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UHRF1 is a Potential Molecular Marker for Diagnosis and Prognosis of Bladder Cancer

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1. Introduction

Bladder cancer is the second most common cancer of the urinary system. An estimated 386,300 new cases and 150,200 deaths from bladder cancer occurred in 2008 worldwide (Jemal et al., 2011). The highest rates of bladder cancer incidence are found in industrially developed countries, particularly in North America and Western Europe (Parkin et al., 2005). Bladder cancer is more common in males. The cancer is the 7th most common cancer in males worldwide and 4th most common cancer in males in industrially developed countries, while the cancer is not ranked in the top 10 most common cancers in females even in industrially developed countries (Jemal et al., 2011). In industrially developed countries, approximately 90% of the cancers are transitional cell carcinomas (TCCs), while the remaining 10% are squamous cell carcinomas and adenocarcinomas (Stein et al., 2001).

There are several potential biomarkers for diagnosis and prognosis for bladder cancer, including Nuclear matrix protein-22 (NMP-22), human complement factor H related protein, telomerase, fibrin degradation product, and hyaluronic acid (Dey, 2004). Among these, only two biomarkers, NMP-22 and human complement factor H related protein, are in clinical use in Japan. Although these two markers are in clinical use, sensitivity and specificity of these markers are not perfect (van Rhijn et al., 2005); NMP-22 staining shows false positivity reactions in patients with hematuria, and the BTA (bladder tumour antigen) stat/BTA TRAK assay, which detects human complement factor H related protein, shows false positivity reactions in patients with urinary tract inflammation, recent genitourinary tumours and in cases of bladder stone (Dey, 2004). Cytology is still the most accurate diagnosis method, although sensitivity is not enough high (van Rhijn et al., 2005). Thus, discovery of a novel biomarker, which is sensitive and specific for bladder cancer, is an urgent subject.

2. UHRF1 is a potential molecular marker for diagnosis and prognosis of bladder cancer

UHRF1 (ubiquitin-like with PHD and ring finger domains 1), also known as ICBP90 (Inverted CCAAT box-binding protein of 90 kDa), was identified as a protein, whose expression is only detectable in proliferating cells, not in quiescent cells (Hopfner et al., 2000; Unoki et al., 2004). UHRF1 plays a central role in transferring DNA methylation status

from mother cells to daughter cells. Its SET and RING finger-associated (SRA) domain recognizes hemi-methylated DNA that appears in newly synthesized daughter DNA strands during duplication of DNA strands through the S phase (Arita et al., 2008; Avvakumov et al., 2008; Hashimoto et al., 2008). UHRF1 recruits DNA methyltransferase 1 (DNMT1) to the site with proliferating cell nuclear antigen (PCNA) and methylates the newly synthesized strands (Achour et al., 2008; Sharif et al., 2007). UHRF1 also recognizes tri/di-methylated H3K9, and recruits the H3K9 methyltransferase G9a, the histone deacetylase 1 (HDAC1), and the histone acetylase Tip60 (Achour et al., 2009; Hashimoto et al., 2009; Karagianni et al., 2008; Kim et al., 2009; Unoki et al., 2004), indicating that UHRF1 links DNA methylation and histone modification status (Fig. 1).

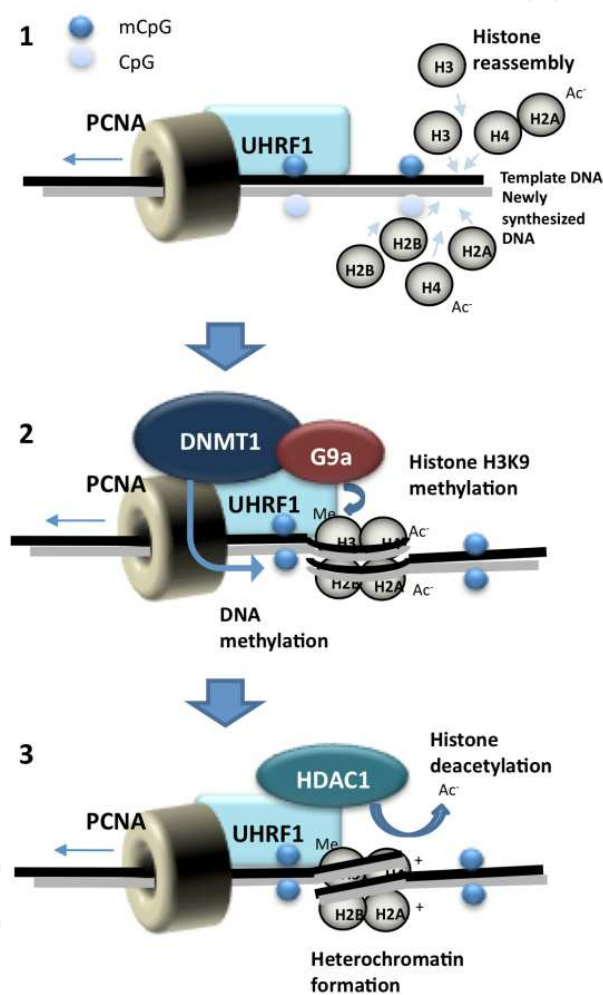


Fig. 1. Proposed mechanism of heterochromatin formation through UHRF1 at DNA replication fork or DNA repair site. 1) UHRF1 binds to PCNA and the SRA domain of UHRF1 recognizes hemi-methylated CpG on newly synthesized DNA. Then histones are reassembled. 2) UHRF1 recruits DNMT1 to methylate both DNA strands to transfer methylation status. UHRF1 also recruits G9a to methylate histone H3K9. Methylated histone H3K9 interacts with the Tudor-PHD domain of UHRF1. 3) UHRF1 recruits HDAC1 to the site and deacetylates histones. Then, histones become charged positively and bind to negatively charged DNA tightly, causing heterochromatin formation. This figure is cited from our article (Unoki et al., 2009a).

UHRF1 promotes G1/S transition (Arima et al., 2004; Jeanblanc et al., 2005) and is a direct target of E2F transcription factor 1 (E2F1) (Abbadly et al., 2005; Mousli et al., 2003; Unoki et al., 2004). The tumour suppressor p53, which is deficient in 50% of all human cancers (Hussain & Harris, 2000), indirectly down-regulates UHRF1 through up-regulation of p21/WAF1 and subsequent deactivation of E2F1 (Arima et al., 2004) (Fig. 2).

