Progress in Neuro-Psychopharmacology & Biological Psychiatry 64 (2016) 334–340

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Genome-wide microarray analysis of gene expression profiling in major depression and antidepressant therapy

Eugene Lin [a,b], Shih-Jen Tsai [c,d,*]

[a] Institute of Clinical Medical Science, China Medical University, Taichung, Taiwan
[b] Vita Genomics, Inc., Taipei, Taiwan
[c] Department of Psychiatry, Taipei Veterans General Hospital, Taipei, Taiwan
[d] Division of Psychiatry, National Yang-Ming University, Taipei, Taiwan

ARTICLE INFO

Available online 20 February 2015

Keywords:
Antidepressants
Genome-wide gene expression profiling
Genome-wide microarray analysis
Major depressive disorder
Transcriptional profiling

ABSTRACT

Major depressive disorder (MDD) is a serious health concern worldwide. Currently there are no predictive tests for the effectiveness of any particular antidepressant in an individual patient. Thus, doctors must prescribe antidepressants based on educated guesses. With the recent advent of scientific research, genome-wide gene expression microarray studies are widely utilized to analyze hundreds of thousands of biomarkers by high-throughput technologies. In addition to the candidate-gene approach, the genome-wide approach has recently been employed to investigate the determinants of MDD as well as antidepressant response to therapy. In this review, we mainly focused on gene expression studies with genome-wide approaches using RNA derived from peripheral blood cells. Furthermore, we reviewed their limitations and future directions with respect to the genome-wide gene expression profiling in MDD pathogenesis as well as in antidepressant therapy.

Contents

Abbreviations: *BDNF*, brain-derived neurotrophic factor; *CAPRIN1*, cell cycle associated protein 1; *CD3D*, CD3d molecule delta; *CD97*, CD97 molecule; *CHL1*, cell adhesion molecule L1-like; *CLEC4A*, C-type lectin domain family 4, member A; CNVs, copy-number variations; *DUSP1*, dual specificity phosphatase 1; *EDN1*, endothelin 1; *ELK3*, ELK3 ETS-domain protein; *FKBP5*, FK506 binding protein 5; *GZMA*, granzyme A; *HIST1H1E*, histone cluster 1 H1e; *IFITM3*, interferon induced transmembrane protein 3; *IL1B*, interleukin 1 beta; *IRF7*, interferon regulatory factor 7; *ITGB3*, integrin beta 3; *KRT23*, keratin 23; LCLs, lymphoblastoid cell lines; lncRNAs, long noncoding RNAs; LPS, lipopolysaccharide; *MATR3*, matrin 3; MDD, major depressive disorder; MDE, major depressive episode; *MET*, MET proto-oncogene receptor tyrosine kinase; *MLC1*, megalencephalic leukoencephalopathy with subcortical cysts 1; mRNAs, messenger RNAs; miRNAs, microRNAs; NESDA, Netherlands Study of Depression and Anxiety; NMDA, N-methyl-D-aspartate; ncRNAs, noncoding RNAs; *NTRK2*, neurotrophic tyrosine kinase receptor type 2; *PAQR6*, progestin and adipoQ receptor family member VI; PBMCs, Peripheral blood mononuclear cells; *PCDH10*, protocadherin 10; *PLSCR1*, phospholipid scramblase 1; *PPL*, periplakin; *PPM1K*, protein phosphatase Mg2+/Mn2+ dependent 1K; *PPT1*, palmitoyl-protein thioesterase 1; *PROK2*, prokineticin 2; *PSMA4*, proteasome subunit alpha type 4; *PSMA6*, proteasome subunit alpha type 6; *RGS7BP*, G-protein signaling 7 binding protein; *RPL5*, ribosomal protein L5; *RPL9*, ribosomal protein L9; *RPL17*, ribosomal protein L17; *RPL24*, ribosomal protein L24; SNPs, single nucleotide polymorphisms; *TAGLN2*, transgelin 2; *TIMP1*, TIMP metallopeptidase inhibitor 1; *TMEM176A*, transmembrane protein 176A; *TNF*, tumor necrosis factor; *TNXB*, tenascin XB; *ZBTB16*, zinc finger and BTB domain containing 16

* Corresponding author at: Department of Psychiatry, Taipei Veterans General Hospital, No. 201, Shih-Pai Road, Sec. 2, 11217 Taipei, Taiwan. Tel.: +886 2 2875 7027x276; fax: +886 2 2872 5643.
E-mail address: tsai610913@gmail.com (S.-J. Tsai).

http://dx.doi.org/10.1016/j.pnpbp.2015.02.008
0278-5846/

1. Introduction

Major depressive disorder (MDD), one of the most prevalent and complex mental disorders worldwide, is estimated to be the second leading cause of disability by 2030 (Mathers and Loncar, 2006). Currently there are no predictive tests for disease state and antidepressant treatment remission in MDD beforehand so that doctors can only take a trial and error approach to prescribe antidepressants, the first line of medication for lifting MDD (Lin and Chen, 2008). In clinical association studies, gene expression can be employed to determine the contribution of genes to pathogenesis of MDD because accumulating evidence suggests that patients with MDD exhibit an altered pattern of expression in relevant genes when compared with healthy controls (Hepgul et al., 2013). Similarly, the analysis of gene expression promises a new approach to cope with the complexity of personalized medication on antidepressant treatment (Menke, 2013). Although further findings in support of this hypothesis are needed, more and more biomarkers in gene expression profiling are being discovered to be associated with MDD as well as antidepressant response (Labermaier et al., 2013). In this paper, we briefly reviewed the few existing transcriptomic studies in assessing and understanding MDD pathogenesis and antidepressant therapy.

With the Human Genome Project completed, a new era for scientific and medical research is set to develop revolutionary technologies such as genome-wide gene expression microarrays, which are different from the candidate-gene approach of hypothesis-driven biomarker search (Seifuddin et al., 2013). An obvious strength of the genome-wide gene expression microarray studies is the hypothesis-free nature about the relevant genes. The genome-wide approach employs high-throughput technologies to analyze biomarkers across the entire human genome in order to find associations with observable traits. This genome-wide approach faces several challenges, such as how to account for the issue of multiple comparisons, which occurs when multiple statistical tests are considered simultaneously (Watanabe, 2011).

