Whole-genome sequencing of 50 LRRK2 G2019S carriers discordant for Parkinson's disease

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Introduction
Parkinson's disease (PD) is one of the most common neurodegenerative disorders, affecting over six million people worldwide. PD symptoms include resting tremor, muscular rigidity, bradykinesia, and postural instability. The pathology of PD is characterized by the loss of dopaminergic neurons in the substantia nigra and is usually accompanied by Lewy bodies, abnormal protein aggregates comprised mainly of alpha synuclein, ubiquitin, and tau proteins. Over 20 single nucleotide variants (SNVs) have been associated with PD susceptibility. Of particular interest is the LRRK2 G2019S mutation, with a population frequency in PD patients ranging from under 1% in Asians to 20% in Ashkenazi Jews and 40% in North African Arabs. G2019S is present in both familial autosomal dominant and sporadic PD and has an estimated penetrance of 28% at age 59 and 74% at age 79 (ref. 4). Higher penetrance estimates in familial cases suggest the presence of additional genetic or environmental penetrance modifiers.

Here we present the results of whole-genome sequencing (WGS) of 50 unrelated European individuals concordant for both the presence of the LRRK2 G2019S mutation and the absence of the PD-associated GBA 84GG, N370S, V394L, and R496H mutations. The cohort, drawn from consenting 23andMe customers, comprises 57 individuals affected by PD and 13 healthy controls with no family history of PD. The goals of the project are three-fold: 1) To establish the feasibility of whole-genome sequencing from 23andMe’s biobanked saliva samples, 2) Search for high-penetrance genetic modifier mutations that confer protection against PD in G2019S carriers, and 3) Identify additional 23andMe customers for WGS to study both PD genetics and Ashkenazi ancestry.

Methods
At least five µg of DNA was extracted from each biobanked saliva sample. Illumina sequencing generated 100 paired-end reads. Read processing followed the Broad Institute’s “best practices” guidelines, using BWA², GATK⁶, Picard⁷, and Pinдель tools to align and call variants (Fig. 1). Variant annotation was performed with Snippy⁸ and RegulomeDB¹⁰.

Results
The age of onset in PD cases ranges from 38-85 with a median of 56 (Fig. 2A). Individuals were sequenced to a median mapped depth of 44.9-fold coverage (Fig. 2B) with the percentage of genome sequenced ranging from 97.6-98.2%. The number of SNVs and insertion/deletion variants (indels) in each genome agree with previous estimates of individual human variation (Fig. 2C, Table 1). Concordance of WGS-called SNVs and indels with 23andMe genotyping chip calls ranged from 99.1-99.97% per individual.

Discussion
The LRRK2 G2019S mutation is present at high frequency in Ashkenazi Jews. The 23andMe database includes 283 Ashkenazi individuals who possess at least one of the LRRK2 G2019S or GBA 84GG, N370S, V394L, or R496H mutations. Identification of these segments between these 283 sequencing candidates and the ~8,000 Ashkenazi individuals in the database shows the effective genome information obtained through imputation (Fig. 3).

References
2. 4. O. et al. (2011). 23andMe, Inc. Mountain View, CA.