PW 9.13

International Surgical Week
The World's Congress of Surgery
isw2024.org
Kuala Lumpur, Malaysia
25-29 August 2024

THE EVOLUTIONARY HISTORY OF METASTATIC ADRENOCORTICAL CARCINOMA

Samuel Backman[1], Fredrik Axling[1], Johan Botling[2], C. Christofer Juhlin[3], Britt Skogseid[4], Jan Zedenius[5], Olov Norlén[1], Peter Stålberg[1], Joakim Crona[4], Tobias Åkerström[1]

[1]Department of Surgical Sciences, Uppsala University, Uppsala, Sweden; [2]Department of Laboratory Medicine, Institute of Biomedicine, University of Gothenburg, Gothenburg, Sweden; [3]Department of Oncology – Pathology, Karolinska Institutet, Stockholm, Sweden; [4]Department of Medical Sciences, Uppsala University, Uppsala, Sweden; [5]Department of Molecular Medicine and Surgery, Karolinska University, Stockholm, Sweden

Conclusion

- Most metastatic ACC undergo LOH followed by WGD (cnLOH)
- cnLOH occur early in the evolution of the tumor
- Mutation heterogeneity is common in advanced ACC
- *FLCN*, *BAP1*, *RNF43, ATR* are novel potential driver genes in ACCs

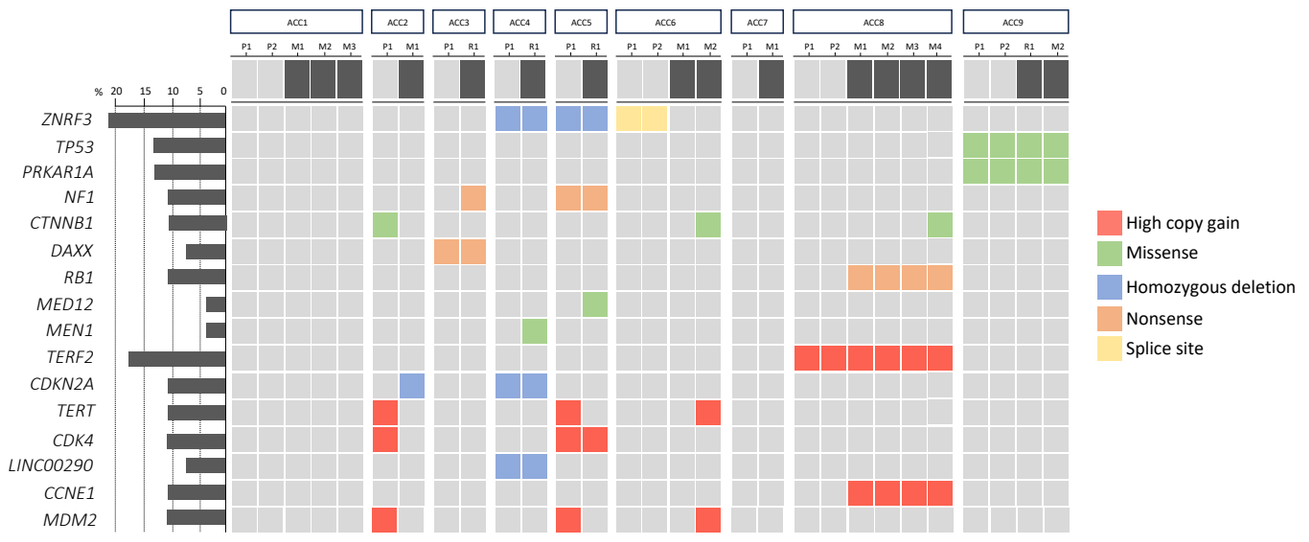

Figure 2. Mutational spectrum and heterogeneity. Top row – Tumors included (P – primary, M - metastatic)

