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Comprehensive investigation of the molecular underpinnings of translocation renal cell carcinoma

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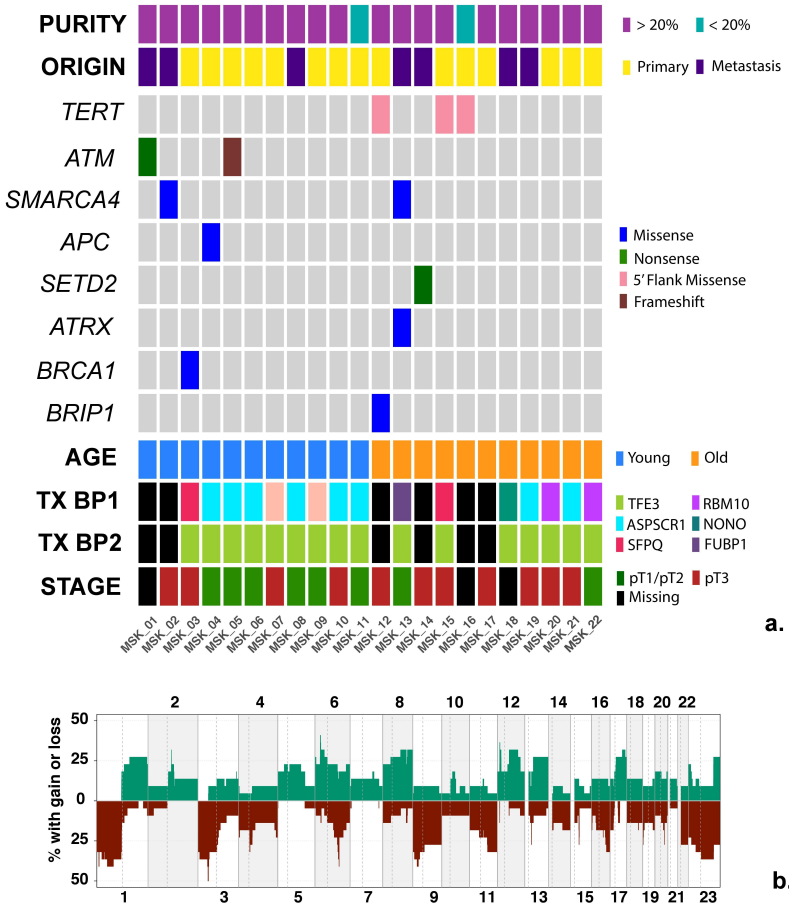
Introduction & Objectives: Translocation renal cell carcinoma (tRCC) is a rare kidney tumor subtype, however, in patients under 45 years the incidence can be up to 15%. Recent studies provided first insights into the genomic landscape of tRCC, but additional cohorts are required to fully comprehend the molecular evolution of these tumors. We performed next-generation sequencing (NGS) and allele-specific copy-number (ASCN) analysis to further investigate the genomic evolution of tRCC.

Materials & Methods: We identified 42 patients with tRCC between 1997 and 2017. Diagnosis of tRCC was established with positive immunohistochemistry and FISH results. The sequencing cohort included 27 patients. Whole-exome sequencing was performed in 13 of the samples. 14 samples were sequenced using our previously validated institutional panel (MSK-IMPACT®). We performed somatic mutation calling and ASCN analysis using our institutional bioinformatics pipeline. In order to infer the relative timing of oncogenic events, we computed clonality estimates, using the purity and ploidy estimates from the copy-number variation (CNV) analysis. Clinical correlates were assessed using non-parametric hypothesis tests, with a pre-rejection alpha of 0.05. Survival estimates were calculated using the Kaplan-Meier method.

Results: Of the sequencing cohort, 11 men and 11 women had complete mutation and copy-number data. Six patients (22%) had distant metastatic disease at presentation. The median age (42.5 years, IQR 33-52) was used to divide patients into old and young groups. The median follow-up time was 27.3 months. Frequent somatic events and translocation binding partners of the sequenced cohort are displayed in Fig.1a, copy-number events are shown in Fig.1b. Patients older than 42.5 years demonstrated a higher burden of mutations in *TERT* (p=0.21) and an elevated rate of CNVs (p=0.11), however, these results were not significant. Overall survival was decreased in patients with 9p-loss (p=0.032). The time to recurrence was reduced in patients with either 3p-loss (p=0.009) or 15q-loss (p=0.0027). Also, there was a significant association between 4q-loss and metastatic disease at presentation (p=0.009).

Fig. 1a: Oncoprint illustrating frequent somatic mutations, translocation binding partners (TX BP1 & TX BP2) and clinical parameters ; Fig. 1b: Copy-number event plot



Conclusions: Our results suggest that the genomic landscape of tRCC may differ depending on the age at diagnosis. Additional oncogenic events in older patients may result in a more aggressive phenotype. Somatic CNVs may play an important role in patient prognosis.