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Editorial:

GENETIC VARIANTS CONFER SUSCEPTIBILITY TO URINARY BLADDER CANCER: AN UPDATED LIST OF CONFIRMED POLYMORPHISMS

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Urinary bladder cancer is the 7th most common cancer in Western Europe (Ferlay et al., 2012). The most relevant risk factors are occupational exposure to aromatic amines and polycyclic aromatic hydrocarbons as well as cigarette smoking (Golka et al., 2012, 2009, 2004; Schwender et al., 2012). Moreover, polymorphisms of phase II metabolizing enzymes are well-known since decades to increase bladder cancer risk, in particular, the deletion variant of the phase II metabolizing enzyme glutathione-S-transferase M1 (GSTM1) (Ovsiannikov et al., 2012; Golka et al., 2009, 1997; Arand et al., 1996) and polymorphisms in the N-acetyltranferase 2 (NAT2) gene leading to a reduced acetylation capacity (Selinski et al., 2011; Moore et al., 2011; Golka et al., 2002, 1996), and currently their influence on prognosis is investigated (Roth et al., 2012; Nørskov et al., 2011). Recently, genome-wide association studies (GWAS) have identified several novel nucleotide polymorphisms (SNPs) as associated with urinary bladder cancer (UBC) risk and most of them could be confirmed in independent follow-up case-control series (review: Golka et al., 2011; Table 1). So far SNPs at ten chromosomal locations, besides GSTM1, have been identified. The functions of the closest genes are related to maintenance of DNA integrity, apoptosis and cell cycle control as well as detoxification of carcinogens. Considering the large size of the case-control series with more than 4,500 cases and 45,000 controls (Rafnar et al., 2011; Kiemeney et al., 2010; Rothman et al., 2010), the high density of polymorphisms on SNP chips as well as the accuracy of SNP imputation algorithms it may be regarded as likely that the most influential SNPs have now been discovered. However, one open question remains: to date it is completely unknown, if the novel SNPs interact. If so, will they result in less than additive, additive or even over additive risks? How high is the population attributable risk of the combined influence of all polymorphisms? And how important is the combined genetic risk compared to the risk attributable to cigarette smoking and occupational exposure to bladder carcinogens? Considering the recent progress in genome-wide association studies it can be expected that answers to these questions will soon be available.

First analyses beyond the standard single SNP analyses in case-control designs yield promising results (Binder et al., 2012; Menashe et al., 2012; Schwender et al., 2012).

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Table 1: Currently confirmed genetic variants that are associated with bladder cancer risk. Polymorphisms and related genes are printed bold, risk alleles are given in brackets.