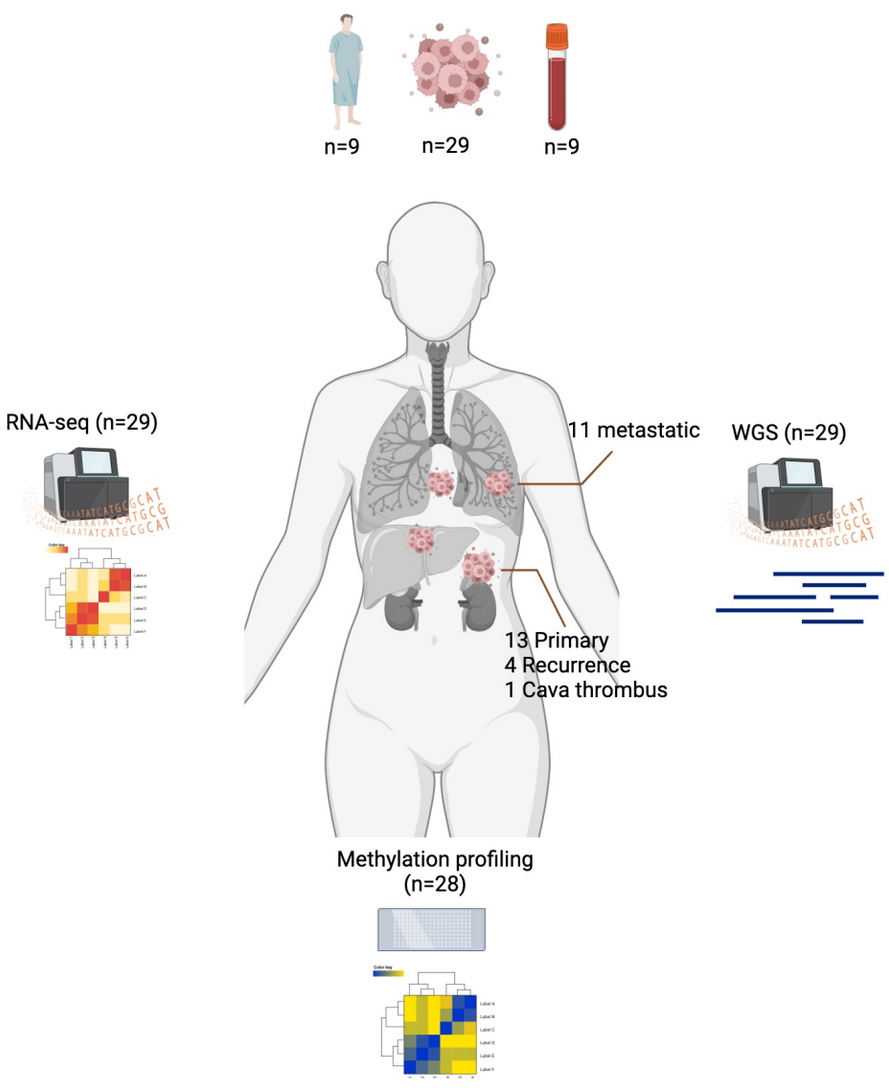

Figure 1. The infrastructure of the current study.

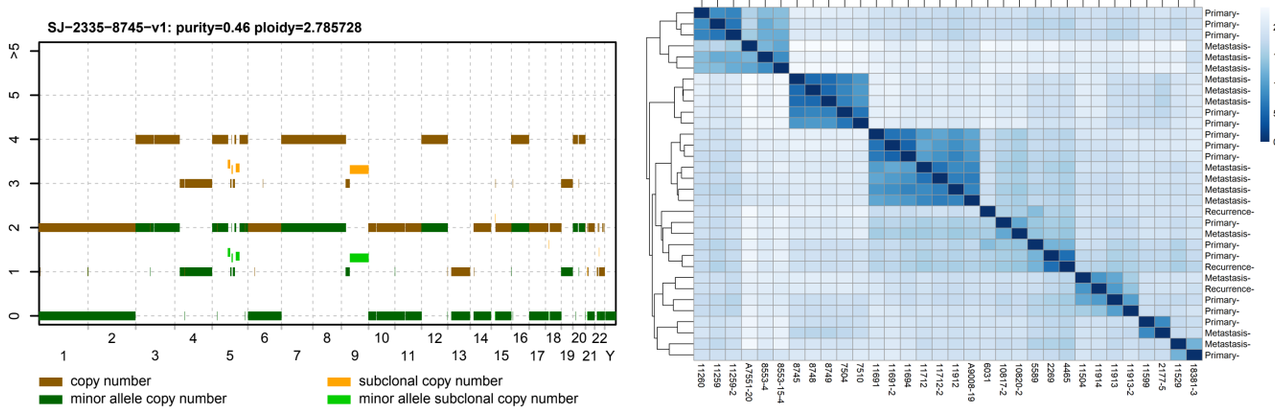

Figure 3. (Left) Example of global LOH followed by WGD. (Right) Paired tumors cluster per patient by RNA sequencing.