Many researchers have investigated MDD-related and transcriptome-based genome-wide approaches in blood tissue, postmortem human brain tissue, and animal brain tissue (Mehta et al., 2010). Blood as a target tissue is readily accessible, and the gene expression levels using blood have shown to be comparable with the ones using prefrontal cortex in MDD-related transcriptomic research (Sullivan et al., 2006). In this review, we provided a synopsis of the genome-wide microarray studies published recently for MDD and antidepressants, mostly with a focus on studies using blood as a target tissue.

First, we surveyed the gene expression profiles and genes that were identified as biomarkers and were linked with MDD in the genome-wide gene expression microarray studies. Furthermore, we assessed some potential gene expression profiles and genes that were investigated in genome-wide gene expression microarray studies and were shown to be associated with drug efficacy for antidepressant medications. Finally, we summarized the limitations and future perspectives with respect to genome-wide gene expression profiling studies. Future replication studies in large and independent samples are needed to confirm the role of the biomarkers discovered in genome-wide transcriptional profiling studies in MDD as well as antidepressant treatment response.

2. RNA molecules

Noncoding RNAs (ncRNAs), including small ncRNAs and long noncoding RNAs (lncRNAs), are different from their counterpart messenger RNAs (mRNAs) owing to the fact that the sequence of nucleotides within ncRNAs does not encode proteins (Nagano and Fraser, 2011). Small ncRNAs, including the microRNAs (miRNAs), are smaller than 200 nucleotides in length. On the other hand, lncRNAs are transcripts over 200 nucleotides in length.

The miRNAs control gene expression by modulating mRNA degradation, translation, or stability (Dwivedi, 2014). The role of mRNAs, miRNAs, and lncRNAs in disease pathogenesis and in monitoring therapeutic responses for MDD is emerging rapidly. Studies are now being geared to examine if gene expression profiles such as mRNAs, miRNAs, and lncRNAs can be developed as possible biomarkers for MDD as well as antidepressant response.

3. Genome-wide gene expression microarray studies in MDD

Table 1 summarizes the relevant gene expression profile and genes associated with MDD in genome-wide microarray studies. This is by no means a comprehensive review of all potential biomarkers reported in the literature. As mentioned previously, increasing numbers of biomarkers are being identified as researchers continue to pay much attention to genome-wide microarray studies in MDD.

3.1. Study by Spijker et al. (2010)

In a stimulated blood-based genome-wide approach, Spijker and colleagues explored the possibility that gene expression profile can distinguish patients suffering from MDD from controls (Spijker et al., 2010). They recruited 21 MDD patients and 21 matched controls from the Netherlands Study of Depression and Anxiety (NESDA) cohort. They chose a lipopolysaccharide (LPS) stimulus to induce gene expression in whole blood and used 44K human whole genome arrays (Agilent Technologies, USA) for genome-wide expression analysis. They employed a microarray analysis tool and constructed a classifier for MDD by using a set of 7 genes including the megalencephalic leukoencephalopathy with subcortical cysts 1 (*MLC1*), prokineticin 2 (*PROK2*), cell cycle associated protein 1 (*CAPRIN1*), C-type lectin domain family 4, member A (*CLEC4A*), keratin 23 (*KRT23*), phospholipid scramblase 1 (*PLSCR1*), and zinc finger and BTB domain containing 16 (*ZBTB16*) genes (Spijker et al., 2010). In their report, the classifier was shown to discriminate MDD patients from control subjects with a sensitivity of 76.9% and a specificity of 71.8% (Spijker et al., 2010). Their results were limited by the small sample size and would need a much larger cohort of patients to better evaluate sensitivity and specificity of the proposed candidate genes.

Table 1
The genome-wide gene expression microarray studies in MDD.

Reference	RNA source	Array platform	Ethnic group	Sample size	Biomarker	Gene expression	Results
Spijker et al. (2010)	Whole blood	44K	Caucasian	42	*MLC1*, *PROK2*, *CAPRIN1*, *CLEC4A*, *KRT23*, *PLSCR1*, *ZBTB16*	mRNA	A classifier for MDD with 76.9% sensitivity and 71.8% specificity
Menke et al. (2012)	Whole blood	HT-12 v3	Caucasian	60	*FKBP5*, *DUSP1*, *TMEM176A*, *ZBTB16*	mRNA	A classifier for MDD with 80.0% sensitivity and 87.5% specificity
Belzeaux et al. (2012)	PBMCs	SurePrint	Caucasian	29	*EDN1*, *ELK3*, *PAQR6*, *PPM1K*, *RGS7BP*	mRNA, miRNA	About 200 candidate genes identified as dysregulated
Garbett et al. (2015)	Dermal fibroblasts	PM Array	Caucasian, African American	32	*PCDH10*, *TNXB*, *PPL*, *MET*, hsa-miR-122	mRNA, miRNA	miRNA and mRNA correlated with each other
Liu et al. (2014)	Peripheral blood	Glue grant	Chinese	20	lncRNAs located at chr10:874695–874794, chr10:75873456–75873642, chr3:47048304–47048512	mRNA, lncRNA	Three lncRNAs as potential regulatory factors in MDD

44K: 44K human whole genome arrays (Agilent, USA); *CAPRIN1*: cell cycle associated protein 1; *CLEC4A*: C-type lectin domain family 4, member A; *DUSP1*: dual specificity phosphatase 1; *EDN1*: endothelin 1; *ELK3*: ELK3 ETS-domain protein; *FKBP5*: FK506 binding protein 5; Glue Grant: Glue Grant Human Transcriptome Array (Affymetrix, USA); HT-12 v3: Human HT-12 v3 Expression BeadChips (Illumina, USA); *KRT23*: keratin 23; *MET*: MET proto-oncogene receptor tyrosine kinase; *MLC1*: megalencephalic leukoencephalopathy with subcortical cysts 1; *PAQR6*: progestin and adipoQ receptor family member VI; PBMCs: peripheral blood mononuclear cells; *PCDH10*: protocadherin 10; *PLSCR1*: phospholipid scramblase 1; PM Array: GeneChip HT HG-U133 + PM Array Plate (Affymetrix, USA); *PPL*: periplakin; *PPM1K*: protein phosphatase Mg2 +/Mn2 + dependent 1K; *PROK2*: prokineticin 2; *RGS7BP*: G-protein signaling 7 binding protein; SurePrint: SurePrint G3 Human GE 8 × 60K (Agilent, USA); *TMEM176A*: transmembrane protein 176A; *TNXB*: tenascin XB; *ZBTB16*: zinc finger and BTB domain containing 16;

