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Guest editorial:

DISCOVERING URINARY BLADDER CANCER RISK VARIANTS: STATUS QUO AFTER ALMOST TEN YEARS OF GENOME-WIDE ASSOCIATION STUDIES

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About ten years ago Kiemeney and colleagues (2008) published the first genome-wide association study (GWAS) discovering two novel single nucleotide polymorphisms (SNPs) near *MYC* (rs9642880) and *TP63* (rs710521) associated with urinary bladder cancer (UBC) risk. Meanwhile, further GWAS and candidate gene studies identified and confirmed a number of susceptibility variants for UBC (Selinski, 2012, 2013, 2014; Dudek et al., 2013; Selinski et al., 2013; Golka et al., 2011). Currently, fifteen genomic regions seem to play a major role in development of this disease (Table 1). It can be assumed that almost all relevant polymorphisms have been discovered now. The most recent UBC GWAS of Figueroa et al. (2016) required 15,058 cases and 286,270 controls to discover a further susceptibility region at 13q34 (*MCF2L* gene), including the Icelandic and the Dutch GWAS (Gudbjartsson et al., 2015; Kiemeney et al., 2008). The odds ratios of the most recent UBC risk SNPs are rather small, e.g. the *MCF2L* intron variant rs4907479, with the strongest signal in the 2016 fine-mapping study of Figueroa et al. (2016) resulted in an odds ratio (OR) of 1.13.

Several UBC risk variants are particularly relevant in persons exposed to bladder carcinogens – mainly by tobacco smoke (Burger et al., 2013; Garcia-Closas et al., 2005, 2011, 2013; Selinski et al., 2013; Moore et al., 2011) but also by occupation and environment (Ebbinghaus et al., 2017; Höhne et al., 2017; Krech et al., 2017; Lukas et al., 2017; Carreón et al., 2014; Golka et al., 2012, 2009, 2004, 2002, 1997, 1996; Delclos and Lerner, 2008; Ovsiannikov et al., 2012; Rushton et al., 2012). However, currently no particular variant that is only relevant in exposed persons could be identified and replicated in GWAS. In 2014, Figueroa et al. (2014a) identified two variants in a genome-wide smoking × SNP interaction study –rs1711973 (*FOXF2*) relevant for never smokers and rs12216499 (*RSPH2-TAGAP-EZR*) in ever smokers, but both could not be confirmed using a large replication series (Figueroa et al., 2016). Nevertheless, interaction analyses and stratification regarding smoking habits and cancer invasiveness are promising future approaches to uncover further susceptibility variants that are relevant for particular subgroups of the UBC patients.

A further challenge is a genome-wide search for variants associated with bladder

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cancer recurrence and progression. This requires a large number of UBC patients with follow-up of several years after first diagnosis. However, it can be assumed that variants relevant for UBC development are also associated with UBC recurrence. Recurrence of this tumor occurs in approximately half of the patients with a median recurrence-free time of almost one year. Selinski et al. (2017a) showed that the ultra-slow N-acetyltransferase 2 (*NAT2*) genotype was associated with a significant reduction of recurrence-free time (8.4 months) compared to rapid acetylators (11 months) and an increased recurrence risk (66 % vs. 50 %, OR=1.89, 95 % CI = 1.06–3.38). Effects were more pronounced in ultra-slow smokers (7.9 months, 73 %) indicating the relevance of gene-environment interaction also for prognosis. Correspondingly, Lukas et al. (2017) showed in a series of 143 UBC cases with suspected occupational bladder cancer the importance of co-occurring susceptibility variants, particularly co-occurring *GSTM1* negative and rs11892031[A/A] for UBC recurrence. They discovered that UBC cases with an elevated number of risk alleles had a significantly shorter median relapse-free time of 8 months compared to cases with few risk alleles.

According to the different importance of several genetic variants depending on exposure to bladder carcinogens, e.g. *GSTM1* and *NAT2*, different variant combinations seem to play a major role in smokers and never smokers (Selinski et al., 2017b; Schwender et al., 2012. Recently, Selinski et al. (2017b) identified and replicated in a large multicentric case-controls series (discovery series: 2969 cases / 3285 controls, replication series: 2080 cases / 2167 controls) four-variant combinations out of twelve well-known UBC risk variants. The highest odds ratios were found in never smokers with the best combination (rs1014971[AA] × rs1058396[AG,GG] × rs11892031[AA] × rs8102137[CC,CT]) resulting in an OR of 2.59 (95 % CI = 1.93-3.47; $P = 1.87 \times 10^{-10}$, frequency in never smoking cases: 25 %). Odds ratios of the best combinations found in smokers were clearly lower (current smokers: 1.56, former: 2.13, ever: 1.55) and different variant combinations were relevant, especially *GSTM1*, rs1058396 (*SLC14A1*) and rs11892031 (*UGT1A*) combinations in current and rs9642880 (*MYC*), rs1495741 (*NAT2*) and rs8102137 (*CCNE1*) combinations in former smokers (Selinski et al., 2017b).

