GENETIC VARIANTS CONTRIBUTING TO FRONTOTEMPORAL DEMENTIA WITH PARKINSONISM

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Background
- Frontotemporal dementia with parkinsonism (FTDP):
  - Neurodegenerative disease
  - Disturbances in cognition, language, personality, and motor function
- Major associated genes: MAPT and GRN
- A large Mennonite kindred (MEN-1) exhibits parkinsonism and dementia in five members of a nuclear family.
- Affected subjects share a novel, non-causal GRN DNA variant [Fig. 1]

Main Question
- Where do affected individuals share haplotypes - closely linked gene variants?

Methods and Results
- Extract DNA from III-7 & III-18
- Next-gen whole exome sequencing
- Identify genetic variants and obtain variant call files (VCF) using the GeneStack pipeline [Fig. 2]

Ongoing Work
- The VCF files, and VCFs from whole genome sequencing of eight other family members are being used to impute genotypes and assess shared haplotypes using SHAPEIT2 on the Oxford Phasing Server

Figure 1. Detail from the MEN-1 kindred. Legend: squares: males, circles: females, confirmed dementia/parkinsonism, suspected disease, c.-22G>A, p.Val8Met GRN variant present/absent available whole genome sequence GRN plasma levels assessed assessed for TDP-43 pathology

Figure 2. Flowchart for GeneStack Whole Exome Sequence Analysis Pipeline

References