which catalyze many reactions associated with drug metabolism as well as reactions associated with the synthesis of cholesterol, steroids and other lipids[68]. CYP2C9 localizes to the endoplasmic reticulum and its expression is induced by rifampin. CYP2C9 is known to metabolize xenobiotics, including phenytoin, tolbutamide, ibuprofen as well as S-warfarin. Studies identifying individuals who are poor metabolizers of phenytoin and tolbutamide suggest associations between metabolism and polymorphisms found within this gene. *CYP2C9* is located within a cluster of cytochrome P450 genes on chromosome 10[69]. Fluoxetine is commonly used in the treatment of OCD; it has been shown to be as effective as clomipramine and causes less side effects[70, 71]. CYP2C9 acts to convert fluoxetine to R-norfluoxetine[72], and so M.A. may not be able to adequately biotransform fluoxetine[73]. However, CYP2C9 does not play a rate-limiting role for other SSRIs or clomipramine. In his own treatment experience, M.A. had no response to an 80 mg daily dose of fluoxetine, although he did experience sexual side effects at that dosage.

The protein encoded by *DPYD* is a pyrimidine catabolic enzyme and it acts as the initial and rate-limiting factor in uracil and thymidine catabolism pathways. M.A. was found to be a carrier of two variations in this gene, p.Ile543Val and p.Arg29Cys, for which he is a heterozygote and homozygote, respectively. Mutations within *DPYD* result in dihydropyrimidine dehydrogenase deficiency, an error in pyrimidine metabolism associated with thymine-uraciluria and an increased risk of toxicity in cancer patients receiving 5-fluorouracil chemotherapy. Two transcript variants encoding different isoforms have been described for *DPYD*[74, 75].

A copy number variant (CNV) analysis was performed using the estimation by read depth with single-nucleotide variants (ERDS) method[42] in combination with the Golden Helix Copy Number Analysis Method (CNAM) optimal segmentation algorithm applied to Illumina HumanOmni2.5-8v1 genotyping array data. ERDS identified 60 putative CNVs, all of which were visually inspected within the Golden Helix Genome Browser. Many of the CNVs detected by the ERDS method were found to be located within chromosomal boundary regions and were determined to be false positives due to highly variable read depth in these regions. The CNAM method detected 35 putative CNVs, which were visually inspected by plotting the LogR and covariate values in Golden Helix SVS. Only six CNVs were simultaneously detected by both the ERDS and CNAM methods, and were visually inspected as further confirmation to be included among the set of highly confident CNVs. High-confidence CNVs are shown in Additional File 9. To our knowledge, these CNVs have not been previously associated in any way with M.A.'s disease phenotype.

Although we believe in archiving and managing all genetic results and not just a small subset of genes, we did analyze the 57 genes that are currently recommended for "return of results" by

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. 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.

the American College of Medical Genetics[76]. These results are shown in Additional File 10.

Clinical results for DBS for treatment-refractory OCD

After healing for one month, the implanted device (equipped with the Kinetra Model 7428 Neurostimulator) was activated on February 14, 2011, with extensive programming by an outpatient psychiatrist, with bilateral stimulation of the ALIC. Final settings were case positive, contact 1 negative on the left side at 2.0 V, frequency 130 Hz, and pulse width 210 usec, and case positive, contact 5 negative on the right side with identical settings.

