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REVIEW ARTICLE

Genetic variants in urinary bladder cancer: collective power of the "wimp SNPs"

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Abstract In recent years, genome-wide association studies (GWAS) have identified more than 300 validated associations between genetic variants and risk of approximately 70 common diseases. A small number of rare variants with a frequency of usually less than 1% are associated with a strongly enhanced risk, such as genetic variants of TP53, RB1, BRCA1, and BRCA2. Only a very small number of SNPs (with a frequency of more that 1% of the rare allele) have effects of a factor of two or higher. Examples include APOE4 in Alzheimer's disease, LOXL1 in exfoliative glaucoma, and CFH in age-related macular degeneration. However, the majority of all identified SNPs have odds ratios between 1.1 and 1.5. In the case of urinary bladder cancer, all known SNPs that have been validated in sufficiently large populations are associated with odds ratios smaller than 1.5. These SNPs are located next to the following genes: MYC, TP63, PSCA, the TERT-CLPTM1L locus, FGFR3, TACC3, NAT2, CBX6, APOBEC3A, CCNE1, and UGT1A. It is likely that these moderate risk or "wimp SNPs" interact, and because of their high number, collectively have a strong influence on whether an individual will develop cancer or not. It should be considered that variants identified so far explain only approximately 5–10% of the overall inherited risk. Possibly, the remaining variance is due to an even higher number of SNPs with odds ratios smaller than 1.1. Recent studies have provided the following information: (1) The functions of genes identified as relevant for bladder cancer focus on detoxification of carcinogens, control of the cell cycle and apoptosis, as well as maintenance of DNA integrity. (2) Many novel SNPs are far away from the protein coding regions, suggesting that these SNPs are located on distant-acting transcriptional enhancers. (3) The low odds ratio of each individual bladder cancer-associated SNP is too low to justify reasonable preventive measures. However, if the recently identified SNPs interact, they may collectively result in a substantial risk that is of preventive relevance. In addition to the "novel SNPs" identified by the recent GWAS, at least 163 further variants have been reported in relation to bladder cancer, although they have not been consistently validated in independent case–control series. Moreover, given that only 60 of these 163 "old SNPs" are covered by the SNP chips used in the recent GWAS, there are in principle 103 published variants still awaiting validation or disproval. In future, besides identifying novel disease-associated rare variants by deep sequencing, it will also be important to understand how the already identified variants interact.

Keywords Genome-wide association study · SNP chip comparison · Bladder cancer risk · Genetic variant · Enzyme polymorphism · Validation · GSTM1

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Frequency and risk factors of urinary bladder cancer

Urinary bladder cancer (UBC) is the 9th most common cancer worldwide, and the 13th most common cause for death from

cancer (Parkin 2008). After removal of primary carcinomas, UBC frequently recurs leading to repeated surgery. The strongest known risk factors are cigarette smoking, occupational exposure to bladder carcinogens, particularly to aromatic amines and polycyclic aromatic hydrocarbons, and male gender. Recent substances drawing interest include azo colourants (Golka et al. 2004) and hair dyes (Bolt and Golka 2007).

Single nucleotide polymorphisms and SNP chip analysis

It is well known that single nucleotide polymorphisms contribute to interindividual differences in cancer susceptibility (Kiemeney et al. 2008, 2010; Hengstler et al. 1998; Arand et al. 1996; Saravana Devi et al. 2008; Hewitt et al. 2007; Gehrmann et al. 2008; Carmo et al. 2006; Cadenas et al. 2010; Hellwig et al. 2010). DNA from different individuals is identical for most base positions; however, variants are observed approximately every 500 bases. If a variant occurs in more than 1% of the population, it is defined as a single nucleotide polymorphism (SNP; Fig. 1a). Today, up to 900,000 SNPs and 900,000 copy number variations can be determined in a single analysis on SNP chips. This technique is based on hybridization of DNA from patients to oligonucleotides immobilized on a chip, which contains oligonucleotides with the two alleles on different spots (Fig. 1b). The patients' DNA (after digestion with endonucleases) is labelled with fluorochromes; therefore, cluster plots can be obtained, which differentiate between the homozygous major allele (green dots in Fig. 1c), the homozygous minor allele (red triangles) and the heterozygous (blue squares) individuals that carry allele A on one and allele B on the other chromosome (Fig. 1c). The automatic clustering of the fluorescence intensities to separate between the three possible genotypes may lead to misclassification of patients in cluster plots—a problem that is frequently underestimated when performing genome-wide association studies (GWAS) with SNP chips. An example is provided in Fig. 1c, where the heterozygous patients have been misclassified, due to the use of a sub-optimal classification algorithm for a specific data set. Although misclassifications can easily be identified by manual inspection, this is not feasible for 900,000 SNPs and large numbers of patients. However, to avoid possible validation of false positive SNPs caused by misclassification in cluster plots, the candidate genes identified from a discovery group (see below) should be manually controlled.

A second major problem is that false positive results are generally caused by multiple testing. When testing with $P < 0.05$ without adjustment for multiple testing, approximately five false positive SNPs will occur in 100 tested SNPs, with a potential outcome of approximately 45,000 false positives in 900,000 SNPs. One possibility to avoid false positives is performing an adjustment for multiple testing, for example by the Bonferroni technique. However, this technique is very conservative and rejects a large number of real positives. Therefore, a good strategy is to establish a "discovery group" where the most promising SNPs are identified. Only a small number of hypotheses will then be validated in an independent group, the so-called "follow-up group". This study design has the additional advantage that analysis in the follow-up groups can be done using much cheaper conventional PCR, whereas the expensive SNP chips are limited to the discovery group.

Combining data from different GWAS to increase the power of the discovery group, it has to be noted that there is little overlap between arrays from different distributors (see Fig. 2a), and also handling data generated with larger arrays of the same distributor results in gaps of thousands of SNPs. To gain information about untyped SNPs, e.g. to investigate candidate regions in more detail or to combine data from different SNP assays, a number of imputation techniques are available (BEAGLE: Browning and Browning 2007, 2009; BIMBAM: Servin and Stephens 2007; fastPHASE: Scheet and Stephens 2006; GenABEL: Aulchenko et al. 2007; IMPUTE/SNPTEST: Marchini et al. 2007; Marchini and Howie 2008; MaCH: Li Y et al. 2010b; Plink: Purcell et al. 2007; TUNA: Nicolae 2006). These approaches are used to infer unknown genotypes using measured loci and linkage disequilibrium information, e.g. from reference panel data usually HapMap (Halperin and Stephan 2009a, b). Comparisons of imputation algorithms can be found in Pei et al. (2008, 2010), Browning (2008), Hao et al. (2009), and Yu and Schaid (2007). Potential difficulties due to ethnic differences between the study group and the reference panel were addressed by Huang et al. (2009).