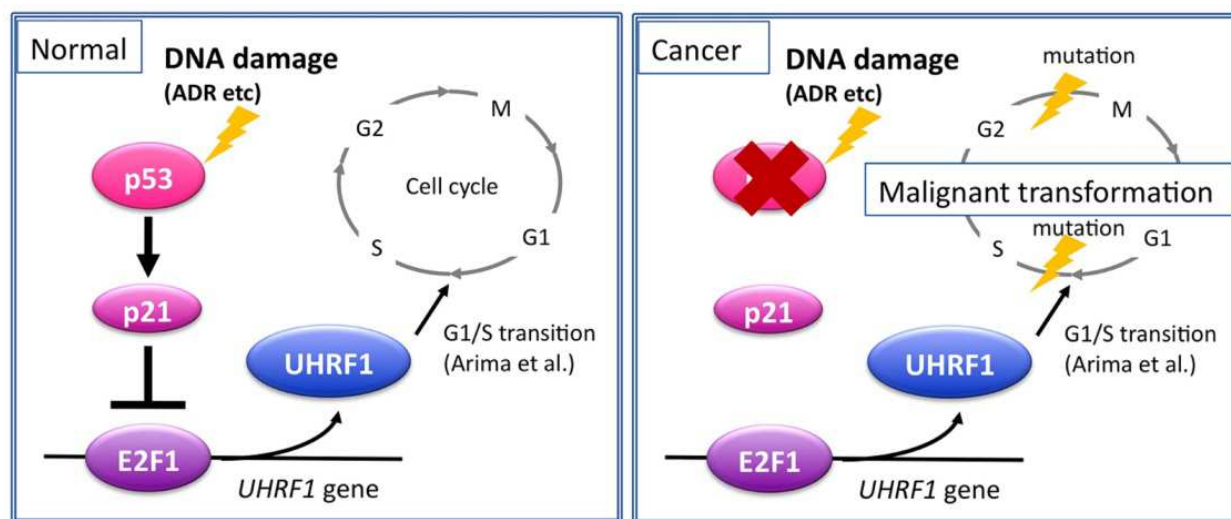


Fig. 2. Proposed p53-UHRF1 pathway model.

Expression of UHRF1 is up-regulated in various cancers, including breast cancer (Fig. 3), lung cancer (Fig. 4), prostate cancer, astrocytoma, pancreatic cancer, cervical cancer, and poorly differentiated thyroid carcinoma (Crnogorac-Jurcevic et al., 2005; Jenkins et al., 2005; Lorenzato et al., 2005; Mousli et al., 2003; Oba-Shinjo et al., 2005; Pita et al., 2009; Unoki et al., 2010; Unoki et al., 2004). Overexpression of UHRF1 in these cancers could be partially due to the inactivation of p53, although there could be several pathways, which regulate expression of UHRF1. Knock down of UHRF1 expression in cancer cells suppressed cell growth, indicating that UHRF1 is essential for progression of cancers and thus could be an anticancer drug target (Tien et al., 2011; Unoki, 2011; Unoki et al., 2009a; Unoki et al., 2004; Yan et al., 2011). Moreover, knockdown or inactivation of UHRF1 is reported to enhance sensitivity against current chemotherapies and radiation therapy *in vitro* (Alhosin et al., 2010; Jenkins et al., 2005; Jin et al., 2010; Li, X. et al., 2011; Li, X. L. et al., 2009; Muto et al., 2002). Therefore, UHRF1 is also an attractive target of cancer combination therapies (Bronner et al., 2007; Unoki, 2011; Unoki et al., 2009a).

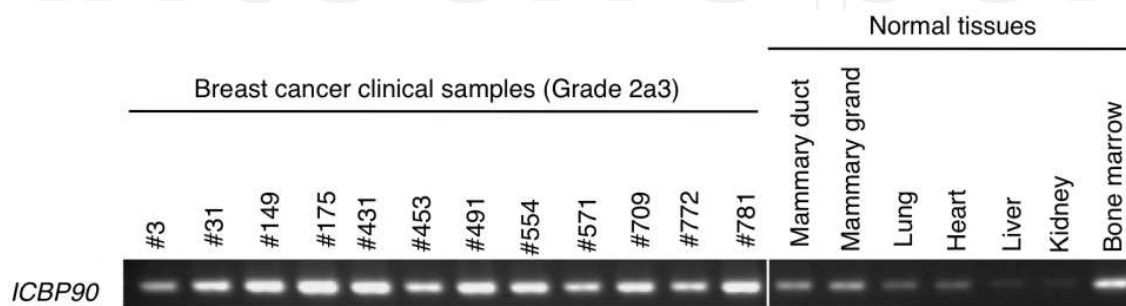


Fig. 3. Expression of *UHRF1* in breast cancer clinical samples detected by semi-quantitative RT-PCR. This figure is cited from our article (Unoki et al., 2004).

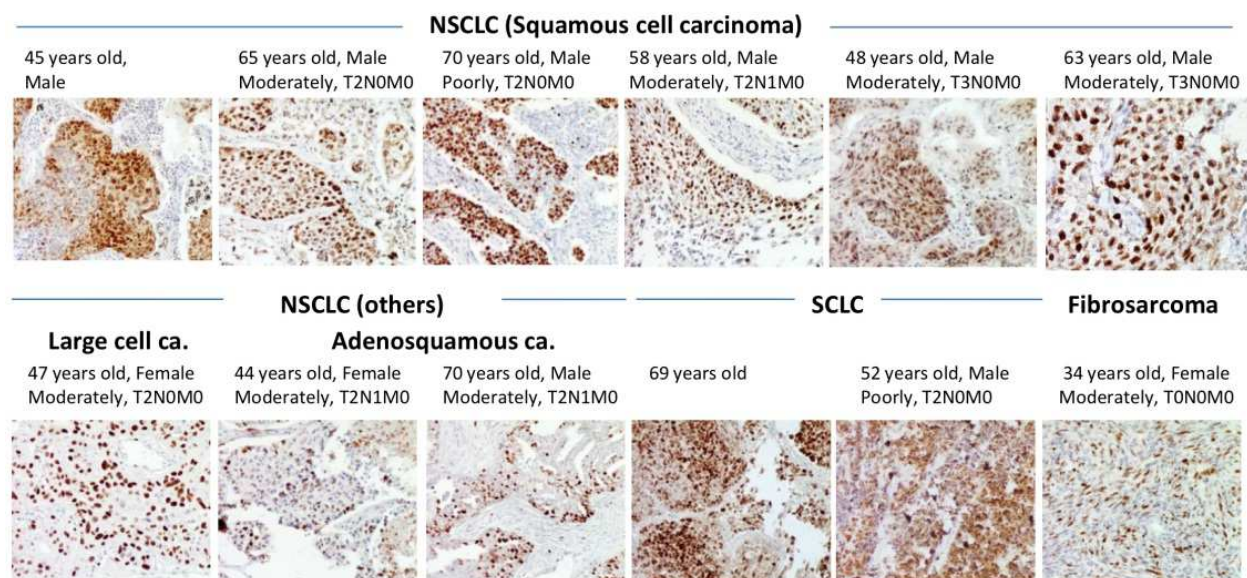


Fig. 4. Expression of UHRF1 in lung cancer clinical samples detected by immunohistochemistry. Representative data of UHRF1 staining in small cell lung carcinoma (SCLC), fibrosarcoma, and non-adenocarcinoma (ADC) histological types of non-small-cell lung carcinoma including squamous cell carcinoma (SCC), large cell carcinoma, and adenosquamous carcinoma (x 200). This figure is cited from our article (Unoki et al., 2010).