Key message	Reference
Rs9642880[T] near proto-oncogene **MYC** (v-myc myelocytomatosis viral oncogene homolog (avian) was associated with UBC in a GWAS (OR=1.22).	Kiemeney et al., 2008
The effect of **rs9642880[T]** was less pronounced in cases with suspected exposure to bladder carcinogens (OR=1.04 and 1.11 exposed study groups; OR=1.36 non-exposed) for which **GSTM1 null** is the more important genetic risk factor (OR=2.43 and 1.38 exposed; OR=1.22 non-exposed).	Golka et al., 2009
Rs710521[A] near the **TP63** (tumor protein 63) gene, that encodes for a member of the p53 family of transcription factors, was associated with UBC in a GWAS (OR=1.19).	Kiemeney et al., 2008
The effect of **rs710521[A]** on UBC risk (OR=1.16) did not depend on exposure to bladder carcinogens via tobacco smoke or occupation.	Lehmann et al., 2010
Rs401681[C] in an intron of **CLPTM1L** (cisplatin resistance related protein CRR9p) and the nearby synonymous **rs2736098[A]** in the 2nd exon of **TERT** (telomerase reverse transcription) were both associated with UBC in a GWAS (OR=1.12; OR=1.16). The CLPTM1L gene associated with cisplatin-induced apoptosis and the nearby TERT that is involved in telomere maintenance and thus in aging are located at a potential cancer susceptibility locus at 5p15.33.	Rafnar et al., 2009
Rs2294008[T] alters the start codon of **PSCA** (prostate stem cell antigen) leading to a reduced promoter activity in vitro and was associated with UBC in a GWAS (OR=1.15). PSCA is over-expressed in prostate and bladder tumors.	Wu et al., 2009
Rs2978974[A] in an alternative untranslated 1st exon of **PSCA** was associated with UBC in a fine-mapping study (OR=1.11) and interacted with rs2294008 10 kb upstream rs2978974.	Fu et al., 2012
Rs798766[T] in an intron of **TACC3** (transforming, acidic coiled-coil containing protein 3), 70 kb of **FGFR3** (fibroblast growth factor receptor 3) was associated with UBC in a GWAS (OR=1.24).	Kiemeney et al., 2010
Rs11892031[C] in an intronic region in the **UGT1A** (UDP glucuronosyltransferase 1 family, polypeptide A complex locus) cluster was associated with UBC in a GWAS (OR=0.84) showing a protective effect of the minor allele [C]. UGT1A proteins are involved in the metabolisms of bladder carcinogens via glucuronidation.	Rothman et al., 2010
Rs11892031[C] showed a more pronounced protective effect in persons with occupational exposure to polycyclic aromatic hydrocarbons and aromatic amines (OR=0.68 exposed; OR=0.83 all combined).	Selinski et al., 2012
Rs17863783[T] a synonymous rare (2 %) SNP in a **UGT1A6** exon was shown to increase UGT1A6.1 mRNA expression in vitro and was associated with UBC in a fine-mapping study (OR=0.55). Rs17863783 explained most of the effect of rs11892031.	Tang et al., 2012
Rs1495741[A] a tagSNP for **NAT2** (N-acetyltransferase 2) activity, 14 kb 3' of NAT2, was associated with UBC in a GWAS ($OR_{A/A}$=1.15). Polymorphisms of NAT2 lead to a reduced acetylation of drugs and xenobiotics ("slow" and "rapid" acetylators) and are a well-known risk factor for UBC. The A/A genotype tags the slow phenotype. Increased risks were observed in current smokers (OR=1.25).	Rothman et al., 2010
NAT2 tagSNP **rs1495741[A/A]** showed an excellent specificity (0.94) regarding the phenotype but was outperformed by the common NAT2 genotype (1.00) and a 2-SNP genotype (1.00) based on the known NAT2 SNPs in Caucasians.	Selinski et al., 2011

Table 1 (cont.): Currently confirmed genetic variants that are associated with bladder cancer risk. Polymorphisms and related genes are printed bold, risk alleles are given in brackets.

Key message	Reference
Rs8102137[C] near **CCNE1** (cyclin E1) involved in the cell cycle G1/S phase transition was associated with UBC in a GWAS (OR=1.13). CCNE1 over-expression seems to be associated with tumorigenesis and UBC prognosis.	Rothman et al., 2010
Rs1014971[T] 25 kb from **CBX6** (chromobox homolog 6) and 64 kb from **APOBEC3A** (apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3A) was associated with UBC in a GWAS (OR=1.14).	Rothman et al., 2010
The well-known increased UBC risk of **GSTM1 null** genotypes was confirmed in a GWAS (OR=1.47).	Rothman et al., 2010
Rs1058396[G] in **SLC14A1** (solute carrier family 14 (urea transporter), member 1 (Kidd blood group)) exon 8 leading to an amino acid exchange and **rs17674580[T]** in an intron of the same gene are associated with UBC in a GWAS (OR=1.14; OR=1.17). SLC14A1 is involved in maintenance of a constant urea concentration gradient in the kidney. Rs1058396 (D280N) determines two alleles of the Kidd blood system. Rs17674580 explained the effect of rs1058396.	Rafnar et al., 2011

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