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Review

Review of renal carcinoma associated with Xp11.2 translocations/*TFE3* gene fusions with focus on pathobiological aspect

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Summary. The concept of Xp11.2 renal cell carcinoma (RCC) was recently established as a tumor affecting 15% of RCC patients <45 years. Many patients present with advanced stage with frequent lymph node metastases. Histologically, Xp11.2 RCC is characterized by mixed papillary nested/alveolar growth pattern and tumor cells with clear and/or eosinophilic, voluminous cytoplasm. Neoplastic cells show intense nuclear immunoreactivity to *TFE3*, while focal immunostaining for melanocytic markers, including melanosome-associated antigen or Melan A in some cases, are also noted. Alpha smooth muscle actin and TFEB are consistently negative. Ultrastructurally, the *ASPL-TFE3* RCC variant contains rhomboid crystals in the cytoplasm, similar to that observed in alveolar soft part sarcoma. The fusion of the *TFE3* gene with several different genes, including *ASPL(*17q25*), PRCC(*1q21*), PSF(*1q34*), NonO (*Xq12*)* and *CLTC (*17q23*)* have been identified to date. The behavior of Xp11.2 RCC in children and young adults is considered as indolent even when diagnosed at advanced stage, including lymph node metastasis. However, Xp11.2 RCC in older patients behaves in a more aggressive fashion. Therapy includes nephrectomy with extended lymphadenectomy. There may be a role for new protease inhibitors in advanced inoperable disease. Further research is required to correlate clinical behavior with the expanding genetic spectrum of this tumor, and to establish standard therapy protocols for primary and metastatic lesions.

Key words: Xp11.2 RCC, TFE3, Immunohistochemistry

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Introduction

Renal carcinoma associated with Xp11.2 translocations/*TFE3* gene fusion, briefly Xp11.2 renal cell carcinoma (RCC), is a recently recognized tumor entity, characterized by chromosome translocations involving the Xp11.2 breakpoint and resulting in gene fusion involving the *TFE3* gene, and was first described by de Jong et al. (1986). Subsequently, RCCs with such features were reported by many investigators (Kovacs et al., 1987; Tomlinson et al., 1991; Meloni et al., 1992, 1993; Ohjimi et al., 1993; Dijkhuizen et al., 1995; Shipley et al., 1995; Tonk et al., 1995; Sidhar et al., 1996; Weterman et al., 1996a-c; Clark et al., 1997; Dal Cin et al., 1998; Kardas et al., 1998; Desangles et al., 1999; Perot et al., 1999; Argani et al., 2001, 2002, 2003b; Heimann et al., 2001). As a result, this disease concept was newly incorporated in the book "Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs" of the 2004 World Health Organization (WHO) classification (Argani and Ladanyi, 2004). In this article, we revisit this disease process with a focus on discussing the pathological, ultrastructural and genetic features coupled to the clinical and therapeutic aspects of this rare but important renal

carcinoma variant.

Epidemiology

Xp11.2 RCC accounts for approximately 20% to 70% of total renal neoplasm in pediatric and adolescent age group (Bruder et al., 2004; Geller et al., 2008). We suggest that the exact percentage is not clear but may be over 50% in this age group. The incidence of adult-onset Xp11.2 RCC represents 1.6% of all renal neoplasms and Xp11.2 RCC accounts for 15% of RCCs in patients <45 years of age (Komai et al., 2009). Some investigators suggest that a previous exposure to cytotoxic chemotherapeutic agents in childhood may be a risk factor for developing Xp11.2 RCC (Argani et al., 2006; Ramphal et al., 2006). A case of Xp11.2 RCC occurring during pregnancy was reported (Armah et al., 2009). One *PRCC-TFE3* RCC occurred in contralateral kidney of a boy with a history of congenital mesoblastic nephroma (Onder et al., 2006). We previously reported a case of Xp11.2 RCC arising in the kidney of a patient receiving hemodialysis (Nouh et al., 2010).

Clinical symptoms

The differences between Xp11.2 RCC and other RCCs are summarized in Table 1. Many patients present with hematuria or abdominal mass, but there are only a few patients that presented with the classic triad of renal cancer, such as abdominal mass, pain and hematuria (Ramphal et al., 2006; Argani et al., 2007; Geller et al., 2008). In a minority, the tumor is incidentally found (Argani and Landanyi, 2004; Argani et al., 2007; Komai et al., 2009).