Table 1: Currently confirmed polymorphisms that are associated with UBC risk, their association with bladder carcinogen exposure and prognosis (update of Selinski, 2014) according to Selinski (2014). Polymorphisms, associated genes and locations are printed in bold, risk alleles or genotypes are given in brackets.

Location Gene(s)	Key message	Reference
1p13.3 *GSTM1* (*glutathione S-transferase mu 1*)	***GSTM1* null** was confirmed as risk factor for increased UBC risk in a GWAS (OR=1.47).	Rothman et al. (2010)
	***GSTM1* null** was associated with recurrence (GSTM1*present/null HR=1.5, GSTM1*null/null HR=2.0 vs. GSTM1*present/present) and mortality (GSTM1*null/null vs. GSTM1* present/null HR=1.9) in the Copenhagen City Heart Study (CCHS).	Nørskov et al. (2011)
	***GSTM1* null × Smoking** (additive interaction) was associated with increased UBC risk ($OR_{SNP\times Smoking}$=4.69, $P_{additive}$=0.008)	Garcia-Closas et al. (2013)
	***GSTM1* null** was not associated with UBC invasiveness or prognosis.	Grotenhuis et al. (2014)
	***GSTM1* null** UBC risk was confirmed in a Chinese study group (1050 cases, 1404 controls, OR=1.37, $P=2.306\times10^{-4}$).	Wang et al. (2014)

Location Gene(s)	Key message	Reference
2q37.1 *UGT1A* (*UDP glucuronosyltransferase 1 family, polypeptide A complex locus*)	**Rs11892031[C]** (***UGT1A*** intron SNP) was associated with decreased UBC in a GWAS (OR=0.84). UGT1A proteins are involved in the metabolisms of bladder carcinogens via glucuronidation.	Rothman et al. (2010)
	Rs17863783[T] (***UGT1A6*** exon variant, MAF 2 %) was associated with UBC in a fine-mapping study (OR=0.55) and explained most of the effect of rs11892031. Rs17863783 increased *UGT1A6.1* mRNA expression *in vitro*.	Tang et al. (2012)
	Rs11892031[C] was particularly associated with a lower UBC risk in persons with occupational exposure to aromatic amines and PAHs (OR=0.68 exposed persons, OR=0.83 total study group).	Selinski et al. (2012)
	Rs17863783[T] × Smoking showed an additive interaction with smoking ($OR_{SNP\times Smoking}$=3.83, $P_{additive}$=8.8 × 10^{-4}). Rs11892031[C] × Smoking was not significant.	Garcia-Closas et al. (2013)
	Rs11892031 and rs17863783 were not associated with UBC invasiveness or prognosis.	Grotenhuis et al. (2014)
3q26.2 *TERC* (*telomerase RNA component*) – ***ACTRT3*** (*actin-related protein T3*) – ***MYNN*** (*myoneurin*) – ***LRRC34*** (*leucine rich repeat containing 34*)	**Rs10936599[C]** (intergenic) was associated with increased UBC risk UBC in a GWAS (OR=1.18). The nearby genes ***MYNN, TERC*** **and*ACTRT3*** were overexpressed in bladder tumor tissue compared to normal bladder tissue. However, rs10936599 did not modify the gene expression.	Figueroa et al. (2014b)
	Rs10936599[C] UBC risk was confirmed in a Chinese study group (1050 cases, 1404 controls, OR=1.22, P=7.179×10^{-4}).	Wang et al. (2014)
3q28 *TP63* (*tumor protein 63*)	**Rs710521[A]** (intergenic) was associated with UBC in a GWAS (OR=1.19).	Kiemeney et al. (2008)
	Rs710521[A] UBC risk (OR=1.16) was not modified by smoking or occupational exposure to bladder carcinogens.	Lehmann et al. (2010)
	Rs710521[A] × Smoking (interaction) was not significant in an interaction analysis.	Garcia-Closas et al. (2013)
	Rs710521 was not associated with UBC invasiveness or prognosis.	Grotenhuis et al. (2014)
	Rs710521[A] UBC risk could not be confirmed in a Chinese study group (1050 cases, 1404 controls, OR=1.14, P=0.061).	Wang et al. (2014)
4p16.3 *TACC3* (*transforming, acidic coiled-coil containing protein 3*) – ***FGFR3*** (*fibroblast growth factor receptor 3*)	**Rs798766[T]** (***TACC3*** intron SNP, 70 kb of ***FGFR3***) was associated with UBC in a GWAS (OR=1.24).	Kiemeney et al. (2010)
	Rs798766[T] × Smoking (interaction) was not significant in an interaction analysis.	Garcia-Closas et al. (2013)
	Rs798766[T] was associated with NMIBC recurrence in non-smokers (P=2.7 × 10^{-5}, $HR_{T/T}$ =2.71, $HR_{C/T}$ =2.43) but not in ever smokers nor in the total case group (P=0.75 and P=0.12, respectively). **Rs798766** was not associated with progression from NMIBC to MIBC nor with mortality in MIBC cases (P=0.28).	Grotenhuis et al. (2014)
	Rs798766[T] UBC risk was confirmed in a Chinese study group (1050 cases, 1404 controls, OR=1.24, P=0.012).	Wang et al. (2014)

