NEAT1-TFE3 and KAT6A-TFE3 renal cell carcinomas, new members of MiT family translocation renal cell carcinoma

Jianming Pei¹ · Harry Cooper² · Douglas B. Flieder² · Jacqueline N. Talarchek¹ · Tahseen Al-Saleem² · Robert G. Uzzo^{3,4} · Essel Dulaimi² · Arthur S. Patchefsky² · Joseph R. Testa^{1,4} · Shuanzeng Wei²

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Abstract

Microphthalmia-associated transcription factor (MiT) family translocation renal cell carcinoma harbors variable gene fusions involving either *TFE3* or *TFEB* genes. Multiple 5' fusion partners for *TFE3* have been reported, including *ASPSCR1*, *CLTC*, *DVL2*, *LUC7L3*, *KHSRP*, *PRCC*, *PARP14*, *NONO*, *SFPQ1*, *MED15*, and *RBM10*. Each of these fusion genes activates *TFE3* transcription which can be detected by immunostaining. Using targeted RNA-sequencing, *TFE3* fusion gene partners were identified in 5 cases of *TFE3* immunohistochemistry positive translocation renal cell carcinoma. Three cases demonstrated known fusions: *ASPSCR1-TFE3*, *MED15-TFE3* and *RBM10-TFE3*. However, two cases showed unreported *NEAT1-TFE3* and *KAT6A-TFE3* fusion transcripts. The *NEAT1-TFE3* RCC arose in a 59-year-old male; which demonstrated overlapping morphological features seen in *NEAT2(MALAT1)-TFEB* t(6;11) renal cell carcinoma, including biphasic alveolar/nested tumor cells with eosinophilic cytoplasm. The *KAT6A-TFE3* renal cell carcinoma demonstrated typical morphological features of *TFE3*/Xp11 renal cell carcinoma including papillae, eosinophilic cytoplasm with focal clearing and abundant psammoma bodies. *KAT6A* gene fusion was reported in some cases of acute myeloid leukemia, which has not been previously reported in solid tumors. This report highlights the genetic complexity of *TFE3* translocation renal cell carcinoma; and RNA-sequencing is a powerful approach for elucidating the underlying genetic alterations.

Introduction

Xp11 translocation renal cell carcinoma was renamed as MiT (microphthalmia-associated transcription factor) family translocation renal cell carcinoma in the 2016 World Health Organization classification [1]. This tumor type harbors variable gene fusions involving either *TFE3* or *TFEB* genes [1]. *TFE3* is a transcription factor gene located at chromosome band Xp11.23. Multiple 5'-fusion partners

for *TFE3* have been reported, including *ASPSCR1*, *CLTC*, *DVL2*, *LUC7L3*, *KHSRP*, *PRCC*, *PARP14*, *NONO*, *SFPQ1*, *MED15*, and *RBM10* [2–11]. Each of these fusion genes activates *TFE3* transcription, which results in the activation of downstream genes including targets normally activated by MiT family transcription factors (Cathepsin K and melanotic markers) [1, 12, 13]. *TFE3*/Xp11 renal cell carcinoma generally has papillary architecture, clear cells and psammoma bodies. The tumor cells are often positive for melanocytic markers, and negative or weakly positive for cytokeratins in contrast to classic clear cell and papillary renal cell carcinomas [6, 14].

Strong nuclear *TFE3* stains using an antibody targeting the C-terminal portion of *TFE3* is a sensitive and specific marker for Xp11 translocation renal cell carcinoma [15, 16]. However, it is difficult to optimize immunostaining for *TFE3*, as it is affected by variable fixation conditions. In clinical practice, it is not uncommon to encounter equivocal findings leading to false positive or false negative results. *TFE3* break-apart fluorescence in situ hybridization (FISH) assay has been demonstrated to be more reliable to detect the presence of the translocation [5, 14, 15]. However, some

✉ Shuanzeng Wei
weishuanzeng@hotmail.com

¹ Genomics Facility, Fox Chase Cancer Center, Philadelphia, PA 19111, USA

² Department of Pathology, Fox Chase Cancer Center, Philadelphia, PA 19111, USA

³ Department of Surgical Oncology, Fox Chase Cancer Center, Philadelphia, PA 19111, USA

