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Editorial:

HIGHLIGHT REPORT: FUNCTIONAL CONSEQUENCES OF URINARY BLADDER CANCER RISK VARIANTS

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About 180,000 new cases of urinary bladder cancer are diagnosed each year in the European Union. The most relevant risk factors are occupational exposure to aromatic amines and cigarette smoking (Golka et al., 2012; Ovsiannikov et al., 2012; Selinski et al., 2013; Kempkes et al., 1996). Recently, genome-wide association studies have successfully identified several urinary bladder cancer susceptibility loci (review: Dudek et al., 2013; Golka et al., 2011; Selinski, 2012; Bolt, 2013a, b). Currently confirmed genetic variants include rs9642880 (MYC, Kiemeney et al., 2008; Golka et al., 2009), rs710521 (TP63, Kiemeney et al., 2008; Lehmann et al., 2010), rs401681 and rs2736098 (CLPTM1L, TERT, Rafnar et al., 2009), rs2294008 and rs2978974 (PSCA, Wu et al., 2009; Fu et al., 2012), rs798766 (TACC3, FGFR3, Kiemeney et al., 2010), rs11892031 (UGT1A, Rothman et al., 2010; Selinski et al., 2012), rs17863783 (UGT1A6, Tang et al., 2012), rs1495741 (NAT2, Rothman et al., 2010; Garcia-Closas et al., 2011; Selinski et al., 2011), rs8102137 (CCNE1, Rothman et al., 2010), rs1014971 (CBX6, Rothman et al., 2010) and rs17674580 and rs1058396 (SLC14A1, Rafnar et al., 2011). Moreover, it has been shown that several high risk alleles of single nucleotide polymorphisms can interact leading to enhanced odds ratios (Schwender et al., 2012). However, relatively little is known about the functional consequences of the novel bladder cancer susceptibility SNPs. Many of them are located in non-coding regions. An example is rs9642880 on chromosome 8q24 that is approximately 30kb upstream of MYC (Kiemeney et al., 2008). Similarly, rs1014971 on 22q13.1 is located 25 kb and 64kb from APOBEC3A and CBX6, respectively (Rothman et al., 2010). Considering these relatively large distances between both SNPs and the closest exons it seems unlikely that an influence can be explained by linkage disequilibrium. Recently, Dudek and colleagues have addressed the open question of the functional consequences of urinary bladder susceptibility loci (Dudek et al., 2013). At least two risk variants, located in PSCA and UGT1A, were confirmed to have functional consequences.

- PSCA (prostate stem cell antigen) is involved in the regulation of stem cell proliferation. Rs2294008 is located in the first exon of PSCA (review: Dudek et al., 2013). It changes a nucleotide in the initiation region, creates a new ATG for translation initiation leading to a PSCA protein which is nine amino acids longer (Dudek et al., 2013). Rs294008 was found to be strongly associated with PSCA protein levels in urinary bladder tumors. Moreover, a second variant, rs2978974, was also identified in exon 1 of PSCA and was found to be associated with urinary bladder cancer risk (Fu et al., 2012; review: Dudek et al., 2013).
- UDP-glucuronosyltransferase (UGT) is a phase II metabolizing enzyme involved in detoxification of numerous

carcinogens (Burkhardt et al., 2012; Hanioka et al., 2011; Luo et al., 2012; Godoy et al., 2013). One bladder cancer susceptibility locus is located in intron 1 of UGT, containing rs11892031 (Rothman et al., 2010; Dudek et al., 2013). Follow-up studies identified the causative variant rs17863783 (Tang et al. 2012). Rs17863783 does not alter the amino acid sequence of UGT1A. However, a possible explanation is that rs17863783 modifies the expression of UGT1A by influencing the exonic splicing enhancer, a DNA sequence motif essential for the identification of splice sites (Dudek et al., 2013).

The current review article of Dudek et al. (2013) describes in a comprehensive way the current concepts by which mechanisms the recently identified bladder cancer risk loci may contribute to carcinogenesis.

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