

The role of lithium in modulation of brain genes: relevance for aetiology and treatment of bipolar disorder

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Abstract

Bipolar disorder is a debilitating disorder of the brain with a lifetime prevalence of 1.0 % for bipolar I, 1.1 % for bipolar II disorder and 2.4–4.7 % for subthreshold bipolar disorder. Medications, including lithium, have demonstrated efficacy in the treatment of bipolar disorder, but their molecular targets and mode of action are largely unknown. A few studies have begun to shed light on potential targets of lithium treatment that may be involved in lithium's therapeutic effect. We have recently conducted a microarray study of rat frontal cortex following chronic treatment (21 days) with lithium. Chronic treatment with lithium led to a significant (at least 1.5-fold) down-regulation of 151 genes and up-regulation of 57 genes. We discuss our results in the context of previous microarray studies involving lithium and gene-association studies to identify key genes associated with chronic lithium treatment. A number of genes associated with bipolar disorder, including *Comt* (catechol-O-methyltransferase), *Vapa* (vesicle-associated membrane protein-associated protein A), *Dtnb* (dystrobrevin β) and *Pkd1* (polycystic kidney disease 1), were significantly altered in our microarray dataset along with genes associated with synaptic transmission, apoptosis and transport among other functions.

Bipolar disorder

Bipolar disorders are a group of mood disorders that are characterized by excessive shifts in mood, resulting in recurring episodes of mania and depression [1]. Bipolar I disorder includes presence of episodes of mania (or mixed mania) and depression or mania alone, and has a lifetime prevalence of 1 % [2,3]. Bipolar II disorder refers to presence of episodes of depression and hypomania and has a lifetime prevalence of 1.1 % [2,3]. Additionally, there is a lifetime prevalence of subthreshold bipolar disorder of approx. 2.4–4.7 % [3]. Lithium is a first-line mood stabilizer used to treat bipolar disorder; however, little is known about the molecular mechanism of lithium drug action.

Microarray studies involving lithium

A few microarray studies of lithium in rodent brain have provided some clues as to potential target genes that may be involved in lithium's efficacy [4–6]. In a microarray

experiment involving juvenile mice, several synaptic vesicle genes, cytoskeletal genes, G-protein signalling and cell adhesion genes were altered in amygdala following treatment with therapeutic doses of lithium [4]. McQuillin et al. [5], in a mouse whole-brain microarray study, demonstrated that 2 weeks of lithium treatment resulted in differential expression of 121 genes, including several myelination genes, protein phosphatase genes, *per2* period gene and the gene for metabolic glutamate receptor 3 [5]. A more recent study of whole-brain mRNA from mice treated for 7 days with lithium revealed differential expression (at least 4-fold change) of 19 genes, five of which were verified by qRT-PCR (quantitative real-time PCR): *Mt3* (metallothionein 3), *Atp1a1* (ATPase Na⁺/K⁺ transporting α 1 polypeptide), *Tceb2* [transcription elongation factor B (SIII) polypeptide 2], *Psm5* (proteasome subunit β type 5) and *Gnb1* (guanine-nucleotide-binding protein β 1) [6]. Taken together, these findings demonstrate that lithium affects multiple pathways in brain, which may explain its efficacy and the underlying pathophysiology of bipolar disorder.

We recently investigated the effect of chronic administration (21 days) of lithium (50 mg/kg of body weight per day intraperitoneally, $n = 20$) on gene expression in rat frontal cortex. Chronic treatment with lithium led to the significant (1.5-fold change, $P < 0.05$) up-regulation of 57 genes and down-regulation of 151 genes in rat frontal cortex (see Supplementary Table S1 at <http://www.biochemsoctrans.org/bst/037/bst0371090add.htm>). Table 1 lists the most substantially up-regulated and down-regulated genes on the basis

Key words: bipolar disorder, catechol-O-methyltransferase (COMT), DNA microarray, frontal cortex, lithium, vesicle-associated membrane protein-associated protein A (VAPA).

Abbreviations used: ABCB1A, ATP-binding cassette, subfamily B, member 1; ATF, activating transcription factor; BMP4, bone morphogenetic protein 4; COMT, catechol-O-methyltransferase; CPLX2, complexin 2; DPC, dystrophin-associated protein complex; DRD1A, dopamine receptor D1A; DTNB, dystrobrevin β ; DTNBP1, dystrobrevin-binding protein 1; FAP, fibroblast-activation protein; HTR2A, 5-hydroxytryptamine receptor 2A; PKD1, polycystic kidney disease 1; qRT-PCR, quantitative real-time PCR; SLC5A7, solute carrier family 5 member 7; SNARE, soluble N-ethylmaleimide-sensitive fusion protein-attachment protein receptor; SNP, single nucleotide polymorphism; TAC1, tachykinin 1; VAMP, vesicle-associated membrane protein; VAPA, VAMP-associated protein A.

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Table 1 | Most substantially down-regulated and up-regulated genes in rat frontal cortex following chronic lithium treatmentAll genes altered significantly ($P < 0.05$). Data mined using MAS5, RMA and LiWong GeneData Expressionist software.

Gene product	Symbol	UniGene	Fold change	Function
CD209b antigen	<i>Cd209b</i>	Rn.138846	0.22	Miscellaneous
Lysosomal-associated membrane protein 3	<i>Lamp3</i>	Rn.19784	0.29	Miscellaneous
Fructose-6-phosphate 2-kinase/fructose-2,6-bisphosphatase	<i>Pfkfb3</i>	Rn.10791	0.30	Metabolism; energy Pathways
ATP-binding cassette, subfamily B, member 1/multidrug resistance protein 1a	<i>Abcb1a</i>	Rn.107444	0.31	Miscellaneous
KH domain-containing, RNA-binding, signal transduction-associated 2	<i>Khdrbs2</i>	Rn.154423	0.33	Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism
Early B-cell factor 1	<i>Ebf</i>	Rn.11257	0.34	Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism
v-Myc myelocytomatosis viral-related oncogene, neuroblastoma-derived (avian)	<i>Mycn</i>	Rn.81116	0.35	Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism
Catecholamine-O-methyltransferase	<i>Comt</i>	Rn.220	0.36	Metabolism; energy Pathways
Dicer1, Dcr-1 homolog (<i>Drosophila</i>)	<i>Dicer1</i>	Rn.205881	0.36	Gene silencing
Histocompatibility 2 class II antigen E α	<i>H2-Ea</i>	Rn.103146	0.36	Immune response
Tachykinin 1	<i>Tac1</i>	Rn.1920	2.62	Regulation of immune response; signal transduction
Rat platelet factor 4	<i>Pf4</i>	Rn.6800	2.29	Immune response
DEAD (Asp-Glu-Ala-Asp) box polypeptide 3, X-linked	<i>Ddx3x</i>	Rn.95841	2.25	Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism
Ns5atp9 protein	<i>Ns5atp9</i>	Rn.7233	1.97	Miscellaneous
T-cell, immune regulator 1, ATPase, H ⁺ -transporting, lysosomal V0 protein isoform A3	<i>Tcirg1</i>	Rn.12627	1.93	Transport
Activating transcription factor 2	<i>Atf2</i>	Rn.9825	1.91	Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism
FBJ murine osteosarcoma viral oncogene homologue	<i>c-fos</i>	Rn.103750	1.90	Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism
UDP-glucuronosyltransferase	<i>LOC286989</i>	Rn.11131	1.82	Miscellaneous
BM259 protein	<i>Bm259</i>	Rn.10826	1.81	Miscellaneous
Dynein, axonemal, heavy polypeptide 12	<i>Dnah12</i>	Rn.198998	1.81	Structural protein

