## **Editorial:**

## ADDITIONAL EVIDENCE FOR THE 'WIMP SNP' CONCEPT OF CARCINOGENESIS

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## Dear Editor,

In 2011 Klaus Golka and colleagues from Dortmund University published the wimp SNP concept of carcinogenesis (Golka et al., 2011). According to this concept, individual genetic variants, usually SNPs, confer only a small cancer risk. However, specific combinations of high risk variants may interact, leading to a much higher risk of affected individuals. Although Golka and colleagues established this concept originally for urinary bladder cancer, it may in principle apply for all types of cancer and any polygenic disease.

Until recently the wimp SNP concept was not much more than a fascinating hypothesis without comprehensive experimental proof. However, with the publication of a recent study including totally more than 10,000 cases and controls the situation has changed (Selinski et al., 2017). Selinski and colleagues identified a statistical interaction of four high risk variants. Each of the individual high risk variants leads to an odds ratio of only 1.1-1.3. However, individuals that carry all four variants have a 2.6-fold increased risk. The four sequences, whose high risk variants interact, are a sequence near APOBEC3A, an exon of SLC14A1, an intron of UGT1A and a variant near CCNE1. Unfortunately, too little is known about each individual variant to understand the mechanism why they interact. However, the fact that wimp SNPs interact to cause high odds ratios has been confirmed.

This progress has been made possible by numerous studies, mostly genome-wide association studies that have identified the individual high risk variants (e.g. Selinski, 2012, 2014a, b; Rafnar et al., 2009, 2011, 2014; Kiemeney et al., 2008, 2010; Garcia-Closas et al., 2011; Figueroa et al., 2014, 2016; Rothman et al., 2010; Schwender et al., 2012; Golka et al., 2011). Currently, most studies on genetic polymorphisms in human disease still focus on individual variants (Huang et al., 2016; Pellé et al., 2016; Anvar et al., 2011; Hashemi et al., 2015; Liaqat et al., 2015; Chu et al., 2016; Fujihara et al., 2016; Geller et al., 2016). However, the recent study of Selinski et al. (2017) has shown that identification of the most powerful interactions of individual SNPs is an attractive perspective of the post-GWAS era.

## REFERENCES

Anvar Z, Saadat I, Namavar-Jahromi B, Saadat M. Genetic polymorphisms of glutathione S-transferase M1 (GSTM1) and T1 (GSTT1) and susceptibility to pre-eclampsia: a case-control study and a meta-analysis. EXCLI J. 2011;10:44-51.

Chu H, Zhong D, Tang J, Li J, Xue Y, Tong N, et al. A functional variant in miR-143 promoter contributes to prostate cancer risk. Arch Toxicol. 2016;90:403-14.

Figueroa JD, Ye Y, Siddiq A, Garcia-Closas M, Chatterjee N, Prokunina-Olsson L, et al. Genome-wide association study identifies multiple loci associated with bladder cancer risk. Hum Mol Genet. 2014;23:1387–98.

Figueroa JD, Middlebrooks CD, Banday AR, Ye Y, Garcia-Closas M, Chatterjee N, et al. Identification of a novel susceptibility locus at 13q34 and refinement of the 20p12.2 region as a multi-signal locus associated with bladder cancer risk in individuals of European ancestry. Hum Mol Genet. 2016;25:1203–14.

Fujihara J, Yasuda T, Iwata H, Tanabe S, Takeshita H. Association of XRCC1 polymorphisms with arsenic methylation. Arch Toxicol. 2016;90:1009-12.

Garcia-Closas M, Ye Y, Rothman N, Figueroa JD, Malats N, Dinney CP, et al. A genome-wide association study of bladder cancer identifies a new susceptibility locus within SLC14A1, a urea transporter gene on chromosome 18q12.3. Hum Mol Genet. 2011;20: 4282–9.

Geller F, Soborg B, Koch A, Michelsen SW, Bjorn-Mortensen K, Carstensen L, et al. Determination of NAT2 acetylation status in the Greenlandic population. Arch Toxicol. 2016;90:883-9.

