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Background: The field of epigenomics holds great promise in understanding and treating disease with advances in machine learning (ML) becoming increasingly important. Recently, DNA methylation (DNAm) measures have been utilised to detect disease and estimate biological traits such as aging. Given the challenge of high-dimensionality of DNAm data, feature-selection techniques are commonly employed to reduce dimensionality and identify the most important subset of features. In this study, our aim was to test and compare a range of feature-selection methods and machine-learning (ML) algorithms in the development of a novel DNAm-based telomere length (TL) estimator.

Results: We found that principal component analysis in advance of elastic-net regression led to the overall best performing estimator when evaluated using a nested cross-validation analysis and two independent test cohorts. This approach achieved a correlation between estimated and actual TL of 0.295 in our validation test set. Contrastingly, the baseline model of elastic-net regression with no prior feature reduction stage performed less well in general—suggesting a prior feature-selection stage may have important utility. Additionally, we observed that different DNAm-based TL estimators, with few common CpGs, are associated with many of the same biological entities.

Conclusion: The variance in performance across tested approaches shows that estimators are sensitive to dataset heterogeneity and the development of an optimal DNAm-based estimator should benefit from our developed methodological approach. Moreover, our methodology which utilises a range of feature-selection approaches and ML algorithms could be applied to other biological markers and disease phenotypes, to examine their relationship with DNAm.

P06 Adapted qPCR Methodology to Detect Oxidative Damage Associated with Induction of Telomere Attrition (TA) in Murine Tissue

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Numerous studies suggest that oxidative stress (OS) is associated with TA but rarely is telomeric oxidative damage (TOD) directly assessed. TOD alters shelterin binding, induces replication fork stalling and inhibits telomerase activity.

We adapted previously published methods to measure TOD, for use in murine tissue. We used C57BL/6J mice, with a naturally occurring nicotinamide nucleotide transhydrogenase (NNT) deficiency, previously used as a model of OS. Relative telomere length (RTL) was measured using mmQPCR and TOD was directly assayed using a formamidopyrimidine DNA glycosylase (FPG) enzyme-based qPCR method. This analysis compares reaction efficiencies before and after FPG treatment. FPG has a role in base excision repairs pathways, removing oxidised Purines (notably 8-Oxo Guanine). A reduction in the efficiency of the reaction indicates the presence of 8-oxo guanine in the telomeric tract ie TOD.

We adapted the assay specifically to investigate the longer murine telomeres. Namely reducing total template, increasing incubation time and adjusting qPCR parameters.

We show that both WT and nnt-/- kidney tissue has high RTL and low OS, testes has low RTL with high OS and BAT has average RTL and high OS. Using this improved method we have been able to show direct oxidative damage in a variety of mouse tissues and to demonstrate that TL and TOD do not always correlate. In light of our findings, care should be taken when interpreting data which use indirect biomarkers of oxidative stress to assess their role in TA. Additionally the nnt-/- mouse model, surprisingly did not show differential TOD.

P07 Diagnostic Yield of Broad Genomic Strategies: An Updated Analysis of The Irish Kidney Gene Project Registry

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Introduction: The prevalence of monogenic nephropathies is underestimated, despite over 700 genes being implicated. Herein, we provide an update on the diagnostic yield of various technologies (exome sequencing, targeted gene panel, and *MUC1* genotyping) employed by the Irish Kidney Gene Project (IKGP).

Methods: Between January 2014 and March 2023, clinic visit records were analyzed for clinical and genetic factors associated with resolved cases. ACMG-defined pathogenic or likely pathogenic variants were considered disease-causing.

Results: 593 IKGP families (976 individuals) have been sequenced to date, of which 58.5% have reached kidney failure, with an average age of 42.3 ± 16.5 years. We identified a disease-causing variant in 47.4% (281/593, following ACMG guidelines) of families, encompassing 52 distinct monogenic entities. Three phenotypes accounted for up to 82% of positive results in genes