Strategy for discovery and validation of SNPs

The study design with a discovery group and follow-up groups has recently been applied in order to identify new SNPs that are associated with urinary bladder cancer risk (Kiemeney et al. 2008, 2010; Wu et al. 2009; Rafnar et al. 2009; Rothman et al. 2010). For example, Kiemeney et al. (2010) studied 4,580 bladder cancer cases and 45,269 controls, where the discovery group consisted of 1,889 cases and 39,310 controls. The follow-up groups included 2,691 cases and 5,959 controls. The twenty most significant SNPs from the discovery group, all with $P \leq 2.5 \times 10^{-5}$, were validated in the follow-up groups. This resulted in the identification of a SNP on chromosome 4p16.3 (rs798766) that was associated with bladder cancer risk in the discovery group ($P = 2.4 \times 10^{-5}$) and in the follow-up group ($P = 8.5 \times 10^{-8}$) (Kiemeney et al. 2010). Odds ratios (OR) for the T allele of rs7998766 were 1.22 (95% confidence interval: 1.11–1.34) in the discovery group and 1.26 (1.16–1.37) in the follow-up

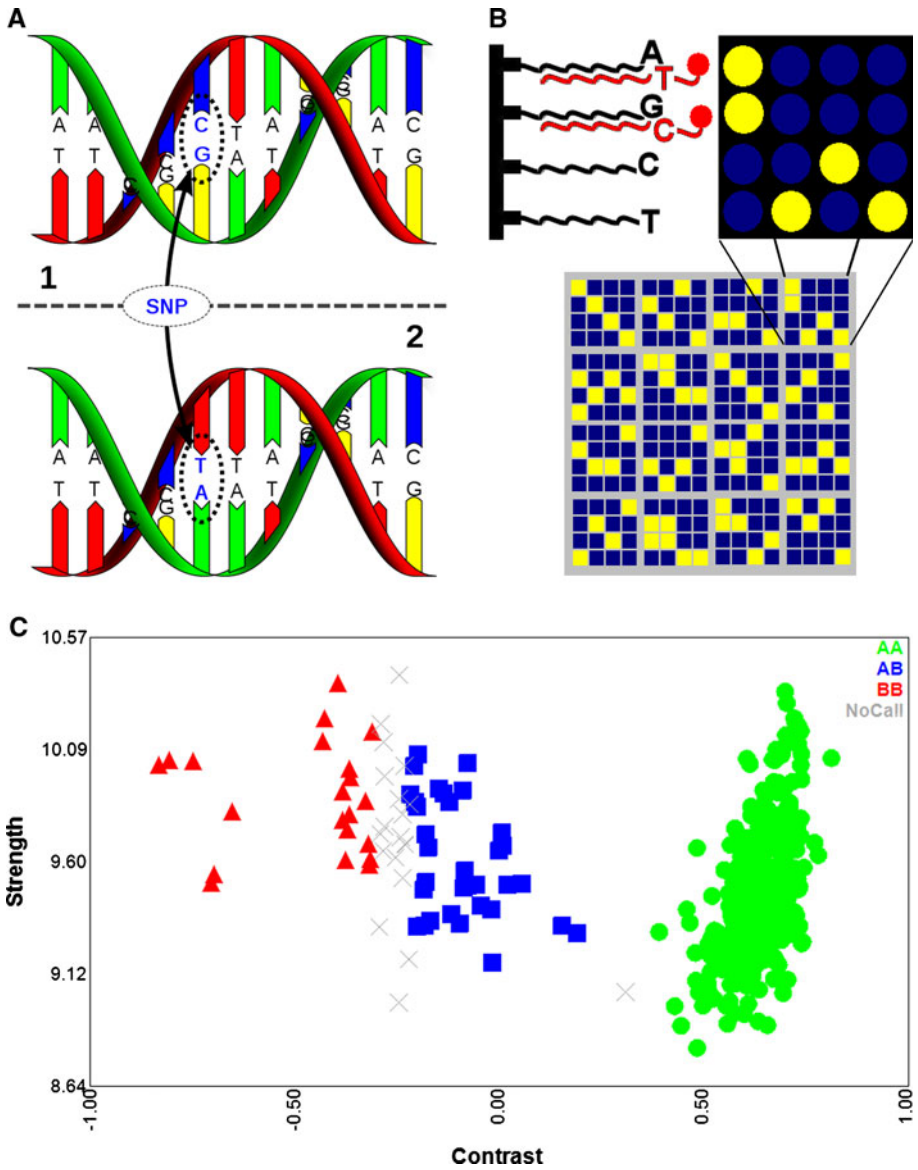

Fig. 1 **a** Exchange of a single base pair present in at least 1% of the population, T:A to C:G in the shown example, is defined as a single nucleotide polymorphism (*SNP*). The human genome contains approximately 3 million SNPs (picture from: "Dna-SNP.svg", Wikipedia, author: David Hall, Gringer, licence: CC-by 2.5, http://creativecommons.org/licenses/by/2.5/deed.de). **b** Principle of a DNA microarray chip. Single-stranded DNA oligonucleotides function as DNA probes by hybridizing DNA fragments from the analysed sample whose nucleotide sequences are homologous. The technique can be applied to differentiate whether an A or a G is present in a certain sequence (from: Carr et al. 2008). **c** Cluster plot obtained from a DNA microarray. The *x*-axis (contrast) and the *y*-axis (strength) indicate transformed values of the two allele intensities S_A and S_B for the [A] and the [B] allele, respectively. They are defined as follows: Contrast = $(S_A - S_B)/(S_A + S_B)$ and Strength = $\log(S_A + S_B)$ (BRLMM whitepaper: BRLMM: an Improved Genotype Calling Method for the GeneChip® Human Mapping 500K Array Set, Revision Date: 2006-04-14; http://media.affymetrix.com/support/technical/whitepapers/brlmm_whitepaper.pdf). Homozygous major alleles are plotted as green dots (*right cluster*), heterozygous genotypes as blue squares (*middle cluster*), homozygous minor alleles as red triangles (*left cluster*), and not determinable genotypes as *grey crosses*. The example illustrates the problem of misclassification of patients in cluster plots using automated systems. Some heterozygous patients have been misclassified as homozygous (*red triangles* instead of *blue squares*)

group. In the combined group, rs798766[T] was associated with an OR of 1.24 ($P = 9.9 \times 10^{-12}$). This association was significant, even after adjustment to cigarette smoking, age, and gender. No association between rs798766[T] and cigarette smoking or smoking quantity was obtained suggesting that rs798766 does not represent a genetic variation that confers susceptibility to addiction.

