MiT Family Translocation Renal Cell Carcinomas: A 15th Anniversary Update

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MiT Family Translocation Renal Cell Carcinomas: A 15th Anniversary Update

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ABSTRACT

Microphthalmia (MiT) family translocation renal cell carcinomas (RCCs) are a heterogeneous category of renal tumors which all express MiT transcription factors, typically from chromosomal translocation and rarely from gene amplification. This tumor family has two major subtypes [i.e., Xp11 translocation RCC and t(6;11) RCC] and several related neoplasms (i.e., TFE3 amplification RCC and melanotic Xp11 translocation renal cancers). Increased understanding of the clinical, pathological, molecular and prognostic heterogeneity of these tumors, since their official recognition in 2004, provides the opportunity to identify prognostic biomarkers and to understand the reasons for tumor aggression. We will review the literature from the past 15 years and highlight the need for a greater understanding of the molecular mechanisms underpinning heterogeneous tumor behavior.

Keywords: renal cell carcinoma, translocation renal cell carcinoma, TFE3, TFEB
INTRODUCTION
Microphthalmia (MiT) family translocation renal cell carcinomas (RCCs) are heterogeneous renal tumors that express one of two basic helix-loop-helix, melanocytic differentiation-inducing MiT family transcription factors – TFE3 or TFEB (Fisher et al., 1991; Zhao et al., 1993; Argani et al., 2003a; Argani et al., 2006a). The two major subtypes, driven by different chromosomal translocations, are termed: Xp11 translocation RCC and t(6;11) RCC. MiT family translocation RCCs also include molecularly-related uncommon variants, such as TFEB amplification RCCs and melanotic Xp11 translocation renal cancers (Argani et al., 2009; Williamson et al., 2017).

Xp11 translocation RCCs were first discovered by Argani et al. as a distinct renal tumor subtype disproportionately more common in pediatric patients and characterized by specific chromosomal translocations (Argani et al., 2001a, 2002). These tumors were officially recognized as a specific subtype by the World Health Organization (WHO) classification of tumors of the urinary system in 2004 (Argani et al., 2004). Almost a decade later, t(6;11) RCC was recognized as another subtype of translocation RCC by the International Society of Urological Pathology Consensus (Srigley et al., 2013). These two subtypes were finally unified under the MiT family translocation RCC category in the 4th edition of the WHO classification of tumors of the urinary system (Argani et al., 2016a).

Despite their clinicopathologic and molecular heterogeneity, several features common to both Xp11 translocation RCCs and t(6;11) RCCs justify placing them within the same category, such as a predisposition for younger patients than other RCCs (Bruder et al., 2004; Altinok et al., 2005; Geller et al., 2008; Sukov et al., 2012); lower level of immunohistochemical expression of epithelial markers such as cytokeratins, compared to other RCCs (Argani et al., 2010a); and
nuclear labeling of TFE3 or TFEB by immunohistochemistry (Argani et al., 2003c, 2005a; Argani et al., 2012).

In this brief review, we will summarize the current body of published literature on this family of tumors, discuss potential clinical and molecular factors that may influence clinical outcomes, and identify critical knowledge gaps of prognostic biomarkers and the molecular mechanisms underlying tumor aggressiveness seen with these cancers.

**Xp11 TRANSLOCATION RENAL CELL CARCINOMA**

**Clinical Features**

Xp11 translocation RCCs have a bimodal age distribution with a mean age of 17 years in the pediatric population (Wu et al., 2008) and 37 years in the adult population (Argani et al., 2007). The median age of onset was 27 years in a mixed cohort of pediatric and adult patients (Liu et al., 2016). Xp11 translocation RCCs comprise approximately 50% of all pediatric RCCs whereas they account for only 1-4% of all adult RCCs (Geller et al., 2008; Ehrlich P. et al., 2012; Geller et al., 2015); other pediatric RCCs include familial and sporadic clear cell RCC, papillary RCC, and unclassified RCC (Wu et al., 2008). The only known predisposing factor for translocation RCC is a prior exposure to DNA topoisomerase II inhibitor/platinum-based chemotherapies or alkylating agents with the latency periods after therapeutic exposure ranging from less than 2 years to 13 years (Argani et al., 2006b; Parikh et al., 2014).