of fold change. Genes significantly altered by lithium treatment were grouped on the basis of function (Table 1 and Supplementary Tables S1 and S2 at <http://www.biochemsoctrans.org/bst/037/bst0371090add.htm>), which revealed involvement of genes from multiple biological pathways, such as signal transduction/cell communication, immune response, transport, protein metabolism, nucleic acid regulation/metabolism and cell growth/maintenance. qRT-PCR verified magnitude and direction of change in ten of the genes of interest (Table 2).

Down-regulation of genes associated with bipolar disorder

Four of the genes from our microarray dataset {*Comt* (catechol-O-methyltransferase), *Vapa* [VAMP (vesicle-associated membrane protein)-associated protein A], *Dtnb*

(dystrobrevin β) and *Pkd1* (polycystic kidney disease 1)} have been known previously to be associated with bipolar disorder.

COMT metabolizes catecholamines [7] including dopamine [8–10]. There are two isoforms of COMT derived from the same gene: one that is soluble, and one that is membrane-bound [7]. COMT has drawn much interest as a modulator of prefrontal cortex function, cognitive abilities and the genetic disposition towards schizophrenia [7,11] and bipolar disorder [7,11–13]. An SNP (single nucleotide polymorphism) of *COMT* has been associated with poorer performance on measures of verbal memory in subjects with bipolar disorder compared with healthy controls [13]. Other studies, however, have found no association between COMT and bipolar disorder [14,15]. Using SDS/PAGE and Western blotting, we have demonstrated previously a significant reduction ($P < 0.0006$) in the 24 kDa

Table 2 | qRT-PCR results for selected genes implicated in lithium treatmentStatistical significance was determined by two-tailed *t* test.

Gene product	Symbol	Fold change	<i>P</i>
ATP-binding cassette, subfamily B, member 1/multidrug resistance protein 1a	<i>Abcb1a</i>	0.526	0.006
Bcl-2-like 1	<i>Bcl2l1</i>	0.593	0.005
Bone morphogenetic protein 4	<i>Bmp4</i>	0.598	0.025
Catecholamine-O-methyltransferase	<i>Comt</i>	0.602	0.003
Complexin 2	<i>Cplx2</i>	0.594	0.032
Dystrobrevin β	<i>Dtnb</i>	0.615	0.036
Fibroblast-activation protein	<i>Fap</i>	0.597	0.004
Polycystic kidney disease 1	<i>Pkd1</i>	0.559	0.003
S100 calcium-binding protein 11a (calizzarin)	<i>S100a11</i>	0.461	0.009
Vesicle-associated membrane protein-associated protein A	<i>Vapa</i>	0.383	6.32×10^{-6}

cytosolic isoform of COMT protein following treatment with lithium [16], supporting further our qRT-PCR data. A decrease in COMT by lithium would increase dopamine levels and enhance dopaminergic neurotransmission.

VAPA associates with VAMP1 and VAMP2 [17] and is widely expressed in brain [18]. VAPA is also required for vesicular neurotransmission, membrane fusion, protein complex assembly and cell motility [19]. Lohoff et al. [20] found two SNPs that associated with bipolar disorder; however, after permutation correction, only one showed a trend towards allelic association ($P < 0.066$). Further evidence is needed to conclusively associate VAPA with bipolar disorder. Interestingly, studies have revealed reduced levels of VAPA's binding partner, VAMP1, in subjects with bipolar disorder [21,22]. It has been hypothesized that variations in VAPA may lead to dysfunctional neurotransmission, ultimately leading to clinical phenotypes of depression and mania [20]. Overexpression of VAPA and VAPB (VAMP-associated protein B) cause retention of endoplasmic reticulum membrane proteins by impeding lateral diffusion and their incorporation into transport vesicles [23]. Thus down-regulation of VAPA by lithium may play a role in the facilitation of intracellular transport of membrane proteins. Interestingly, Youngs et al. [4] also observed down-regulation of a number of synaptic vesicle genes, including *Vamp1*, *Rims2* (encoding synaptotagmin 3) and *Stxbp1* (syntaxin-binding protein 1) in amygdala following lithium treatment. VAPA, on the other hand, was found to be increased in amygdala 2 weeks after the last lithium dose [4]. This may represent a regional difference, or the restoration of pre-clinical VAPA expression following the end of treatment.

DTNB is a component of the DPC (dystrophin-associated protein complex). The DPC consists of dystrophin and several integral and peripheral membrane proteins, including dystroglycans, sarcoglycans, syntrophins and dystrobrevin α and β . The DPC localizes to the sarcolemma, and its disruption is associated with various forms of muscular dystrophy. In brain, DTNB is found on neurons primarily in the cortex and hippocampus and it is expressed in postsynaptic membranes, suggesting a role in synaptic transmission [24]. Gaysina et al. [25] found evidence for an

association of the *DTNBP1* (dystrobrevin-binding protein 1) gene with bipolar disorder, and Talbot et al. [26] found a link between *DTNBP1* and schizophrenia.

The *Pkd1* gene encodes a member of the polycystin protein family (polycystin 1). *Pkd1* is found on chromosome 16p, a region linked to bipolar disorder, autism and epilepsy [27]. Polycystin 1 contains a large N-terminal extracellular region, multiple transmembrane domains and a cytoplasmic C-tail. It is an integral membrane protein that functions as a regulator of calcium-permeable cation channels and intracellular calcium homeostasis. Polycystin 1 is also involved in actin cytoskeleton rearrangement in response to microenvironmental cues and may be involved in synaptic remodelling and plasticity [28].

