Application number/Title: 16009 - A meta-analytic genome-wide association study for Vitamin D Levels

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

GWAS, vitaminD, rare/low-frequency variants

Application Lay Summary:

1a: We propose to run a large scale analysis of genome-wide association studies (GWAS) to identify novel common, low-frequency and rare genetic variants associated with vitamin D (specifically 25-hydroxyvitamin D (25OHD)). We are aiming to expand the understanding of how genetic variation contributes to levels of vitamin D which is known to be associated with a host of different disorders and also with biological pathways important for diseases such as cancer. This understanding will not only help us to understand what determines levels, but also apply this knowledge to assess the impact of vitamin D levels on disease.

1b: Vitamin D insufficiency affects up to half of otherwise healthy adults with detrimental impacts on public health. Approximately 50% of the variability in 25OHD levels is attributable to genetic factors. Although genetic factors are speculated to contribute substantially to this variability, the identified to date four common variants explain little of the heritability. The objective of the present study is to detect additional common, low-frequency and rare variants in novel genetic loci of large effect, associated with 25OHD levels, enabling the identification of novel pathways implicated in 25OHD metabolism and groups of individuals at risk for 25OHD insufficiency.

1c: We have collected 12 participating studies, with approximately 30,000 individuals with genome-wide genotypes and 25OHD levels. All cohorts have assessed the effect of genetic variants on 25OHD levels. We have imputed each cohort to the UK10K/1000Genomes

reference panel which enables more accurate estimation of low frequency and rare genotypes. While we have identified preliminarily interesting findings, we aim to include the UKBiobank data to replicate our findings and identify potential novel loci. To do so, we will undertake a fixed-effects meta-analysis of all cohorts of the effect of each genetic variant on 25OHD levels.

1d: For these analyses we request access to genome-wide genotyping data, serum levels of 25OHD, and the following covariates: sex, age, body mass index, date of vitamin D measurement and reported vitamin D intake through food and supplemental sources. Specifically we request the above data for the entire UKBiobank cohort as and when available. We would like to use and extend (with the full release when available) imputed GWAS data generated as part of UKBiobank project 8786. This will greatly speed up our project and prevent replication of effort and minimise the amount of storage we use for this project.

We propose to run a large scale analysis of genome-wide association studies (GWAS) to identify novel common, low-frequency and rare genetic variants associated with vitamin D (specifically 25-hydroxyvitamin D (25OHD)). We are aiming to expand the understanding of how genetic variation contributes to levels of vitamin D which is known to be associated with a host of different disorders and also with biological pathways important for diseases such as cancer. This understanding will not only help us to understand what determines levels, but also apply this knowledge to assess the impact of vitamin D levels on disease.

Extension: In our original proposal, we aimed to use genetic variants associated with vitamin D to test for causal associations with down-stream factors. To add to this, we aim to test the association between vitamin D and down-stream biological pathways (including lipids and IGF-I) and how these down-stream biological pathways impact on various disease outcomes including cancer using both observational and Mendelian randomization analyses.