⁴ Cancer Biology Program, Fox Chase Cancer Center, Philadelphia, PA 19111, USA

Table 1 Clinicopathological characteristics of five cases of renal cell carcinoma

No.	Age	Sex	Fusion	Tumor size	Stage	Biphasic	Cytoplasm	Furhman grade	Psammoma body	Pigment	Necrosis
1	59	M	NEAT1-TFE3	7 cm	pT1b	Y	Clear/eosinophilic	2	Y	Y	N
2	23	F	ASPCR1-TFE3	4 cm	pT1a	N	Clear	3	Y	N	N
3	22	F	MED15-TFE3	2 cm	pT1a	N	Clear/granular	2	N	N	N
4	54	F	RBM10-TFE3	10 cm	pT3a	Y	Clear/granular	4	N	N	FOCAL
5	73	M	KAT6A-TFE3	5 cm	pT1b	N	Clear/eosinophilic	3	Y	N	Y

M, male; *F*, female; *Y*, yes; *N*, no; *FOCAL*, focally present

renal cell carcinomas with morphological features of translocation renal cell carcinoma remain negative by immunostaining and FISH studies [5]. With the recent advancement of next-generation sequencing technology, RNA sequencing not only can identify cases not detected by other means, but also can identify various specific translocations in a single assay. In this study, we used targeted RNA-sequencing to identify the fusion genes in five cases of MiT family translocation renal cell carcinoma which had been diagnosed through TFE3 immunohistochemistry and/or FISH analysis for *TFE3* fusions.

Materials and methods

Patients and samples

Five archived cases of renal cell carcinoma with expression of TFE3 by immunohistochemistry were retrieved from the Department of Pathology, Fox Chase Cancer Center (Table 1). Medical record review provided pertinent clinical information. Adequate tumor sampling for each case had been performed (case 1 (9 sections), case 2 (6 sections), case 3 (12 sections), case 4 (14 sections), case 5 (13 sections)). This study was approved by the Institutional Review Board.

Immunohistochemistry

Immunohistochemistry was performed on 4-μm sections from formalin-fixed, paraffin-embedded (FFPE) tissue using a Ventana Benchmark XT automated stainer (Ventana Medical Systems, Tucson, AZ). The following antibodies were used: Melan-A (monoclonal mouse anti-human antibody, A103; DAKO; 1:100), TFE3 (monoclonal mouse anti-human antibody, MRQ37, Cell Marque; prediluted), PAX8 (monoclonal mouse anti-human antibody, MRQ50, Cell Marque; prediluted), cytokeratin AE1/AE3 (monoclonal mouse anti-human antibody, AE1/AE3, Ventana; prediluted), cytokeratin 7 (monoclonal mouse anti-human antibody, OV-TL 12/30, Dako; 1:800), CAM 5.2 (monoclonal mouse anti-human antibody, BD, 1:100), Cathepsin K (monoclonal mouse anti-human antibody, 3F9, Cell

marque, prediluted) and HBM45 (monoclonal mouse anti-human antibody, Dako; 1:60). The corresponding positive and negative controls were shown to be adequate.

RNA-sequencing and data analysis

RNA was isolated from FFPE samples using five 10 μm thick tissue sections. A High Pure FFPE RNA Isolation Kit (Roche, Indianapolis, IN) was used according to the manufacturer's protocol. RNA was quantified using a Nanodrop apparatus and evaluated with an Agilent 2100 bioanalyzer.

Next-generation sequencing-based targeted RNA-sequencing analysis was performed using the Illumina TruSight RNA Fusion Panel and a MiniSeq sequencer according to the manufacturer's recommendation (Illumina, San Diego, CA). This targeted RNA fusion panel consists of 507 of the most well-known cancer-related fusion genes (including TFE3), and the gene list is available at www.illumina.com. The Trusight RNA fusion panel covers 7690 exonic regions that are targeted with a total of 21,283 probes.