The *MLC1* gene encodes a protein highly expressed in the brainstem, cerebellum, olfactory tract, and thalamus, and has been linked with bipolar disorder and schizophrenia in a Southern Indian population (Verma et al., 2005). The protein encoded by the *PROK2* gene is expressed in the circadian clock, and the *PROK2* receptor (*PROKR2*) gene was found to be associated with MDD in a Japanese population (Kishi et al., 2009). A previous study by Menke et al. (2012) also identified the *ZBTB16* gene to have potential relevance to MDD in a stimulated blood-based genome-wide approach. To our knowledge, the *MLC1*, *PROK2*, *CAPRIN1*, *CLEC4A*, *KRT23*, and *PLSCR1* genes had not been indicated in MDD in other previous studies.

3.2. Study by Menke et al. (2012)

Similarly, in a stimulated blood-based genome-wide approach, Menke and colleagues tested whether gene expression profile can identify differences between MDD patients and controls (Menke et al., 2012). They recruited 29 male MDD patients and 31 matched male controls from the Munich-Antidepressant-Response-Signature (MARS) project. They used an in vivo dexamethasone challenge test to induce gene expression in whole blood and employed HumanHT-12 v3 Expression BeadChips (Illumina, USA) for genome-wide expression analysis. They performed random forest analyses for classification and constructed a classifier for MDD by using a set of 19 genes including FK506 binding protein 5 (*FKBP5*), dual specificity phosphatase 1 (*DUSP1*), transmembrane protein 176A (*TMEM176A*), and *ZBTB16* (Menke et al., 2012). In their report, the classifier was shown to discriminate MDD patients from control subjects with a sensitivity of 80.0% and a specificity of 87.5% (Menke et al., 2012). Their results were limited by the small sample size and would need a much larger cohort of patients to better evaluate sensitivity and specificity of the proposed candidate genes.

The protein encoded by the *FKBP5* gene may play a role in immunoregulation, and genetic variants within the *FKBP5* gene have been associated with MDD (Szczepankiewicz et al., 2014). The *DUSP1* gene was reported to be expressed more strongly in postmortem hippocampus tissue of MDD patients as compared with matched controls (Duric et al., 2010). In a genetic animal model of depression, gene expression of the *TMEM176A* gene was found to be altered in the hippocampus and prefrontal cortex (Blaveri et al., 2010). A previous study by Spijker et al. (2010) also found the *ZBTB16* gene to be linked with MDD in a stimulated blood-based genome-wide approach.

3.3. Study by Belzeaux et al. (2012)

In a transcriptome-based genome-wide approach, Belzeaux and colleagues tested the hypothesis that a convergent analysis of the gene expression profile of both mRNAs and miRNAs can distinguish patients suffering from a major depressive episode (MDE) from controls (Belzeaux et al., 2012). They recruited 16 MDE patients and 13 matched controls and employed SurePrint G3 Human GE 8 × 60K (Agilent Technologies, USA) for genome-wide expression analysis. In their analysis for transcripts, about 200 candidate genes were identified as dysregulated when MDE patients were compared with controls (including the regulator of endothelin 1 (*EDN1*), ELK3 ETS-domain protein (*ELK3*), progestin and adipoQ receptor family member VI (*PAQR6*), protein phosphatase Mg2 +/Mn2 + dependent 1K (*PPM1K*), and G-protein signaling 7 binding protein (*RGS7BP*) genes). The *EDN1*, *ELK3*, *PAQR6*, *PPM1K*, and *RGS7BP* genes have also been previously identified as dysregulated in brain tissues with MDD (Guilloux et al., 2012; Sequeira et al., 2006, 2007).

Belzeaux and colleagues also tested the hypothesis that gene expression profile (including mRNA and miRNA expression) can predict response to antidepressants with MDE patients (Belzeaux et al., 2012). We will discuss their report in the next section.

3.4. Study by Garbett et al. (2015)

In another transcriptome-based genome-wide approach, Garbett and colleagues studied dermal fibroblasts from patients with MDD and tested whether gene expression profiling could be used as peripheral biomarkers of MDD (Garbett et al., 2015). They assayed dermal fibroblast samples (n = 32) from MDD patients and matched controls using genome-wide mRNA expression analysis with GeneChip HT HG-U133 + PM Array Plate (Affymetrix, USA) (Garbett et al., 2015). In order to investigate the relationship between the mRNA and miRNA expression changes, they also performed quantitative polymerase chain reaction-based experiments of miRNA species (Garbett et al., 2015). Garbett and colleagues revealed that there was a strong mRNA gene expression pattern change in multiple molecular pathways, such as cell-to-cell communication (including protocadherin 10 (*PCDH10*), tenascin XB (*TNXB*), periplakin (*PPL*), and MET proto-oncogene receptor tyrosine kinase (*MET*) genes) when they compared MDD fibroblasts with matched controls. The most prominent miRNA candidate was hsa-miR-122, which is highly expressed in the hippocampus (Garbett

et al., 2015). Furthermore, the miRNA and mRNA expression changes were found to be functionally correlated with each other. To our knowledge, the *PCDH10*, *TNXB*, *PPL*, and *MET* genes had not been suggested in MDD in other previous studies.

The pathway analyses by Garbett et al. (2015) suggested that most of the identified molecular pathways were relevant to cell-to-cell communication, which plays a role in the innate and adaptive immune system. Their results were aligned with the view of inflammatory and immune system biomarkers. With the emergence of neuroinflammation in MDD, there is evidence to support a role of inflammation in the pathophysiology of MDD (Krishnadas and Cavanagh, 2012; Patel, 2013). Several inflammatory biomarkers, such as C reactive protein (CRP) and interleukin 6 (IL-6), have been shown to be predictive of MDD due to increased serum levels of these inflammatory biomarkers in MDD patients compared with controls in recent studies (Valkanova et al., 2013). Further studies are needed and may shed additional light on the links between MDD and inflammation.