The rs798766 is located on intron 5 of TACC3 (transforming acidic coiled-coil containing protein 3), which is involved in the regulation of microtubule dynamics. TACC3's relevance for bladder carcinogenesis is currently unknown; however, FGFR3, a neighbouring gene approximately 70 kb away from rs798766, contains activating mutations in about one-third of all bladder carcinomas. The

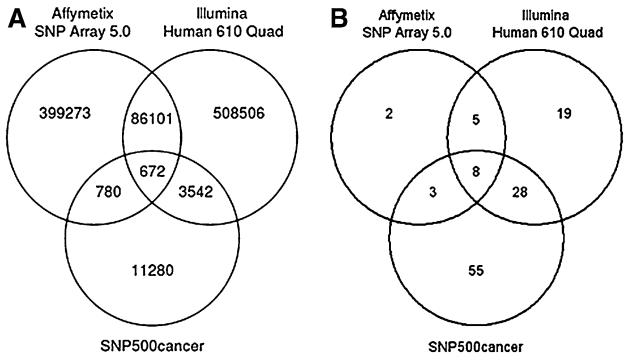

Fig. 2 **a** The Venn diagram illustrates relatively little overlap between two frequently applied SNP chips, the Affymetrix SNP Array 5.0 and the Illumina Human 610 Quad, and the SNP500Cancer database. **b** An overview of how many of the previously analysed SNPs (the so-called "old SNPs" in bladder cancer case–control series; Table 2, Supplemental Table 1) are present on currently used SNP chips. Considering that the recent large GWAS (Table 1) have been performed with Illumina chips only 60 of the 163 "old SNPs" could have been discovered by these SNP chip studies. Presence or absence of SNPs if identified by rs numbers was determined using the software R, version 2.12.1 and annotation from the meta-data packages pd.genomewidesnp.5 version 1.1.0 (Affymetrix SNP Chip 5.0) and human610quadv1bCrlmm version 1.0.2 (Illumina Human 610 Quad) and from the SNP500Cancer database (from: ftp://ftp-snp500cancer.nci.nih.gov/snp500Cancer/Genotypes/allgenes.tab, access date 05 Jan 2011)

critical role of FGFR3 in urinary bladder carcinogenesis led to the question whether the rs798766 polymorphism correlates with RNA levels of both FGFR3 and TACC3 (Kiemeney et al. 2010). Ideally, the optimal model for this study is cells originating from urinary bladder cancer, namely the epithelial cells of the bladder. Unfortunately, availability of bladder epithelial cells from tissue banks is limited; therefore, the analysis was performed in adipose tissue from 604 individuals. Interestingly, there was a significant correlation between rs798766 and RNA levels of both FGFR3 and TACC3 (Fig. 3). The highest RNA levels were obtained for the homozygous T allele, intermediate expression for the heterozygous C/T genotype, and lowest levels for the homozygous C allele. Currently, it is not known how the polymorphism of rs798766 influences expression of FGFR3 which is 70 kb away. A potential explanation is rs798766[T] leads to a conformational alteration of this region of the chromosome that improves accessibility of the transcriptional machinery. However, this remains speculative.

A possible mechanism how rs798766[T] may contribute to bladder cancer risk is via the increased production of the FGFR3 protein as a consequence of enhanced gene expression, leading to an increased rate of proliferation and an increased probability for accumulation of mutations. The example of rs798766 illustrates that GWAS with discovery plus follow-up group design and sufficient case numbers can successfully be applied to identify novel disease-relevant SNPs.

State of the art: overview of recently discovered, validated SNPs

Using the above-described strategy for GWAS, nine SNPs have been identified since 2008 that are associated with bladder cancer risk (Table 1). Importantly, none of these SNPs have been previously described in relation to bladder cancer. In contrast to the newly discovered polymorphisms, the relevance of GSTM1 0/0, a deletion in the glutathione *S*-transferase M1 gene leading to loss of enzyme activity and the NAT2 polymorphism, was described by our group 15 years ago (Golka et al. 1996; Kempkes et al. 1996; Hengstler et al. 1998) and has been confirmed in the recent studies (Golka et al. 2009; Rothman et al. 2010).

An overview of the closest genes to the newly discovered and validated SNPs is given in Table 1. The well-known proto-oncogene c-Myc encodes a DNA-binding factor that activates or suppresses transcription, thus explaining its regulation of many target genes involved in the proliferation and cell cycle progression (Dominguez-Sola et al. 2007). TP63 shows strong homology to the tumour suppressor P53 and, similar to P53, is also involved in cell cycle and apoptosis control (Sayan et al. 2007; Lefkimmiatis

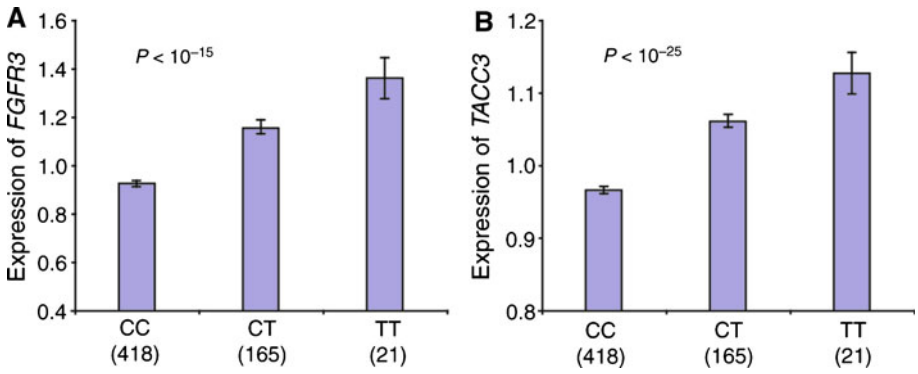

Fig. 3 Correlation between rs798766 and RNA levels of FGFR3 and TACC3 in adipose tissue (from: Kiemeney et al. 2010)

Table 1 Overview of confirmed genetic variants in GWAS that are associated with urinary bladder cancer risk