Over the next few months, his voltage was increased monthly in increments of 0.2-0.5 V by an outpatient psychiatrist. He returned to one of the author's (GJL) for psychiatric treatment in July 2011, at which time his voltage was set at 4.5 V bilaterally. His depression had immediately improved after the surgery, along with many of his most irrational obsessions, but his YBOCS score still remained in the 35-38 range. From July 2011-December 2011, his voltage was increased bilaterally on a monthly basis in increments of 0.2 V, with steady improvement with his OCD until his battery started to lose charge by December 2011. This caused him considerable anxiety, prompting him to turn off his battery in order to "save battery life", which unfortunately led to a complete relapse to his baseline state in a 24 hour period, which was reversed when he turned the battery back on. The battery was surgically replaced with a rechargeable *Activa RC* neurostimulator battery in January 2012, and the voltage has been increased monthly in 0.1-0.2 V increments until the present time (May 2013). At every visit, M.A. has reported improvements, with reductions of his obsessions and compulsions, marked by a steady decline in his YBOCS score (Figure 2). M.A. has started to participate in many activities that he had never previously been able to engage in. This includes: exercising (losing 50 pounds in two years) and volunteering at the church and other organizations. In fact, M.A. started dating and recently became engaged to be married, highlighting his improvement in daily functioning. New issues that M.A. reports are consistent tenesmus, occasional diarrhea (which he can now tolerate despite prior contamination obsessions) and improved vision (going from 20/135 to 20/40 vision, as documented by his optometrist), with him no longer needing to wear glasses. It is unknown whether the 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. M.A. still receives an injection of 37.5 mg

risperidone every two weeks for his past history of psychoses; otherwise, he no longer takes any other medications.

The most significant aspect of this presentation is the rechargeable, and hence depletable, nature of the *Activa RC* neurostimulator battery, which serves to illustrate the efficacy of DBS for OCD for this individual. On one such occasion, M.A. forgot to take the recharging device on a four-day weekend trip. Once his battery was depleted, all of his symptoms gradually returned to their full level over a ~24 hour period, including severe OCD, depression and suicidality. Since that episode, M.A. always takes his recharging device with him on extended trips, but there have been other such instances in which his battery has become depleted for several hours, with the noticeable and intense return of his OCD symptoms and the cessation of his tenesmus. The electrical stimulation is clearly having an effect on his OCD, and these data are complementary to other data-sets involving turning DBS devices off for one week at a time[77]. The efficacy is also in agreement with a burgeoning literature related to the mechanism and efficacy of deep brain stimulation for OCD in some people[77-92].

It is worth noting that M.A. was declined for DBS at three centers due to his prior history of suicidality, suicide attempts, and possible psychoses. Although there is a considerable degree of caution and outright skepticism in the medical community regarding the use of DBS for OCD, it is a fact that many people with severe OCD also have severe depression, usually with passive (and sometimes active) suicidal ideation[93-95]. In addition, the obsessions and compulsions can be quite severe, sometimes to a delusional or psychotic degree, and there can also be co-occurring psychoses in any individual. In this regard, there has not been any exacerbation of psychoses in this individual during the prior two years of treatment, and the benefits of DBS have clearly outweighed the risks related to his prior history of psychoses.

Discussion

There is a rich case literature and N=1 studies that have been incredibly illustrative over the years (for just a small sampling, see[96-103]). We anticipate that others will be able to capture and document many more such cases going forward, as we are entering an era of individualized medicine, made possible mainly by the introduction of the internet and the "networking of science" revolution that is currently underway[27, 32, 104-109]. We document here what we believe to be the first integration of whole genome sequencing and deep brain stimulation in the evaluation and treatment of one severely mentally ill individual, M.A.

We found that M.A. carries at least three alleles that have been associated with neuropsychiatric phenotypes, including variants in *BDNF*, *MTHFR*, and *ChAT* (Table 1). There are certainly other mutations and/or environmental interactions that have influenced or will influence his clinical course, and we subscribe to the model that there will be numerous gene-gene and gene-environment interactions occurring over the lifetime of M.A. to influence his course[110-122]. That is why it is so important to archive and re-interpret his genome going forward.