3.5. Study by Liu et al. (2014)

Recently, the characterization of lncRNAs, which are highly expressed in the brain, has become a fruitful area of research in MDD due to their importance in gene regulatory networks (Nagano and Fraser, 2011; Ng et al., 2013). In a similar transcriptome-based genome-wide approach, Liu and colleagues explored whether genome-wide lncRNA expression and co-expression with mRNA patterns may serve as tentative biomarkers for MDD (Liu et al., 2014). They recruited 10 MDD patients and 10 matched controls. Glue Grant Human Transcriptome Array (Affymetrix, USA), which detected 34,834 lncRNAs and 39,224 mRNAs in peripheral blood, was employed for genome-wide expression analysis (Liu et al., 2014). In their report, there were 1556 upregulated lncRNAs and 441 down-regulated lncRNAs as well as 759 up-regulated mRNAs and 1007 downregulated mRNAs between MDD patients and controls. Furthermore, in co-expression analysis of lncRNAs and mRNAs, the lncRNAs located at chr10:874695–874794, chr10:75873456–75873642, and chr3:47048304–47048512 were each connected to four differentially regulated mRNAs in the MDD sub-network. However, these connections were not found in the control's sub-network. Therefore, Liu et al. (2014) suggested these three lncRNAs as potential regulatory factors in MDD.

4. Genome-wide gene expression microarray studies in antidepressants

Table 2 summarizes the relevant gene expression profile and genes associated with antidepressant response in genome-wide microarray studies. This is by no means a comprehensive review of all potential biomarkers reported in the literature. As mentioned previously, increasing numbers of biomarkers are being discovered as researchers continue to pay much attention to genome-wide microarray studies of antidepressants in MDD.

4.1. Study by Mamdani et al. (2011)

In the first transcriptome-based genome-wide study, Mamdani and colleagues explored whether genome-wide RNA expression may serve as potential biomarkers to antidepressant treatment in MDD (Mamdani et al., 2011). They recruited 63 MDD patients treated with citalopram for 8 weeks and employed GeneChip Human Genome U133 Plus 2.0 array (Affymetrix, USA) for genome-wide expression analysis (Mamdani et al., 2011). In their report, there were 32 differentially expressed probesets shown to be associated with response to citalopram treatment (Mamdani et al., 2011). Among the 32 probesets, probeset 208436_s_at, which maps the interferon regulatory factor 7 (*IRF7*) gene, was the most significant differentially expressed one (Mamdani et al., 2011). To our knowledge, no other previous studies had implicated *IRF7* in antidepressant treatments or in MDD.

4.2. Study by Morag et al. (2011)

In the second transcriptome-based genome-wide study, Morag and colleagues studied gene expression profiling as a biomarker of antidepressant drug treatment (Morag et al., 2011). They used drug-effect phenotypes in human lymphoblastoid cell lines (LCLs) and selected 14 human LCLs from healthy adult female individuals with relatively high versus low sensitivities to antidepressant paroxetine (Morag et al., 2011). GeneChip Human Gene 1.0 ST arrays (Affymetrix, USA) were employed for genome-wide expression analysis (Morag et al., 2011). Morag and colleagues revealed the cell adhesion molecule L1-like (*CHL1*) gene as a predictor of antidepressant drug treatment due to the lower levels of *CHL1* expression by 6.3-fold ($p = 0.0000256$) in the paroxetine-sensitive cell lines when they compared the two phenotypic groups (Morag et al., 2011). However, a major drawback for the study by Morag and colleagues is that the observations were based on cell lines representing healthy individuals instead of major depression patients' peripheral blood lymphocytes (Morag et al., 2011). The implication of gene expression profiling should ideally be assessed with the blood samples of much larger cohorts of MDD patients, both before and after several weeks of antidepressant treatment, by comparing transcriptomic changes between good and poor responders.

The protein encoded by the *CHL1* gene is a member of the neural cell adhesion molecules of the immunoglobulin superfamily, which is a neural recognition molecule and may play a key role in signal transduction pathways and structural reorganization indicated in learning and memory (Maness and Schachner, 2007). Clark and colleagues suggested further evidence of an association between the *CHL1* gene and adverse effects to antidepressant medication in major depressive disorder from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study (Clark et al., 2012).

Human LCLs consist of a promising model system in the pharmacogenomic studies of drug response including chemotherapeutics, statins, and antidepressants (Wheeler and Dolan, 2012). The main advantage of LCLs is the ease of experimental manipulation; on the other hand, a major disadvantage is that the complexity of drug effects in the human body cannot be characterized by a single-model system such as LCLs (Wheeler and Dolan, 2012).

4.3. Study by Oved et al. (2012)

In a similar genome-wide gene-expression profiling approach for antidepressant response to therapy, Oved and colleagues expanded the previous study by Morag et al. (2011) to investigate whether miRNAs may serve as tentative biomarkers for antidepressant response (Oved et al., 2012). They chose 8 human LCLs from healthy adult female individuals with reproducible high or low sensitivities to growth inhibition by antidepressant paroxetine (Oved et al., 2012). GeneChip miRNA 2.0 arrays (Affymetrix, USA) were employed for genome-wide expression analysis (Oved et al., 2012). In their report, the miRNA miR-151-3p was identified as a tentative biomarker because it exhibited 6.71-fold higher expression in LCLs with higher paroxetine sensitivity (Oved et al., 2012). Their results were in agreement with those of the study by Morag et al. (2011) such that the *CHL1* gene was identified as a leading tentative biomarker for antidepressant sensitivity because *CHL1* is a target of miR-151-3p (Oved et al., 2012). Again, a major drawback for the study by Oved and colleagues is that the observations were based on cell lines representing healthy individuals instead of major depression patients' peripheral blood lymphocytes.

4.4. Study by Belzeaux et al. (2012)

As mentioned in the previous section, Belzeaux and colleagues also tested the hypothesis that a convergent analysis of both mRNA and miRNA profiling can predict response to antidepressants with MDE patients in a transcriptome-based genome-wide approach (Belzeaux et al.,

Table 2
The genome-wide gene expression microarray studies in antidepressant response in MDD.