Golka K, Selinski S, Lehmann ML, Blaszkewicz M, Marchan R, Ickstadt K, et al. Genetic variants in urinary bladder cancer: collective power of the "wimp SNPs". Arch Toxicol. 2011;85:539–54.

Hashemi M, Sharifi-Mood B, Rasouli A, Amininia S, Naderi M, Taheri M. Macrophage migration inhibitory factor -173 G/C polymorphism is associated with an increased risk of pulmonary tuberculosis in Zahedan, Southeast Iran. EXCLI J. 2015;14:117-22.

Huang CY, Pu YS, Shiue HS, Chen WJ, Lin YC, Hsueh YM. Polymorphisms of human 8-oxoguanine DNA glycosylase 1 and 8-hydroxydeoxyguanosine increase susceptibility to arsenic methylation capacity-related urothelial carcinoma. Arch Toxicol. 2016;90: 1917-27.

Kiemeney LA, Thorlacius S, Sulem P, Geller F, Aben KK, Stacey SN, et al. Sequence variant on 8q24 confers susceptibility to urinary bladder cancer. Nat Genet. 2008;40:1307–12.

Kiemeney LA, Sulem P, Besenbacher S, Vermeulen SH, Sigurdsson A, Thorleifsson G, et al. A sequence variant at 4p16.3 confers susceptibility to urinary bladder cancer. Nat Genet. 2010;42:415–9.

Liaqat S, Hasnain S, Muzammil S, Hayat S. Polymorphism analysis in estrogen receptors alpha and beta genes and their association with infertile population in Pakistan. EXCLI J. 2015;14:1085-94.

Pellé L, Cipollini M, Tremmel R, Romei C, Figlioli G, Gemignani F, et al. Association between CYP2E1 polymorphisms and risk of differentiated thyroid carcinoma. Arch Toxicol. 2016;90:3099-109.

Rafnar T, Sulem P, Stacey SN, Geller F, Gudmundsson J, Sigurdsson A, et al. Sequence variants at the TERT-CLPTM1L locus associate with many cancer types. Nat Genet. 2009;41:221–7.

Rafnar T, Vermeulen SH, Sulem P, Thorleifsson G, Aben KK, Witjes JA, et al. European genome-wide association study identifies SLC14A1 as a new urinary bladder cancer susceptibility gene. Hum Mol Genet. 2011;20:4268–81.

Rafnar T, Sulem P, Thorleifsson G, Vermeulen SH, Helgason H, Saemundsdottir J, et al. Genome-wide association study yields variants at 20p12.2 that associate with urinary bladder cancer. Hum Mol Genet. 2014;23: 5545–57.

Rothman N, Garcia-Closas M, Chatterjee N, Malats N, Wu X, Figueroa JD, et al. A multi-stage genome-wide association study of bladder cancer identifies multiple susceptibility loci. Nat Genet. 2010;42:978–84.

Schwender H, Selinski S, Blaszkewicz M, Marchan R, Ickstadt K, Golka K, et al. Distinct SNP combinations confer susceptibility to urinary bladder cancer in smokers and non-smokers. PloS One. 2012;7:e51880.

Selinski S. Genetic variants confer susceptibility to urinary bladder cancer: an updated list of confirmed polymorphisms. EXCLI J. 2012;11:743-7.

Selinski S. The post GWAS era: strategies to identify gene-gene and gene-environment interactions in urinary bladder cancer. EXCLI J. 2014a;13:1198–203.

Selinski S. Urinary bladder cancer risk variants: recent findings and new challenges of GWAS and confirmatory studies. Arch Toxicol. 2014b;88:1469–75.

Selinski S, Blaszkewicz M, Ickstadt K, Gerullis H, Otto T, Roth E, et al. Identification and replication of the interplay of four genetic high risk variants for urinary bladder cancer. Carcinogenesis. 2017; epub ahead of print;

http://dx.doi.org/10.1093/carcin/bgx102.