2.1 UHRF1 is overexpressed in bladder cancer

Considering these features of UHRF1, we thought that UHRF1 could be also important for bladder carcinogenesis, and examined expression of UHRF1 in bladder cancer specimens obtained from 124 UK cases (Table 1) and 36 Japanese cases (Unoki et al., 2009b). As a result, we found that UHRF1 was significantly overexpressed in bladder cancers at the mRNA and protein level (Fig. 5 and Fig. 6).

Because overexpression of UHRF1 in the cancer was detected both in UK cases and also in Japanese cases, the overexpression of UHRF1 could be common worldwide. Recently, another group showed that UHRF1 is also overexpressed in superficial, non-muscle-invasive bladder cancer of Chinese cases (Yang et al., 2011). Their result supports our observation. We also examined correlation between expression of UHRF1, p53, and *p21/WAF1*, and observed accumulation of stabilized p53 protein, which is probably mutated, in cancer tissues at grade II-III. However, we did not observe any accumulation of p53 in cancer tissues at grade I, although overexpression of UHRF1 was observed in this grade (Fig. 7). There was no relationship between expression levels of UHRF1 and *p21* mRNA. Therefore, UHRF1 seems to be superior to p53 as a potential diagnostic marker of bladder cancer. This result is concordant with the fact that p53 is mutated only in 10-30 % of bladder cancer cases (Berggren et al., 2001; Lorenzo Romero et al., 2004).

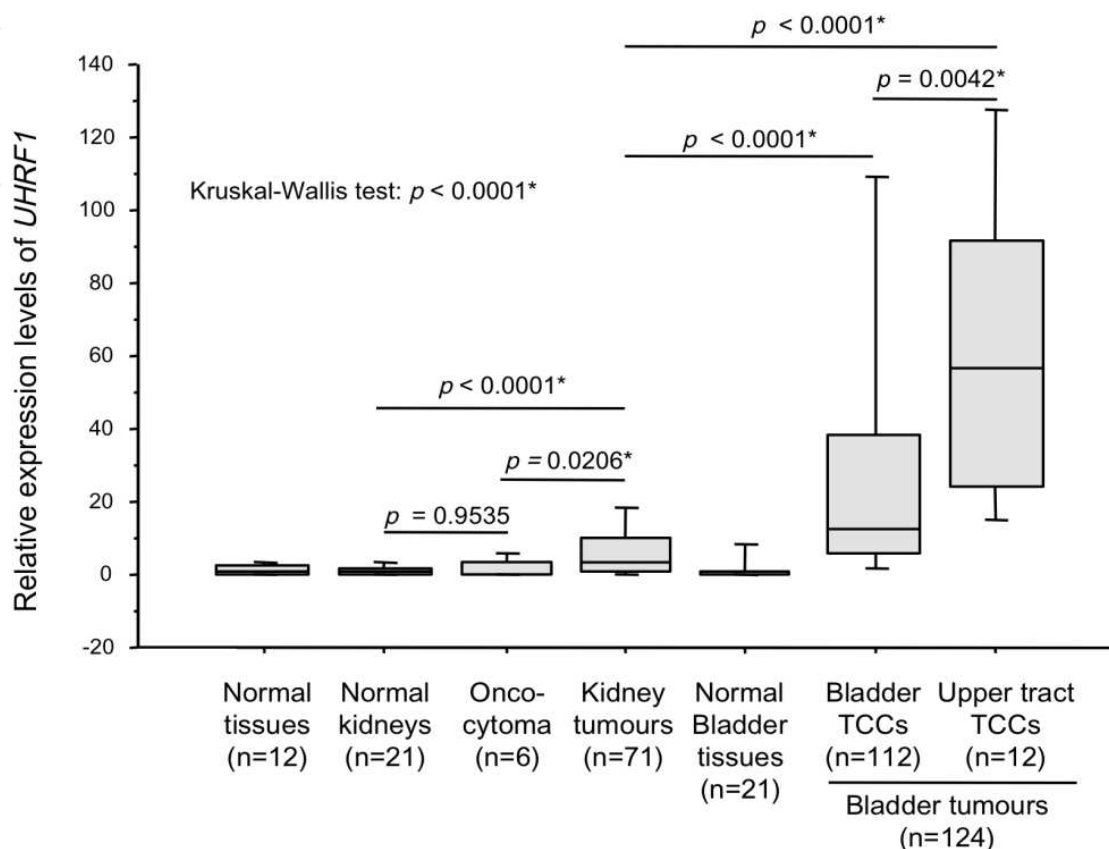


Fig. 5. Expression levels of *UHRF1* mRNA in urinary system tumours and normal tissues detected by TaqMan qRT-PCR. Expression of *UHRF1* in 12 different normal tissues, 21 normal kidneys, 6 oncocytomas, 71 kidney tumours, 21 normal bladders, and 124 bladder tumours, including 112 bladder located transitional cell carcinomas (TCCs) and 12 TCCs occurred in upper tract, were compared. Expression of *UHRF1* differed among the seven groups ($p < 0.0001$, Kruskal-Wallis' test). Expression of *UHRF1* in the kidney cancers was higher than that in the normal kidneys and also in the oncocytomas significantly ($p < 0.0001$, and $p = 0.0206$, respectively, Mann-Whitney's U-test), but expression levels of *UHRF1* in the bladder cancers were much higher than those in the kidney cancers ($p < 0.0001$, Mann-Whitney's U-test). Among the bladder cancers, expression of *UHRF1* was significantly high in upper tract TCCs ($n = 12$) compared with the bladder-origin bladder tumours ($n = 112$) (Mann-Whitney's U-test; $p = 0.0042$). $\beta 2$ -microglobulin was used for normalization. Asterisk indicates statistically significant p -values. This figure is cited from our article (Unoki et al., 2009b).

Characteristics	n (%)	Characteristics	n (%)
Total numbers of patients	124	Sex	
Anatomic site		Male	75 (72%)
Bladder	112 (90%)	Female	29 (28%)
Upper tract	12 (10%)	Numbers of tumours	
Type		<4	53 (85%)
TCC	122 (>99%)	>4	9 (15%)
Others	1 (<1%)	Tumour size	
Invasiveness		<5	38 (66%)
Superficial	71 (63%)	>5	20 (34%)
Invasive	41 (37%)	Growth pattern	
T-category		°CIS	1 (2%)
Ta	40 (35%)	Papillary	32 (52%)
T1	32 (28%)	Solid	19 (31%)
T2	24 (21%)	Solid/Papillary	9 (15%)
T3	14 (12%)	Recurrence	
T4	4 (4%)	No	19 (29%)
WHO grading		Yes	46 (71%)
Grade 1	9 (8%)	5-years survival	
Grade 2	59 (51%)	Alive	46 (49%)
Grade 3	47 (41%)	Dead	48 (51%)
Risk after °TURBT		Smoking	
Low	7 (13%)	Non-smoker	22 (35%)
Intermediate	26 (46%)	Smoker	40 (65%)
High	23 (41%)		

^aTotal numbers of the patients are not always 124, because not all patients have all the clinical information; ^bTURBT, transurethral resection of the bladder tumour; ^cCIS, carcinoma *in situ*.

