GENETIC VARIANTS CONTRIBUTING TO FRONTOTEMPORAL DEMENTIA WITH PARKINSONISM

Elizabeth Oduwo
Neuroscience Program, University of Nebraska at Omaha, NE 68182

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]

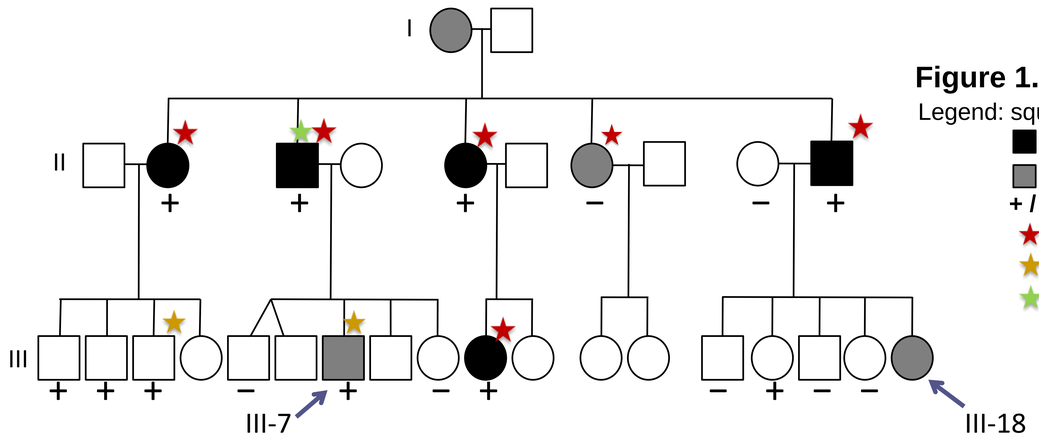

Figure 1. Detail from the MEN-1 kindred.
Legend: squares: males, circles: females,
confirmed dementia/parkinsonism,
suspected disease
+ / – c.22G>A, pVal8Met GRN variant present/absent
available whole genome sequence
GRN plasma levels assessed
assessed for TDP-43 pathology

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]

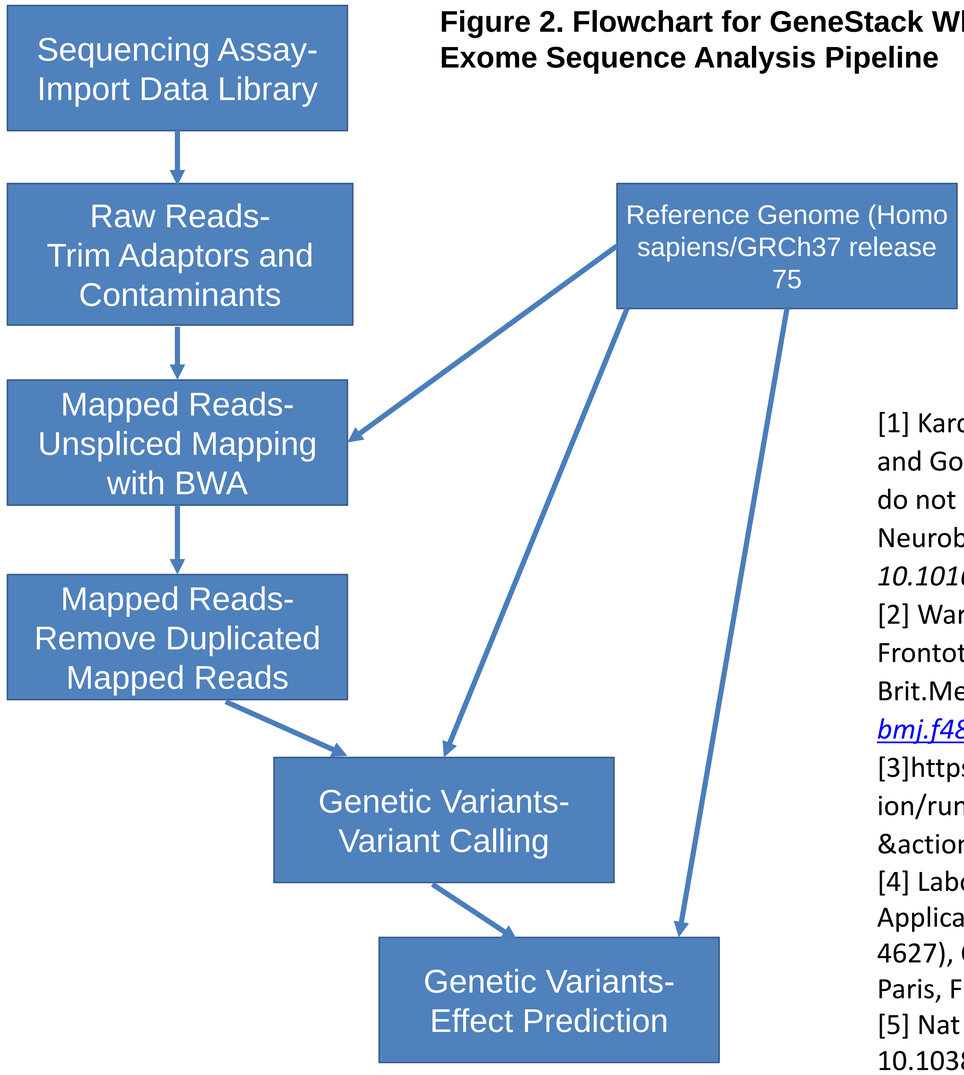

Figure 2. Flowchart for GeneStack Whole Exome Sequence Analysis Pipeline

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

References

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