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学位論文の題名	Genomic landscape of experimental bladder cancer in rodents and its application to human bladder cancer: gene amplification and potential overexpression of Cyp2a5/CYP2A6 are associated with the invasive phenotype （齧歯動物モデルにおける膀胱がんのゲノム全体像とヒトへの応用 ：Cyp2a5/CYP2A6 遺伝子の増幅と潜在的過剰発現は浸潤型と関連する） PLoS One. 11(11):e0167374, 2016
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Human cancers develop because of genetic and epigenetic changes induced by environmental and hereditary factors. Bladder cancer is one of several types of tumors arising in the urinary tract. Non-muscle invasive (superficial) bladder cancer is a low-grade malignancy with good prognosis, while muscle invasive (invasive) bladder cancer is a high-grade malignancy with poor prognosis. *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine (BBN) induces superficial bladder cancers with papillary morphology in rats and invasive bladder cancers with infiltrating phenotype in mice. In this study, we analyzed genomic landscapes of rodent BBN-induced bladder cancers using array-based comparative genomic hybridization (array CGH). While no significant copy number alterations were detected in superficial bladder tumors in rats, copy number gains in chromosomal regions 2D-E1, 7qA3, 9F2, and 11C-D were detected in invasive bladder tumors in mice. Amplification of representative genes located on 2D-E1 and 7qA3 chromosomal regions was confirmed by quantitative PCR. *Cyp2a22* and *Cyp2a5* genes but not *Cyp2g1, Cyp2a12*, and *Rab4b* genes on mouse chromosome 7qA3 were amplified in invasive bladder cancers. Although the human ortholog gene of *Cyp2a22* has not been confirmed, the mouse *Cyp2a5* gene is the ortholog of the human *CYP2A6* gene located in chromosomal region 19q13.2, and *CYP2A6* was identified by database search as one of the closest human homolog to mouse *Cyp2a22*. Considering a possibility that this region may be related to mouse 7qA3, we analyzed *CYP2A6* copy number and expression in human bladder cancer using cell lines and resected tumor specimens. Although only one of eight cell lines showed more than one copy increase of the *CYP2A6* gene, *CYP2A6* amplification was

detected in six out of 18 primary bladder tumors where it was associated with the invasive phenotype. Immunohistochemical analyses of 118 primary bladder tumors revealed that CYP2A6 protein expression was also higher in invasive tumors, especially in those of the scattered type. Together, these findings indicate that the amplification and overexpression of the *CYP2A6* gene are characteristic of human bladder cancers with increased malignancy and that *CYP2A6* can be a candidate prognostic biomarker in this type of cancer.