Table 1. Base line characteristics of bladder cancer patients used for our analyses (Unoki et al., 2009b).

We also examined expression of UHRF1 in kidney cancer, another urinary system tumour, together with the bladder cancer by immunohistochemistry. Although overexpression of *UHRF1* is significant at mRNA level (Fig. 5), expression of UHRF1 in kidney cancer was not detected at protein level (Fig. 8A). Therefore, immunohistochemical staining of UHRF1 in the cancer seems not to be useful. However, overexpression of *UHRF1* at the mRNA level was associated with several characteristics of kidney cancer patients including 5-year survival rates, pathological staging and histological grade (Fig. 8B-D). Thus, detection of

UHRF1 mRNA overexpression in surgical specimen might be useful as a prognosis tool in kidney cancer.

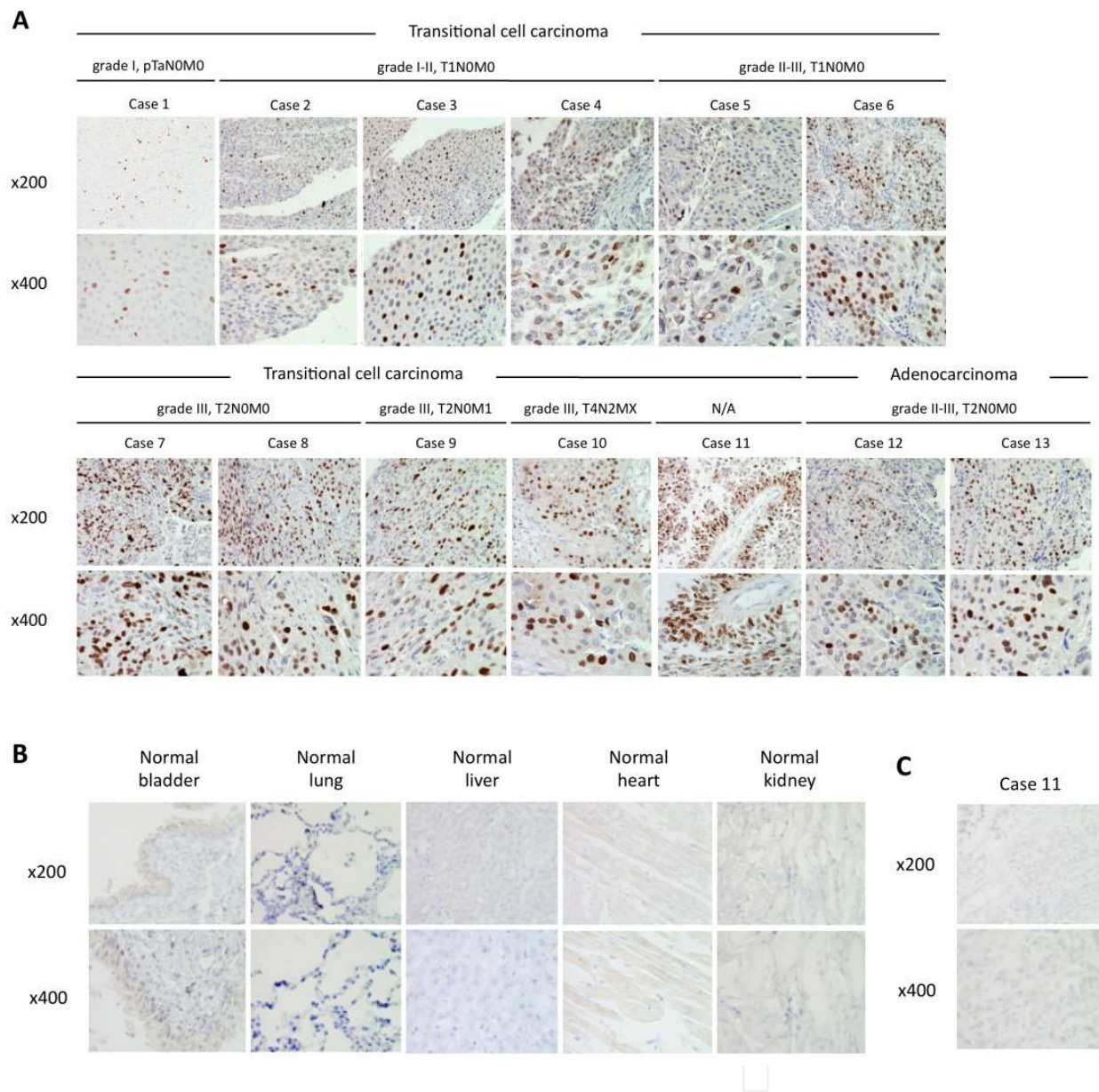


Fig. 6. Immunohistochemical staining of UHRF1 in 13 bladder tumour cases. A. Expression of UHRF1 in 11 transitional cell carcinomas and two adenocarcinomas with the different stage and grade. High expression of UHRF1 was detected only in nucleus of cancer cells, not in stromal cells. B. Expression of UHRF1 in normal tissues including bladder, lung, liver, heart, and kidney. No expression was observed in these normal tissues. Original magnifications, x 200 (top), and x 400 (bottom). C. Representative images of normal IgG staining as a negative control (Case 11 used for Fig. 6A). Original magnifications, x 200 (top), and x 400 (bottom). This figure is cited from our article (Unoki et al., 2009b).

