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 (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.

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

<table>
<thead>
<tr>
<th>Gene name</th>
<th>Genomic coordinates</th>
<th>Amino acid change</th>
<th>Zygosity</th>
<th>Mutation type</th>
<th>Population Frequency</th>
<th>Clinical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTHFR</td>
<td>chr1: 11854476</td>
<td>Glu&gt;Ala</td>
<td>heterozygous</td>
<td>non-synon</td>
<td>T:77% G:23%</td>
<td>Susceptibility to psychoses, schizophrenia, obsessive compulsive disorder, and methylenetetrahydrofolate reductase deficiency</td>
</tr>
<tr>
<td>BDNF</td>
<td>chr11: 27679916</td>
<td>Val&gt;Met</td>
<td>heterozygous</td>
<td>non-synon</td>
<td>C:77% T:23%</td>
<td>Susceptibility to OCD, psychosis, and methylenetetrahydrofolate reductase deficiency</td>
</tr>
<tr>
<td>CHAT</td>
<td>chr10: 50824117</td>
<td>Asp&gt;Asn</td>
<td>heterozygous</td>
<td>non-synon</td>
<td>G:85% A:15%</td>
<td>Susceptibility to schizophrenia and other psychopathological disorders.</td>
</tr>
</tbody>
</table>

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.