**University of Leicester**

**Future 50 PhD Scholarship**

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| **Project Reference** | CVS Codd |

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| **Additional Supervisor** |  |

**Section 2 – *Project Information***

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| **Project Title** | Telomere length in humans, going beyond simple genetic variants: The effect of copy number and mitochondrial variation on telomere length and disease risk. |
| **Project Highlights:** | 1. | Understanding genetic variation that contributes to disease risk through telomere length regulation |
| 2. | Working with large-scale (UK Biobank) data |
| 3. | Training in both statistical and laboratory techniques |
| **Project Summary**  |
| Telomere length is highly variable between individuals and has been causally associated with a number of diseases, including coronary artery disease, hypertension and a range of cancers and proliferative disorders. Our recent genome-wide association (GWAS) study identified 197 genetic variants (SNP) that associate with human leucocyte telomere length (LTL, Codd et al., Nat Genetics 2021). However, the GWAS analysis only explains 5.64% of the variability between individuals and SNP based heritability is lower than that estimated by other means. It is therefore likely that other types of genetic variation contribute to LTL and subsequent disease risk.Copy number variation (CNV) has been shown to associate with increased risk of asthma (Fawcett et al., BMC Medical Genomics, 2022) and a range of common traits and diseases, including CAD (Aguirre, Rivas and Priest, AJHG, 2019). The scale of data available within UK Biobank has also allowed the identification of mtDNA variants that associate with a range of traits and diseases for the first time (Yonova-Doing et al., Nat Genet. 2021). There is an established relationship between mitochondrial function and telomere length, with mitochondrial dysfunction leading to telomere attrition and the telomerase subunit TERT protecting mitochondria from oxidative stress.The aim of this project is to gain skills in statistical, bioinformatic and experimental approaches to explore how CNV and/or mitochondrial variants may influence LTL. CNVs will be identified in UK Biobank using both genotype array and sequencing data established methods (PennCNV, ClinCNV). We will test these for association with LTL using both individual CNVs and gene-based aggregate burden scores. For mtDNA we will test both individual variants and mtDNA haplotypes. We will also test for interaction between CNVs and mtDNA variants and genomic SNPs that associate with LTL. Once significant associations and/or interactions are identified these will be further explored to establish how they contribute to disease risk and understanding the biological mechanisms through which they influence LTL using a variety of molecular and cellular laboratory-based techniques. The successful applicant will work alongside world-leaders in the field of LTL genetics and will receive training in both statistical and laboratory techniques. |