Revisiting the effects of MDR1 Variants using computational approaches

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Abstract

P-glycoprotein, encoded by the MDR1 gene, is an ATP-dependent efflux pump that is interleaved in the cell membrane and exports various substances out of the cell. It was shown to be overexpressed and related to acquired multi drug resistance in many cancers. Over the past three decades numerous studies were conducted to identify the effects of MDR1 variants on p-gp expression and function as well as on patient survivability. T1236C, T2677C and T3435C are highly prevalent MDR1 variants that are the most widely studied, typically using in-vitro and in-vivo methodologies. Results of these studies are remarkably inconsistent and even contradictory. In this paper we perform multiple computational, data-driven analyses to assess the effects of these variants in a different approach. We exploit knowledge of gene expression regulation to elucidate the impact of the variants on biological mechanisms and use extensive genomic databases to discern their expected effects. Our results indicate that T1236C increases MDR1 mRNA levels by 2-fold ($p = 0.06$) and is correlated with worse patient prognosis ($p = 0.02$). Additionally, our novel approach of examining the mRNA folding strength suggests that T3435C is in a region of evolutionarily conserved slow translation and is deemed to cause an increase in local translation rates, indicating a potential modification of co-translational folding. These results support several hypotheses that have been suggested by previous major studies. To the best of our knowledge, this study is the first to apply a computational approach to examine the effects of MDR1 variants. Its advantages and disadvantages substantially differ from those of in-vivo and in-vitro methods, making it beneficial to use as a complimentary approach to settle disputes regarding the effects of MDR1 variants.