We have previously argued in favor of an analytic-interpretive split in the area of clinical genomics, in which WGS can be a discrete deliverable clinical unit, allowing for multiple downstream interpretive analyses, by any number of people, including the individual and/or his/her health care providers[39]. We have implemented that model here with M.A. by archiving and offering to him the encrypted hard drive containing his "raw" sequencing data, along with analyzing the data with several downstream pipelines. Due to the incomplete and sometimes proprietary nature of databases containing information pertaining to human genetic variation, it is likely that analyses and medical guidance gleaned from these data will differ from institution to institution. For this reason, we stress the need to collate and offer these raw data to individuals so that they can, like with many other traditional medical tests, obtain "second opinions". We hope to eventually incorporate his genetic data into his electronic health record, which is made easier by the fact that he is a U.S. veteran, meaning that we can attempt to incorporate his WGS data information into the highly successful VistA health information system (HIS)[123-126], perhaps using the GVFclin format[127]. We did already counsel M.A. regarding several genetic variants that may be clinically relevant to predisposing him to his psychiatric disorder[128].

We believe that anyone should be able to access and manage their own genome data[129], just like how anyone should be able to own and manage their medical and radiology test results[130], particularly if the testing is performed with suitably appropriate clinical standards in place, i.e. CLIA in America[131, 132]. Others have described the extraordinary amount of hype and genetic

exceptionalism in the field of genomics[133], alongside the rise of genetic determinism[134]. We tend to think that whole genome sequencing will eventually become like many other laboratory tests, and it certainly won't be as dangerous as the many thousands of surgical procedures and other interventions that occur every day in medicine. There is currently an ongoing project in America to collect phenotype and genetic data on one million U.S. veterans[135]. We sincerely hope that the Million Veteran Program will reconsider their current position of not returning any genetic results, as they currently claim in their current consent form (accessed April 27, 2013)[136]. We have readily demonstrated herein that it is possible to sequence the whole genome in a CLIA-certified laboratory, so that these results can be offered to this veteran (and other veterans), and we are working now to determine if we can incorporate any of these results into his electronic medical record at the VA. We also note that there are efforts underway to create "a national resource with linked genealogy and phenotypic data: the Veterans Genealogy Project", and the authors of that paper note the potential of linking this with the genetic information obtained via the Million Veteran Program[137].

There has also been a substantial reluctance among most members of the neurologic and neurosurgical community (in America at least) to work with psychiatrists to implement any further neurosurgical procedures in the field of psychiatry. This is primarily the legacy of an era of psychosurgery with the completely indiscriminate and imprecise use of lobotomy in the field of psychiatry[20, 21]. It is also a byproduct of the artificial separation of the disciplines of psychiatry, neurology and neurosurgery, which has created departmental siloes and turf battles over which diseases "belong" to which discipline, despite the fact that these diseases all involve mainly one organ: the brain[138]. There is an ongoing clinical trial testing the "Effectiveness of Deep Brain Stimulation for Treating People With Treatment Resistant Obsessive-Compulsive Disorder"[76]. However, some of the extensive exclusion criteria in that trial include: "current or past psychotic disorder", "a clinical history of bipolar mood disorder", and/or "an inability to control suicide attempts, imminent risk of suicide in the investigator's judgment, or a history of serious suicidal behavior, which is defined using the Columbia-Suicide Severity Rating Scale (C-SSRS) as either (1) one or more actual suicide attempts in the 3 years before study entry with the lethality rated at 3 or higher, or (2) one or more interrupted suicide attempts with a potential lethality judged to result in serious injury or death".

