Combined presence of four individually weak genetic variants strongly increases cancer risk

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Recently, large efforts have been invested into genome-wide association studies to identify genetic variants that confer urinary bladder cancer risk (Rothman et al. 2010; Selinski 2014C; Rafnar et al. 2014, 2011, 2009; Kiemeny et al. 2008, 2010; Garcia-Closas et al. 2011; Figueroa et al. 2016, 2014). Usually, the odds ratios of individual variants are low and do not exceed 1.4 (Selinski 2012, 2014a, b; Golka et al. 2011; Schwender et al. 2012). Recently, Selinski et al. (2017) have performed a large study including most of the currently known high-risk genetic variants of urinary bladder cancer. All individual variant odds ratios were only between 1.11 and 1.30 (Selinski et al. 2017). However, the authors discovered a four-variant combination that confers an odds ratio of 2.59 (95% confidence interval of 1.93–3.47). Importantly, this combination of four risk variants is relatively frequent, with approximately 25% in bladder cancer cases and 11% in controls of a European population (Selinski et al. 2017). The interaction of risk variants was stronger in never smoking individuals than in smokers. This example demonstrates that relatively weak individual genetic variants, also named ‘wimp SNPs’ (Golka et al. 2011), can statistically interact to confer a much higher risk in combination.

Urinary bladder cancer is known to be caused by a combination of environmental factors, such as aromatic amines and genetic predisposition (Höhne et al. 2017; Krech et al. 2017; Lukas et al. 2017; Selinski et al. 2015). The majority of currently published studies on genetic polymorphisms still focusses on individual SNPs (Pellé et al. 2016; Huang et al. 2016; Geller et al. 2016; Fujihara et al. 2016; Chu et al. 2016; Liaqat et al. 2015; Hashemi et al. 2015; Anvar et al. 2011). However, the present study of Selinski et al. (2017) demonstrates that it is particularly important to identify

combinations of SNPs that together have a much stronger impact than the sum of individual variants. However, this approach is challenging, because extremely high numbers of cases and controls are needed. The present study (Selinski et al. 2017) included 5049 bladder cancer cases and a similar number of controls to identify statistical interactions of four genetic variants. However, it can be expected that even higher numbers of SNPs interact, which in future confronts scientists with the challenge to organize much larger cohorts of cases and controls.

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