Stage of presentation varies across different institutional studies with incidences of regional lymph node involvement or metastases ranging from 25% to 85% (Camparo et al., 2008; Geller et al., 2008; Wu et al., 2008). In a study on pediatric RCCs, 65% of non-translocation associated
RCCs presented at a lower stage (stage I or II); whereas, 65% of Xp11 translocation RCCs presented with higher stage tumors (stage III or IV) (Geller et al., 2008). In another study of mixed cohort of children and adults, the majority (66%) of Xp11 translocation RCCs presented at an advanced stage disease (Wu et al., 2008). A separate study found similar results of a high pathologic stage (pT3 or pT4) in approximately 50% of children and adults with Xp11 translocation RCC (Camparo et al., 2008).

Nodal metastasis is relatively common, even with small-sized primary tumors (Argani et al., 2007). Although patients with Xp11 translocation RCCs are more likely to present with a higher stage disease, the presence of lymph node metastases alone (without hematogenous spread) does not seem to portend a worse prognosis, at least in the short term and especially in the pediatric population (Geller et al., 2008). Late recurrences after a prolonged latency, however, have been reported (Ellis et al., 2014), suggesting that a longer follow-up period may be needed to appreciate the full biological potential of these tumors. Nonetheless, those who develop hematogenous metastases with systemic involvement seem to have a dismal prognosis (Geller et al., 2008; Ellis et al., 2014).

**Molecular Features**

At the cytogenetic level, Xp11 translocation RCCs are characterized by balanced chromosomal translocations at the Xp11.2 locus. These translocations result in TFE3 gene fusions and overexpression of chimeric proteins retaining the TFE3 C-terminal DNA binding domain. Reported fusion partners include ASPSCR1 (ASPL), PRCC, NonO (p54nrb), SFPQ (PSF), CLTC, PARP14, LUC7L3, KHSRP, DVL2, and unknown genes on chromosomes 3 and 10 (Argani et al., 2003b, 2016b; Wang et al., 2017). The two most frequent Xp11 translocation RCC subtypes are
the \textit{ASPSCR1-TFE3 (ASPL-TFE3)} and the \textit{PRCC-TFE3} subtypes, resulting from (X;17) (p11;q25) and (X;1)(p11;q21) translocations, respectively. In some tumors lacking rearrangement, \textit{TFE3} amplification accounts for \textit{TFE3} expression (Macher-Göppinger et al., 2012).

\textit{TFE3} rearrangements are not unique to translocation RCCs and are also found in all alveolar soft part sarcomas [unbalanced (X;17) (p11;q25) translocations] as well as in a subset of perivascular epithelioid cell tumors (PEComas) (Argani et al., 2010b; Hodge et al., 2014).

**Pathologic Features**

Xp11 translocation RCCs are often grossly described as having a tan-yellow appearance with areas of hemorrhage and necrosis (Wu et al., 2008) (Figure 1). Microscopically, most tumors have a papillary/pseudopapillary architecture with epithelioid cells containing voluminous clear to eosinophilic cytoplasm and large, round nuclei with variably prominent nucleoli (Figures 1 and 2). Psammomatous calcifications are present in many cases (Argani et al., 2003a, 2007; Wu et al., 2008). Common morphologic variations include short papillary structures; lining of cells with less abundant cytoplasm; and small, irregular nuclei with inconspicuous nucleoli. The latter feature may have histological resemblance to chromophobe RCC. Some tumors contain a prominent eosinophilic cell population and may mimic a rare subtype of renal cancer termed tuberous sclerosis-associated RCC (Guo et al., 2014; Yang et al., 2014).

The histological features of Xp11 translocation RCCs vary depending on the underlying fusion partner gene (Table 1). For example, Xp11 translocation RCCs harboring the \textit{ASPSCR1-TFE3} fusion gene often have the architectural and cytologic features described earlier (Figure 1), with abundant psammoma bodies (Argani et al., 2002). In contrast, tumors with the \textit{PRCC-TFE3}}
fusion gene typically have neoplastic cells with less abundant cytoplasm, fewer psammoma bodies, and a more compact growth pattern (Argani et al., 2007; Wu et al., 2008) (Figure 2). Xp11 translocation RCC with NONO-TFE3 and SFPQ-TFE3 are less common subtypes (Wang et al., 2017; Xia et al., 2017), which exhibit a secretory endometrioid appearance with nuclear palisading and sub-nuclear vacuoles, resembling clear cell papillary RCC (Wang et al., 2017). Tumors with MED15-TFE3 fusions are characterized by multicystic growth pattern with thin fibrous septae that closely resemble the recently described entity termed “multilocular cystic renal neoplasm of low-malignant potential” (Wang et al., 2018). Tumors with NEAT1-TFE3 fusions have an alveolar or nested architecture with biphasic tumor cells, composed of larger epithelioid cells and smaller lymphocyte-like cells and abundant psammoma bodies (Pei et al., 2019).