Additional genes down-regulated by lithium

Complexins are cytosolic proteins that bind preferentially to syntaxin within the SNARE (soluble *N*-ethylmaleimide-sensitive fusion protein-attachment protein receptor) complex and promote the oligomerization of SNAREs, which, if blocked, prevent vesicular release of neurotransmitters [29]. Further animal studies found that complexins are vital to transmitter release immediately before vesicle fusion [30]. CPLX2 (complexin 2) is a cytosolic protein that binds preferentially to syntaxin within the SNARE complex and promotes the oligomerization of SNAREs. *Cplx2*-knockout mice display deficits in interactive grooming behaviours and exploratory behaviour [31]. The decrease of both VAPA and CPLX2 expression following treatment with lithium, together with the study by Youngs et al. [4], suggests that lithium modulates synaptic transmission as part of its efficacy. A down-regulation of *Cplx2* by lithium may increase intracellular uptake of the SNARE complex.

The S100 superfamily consists of 22 members which share conserved structural motifs consisting of two EF-hand Ca^{2+} -binding domains connected by a hinge region [32]. S100 proteins are involved in multiple intracellular functions, including maintenance of calcium homeostasis, cytoskeletal

rearrangement, transcription and enzyme regulation [32]. S100A8/A9, S100B and S100A11 and other S100 proteins can be secreted and extracellularly exhibit cytokine-like functions related to inflammation [33,34]. S100A11 has been observed to be overexpressed in colorectal, gastric, prostate and pancreatic cancers [35]. Previous work by us and others have shown an increase in expression of S100A8, S100A9 and S100A10 in mouse or rat brain in response to chronic treatment with antidepressants and olanzapine [7,36,37]. Future studies are needed to determine whether the changes in *S100a11* gene expression observed in rat frontal cortex are medication effects or markers of inflammation. A possible explanation for lithium's effect on down-regulating S100 protein may be to exhibit anti-inflammatory and antioxidative responses in the brain.

We observed down-regulation of two genes associated with apoptosis. *FAP* (fibroblast-activation protein) is overexpressed in chronic liver disease and has been shown to promote apoptosis in two liver cell lines [38]. The down-regulation of *Fap* mRNA in rat frontal cortex in response to chronic treatment with lithium may be an anti-apoptotic mechanism. Bcl-2L1 (also known as Bcl-X) also regulates apoptosis. It codes for two isoforms, Bcl-X_S, which is pro-apoptotic and Bcl-X_L, which is anti-apoptotic [39]. This gene is important for the survival of differentiating neurons. It is possible that lithium decreases levels of the pro-apoptotic isoform Bcl-X_S in favour of Bcl-X_L to promote its anti-apoptotic effects. Bcl-2L1 can inhibit apoptosis following withdrawal of growth factors [40], and the smaller variant, Bcl-X_S, encodes a protein that inhibits the ability of Bcl-2 to enhance survival of growth factor-deprived cells [40]. Previous work has shown that lithium up-regulates Bcl-X_L [41] and Bcl-2 in frontal cortex, hippocampus and striatum [42]. It has been suggested that this action is part of its efficacy in provision of neuroprotective effect to the brain [43].

Abcb1a (ATP-binding cassette, subfamily B, member 1) codes a transmembrane protein localized to the blood-brain barrier that functions as a drug-transport pump, regulating movement of drugs across the barrier [44]. Decreasing ABCB1A may represent a feedback loop in response to lithium treatment in order to regulate the amount of lithium that may cross the blood-brain barrier.

BMP4 (bone morphogenetic protein 4) is a member of the transforming growth factor- β superfamily. The superfamily includes large families of growth and differentiation factors, which induce cartilage and bone formation and also acts in mesoderm induction, tooth development, limb formation and fracture repair. BMP4 is widely expressed in the brain and may have specialized functions in the adult brain [45], such as involvement in neural induction and synaptic plasticity. A decrease in BMP4 by lithium may result in altered dendritic remodelling.

Genes up-regulated by lithium

Dnah12 (dynein, axonemal, heavy chain polypeptide 12) was up-regulated in rat frontal cortex. Dyneins are microtubule-

based motor proteins that transport membranes in cells [46]. Up-regulation of another dynein gene, *Dnah3* (dynein, axonemal, heavy chain polypeptide 3), by paroxetine, an antidepressant, was found after 12 days of administration in rat hippocampus [47]. Disruption of dynein function results in inefficient recycling of transferrin intracellularly [48]. It is possible that lithium helps in recycling of various molecules, such as transferrin.

Fos is part of a gene family encoding nuclear transcription factors. *Fos* is expressed following stimulation of cells and during differentiation. Lithium is well known to activate *Fos* in various areas of the brain [49,50]. The current result is a confirmation of the specificity of this study.

Members of the CREB (cAMP-response element-binding protein)/ATF (activating transcription factor) family are part of signalling cascades that ultimately activate genes involved in neuronal growth and differentiation [51]. Using a rat model, Laifenfeld et al. [52] found that prolonged stress increased phosphorylation of ATF2 in prefrontal cortex. Treatment with the antidepressants desipramine and fluoxetine, reduced phosphorylation of ATF2, suggesting that ATF2 may be involved in the pathology of major depression and a potential target for therapeutic intervention [52].

Tac1 (tachykinin 1) gene produces substance P and neurokinins that are involved in multiple pathways including inflammation and the potentiation of glutamatergic excitatory synaptic transmission [53]. *Tac1*-knockout mice display reduced anxiety and depression related behaviours [54] and has been identified as a bipolar disorder candidate gene on the basis of convergent functional genomics [55].

Ddx3x (DEAD box protein 3, X-linked) was significantly up-regulated following treatment with lithium in rat frontal cortex. DEAD box proteins, characterized by the conserved motif DEAD (Asp-Glu-Ala-Asp), are putative RNA helicases. They are implicated in a number of cellular processes involving alteration of RNA secondary structure such as translation initiation, nuclear and mitochondrial splicing, and ribosome and spliceosome assembly.

Other important genes involved in neuropsychiatric illnesses

A number of genes associated with neurotransmission and psychiatric disorders were significantly altered by chronic lithium treatment as determined by microarray analysis. *SLC5A7* (solute carrier family 5 member 7) was significantly up-regulated and is a Na⁺/Cl⁻ transporter responsible for the uptake of choline for the synthesis of acetylcholine. Polymorphisms of *SLC5A7* have been associated with major depression [56]. *DRD1A* (dopamine receptor D1A) was also up-regulated by lithium treatment. DRD1A mediates the actions of dopamine intracellularly by stimulating signalling pathways via adenylate cyclase and has been shown to play important roles in cognition and prefrontal cortex activity [57]. A number of studies have shown an association between *DRD1A* polymorphisms and bipolar disorder (reviewed

in [57]). Moreover, variations in DRD1A are associated with response to lithium treatment with the G/G genotype resulting in a poorer response to lithium treatment [58]. The increase in DRD1A by lithium would increase dopamine neurotransmission. *Htr2a* (5-hydroxytryptamine receptor 2A) was significantly down-regulated following lithium treatment in rat frontal cortex and has been associated with bipolar disorder and may mediate the effects of certain antidepressants (reviewed in [3]). A decrease in HTR2A by lithium would help with improving symptoms of depression. *Syng1* (synaptogyrin 1) was also down-regulated and it encodes a membrane protein associated with synaptic vesicles and is important for neurotransmitter release. Five polymorphisms of *Syng1* have been identified and are associated with schizophrenia and bipolar disorder in an Indian population sample [59]. Also down-regulated and associated with vesicles is *Syn3* (synapsin III), encoding a phosphoprotein that is involved in neurotransmitter release. Preliminary results suggest that the SYN3-196 promoter mutation is associated with schizophrenia in Caucasians, but not African Americans [60].