Reference	RNA source	Array platform	Ethnic group	Sample size	Biomarker	Gene expression	Results
Mamdani et al. (2011)	Whole blood	U133	Caucasian	63	*IRF7*	mRNA	32 probesets associated with antidepressant response
Morag et al. (2011)	LCLs	GeneChip	Caucasian	14	*CHL1*	mRNA	*CHL1* associated with antidepressant response
Oved et al. (2012)	LCLs	GeneChip 2.0	Caucasian	8	*CHL1*	miRNA	*CHL1* associated with antidepressant response
Belzeaux et al. (2012)	PBMCs	SurePrint	Caucasian	29	*PPT1*, *TNF*, *IL1B*, *HIST1H1E*, miR-941, miR-589	mRNA, miRNA	Four mRNAs associated with antidepressant response
Oved et al. (2013)	LCLs	GeneChip or GeneChip 2.0	Caucasian	4	*ITGB3*, miR-221, miR-222	mRNA, miRNA	*ITGB3* associated with antidepressant response
Guilloux et al. (2015)	Whole blood	HT12-v4.0	Caucasian	67	*CD3D*, *CD97*, *IFITM3*, *RPL5*, *GZMA*, *TAGLN2*, *TIMP1*, *RPL24*, *PSMA4*, *MATR3*, *RPL9*, *PSMA6*, *RPL17*	mRNA	A classifier for antidepressant response with 66.7% sensitivity and 89.5% specificity

CD3D: CD3d molecule delta; *CD97*: CD97 molecule; *CHL1*: cell adhesion molecule L1-like; GeneChip: GeneChip Human Gene 1.0 ST arrays (Affymetrix, USA); GeneChip 2.0: GeneChip miRNA 2.0 arrays (Affymetrix, USA); *GZMA*: granzyme A; *HIST1H1E*: histone cluster 1 H1e; HT12-v4.0: HT12-v4.0 gene array (Illumina, USA); *IFITM3*: interferon induced transmembrane protein 3; *IL1B*: interleukin 1 beta; *IRF7*: interferon regulatory factor 7; *ITGB3*: integrin beta 3; LCLs: lymphoblastoid cell lines; *MATR3*: matrin 3; PBMCs: peripheral blood mononuclear cells; *PPT1*: palmitoyl-protein thioesterase 1; *PSMA4*: proteasome subunit alpha type 4; *PSMA6*: proteasome subunit alpha type 6; *RPL5*: ribosomal protein L5; *RPL9*: ribosomal protein L9; *RPL17*: ribosomal protein L17; *RPL24*: ribosomal protein L24; SurePrint: SurePrint G3 Human GE 8 × 60K (Agilent, USA); *TAGLN2*: transgelin 2; *TIMP1*: TIMP metallopeptidase inhibitor 1; *TNF*: tumor necrosis factor; U133: GeneChip Human Genome U133 Plus 2.0 array (Affymetrix, USA).

2012). They recruited 16 MDE patients and 13 matched controls and employed SurePrint G3 Human GE 8 × 60K (Agilent Technologies, USA) for genome-wide expression analysis. In their report, a combination of four mRNAs was identified to be predictive of treatment response (including the palmitoyl-protein thioesterase 1 (*PPT1*), tumor necrosis factor (*TNF*), interleukin 1 beta (*IL1B*), and histone cluster 1 H1e (*HIST1H1E*) genes). Two miRNAs (such as miR-941 and miR-589) were also shown to be stable overexpression in MDE patients in comparison with the miRNA expression between MDE patients and controls at 8 weeks.

The protein encoded by the *PPT1* gene is a small glycoprotein in the brain, and deficiency of this protein leads to infantile neuronal ceroid lipofuscinosis, a neurodegenerative storage disorder in childhood (Kim et al., 2008). To our knowledge, no other previous studies had implicated *PPT1*, *TNF*, *IL1B*, and *HIST1H1E* in antidepressant treatments or in MDD.

4.5. Study by Oved et al. (2013)

Similarly, in a genome-wide expression profiling study for the mode of action of antidepressants, Oved and colleagues conducted microarray expression profiling experiments in human LCLs chronically treated with paroxetine from four unrelated adult male donors (Oved et al., 2013). GeneChip Human Gene 1.0 ST arrays or GeneChip miRNA 2.0 arrays (Affymetrix, USA) were employed for detecting the expression levels of genes and miRNAs, respectively (Oved et al., 2013). Their data revealed that the integrin beta 3 (*ITGB3*) gene exhibited 1.925-fold increased expression ($P = 7.5 \times 10(-8)$) for the four LCLs with chronic paroxetine exposure (Oved et al., 2013). In addition, they observed a decrease in the expression levels of two miRNAs, miR-221 and miR-222, which were both predicted to target the *ITGB3* gene (Oved et al., 2013).

A recent study suggested genetic interactions of the Itgb3 and serotonin transporter (Slc6a4) genes to modulate serotonin uptake in mouse brain (Whyte et al., 2014). To our knowledge, no other previous studies had implicated *ITGB3* in antidepressant treatments or in MDD.

4.6. Study by Guilloux et al. (2015)

Very recently, Guilloux and colleagues tested the hypothesis that the gene expression profile can predict response to antidepressants prior to treatment initiation for MDD patients in a transcriptome-based genome-wide approach (Guilloux et al., 2015). They recruited 34 MDD patients with co-occurring anxiety and 33 matched controls and employed HT12-v4.0 gene array (Illumina, USA) for genome-wide expression analysis. By using a machine learning method with support vector machines, a predictive 13-gene model was indicated to predict non-remission with 79.4% accuracy (sensitivity of 66.7% and specificity of 89.5%). The 13-gene predictive model includes the CD3d molecule delta (*CD3D*), CD97 molecule (*CD97*), interferon induced transmembrane protein 3 (*IFITM3*), ribosomal protein L5 (*RPL5*), granzyme A (*GZMA*), transgelin 2 (*TAGLN2*), TIMP metallopeptidase inhibitor 1 (*TIMP1*), ribosomal protein L24 (*RPL24*), proteasome subunit alpha type 4 (*PSMA4*), matrin 3 (*MATR3*), ribosomal protein L9 (*RPL9*), proteasome subunit alpha type 6 (*PSMA6*), and ribosomal protein L17 (*RPL17*) genes. To our knowledge, these genes had not been indicated in antidepressant treatments or in MDD in other previous studies.