Immunohistochemical staining is routinely used for Xp11 translocation RCC diagnosis since the morphologic features of these tumors commonly overlap those of other RCCs (Argani et al., 2007, 2016b; Suzigan et al., 2007; Ellis et al., 2014; Kryvenko et al., 2014). TFE3 immunohistochemical staining is helpful in labeling TFE3 protein, which is generally undetectable by immunohistochemistry in normal tissues (Argani et al., 2003c). However, TFE3-staining can be technically challenging (particularly using automated immunohistochemistry stainers). A positive signal should be interpreted with caution – only moderate to strong nuclear TFE3 expression should be considered as genuinely positive, and background normal tubules and parenchyma should be negative (Argani et al., 2010a; Argani, 2015).

Melanocytic markers (Melan-A, HMB-45) show variable levels of expression in almost all cases (Campaor et al., 2008). The renal tubular transcription factor PAX8 is expressed in more than 50% of cases (Argani et al., 2010a) and cathepsin-K in approximately 60% of cases. Other renal markers, such as CD10 and renal cell carcinoma marker (RCC-Ma), are also consistently
positive. Unlike other adult renal cell carcinomas, Xp11 translocation RCC tend to underexpress epithelial markers (Argani et al., 2010a). A minimally positive carbonic anhydrase 9 (CA-9) signal differentiates Xp11 translocation RCCs from clear cell RCCs, which consistently show diffuse CA-9 positivity (Argani et al., 2010a).

TFE3 fluorescence in situ hybridization (FISH) with a break-apart probe is particularly useful for diagnosis in cases with unusual histology or equivocal immunohistochemistry results (Green et al., 2013) (Figure 1). Knowledge about the exact TFE3 fusion partner is currently not essential in routine practice. Some recent examples have shown that TFE3-rearrangements caused by subtle chromosome X inversions, resulting in RBM10-TFE3 or NONO-TFE3 fusions, may not be detected by FISH. In such cases, other molecular methods such as RNA sequencing may be used to detect alterations when the morphology is typical, but immunohistochemistry or FISH is non-conclusive (Argani et al., 2017).

**Prognostic Factors**

Although the first reported cases in children had an indolent course, it is now recognized that Xp11 translocation RCCs are commonly aggressive, especially in adult patients (Argani et al., 2007). Adult Xp11 translocation RCCs have a worse prognosis than papillary RCC and a similar or worse prognosis than clear cell RCC (Sukov et al., 2012; Choo et al., 2017). By contrast, a subset of pediatric tumors, with or without nodal metastasis, have an indolent clinical course (Geller et al., 2008). Supporting the age-related prognosis of translocation RCCs, independent multivariate analyses by Ellis et al. and Marchionni et al. showed that older age and distant visceral metastasis were the only two independent poor prognosis predictors (Ellis et al., 2014; Marchionni et al., 2017). Efforts to histologically grade translocation RCCs based on Fuhrman nuclear grade or
WHO grading system have not been substantiated (Sika-Paotonu et al., 2006; Delahunt et al., 2011; Marchionni et al., 2017).

The impact of nodal metastasis on Xp11 translocation RCC outcome is debatable and probably age-dependent (Malouf et al., 2013). For example, pediatric cases commonly maintain a favorable prognosis even with lymph node metastasis. In a pediatric cohort of Xp11 translocation RCC, Geller et al. found that 93.3% of patients with stage III and stage III/IV RCC due to lymph node spread (N1 M0) remain disease free with a median and mean follow-up of 4.4 and 6.3 years, respectively (range, 0.3-15.5). (Geller et al., 2008). By contrast, a cohort of adult patients followed a fatal clinical course, with a mean survival of 18 months after diagnosis (range, 10-24 months) (Meyer et al., 2007).