Conclusions

Our results represent a pilot study examining the effect of lithium on gene expression in rat frontal cortex. We observed significant down-regulation of 151 genes and up-regulation of 57 genes involved with multiple metabolic pathways. As with other microarray studies [4–6], we observed that lithium altered the expression of genes involved in multiple biological functions. The direction and magnitude of change for ten genes was verified by qRT-PCR, including four genes that have been associated with bipolar disorder: *Comt*, *Vapa*, *Dtnb* and *Pkd1*. Our results show that lithium causes changes in levels of several important genes that may be involved in the aetiology and treatment of bipolar disorder.

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SUPPLEMENTARY ONLINE DATA

The role of lithium in modulation of brain genes: relevance for aetiology and treatment of bipolar disorder

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Table S1 | Significantly (all values $P < 0.05$) altered genes in rat frontal cortex following 21-day lithium treatment

(a) Genes down-regulated by lithium

Gene product	Symbol	UniGene	Fold change	Function
5,10-Methenyltetrahydrofolate synthetase (5-formyltetrahydrofolate cycloligase)	<i>Mthfs</i>	Rn.2215	0.60	Metabolism; energy Pathways
5-Hydroxytryptamine (serotonin) receptor 2 A	<i>Htr2a</i>	Rn.10294	0.53	Cell communication; signal transduction
A-kinase (PRKA) anchor protein 8	<i>Akap8</i>	Rn.10248	0.66	Cell communication; signal transduction
ABI gene family, member 3	<i>Abi3</i>	Rn.95169	0.61	Cell communication; signal transduction
Adducin 1 α	<i>Add1</i>	Rn.5788	0.57	Cell growth and/or maintenance
Aldo-keto reductase family 1, member B10 (aldose reductase)	<i>Akr1b10</i>	Rn.8475	0.54	Metabolism; energy pathways
α -Thalassaemia/mental retardation syndrome X-linked homologue (human)	<i>Atrx</i>	Rn.107838	0.63	Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism
Arginase 2	<i>Arg2</i>	Rn.11055	0.55	Metabolism; energy pathways
Arrestin domain containing 2	<i>Arrdc2</i>	Rn.22831	0.50	Miscellaneous
Arrestin β 2	<i>Arrb2</i>	Rn.32973	0.45	Cell communication; signal transduction
ATP-binding cassette, subfamily C (CFTR/MRP), member 8	<i>Abcc8</i>	Rn.11187	0.39	Transport
Bcl-2-like 1	<i>Bcl2l1</i>	Rn.10323	0.43	Apoptosis
Biphenyl hydrolase-like (serine hydrolase, breast epithelial mucin-associated antigen)	<i>Bphl</i>	Rn.22050	0.56	Metabolism; energy pathways
Bone morphogenetic protein 4	<i>Bmp4</i>	Rn.10318	0.50	Cell communication; signal transduction
Calcium channel, voltage-dependent, L type, α 1C subunit	<i>Cacna1c</i>	Rn.9827	0.52	Transport
Calcium/calmodulin-dependent protein kinase IV	<i>Camk4</i>	Rn.11046	0.58	Cell communication; signal transduction
Calpain 8	<i>Capn8</i>	Rn.80837	0.65	Protein metabolism
cAMP-responsive element-binding protein 3-like 1	<i>Creb3l1</i>	Rn.24541	0.64	Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism
cAMP-regulated guanine-nucleotide-exchange factor I (cAMP-GEFI)	<i>Rapgef3</i>	Rn.42899	0.51	Cell communication; signal transduction
CAP-GLY domain-containing linker protein 1	<i>Clip1</i>	Rn.22069	0.49	Cell growth and/or maintenance
Catecholamine-O-methyltransferase	<i>Comt</i>	Rn.220	0.36	Metabolism; energy pathways
CCAAT/enhancer-binding protein γ	<i>Cebpg</i>	Rn.10332	0.65	Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism
CD209b antigen	<i>Cd209b</i>	Rn.138846	0.22	Cell communication; signal transduction
CDC16 cell division cycle 16 homologue (<i>Saccharomyces cerevisiae</i>)	<i>Cdc16</i>	Rn.66098	0.53	Cell communication; signal transduction
Cell adhesion molecule 1	<i>Cadm1</i>	Rn.19928	0.63	Cell communication; signal transduction