Their results were limited by the small size of the cohort and would need a much larger cohort of patients to better assess sensitivity and specificity of the proposed predictive model and biomarkers.

5. Limitations in current genome-wide gene expression microarray studies

With respect to the aforementioned genome-wide gene expression profiling studies, there were several limitations. First, the small size of the cohort warrants no definite conclusions. Small cohort size can cause no biomarkers reaching genome-wide significance because of insufficient statistical power (Novianti et al., 2014). In future work, independent replication studies in much larger cohort sizes are needed to validate the role of the biomarkers discovered in these studies.

Further, many biomarkers did not replicate well across studies, making us question whether the novel associations were valid. In addition, the co-medications may affect treatment response and should be tested for future personalized medicine in the treatment of MDD (Ulrich-Merzenich et al., 2012). And combined substance use (such as alcohol and smoking) should also be addressed as a response modifier.

Moreover, it could be possible that different antidepressants may be possessing different biomarkers due to different mechanisms of action as well as administered drug dose (Serretti et al., 2008). It is also important to examine the biomarkers between different ethnic groups because different populations could result in different findings (Serretti et al., 2008). This comparison may implicate proper MDD treatment for different ethnic backgrounds.

Because the aforementioned genome-wide gene expression profiling studies investigated RNA derived from different cell populations such as whole blood or isolated lymphocytes, some of the discrepancies could be associated with the cell types used for the analysis. miRNA

studies have been done in serum and plasma, whereas mRNA studies have been done in either lymphocytes or RNAs isolated from peripheral blood mononuclear cells (PBMCs) (Blondal et al., 2013).

6. Future outlook

In future work, it will be indispensably necessary to generate a panel of biomarkers that are highly reproducible as an indicator of MDD or antidepressant response. At this point, no biomarkers found in the previous genome-wide gene expression microarray studies would really qualify to be listed in the set because of the limitations as described above. We will also need to consider what kind of selection criteria for prioritizing biomarkers to be listed in such a panel.

As discussed in this review, an increasing amount of evidence supports the hypothesis that mRNA, miRNA, and lncRNA expression profiles have active roles in various biological processes in MDD or in antidepressant therapy. Therefore, it may make great contributions to the unveiling of the complex mechanisms underlying MDD or antidepressant therapy by considering systematic and integrative analyses of different RNA molecules, such as mRNAs, miRNAs, and lncRNAs, with potentially cooperative functions (Guo et al., 2014).

Furthermore, machine learning techniques such as the artificial neural network approach may provide a plausible way to predict drug efficacy in antidepressant therapy and establish models for predicting MDD (Lin et al., 2006). In future research, statistical models will be established to predict the probability of disease status or drug efficacy to guide clinicians in choosing medications. Machine learning techniques such as the artificial neural network approach may also play a key role in assessing gene–environment interactions or RNA–RNA molecule correlations such as correlations between miRNA and mRNA (Lin and Hsu, 2009; Lin et al., 2007). Statistical modeling is essential to root out the false positive biomarkers discovered at the current association analyses of genome-wide gene expression microarray studies by using meta-analysis, pathway analysis, and gene–gene expression correlations (Gaiteri et al., 2014; Rezola et al., 2014).

In addition, accumulating evidence suggests that single nucleotide polymorphisms (SNPs) can be employed to determine the contribution of genes to MDD and antidepressant response in genetic association studies (Gatt et al., 2015; Lin and Chen, 2008). For example, the brain-derived neurotrophic factor (*BDNF*) gene and its receptor, the neurotrophic tyrosine kinase receptor type 2 (*NTRK2*) gene, have been indicated in MDD and antidepressant response (Hwang et al., 2006; Lin and Chen, 2008; Lin et al., 2009). The expression of a gene could be affected by SNPs or copy-number variations (CNVs). Future research may incorporate SNPs, CNVs, and other biomarkers as discussed in this review to fully investigate their role in MDD and antidepressant response.

Finally, it seems that MDD has a strong environmental cause as well as a genetic cause (Fass et al., 2014). Furthermore, other approaches such as epigenetics should be considered to obtain clinically meaningful prediction of antidepressant treatment if genome-wide gene expression microarray studies alone could not obtain replicable biomarkers (Fass et al., 2014). Epigenetic mechanisms are modulated by environmental factors and may be associated with therapeutic effects of antidepressant drugs (Menke and Binder, 2014). Ultimately, future studies may need to propose an integrative use of biomarkers, such as clinical, genetic, epigenetic, metabolomic, transcriptomic, proteomic, and imaging data, in order to precisely understand MDD pathogenesis as well as antidepressant therapy (Breitenstein et al., 2014).

7. Summary

In summary, modeling tools based on biomarkers play a crucial role in distinguishing MDD from controls as well as in predicting the possible outcomes of antidepressant treatment. Future research using machine learning approaches is needed in order to model the interactions among biomarkers as well as to evaluate associations between antidepressant response and biomarkers in genome-wide gene expression microarray studies (Lin, 2012; Lin and Tsai, 2011, 2012). These machine learning techniques may provide tools for clinical genome-wide transcriptional profiling studies and assist in finding biomarkers involved in responses to therapeutic drugs and adverse drug reactions (Lin, 2012; Lin and Tsai, 2011, 2012). Over the next few years, novel machine learning methods could be employed to develop molecular diagnostic and prognostic tools with big data technology, which manages massive clinical datasets in genomics and personalized medicine (Lin, 2012; Lin and Tsai, 2011, 2012). However, the results of genome-wide gene expression profiling studies can be integrated into routine clinical practice only after we overcome a number of major challenges (Lin, 2012; Lin and Tsai, 2011, 2012). Personalized therapy for MDD will become a reality after larger prospective clinical trials have been conducted in more diverse human populations to confirm biomarkers and clinical factors associated with MDD and antidepressant treatment response.