Radiological findings

No specific imaging findings have been described yet, but there were some reported cases presenting as heavily calcified lesions, masses, cysts or cystic neoplasms (Argani et al., 2007). Radiologists and urologists need to suspect Xp11.2 RCC in young patients, particularly if lymph node metastases are prominent (Prasad et al., 2006; Komai et al., 2009).

Pathological findings

Macroscopic findings

Grossly, the tumor is well circumscribed but not encapsulated. The cut surface of the tumor is often a yellow-tan color with a soft consistency. Necrosis, hemorrhage, calcification, ossification and cystic change may be observed (Yan et al., 2009) and these lesions are macroscopically inseparable from other forms of RCC. A case of Xp11.2 RCC showing multilocular cystic RCC-like appearance was reported (Suzigan et al., 2007).

Microscopic findings

In general, Xp11.2 RCC is histologically characterized by mixed papillary nested/alveolar growth pattern, tumor cells with clear and/or eosinophilic, voluminous cytoplasm, distinct cell border, vesicular chromatin and prominent nucleoli (Argani et al., 2001, 2002; Argani and Ladanyi, 2004; Armah et al., 2009). From a practical point of view, this tumor is characterized by the presence of features which do not fit in one of most frequent histological subtypes. Namely, if pathologists find a tumor composed of predominant clear cells with mixed papillary and solid/alveolar pattern and some microcalcification in which they are not able to find expression of epithelial markers, pathologists have to start to include this tumor in the differential diagnosis. The *ASPL-TFE3* RCC variant features a more nested (Fig. 1A) and papillary architecture (Fig. 1B), with frequent psammoma bodies (Fig. 1C), hyaline nodules and cytoplasm that ranges from eosinophilic to clear (Argani et al., 2001; Argani and Ladanyi, 2004). The proliferating pattern indistinguishable from clear cell RCC can be seen (Fig. 1D). In contrast, the *PRCC-TFE3* RCC variant has a more solid, compact architecture, slightly less voluminous cytoplasm, usually less frequent psammoma bodies and hyaline nodules, and less prominent nucleoli

Table 1. Comparison of clinical and prognostic features of Xp11.2 RCC and other RCCs.

Clinical features	Xp11. 2 RCC	Clear cell RCC	Papillary RCC, type 2
age	Children~adolescents approximately 1% in adult	Usually adult	Usually adult
symptom	Painless mass, hematuria asymptomatic incidentally found	Mass, pain hematuria	Mass, pain hematuria
previous exposure to cytotoxic chemotherapy	10-15%, +	-	-
Prognosis	Poor particularly in adult *ASPL-TFE3* RCC	Poorer than papillary RCC, type 1 and chromophobe RCC	Poorer in type 2 than in type 1

RCC: renal cell carcinoma.

(Argani et al., 2002; Argani and Ladanyi, 2004). The *PSF-TFE3* RCC variant may contain pleomorphic neoplastic cells with a hobnail pattern (Argani et al., 2007). Xp11 RCC with t(X;3)(p11;q23) may have morphologically overlapping features with the *ASPL-TFE3* RCC (Argani et al., 2007).

Immunohistochemical findings

The most distinctive feature for the diagnosis of this tumor is a strong nuclear labeling for TFE3 (Fig. 2A), and this finding is observed in the majority of cases with Xp11.2 RCC (Argani et al., 2003a). The immunoreactivity for TFE3 is a highly sensitive (82 to 97.5%) and specific (99.6%) marker of Xp11.2 RCC, in contrast to clear cell RCC (Fig. 2B) or other renal tumors. TFE3 is also positive in alveolar soft part sarcoma (Argani et al., 2003a, Camparo et al., 2008). Positive TFE3 immunostaining is recognized by strong nuclear labeling, obvious at low power magnification. More than 5% of the total neoplastic cells should be stained. (Argani et al., 2003a; Camparo et al., 2008). Excessive antigen retrieval may lead to false positivity because native TFE3 is ubiquitously distributed (Argani et al., 2003a). Cathepsin-K is expressed in 60% of cases and it is very useful in distinguishing other renal tumors,

