# The Mutational Landscape of Resected Clear Cell Renal Cell Carcinoma with Cystic components

Laura Bukavina, Johnathan Drevik, Spencer Bell, Ilaha Isali, Adam Calaway, Diana Magee, Alexander Kutikov, Robert Uzzo, Andres Correa, Philip Abbosh

FOX CHASE CANCER CENTER
TEMPLE HEALTH

## Background

- Clear cell renal cell carcinoma (ccRCC) with cystic components poses clinical and diagnostic challenges
- Cystic ccRCC (defined as <25% solid) are predominantly low-stage and low-grade tumors, but there is significant variability in morphology and oncologic outcomes
- We characterized the mutational landscape and long-term oncological outcomes of resected cystic masses within the cancer genome atlas (TCGA) database

## Methods

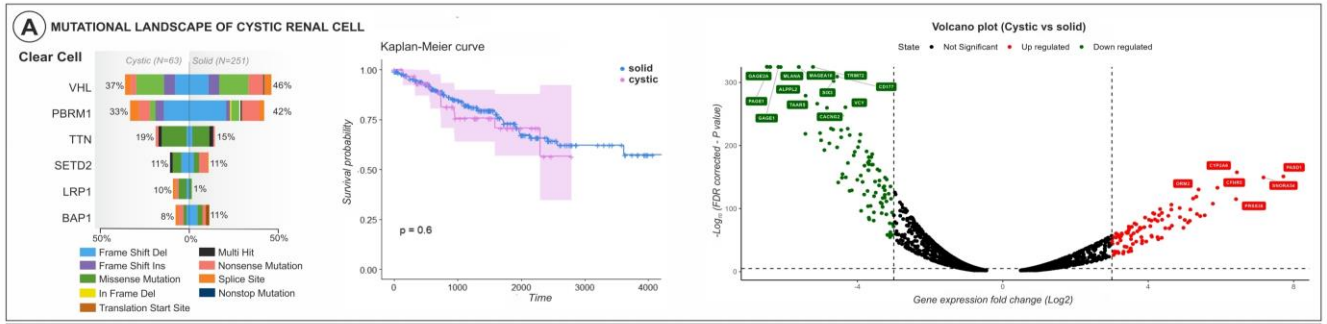
- We stratified tumor samples from kidney renal clear cell carcinoma (KIRC) within TCGA into 63 cystic ccRCC masses and 251 solid ccRCC masses based on pathology reports and DICOM images
- We compared transcriptome profiles (HTSeq-Count) of the masses and collected corresponding patient clinical data
- We also evaluated differences in overall survival (OS) between cystic and solid ccRCC patients using KM survival and log-rank test
  - Repeated this in a sub-cohort of patients with radiographically confirmed cystic ccRCC
- Pairwise differential expression (DESeq) and principal component analysis was performed (*Costalab R*) and functional analysis was performed vis *gprofiler2*

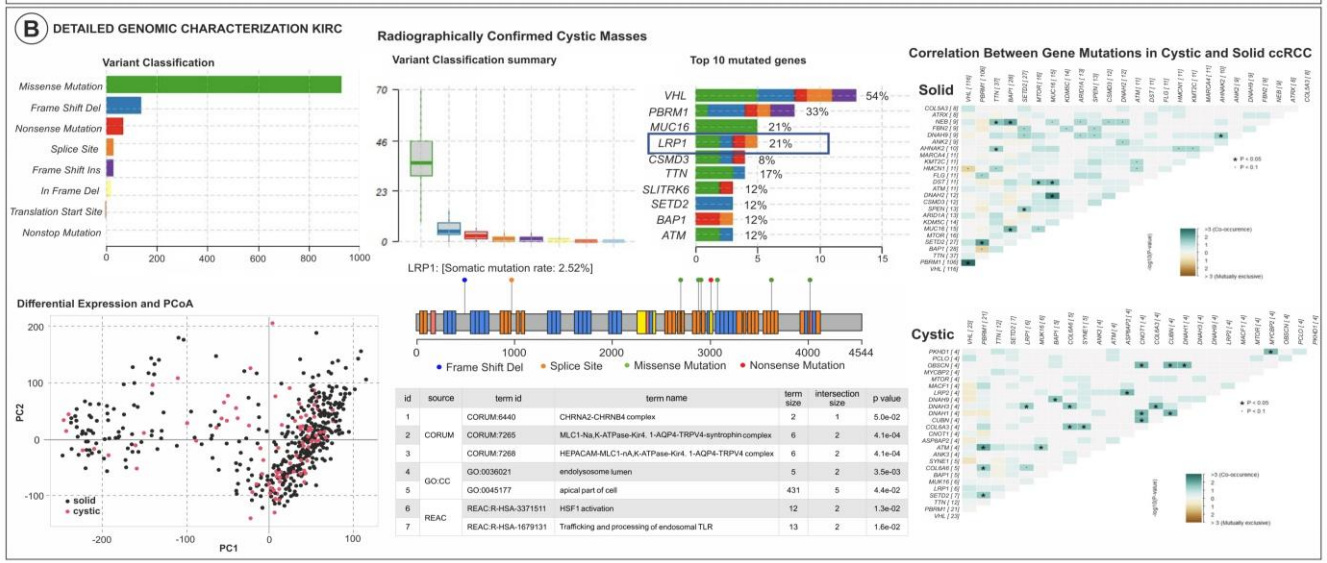
## Results

- We identified a median of 44 mutations per sample for both cohorts
  - Most frequent arm-level event involving loss of chromosome 3p (*VHL, PBRM1, BAP1, SETD2*) in both cohorts
- Arm level losses of chromosome 12q *LRP1* (low-density lipoprotein receptor, total somatic mutation rate of 2.52%) was more frequently mutated among cystic ccRCC, particularly within the radiographically confirmed cohort (21%)
- Pathways affected by mutations within cystic ccRCC include:
  1) *HSF1* activation
  2) Trafficking
  3) Processing of endosomal TLR, MLC1-Na, K-ATPase-Kir4 complex, and HEPACAM-MLC complex
- No OS differences despite upregulation of oncogenes serine protease 38 (*PRSS38*) and *PASD1* within cystic masses
- *LRP1* mutation strongly correlated with *DNAH3* mutation (constituents of microtubule-associated motor protein complex) within cystic ccRCC (p<0.05)

## Results

A) Mutation events per sample and top 10 mutations present in solid vs. cystic ccRCC. KM curve representing OS between tumors identified as large cystic components vs. none. Differentially expressed genes (DEGs) within cystic ccRCC compared to solid ccRCC with p<0.001 (FDR adjusted).




B) Distribution of mutation within a radiographically confirmed ccRCC with cystic features, including high prevalence of *LRP1* mutation. Lollipop plot illustrating *LRP1* variants in our cohort, and correlation analysis among cystic and solid RCC. *FDR, False discovery rate

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## Conclusions

- **We present the first study evaluating genetic differences between cystic and solid ccRCC**
- **This data reveals the genetic heterogeneity of disease with possible therapeutic targets unique to cystic ccRCC**
- **Further mechanistic and immunogenic details remain to be defined**