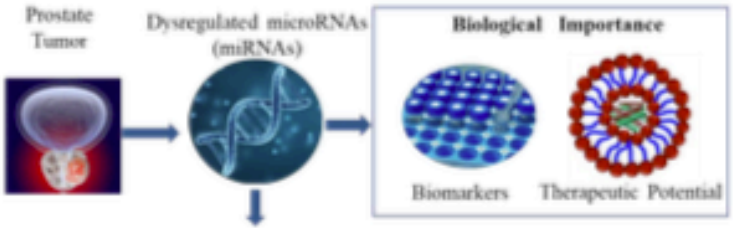
Identifying microRNA Biomarkers in Prostate Cancer: A Transcriptome-Wide Association Study (TWAS)

Dulari K. Jayarathna[1,2], Miguel E. Rentería[2], Jyotsna Batra[3,4], Emilie Sauret [5], Samaneh Farashi[3,4] & Neha S. Gandhi[1]

1. Queensland University of Technology (QUT), Centre for Genomics and Personalised Health, School of Chemistry and Physics, Faculty of Science and Engineering, Institute of Health and Biomedical Innovation, 2 George Street, Brisbane, QLD 4000, Australia., 2. Department of Genetics and Computational Biology, QIMR Berghofer Medical Research Institute, Brisbane, QLD 4006, Australia, 3. Australian Prostate Cancer Research Centre- Queensland, Translational Research Institute, Brisbane, QLD 4102, Australia, 4. Cancer Program, School of Biomedical Sciences, Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, QLD 4102, Australia., and 5. School of Mechanical, Medical & Process Engineering, Queensland University of Technology, 2 George Street, Brisbane, QLD 4000, Australia.

Introduction



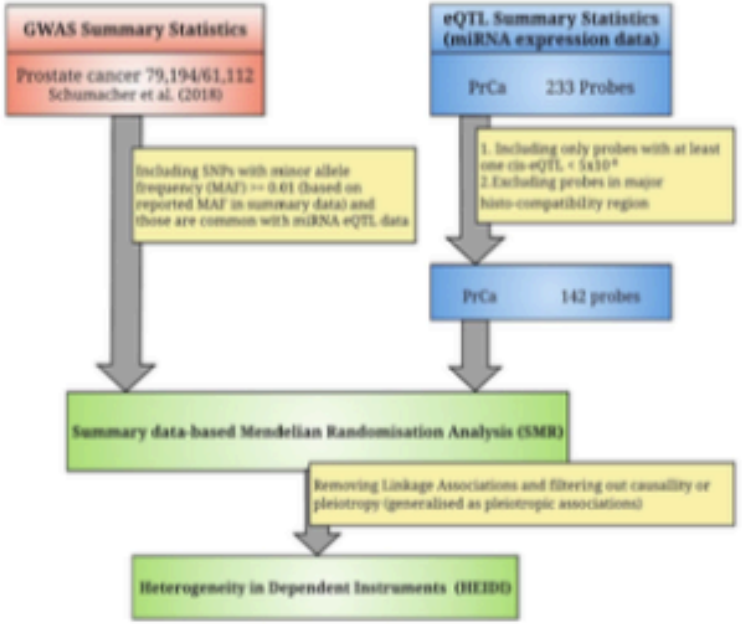
Computational Methods

(to identify Prostate Cancer (PrCa) risk-associated miRNAs)

GWAS (genome-wide association studies)	eQTL (expression quantitative trait loci)	TWAS (transcriptome-wide association studies)
Found PrCa risk loci associated with miRNA regions [1]	Found risk loci-miRNA expression level associations	Integrates GWAS and eQTL to find miRNA-PrCa associations

Computational Method Workflow

A GWAS and eQTL summary data-based TWAS method, SMR (summary data-based Mendelian randomisation)-HEIDI (Heterogeneity in dependent instruments) was used to identify miRNA-PrCa risk associations.