It is therefore sad and ironic that some people in America with the most severe cases of OCD are being excluded from the ongoing clinical trial for DBS due to the above exclusion criteria[76]. We are publishing our initial two-year experience with this one individual, so that others in the world can learn about this result. This is not an instance of selective reporting[139], as the clinician and corresponding author on this paper has only been intimately involved with this single case, although he is aware of two other successful unpublished outcomes obtained by others. There are a considerable number of ethical and regulatory issues relating to deep brain stimulation that have been discussed elsewhere[140-146], and we simply wish to report our one very positive experience, only made possible when the US Food and Drug Administration granted a Humanitarian Device Exemption (HDE) to allow clinicians to use this intervention on American soil. The rechargeable nature of the new battery has also been very reassuring to M.A., as he is able to exert self-control over his battery life, whereas he previously had no control with the original "single-use" battery that must be replaced when the battery depletes (usually at least once annually). We assume that other persons treated with DBS for OCD will likely also start receiving rechargeable batteries. Unfortunately, the artificial split between neurology, psychiatry and neurosurgery has made it incredibly difficult to develop teams that can easily push forward the re-emerging field of neuromodulation, mainly due to the fact that most neurosurgeons and neurologists do not obtain sufficient training or expertise with these severe psychiatric phenotypes, and conversely most psychiatrists get very little training or exposure to neurosurgery and even in some cases neurology.

It is also worth noting that the recent development of an injectable class of cellular-scale optoelectronics paves the way for implanted wireless devices[147], and we fully expect that there will be more brain-machine neural interfaces used in humans in the future[148-152]. We hope very much that the recently announced BRAIN initiative [148, 149] will incorporate feedback and advice from clinical investigators in the fields of psychiatry, neurology, neurosurgery and neuropathology.

We close with an excerpt of a quote from M.A. upon turning on his device, after leaving it off for one day:

> "*I turned back on the device Saturday afternoon after I became suicidal, and my mood immediately improved in a surprising and dramatic fashion. One second the battery was off and I was not just wishing I were dead, but realizing I needed to kill myself to spare myself future misery, and the next second I came to the realization that my battery wasn't working. I turned on the battery and a second later I was no longer wishing I were dead and was smiling because the internal pain was gone.*"

Contributions

GJL conceived of the project, conducted psychiatric evaluations, provided clinical care, analyzed data, supervised other data analyses, and wrote the manuscript. JO, GH, ESK and MGR analyzed and interpreted the whole genome data. RR leads the Utah Foundation for Biomedical Research. All authors read, commented on, and approved the final manuscript.

Conflicts of Interest

The corresponding author (GJL) has had informal discussions with representatives from Medtronic, Illumina, and Omicia, Inc., but he has not had any formal consulting role, nor received financial compensation or grants from these or any other for-profit companies performing deep brain stimulation, DNA collection or sequencing. GJL does not hold any patents, and he is unaware of any conflicts of interest on his part. Revenue earned by GJL from providing medical care in Utah is currently donated to the Utah Foundation for Biomedical Research for genetics research. ESK and MGR are co-founders and officers of Omicia, Inc., and GH is an employee of Assure Rx, Inc. All authors read and approved of the content in the manuscript.

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Description of additional files

The following additional data files are associated with this paper and can be downloaded on request to the corresponding author:

Additional File 1. Genotyping was performed as part of the Illumina CLIA WGS pipeline using the HumanOmni2.5-8v1 BeadChip. The genotyping report is included as a tab-delimited text file and includes a header followed by a number of columns that describe the data within, including: the SNP name, GC score, Allele A – Forward, Allele B – Forward, Allele A – Design and Allele B – Design. The allele calls for the genotyping array are listed in forward orientation.

Additional File 2. The Illumina CLIA WGS clinical report, which includes the clinical evaluation of 140 conditions associated with 344 genes. Clinical interpretation was performed using interpretation guidelines and recommendations from the American College of Medical Genetics. A cumulative total of 1247 variants were detected and evaluated for clinical significance with one single variation being determined as "likely pathogenic", a p.Arg245Gln change in *PHYH*.

Additional File 3. The 344 gene list analyzed by Illumina as part of the Understand your Genome Symposium in 2012.

Additional File 4. Variant prioritization was performed on all variants discovered by the Illumina CLIA WGS pipeline using the Omicia Opal version 1.5.0 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.