SNP	Chromosome	Reported OR and 95% CI	Closest genes	Reference
rs9642880	8q24.21	1.22 (1.15–1.29)	c-Myc	Kiemeney et al. (2008); Golka et al. (2009)
rs710521	3q28	1.19 (1.12–1.27)	TP63	Kiemeney et al. (2008); Lehmann et al. (2010)
rs401681	5p15.33	1.12 (1.06–1.18)	TERT-CLPTM1L	Rafnar et al. (2009)
rs2736098	5p15.33	1.16 (1.08–1.23)	Neighbour SNP of rs401681	Rafnar et al. (2009)
rs2294008	8q24.3	1.15 (1.10–1.20)	PSCA	Wu et al. (2009)
rs798766	4p16.3	1.24 (1.17–1.32)	FGFR3, TACC3	Kiemeney et al. (2010)
rs11892031	2q37.1	1.19 (1.12–1.27)	UGT1A	Rothman et al. (2010)
rs1495741	8p22	1.15 (1.10–1.20)	Tagging SNP for NAT2 status	Rothman et al. (2010)
rs8102137	19q12	1.13 (1.09–1.17)	CCNE1	Rothman et al. (2010)
rs1014971	22q13.1	1.14 (1.10–1.18)	CBX6, APOBEC3A	Rothman et al. (2010)
GSTM1 deletion	1p13.3	1.47 (1.38–1.57)[1]	GSTM1	For example: Golka et al. (2009); Rothman et al. (2010)

OR Allelic OR of discovery and follow-up study groups combined, *95% CI* 95% confidence interval

[1] Reported in Rothman et al. (2010), study groups of Golka et al. (2009), see Table 4B

et al. 2009). Prostate stem cell antigen (PSCA) is a cell surface protein associated with prostate and other types of cancer (Watabe et al. 2002). The TERT gene represents the reverse transcriptase component of telomerase that is essential for the maintenance of DNA length and cellular immortality (Cheung and Deng 2008; Florl and Schulz 2008). Little is known about the function of cleft lip and palate transmembrane 1-like gene (CLPTM1L). CLPTM1L is upregulated in cisplatin-resistant cell lines and might be involved in apoptosis control (Liu et al. 2010). Fibroblast growth factor receptor 3 (FGFR3) belongs to a family of polypeptide growth factors containing a cytoplasmic tyrosine kinase domain and extracellular immunoglobulin-like domains and is involved in mitogenesis, angiogenesis, and wound healing (Keegan et al. 1991). TACC3 plays a role in the maintenance of nuclear envelope structure and in cell division control (Gómez-Baldó et al. 2010). NAT2 is a phase II metabolizing enzyme involved in detoxification, but also bioactivation of xenobiotics (Hengstler et al. 1998). Low NAT2 activity is associated with increased bladder cancer risk in Caucasians. Chromobox homolog 7 (CBX7) positively regulates E-cadherin expression by interacting with histone deacetylase 2 (Federico et al. 2009), possibly explaining why loss of CBX7 expression is associated with a highly malignant phenotype of carcinomas. APOBEC3 deaminases cause G to A hypermutation in nascent DNA of hepatitis B viruses which seems to play a role in antiviral defence (Abe et al. 2009). Overexpression of APOBEC3 genes may lead to mutations in the genome and influence the development of tumours (Vartanian et al. 2008). Cyclin E (CCNE1) controls cell cycle progression at the G1/S transition (Koff et al. 1991). UDP-glucuronosyltransferase 1A (UGT1A) is a phase II metabolizing enzyme that catalyses glucuronidation and elimination of numerous lipophilic xenobiotics, thereby acting as a detoxifying enzyme (Hengstler et al. 2000; Strassburg et al. 2008). Glutathione *S*-transferase M1 is also a phase II metabolizing enzyme (Bolt and Thier 2006) that upon conjugation with glutathione detoxifies numerous xenobiotics including polycyclic aromatic hydrocarbons that are known bladder carcinogens (Golka et al. 2009). In conclusion, the functions of the discussed genes focus on carcinogen detoxification, control of the cell cycle as well as apoptosis, and maintenance of DNA integrity.

More than 75 further studies of SNPs and bladder cancer risk

A literature search on SNPs and bladder cancer identified more than 75 further studies reporting on genetic variants in bladder cancer (Tables 2, 3, Supplemental Table 1). Most of these SNPs ($n = 34$) affect genes encoding xenobiotic metabolizing enzymes (Table 2). Moreover, variants of genes have been reported that play a role in DNA repair and damage signalling ($n = 58$), cell cycle control, DNA replication, translesion synthesis and transcription ($n = 14$), inflammation ($n = 13$), apoptosis ($n = 8$), methylation ($n = 4$), growth factors ($n = 5$), matrix metalloproteinases ($n = 5$), mTOR and associated factors ($n = 4$), and others ($n = 18$) (Table 3, Supplemental Table 1). However, in contrast to the SNPs summarized in the previous paragraph and

Table 2 Polymorphic xenobiotic metabolizing enzymes ("old SNPs"), reported to influence bladder cancer risk and the coverage by the five SNP chips Affymetrix 5.0, 6.0, Illumina Hap300Duo, Human610quad, Omni1Mduo, and the SNP500Cancer database

