Assessing Phenotypic Associations with Relative Average Telomere Length

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Background: Cells in mitotic arrest can induce inflammation and, in excess, tissue failure; this constitutes one mechanism that connects **T**elomere **L**ength (TL) to geriatric diseases. Telomeres are repetitive sequences of non-coding DNA that protect genomic information by capping the ends of chromosomes. TL becomes shorter each time a mitotic cell replicates. When reduction in TL becomes too short, cells become senescent or apoptotic. This phenomenon, known as "biological ageing," can be exploited by using a **Phe**nome-**W**ide **A**ssociation **S**tudy (PheWAS) to identify phenotypic associations between TL and genetic diseases and possibly detect early onset of disease in predisposed individuals.

Methods: DNA samples isolated from white blood cells were provided by Vanderbilt University's BioVU cohort (n ~65000) and Marshfield Clinic's **P**recision **M**edicine **R**esearch **P**rogram (PMRP) cohort (n ~20000). High throughput quantitative PCR measured the **r**elative **a**verage **T**elomere **L**ength (raTL) by comparing the amplification signals of telomeres to that of a single copy gene (stable internal control). A precursory PheWAS was run on Marshfield Clinic's PMRP raTL data to identify diseases associated with abnormal TL. raTLs from the first ~20,000 samples from Vanderbilt were assessed with age and compared with the PMRP cohort.

Results: The raTLs from Vanderbilt's BioVu cohort were correlated with age, producing a similar linear model (with a comparable regression coefficient) to that of the PMRP cohort. PheWAS analysis with the PMRP identified several phenotypes associated with short TL including tobacco use disorder, obesity, chronic airway obstruction, and type II diabetes. Long TL was associated with benign neoplasms of the skin and breast.

Conclusions: PheWAS data from the PMRP cohort suggests an association between TL and cellular senescence exists, providing an explanation for the onset of certain clinical phenotypes later in life. Future PheWAS associations from the BioVu cohort will likely support this conclusion.