Location Gene(s)	Key message	Reference
5p15.33 *CLPTM1L* (*cisplatin resistance related protein CRR9p*) – ***TERT*** (*telomerase reverse transcription*)	**Rs401681[C]** (***CLPTM1L*** intron SNP) and the nearby synonymous **rs2736098[A]** (synonymous ***TERT*** exon SNP) were both associated with UBC in a GWAS (OR=1.12 and 1.16, respectively). ***CLPTM1L*** is involved in cisplatin-induced apoptosis. ***TERT*** is associated with telomere maintenance and aging. Both genes are located at a cancer susceptibility locus at 5p15.33.	Rafnar et al. (2009)
	Rs401681[C] × Smoking (interaction) was not significant in an interaction analysis.	Garcia-Closas et al. (2013)
	Rs401681 and **rs2736098** were not associated with UBC invasiveness or prognosis.	Grotenhuis et al. (2014)
	Rs401681[C] and **rs2736098[G]** UBC risk could not be confirmed in a Chinese study group (1050 cases, 1404 controls, OR=1.02 and 1.01, P=0.779 and 0.858, respectively).	Wang et al. (2014)
8p22 *NAT2* (*N-acetyltransferase 2*)	**Rs1495741[A/A]** (intergenic, 14 kb 3' of ***NAT2*, *NAT2*** tagSNP), was associated with UBC in a GWAS ($OR_{A/A}$=1.15). ***NAT2*** variants result in a reduced acetylation of bladder carcinogens and are an established susceptibility factor for UBC in persons exposed to bladder carcinogenic aromatic amines, e.g. smokers. **Rs1495741[A/A]** corresponds to the slow phenotype. Increased risks were observed in current smokers (OR=1.25).	Rothman et al. (2010)
	Rs1495741[A/A] showed a very good specificity (94 %) for the prediction of the *NAT2* phenotype. However, a perfect specificity was obtained by the common 7-SNPs *NAT2* genotype (1.00) and a 2-SNPs genotype (1.00) based on the estabished 7 *NAT2* SNPs in Caucasians.	Selinski et al. (2011)
	Rs1495741[A] × Smoking interaction increased UBC risk significantly ($OR_{SNP\times Smoking}$=2.48, $P_{additive}=6.6 \times 10^{-4}$, $P_{multiplicative}$=0.029).	Garcia-Closas et al. (2013)
	Rs1495741[A/A] was associated with NMIBC recurrence (P=0.02, HR=1.29) but not progression in ever smokers (P=0.27) and reduced NMIBC progression risk in non-smokers (P=0.03, HR=0.42).	Grotenhuis et al. (2014)
	Rs1495741[A] UBC risk could be confirmed in a Chinese study group (1050 cases, 1404 controls, OR=1.13, P=0.034).	Wang et al. (2014)
8q24.3 *PSCA* (*prostate stem cell antigen*)	**Rs2294008[T]** was associated with UBC in a GWAS (OR=1.15). Rs2294008[T] altered the start codon of **PSCA** leading to a reduced promoter activity *in vitro*. Overexpression of PSCA in prostate and bladder tumors is well-known.	Wu et al. (2009)
	Rs2978974[A] (in an alternative untranslated 1st exon of **PSCA**) was detected in a fine-mapping study (OR=1.11) and showed a significant interaction effect (P=0.035) with **rs2294008** (10 kb upstream **rs2978974**) instead of capturing the same signal.	Fu et al. (2012)
	Rs2294008[T] × Smoking interaction (additive) increased UBC risk significantly ($OR_{SNP\times Smoking}$=2.90, $P_{additive}$=0.033).	Garcia-Closas et al. (2013)
	Rs2294008 and **rs2978974** were not associated with NMIBC or MIBC prognosis.	Grotenhuis et al. (2014)
	Rs2294008 UBC risk could be confirmed in a Chinese study group (1050 cases, 1404 controls, OR=1.21, P=0.003).	Wang et al. (2014)