Polymorphism/SNP	Rs number	Affy 5.0	Affy 6.0	IllHap300	IllHum610 Quad	IllOmni1 Mduo	SNP500-Cancer	References Bladder cancer risk (rs number)
ADH3 $\gamma 1\gamma 1$, exon 8 (syn.: ADH3 $\gamma 1$, ADH3*1, ADH1C 349Ile)	rs698	–	–	–	X	X	X	Van Dijk et al. (2001); (Reddy et al. 2006) (for synonym, see also Verlaan et al. 2004, Pharmacogenomics Knowledge Base (2010))
AKR1C3 promoter	rs1937845	–	–	–	–	X	X	Figueroa et al. (2008)
ARNT promoter	rs7517566	–	–	–	–	X	X	Figueroa et al. (2008)
CYP1A1	rs2472299	X	X	X	X	X	X	Figueroa et al. (2008)
CYP1A2 2467T/delT	rs35694136	–	–	–	–	–	X	Pavanello et al. (2010)
CYP2A6*4 (syn.: CYP2A6 gene deletion)	rs1801272	–	–	–	X	X	X	Song et al. (2009); (Kotsopoulos et al. 2009); (for synonym, see Oscarson 2001)
CYP1B1 promoter	rs162555	–	–	–	–	X	X	Figueroa et al. (2008)
CYP2C19 PM	rs4244285 (*2)	–	–	–	–	–	X	Shi and Chen (2004); (Lee et al. 2009); (Both SNPs are responsible for almost all PM!)
	rs4986893 (*3)	–	–	–	X	X	X	
CYP2E1 C1019T in the 5′ flanking region c1/c1 (syn.: CKP2E1*5B)	rs3813867	–	–	–	X	X	X	Choi et al. (2003); (Prieto-Castelló et al. 2010)
CYP4B1*1/*2 or *2/*2		–	–	–	–	–	–	Sasaki et al. (2008)
CYP4B1*1 (wild-type), CYP4B1*2 (AT881–882del, 993G > A, 1018C > T and 1123C > T), CYP4B1*2: 3 missense mutations and a double nucleotide deletion (AT881-882del)								(NCBI CYP4B1*2)
Met331Ile	rs2297810	X	X	X	X	X	–	
Arg340Cys	rs4646491	X	X	X	X	X	–	
Arg375Cys	rs2297809	–	–	X	X	X	–	
GSTM3 mutation of intron 6	rs1799735	–	–	–	–	–	X	Schnakenberg et al. (2000); (Li Y et al. 2010a)
GPX-1 Pro198Leu	rs1050450	–	–	–	–	–	X	Paz-y-Miño et al. (2010); (Cox et al. 2004)
GSTP1 A1578G (Ile105Val)	rs1695 (new)	–	–	X	X	X	X	Harries et al. (1997); (Reddy et al. 2010)
	rs947894 (old)							
mEH exon 3 Tyr > His	rs1051740	–	–	X	X	X	X	Srivastava et al. (2008); (Tranah et al. 2004)
MnSOD Val/Val	rs1799725	–	–	–	–	–	–	Hung et al. (2004); (Gaudet et al. 2005)
MPO G-463A homozygous variant	rs2333227	–	–	–	–	–	X	Hung et al. (2004); (Mølle et al. 2008)
NAT1*10								Cascorbi et al. (2001); (Human Arylamine *N*-Acetyltransferase Gene Nomenclature (2010))
T1088A	rs1057126	–	–	–	–	–	X	
C1095A	rs15561	–	–	–	–	X	X	

Table 2 continued

Polymorphism/SNP	Rs number	Affy 5.0	Affy 6.0	IllHap300	IllHum610 Quad	IllOmni1 Mduo	SNP500-Cancer	References Bladder cancer risk (rs number)
NAT2 (relevant in Caucasians)								Brockmöller et al. (1996); Golka et al. (1996); (Human Arylamine *N*-Acetyltransferase Gene Nomenclature (2010))
G191A	rs1801279	–	–	–	–	X	X	
C282T	rs1041983	–	–	–	X	X	X	
T341C	rs1801280	–	–	–	X	X	X	
C481T	rs1799929	X	X	–	X	X	X	
G590A	rs1799930	X	X	–	X	X	X	
A803G	rs1208	–	X	X	X	X	X	
G857A	rs1799931	–	–	–	X	X	X	
NQO1 C/T and T/T (Pro187Ser) nucleotide 609 of exon 6	rs1800566	X	X	X	X	X	X	Chao et al. (2006)
PTGS2 3′-untranslated region	rs5275	–	–	–	X	X	X	Yang et al. (2008)
SULT1A1 Arg213His (syn.: SULT1A1*2)	rs9282861	–	–	–	–	–	X	Zheng et al. (2003); (Hebbring et al. 2007) (for synonym, see Pharmacogenomics Knowledge Base (2010))
SULT1A2	rs4987024	–	–	–	–	–	X	Figueroa et al. (2008)
UGT2B7 C802T (His268Tyr)	rs7439366	–	–	–	–	–	–	Lin et al. (2005); (Rouguieg et al. 2010)

If the reference does not include the rs number, the source is given in brackets

in Table 1, the latter variants have not been consistently validated in independent case–control series. Therefore, we analysed the fraction of the 163 SNPs from Table 3, Supplemental Table 1 ("old SNPs") that are represented on the SNP chips from the previously published GWAS (Table 1), because in this case it is unlikely that the "old SNPs" could be verified in genome-wide studies. Considering that the recent GWAS (Table 1) were performed with Illumina chips, it can be concluded that 60 of the "old SNPs" were re-analysed in the Illumina SNP chip studies but not confirmed. However, 103 of the "old SNPs" are not currently present on the Illumina SNP chip and therefore represent candidates that could be validated (or disproven) in future. Of course, most of the mentioned SNPs are likely to be in linkage disequilibrium with markers on the SNP chips and some of their neighbouring SNPs might indeed show small *P* values. However, not reaching genome-wide significance, the association with "old SNPs" is unlikely to be recognized. Nevertheless, final answers will most probably be provided when the next generation sequencing studies (see paragraph below) are finished.

Implications for prevention?

A common feature of the novel bladder cancer-associated SNPs is the relatively low odds ratio (<1.5), when compared to heavy cigarette smoking that is associated with an odds ratio of approximately four (e.g. OR = 3.69; 95% CI = 2.97–4.67; $P = 8.1 \times 10^{-33}$ in Lehmann et al. 2010). Generally, an odds ratio of 1.5 is of minor relevance for an individual and would not justify additional medical precautionary measures. However, a relevant question is whether the high-risk alleles of several of the SNPs in Table 1 interact, leading to odds ratios that are similar or even higher than that of cigarette smoking. If so, one should consider that individuals carrying combinations of several high-risk alleles are rare. For example, only approximately eight in 1,000 individuals may carry a combination of four high-risk alleles if the frequency of the individual high-risk alleles is 0.3. Nevertheless, identifying these individuals would be advantageous, especially if adequate measures of precaution such as cystoscopy or specific imaging techniques, in the case of bladder cancer, are too expensive or too invasive to be applied to the general population. The above example illustrates that studies are required to test whether influential SNPs interact and add together to create odds ratios that would justify preventive measures.