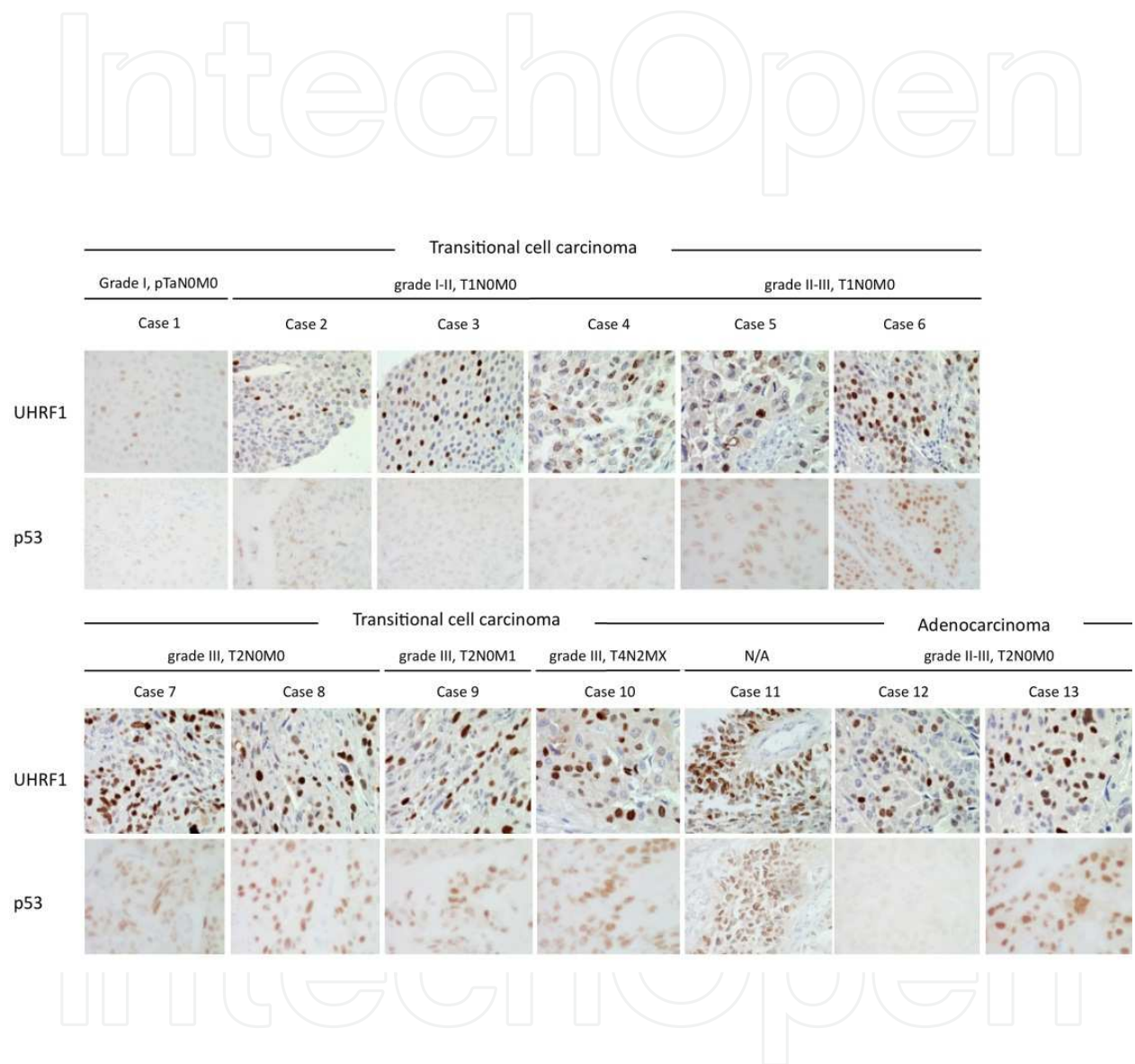


Fig. 7. Expression of p53 and UHRF1 in bladder cancers detected by immunohistochemistry. This figure is cited from our article (Unoki et al., 2009b).