Location Gene(s)	Key message	Reference
8q24.21 *MYC* (*v-myc myelocytomatosis viral oncogene homolog (avian)*	**Rs9642880[T]** (intergenic, 30 kb MYC) was associated with UBC in a GWAS (OR=1.22).	Kiemeney et al. (2008)
	Rs9642880[T] UBC risk was less pronounced in cases with suspected exposure to bladder carcinogens (OR=1.04 and 1.11 exposed study groups) than in non-exposed persons (OR=1.36) in contrast to ***GSTM1*** **null** (OR=2.43 and 1.38 in exposed study groups, OR=1.22 non-exposed persons).	Golka et al. (2009)
	Rs9642880[T] × Smoking interaction (additive) increased UBC risk significantly ($OR_{SNP\times Smoking}$=3.49, $P_{additive}$=0.035).	Garcia-Closas et al. (2013)
	Rs9642880[G] was associated with NMIBC progression ($P_{trend}=2.6 \times 10^{-3}$, $HR_{G/G}$ =1.81, $HR_{G/T}$ =1.06) but not with NMIBC recurrence (P=0.98) nor with mortality among MIBC cases (P=0.56).	Grotenhuis et al. (2014)
	Rs9642880[T] UBC risk could be confirmed in a Chinese study group (1050 cases, 1404 controls, OR=1.24, P=0.010).	Wang et al. (2014)
11p15.5 *LSP1* (*lymphocyte-specific protein 1, longer transcript*)	**Rs907611[A]** (130 bp upstream ***LSP1*** transcription start site) was associated with UBC in a GWAS (OR=1.15). **Rs907611[A]** did not modify ***LSP1*** and **miRNA-4298** expression in bladder tissue. **MiRNA-4298** is located in the **LSP1** gene and in the same haploblock as **rs907611**.	Figueroa et al. (2014b)
	Rs907611 UBC risk could not be confirmed in a Chinese study group (1050 cases, 1404 controls, OR=1.12, P=0.129).	Wang et al. (2014)
13q34 *MCF2L* (*MCF.2 cell line derived transforming sequence like*)	**Rs4907479** (***MCF2L*** intron SNP) was associated with UBC in a GWAS (OR = 1.13). No association was found with ***MCF2L*** mRNA expression in bladder tumors. ***MCF2L*** encodes a guanine nucleotide exchange factor that is involved in the Rho/Rac signaling pathways.	Figueroa et al. (2016)
18q12.3 *SLC14A1* (*solute carrier family 14 (urea transporter), member 1 (Kidd blood group)*)	**Rs1058396[G]** (***SLC14A1*** exon 8 missense SNP) and **rs17674580[T]** (***SLC14A1*** intron SNP) both increased UBC risk in a GWAS (OR=1.14, OR=1.17) but captured the same signal. Rs17674580 explained the effect of rs1058396.***SLC14A1*** plays a role in maintenance of a constant urea concentration gradient in the kidney. The exon missense SNP rs1058396 (D280N) determines two alleles of the Kidd blood system.	Rafnar et al. (2011)
	Rs7238033[T] (OR=1.20) as well as **rs10775480[T]** and **rs10853535[C]** (both: OR=1.16) were associated with UBC in a GWAS. **Rs1058396** was in strong LD with **rs7238033**, **rs10775480** and **rs11082469** (r^2=0.71, 0.64, and 0.93, respectively). The highly correlated rs10775480[T] and rs10853535[C] (r^2=1.00) were used as mutual tagSNPs.	Garcia-Closas et al. (2011)
	rs10775480[T]/rs10853535[C] × Smoking interactions were not significant in an interaction analysis ($P_{additive}$=0.053, $P_{multiplicative}$=0.833).	Garcia-Closas et al. (2013)
	Rs1058396 was not associated with UBC prognosis.	Grotenhuis et al. (2014)
	Rs17674580[C] UBC risk could be confirmed in a Chinese study group (1050 cases, 1404 controls, OR=1.65, $P=8.507\times10^{-8}$).	Wang et al. (2014)