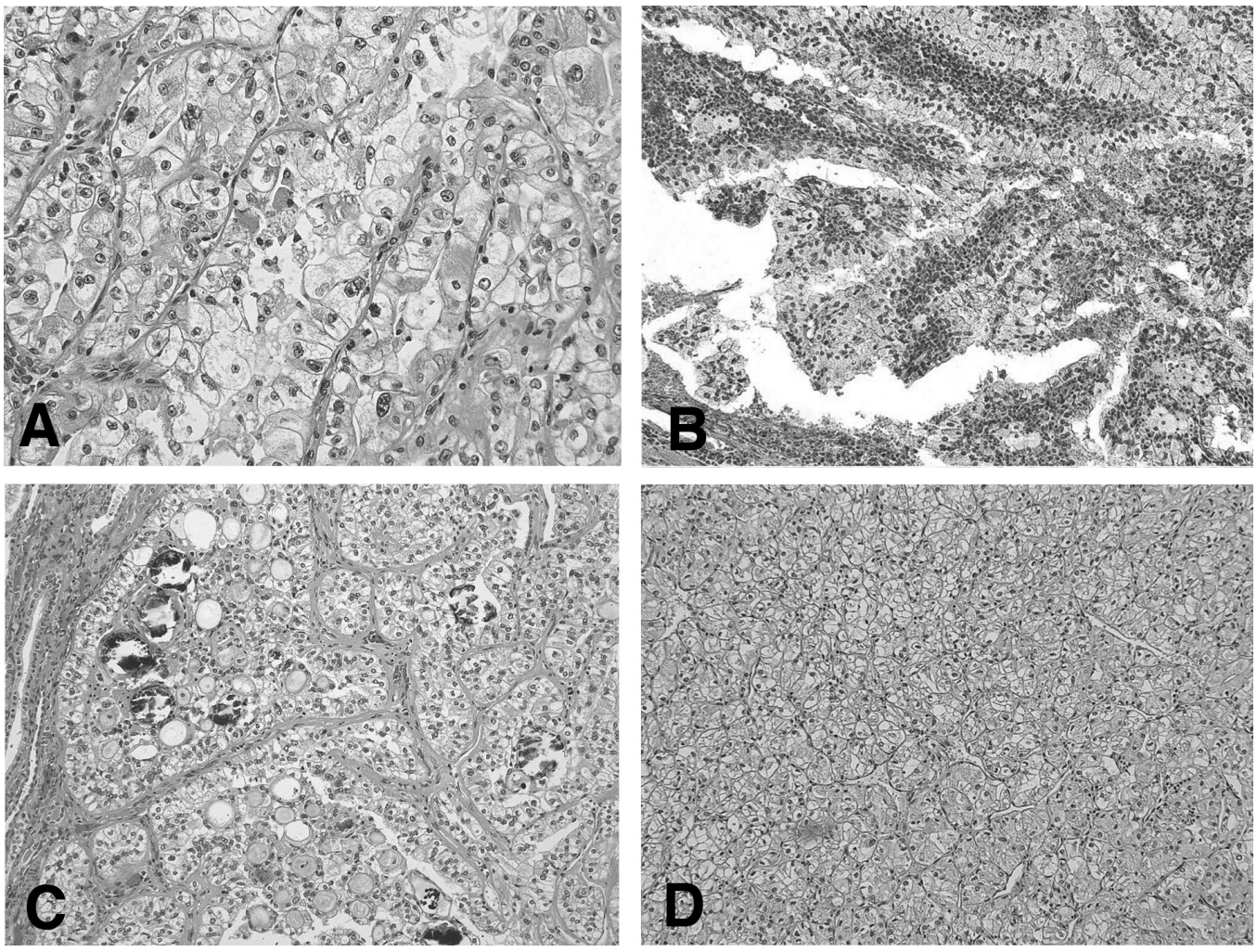

Fig. 1. Microscopic findings of *ASPL-TFE3* RCC. **A.** Voluminous tumor cells with clear to eosinophilic cytoplasm with nested/alveolar pattern. **B.** The papillary growth pattern with clear cytoplasm is seen. **C.** Psammoma bodies are identified in the stroma. **D.** The growth pattern indistinguishable from clear cell RCC can be observed. A, x 200; B-D, x 100