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Table S1 | Continued

Gene product	Symbol	UniGene	Fold change	Function
Cell division cycle 25A	<i>Cdc25a</i>	Rn.11390	0.47	Cell communication; signal transduction
Cerebellar degeneration-related 2	<i>Cdr2</i>	Rn.3537	0.61	Miscellaneous
Cholinergic receptor, nicotinic, α polypeptide 5	<i>Chrna5</i>	Rn.40125	0.65	Cell communication; signal transduction
Coiled-coil domain containing 52	<i>Ccdc52</i>	Rn.138747	0.66	Miscellaneous
Colony-stimulating factor 2 receptor, β 1, low-affinity (granulocyte/macrophage)	<i>Csf2rb1</i>	Rn.42930	0.53	Cell communication; signal transduction
Complexin 2	<i>Cplx2</i>	Rn.10134	0.63	Vesicle docking
Core binding factor β	<i>Cbfb</i>	Rn.7308	0.60	Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism
Cyclin E	<i>Ccne</i>	Rn.15455	0.58	Cell communication; signal transduction
Cytoplasmic dynein heavy chain 2	<i>Dync2h1</i>	Rn.44896	0.66	Cell growth and/or maintenance
Dicer1, Dcr-1 homologue (<i>Drosophila</i>)	<i>Dicer1</i>	Rn.205881	0.36	Gene silencing
Dystrobrevin β	<i>Dtnb</i>	Rn.61275	0.44	Cell growth and/or maintenance
Early B-cell factor 1	<i>Ebf</i>	Rn.11257	0.34	Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism
ELAV (embryonic lethal, abnormal vision, <i>Drosophila</i>)-like 2 (Hu antigen B)	<i>Hub</i>	Rn.12662	0.53	Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism
Family with sequence similarity 5, member B	<i>fam5b</i>	Rn.22596	0.59	Cell growth and/or maintenance
Farnesyl diphosphate synthase	<i>Fdps</i>	Rn.2848	0.58	Metabolism; energy pathways
Ferritin, heavy polypeptide 1	<i>Fth1</i>	Rn.54447	0.50	Transport
Fibroblast activation protein α	<i>Fap</i>	Rn.82756	0.59	Cell communication; signal transduction
FMS-like tyrosine kinase 1	<i>Flt1</i>	Rn.10239	0.58	Cell communication; signal transduction
Fructose-6-phosphate 2-kinase/fructose-2,6-bisphosphatase	<i>Pfkfb3</i>	Rn.10791	0.30	Metabolism; energy pathways
FXFD domain-containing ion transport regulator 6	<i>Fxyd6</i>	Rn.839	0.63	Transport
G-protein-coupled receptor 108	<i>Gpr108</i>	Rn.203125	0.60	Cell communication; signal transduction
G-protein-coupled receptor 34	<i>Gpr34</i>	Rn.16344	0.55	Cell communication; signal transduction
γ -Aminobutyric acid (GABA _A) receptor, subunit β 1	<i>Gabrb1</i>	Rn.207157	0.57	Cell communication; signal transduction
General transcription factor IIB	<i>Gtf2b</i>	Rn.6109	0.49	Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism
Glutamic acid decarboxylase 2 (GAD65)	<i>Gad2</i>	Rn.29951	0.49	Metabolism; energy pathways
Glycophorin C (Gerbig blood group)	<i>Gypc</i>	Rn.7693	0.56	Cell growth and/or maintenance
Guanine-nucleotide-binding protein, α stimulating, olfactory type	<i>Gnal</i>	Rn.203753	0.45	Cell communication; signal transduction
Hairless protein	<i>Hr</i>	Rn.41543	0.38	Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism
Heat-shock 70 kDa protein 1A	<i>Hspa1a</i>	Rn.1950	0.37	Protein metabolism
Heparan sulfate (glucosamine) 3-O-sulfotransferase 1	<i>Hs3st1</i>	Rn.17364	0.58	Metabolism; energy pathways
High-molecular-mass neurofilament	<i>Nefh</i>	Rn.108194	0.66	Cell growth and/or maintenance
Histocompatibility 2 class II antigen E α	<i>H2-Ea</i>	Rn.103146	0.36	Immune response
Inner membrane protein, mitochondrial	<i>Immt</i>	Rn.47124	0.48	Cell growth and/or maintenance
Inositol phosphate 5 phosphatase F	<i>Inpp5f</i>	Rn.60475	0.66	Metabolism; energy pathways
Insulin-like growth factor-binding protein 6	<i>Igfbp6</i>	Rn.6431	0.52	Cell communication; signal transduction
Integrin β 3-binding protein (β 3-endonexin)	<i>Itgb3bp</i>	Rn.91426	0.58	Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism
KH domain-containing, RNA-binding, signal transduction-associated 1	<i>Khdrbs1</i>	Rn.162107	0.58	Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism
KH domain-containing, RNA-binding, signal transduction-associated 2	<i>Khdrbs2</i>	Rn.154423	0.33	Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism
KH-type splicing regulatory protein	<i>Khsrp</i>	Rn.92643	0.51	Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism
Lactamase, β 2	<i>Lactb2</i>	Rn.1263	0.46	Miscellaneous
Lamin B1	<i>Lmnb1</i>	Rn.11362	0.37	Cell growth and/or maintenance

Table S1 | Continued

Gene product	Symbol	UniGene	Fold change	Function
Latent transforming growth factor β -binding protein 4	<i>Ltbp4</i>	Rn.7961	0.56	Cell growth and/or maintenance
Lectin, galactose-binding, soluble 1	<i>Lgals1</i>	Rn.57	0.46	Immune response
Lectin, galactose-binding, soluble 8	<i>Lgals8</i>	Rn.10069	0.45	Signal transduction
Leptin receptor overlapping transcript-like 1	<i>Leprotl1</i>	Rn.94288	0.59	Cell communication; signal transduction
Low-density lipoprotein receptor-related protein3	<i>Lrp3</i>	Rn.87059	0.65	Cell communication; signal transduction
Lymphocyte cytosolic protein 1	<i>Lcp1</i>	Rn.14256	0.39	Cell communication; signal transduction
Lysosomal-associated membrane protein 3	<i>Lamp3</i>	Rn.19784	0.29	Miscellaneous
Methionine adenosyltransferase II α	<i>Mat2a</i>	Rn.41420	0.56	Metabolism; energy pathways
Methyltransferase-like 7A	<i>Mettl7a</i>	Rn.3341	0.52	Metabolism; energy pathways
Midkine	<i>Mdk</i>	Rn.17447	0.49	Cell communication; signal transduction
Mitochondrial transcription termination factor 1	<i>Mterf</i>	Rn.64629	0.45	Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism
Mitochondrial tumour suppressor 1	<i>Mtsq1</i>	Rn.95344	0.66	Cell communication; signal transduction
Mitogen-activated protein kinase kinase 2	<i>Map2k2</i>	Rn.82693	0.63	Cell communication; signal transduction
Mki67 (FHA domain)-interacting nucleolar phosphoprotein	<i>Mki67ip</i>	Rn.20901	0.63	Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism
Multidrug-resistance protein 1a	<i>Abcb1a</i>	Rn.107444	0.31	Miscellaneous
N-acylaminoacyl-peptide hydrolase	<i>Apeh</i>	Rn.11057	0.54	Metabolism; energy pathways
NADH dehydrogenase (ubiquinone) flavoprotein 3-like	<i>Ndufv3</i>	Rn.6452	0.41	Miscellaneous
Natural cytotoxicity triggering receptor 3	<i>Ncr3</i>	Rn.203206	0.40	Immune response
Nuclear fragile X mental retardation protein-interacting protein 1	<i>Nufip1</i>	Rn.154742	0.57	Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism
Nudix (nucleoside diphosphate-linked moiety X)-type motif 2	<i>Nudt2</i>	Rn.40265	0.50	Metabolism
Nudix (nucleoside diphosphate-linked moiety X)-type motif 6	<i>Nudt6</i>	Rn.83600	0.54	Regulation of cell proliferation
Peroxioredoxin 6	<i>Prdx6</i>	Rn.42	0.62	Metabolism; energy pathways
Phosphodiesterase 1C	<i>Pde1c</i>	Rn.10289	0.48	Metabolism; energy pathways
Phosphodiesterase 4A	<i>Pde4a</i>	Rn.91357	0.52	Cell communication; signal transduction
Polycystic kidney disease 1	<i>Pkd1</i>	Rn.127770	0.59	Cell-matrix adhesion
Potassium channel, subfamily K, member 3	<i>Kcnk3</i>	Rn.15536	0.46	Ion transport
Potassium voltage-gated channel, Shal-related family, member 2	<i>Kcnd2</i>	Rn.87841	0.40	Transport
Potassium voltage-gated channel, Shaw-related subfamily, member 3	<i>Kcnc3</i>	Rn.9885	0.47	Transport
Potassium voltage-gated channel, delayed-rectifier, subfamily S, member 3	<i>Kcns3</i>	Rn.10878	0.47	Transport
Prolactin-releasing hormone	<i>Prlh</i>	Rn.91303	0.57	Cell communication; signal transduction
Protein kinase D3	<i>Prkd3</i>	Rn.3990	0.50	Cell communication; signal transduction
Protein phosphatase 1, catalytic subunit, β isoform	<i>Ppp1cb</i>	Rn.39034	0.57	Cell growth and/or maintenance
Rab geranylgeranyl transferase A subunit	<i>Rabggta</i>	Rn.29434	0.42	Protein modification
RAB15, member Ras oncogene family	<i>Rab15</i>	Rn.24234	0.64	Cell communication; signal transduction
RAB34, member of Ras oncogene family	<i>Rab34</i>	Rn.98493	0.58	Cell communication; signal transduction
Radial spoke head 1 homologue (<i>Chlamydomonas</i>)	<i>Rsph1</i>	Rn.14627	0.64	Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism
Ras homologue gene family, member Q	<i>Rhoq</i>	Rn.4169	0.44	Cell communication; signal transduction
Ras, dexamethasone-induced 1	<i>Rasd1</i>	Rn.54720	0.57	Cell communication; signal transduction
Rcd1 (required for cell differentiation) homologue 1 (<i>Schizosaccharomyces pombe</i>)	<i>Rqcd1</i>	Rn.18033	0.39	Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism
Receptor accessory protein 6	<i>Reep6</i>	Rn.9353	0.55	Miscellaneous
Reticulon 4 receptor	<i>Rtn4r</i>	Rn.45686	0.59	Cell communication; signal transduction
Ribonuclease III, nuclear	<i>Rnasen</i>	Rn.41113	0.40	Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism

Table S1 | Continued

Gene product	Symbol	UniGene	Fold change	Function
Ribosomal protein s25	<i>Rps25</i>	Rn.60855	0.48	Protein metabolism
RNA terminal phosphate cyclase-like 1	<i>Rcl1</i>	Rn.22496	0.60	Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism
S100 calcium-binding protein A11 (calizzarin)	<i>S100a11</i>	Rn.104930	0.61	Cell communication; signal transduction
Sex hormone-binding globulin or androgen-binding protein (other gene product from <i>ABP</i> gene)	<i>Shbg</i>	Rn.37473	0.56	Metabolism; energy pathways
Small glutamine-rich protein with tetratricopeptide repeats 2	<i>Sgt2/Sgtb</i>	Rn.23400	0.47	Miscellaneous
Small nuclear ribonucleoprotein polypeptides B and B1	<i>Snrpb</i>	Rn.3437	0.53	Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism
Solute carrier family 2 (facilitated glucose transporter), member 4	<i>Slc2a4</i>	Rn.1314	0.60	Transport
Solute carrier family 35, member B1	<i>Slc35b1</i>	Rn.124916	0.44	Transport
Solute carrier family 5 (sodium iodide symporter), member 5	<i>Slc5a5</i>	Rn.10505	0.53	Transport
Sortilin 1	<i>Sort1</i>	Rn.11286	0.60	Cell communication; signal transduction
Sorting nexin 25	<i>Snx25</i>	Rn.16962	0.47	Cell communication; signal transduction
Sorting nexin 7	<i>Snx7</i>	Rn.29845	0.57	Miscellaneous
START domain-containing 10	<i>Stard10</i>	Rn.143765	0.55	Miscellaneous
STEAP family member 3	<i>Steap3</i>	Rn.16304	0.38	Cell communication; signal transduction
Sulfite oxidase	<i>Suox</i>	Rn.25720	0.58	Metabolism
Suppression of tumorigenicity 14	<i>St14</i>	Rn.49170	0.44	Protein metabolism
Synapse-associated protein 1	<i>Syap1</i>	Rn.63210	0.52	Cell communication; signal transduction
Synapsin III	<i>Syn3</i>	Rn.162920	0.60	Transport
Synaptogyrin 1	<i>Syng1</i>	Rn.88235	0.62	Transport
TBC1 domain family, member 10a	<i>Tbc1d10a</i>	Rn.105859	0.48	Cell communication; signal transduction
Transcribed locus		Rn.15974	0.59	Miscellaneous
Transcribed locus		Rn.2815977	0.40	Miscellaneous
Transcribed locus		Rn.209650	0.63	Miscellaneous
Transcribed locus		Rn.69724	0.60	Miscellaneous
Transcribed locus		Rn.22224	0.58	Miscellaneous
Transcribed locus		Rn.9230	0.43	Miscellaneous
Transcribed locus		Rn.38577	0.65	Miscellaneous
Transcribed locus		Rn.82343	0.45	Miscellaneous
Tropomyosin 1 α	<i>Tpm1</i>	Rn.87540	0.52	Cell growth and/or maintenance
Tropomyosin 3 γ	<i>Tpm3</i>	Rn.37575	0.54	Cell growth and/or maintenance
Troponin C type 2 (fast)	<i>Tnnc2</i>	Rn.43529	0.64	Cell communication; signal transduction
Tyrosyl protein sulfotransferase 1	<i>Tpst1</i>	Rn.144004	0.62	Metabolism; energy pathways
UDP-N-acetyl- α -D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 14	<i>Galnt14</i>	Rn.24642	0.62	Metabolism; energy pathways
Unc-84 homologue A (<i>Caenorhabditis elegans</i>)	<i>Unc84a</i>	Rn.100642	0.56	Cell growth and/or maintenance
Upstream of N-Ras	<i>Csde1</i>	Rn.3562	0.66	Regulation of gene expression, epigenetic
Uridine-cytidine kinase 2	<i>Uck2</i>	Rn.24811	0.60	Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism
Vacuolar protein sorting 45 (yeast)	<i>Vps45</i>	Rn.9316	0.52	Transport
Vesicle-associated membrane protein-associated protein A	<i>Vapa</i>	Rn.162275	0.54	Vesicle docking; transport
v-Myc myelocytomatosis viral-related oncogene, neuroblastoma-derived (avian)	<i>Mycn</i>	Rn.81116	0.35	Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism
Von Willebrand factor	<i>Vwf</i>	Rn.35561	0.59	Protein metabolism
YTH domain family 1	<i>Ythdf1</i>	Rn.16949	0.52	Miscellaneous
Zinc-finger homeobox 1b	<i>Zeb2</i>	Rn.59710	0.61	Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism
Zinc-finger protein 91	<i>Zfp91</i>	Rn.1772	0.60	Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism

Table S1 | Continued
(b) Genes up-regulated by lithium

Gene	Symbol	UniGene	Fold change	Function
Acidic (leucine-rich) nuclear phosphoprotein 32 family, member E	<i>Anp32e</i>	Rn.4268	1.50	Miscellaneous
Activating transcription factor 2	<i>Atf2</i>	Rn.9825	1.91	Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism
Aldehyde oxidase 1	<i>Aox1</i>	Rn.15681	1.59	Metabolism; energy pathways
All- <i>trans</i> -13,14-dihydroretinol saturase	<i>Rmt7</i>	Rn.55275	1.53	Vitamin metabolism
Basic helix-loop-helix domain-containing, class B2	<i>Bhlhb2</i>	Rn.81055	1.68	Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism
Bone morphogenetic protein receptor, type 1A	<i>Bmpr1a</i>	Rn.88925	1.60	Cell communication; signal transduction
Calcium channel, voltage-dependent, β 2 subunit	<i>Cacnb2</i>	Rn.10739	1.59	Transport
cAMP-responsive element-binding protein-like 2	<i>Crebl2</i>	Rn.107553	1.69	Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism
Caveolin 2	<i>Cav2</i>	Rn.81070	1.54	Cell communication; signal transduction
CD209b antigen	<i>Cd209b</i>	Rn.138846	1.88	Miscellaneous
Cell division cycle-associated 2	<i>Cdca2</i>	Rn.49950	1.56	Miscellaneous
Ceramide UDP-galactosyltransferase	<i>Ugt8</i>	Rn.9744	1.54	Metabolism; energy pathways
Cyclin D1	<i>Ccnd1</i>	Rn.22279	1.68	Cell communication; signal transduction
DEAD (Asp-Glu-Ala-Asp) box polypeptide 3, X-linked	<i>Ddx3x</i>	Rn.95841	2.25	Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism
Degenerative spermatocyte homologue 1 (<i>Drosophila</i>)	<i>Degs1</i>	Rn.34792	1.56	Energy pathways; lipid metabolism
Discoidin domain receptor [neurotrophic tyrosine kinase, receptor, type 4 (cell adhesion kinase)]	<i>Ddr1</i>	Rn.7807	1.54	Cell communication; signal transduction
Dopamine-1A receptor	<i>Drd1a</i>	Rn.24039	1.60	Cell communication; signal transduction
Dyenin, axonemal, heavy chain polypeptide 12	<i>Dnah12</i>	Rn.198998	1.81	Miscellaneous
FBJ murine osteosarcoma viral oncogene homologue	<i>c-fos</i>	Rn.103750	1.90	Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism
Fucosyltransferase 2	<i>Fut2</i>	Rn.10678	1.61	Metabolism; energy pathways
Gap junction protein, α 1, 43 kDa (connexin43)	<i>Gja1</i>	Rn.10346	1.74	Transport
Gastrin-releasing peptide	<i>Grp</i>	Rn.10930	1.74	Signal transduction
Guanine-nucleotide-binding protein (G-protein), γ 7 subunit	<i>Gng7</i>	Rn.11335	1.51	Miscellaneous
Guanine-nucleotide-binding protein, α 11	<i>Gna11</i>	Rn.21925	1.79	Cell communication; signal transduction
Inhibitor of nuclear factor κ B kinase β	<i>Ikbkb</i>	Rn.19222	1.69	Cell communication; signal transduction
JunB proto-oncogene	<i>Junb</i>	Rn.15806	1.75	Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism
Kit ligand	<i>Kitl</i>	Rn.44216	1.74	Cell communication; signal transduction
Krüppel-like factor 4 (gut)	<i>Klf4</i>	Rn.7719	1.61	Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism
Lin-7-C	<i>Lin7c</i>	Rn.44269	1.78	Cell communication; signal transduction
Matrix metalloproteinase 23	<i>Mmp23</i>	Rn.22562	1.53	Protein metabolism
Melanoma inhibitory activity 1	<i>Mia</i>	Rn.10660	1.53	Cell communication; signal transduction
MT-protocadherin	<i>Pcdh21</i>	Rn.19780	1.55	Cell communication; signal transduction
Myxovirus (influenza) resistance, homologue of murine Mx (also interferon-inducible protein IFI78)	<i>Mx2</i>	Rn.10374	1.51	Immune response
Neurofibromatosis type 1	<i>Nf1</i>	Rn.10686	1.64	Cell communication; signal transduction
Ns5atp9 protein	<i>Ns5atp9</i>	Rn.7233	1.97	Miscellaneous
Paired box homoeotic gene 6	<i>Pax6</i>	Rn.89724	1.54	Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism
Patatin-like phospholipase domain-containing 7	<i>Pnpla7</i>	Rn.162643	1.71	Metabolism; energy pathways
PDZ and LIM domain 3	<i>Pdlim3</i>	Rn.13361	1.78	Cell growth and/or maintenance
Phosphatidylinositol 3-kinase, regulatory subunit, polypeptide 1	<i>Pik3r1</i>	Rn.10599	1.68	Cell communication; signal transduction

Table S1 | Continued

Gene	Symbol	UniGene	Fold change	Function
Phosphodiesterase 10A	<i>Pde10a</i>	Rn.44869	1.58	Cell communication; signal transduction
Ras homologue enriched in brain	<i>Rheb</i>	Rn.859	1.62	Cell communication; signal transduction
Rat platelet factor 4 (PF4)	<i>Pf4</i>	Rn.6800	2.29	Immune response
Retinoid X receptor γ	<i>Rxrg</i>	Rn.40816	1.61	Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism
Small inducible cytokine A4-like	<i>ccl4l1</i>	Rn.37880	1.58	Immune response
Solute carrier family 5 (choline transporter), member 7	<i>Slc5a7</i>	Rn.44872	1.66	Transport
Solute carrier family 6 (monocarboxylic acid transporter), member 3	<i>Slc16a3</i>	Rn.10826	1.81	Transport
Tachykinin 1	<i>Tac1</i>	Rn.1920	2.62	Regulation of immune response; signal transduction
T-cell, immune regulator 1, ATPase, H ⁺ -transporting, lysosomal V0 protein A isoform A3	<i>Tcirg1</i>	Rn.12627	1.93	Transport
Thyroid hormone receptor β [avian erythroblastic leukaemia viral (v-erb-a) oncogene homologue 2]	<i>Thrb</i>	Rn.88692	1.76	Cell communication; signal transduction
Transcribed locus		Rn.44826	1.51	Miscellaneous
Transforming growth factor α	<i>Tgfa</i>	Rn.9952	1.65	Cell communication; signal transduction
Translocating chain-associating membrane protein	<i>Tram1</i>	Rn.104193	1.56	Transport
Transmembrane protein 49	<i>tmem49</i>	Rn.109048	1.61	Apoptosis
UDP-glucuronosyltransferase	<i>LOC286989</i>	Rn.11131	1.82	Miscellaneous
WD SOCS-box protein 2	<i>Wsb2</i>	Rn.4063	1.54	Protein metabolism
Wingless-related MMTV integration site 2	<i>Wnt2</i>	Rn.203764	1.61	Cell communication; signal transduction