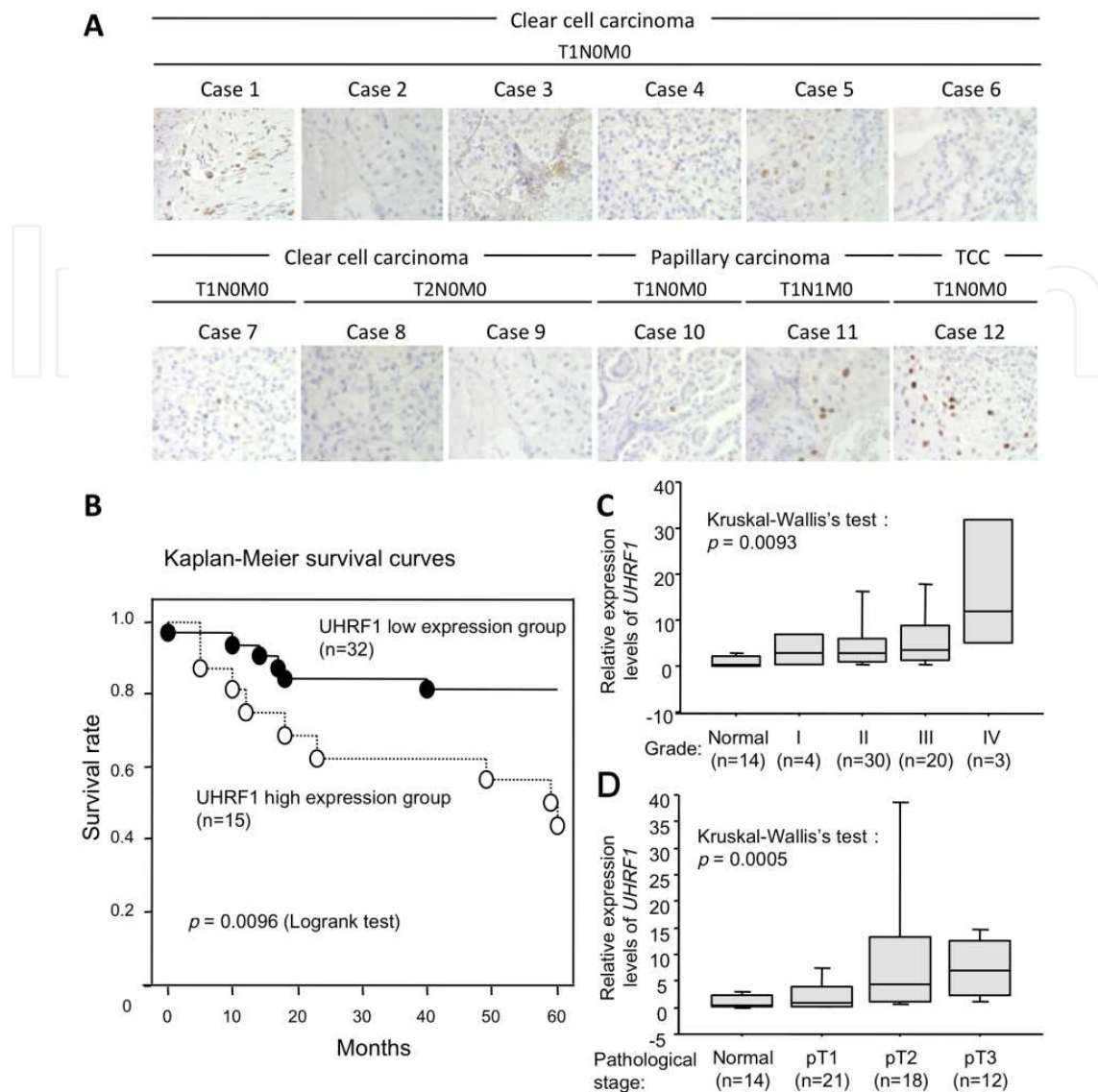


Fig. 8. Expression of UHRF1 in kidney cancer. A. UHRF1 expression in kidney cancers examined by immunohistochemistry. Magnification level is x400. B. Expression levels of *UHRF1* correlate with 5-years' survival rate of kidney tumours detected by TaqMan qRT-PCR. Patients were categorized into two groups by expression levels of *UHRF1*. The *UHRF1* high expression group is a group, which expresses *UHRF1* eight or more (≥ 8) and the low expression group is a group, which expresses *UHRF1* less than eight fold (< 8) compared with average of *UHRF1* expression level in normal kidney from 21 individuals as 1.0. In the result of Kaplan-Meier survival analysis, the *UHRF1* high expression group showed significantly poor survival rate compared with the *UHRF1* low expression group ($p=0.0096$: Logrank test). $\beta 2$ -microglobulin was used for normalization. C. Expression levels of *UHRF1* correlated with histological grade of kidney tumours detected by TaqMan qRT-PCR. Patients were categorized into four groups by histological grade (I to IV). High expression of *UHRF1* correlated with advanced grade ($p=0.0093$: Kruskal-Wallis's test). $\beta 2$ -microglobulin was used for normalization. D. Expression levels of *UHRF1* correlated with pathological staging and histological grade of renal cancers detected by TaqMan qRT-PCR. Patients were categorized into three groups with pathological stages, pT1 to pT3. High expression of

UHRF1 correlated with advanced stage ($p=0.0005$: Kruskal-Wallis's test). $\beta 2$ -microglobulin was used for normalization. This figure is cited from our article (Unoki et al., 2009b).

2.2 Expression level of *UHRF1* correlates with malignancy of bladder cancer

We examined correlations between *UHRF1* expression in bladder cancer and various clinical features of the patients (Table 1). Among these features, the expression of *UHRF1* correlated with the T-category and the WHO histological grading significantly (Fig. 9A and 9B). Expression level of *UHRF1* in superficial bladder cancers (T-category: Ta and T1) and invasive bladder cancers (T-category classification: T2, T3 and T4) was both significantly higher than that in normal bladders. This result is concordant with data from the another group (Yang et al., 2011). In addition, expression of *UHRF1* in invasive bladder cancers was higher than that in superficial cancers, when we compared the three groups, normal bladders, invasive bladder cancers (pTa, pT1), and superficial bladder cancers (pT2-4), by Kruskal-Wallis's test (Fig. 9A). In addition, expression level of *UHRF1* in cancers with grade-II and -III was up-regulated compared with that in normal bladders (Fig. 9B). Therefore, up-regulation level of *UHRF1* reflects progression level of bladder cancer.

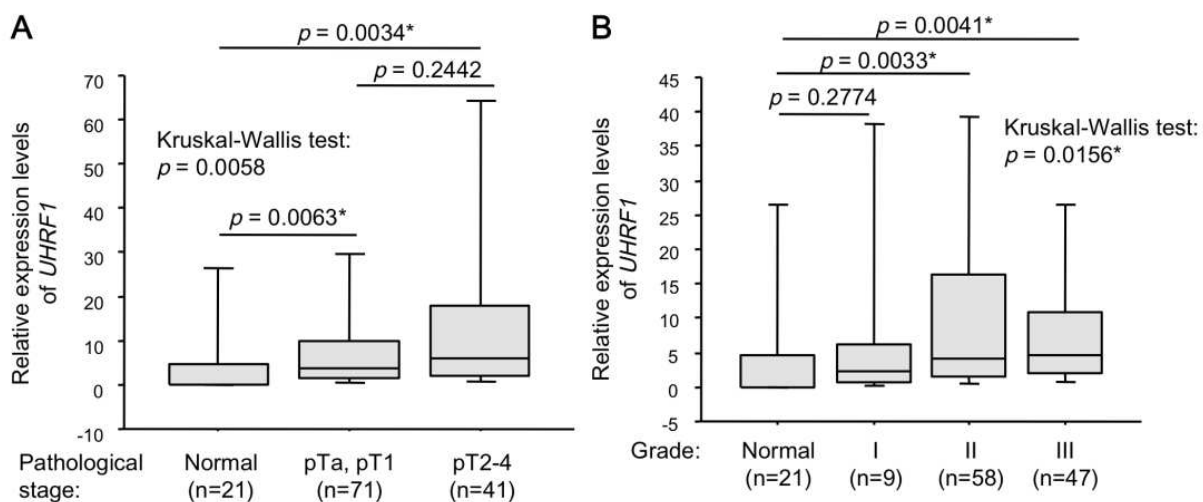


Fig. 9. Expression of *UHRF1* correlated with the stage, and grade. A. Expression of *UHRF1* in 21 normal bladders, 71 superficial bladder tumours (T-category is pTa and pT1), and 41 invasive bladder tumours (T-category is pT2, pT3, and pT4) detected by TaqMan qRT-PCR. Expression levels of *UHRF1* in superficial bladder tumours and in invasive tumours were significantly higher compared with those in normal bladders by Mann-Whitney's U-test ($p=0.0063$ and $p=0.0034$, respectively). Although its expression in superficial tumours and invasive tumours did not differ ($p=0.2442$, Mann-Whitney's U-test), it differed among the three different groups ($p=0.0058$, Kruskal-Wallis' test). $\beta 2$ -microglobulin was used for normalization. B. Expression of *UHRF1* differed among four groups with the different grade ($p=0.0156$, Kruskal-Wallis' test) detected by TaqMan qRT-PCR. Expression of *UHRF1* in grade II, and III tumour was higher than that in the normal bladders ($p=0.0033$ and $p=0.0041$). $\beta 2$ -microglobulin was used for normalization.

In our result, expression of *UHRF1* was not associated with difference of gender, numbers of tumour, tumour size, growth pattern (papillary or solid), incidence of recurrence, survival status after five years from surgery, and smoking history (Fig. 10), although the another

group showed an association between UHRF1 expression levels and tumour recurrence in superficial bladder cancer of Chinese cases (Yang et al., 2011). Therefore, UHRF1 could be a molecular marker for predicting the recurrence of superficial bladder cancers in some ethnic groups.

