Germline mutations of renal tumor predisposition genes in early-onset patients

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Poster MP28-01

BACKGROUND

Inherited susceptibility to renal tumors has been associated with an array of RCC predisposing genes, but most screening has been limited patients with a strong family history of RCC. Next generation sequencing (NGS-) based multi-gene panel analysis provides an economic, efficient, and adaptable tool for investigating the frequency of germline pathogenic mutation on a wider scale. This study investigated the frequency of germline pathogenic mutations of renal tumor predisposition genes in sporadic, early-onset RCC.

Materials and Methods

An NGS-based array for 23 known and potential RCC predisposition genes was used to perform germline mutation analysis on 190 unrelated Chinese patients who presented with renal tumors at under 45 years old. Variants detected were filtrated for pathogenicity and frequencies were calculated and correlated with clinical features.

Table 1. Gene Selection

RCC related genes	Syndrome	Recommended genes
VHL	VHL	*BRCA1/2*
TSC1/2	Tuberous sclerosis complex	*KDM5C*
PTEN	PTEN hamartoma syndrome	*KDM6A*
MET	Hereditary papillary renal carcinoma (HPRC)	*NF2*
FH	Hereditary Leiomyomatosis and renal cell carcinoma (HLRCC)	*SETD2*
SDHB/C/D	SDH-associated kidney cancer	*CDKN2A*
FLCN	BHD syndrome	*TCEB1*
BAP1	Predisposition gene to familial ccRCC	*TP53*
MITF	MiT family kidney cancer	
HNF1B	Renal cysts and diabetes syndrome, predisposition gene	
PBRM1	Predisposition gene to familial ccRCC	

Characteristics	RCC patients
Gender, N (%)	
Male	117 (61.6)
Female	73 (38.4)
Median (range)	
Age, years	36 (17-42)
BMI, kg/m²	23.19 (13.39-46.30)
N (%)	
Pathogenic mutation carrier	18 (9.5)
Smoking status	37 (19.5)
Family history	41 (21.6)
First-degree relative	32 (16.8)
Second-degree relative	14 (7.4)
Personal history	16 (8.4)
Histological types[a]	
Clear cell	129 (67.9)
Papillary	12 (6.3)
Chromophobe	21 (11.1)
Angiomyolipoma	29 (15.3)

Table 2. Clinical characteristics and patient demographics

Note：One patient in our cohort had both clear cell renal cell carcinoma and papillary renal cell carcinoma

Results

Eighteen of 190 patients (9.5%) had germline pathogenic mutations in 10 out of 23 selected RCC predisposition genes. Twelve patients had alterations in known RCC predisposition genes (6.3%), including 3 germline *BAP1* mutations. While, 6 patients had mutations in potential RCC predisposition genes, such as *BRCA1/2*.

Carrier status was significantly associated with second-degree relative tumor history ($p < 0.001$) only.

Several germline variants of unknown clinical significance in *FH* and *BAP1* demonstrated evidence of additional somatic loss in tumors consistent with pathogenic mutations.

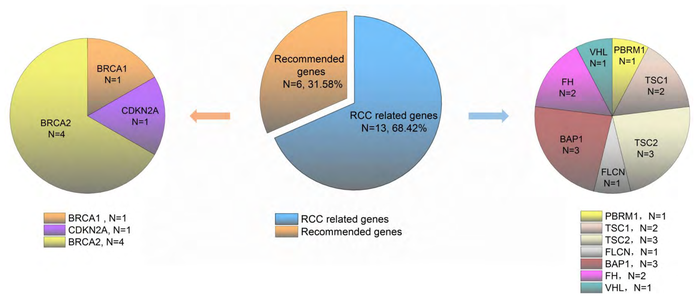

Figure 1. Pathogenic mutations identified with a 23-gene panel among 190 early-onset renal tumor patients. Proportion of mutated RCC-related genes and recommended sequenced genes are separately presented in the middle. The right pie chart shows details of mutated RCC-related genes and the left pie chart presents details of mutated recommended sequenced cancer predisposition genes.

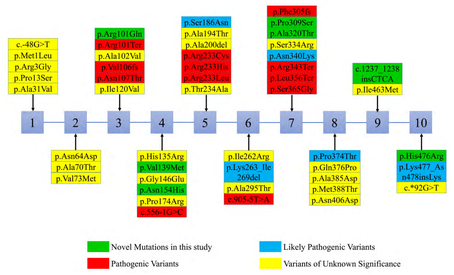

Figure 2. Schematic of FH exons showing the positions of novel mutations of FH.

(Data based on ClinVar database)

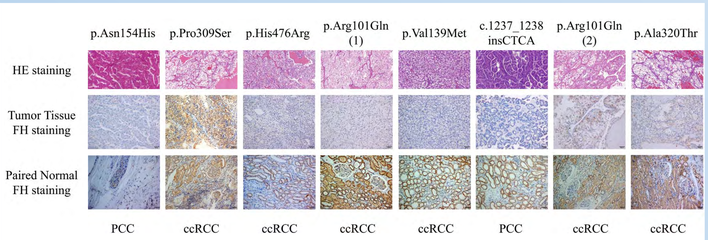

Figure 3. HE staining tumor images, tumor tissue FH staining images and paired normal tissue FH staining images (All in 200X) of 8 patients with FH germline pathogenic mutations or VUS identified.

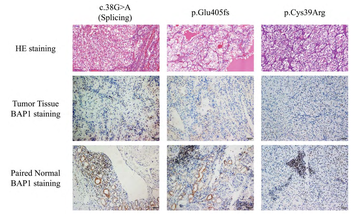

Figure 4. HE staining images, tumor tissue BAP1 staining images and paired normal tissue/infiltrating lymphcytes BAP1 staining images of 3 patients with BAP1 germline pathogenic mutations or VUS

Table 3. Difference between pathogenic mutation carriers and non-pathogenic mutation carriers in clinical categorical variable

Items	Pathogenic mutation carriers (N=18)	Non-pathogenic mutation carriers (N=172)	*P* value
Number (%)			
Gender			0.966
Male	11 (61.1)	106 (61.6)	
Female	7 (38.9)	66 (38.4)	
Family history (ALL)			0.502
Yes	5 (27.8)	36 (20.9)	
No	13 (72.2)	136 (79.1)	
First-degree relative history			0.983
Yes	3 (16.7)	29 (16.9)	
No	15 (83.3)	143 (83.1)	
Second-degree relative history			**<0.001**
Yes	5 (27.8)	9 (5.2)	
No	13 (72.2)	163 (94.8)	
Smoking status			0.757
Yes	4 (22.2)	33 (19.2)	
No	14 (77.8)	139 (80.8)	
Personal history			0.803
Yes	2 (11.1)	16 (9.3)	
No	16 (88.9)	156 (90.7)	
Histological type			0.872
Clear cell	11 (61.1)	117 (68.4)	
Papillary	1 (5.6)	10 (5.8)	
Chromophobe	3 (16.7)	18 (10.5)	
Angiomyolipoma	3 (16.7)	26 (15.2)	
Mean (SD)			
Age at diagnosis	35.06 (5.06)	35.14 (5.27)	0.949
BMI (kg/m²)	22.67 (3.23)	23.60 (3.78)	0.314

Conclusion

In early-onset patients, multi-gene panel testing identified pathogenic germline mutations in known and potential RCC predisposition genes. This emphasizes the importance of screening these early-onset patients, irrelevant of family history, and provides valuable epidemiological information. Germline mutation screening for RCC susceptibility represents an achievable aspect of personalized medicine that can improve patient outcomes.