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

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Abstract

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. Here we present our experience with an alternative approach, based on genome-wide transcriptomic profiling of a panel of human lymphoblastoid cell lines (LCLs) representing unrelated healthy donors. LCLs can be obtained from most large biobanks and our approach offer simple and inexpensive discovery of tentative drug response biomarkers. The expression of candidate biomarker genes and microRNAs (miRNAs) is subsequently measured by qPCR in blood samples of patient cohorts.

We applied genome-wide expression profiling of human LCLs for searching tentative SSRI antidepressant drug response biomarkers. 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.

Next, our studies with commercial miRNA arrays have identified miR-151-3p, predicted to target *CHL1*, as an additional biomarker for SSRI sensitivity. Other miRNAs showing differential expression levels in the two groups of human LCLs, which corresponds with the differential expression of other tentative biomarker genes, included miR-132, miR-212, miR-30b* (miR-30b-3p), let-7b and let-7c, all of which are also implicated in CNS function.

Findings will be presented from our ongoing studies with DNA samples from major depression patients with known SSRI response phenotypes.

In vitro drug sensitivity phenotyping of LCLs from unrelated donors, followed by their genome-wide expression profiling for both genes and miRNAs, appears to be a powerful and cost-effective tool for early studies on tentative drug response biomarkers (prior to collection of clinical samples) for aiding clinical trial design. The method is applicable for any CNS drug whose target is functionally expressed by LCLs. This approach builds upon the utility of LCLs of healthy donors to faithfully represent the complex human genomic and epigenomic repertoire.

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