Location Gene(s)	Key message	Reference
19q12 ***CCNE1*** (*cyclin E1*)	**Rs8102137[C]** (intergenic) transition was associated with UBC in a GWAS (OR=1.13). ***CCNE1*** is involved in the cell cycle G1/S phase ***CCNE1*** over-expression seemed to be associated with tumorigenesis and UBC prognosis.	Rothman et al. (2010)
	Rs8102137[C] × Smoking did not modify UBC risk in an interaction analysis ($P_{additive}$=0.961, $P_{multiplicative}$=0.133).	Garcia-Closas et al. (2013)
	Rs8102137 was not associated with UBC prognosis.	Grotenhuis et al. (2014)
	Rs8102137[C] UBC risk could not be confirmed in a Chinese study group (1050 cases, 1404 controls, OR=1.12, P=0.253).	Wang et al. (2014)
20p12.2 ***JAG1*** (*jagged 1*)	**Rs6104690[A]** (intergenic, 300 kb of ***JAG1***) was associated with UBC in a GWAS (OR=1.12).	Figueroa et al. (2014b)
	Rs**62185668[A]** and **rs4813953[T]** (OR=1.19 and 1.16, resp.) as well as the indel **rs148953085** (all: intergenic, 300 kb of ***JAG1***) were associated with UBC in a GWAS. **Rs62185668** represented the signal best. **Rs62185668** and **rs148953085** (both in a predicted DNaseI hotspot) showed a high correlation (r^2=0.96). The correlation between **rs62185668** and **rs4813953** was moderate (r^2=0.50). The effect of **rs6104690[A]** could be fully explained by the nearby SNP **rs62185668** (**rs6104690**: OR_{adj}=0.99, P_{adj}=0.85, r^2=0.30). Expression of the NOTCH ligand ***JAG1*** was reduced in bladder tumors compared to normal urothelium. **Rs62185668[A]** led to a reduced expression of ***JAG1*** in low-passage urothelial cells.	Rafnar et al. (2014)
	Rs6108803 (intergenic, 300 kb of ***JAG1***) was associated with UBC in a fine-mapping study (OR=1.18) and explained most of the effect of **rs62185668** (P_{adj}=0.25). The effect of **rs6104690** (OR=1.11) could be confirmed in 8,147 additional cases and 274,456 controls (in total: 15,058 / 286,270) compared to Figueroa et al. (2014b). **Rs6108803-rs6104690** haplotypes had a maximum OR=1.21, indicating that the signal in 20p12.2 can be captured by these two SNPs. The association with MIBC was stronger than with NMIBC for **rs6108803** (OR_{MIBC}= 1.36, OR_{NMIBC}=1.10, $P_{OR\ difference}$=0.02) and **rs62185668** (OR_{MIBC}= 1.39, OR_{NMIBC}=1.13, $P_{OR\ difference}$=0.01) but not for **rs6104690** (OR_{MIBC}= 1.22, OR_{NMIBC}=1.10, $P_{OR\ difference}$=0.20).	Figueroa et al. (2016)
22q13.1 ***CBX6*** (*chromobox homolog 6*) – ***APOBEC3A*** (*apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3A*)	**Rs1014971[T]** (intergenic, 25 kb from ***CBX6***, 64 kb from ***APOBEC3A***) was associated with UBC in a GWAS (OR=1.14).	Rothman et al. (2010)
	Rs1014971[T] × Smoking interaction (additive) increased significantly UBC risk ($OR_{SNP×Smoking}$=2.71, $P_{additive}$=0.036).	Garcia-Closas et al. (2013)
	Rs1014971 was not associated with UBC prognosis.	Grotenhuis et al. (2014)
	Rs1014971 UBC risk could not be confirmed in a Chinese study group (1050 cases, 1404 controls, OR=1.14, P=0.050).	Wang et al. (2014)

OR: odds ratio, P: P value, HR: hazard ratio, 95 % CI: 95 % confidence interval, adj.: adjusted
NMIBC: non-muscle invasive bladder cancer, MIBC: muscle-invasive or metastatic bladder cancer, PAHs: polycyclic aromatic hydrocarbons

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