Oslo University Hospital

UiO : Faculty of Medicine — University of Oslo

AKERSHUS UNIVERSITY HOSPITAL

GRIN3A – a novel biomarker identifying a subtype of intraductal prostate cancer (IDC-P)

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Background

- Histopathological grading with determination of the Gleason score/Grade Group is one of the best prognosticators in prostate cancer

- Specific morphological features, *e.g.*, a cribriform pattern (intraductal carcinoma and/or invasive cribriform carcinoma), have gained increasing attention as prognostic biomarkers due to findings of associations with a poorer prognosis

- The molecular mechanism contributing to the association between a cribriform pattern and a poorer prognosis is not fully understood. Further, there are still no specific molecular markers for a cribriform pattern warranting further research

Main Aim

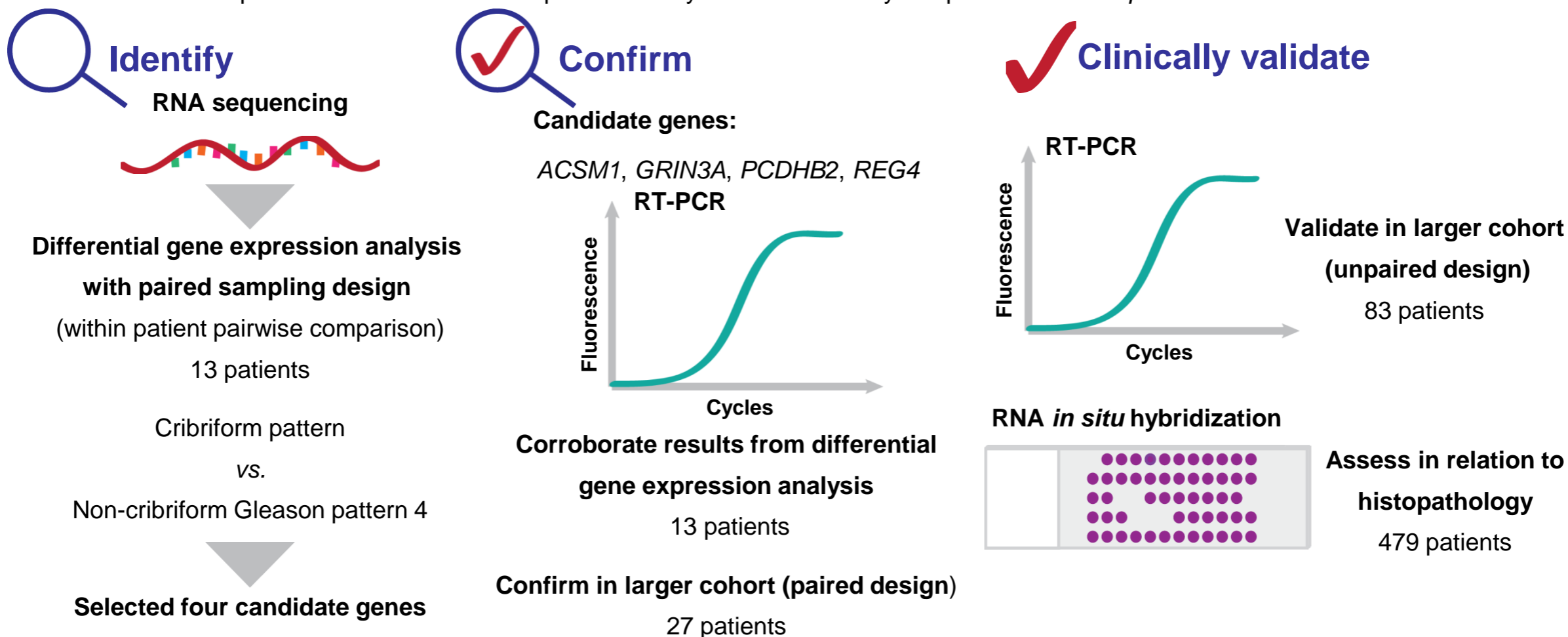To identify molecular markers specific for a cribriform pattern in prostate cancer
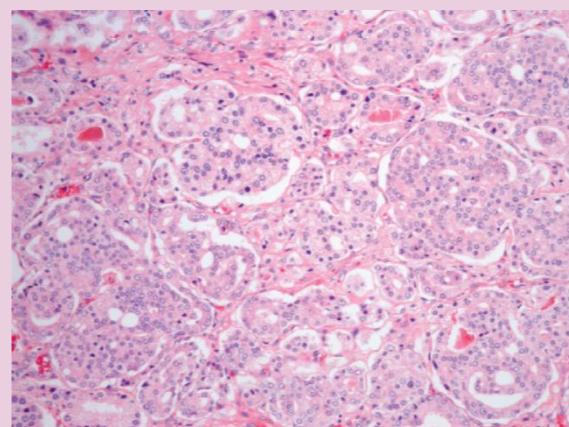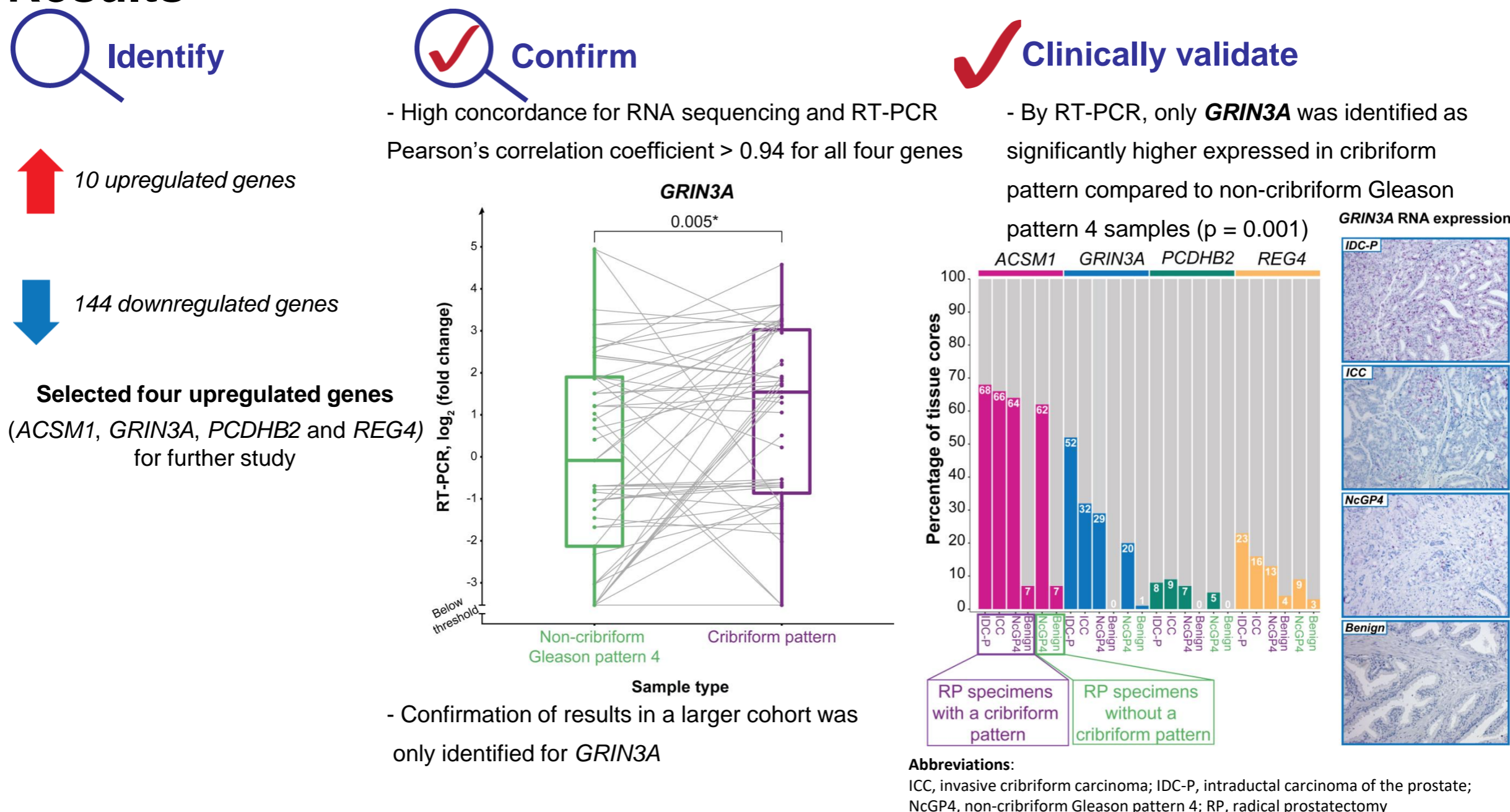