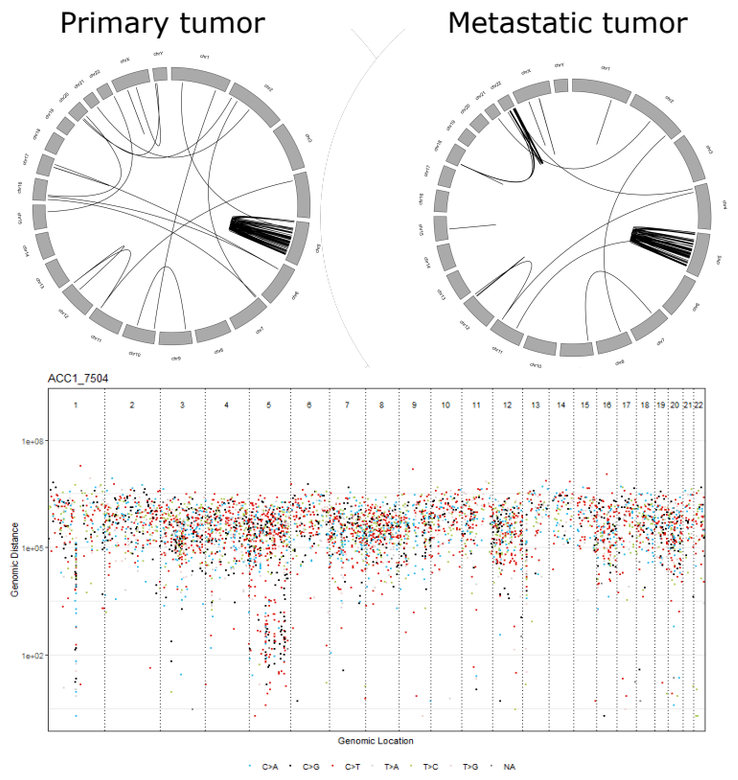

Figure 4. (Top) circos plots depicting small copy number alterations. In this patient Chr 5 is affected by a large number of structural alterations. In this area a hypermutation phenomenona occurs called kataegis (bottom).

Introduction

Adrenocortical carcinoma (ACC) is a rare and aggressive cancer with a prevalence of 1-2 per million individuals and a 5-year survival of 40%. Intratumoral heterogeneity is part of most cancers' evolution towards a metastatic state and evasion of systemic treatment. Large scale genomic investigations of different tumors have revealed a complex pattern of clonal and subclonal alterations in both single nucleotide variants (SNV) and copy number alterations (CNV).

To further extend our knowledge on intratumoral heterogeneity in advanced ACC, we performed a detailed pan-genomic investigation on paired primary and metastatic ACC.

Materials and methods

A total of 29 tumor samples from 9 patients were eligible for inclusion. All had matched primary and relapse samples (four with recurrent, eleven with metastatic). Four patients had multiple primary and metastatic tissues included. All tumors were subjected to whole-genome sequencing to a minimum of 60X, RNA sequencing (>45 million reads/sample), and methylation array (Illumina EPIC DNA methylation array) (Figure 1).

Acknowledgments

CANCERFONDEN
SciLifeLab
UPPSALA UNIVERSITET
LIONS INTERNATIONAL

Results

Previously described ACC driver mutations were heterogeneous in 44% (Figure 2)

In 8/9 patients the tumor underwent global LOH which in most cases (7/8) was followed by WGD (Figure 3). This occurred early as only a mean of 24% of SNV were present before this event.

To discover potential new candidate driver genes we selected clonal mutations also occurring in all tumor cells; *FLCN*, *BAP1*, *RNF43, ATR* were identified as new potential driver genes in ACC

Structural alterations were stable among paired tumors from the same patient, suggesting early events in tumor development (Figure 4)

RNA expression revealed upregulation of chromatin associated genes in metastatic samples.