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 antituberculosis 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; Vines 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-Garcia 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.
REFERENCES


Chen SC, Chen CC, Kuo CY, Huang CH, Lin CH, Lu ZY et al. Elevated risk of hypertension induced by arsenic exposure in Taiwanese rural residents: possible effects of manganese superoxide dismutase (MnSOD) and 8-oxoguanine DNA glycosylase (OGG1) genes. Arch Toxicol 2012;86:869-78.

Costa GN, Magno LA, Santana CV, Konstantinovas C, Saito ST, Machado M et al. Genetic interaction between NAT2, GSTM1, GSTT1, CYP2E1, and environmental factors is associated with adverse reactions to anti-tuberculosis drugs. Mol Diagn Ther 2012;16:241-50.


Hein DW. Molecular genetics and function of NAT1 and NAT2: role in aromatic amine metabolism and carcinogenesis. Mutat Res. 2002;506-507:65-77.


Hein DW, Doll MA. A four-SNP NAT2 genotyping panel recommended to infer human acetylator phenotype. Pharmacogenomics 2012a;13:855.

Hein DW, Doll MA. Accuracy of various human NAT2 SNP genotyping panels to infer rapid, intermediate and slow acetylator phenotypes. Pharmacogenomics 2012b;13:31-41.


Lehmann ML, Selinski S, Blaszkewicz M, Ovsianikov D, Moormann O, Guballa C et al. Genotyping NAT2 with only two SNPs (rs1041983 and rs1801280) outperforms the tagging SNP rs1495741 and is equivalent to the conventional 7-SNP NAT2 genotype. Pharmacogenet Genomics 2011;21:673-8.