Invasive cribriform carcinoma
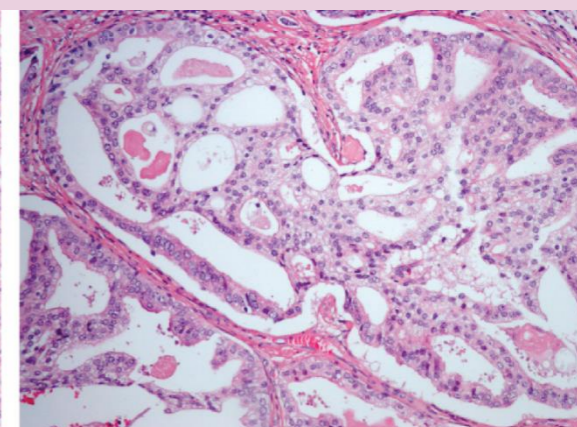
Intraductal carcinoma

Materials and methods

Patient cohort: 515 patients treated with radical prostatectomy at Oslo University Hospital–*Radiumhospitalet* between 2010 and 2012

Identify

RNA sequencing

Differential gene expression analysis with paired sampling design

(within patient pairwise comparison)

13 patients

Cribriform pattern

vs.

Non-cribriform Gleason pattern 4

Selected four candidate genes

Confirm

Candidate genes:

ACSM1, *GRIN3A*, *PCDHB2*, *REG4*

RT-PCR

Corroborate results from differential gene expression analysis

13 patients

Confirm in larger cohort (paired design)

27 patients

Clinically validate

RT-PCR

Validate in larger cohort (unpaired design)

83 patients

RNA *in situ* hybridization

Assess in relation to histopathology

479 patients

Results

Identify

↑ *10 upregulated genes*

↓ *144 downregulated genes*

Selected four upregulated genes

(*ACSM1*, *GRIN3A*, *PCDHB2* and *REG4*) for further study

Confirm

- High concordance for RNA sequencing and RT-PCR Pearson's correlation coefficient > 0.94 for all four genes

GRIN3A

0.005*

RT-PCR, $\log_2$ (fold change)

Non-cribriform Gleason pattern 4 — Cribriform pattern

Sample type

- Confirmation of results in a larger cohort was only identified for *GRIN3A*

Clinically validate

- By RT-PCR, only *GRIN3A* was identified as significantly higher expressed in cribriform pattern compared to non-cribriform Gleason pattern 4 samples (p = 0.001)

GRIN3A RNA expression

IDC-P

ICC

NcGP4

Benign

Abbreviations:
ICC, invasive cribriform carcinoma; IDC-P, intraductal carcinoma of the prostate; NcGP4, non-cribriform Gleason pattern 4; RP, radical prostatectomy

Conclusion

Through the use of RNA sequencing, RT-PCR and RNA *in situ* hybridization methods on radical prostatectomy specimens, we have identified a potential RNA-based marker, *GRIN3A*, for the presence of a cribriform pattern in prostate cancer, and specifically a subtype of intraductal carcinoma. Further, *GRIN3A* was identified as a tumor marker as it was only rarely expressed in benign tissue. Additional studies are needed to elucidate the functional role of *GRIN3A* in tumors with a cribriform pattern and whether it may be used in a diagnostic setting.

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