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Editorial:

IMPROVED GENOTYPING OF N-ACETYLTRANSFERASE 2: ROLE OF THE ULTRA-SLOW ACETYLATORS

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N-acetyltransferase 2 polymorphisms are of high relevance in clinical toxicology (Lück et al., 2009; Bing et al., 2011; Costa et al., 2012). The slow acetylator genotype of NAT2 has been demonstrated to be associated with an increased risk of anti-tuberculosis drug-induced liver damage (Cai et al., 2012; Lv et al., 2012; An et al., 2012; Ben Mahmoud et al., 2012; Bose et al., 2011). Moreover, many urinary bladder carcinogens are substrates of NAT2 (Golka et al., 1996; 2002; Vineis et al., 2001; Hung et al., 2004; Moore et al., 2011). Large meta-analyses have clearly shown an association between slow acetylation genotypes and increased risk of bladder cancer (Garcia-Closas et al., 2005; 2011; Sanderson et al., 2007; Agúndez et al., 2008; Hein, 2002, 2006, 2009; Hein and Doll, 2012a, b). However, at the level of individual studies the results remain controversial. Of 46 studies included into one of the recent meta-analysis 35 did not reach statistical significance (Moore et al., 2011).

To clarify the situation a recent study has been performed to identify the role of 'extreme' genotypes (Selinski et al., 2013). This study is based on a population of 344 individuals that have been phenotyped by the caffeine test (Blaszkewicz, 2004; Hakooz, 2009; Jetter et al., 2009). This test quantitatively determines the activity of NAT2 *in vivo*. A subgroup with an `ultra-slow´ *in vivo* metabolism of caffeine was identified.

Interestingly, these individuals with the ultra-slow NAT2 phenotype carried several slow acetylator alleles and could be identified as *6A/*6A, *6A/*7B and *7B/*7B genotypes. This combination of slow alleles, the 'ultra-slow genotype' was further tested in 1,712 bladder cancer cases and 2,020 controls. Remarkably, individuals with the 'ultra-slow' genotype showed an increased odds ratio for bladder cancer risk (OR=1.31, P=0.012) whereas the slow acetylators in general were not significantly associated with cancer risk.

Currently, a huge number of studies is performed to understand the association between genetic variations and phenotype (Daly, 2013; Stewart and Marchan, 2012; Partosch et al., 2013; Sobin et al., 2011; Tumer et al., 2012; Zeller et al., 2012; Escobar-García et al., 2012). A special focus are drug metabolizing enzymes and their role in carcinogenesis (Chen et al., 2012; Hanioka et al., 2011; Santovito et al., 2011; Fujihara et al., 2011; Lankisch et al., 2008; Ulusoy et al., 2007). Genome-wide association studies have identified to which degree genetic variants influence bladder cancer risk (Golka et al., 2011; Selinski et al., 2011, 2012a, b; Safarinejad et al., 2011; Lehmann et al., 2010). However, most of these approaches considered only the genotype in relation to disease. The present study (Selinski et al., 2013) demonstrates the importance of understanding the association of haplotypes with enzyme activity and the relevance of extreme phenotypes.

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