including clear cell RCC, papillary RCC, chromophobe RCC and renal oncocytoma (Martignoni et al., 2009). In contrast to renal carcinoma with t(6;11)(p21;q12-13), melanocytic markers such as melanosome-associated antigen and Melan A are negative in *ASPL-TFE3* RCC (Argani et al., 2009). However, melanocytic markers are positive in only a subset of Xp11.2 RCC, and staining is generally focal (Camparo et al., 2008). However, MiTF is nonimmunoreactive in the majority of cases (Argani et al., 2010b). Neoplastic cells in most cases show diffuse immunoreactivity for CD10, AMACR and E-cadherin (Camparo et al., 2008). Many tumors show nuclear labeling for PAX2 and PAX8 (Argani et al., 2010b). In contrast, Gupta et al. (2009) reported that all tumors with Xp11.2 RCC are nonimmunoreactive with PAX2. Carbonic anhydrase IX expression is generally focal (Gupta et al., 2009; Argani et al., 2010b). Epithelial markers including cytokeratin detected by AE1/AE3 and EMA are frequently negative or only weakly positive (Armah et al., 2009). Vimentin immunoreactivity is variable in adult cases of Xp11.2 RCC (Argani et al., 2007; Camparo et al., 2008). Tumor cells in all cases with Xp11.2 RCC show no immunoreactivity to TFEB (Argani et al., 2005).

Ultrastructural findings

In *ASPL-TFE3* RCC, tumor cells may contain alveolar soft part sarcoma-like structures, such as dense granules and rhomboid crystals, as well as epithelial structures such as cell junctions, microvilli and glandular lumens (Argani et al., 2001; Meyer et al., 2007; Yamaguchi et al., 2009). In *PRCC-TFE3* RCC, neoplastic cells have features consistent with clear cell RCC, but some tumors may contain distinctive intracisternal microtubules similar to those observed in melanoma (Argani et al., 2002).

Cytological findings

Imprint cytology of primary tumor shows tight clusters of papillary formation with branching fibrovascular cores, and tumor cells have abundant cytoplasm, irregular-shaped large, oval nuclei with prominent nucleoli (Yamaguchi et al., 2009). The stromal change, such as hyaline nodules or psammoma bodies may become cytologic diagnostic clues (Mansouri et al., 2006; Yamaguchi et al., 2009). Fine-needle aspiration material of pulmonary metastatic lesion show follicular structures surrounding dense hyalinizing central cores, and neoplastic cells display bland nuclei and have granular to vacuolated cytoplasm (Schinstine et al., 2006).

Molecular genetic findings

Several chromosomal translocation partners can be fused to the *TFE3* gene at Xp11.2. Two common forms are t(X;17)(p11.2;q25) which fuses the *TFE3* gene with the *ASPL* gene located on 17q25, and t(X;1)(p11.2;q21) which fuses the *TFE3* gene with the *PRCC* gene situated at 1q21 (Tomlinson et al., 1991; Meloni et al., 1992, 1993; Shipley et al., 1995; Sidhar et al., 1996; Weterman et al., 1996a-c; Dal Cin et al., 1998; Kardas et al., 1998; Perot et al., 1999; Argani et al., 2001, 2002; Heimann et al., 2001; Ramphal et al., 2006). Additionally, less common translocations involving the *TFE3* gene include t(X;1)(p11.2;p34), which results in the *PSF-TFE3*