Strong impact of "wimp SNPs"

To date, GWAS have identified more than 300 validated associations between genetic variants and approximately 70 common diseases (Hindorff et al. 2009; http://www.genome.gov/gwastudies). Only a small number of rare variants with

Table 3 Polymorphic genes (and loci) ("old SNPs") not involved in xenobiotic metabolism but reported to influence bladder cancer risk and its rs numbers

Functional classes/groups: genes and loci	Rs number
Repair, damage signalling	
APE1[1]	rs1760944[A1]
ATM[2]	rs189037[A2]
ERCC1[3]; ERCC1[4]; ERCC1[4]; ERCC1[4]; ERCC2[5]; ERCC2[6]; ERCC5[3]; ERCC6[7]; ERCC6[2] (ERCC2 syn.: XPD)	rs3212961[A3], rs967591[A4]; rs735482[A4]; rs2336219[A4]; rs1799793[A5]; 238406[A6]; rs1047769[A7]; rs2228528[A8]; rs3750751[A2]
FANCA[2]; FANCA[2]; FANCA[2]; FANCA[2]; FANCA haplotype 3[2]	rs11644967[A2]; rs11649162[A2]; ss69355534[A2]; rs2074963[A2]; rs17684004[A2], rs11644967[A2], ss69355540[A2]
Ku80[8]	rs828907[A9]
MLH1[2]	rs4647255[A2]
MRE11[9]	rs2155209[A10]
NBN[5]	rs1805794[A5]
NBS1[10]	rs709816[A11]
OGG1[11]; OGG1[12]; OGG1 haplotype 2[2]	rs1052133[A12, A13]; rs125701[A14]; rs2304277[A2], rs3218995[A2]
PARP1[12]	rs1136410[A14]
PCNA[13]	rs3626[A15]
POLB[12]; POLB haplotype 2[2]	rs3136717[A14]; rs2272615[A2], rs2953983[A2], rs3136717[A14], rs3136795[A2]
RAD23B[3]	rs1805335[A16]
RAG1[14]	rs2227973[A17]
XPC[5]; XPC[15]; XPC (PAT, ∓)[16]; (XPC syn.: XPD3)	rs2228000[A5]; rs2228001[A18]; n.a.[A19];
XPD[6]; XPD[14]; XPD[17]; XPD[6] (XPD syn.: ERCC2), (XPD3 syn.: XPC)	rs238406[A6]; rs1799793[A17]; rs13181[A20]; rs10525559[A6]
XPF[18]	rs744154[A21]
XRCC1[1]; XRCC1[1]; XRCC1[13]; XRCC1[19]; XRCC2[12]; XRCC2[12]; XRCC2[12]; XRCC2[12]; XRCC3[20]; XRCC4[21]; XRCC4[12]; XRCC4 haplotypes[12]; XRCC7[12]	rs1799782[A22]; rs25489[A22]; rs915927[A15]; rs25487[A12]; rs10234749[A14]; rs6464268[A14]; rs3218373[A14]; rs3218536[A14]; rs861539[A22]; rs 6869366[A23]; rs1805377[A14]; rs2075685[A14], rs2662238[A14]; rs7003908[A13]
Cell cycle control	
CCND1[22]	rs603965[A24]
MDM2[23]; MDM2[24]	rs937282[A25]; rs2279744[A25]
P21 codon 31 (syn.: Waf1/Cip1/CDKN1A)[25, 26]	rs1801270[A26]
p53 intron 3[14]; P53 codon 72[27]	rs17883323[A27]; rs1042522[A28]
DNA replication, translesion synthesis, transcription (close to cell cycle)	
POLR2E[2]; POLR2E[2]; POLR2E[2]; POLR2K[2]; POLR2K[2]; POLR2K[2]; POLR2K[2]; POLR2K[2]	rs2238586[A2]; rs1046911[A2]; rs3787016[A2]; rs2453639[A2]; rs2254883[A2]; rs2453640[A2]; rs2453641[A2]; rs2453643[A2]
Inflammation	
CCR2[28]	rs1799864[A29]
COX-2[29]	rs20417[A30]
IL-6[30]; IL-8[31]; IL8RB[32]	rs1800796[A31]; rs4073[A32]; rs1126579[A33]
NFKB1[33]	n.a.[A34];
PTGS2[34]	rs5275[A35]
TGFBR1[35]	rs334354[A36]
TNF[36]; TNF[36]	rs1800629[A37]; n.a.[A37]
TNF-alpha[37]; TNF-alpha haplotype[37]	rs1799964[A38]; n.a.[A38]
TNFß (syn.: lymphotoxin-α (LTA))[38]	rs909253[A39]
Apoptosis	
CASP8[39]; CASP9[40]	rs3834129[A40]; rs4645978[A41]
DR4 (syn.: TNFRSF10A, TRAIL-R1)[41]; DR4 (syn.: TNFRSF10A, APO2L/TRAIL R1)[42]; DR4 TagSNP[43]	rs20576[A42]; rs4871857[A43]; rs13278062[A44]
FAS haplotype[44]	rs2234767[A45], rs1800682[A45]
FASL (syn.: FASLG)[44]	rs763110[A45]

Table 3 continued

Functional classes/groups: genes and loci	Rs number
Cell adhesion	
CDH1 (syn.: E-cadherin)[45]	rs16260[A46]
Methylation	
MS[46]	rs1805087[A47]
MTHFR[47]; MTHFR[48]; MTHFR TTAA haplotype[48]; MTHFD2[32]	rs1801131[A48]; rs1801133[A49]; rs1667627[A33]
Growth factors	
IGFBP-3[49]	rs2854744[A50]
VEGF[50]; VEGF[50]; VEGF[50]; VEGF[50]	rs833052[A51]; rs1109324[A51]; rs1547651[A51]; rs3024994[A51]
Matrix metalloproteinases	
MMP-1[51]; MMP-3[52]; MMP-7[51]; MMP-9[52]; MMP-9[52]	rs1799750[A52]; rs3025058[A53]; rs11568818[A54]; rs17576[A55]; rs2274756[A56]
mTOR and associated structures	
RAPTOR[53], RAPTOR[53], RAPTOR[53], RAPTOR[53]	rs11653499[A57], rs7211818[A57]; rs7212142[A57], rs9674559[A57]
Others	
CDKN2A[2]	rs3731238[A2]
CTH[54]	rs6413471[A58]; rs559062[A58]
H19[55]	rs2839698[A59]; rs2107425[A59]
H-ras[56]	rs12628[A60]
JWA[57]; JWA[57]; JWA[57]	rs10489[A61]; rs7038[A61]; n.a.[A61]
PSCA[58]	rs2294008[A62]
RGS6[59]	rs2074647[A63]
RUNX3[60]	rs760805[A64]
TEP1[32]	rs1760897[A33]
Urokinase gene[61]	rs4065[A65, A66]
VDR[62]; VDR[62]; F-T haplotype[62]; f-T haplotype[62]	rs10735810[A67]; rs731236[A67]; n.a.[A68]