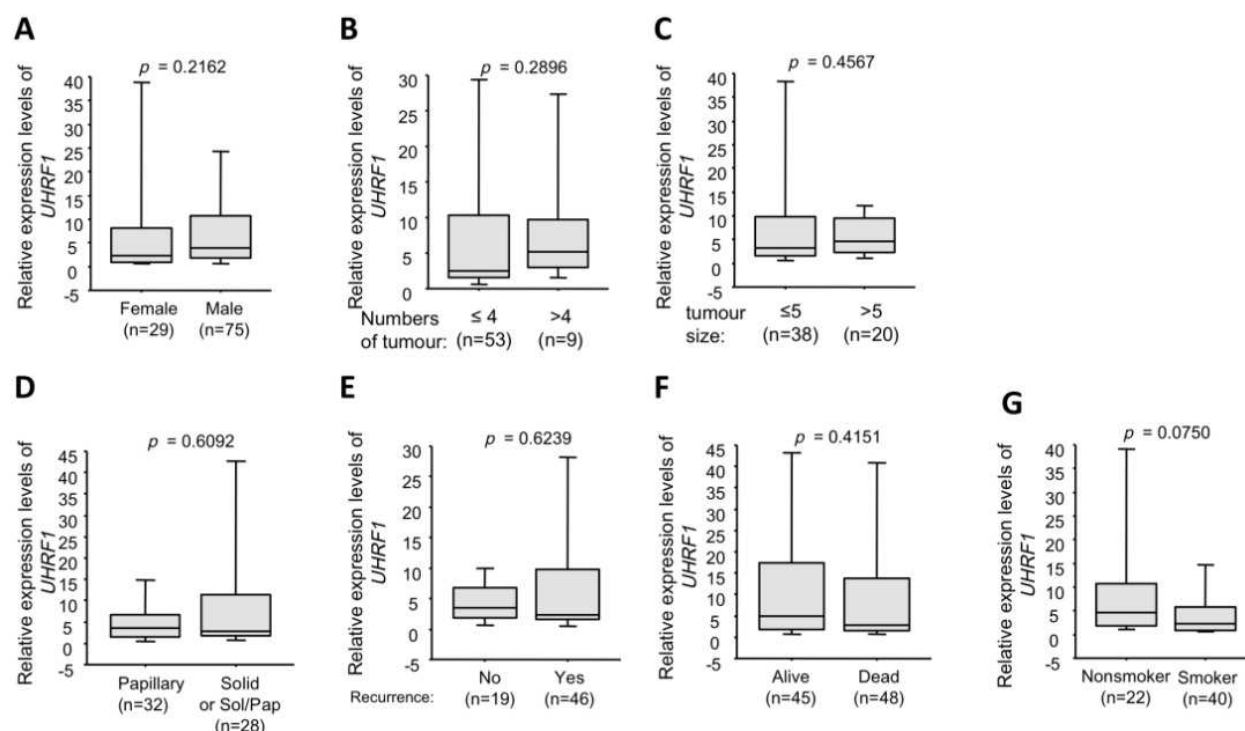


Fig. 10. Expression of *UHRF1* detected by TaqMan qRT-PCR and many characteristics of patients were compared by Mann-Whitney's U-test. A. Expression levels of *UHRF1* in female patients (n=29) and male patients (n=75). Gender was not associated with expression levels of *UHRF1* ($p=0.2162$). B. Expression levels of *UHRF1* in patients with tumours four and less (n=53) and more than four (n=9) were not different ($p=0.2896$). C. Expression levels of *UHRF1* in patients with ≤ 5 cm tumours (n=38) and with >5 cm tumours (n=20) were not different ($p=0.4567$). D. Expression levels of *UHRF1* in patients with papillary type tumours (n=32) and with solid or solid/papillary tumours (n=28) were not different ($p=0.4567$). E. Expression levels of *UHRF1* in patients who did not have a recurrence (n=19) and have a recurrence (n=46) were not different ($p=0.6239$). F. Expression levels of *UHRF1* in patients who survived 5 years after surgery (n=45) and died within 5 years (n=48) were not different ($p=0.4151$). G. Expression levels of *UHRF1* in non-smoker patients (n=22) and smoker patients including 4 ex-smokers (n=40) was not different ($p=0.0750$). $\beta 2$ -microglobulin was used for normalization.

2.3 Expression *UHRF1* can be used for predicting recurrence risk after TURBT

Over 75% bladder cancer patients have one or more superficial bladder cancers, and two thirds of them will develop recurrent disease (Lutzeyer et al., 1982), with 10–20% progressing to an invasive phenotype (Torti & Lum, 1984). The outcome of patients with invasive tumours remains still poor, with distant metastasis occurring in over 50% within 2 years and an average 5-year survival of only 50% (Raghavan et al., 1990). Currently, superficial bladder cancers are resected by a procedure called TURBT (TransUrethral

Resection of Bladder Tumour), and patients are treated differently based on estimated recurrence risk after TURBT. Thus, diagnosis of bladder cancer at non-advanced stage and also precise estimation of the risk after the TURBT, are very important for prognosis of patients. Currently, the risk after the surgery is estimated by a scoring system and risk tables developed by European Organization for Research and Treatment of Cancer (EORTC). The EORTC scoring system was developed based on the six most significant clinical and pathological factors, which are tumour stage, tumour grade, numbers of tumour, tumour size, prior recurrence rate, and presence of carcinoma *in situ* (CIS). Bladder cancer patients with pTaG1 tumours (50% of all patients) are at very low risk, and those with CIS or with pT1G3 tumours are at the highest risk (15% of all patients). Intermediate risk patients are those with pTa/pT1 G1/G2 disease who develop multiple recurrent cancers (35% of all patients). Our TaqMan qRT-PCR result showed that high expression of *UHRF1* was associated with high risk after TURBT (Fig. 11), probably because reflecting the association between high expression of *UHRF1* and stage, and/or grade (Fig. 9A and 9B). Based on these results, detection of *UHRF1* in tissue samples after TURBT will be a prognostic marker of future recurrence and may help to determine the risk together with the current prognostic factors.

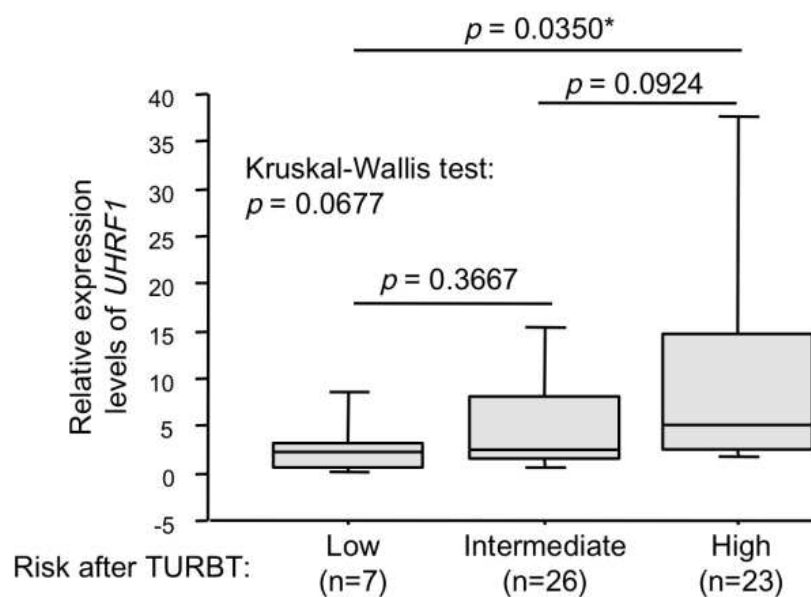


Fig. 11. Expression of *UHRF1* correlated with the recurrence risk after TURBT. Significant high expression of *UHRF1* in the high risk group after TURBT (n=23) was observed compared with that in the low risk group (n=7) by Mann-Whitney's U-test ($p=0.0350$). Asterisk indicates statistically significant p -values. β -microglobulin was used for normalization. This figure is cited from our article (Unoki et al., 2009b).