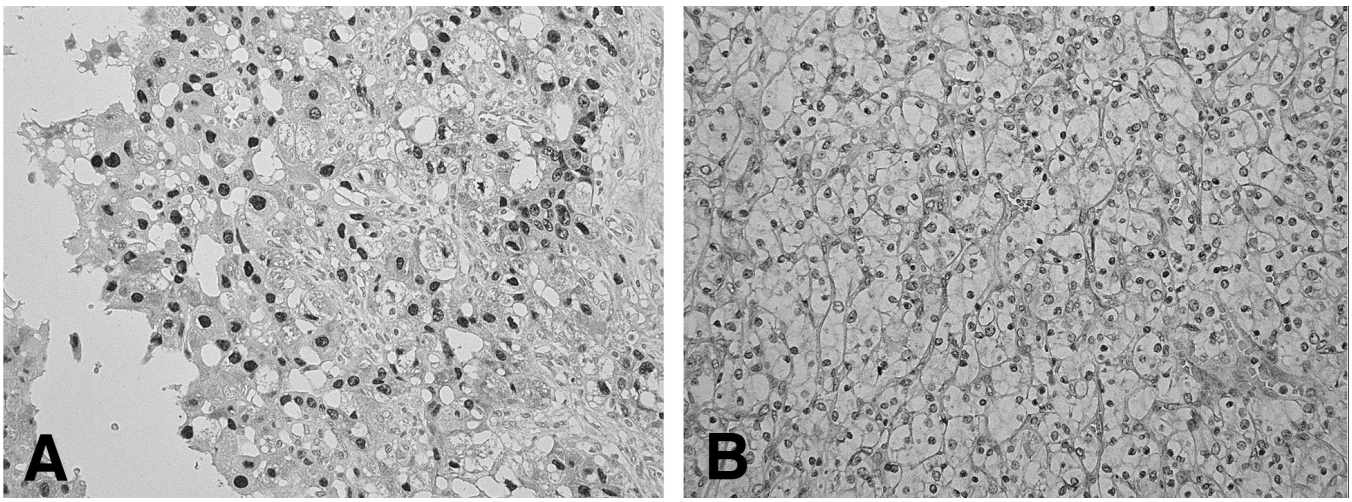

Fig. 2. Immunohistochemical findings. **A.** Xp11.2 RCC shows diffuse intense nuclear labeling for TFE3. The adjacent benign renal parenchyma is negative for TFE3. **B.** Clear cell RCC demonstrates no immunoreaction with TFE3. A, x 200; B, x 100

chimera, inv(X)(p11.2;q12), which gives rise to *NonO*(*p54^{nrb}*)-*TFE3* chimera, and t(X;17)(p11.2;q23), which fuses the *CLTC* gene to the *TFE3* gene (Kovacs et al., 1987; Dijkuizen et al., 1995; Clark et al., 1997; Argani et al., 2003b). Additionally, novel chromosomal translocations of t(X;10)(p11.2;q23), t(X;3)(p11;q23) and t((X;19)((p11.2;q13.1) have been identified (Dijkuizen et al., 1995; Argani et al., 2007; Armah et al., 2009). However, these partner genes remain unknown. No *VHL* mutations have been observed, but deletion of 3p25-26 was found in one case (Bruder et al., 2004). The break apart FISH assay on paraffin-embedded tumor tissue may be a helpful ancillary technique in small biopsies or fine needle aspiration materials for Xp11.2 RCC (Zhong et al., 2010). The fusion of the *TFE3* gene to the *PRCC, PSF, NONO, ASPL* and *CLTC* genes leads to activation and/or upregulation of the respective *MiTF* genes (Medendorp et al., 2007). *ASPL-TFE3* fusion protein binds to the MET promoter and strongly activates it. Likewise, *PSF-TFE3* and *NONO-TFE3* fusion proteins also bind to this promoter (Tsuda et el., 2007).

Differential diagnosis

The histological distinction of Xp11.2 RCC from clear cell RCC, papillary RCC, chromophobe RCC, collecting duct carcinoma, mucinous tubular and spindle cell carcinoma, sarcomatoid carcinoma, clear cell papillary RCC, epithelioid angiomyolipoma, and renal carcinoma with t(6;11)(p21;q12-13) is important. The differences between Xp11.2 RCC and two RCCs, namely clear cell RCC and papillary RCC, in the most likely differential diagnosis are summarized in Table 2. In clear cell RCC, papillary growth pattern is generally focal, and stromal changes such as hyaline nodules and psammoma bodies are rare. In typical papillary RCC, nested/alveolar growth pattern is not prominent and voluminous neoplastic cells are not intermingled. *ASPL-TFE3* RCC generally has distinct cell borders and variation of the size of neoplastic cells. Such findings may resemble chromophobe RCC (Kuroda et al., 2010). *PSF-TFE3* RCC may resemble collecting duct carcinoma or renal angiomyolipoma (Argani et al., 2007). Renal angiomyolipoma shows strong immunoreactivity for alpha smooth muscle actin, which is different from that of Xp11.2 RCC, and melanosome-related antigen positivity is usually much more prominent compared to Xp11.2 RCC (Aydin et al., 2009). Xp11.2 RCC may rarely show myxoid change and slit-like lumina frequently encountered in mucinous tubular and spindle cell carcinoma (Argani et al., 2007). Additionally, spindle neoplastic cells rarely appear in Xp11.2 RCC. These spindle cells occurring in mucinous tubular and spindle cell carcinoma generally show low-grade morphology, different from sarcomatoid RCC (Argani et al., 2007). Clear cell papillary RCC immunohistochemically shows typically positive labeling for cytokeratin 7 and negative labeling for AMACR (Gobbo et al., 2008). Rare cases of Xp11.2 RCC may possess two populations of cells: large polygonal cells and small cells around hyaline materials. Such findings are typical for RCC with t(6;11)(p21;q12-13). In such a setting, staining with TFEB is very useful (Argani et al., 2005). Finally, correctly performed and interpreted TFE3 immunohistochemistry remained the most useful marker in identifying this tumor sub-type (Argani et al., 2003a).

