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The genome-wide search of SNPs in 3'-UTR microRNA target sequences associated with individual drug susceptibility

Rykova E.[1, 2, 3]*, Ershov N.[1], Merkulova T.[1]

[1] *Institute of Cytology and Genetics, SB RAS, Novosibirsk, Russia*

[2] *Institute of Chemical Biology and Fundamental Medicine, SB RAS, Novosibirsk, Russia*

[3] *Novosibirsk State Technical University, Novosibirsk, Russia*

** rykova.elena.2014@gmail.com*

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Motivation and Aim: The development of approaches to the large-scale identification of genetic determinants of individual sensitivity to drugs is one of the central tasks of fundamental medicine. Many SNPs in 3'-UTR microRNA (miRNA) target sequences are associated with various diseases [2] however, their role in response to therapy remains poorly understood. The aim of this study was the identification of SNPs in 3'-UTR miRNA target sequences, underlining individual drug susceptibility, based on available data on eQTL and allele-specific expression (ASE) analysis.
Methods and Algorithms: The search for SNPs in 3'-UTR miRNA target sites was carried out in 5402 eQTLs that appeared upon treatment of CD14+ monocytes with IFN-g [3] and in 253 ASE events identified upon exposure of 5 human cell types (LCLs, PBMCs, HUVECs, SMCs and melanocytes) to various drugs, nutrients and pollutants [4]. Data on the functional impact of SNPs on predicted miRNA sites were taken from the PolymiRTS database [1]. ASE events that showed inconsistent changes across replicates were filtered out additionally.
Results: Of the 5402 eQTLs (5270 SNPs and 4173 genes) identified under IFN-g treatment, 317 (307 SNPs and 298 genes) contained predicted miRNA binding sites affected by the nucleotide substitution. Since 317 eQTLs were shown not to be significantly enriched in GO/KEGG terms relative to 5402 eQTLs, it can be assumed that they all belong to the same functional groups. The highest enrichment in the group of 317 eQTLs was shown for the terms "cellular response to stress" (41 genes, FDR = 3.71 e-8) and "immune response" (36 genes, FDR = 5.59 e-6). According to the mSigDB database, the greatest enrichment (44 genes, FDR = 1.66 e-11) was shown for the genes up-regulated in PBMCs after exposure to FluMist live virus vaccine. In addition, predicted target genes of hsa-miR-8485 (28 genes FDR = 4.3e-7) were also enriched. Out of 253 ASE events, 58 coincided with the predicted SNPs in 3'-UTR miRNA target sequences; allele asymmetry in these sites in response to drugs was shown for 14 (Acetaminophen – 2 ASE; Triclosan – 1 ASE; Tunicamycin – 1 ASE; Dexamethasone – 5 ASE; Caffeine – 5 ASE). In most cases, reduced expression of the allelic variant corresponded to the appearance of a binding site for a particular Mir(s).
Conclusion: Both eQTL and ASE analysis are effective tools to identify SNPs located in 3'-UTR miRNA target sequences and associated with individual drug response.
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