Several molecular markers have been discussed in the literature for Xp11 translocation RCCs, but none is proven to be prognostically reliable. For example, the ASPSCR1-TFE3 fusion was initially considered to be a predictor of poor prognosis, however by multivariate analysis it did not prove to be an independent factor in predicting outcome (Ellis et al., 2014). Studies by Marchionni et al. showed that the microRNA profiles seen in Xp11 translocation RCCs closely resemble that of clear cell papillary RCC, an indolent renal carcinoma subtype, and least to that of papillary RCC (Marchionni et al., 2017). A high number of copy number alterations (Pan et al., 2013) or TFE3 amplification, either with or without TFE3 gene rearrangement (but not TFE3 rearrangement alone), are also associated with aggressive tumor behavior (Macher-Goeppinger et al., 2012; Argani et al., 2016c; Williamson et al., 2017). Genetic profiling of Xp11 translocation RCCs performed by Malouf et al. divided these tumors into four groups: those with profiles similar to clear cell RCC, i.e. with 3p loss and other imbalances (Group I); those with profiles similar to papillary RCC, i.e. with gains of chromosomes 7, 12, and 17 (Group II); those with novel
cytogenetic profiles not found in other renal tumor subsets (Group III); and those with balanced chromosomal complement profiles (Group IV) (Malouf et al., 2013). In addition, epigenetic profiling discovered that adult tumors display distinct aberrations, such as lower LINE-1 methylation (a surrogate marker of DNA methylation) and frequent 17q partial gain when compared to pediatric (<18 years) tumors. These differences in pediatric and adult translocation RCCs provide useful insight to the biology of these tumors, which may be used to develop prognostic biomarkers in the future (Malouf et al., 2013). However, the biological differences between the two age groups for translocation RCCs are still being unraveled.

**Future Perspective**

The clinical heterogeneity in Xp11 translocation RCC is likely multifactorial, involving both tumor- and host-related parameters. To allow a more precise outcome assessment, a risk stratification scheme needs to be developed that uses both intrinsic tumor biologic factors and clinical parameters. The molecular mechanisms underlying disease aggressiveness need to be further explored to identify prognostically reliable molecular markers.

Mammalian target of rapamycin (mTOR) inhibitors are being investigated for treating MiT family RCCs, given one reported case of a good response (Rua Fernandez et al., 2018). In preclinical models of TFE3 translocation RCC, targeting PI3K and mTOR concurrently achieved a greater antitumor response than did single pathway inhibition, but the reported toxicity was a major downfall (Damayanti et al., 2018). VEGFA (vascular endothelial growth factor A) inhibitors should be further investigated for treating adult and pediatric populations given some efficacy in treating Xp11 translocation RCC metastases in adults (Choueiri et al., 2010; Giles et al., 2017).
PD1/PD-L1 immune checkpoint inhibitors also have therapeutic potential since PD-L1 is expressed in 25% of Xp11 translocation RCCs (Chang et al., 2017).

**t(6;11)/ TFEB-REARRANGED RENAL CELL CARCINOMA**

**Clinical Features**

t(6;11) RCCs, initially described in 2001, are rare tumors and only ~78 cases have been reported in the literature to date (Argani et al., 2001a; Wyvekens et al., 2019). The average age of onset is 34 years (Wyvekens et al., 2019). Based on the presently available data, t(6;11) RCCs are more indolent than Xp11.2 translocation RCCs, although a few aggressive forms have recently been described (Peckova et al., 2014; Calio et al., 2018a; Wyvekens et al., 2019). Due to the limited number of reported cases with available follow-up, the full biological potential of t(6; 11) RCCs has yet to be fully understood.

**Molecular Features**

The molecular event underlying t(6; 11) RCC pathogenesis is the fusion of the non-coding *MALAT1* locus (11q12) with *TFEB* (6p21), resulting in dysregulated full-length TFEB expression (Argani et al., 2006a). Other *TFEB* fusion partners include *COL21A1*, *CADM2*, (Linehan et al., 2016) and *KHDRBS2* (Malouf et al., 2014).
Pathologic Features

Grossly, t(6;11) RCCs resemble renal onc cytoma, often having a mahogany/tan-brown, cystic to solid cut surface (Argani et al., 2001a; Magers et al., 2015). Microscopically, they exhibit a distinctive biphasic appearance (Figure 3), composed of nests of larger epithelioid cells with clear to eosinophilic cytoplasm and a second population of smaller cells with condensed chromatin that is usually clustered around the basement membrane material, resembling Call-Exner bodies of adult granulosa cell tumors (Argani et al., 2001a). Histological variations, which can be potentially misconstrued as other diagnoses, include a multicystic appearance resembling multilocular cystic RCC; abundant clear cytoplasm mimicking conventional clear cell RCC; paucity or absence of the small cell population; and high-grade nuclear features (Smith et al., 2014).

