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SSRI response biomarkers: Lessons from genome-wide transcriptomic profiling of human lymphoblastoid cell lines

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Genome-wide pharmacogenomic studies for developing targeted therapies offer the advantage of hypothesis-free search for tentative drug response biomarkers (efficacy and safety). However, they require large patient cohorts and are therefore laborious and quite costly. We present an alternative approach based on genome-wide transcriptomic profiling of a panel of human lymphoblastoid cell lines (LCLs) representing unrelated healthy donors. Eighty LCLs from healthy adult female individuals were phenotyped for growth inhibition by paroxetine. Fourteen LCLs were chosen for comparative expression profiling with affymetrix microarrays. The most notable difference between LCLs displaying high vs. low paroxetine sensitivities was a 6.3-fold lower basal expression ($p=0.0000256$) of CHL1 (close homologue of L1), coding for neuronal cell adhesion protein implicated in thalamo-cortical circuitry. This was confirmed by qPCR. Studies with miRNA arrays have identified miR-151-3p, predicted to target CHL1, as an additional biomarker for SSRI sensitivity. This supports CHL1 expression levels as tentative biomarker for SSRI sensitivity. Preliminary findings will be presented from our ongoing studies with DNA samples from major depression patients with known SSRI response phenotypes.

Our studies demonstrate that drug sensitivity phenotyping in LCLs from unrelated healthy donors, followed by their genome-wide transcriptomic profiling for genes and miRNAs, is a powerful and cost-effective tool for searching drug response biomarkers (prior to collection of clinical samples). The method is applicable for drugs, including CNS drugs, whose targets are functionally expressed by LCLs. This approach builds upon the utility of LCLs of healthy donors to faithfully represent the intricate human transcriptomic repertoire.

Biography

David Gurwitz is the Director of The National Laboratory for the Genetics of Israeli Populations (NLGIP) at the Department of Human Molecular Genetics and Biochemistry, Sackler Faculty of Medicine, Tel-Aviv University, since 1995. He earned a Ph.D. in Biochemistry from Tel-Aviv University in 1986 and conducted post-graduate studies at the University of California, Irvine.

His research is focused on pharmacogenomics and on finding biomarkers for CNS drug response. He is affiliate member of the NIH Pharmacogenetics Research Network (PGRN) and of international biobanking organizations.

He published over 140 manuscripts, including in Nature and Science, serves as a senior editor of the journal Pharmacogenomics, and as Associate Editor for several additional journals including Drug Development Research and Pharmaceutical Biology.

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