FISH analysis

FISH/TFE3 analysis for case 1 and 2 were performed at the Hospital of the University of Pennsylvania (Philadelphia, PA) using dual-color DNA break-apart probes (KREATECH Repeat-Free Poseidon TFE3 (Xp11) Break probes, Leica Biosystems). FISH/TFE3 analysis on case 5 was performed at the Mayo Clinic (Rochester, MN) using break-apart probes Xp11.23 (3'TFE3, 5'TFE3) and probe XCEN (DXZ1). FISH for TFEB on case 1 was done at Mayo Clinic (Rochester, MN) using break-apart probes 6p21.1 (3'TFEB, 5'TFEB).

Results

Clinical characteristics

The patients consisted of three females and two males ranging in age from 22 to 73 (mean, 46 years) (Table 1). Three patients underwent partial nephrectomies, and two patients had radical nephrectomies.

Fig. 1 *NEAT1-TFE3* renal cell carcinoma with alveolar/nested growth pattern and psammoma bodies (a). Biphasic morphology with both larger epithelial cells and smaller cells (inset) (b). The larger cells have

eosinophilic/granular appearance with focal vacuolation/clearing. Some of the cells have brown pigments (inset) (c). Expression of TFE3 (d)

Pathological findings

The pathological features are summarized in Table 1. Three cases demonstrated known fusions: *ASPSCR1-TFE3*, *MED15-TFE3*, and *RBM10-TFE3*. However, case 1 showed a *NEAT1-TFE3* fusion gene due to a t(X;11)(p11.23; q13.1). Morphologically, the distinct features observed in this case include abundant psammoma bodies and predominantly alveolar/nested growth pattern as opposed to the papillary architecture observed in the other four cases. This case also demonstrated biphasic tumor cells, i.e., larger epithelioid cells and small lymphocyte-like cells (Fig. 1a–c). Distinct basement membrane globules were not identified, as typically found in *TFEB/t* (6;11) renal cell carcinoma. The large epithelioid cells had eosinophilic cytoplasm with focal clearing (Fig. 1c), which were only focally positive for cytokeratins, including AE1/3, CAM5.2, and CK7. Melanin pigment was noted focally (Fig. 1c); and Melan A immunostaining was focally and weakly positive. These tumor cells were negative for HMB45 and Cathepsin K. Since TFE3 immunohistochemistry was focally positive (Fig. 1d), FISH analysis with TFE3 (Xp11) break-apart probes was performed, and this study confirmed the presence of a *TFE3* translocation. FISH for *TFEB* translocation was negative.

Another case had a *KAT6A-TFE3* fusion gene due to a t(X;8)(p11.23; p11.21). This tumor featured typical TFE3/Xp11 morphology including papillae and abundant psammoma bodies. The tumor cells had eosinophilic cytoplasm with focal clearing (Fig. 2a, b). The tumor cells were positive for CAM5.2, and only focally positive for AE1/3, CK7 and Melan A. Similar to the *NEAT1-TFE3* renal cell carcinoma, the TFE3 immunohistochemistry was only focally positive. FISH analysis with *TFE3* (Xp11) break-apart probes was positive for a *TFE3* translocation (Fig. 2c).

Interestingly, the *RBM10-TFE3* renal cell carcinoma (case 4, Fig. 2e, f) also showed biphasic tumor cells without basement membrane globules. However, unlike *NEAT1-TFE3* renal cell carcinoma, the *RBM10-TFE3* renal cell carcinoma did not feature eosinophilic cytoplasm. These tumor cells were positive for Melan A and Cathepsin K, negative for AE1/3, CAM5.2, CK7, and PAX8. The *ASPSCR1-TFE3* renal cell carcinoma (case 2) case had typical *TFE3/Xp11* morphology including papillae with clear cytoplasm and abundant psammoma bodies. The *MED15-TFE3* renal cell carcinoma (case 3, Fig. 2d) showed papillae and granular cytoplasm with clearing; however, no psammoma bodies were identified. The tumor cells were focally positive for CAM5.2, Cathepsin K and Melan A,