Immunophenotypically, t(6;11) RCCs express renal markers (PAX8, CD10, RCC Ma) and cathepsin-K (Smith et al., 2014). Similar to Xp11 translocation RCCs, these tumors also underexpress cytokeratins (Martignoni et al., 2009; Argani et al., 2010a; Zheng et al., 2013; Smith et al., 2014). Melanoma markers such as HMB45 and Melan-A are usually positive (Argani et al., 2009; Argani et al., 2016a; Saleeb et al., 2017; Wyvekens et al., 2019) and can potentially mislead to a diagnosis of epithelioid angiomyolipoma (Argani et al., 2005b). In such cases, CD68 (PG-M1) can be used since it is expressed in PEComa/epithelioid angiomyolipoma but not in t(6;11) RCCs (Calio et al., 2018b). TFEB is a sensitive and specific diagnostic marker and its nuclear labeling is consistent with the TFE3 gene rearrangement or amplification status. However, similar to TFE3, the TFEB stain may be technically difficult to validate and therefore FISH testing represents the most useful tool for the detection of gene rearrangement in t(6;11) RCCs (Figure 3) (Argani et al., 2012). An added advantage of performing FISH is that it can identify concurrent 6p
amplification, which is associated with an aggressive clinical course (detailed below) (Williamson et al., 2017).

**Prognostic Factors**

t(6;11) RCCs are associated with a more indolent clinical behavior than Xp11 translocation RCCs with only a few reported cases showing aggressive behavior (Peckova et al., 2014; Calio et al., 2018b). Although strict criteria to indicate aggressiveness are not well-established, few features that can help identify an aggressive subtype include older age group; lack of the small cell component; histologic resemblance to clear cell RCC; grossly visible necrosis; and concurrent TFEB amplification (Peckova et al., 2014).

**RARE VARIANTS**

**TFEB-Amplified Renal Cell Carcinoma**

Only 54 cases of TFEB-amplified RCCs have been published to date with a small proportion showing concurrent TFEB translocation (Wyvekens et al., 2019). After the first study that documented TFEB amplification (Peckova et al., 2014), Argani et al. described 6 TFEB-amplified carcinomas without concurrent TFEB-translocation, distinguishing them from the conventionally described t(6;11) RCCs (Argani et al., 2016c). Subsequently, Williamson et al. reported 9 cases with chromosome 6p amplification including TFEB, most of which were in the elderly and associated with advanced stage disease (Williamson et al., 2017). In their series of 11 TFEB-amplified RCCs, Gupta et al. also found VEGFA co-amplification in a subset of cases (Gupta et al., 2017), an observation with potential significance for VEGFA inhibitors as treatment options.
**TFEB**-amplified tumors generally occur in a significantly older age group (6-7th decade). Most of these tumors are large, uncircumscribed, and occupy the entire kidney, usually with visible necrosis and evidence of retrograde large venous invasion (Argani et al., 2016c; Williamson et al., 2017; Mendel et al., 2018; Skala et al., 2018). Microscopically, these tumors are characterized by nested, alveolar, and pseudopapillary architectures. The cells are typically polygonal with eosinophilic cytoplasm and display high-grade nuclear features with prominent nucleoli, similar to what is seen in high-grade clear cell RCC (Figure 4). Some tumors may contain true papillae and psammomatous calcifications. Resemblance to fumarate hydratase-deficient RCCs is observed occasionally when prominent nucleoli and perinuclear halos are present (Argani et al., 2016c). The most remarkable characteristic of **TFEB**-amplified RCCs is their aggressive behavior, which is very different from RCCs which harbor **TFEB**-translocations only (Peckova et al., 2014; Argani et al., 2016c; Gupta et al., 2017; Mendel et al., 2018). These neoplasms diffusely express PAX8 and TFEB; variably express melanocytic markers (HMB45 and Melan-A), with at least patchy immunoreactivity for low molecular weight cytokeratins (CAM5.2) and pan-cytokeratin in all cases (Argani et al., 2016c; Wyvekens et al., 2019). When subjected to FISH testing, **TFEB** gene amplification is considered when the signal is greater than a 10:1 ratio relative to the control gene signal (Argani et al., 2016c) (Figure 4).