In this study, we reviewed several recent findings and relevant studies in genome-wide gene expression profiling for MDD as well as for antidepressants. The work also underscores the importance of large-scale genome-wide studies to examine a greater diversity of populations in the clinical settings of mental diseases and their treatments. Now we obtain a major new piece in the puzzle after some pieces fitting the puzzle for gene expression profiling of MDD pathogenesis and antidepressant therapy have been investigated. To improve and personalize MDD treatment and prevention worldwide, the future effort will have to correlate these findings with other pieces until the picture of MDD treatment and prevention is sufficiently clear. Furthermore, these findings suggested that modeling tools based on clinical factors such as gene expression data may help patients and doctors make more informed and personalized decisions.

Role of the funding source

None.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgments

The authors extend their sincere thanks to Vita Genomics, Inc. for funding this research.

References

Belzeaux R, Bergon A, Jeanjean V, Loriod B, Formisano-Tréziny C, Verrier L, et al. Responder and nonresponder patients exhibit different peripheral transcriptional signatures during major depressive episode. Transl Psychiatry 2012;2:e185.
Blaveri E, Kelly F, Mallei A, Harris K, Taylor A, Reid J, et al. Expression profiling of a genetic animal model of depression reveals novel molecular pathways underlying depressive-like behaviours. PLoS One 2010;5:e12596.
Blondal T, Jensby Nielsen S, Baker A, Andreasen D, Mouritzen P, Wrang Teilum M, et al. Assessing sample and miRNA profile quality in serum and plasma or other biofluids. Methods 2013;59:S1–6.
Breitenstein B, Scheuer S, Holsboer F. Are there meaningful biomarkers of treatment response for depression? Drug Discov Today 2014;19:539–61.
Clark SL, Adkins DE, Aberg K, Hettema JM, McClay JL, Souza RP, et al. Pharmacogenomic study of side-effects for antidepressant treatment options in STAR*D. Psychol Med 2012;42:1151–62.
Duric V, Banasr M, Licznerski P, Schmidt HD, Stockmeier CA, Simen AA, et al. A negative regulator of MAP kinase causes depressive behavior. Nat Med 2010;16:1328–32.
Dwivedi Y. Emerging role of microRNAs in major depressive disorder: diagnosis and therapeutic implications. Dialogues Clin Neurosci 2014;16:43–61.
Fass DM, Schroeder FA, Perlis RH, Haggarty SJ. Epigenetic mechanisms in mood disorders: targeting neuroplasticity. Neuroscience 2014;264:112–30.
Gaiteri C, Ding Y, French B, Tseng GC, Sibille E. Beyond modules and hubs: the potential of gene coexpression networks for investigating molecular mechanisms of complex brain disorders. Genes Brain Behav 2014;13:13–24.