Fig. 2 *KAT6A-TFE3* renal cell carcinoma shows psammoma bodies, papillae and eosinophilic cytoplasm with clearing (**a**). High power of Fig **a** (**b**). FISH for *KAT6A-TFE3* renal cell carcinoma shows TFE3

break-apart signals (green: 3'TFE3[Xp11.23], red: 5'TFE3[Xp11.23], azure: DXZ1[Xcen]) (**c**). *MED15-TFE3* renal cell carcinoma (**d**). *RBM10-TFE3* renal cell carcinoma (**e**). High power of Fig **e** (**f**)

negative for AE1/3 and CK7, and they had no melanin pigments.

Discussion

Xp11 translocation renal cell carcinoma was first recognized as a specific category of renal cell carcinoma in the 2004 WHO classification [17]. In 2016, This group of renal cell carcinoma was renamed MiT family translocation renal cell carcinoma in the new World Health Organization classification [1]. This tumor type harbors variable gene fusions involving either *TFE3* or *TFEB* genes [1]. The first fusion/translocation was cloned in 1996, which was found

to fuse the *TFE3* transcription factor gene on Xp11.2 to the *PRCC* gene located at 1q21.2 [18, 19]. Since that time, other various *TFE3* fusion gene partners have been described, including *ASPSR1*, *CLTC*, *DVL2*, *LUC7L3*, *KHSRP*, *PARP14*, *NONO*, *SFPQ1*, *MED15*, and *RBM10* [2–11].

The predominant histological pattern of *TFE3*/Xp11 renal cell carcinoma is papillary architecture with clear cells and psammoma bodies. The tumor cells are frequently positive for melanocytic markers with negative or low expression of cytokeratins, which distinguishes them from other renal cell carcinoma subtypes [6, 14]. Renal cell carcinomas with MALAT1 (Alpha)-TFEB /t(6;11) are biphasic neoplasms composed of nested larger epithelioid cells with eosinophilic and vacuolated/clear cytoplasm

and smaller cells surrounding basement membrane material [1, 20, 21]. The *NEAT1-TFE3* renal cell carcinoma case reported here demonstrated a similar phenotype with an alveolar/nested growth pattern and only focal papillary architecture. The cytoplasm showed eosinophilic appearance with clearing. Our example lacks basement membrane material [21]. Interestingly, the *MALAT1* (metastasis-associated lung adenocarcinoma transcript 1) is also known as *NEAT2* (nuclear-enriched abundant transcript 2) [22].

The Nuclear Enriched Abundant Transcript 1 (*NEAT1*) gene, located at 11q13.1, produces a long non-coding RNA (lncRNA), a class of intergenic non-coding RNAs longer than 200 nucleotides that can regulate specific gene expression at multiple steps. *NEAT1* is a lncRNA localizing to a nuclear structure called paraspeckles [23]. *NEAT1* is aberrantly up-regulated in various types of cancer including carcinomas of the ovary, colon and genitourinary system [24–26]. *NEAT1* has been shown to be overexpressed in clear cell renal cell carcinoma, and upregulation of *NEAT1* was positively correlated with tumor size, higher Fuhrman grade, and lymph node metastasis [26]. Interestingly, *NEAT1* is involved in organizing a paraspeckle protein known as NONO (Non-POU domain-containing octamer-binding protein), which is one of the *TFE3* fusion gene partners [6, 8, 27]. Similar to *NEAT1*, the *TFEB/t(6;11)* fusion partner *MALAT1/NEAT2* is a lncRNA; and the fusion of *NEAT2* and *TFEB* results in overexpression of *TFEB* [1, 21, 22, 28]. Although the *NEAT2* promoter drives expression of the *NEAT2-TFEB* fusion gene, the *NEAT2* gene does not contribute to the open reading frame [28, 29].