**Melanotic Xp11 Translocation Renal Cancers / Xp11 translocation PEComas**

Melanotic Xp11 translocation renal cancers are exceedingly rare tumors with close morphological and immunohistochemical resemblance to PEComa and malignant melanoma (Argani et al., 2009). Due to their overlapping properties, some of these tumors cannot be distinguished with certainty from PEComas with **TFE3** rearrangement. It is important however to recognize this entity from
malignant melanoma, as highlighted by Argani et al. (Argani et al., 2010b). To our knowledge, only 20 cases have been reported so far (age range, 11-46 years) and based on the available data, it appears that these tumors are associated with an unfavorable prognosis (Argani et al., 2009; Jing et al., 2018).

*PSF/SFPQ* is a known gene fusion partner with *TFE3* in melanotic Xp11 translocation renal cancers. These tumors generally demonstrate a solid, nested to alveolar architecture composed of epithelioid cells with clear to focally eosinophilic cytoplasm. One case of a novel *ARID1B-TFE3* fusion has also been reported. Cytoplasmic melanin pigment is readily identifiable on hematoxylin and eosin sections. These neoplasms are immunoreactive to TFE3 and CD68 (PGM1) (Argani et al., 2016c; Calio et al., 2018b) and immunonegative to renal tubular markers, such as PAX-8, and epithelial markers (Rao et al., 2015; Argani et al., 2016c).

**CONCLUSION**

Since their official recognition as a distinct category of renal tumors in the 2004 WHO blue book 15 years ago, our knowledge base has increased exponentially on MiT family translocation RCC characteristics. However, there remain important gaps in our understanding of their heterogeneous biological behaviors. Distant metastasis and older age predict worse outcomes, but we do not know of the molecular reasons why prognosis depends on age. Furthermore, some tumors are indolent while others are aggressive even within the same pediatric age group. Future studies must focus on prognostic biomarker discovery to facilitate more precise stratification of patients with MiT family translocation RCC.
Table 1. Summary of common histologic patterns described for specific gene fusions in MiT family translocation renal cancers

<table>
<thead>
<tr>
<th>Gene fusions</th>
<th>Summary of common morphologic patterns linked to fusion gene partners</th>
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<tbody>
<tr>
<td>ASPL-TFE3 RCC (Argani et al., 2001b; Ellis et al., 2014)</td>
<td>Papillary/pseudopapillary architecture; voluminous cytoplasm; psammoma bodies</td>
</tr>
<tr>
<td>PRCC-TFE3 RCC (Argani et al., 2002)</td>
<td>Compact architecture; less voluminous cytoplasm; few psammoma bodies</td>
</tr>
<tr>
<td>SFPQ-TFE3 RCC (Argani et al., 2016b)</td>
<td>Papillary architecture; subnuclear vacuolization; pseudorosettes; may have variable amounts of finely brown melanin pigment</td>
</tr>
<tr>
<td>NONO-TFE3 RCC (Argani et al., 2016b)</td>
<td>Secretory endometrioid, subnuclear vacuolization</td>
</tr>
<tr>
<td>RBM10-TFE3 RCC (Argani et al., 2017)</td>
<td>Solid, papillary, and trabecular architecture; epithelioid cells with clear to eosinophilic cytoplasm (biphasic morphology); cytoplasmic vacuolization; pseudorosettes architectures may mimic TFEB/t (6;11) RCC</td>
</tr>
<tr>
<td>MED15-TFE3 RCC (Wang et al., 2018) (Huang et al., 2015)</td>
<td>Variable morphologies; solid/nested, papillary or cystic growth pattern; calcification/ossification; can be extensively cystic with thin fibrous septa, reminiscent of multilocular cystic renal neoplasm of low malignant potential</td>
</tr>
<tr>
<td>CLTC-TFE3 RCC (Argani et al., 2003d)</td>
<td>Overlapping features with ASPL-TFE3 and PRCC-TFE3 RCC</td>
</tr>
<tr>
<td>DVL2-TFE3 RCC (Argani et al., 2016b)</td>
<td>Variable histologic patterns composed of papillary and solid architecture; variably eosinophilic cytoplasm</td>
</tr>
<tr>
<td>LUC7L3-TFE3 RCC (Malouf et al., 2014)</td>
<td>No distinctive histological patterns (detected on next generation sequencing)</td>
</tr>
<tr>
<td>KHSRP-TFE3 RCC (Malouf et al., 2014)</td>
<td>No distinctive histologic patterns (detected on next generation sequencing)</td>
</tr>
<tr>
<td>KHDRBS2-TFE3 RCC (Malouf et al., 2014)</td>
<td>No distinctive histologic patterns (detected on next generation sequencing)</td>
</tr>
<tr>
<td>PARP14-TFE3 RCC (Huang et al., 2015)</td>
<td>No distinctive histologic patterns; can have papillary or alveolar pattern, polygonal cells with well-demarcated, predominantly clear, voluminous cytoplasm; psammoma bodies</td>
</tr>
<tr>
<td>KAT6A-TFE3 RCC (Pei et al., 2019)</td>
<td>No distinctive histologic patterns. May have papillary pattern with abundant psammoma bodies</td>
</tr>
<tr>
<td>GRIPAP1-TFE3 RCC (Classe et al., 2017)</td>
<td>No distinctive histologic patterns</td>
</tr>
<tr>
<td>NEAT1-TFE3 RCC (Pei et al., 2019)</td>
<td>Alveolar/nested growth pattern; psammoma bodies; biphasic morphology with both larger epithelial cells and smaller cells with eosinophilic/granular cytoplasm with focal vacuolation/clearing; +/- pigment</td>
</tr>
<tr>
<td>t(6;11) RCC (Argani et al., 2005b)</td>
<td>Pseudorosettes; 2 cell types; hyaline material; psammoma bodies; pigmentation; can have papillary/pseudopapillary and chromophobe like nuclear features</td>
</tr>
<tr>
<td>TFEB amplified RCC (Argani et al., 2016c)</td>
<td>Variable morphologies; nested, papillary/pseudopapillary architecture; polygonal eosinophilic cells (rhabdoid) with prominent nucleoli; similar to the type commonly seen in high grade clear cell RCC, tumor necrosis common</td>
</tr>
<tr>
<td>Melanotic translocation renal cancers with SFPQ-TFE3 (Rao et al., 2015)</td>
<td>Nested or sheet-like architecture separated by a delicate vascular network, epithelioid cells containing a clear or granular eosinophilic cytoplasm, a lack of papillary structures and spindle cell or fat components, uniform round or oval nuclei containing small visible nucleoli, and variable amounts of melanin pigmentation.</td>
</tr>
<tr>
<td>Melanotic translocation renal cancers with ARID1B-TFE3 (Antic et al., 2017)</td>
<td>Nested and papillary architecture with infiltrative growth pattern at the periphery; biphasic morphology with clear and eosinophilic cells; sparse melanin pigment</td>
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References:


