AB130. Comprehensive analysis of CYP2D6 and copy number variants using reverse-hybridization and real-time PCR-based assays

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Background: The cytochrome P450 2D6 (CYP2D6) is an important liver enzyme involved in the metabolism of up to 25% of clinically used drugs. The CYP2D6 gene is highly polymorphic, with numerous (sub)variants described in the Human Cytochrome P450 Database (www.cypalleles.ki.se). While the most frequent allelic variations are caused by single nucleotide polymorphisms and small insertions/deletions, highly homologous regions in the CYP2D6 gene locus facilitate unequal cross-over, leading to large deletions, duplications and gene conversions.

Methods: We developed a reverse-hybridization assay (PGX-CYP2D6 XL StripAssay) for the simultaneous detection of 19 sequence variations in the CYP2D6 gene, which define the most prevalent alleles impacting enzyme activity in Caucasians. For the detection of copy number variations, a real-time PCR based assay (CYP2D6 RealFast CNV Assay) was established. The StripAssay and real-time PCR assay were validated on 118 and 98 samples, respectively.

Results: The PGX-CYP2D6 XL StripAssay correctly identified allelic variants with normal (*1, *2, *35, *39), reduced (*9, *10, *17, *29, *41) and no (*3 to *8, *11, *12, *14, *15, *40, *58) enzyme activity, hence allowing the classification of individuals into extensive (EM), intermediate (IM) and poor (PM) metabolizers. In addition, ultrarapid (UM) metabolizers and CYP2D6*5 carriers can be identified by quantifying their abnormal copy number status using the CYP2D6 RealFast CNV Assay. Both assays demonstrated a test accuracy of >0.99.

Conclusions: The metabolizer phenotype of patients treated with CYP2D6 substrates can be accurately determined by the combined use of PGX-CYP2D6 XL StripAssay and CYP2D6 RealFast CNV Assay.

Keywords: CYP2D6; cytochrome P450; drug metabolizer; genotyping

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