Garbett KA, Vereczkei A, Kálmán S, Brown JA, Taylor WD, Faludi G, et al. Coordinated messenger RNA/microRNA changes in fibroblasts of patients with major depression. Biol Psychiatry 2015;77:256–65.
Gatt JM, Burton KL, Williams LM, Schofield PR. Specific and common genes implicated across major mental disorders: a review of meta-analysis studies. J Psychiatr Res 2015;60:1–13.
Guilloux JP, Douillard-Guilloux G, Kota R, Wang X, Gardier AM, Martinowich K, et al. Molecular evidence for BDNF- and GABA-related dysfunctions in the amygdala of female subjects with major depression. Mol Psychiatry 2012;17:1130–42.
Guilloux JP, Bassi S, Ding Y, Walsh C, Turecki G, Tseng G, et al. Testing the predictive value of peripheral gene expression for nonremission following citalopram treatment for major depression. Neuropsychopharmacology 2015;40:701–10.
Guo L, Zhao Y, Yang S, Zhang H, Chen F. An integrated analysis of miRNA, lncRNA, and mRNA expression profiles. Biomed Res Int 2014;2014:345605.
Hepgul N, Cattaneo A, Zunszain PA, Pariante CM. Depression pathogenesis and treatment: what can we learn from blood mRNA expression? BMC Med 2013;11:28.
Hwang JP, Tsai SJ, Hong CJ, Yang CH, Lirng JF, Yang YM. The Val66Met polymorphism of the brain-derived neurotrophic-factor gene is associated with geriatric depression. Neurobiol Aging 2006;27:1834–7.
Kim SJ, Zhang Z, Sarkar C, Tsai PC, Lee YC, Dye L, et al. Palmitoyl protein thioesterase-1 deficiency impairs synaptic vesicle recycling at nerve terminals, contributing to neuropathology in humans and mice. J Clin Invest 2008;118:3075–86.
Kishi T, Kitajima T, Tsunoka T, Okumura T, Ikeda M, Okochi T, et al. Possible association of prokineticin 2 receptor gene (PROKR2) with mood disorders in the Japanese population. Neuromolecular Med 2009;11:114–22.
Krishnadas R, Cavanagh J. Depression: an inflammatory illness? J Neurol Neurosurg Psychiatry 2012;83:495–502.
Labermaier C, Masana M, Müller MB. Biomarkers predicting antidepressant treatment response: how can we advance the field? Dis Markers 2013;35:23–31.
Lin E. Novel drug therapies and diagnostics for personalized medicine and nanomedicine in genome science, nanoscience, and molecular engineering. Pharm Regul Aff Open Access 2012;1:e116.
Lin E, Chen PS. Pharmacogenomics with antidepressants in the STAR*D study. Pharmacogenomics 2008;9:935–46.
Lin E, Hsu SY. A Bayesian approach to gene–gene and gene–environment interactions in chronic fatigue syndrome. Pharmacogenomics 2009;10:35–42.
Lin E, Tsai SJ. Gene–gene interactions in a context of individual variability in antipsychotic drug pharmacogenomics. Curr Pharmacogenomics Person Med 2011;9:323–31.
Lin E, Tsai SJ. Novel diagnostics R&D for public health and personalized medicine in Taiwan: current state, challenges and opportunities. Curr Pharmacogenomics Person Med 2012;10:239–46.
Lin E, Hwang Y, Wang SC, Gu ZJ, Chen EY. An artificial neural network approach to the drug efficacy of interferon treatments. Pharmacogenomics 2006;7:1017–24.
Lin E, Hwang Y, Liang KH, Chen EY. Pattern-recognition techniques with haplotype analysis in pharmacogenomics. Pharmacogenomics 2007;8:75–83.
Lin E, Hong CJ, Hwang JP, Liou YJ, Yang CH, Cheng D, et al. Gene–gene interactions of the brain-derived neurotrophic-factor and neurotrophic tyrosine kinase receptor 2 genes in geriatric depression. Rejuvenation Res 2009;12:387–93.
Liu Z, Li X, Sun N, Xu Y, Meng Y, Yang C, et al. Microarray profiling and co-expression network analysis of circulating lncRNAs and mRNAs associated with major depressive disorder. PLoS One 2014;9:e93388.
Mamdani F, Berlim MT, Beaulieu MM, Labbe A, Merette C, Turecki G. Gene expression biomarkers of response to citalopram treatment in major depressive disorder. Transl Psychiatry 2011;1:e13.
Maness PF, Schachner M. Neural recognition molecules of the immunoglobulin superfamily: signaling transducers of axon guidance and neuronal migration. Nat Neurosci 2007;10:19–26.
Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med 2006;3:e442.
Mehta D, Menke A, Binder EB. Gene expression studies in major depression. Curr Psychiatry Rep 2010;12:135–44.
Menke A. Gene expression: biomarker of antidepressant therapy? Int Rev Psychiatry 2013;25:579–91.
Menke A, Binder EB. Epigenetic alterations in depression and antidepressant treatment. Dialogues Clin Neurosci 2014;16:395–404.
Menke A, Arloth J, Pütz B, Weber P, Klengel T, Mehta D, et al. Dexamethasone stimulated gene expression in peripheral blood is a sensitive marker for glucocorticoid receptor resistance in depressed patients. Neuropsychopharmacology 2012;37:1455–64.
Morag A, Pasmanik-Chor M, Oron-Karni V, Rehavi M, Stingl JC, Gurwitz D. Genome-wide expression profiling of human lymphoblastoid cell lines identifies CHL1 as a putative SSRI antidepressant response biomarker. Pharmacogenomics 2011;12:171–84.
Nagano T, Fraser P. No-nonsense functions for long noncoding RNAs. Cell 2011;145:178–81.
Ng SY, Lin L, Soh BS, Stanton LW. Long noncoding RNAs in development and disease of the central nervous system. Trends Genet 2013;29:461–8.
Novianti PW, Roes KC, Eijkemans MJ. Evaluation of gene expression classification studies: factors associated with classification performance. PLoS One 2014;9:e96063.
Oved K, Morag A, Pasmanik-Chor M, Oron-Karni V, Shomron N, Rehavi M, et al. Genome-wide miRNA expression profiling of human lymphoblastoid cell lines identifies tentative SSRI antidepressant response biomarkers. Pharmacogenomics 2012;13:1129–39.
Oved K, Morag A, Pasmanik-Chor M, Rehavi M, Shomron N, Gurwitz D. Genome-wide expression profiling of human lymphoblastoid cell lines implicates integrin beta-3 in the mode of action of antidepressants. Transl Psychiatry 2013;3:e313.
Patel A. Review: the role of inflammation in depression. Psychiatr Danub 2013;25(Suppl. 2):S216–23.
Rezola A, Pey J, Tobalina L, Rubio A, Beasley JE, Planes FJ. Advances in network-based metabolic pathway analysis and gene expression data integration. Brief Bioinform 2014. [Mar 13. [Epub ahead of print]].
Seifuddin F, Pirooznia M, Judy JT, Goes FS, Potash JB, Zandi PP. Systematic review of genome-wide gene expression studies of bipolar disorder. BMC Psychiatry 2013;13:213.
Sequeira A, Gwadry FG, Ffrench-Mullen JM, Canetti L, Gingras Y, Casero Jr RA, et al. Implication of SSAT by gene expression and genetic variation in suicide and major depression. Arch Gen Psychiatry 2006;63:35–48.
Sequeira A, Klempan T, Canetti L, Ffrench-Mullen J, Benkelfat C, Rouleau GA, et al. Patterns of gene expression in the limbic system of suicides with and without major depression. Mol Psychiatry 2007;12:640–55.
Serretti A, Kato M, Kennedy JL. Pharmacogenetic studies in depression: a proposal for methodologic guidelines. Pharmacogenomics J 2008;8:90–100.
Spijker S, Van Zanten JS, De Jong S, Penninx BW, van Dyck R, Zitman FG, et al. Stimulated gene expression profiles as a blood marker of major depressive disorder. Biol Psychiatry 2010;68:179–86.
Sullivan PF, Fan C, Perou CM. Evaluating the comparability of gene expression in blood and brain. Am J Med Genet B Neuropsychiatr Genet 2006;141B:261–8.
Szczepankiewicz A, Leszczyńska-Rodziewicz A, Pawlak J, Narozna B, Rajewska-Rager A, Wilkosc M, et al. FKBP5 polymorphism is associated with major depression but not with bipolar disorder. J Affect Disord 2014;164:33–7.
Ulrich-Merzenich G, Kelber O, Koptina A, Freischmidt A, Heilmann J, Müller J, et al. Novel neurological and immunological targets for salicylate-based phytopharmaceuticals and for the anti-depressant imipramine. Phytomedicine 2012;19:930–9.
Valkanova V, Ebmeier KP, Allan CL. CRP, IL-6 and depression: a systematic review and meta-analysis of longitudinal studies. J Affect Disord 2013;150:736–44.
Verma R, Mukerji M, Grover D, B-Rao C, Das SK, Kubendran S, et al. MLC1 gene is associated with schizophrenia and bipolar disorder in Southern India. Biol Psychiatry 2005;58:16–22.
Watanabe RM. Statistical issues in gene association studies. Methods Mol Biol 2011;700:17–36.
Wheeler HE, Dolan ME. Lymphoblastoid cell lines in pharmacogenomic discovery and clinical translation. Pharmacogenomics 2012;13:55–70.
Whyte A, Jessen T, Varney S, Carneiro AM. Serotonin transporter and integrin beta 3 genes interact to modulate serotonin uptake in mouse brain. Neurochem Int 2014;73:122–6.