Highlight report: gene dose response in *N*-acetylation capacity

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Recently, Mark A. Doll and David W. Hein from the University of Louisville have identified a gene dose response in *N*-acetylation capacity (Doll and Hein 2017). The authors determined *N*-acetyltransferase activity in cultivated human hepatocytes that were incubated with substrates. Moreover, the phenotype was characterized by an *N*-acetyltransferase assay with human hepatocyte lysate. The NAT2 acetylator genotype was determined in DNA isolated from hepatocytes of the same donors. The authors observed a clear gene dose response, where *N*-acetylation capacity increased in the order NAT2*6A/*6A, NAT2*5B/*6A, NAT2 *5B/*5B (Doll and Hein 2017).

Numerous studies have reported an association of NAT2 slow genotypes with urinary bladder cancer risk (Hein et al. 1988, 1993, 1994, 1995, 2006; Lukas et al. 2017; Ebbinghaus et al. 2017; Krech et al. 2017; Selinski 2014a, b, c; 2015; Golka et al. 2014). The relevance of NAT2 polymorphisms seems to depend on exposure to carcinogenic substrates of NAT2, such as aromatic amines. Since exposure of humans to aromatic amines has decreased in the past decades, more recent studies observed only a minor influence of NAT2, while other genetic variants were reported to be more relevant for urinary bladder cancer risk (Höhne et al. 2017; Isermann et al. 2017; Selinski et al. 2017, 2016a, b; Gundert-Remy et al. 2015; Mohamed 2017; Figueroa et al. 2016; Bolt 2014; Rota et al. 2014; Schwender et al. 2012, 2015; Hammad et al. 2015; Wang et al. 2014; Rafnar et al. 2014; Piletic and Kuney 2016). Besides bladder cancer risk and the well-established risk for drug-induced liver injury (Hughes et al. 1954; Daly 2013; Du et al. 2013), slow NAT2 has also been reported to be associated with sensory hearing functions (Selinski et al. 2015) and age-related cataract (Tamer et al. 2005; Meyer et al. 2003), although independent confirmation in larger studies is still required.

Considering the current state of the art, the highlighted study of Doll and Hein is particularly valuable, because it carefully characterized metabolic activity of a specific cell type, the human hepatocyte. Therefore, the reported gene dose response can clearly be assigned to the metabolic activity of the liver, which is not the case, when NAT2 substrates are analyzed in human blood.

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