Except for the *NEAT1-TFE3* renal cell carcinoma, the other four Xp11 renal cell carcinoma cases reported here had predominantly papillary architecture, cytoplasmic clearing and low/negative cytokeratin expression; and three of four cases were positive for Melan A. Two cases had psammoma bodies (Tables 1, 2). The *KAT6A-TFE3* renal cell carcinoma case demonstrated typical morphological features of *TFE3*/Xp11 renal cell carcinoma including papillae and abundant psammoma bodies. In addition, the tumor cells had eosinophilic cytoplasm with focal clearing. Lysine acetyltransferase 6A (*KAT6A*) belongs to the histone acetyltransferase (HAT) family, which was reported to fuse to CREB-binding protein

(CBP) in some cases of acute myeloid leukemia [30–32]. These proteins have histone acetyltransferase activity and are involved in transcriptional regulation and cell cycle control [33, 34]. Notably, gene fusions involving *KAT6A* have not been previously reported in solid tumors.

Only ten cases of *RBM10-TFE3* renal cell carcinoma have been reported. These cases can have sheets of small cells with “pseudo-rosette-like” architectures, mimicking the typical morphology of *TFEB/t(6;11)* renal cell carcinoma [5, 7]. The *RBM10-TFE3* renal cell carcinoma case reported here not only was completely negative for AE1/3, CAM5.2, and CK7, it also did not express PAX8. However, it was positive for Melan A and Cathepsin K. This tumor might belong to melanotic Xp11 translocation renal cell carcinoma/perivascular epithelioid cell neoplasms, which can be keratin(-)PAX8(-)Cathepsin K(+) Melan A(+), although the most reported melanotic Xp11 translocation renal cell carcinoma/perivascular epithelioid cell neoplasms had SFPQ-TFE3 fusion. It may contain variable amounts of finely brown melanin pigment which was not identified in this case [6, 35, 36]. It should be mentioned that both *TFE3* and *RBM10* are located on the same chromosome sub-band (Xp11.23), only 1.82 Mb apart, so a rearrangement involving these two genes is very unlikely to be detected by conventional FISH analysis [5].

As noted by Argani et al., it is difficult to optimize TFE3 immunostaining due to variable fixation conditions [5, 16]. In our study, three of five cases only had focal or weak positivity for TFE3 staining. Therefore, one should interpret TFE3 immunostaining cautiously. Furthermore, even the use of FISH testing with break-apart probes can sometimes be problematic, as it may be difficult or impossible to detect an inversion or translocation of chromosome X, such as *NONO-TFE3* and *RBM10-TFE3* rearrangements [5–7, 37]. Thus, RNA-sequencing or targeted multiplex RT-PCR would be a better option for identifying such cases [37].

Conclusion

In this study, two new members of MiT family translocation renal cell carcinoma, *NEAT1-TFE3* and *KAT6A-TFE3* renal

Table 2 Immunohistochemistry profile of 5 cases of renal cell carcinoma

No.	Age	Sex	Fusion	TFE3/FISH	TFE3	PAX8	Melan A	HMB45	AE1/3	CAM5.2	CK7	Cathepsin K
1	59	M	NEAT1-TFE3	>10%+	20%+	20%+	5%+	NEG	5%+	5%+	5%+	NEG
2	23	F	ASPSR1-TFE3	>30%+	95%+	90%+	NEG	5%+	90%+	20%+	30%+	NEG
3	22	F	MED15-TFE3	N/A	80%+	90%+	25%+	NEG	NEG	20%+	NEG	95%+
4	54	F	RBM10-TFE3	N/A	10%+	NEG	70%+	NEG	NEG	NEG	NEG	95%+
5	73	M	KAT6A-TFE3	>50%+	50%+	70%+	10%+	NEG	15%+	75%+	25%+	NEG

NEG, negative; +, positive

cell carcinomas, are reported. The renal cell carcinoma bearing a t(X;11)(p11.2;q13.1)/*NEAT1-TFE3* gene fusion demonstrates overlapping morphological features with *TFEB/t(6;11)* renal cell carcinoma. The *KAT6A-TFE3* renal cell carcinoma demonstrated typical features of *TFE3/Xp11* renal cell carcinoma. This study further emphasizes the genetic complexity of this unusual group of renal tumors.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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