Application number/Title: 27449 - Genetic Association to Phenotypic Variance and its Role in Human Health

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Keywords provided by the Applicant PI to describe the research project:

Phenotypic variance, genome-wide association.

Application Lay Summary:

1a: Disease may arise when the phenotype of an individual surpasses a given threshold, such as fasting glucose level in type 2 diabetes. Thus, changes in DNA sequence associated with greater fluctuation, or variance, in phenotype may result in a greater number of individuals at increased disease risk, despite possessing the same average phenotype as individuals carrying no change in DNA sequence. The aim of this research program is to identify changes in DNA sequence associated to phenotypic variance across multiple traits. It will determine the extent to which phenotypic variance due to genetic variation contributes to overall disease susceptibility.

1b: A DNA change's effect on phenotypic variance represents an important part of genetics' contribution to differences in phenotype between individuals. Currently, only a few studies have found genetic variants associated to phenotypic variance of human phenotypes[1], [2]. Therefore, a large part of the genetic landscape that contributes to our understanding of human health, including contributions to disease susceptibility, remains unexplored. Identifying genetic variation associated to phenotypic variance across multiple traits would better inform public health policy, such as limiting certain biological or environmental exposures that push the phenotype of at-risk individuals over the disease-risk threshold.

1c: Utilizing UK Biobank, we will associate differences in DNA sequence at

specific genome positions to the extent that a trait is spread about the mean (i.e. variance). We will remove bias due to genetically related individuals and the correlation between traits. Due to increased error inherent in measuring trait variance, and expected small effect of genetic changes on phenotype, only a comprehensive analysis of multiple traits using a very large number of individuals will make this analysis possible. Results will determine if there exists DNA changes that associate to phenotypic variance across multiple traits.

1d: We request the full cohort, ~500,000 participants (ETA Q2 2017) of which currently ~150,000 are available, to maximize statistical power and phenotype coverage.