FIGURE LEGENDS

Figure 1. Pathologic features of an Xp11 translocation RCC with *ASPL-TFE3* fusion from an adolescent male patient. A, Gross image of nephrectomy showing a circumscribed renal mass with foci of hemorrhage. B, Low-power image of Hematoxylin and eosin (H&E)-stained section shows a papillary architecture with intervening fibrous bands. C, Higher-power view shows papillary cores covered by tumor cells. D, Tumor cells have voluminous eosinophilic cytoplasm containing enlarged nuclei with prominent nucleoli. E, Lymph node excised showing a focus of metastasis. F, Fluorescent in situ hybridization (FISH) using break apart *TFE3* probe shows split signals.

Figure 2. An Xp11 translocation RCC with *PRCC-TFE3* fusion from a child. A and B, H&E stained photomicrographs show a compact architecture composed of clear cells with distinct cell boundaries and low-grade nuclei, and interspersed thin-walled blood vessels, closely resembling conventional clear cell RCC. C, TFE3 immunohistochemical staining shows strong and diffuse nuclear labeling of the tumor cells. D, FISH using break apart *PRCC* probe shows split signals.

Figure 3. Morphological features of an t(6;11) translocation RCC in an adult patient. A and B, H&E stained photomicrographs of the tumor showing a nested architecture and a characteristic biphasic appearance, composed of larger cells with clear and eosinophilic cytoplasm and smaller cells clustered around hyaline material. C, FISH using break apart *TFEB* probe shows split signals.

Figure 4. *TFEB*-amplified RCC in an adult patient. A, Gross photograph shows a poorly circumscribed renal mass with a tan brown cut surface. B and C, H&E stained photomicrographs of the tumor show a lobular architecture with a nested solid growth pattern and intra-tumoral
necrosis. High magnification shows tumor cells with abundant eosinophilic cytoplasm and high-grade nuclear features. D, FISH using break apart \textit{TFEB} probe shows high level amplification and no rearrangement.