2.4 UHRF1 is a possible marker of bladder cancers and upper tract TCCs

Because *UHRF1* was significantly overexpressed in bladder cancers and upper tract TCCs (Fig. 5), *UHRF1* might be a useful diagnostic marker especially for upper tract TCCs. Upper tract TCCs are often very malignant when it is diagnosed, partially because it is relatively difficult to find at an early stage. If the cancer is found at an early stage, the

prognosis of patients is improved. The development of a sensitive urine based detection marker is still being sought. Examination of voided urine or bladder barbotage for exfoliated cancer cells is useful for diagnosis of urothelial tumours anywhere in the urinary tract, from the calyx, through the ureters, into bladder and urethra. However, cytological interpretation can be problematic; low cellular yields, atypia, degenerative changes, urinary tract infections, stones and intravesical instillations hamper a correct diagnosis. Because the current two biomarker tests in clinical use, NMP-22 detection and BTA stat/BTA TRAK assay, can be hampered by existence of bleeding, inflammation, recent genitourinary tumours, and bladder stone (Dey, 2004), these markers have not improved the traditional cytology-based bladder cancer diagnosis largely. Thus, cytology is still the mainstay for diagnosing bladder cancer. Because the expression of *UHRF1* in peripheral blood mononuclear cells (PBMCs) was under detection limit of qRT-PCR (Fig. 12), the presence of these cells in urine would not impede the diagnosis. Additionally, expression of *UHRF1* was not detected in adjacent normal bladder tissues by immunohistochemistry (Fig. 6A and 6B). Thus, contamination of these stromal cells also would not disturb the diagnosis, either. Therefore, an immunohistochemistry or Enzyme-Linked ImmunoSorbent Assay (ELISA)-based *UHRF1* detection in urine sediment can be a sensitive and cancer-specific diagnostic method, and may greatly improve the current diagnosis based on cytology.

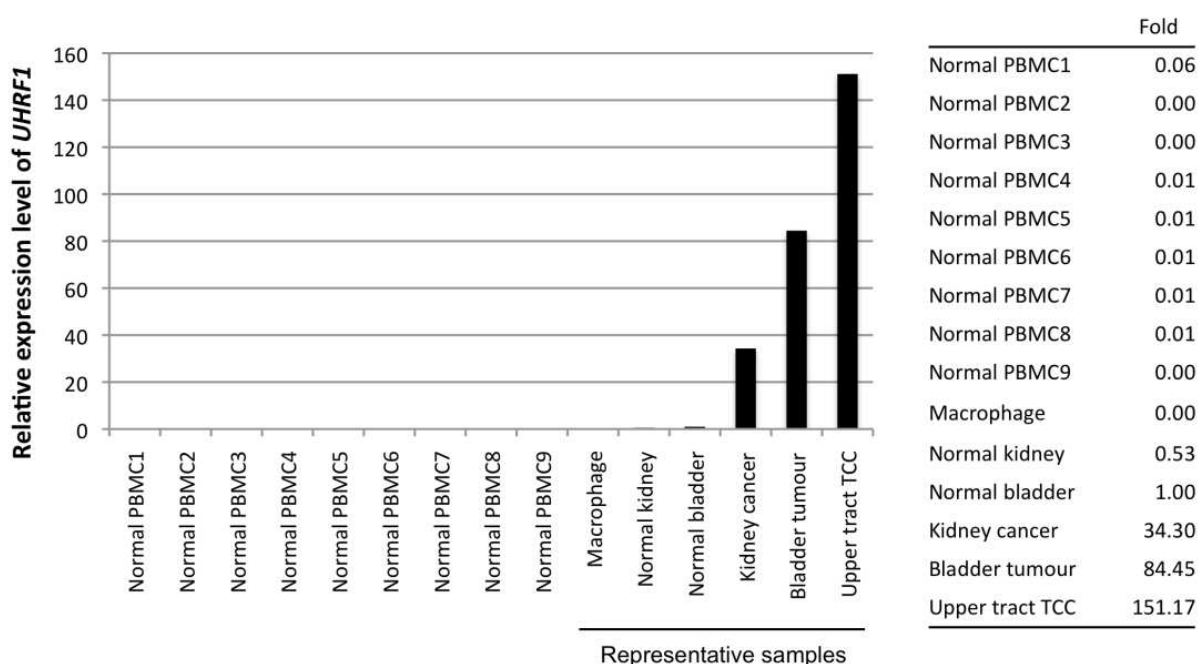


Fig. 12. Relative expression levels of *UHRF1* in peripheral blood mononuclear cells (PBMCs) were examined by TaqMan qRT-PCR. Almost no expression of *UHRF1* was detected in PBMCs.

3. Conclusion

Although UHRF1 expression in muscle invasive cancer was greater than in non-invasive (pTa) or superficially invasive (pT1) cancers, UHRF1 could still be detected by immunohistochemistry in the early stage bladder cancers. In addition, overexpression of *UHRF1* was associated with increased risk of progression after TURBT. Therefore, our result indicates that detection of UHRF1 may be a useful marker for early stage bladder cancers, and also for estimation of risk after TURBT, although it should be tested in larger series to determine if it can improve current strategies for diagnosis and prognosis of bladder cancer.

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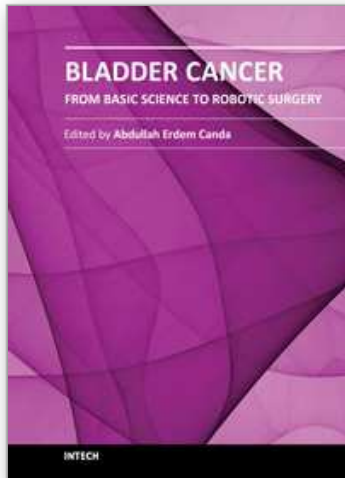
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This book is an invaluable source of knowledge on bladder cancer biology, epidemiology, biomarkers, prognostic factors, and clinical presentation and diagnosis. It is also rich with plenty of up-to-date information, in a well-organized and easy to use format, focusing on the treatment of bladder cancer including surgery, chemotherapy, radiation therapy, immunotherapy, and vaccine therapy. These chapters, written by the experts in their fields, include many interesting, demonstrative and colorful pictures, figures, illustrations and tables. Due to its practicality, this book is recommended reading to anyone interested in bladder cancer.

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