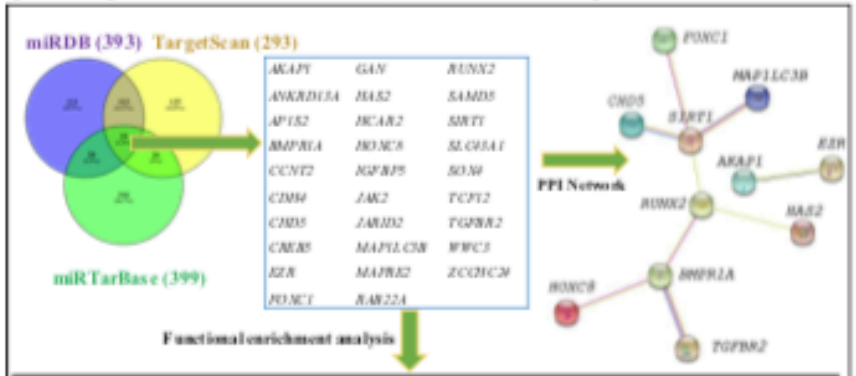


Results

Table1. SMR-HEIDI results for miRNAs in PrCa

microRNA	Top-SNP ID	Effect sizes	FDR (SMR)	p-value (HEIDI)
hsa-miR-22-5p	rs684232	-0.52	2.65E-04	NA
hsa-miR-5699-5p	rs10904588	-0.1511	1.41E-02	NA
hsa-miR-4661-5p	rs6999873	-0.0898	1.74E-02	2.02E-01
hsa-miR-155-5p	rs2829580	0.1625	2.16E-02	NA
hsa-miR-194-3p	rs3741389	0.0932	3.77E-02	NA
hsa-miR-204-5p	rs10124022	-0.0517	4.01E-02	8.92E-01

Three miRNA target prediction tools (miRDB, miRTarBase, and TargetScan) identified miRNA targets for SMR-HEIDI significant. The STRING server was used to enrichment analysis and construct protein-protein interaction (PPI) network (see Figure 1).



Gene Ontology pathway	Genes associated with pathway	FDR
Regulation of developmental growth	*FOXC1, CDH4, WWC3, BMPR1A, TGFBR2, JARID2, SLC43A1*	0.00044
Regulation of organ growth	*FOXC1, WWC3, BMPR1A, TGFBR2, JARID2*	0.00044
Regulation of growth	*FOXC1, CDH4, WWC3, BMPR1A, TGFBR2, JARID2, SIRT1, TGFBR2, EZR*	0.00044
Heterochromatin	*FOXC1, CHD5, SIRT1*	0.0253
bHLH transcription factor binding	*SIRT1, RUNX2, CF12*	0.0028

Figure1. The PrCa risk associated miRNAs target genes were predicted by three databases, miRDB, TargetScan, and miRTarBase. The shared target genes among three tools were input for STRING online server to construct PPI network and performed functional enrichment analysis. The PPI network analysis exhibits a network of eleven out of twenty-nine genes. Three pathways among top-five are associated with growth regulation pathways. Heterochromatin and bHLH transcription binding factor were most significant for cellular component and molecular function sub ontologies.

Discussion

- Six-miRNAs were identified by SMR and they were further analysed using HEIDI method to avoid linkage associations.
- The HEIDI test recognised hsa-miR-204-5p and hsa-miR-4661-5p as significant in PrCa risk and predicted as tumor-suppressive by negative effect sizes. Lin *et al* have shown that hsa-miR-204-5p repress PrCa oncogenes [2].
- Twenty-nine miRNA targets were found for hsa-miR-204-5p and no shared miRNA targets were found for hsa-miR-4661-5p.
- Eleven out of twenty-nine miRNA targets involved in a significant PPI network including known mutated genes in PrCa.
- In functional enrichment analysis, the top three significant are associated with growth related regulation in biological process where Heterochromatin and bHLH transcription factor binding were significant from cellular component and molecular function, respectively (see Figure 1).
- The given analytical approach can be implemented for other cancers which would be helpful to build up comprehensive miRNA profile in cancers.

Conclusion

- SMR-HEIDI provides a means of using summary statistics from GWAS and miRNA eQTL to identify likely functionally relevant miRNAs in previously identified GWAS loci.

References

1.Benaff, S., Z. Kote-Jarai, and R.A. Eeles, A Review of Prostate Cancer Genome-Wide Association Studies (GWAS). Cancer Epidemiol Biomarkers Prev, 2018. 27(8): p. 845-857.

2.Lin, Y.C., et al., Tumor suppressor microRNA-204-5p promotes apoptosis by targeting BCL2 in prostate cancer cells. 2017. 40(5): p. 396-406.

Acknowledgement

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