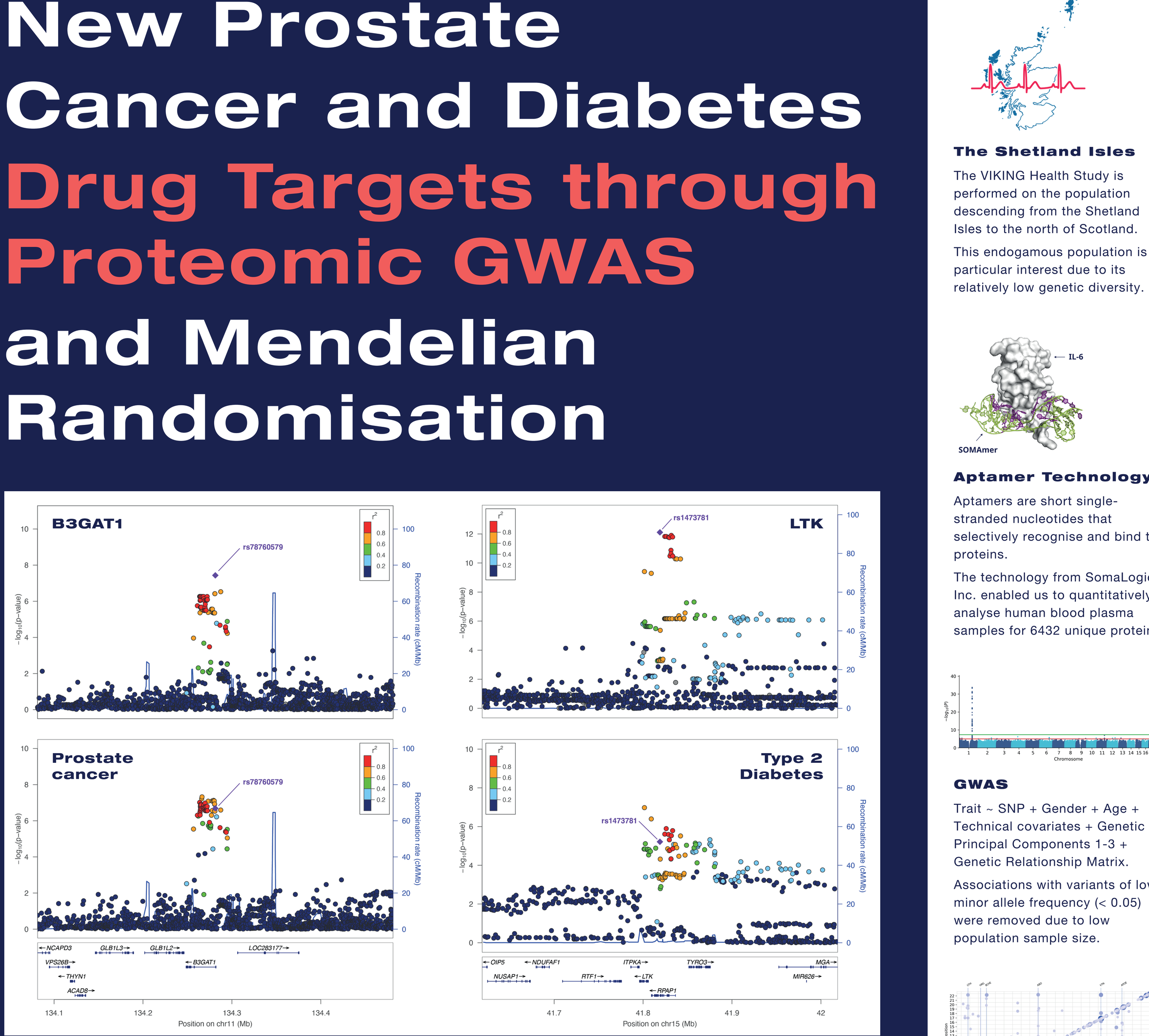
New Prostate Cancer and Diabetes Drug Targets through Proteomic GWAS and Mendelian Randomisation



These protein level and disease GWAS colocalize with Posterior Probability of Hypothesis 4 (PP4) >90% indicating a common signal between the datasets

Study design

In this study we performed a GWAS of 7596 protein-targeting aptamers with the aim of identifying genetic factors that lead to increased disease risk. We focused on 1790 largely unstudied proteins.

Combining broad-capture proteomics with genomic variation across a population is a valuable resource with implications in elucidating complex traits and disease in multiple tissues, drug development or repurposing, and precision medicine.

- 200 Participants
- 6432 proteins
- 505 pQTL
- 382 cis ($p<5*10-8$)
- 123 trans ($p<6.6*10-12$)

In-depth investigation of 31 cis pQTL for 31 little-studied proteins.

Main findings

Two-sample Mendelian Randomisation and Colocalisation were performed using public datasets to assess causality for cis associations.

These five colocalising associations (posterior probability that the underlying signals are the same >80%) point to plausible causal roles for the measured proteins in the outcomes shown (main table). Examples of colocalisation locus zoom plots are given for 3-beta-glucuronosyltransferase 1 (B3GAT1) & prostate cancer and leukocyte receptor tyrosine kinase (LTK) & type-2-diabetes (main figure).

HUGO	GWAS - log(p)	GWAS Effect size	MR Outcome	MR - log(p)	MR Effect size
B3GAT1	7.4	-0.80	Prostate cancer	6.7	-0.080
LTK	12	0.69	Type 2 Diabetes	5.2	0.054
NIF3L1	12	0.88	Macular degeneration	5.7	-0.11
NTAQ1	11	-0.62	Testosterone levels	6.3	-0.026
SEMA5B	7.8	0.55	Depression	4.4	0.019

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Authors declare no conflicts of interest.

The Shetland Isles

The VIKING Health Study is performed on the population descending from the Shetland Isles to the north of Scotland.

This endogamous population is of particular interest due to its relatively low genetic diversity.

Aptamer Technology

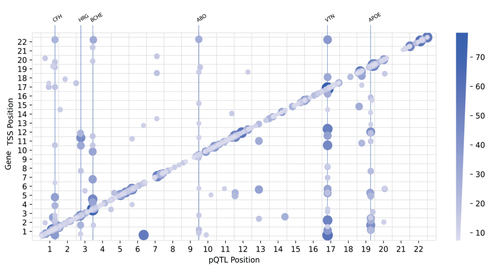
Aptamers are short single-stranded nucleotides that selectively recognise and bind to proteins.

The technology from SomaLogic Inc. enabled us to quantitatively analyse human blood plasma samples for 6432 unique proteins.

GWAS

Trait ~ SNP + Gender + Age + Technical covariates + Genetic Principal Components 1-3 + Genetic Relationship Matrix.

Associations with variants of low minor allele frequency (< 0.05) were removed due to low population sample size.



Association mapping

Plotting all significantly associated protein Quantitative Trait Loci (pQTL) across the proteome against their corresponding gene transcription start site (TSS) shows cis associations on the diagonal.

Previously reported pleiotropic hubs are visible as vertical lines in the plot and the association strength is denoted by the size of the data point.

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