Therapy

Radical nephrectomy is recommended, but partial

Table 2. Comparison of morphological and immunohistochemical data of X11.2 RCC and other RCCs.

	Xp11.2 RCC	Clear cell RCC	Papillary RCC, type 2
Morphology			
Cytoplasmic color	Clear to eosinophilic	Clear	Eosinophilic
Cytoplasmic size or shape	Voluminous	Intermediate	Columnar
Nuclei	Moderate~large	Usually small	Moderate~large
Nucleoli	Usually prominent	Usually inconspicuous	Various
Growth pattern	Alveolar/solid	Alveolar/solid	Papillary
Papillary	tubular, cystic	Tubulopapillary	
Psammoma bodies	Frequent	Rare	Occasional
Hyaline nodules	Frequent	Absent	Absent
Immunohistochemistry			
RCC Ma	+	+	+
CD10	+	+	+
Cytokeratin 7	-	-	+
AMACR (P504S)	+	-	+
E-cadherin	+	-	+
Cathepsin K	+	-	-
TFE3	+	-	-

RCC: renal cell carcinoma; +, positive; -, negative.

nephrectomy may be occasionally considered if the tumor is small and superficial. Although some patients with Xp11.2 RCC were received immunotherapy, some patients did not show any response to immunotherapy such as interferon or interleukin-2 (Mansouri et al., 2006; Komai et al., 2009). Therefore, radical nephrectomy with extended lymphadenectomy should be considered when there is preoperative evidence of lymph node involvement or when there is increased risk for having lymph node metastasis (Komai et al., 2009). Target therapy with Sunitinib and Sorafenib, the vascular endothelial growth factor (VEGF) inhibitors, or Temsirolimus, an inhibitor of mammalian target of rapamycin (mTOR) kinase, may lead to a successful outcome for the metastatic lesions (Choueiri et al., 2009, 2010; Parikh et al., 2009; Malouf et al., 2010). MET tyrosine kinase or mTOR kinase may be a potential therapeutic target in the future (Argani et al., 2007, 2010b; Tsuda et al., 2007; Sagara et al., 2009; Armah et al., 2009; Choueiri et al., 2010).

Prognosis

The differences between Xp11.2 RCC and other RCCs are summarized in Table 1. Xp11.2 RCC in children and young adults are believed to be indolent even when diagnosed at advanced stage with regional lymph node metastasis and without distant metastasis (Ramphal et al., 2006; Geller et al., 2008; Armah et al., 2009). In adults, Xp11.2 RCC seems to behave in more aggressive fashion than in pediatric patients (Argani et al., 2007; Meyer et al., 2007). Recently, patients with Xp11.2 RCC have a grim prognosis due to their advanced stage at presentation and aggressive biologic features compared with the TFE-negative unclassified RCC cases (Mir et al., 2011). *ASPL-TFE3* RCC seems to be more likely to present at advanced stage than *PRCC-TFE3 RCC* (Camparo et al., 2008; Komai et al., 2009). However, as *PRCC-TFE3* RCC may have a potential to recur later, long-term follow-up is needed.

Perspectives

Gene partners of novel chromosomal translocations such as t(X;10)(p11.2;q23), t(X;3)(p11;q23) and t((X;19)((p11.2;q13.1) that were previously elucidated by cytogenetic studies need to be identified by further molecular studies (Dijkuizen et al., 1995; Argani et al., 2007; Armah et al., 2009). Additionally, only a subset of Xp11.2 RCC share features with malignant melanoma or perivascular epithelioid cell tumor (Argani et al., 2009; Kuroda et al., 2009; Tanaka et al., 2009; Argani et al., 2010a). In particular, both Xp11.2 RCC and perivascular epithelioid cell tumor immunohistochemically express melanocytic markers and TFE3 protein and, furthermore, translocation of the *TFE3* gene was confirmed in both tumors. The difference of clinical behavior of Xp11.2 RCC arising in children, youth and adults needs further investigation. Finally, as parts of renal carcinoma with t(6;11)(p21;q12-13) may share histologic features such as Xp11.2 RCC, further investigation on a large-scale study will be required in order to clarify the histological and molecular differences between both tumors (Petersson et al., 2011).

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