DETECTION OF DPYD*2A ALLELE IN DIHYDROPYRIMIDINE DEHYDROGENASE GENE: PERSPECTIVE FOR FLUOROPYRIMIDINE-TREATED PATIENTS

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*ABSTRACT – Dihydropyrimidine dehydrogenase is a key enzyme involved in the metabolism of fluoropyrimidine anticancer drugs. Several studies have demonstrated that diminished DPD activity as a consequence of genetic variations in the DPYD gene limits carrier's ability to fully metabolize the drug, resulting in toxicity and adverse events. DPYD*2A (IVS14+1G>A) represents the most abundant variant allele in the European Caucasian population. Cancer patients with this gene variant represent a subgroup with higher risk of toxicity when treated with fluoropyrimidines. Therefore, we have implemented a method for DPYD*2A allele genotyping. In our pilot study performed in a group of individuals derived from our regional reference population, we found that none out of 47 subjects was a carrier of the DPYD*2A variant allele.*

INTRODUCTION

Dihydropyrimidine dehydrogenase (DPD; EC 1.3.1.2) is the initial and rate-limiting enzyme of pyrimidine bases (uracil and thymine) catabolic pathway. DPD is also the key enzyme involved in metabolism of pyrimidine analog drugs including 5-fluorouracil (5-FU) and its derivates (e. g. capecitabine) (Amstutz *et al.*, 2011) (Fig. 1). Fluoropyrimidine drugs are widely used as chemotherapeutic agents in the treatment of solid carcinomas including gastrointestinal (CRC – colorectal cancer) and breast cancer. The human gene encoding DPD (DPYD; OMIM 612779) maps to chromosome 1p21.3 and consists of 23 exons (Wei *et al.*, 1998). Polymorphisms or mutations in genes encoding drug-metabolizing enzymes are responsible for wide variability in individual response to standard doses of anticancer drugs. In up to 40% of patients, the use of 5-fluorouracil therapy is compromised by development of severe gastrointestinal and hematological toxicity and neurotoxicity (Caudle *et al.*, 2013). As DPD is the main enzyme involved in fluoropyrimidine metabolism it is assumed that genotyping of DPYD gene helps to identify individuals predisposed to high risk of adverse events related to fluoropyrimidine toxicity.