Comprehensive analysis of CYP2D6 mutations in human cancers

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The cytochrome P450 (CYP) enzymes are responsible for the metabolism of many drugs. Single nucleotide polymorphisms (SNPs) have large impacts on the activity of these enzymes and result in altered metabolism for a variety of drugs. Cancer patients frequently suffer from both chronic pain and depression, leading to co-administration of selective serotonin reuptake inhibitors (ssRIs) and opioids. CYP2D6 is necessary to convert ssRIs into their inactive metabolites and to activate several prodrug opioids. Ideally, to avoid drug-drug interactions in cancer patients when prescribing ssRI-opioid combinations, careful analysis of relevant SNPs through PCR in individual patients would be employed. However, this approach remains technically and economically inaccessible to many cancer demographics and clinical settings. To address these limitations and provide genomic-based alternatives, we analyzed the frequency of CYP2D6 mutations in sequenced specimens from a varied pool of cancer patients. The primary goal of this study is to use cancer data trends linked to CYP2D6 DNA sequence disruptions to improve informed selection of ssRI-opioid treatments based on specific patient characteristics. We mined the Catalogue of Somatic Mutations in Cancer (COSMIC) from the Sanger Institute to identify CYP2D6 mutations occurring in patients with various cancers types. We also used the CHASM-3.1 and VEST-4 artificial intelligence algorithms from the Cancer-Related Analysis of Variants Toolkit (CRAVAT) to evaluate the functional significance of missense mutations. Results from CHASM reveal the probability of mutations either being drivers or passengers in cancer, while VEST indicates the likelihood of mutations being pathogenic. We found that 188 of 409 patients showed CYP2D6 mutations localized to the coding region. A majority of these (126) were missense mutations, 18 showed high pathogenicity, and no cancer drivers were identified. The three tissue types most frequently affected by CYP2D6 mutations were the large intestine (60), lung (58), and upper aerodigestive tract (49). The mean age at time of sequencing (MATS) for all tissues was 58.2 years. Three tissues showed significant age differences relative to the MATS of all tissue types: the urinary tract (mean=69.5, p=0.0080), hematopoietic and lymphoid tissue (mean=49.1, p=0.0039), and the stomach (mean=66.0, p=0.0027). The primary histology associated with CYP2D6 mutations was carcinoma (327 of 409 patients). Intriguingly, cancers linked to lymphoid neoplasm histology had a significantly different MATS (mean=41.4 years, p=0.0002) relative to all histology types (mean=58.2). The observed missense mutations in the conserved P450 domain of CYP2D6 suggest structural changes that likely affect protein function, thereby precluding effective metabolism of this enzyme’s drug substrates. Therefore, these results indicate that cautious, personalized, and deliberate prescription should be used when co-administering opioids and ssRIs to patients who meet criteria associated with decreased CYP2D6 metabolism in the cancer contexts herein reported.