The reference for bladder cancer risk is provided in superscript, the reference for the rs number is noticed in superscript beginning with A. More detailed information, as provided in Table 2 for xenobiotic metabolizing enzymes, is given in the electronical supplemental Table 1

n.a. not available

References: 1 Wang et al. (2010a), 2 Michiels et al. (2009), 3 García-Closas et al. (2006), 4 Ricceri et al. (2010), 5 Stern et al. (2009), 6 Shao et al. (2007), 7 Chang et al. (2009a), 8 Chang et al. (2009b), 9 Choudhury et al. (2008), 10 Park et al. (2010), 11 Gangwar et al. (2009a), 12 Figueroa et al. (2007), 13 Matullo et al. (2005), 14 Wu et al. (2006), 15 Wen et al. (2009), 16 de Verdier et al. (2010), 17 Chang et al. (2009c), 18 Wang et al. (2010b), 19 Arizono et al. (2008), 20 Sun et al. (2010), 21 Chang et al. (2009d), 22 Yuan et al. (2010), 23 Wang et al. (2008), 24 Onat et al. (2006), 25 Chen et al. (2002), 26 Yang et al. (2010), 27 Li DB et al. (2010), 28 Narter et al. (2010), 29 Gangwar et al. (2011), 30 Leibovici et al. (2005), 31 Ahirwar et al. (2010), 32 Andrew et al. (2009), 33 Tang et al. (2010), 34 Yang et al. (2008), 35 Chen et al. (2004), 36 Marsh et al. (2003), 37 Ahirwar et al. (2009), 38 Nonomura et al. (2006), 39 Wang et al. (2009b), 40 Gangwar et al. (2009b), 41 Wolf et al. (2006), 42 Hazra et al. (2003), 43 Wang et al. (2009c), 44 Li et al. (2006), 45 Kiemeney et al. (2006), 46 Ouerhani et al. (2007), 47 Safarinejad et al. (2010), 48 Cai et al. (2009), 49 Safarinejad et al. (2011), 50 García-Closas et al. (2007), 51 Srivastava et al. (2010a), 52 Srivastava et al. (2010b), 53 Chen et al. (2009), 54 Moore et al. (2007), 55 Verhaegh et al. (2008), 56 Johne et al. (2003), 57 Li et al. (2007), 58 Wang et al. (2010c), 59 Berman et al. (2004), 60 Zhang et al. (2008b), 61 Manchanda et al. (2006), 62 Mittal et al. (2007)

A1 Lo et al. (2009), A2 Michiels et al. (2009), A3 Abbasi et al. (2009), A4 Ricceri et al. (2010), A5 Stern et al. (2009), A6 Shao et al. (2007), A7 García-Closas et al. (2006), A8 Chang et al. (2009a), A9 Wang et al. (2009a), A10 Choudhury et al. (2008), A11 Park et al. (2010), A12 Mateuca et al. (2008), A13 Gangwar et al. (2009a), A14 Figueroa et al. (2007), A15 Matullo et al. (2005), A16 Reif (2006), A17 Wu et al. (2006), A18 Wen et al. (2009), A19 de Verdier et al. (2010), A20 Pabalan et al. (2010), A21 Wang et al. (2010b), A22 Skjelbred et al. (2006), A23 Chiu et al. (2008), A24 Lu et al. (2009), A25 Wang et al. (2008), A26 Sun et al. (2009), A27 Galli et al. (2009), A28 Li DB et al. (2010), A29 Nyquist et al. (2009), A30 Gangwar et al. (2011), A31 Slattery et al. (2007), A32 Savage et al. (2006), A33 Andrew et al. (2009), A34 Tang et al. (2010), A35 Yang et al. (2008), A36 Castillejo et al. (2009), A37 Puthothu et al. (2009), A38 Zhou et al. (2011), A39 Yang et al. (2009), A40 Pittman et al. (2008), A41 Gangwar et al. (2009b), A42 Wolf et al. (2006), A43 Frank et al. (2005), A44 Wang et al. (2009c), A45 Park et al. (2009), A46 Kiemeney et al. (2006), A47 Ott et al. (2008), A48 Platek et al. (2009), A49 Bezemer et al. (2007), A50 Safarinejad et al. (2011), A51 García-Closas et al. (2007), A52 Su et al. (2006), A53 Tsironi et al. (2009), A54 Alakus et al. (2010), A55 Haq et al. (2010), A56 Pinto et al. (2010), A57 Chen et al. (2009), A58 Moore et al. (2007), A59 Verhaegh et al. (2008), A60 Zhang et al. (2008a), A61 Li et al. (2007), A62 Wang et al. (2010c), A63 Berman et al. (2004), A64 Zhang et al. (2008b), A65 Bégin et al. (2007), A66 Shih et al. (2011), A67 Maalej et al. (2005), A68 Mittal et al. (2007)

a frequency of usually much less than 1% is associated with a strongly enhanced risk, such as genetic variants of TP53, RB1, BRCA1, and BRCA2. A very small number of SNPs have effects of a factor of two or higher, for example APOE4 in Alzheimer's disease, LOXL1 in exfoliative glaucoma, and CFH in age-related macular degeneration (Altshuler et al. 2008). Nevertheless, the majority of all identified SNPs have odds ratios between 1.1 and 1.5. In the case of urinary bladder cancer, all known SNPs increase risk by a factor smaller than 1.5. It is likely that these "wimp SNPs"

interact and that complex combinations of several SNPs have a strong influence on whether an individual will develop cancer or not.

However, no comprehensive studies on "wimp SNPs" and "wimp-SNP"-environment interactions are currently available. It should also be noted that variants identified so far, including the novel SNPs identified by GWAS, explain only approximately 5–10% of the overall inherited risk (Altshuler et al. 2008). The remaining variance may be due to an even higher number of SNPs with odds ratios smaller than 1.1; however, the case numbers of most completed GWAS were too small to identify variants associated with such low risk. Nevertheless, it is likely that the "wimpiest-wimp SNPs" with odds ratios smaller than 1.1 are collectively even stronger (Varghese and Easton 2010). Additionally, the locus-attributable risk may have been underestimated, because the marker SNPs identified in GWAS were suboptimal proxies for the causal mutations (Altshuler et al. 2008). The genetic variance explained by the variants identified so far may also have been underestimated, because gene–gene and gene–environment interactions have not yet been adequately considered. Finally, many rare variants may remain undiscovered, because they cannot be identified by SNP chip analysis but require systematic sequencing.