Additional File 5. Less stringent variant prioritization was performed on all variants discovered by the Illumina CLIA WGS pipeline using the Omicia Opal version 1.5.0 platform. A more inclusive set of variants was derived by performing less stringent prioritization on all genomic variations. Variants called by the Illumina CLIA WGS and bioinformatics pipeline were imported into the Omicia Opal clinical variant annotation and prioritization platform. Variants were then prioritized by only requiring each variant to have supporting evidence in OMIM.

Additional File 6. Variants discovered by the Illumina CLIA WGS pipeline to have pharmacogenomic significance were evaluated and prioritized using the Omicia Opal version 1.5.0 platform. Pharmacogenomic variant prioritization was performed by importing all variants called by the Illumina CLIA WGS and bioinformatics pipeline into the Omicia Opal cloud based variant prioritization platform. Variants were filtered by activating the "Drugs and Pharmacology" track in Opal, and further filtered to those that also had prior evidence in a variety of supporting databases, including: OMIM, HGMD, PharmGKB, LSDB and GWAS.

Additional File 7. Variants discovered by the Illumina CLIA WGS pipeline to have pharmacogenomic significance were evaluated using less conservative prioritization requirements. Less stringent pharmacogenomic variant prioritization was performed by first importing variants called by the Illumina CLIA WGS sequencing and bioinformatics pipeline into the Omicia Opal cloud based variant prioritization platform version 1.5.0. Variants were then filtered only by activating the "Drugs and Pharmacology" track in Opal.

Additional File 8. Expert curation of pharmacogenetic variants identified by Omicia Opal pipeline. All single nucleotide variants (SNPs), copy number variants (CNVs), indels and other variants identified as important and provided by Omicia's Opal Annotation Pipeline were investigated further using GenomePharm and manual review of the published literature and clinical trial data. These were compared to genes listed in Pharma DMET, Pharma ADME, and the ADME Pharma consortium. Comparisons were made of known gene-variant-drug-disease interactions as identified in GenomePharm and stored in a temporary NoQL database. Judgments were made by GH, in which a given pharmacogenomic variant had to have been replicated >6 times in adequately powered randomized controlled trials using individuals of European American ancestry.

Additional File 9. A list of 6 high confidence copy number variations (CNVs) that were called by the ERDS and CNAM CNV detection methods. ERDS (version 1.06.04) derived CNVs were required to be >200 kb in length, with confidence scores of >300. CNAM (Golden Helix SVS version 7.7.5) CNVs were also required to be >200kb in length with average segment LogR values of > 0.15 and < -0.15 for duplications and deletions, respectively. CNVs detected by both methods were visually inspected to eliminate obvious false positive calls. The 6 CNVs shown here were detected by each method, visually confirmed, and are thus considered high confidence.

Additional File 10. 57 genes recommended by the ACMG as candidates for returning results were analyzed and annotated by the Omicia Opal system. Only two variants, one in CACNA1S and one in MYLK, were interpreted as being of putative interest but not rising to the level of "pathogenicity".

Additional File 11, Figure S1. Data statistics and SNP characteristics for the Illumina CLIA WGS pipeline. WGS was performed using the Illumina CLIA WGS pipeline. We report the volume of data, the quality of the data as well as whole genome SNP characteristics and more general characteristics of SNVs reported by the Illumina CLIA WGS pipeline, including: the total number of SNVs, the total number of SNVs that are within genes, coding regions, UTRs, splice site regions as well as the number of SNVs that were stop gained, stop lost, non-synonymous, synonymous and mature mRNA.

Additional File 12, Figure S2. Screen shot of the Omicia Opal system showing the list of prioritized variants.

Additional File 13, Figure S3. Screen shot of Summary from the Omicia Opal system on *ChAT*, encoding choline O-acetyltransferase, which synthesizes the neurotransmitter acetylcholine

Additional File 14, Figure S4. Screen shot of the Omicia Opal system showing the list of prioritized pharmacogenetic variants.

Additional File 15. Supplementary Methods and Clinical Descriptions.

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