SNPs of distant-acting enhancers

Many of the recently discovered SNPs associated with bladder cancer risk are located in non-coding regions. Examples are the sequence variant rs9642880 on chromosome 8q24, which is 30 kb upstream of Myc (Kiemeney et al. 2008) and rs798766 on 4q16.3, 70 kb from FGFR3 (Kiemeney et al. 2010). Both SNPs are located so far from the exons whose expression they influence that the effect cannot be explained by linkage disequilibrium. In principle, it is not surprising that non-coding sequences can play an important role. It is well known that approximately 5% of the human genome is evolutionary conserved, and only less than one-third of this 5% consists of coding genes (Mouse Genome Sequencing Consortium et al. 2002). One possibility that might therefore explain these hits from GWAS is that the respective non-coding regions contain distant-acting enhancers (Visel et al. 2009). Distant-acting transcriptional enhancers represent sequences that can be located either downstream or upstream of the target gene or even within other genes. They consist of aggregations of transcription factor binding sites. Occupancy of these transcription factor binding sites leads to recruitment of transcriptional co-activators and chromatin remodelling. The protein aggregates at the distant-acting enhancer facilitate DNA looping, whereby the enhancer relocates to physical proximity of the target gene promoter and finally activates transcription by RNA polymerase II (Visel et al. 2009). This mechanism would also explain why some of the novel SNPs act in a tissue specific manner enhancing, for example, the risk of urinary bladder cancer but not that of breast cancer (Kiemeney et al. 2008). In any tissue, only a subset of enhancers is active, because only a specific set of transcription factors is formed. Therefore, it is plausible that rs9642880 and rs798766 are located within urothelium-specific enhancers. In future, it will be interesting to study whether the relatively high number of cancer-associated SNPs in non-coding regions identify distant-acting transcriptional enhancers.

Do SNPs differentiate between bladder cancer with and without exposure to bladder carcinogens?

In most countries, the eligibility criteria for occupational disability compensation are restrictive. Additional criteria that help identify cases where past occupational exposure has contributed to carcinogenesis are welcome. Therefore, it would be relevant to analyse whether specific SNP patterns can differentiate between urinary bladder carcinomas with and without occupational exposure to carcinogens. Recent evidence suggests that such differentiation is possible (Golka et al. 2009). Occupational exposure to aromatic amines and polycyclic aromatic hydrocarbons (PAHs) has been documented in several case–control series (Table 4A). The Wittenberg case–control series is a hospital-based study comprising only a relatively small fraction of individuals with occupational exposure to aromatic amines or PAHs (Table 4A). In contrast, the "Occupational case–control series" comprises individuals that have been evaluated for bladder cancer as an occupational disease, showing a high fraction of individuals exposed to aromatic amines (61%) and PAHs (27%). The Dortmund case–control series comprises former workers from the coal, iron, and steel industries and contains the highest fraction of individuals exposed to PAHs (52%) but not to aromatic amines (0%). Interestingly, GSTM1 0/0 was significantly associated with bladder cancer in the two case–control series with relatively high exposure to PAHs (Table 4B). In contrast, no significant association of GSTM1 0/0 was obtained in the Wittenberg case–control series with a relatively low number of individuals exposed to PAHs. On the other hand, rs9642880[T] was significantly associated with bladder cancer risk in the Wittenberg and not in the occupational as well as the Dortmund case–control series (Table 4B). This result suggests that the quality and quantity of exposure to bladder carcinogens determines which SNPs are relevant. In the case of exposure to certain carcinogens, the influence of SNPs on relevant detoxifying enzymes may increase.

Table 4 Association of bladder cancer risk with rs9642880 and GSTM1 in three case–control series with different exposure to bladder carcinogens

Study population	Occupational exposure to bladder carcinogens (%)	
	Aromatic amines (%)	Polycyclic aromatic hydrocarbons (%)
(A) Exposure to aromatic amines and polycyclic aromatic hydrocarbons		
Wittenberg, cases	6	8
Wittenberg, controls	1	1
Occupational case–control series, cases	61	27
Dortmund case–control series, cases	0	62

Study population (*N* cases/*N* controls)	rs9642880[T]					GSTM1 0/0				
	Frequency					Frequency				
	Cases	Controls	OR	95% CI	*P* value	Cases	Controls	OR	95% CI	*P* value
(B) Association of rs9642880 and GSTM1 with bladder cancer risk										
Wittenberg case–control series (212/194)	0.56	0.48	1.362	1.023–1.813	0.029	0.58	0.53	1.223	0.826–1.809	0.320
Occupational case–control series (216/699)	0.51	0.49	1.112	0.891–1.389	0.350	0.56	0.48	1.383	0.9950–1.921	0.017
Dortmund case–control series (87/699)	0.49	0.49	1.038	0.747–1.441	0.872	0.69	0.48	2.431	1.468–4.104	<0.001

However, this concept must be discussed with caution for different reasons: firstly, because of the relatively small case numbers in the current study and secondly because of the lack of a consistent interaction of GSTM1 0/0 and cigarette smoking. In a recently published meta-analysis, GSTM1 0/0 was reported to be associated with a similarly increased risk in smokers and non-smokers (García-Closas et al. 2005), which speaks against an enhanced role of GSTM1 0/0 in the presence of cigarette smoke-associated carcinogens. On the other hand, *NAT2* slow acetylators have been reported to be especially susceptible to the adverse effects of cigarette smoking on bladder cancer risk (García-Closas et al. 2005). Further studies are needed to analyse whether bladder carcinomas with and without occupational exposure to carcinogens can be differentiated by SNP patterns. Such gene–environment interactions may be particularly interesting for the recently discovered SNP of the detoxifying enzyme UGT1A (Table 1).

Future perspective: next generation sequencing

Sequencing of the first human genome took approximately 50 years and an investment of more than two billion Euros. With the advent of deep sequencing, the required time has been reduced to weeks. Within the next 10 years, the time required for sequencing of a human genome may be reduced to less than 1 day. Therefore, it can be expected that GWAS with SNP chips will soon be replaced by whole genome sequencing, thus allowing access to critical further information, particularly rare mutations. As a consequence, this will further increase the problem of multiple testing and even larger case–control series will be needed. Nevertheless, deep sequencing will, for the first time, give the opportunity to analyse comprehensively and quantitatively the degree to which interindividual differences within our genome contribute to our overall cancer risk.

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