Table S2 | Genes associated with neuropsychiatric disease significantly ($P < 0.05$) altered by lithium in rat frontal cortex as determined by microarray

AUT, autism; BPD, bipolar disorder; MDD, major depressive disorder; SCZ, schizophrenia.

(a) Genes down-regulated by lithium

Gene product	Fold change	Symbol	UniGene	Gene name	Function	Disease
5-hydroxytryptamine (serotonin) receptor 2 A	0.53	<i>Htr2a</i>	Rn.10294	1369124_at	Cell communication; signal transduction	AUT [1], SCZ [2], BPD [3], MDD [4]
α -Thalassaemia/mental retardation syndrome X-linked homologue (human)	0.63	<i>Atrx</i>	Rn.107838	1389989_at	Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism	AUT [5]
Arrestin β 2	0.45	<i>Arrb2</i>	Rn.32973	1370265_at	Cell communication; signal transduction	SCZ [6]
Bcl-2-like 1	0.43	<i>Bcl2l1</i>	Rn.10323	1370485_a_at	Apoptosis	SCZ (animal model) [7]
Benzodiazepine receptor-associated protein 1	0.59	<i>Bzrap1</i>	Rn.15974	1380450_at	Cell communication; signal transduction	Altered by antidepressant, fluoxetine [8]
Calcium channel, voltage-dependent, L type, α 1C subunit	0.52	<i>Cacna1c</i>	Rn.9827	1379157_at	Transport	BPD [9]

Table S2 | Continued

Gene product	Fold change	Symbol	UniGene	Gene name	Function	Disease
Calcium/calmodulin-dependent protein kinase IV	0.58	<i>Camk4</i>	Rn.11046	1369753_at	Cell communication; signal transduction	Decreased by lithium in hippocampus [10]
Catecholamine-O-methyltransferase	0.36	<i>Comt</i>	Rn.220	1368826_at	Metabolism; energy pathways	SCZ [11], BP [11], MDD [12]
Colony-stimulating factor 2 receptor, β 1, low-affinity (granulocyte/macrophage)	0.53	<i>Csf2rb1</i>	Rn.42930	1377671_at	Cell communication; signal transduction	SCZ [13]
Complexin 2	0.63	<i>Cplx2</i>	Rn.10134	1368584_a_at	Vesicle Docking	SCZ [14]
FXRD domain-containing ion transport regulator 6	0.63	<i>Fxyd6</i>	Rn.839	1370248_at	Transport	SCZ [15]
γ -Aminobutyric acid (GABA _A) receptor subunit β 1	0.57	<i>Gabrb1</i>	Rn.207157	1369904_at	Cell communication; signal transduction	SCZ [16]
Glutamate decarboxylase 2 (islet)	0.49	<i>Gad2 GAD65</i>	Rn.29951	1369462_at	Metabolism; energy pathways	SCZ [17], BPD [16]
Guanine-nucleotide-binding protein, α -stimulating, olfactory type	0.45	<i>Gnal</i>	Rn.57564	1394575_at	Cell communication; signal transduction	SCZ [18], BPD [18]
Heat-shock 70 kDa protein 1A	0.37	<i>Hspa1a</i>	Rn.1950	1370912_at	Protein metabolism	SCZ [19], MDD [20]
Insulin-like growth factor-binding protein 6	0.52	<i>Igfbp6</i>	Rn.6431	1372168_s_at	Cell communication; signal transduction	BPD [21]
MAD homologue 2	0.69	<i>smad2</i>	Rn.2755	1368214_at	Regulation of gene expression, epigenetic; Signal Transduction	MDD (animal model) [22]
Midkine	0.49	<i>Mdk</i>	Rn.17447	1367682_at	Cell communication; signal transduction	SCZ [23]
Multidrug-resistance protein 1a	0.31	<i>Abcb1a</i>	Rn.107444	1370465_at	Transport	BPD [24], MDD [25]
Phosphodiesterase 4A	0.52	<i>Pde4a</i>	Rn.91357	1368670_a_at	Cell communication; signal transduction	AUT [26], BPD [27]
Polycystic kidney disease 1	0.59	<i>Pkd1</i>	Rn.127770	1371029_at	Cell-Matrix Adhesion	AUT [28], BPD [28]
Ras, dexamethasone-induced 1	0.57	<i>Rasd1</i>	Rn.54720	1387908_at	Cell communication; signal transduction	AUT [29]
Reticulon 4 receptor	0.59	<i>Rtn4r</i>	Rn.45686	1369293_at	Cell communication; signal transduction	SCZ [30]
Synapsin III	0.60	<i>Syn3</i>	Rn.98839	1389836_a_at	Transport	SCZ [31]
Synaptogyrin 1	0.62	<i>Syng1</i>	Rn.88235	1396512_at	Transport	SCZ [32], BPD [33]
Farnesyl diphosphate synthase	0.58	<i>Fdps</i>	Rn.2848	1367667_at	Metabolism; energy pathways	SCZ (cell line response to clozapine) [34]
Vesicle-associated membrane protein-associated protein A	0.54	<i>Vapa</i>	Rn.40583	1397977_at	Vesicle Docking; Transport	SCZ [35], BPD [36]
Von Willebrand factor	0.59	<i>Vwf</i>	Rn.35561	1389234_at	Protein metabolism	BPD [37]

Table S2 | Continued

Gene product	Fold change	Symbol	UniGene	Gene name	Function	Disease
Ataxin 2-binding protein 1	0.67	<i>A2bp1</i>	Rn.92540	1380516_at	Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism	AUT [38]
Lysosomal-associated membrane protein 3	0.29	<i>Lamp3</i>	Rn.19784	1383145_at	Miscellaneous	MDD (decreased by escitalopram) [39]
(b) Genes up-regulated by lithium						
Activating transcription factor 2	1.91	<i>Atf2</i>	Rn.9825	1383691_at	Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism	SCZ [40], MDD (animal model) [41]
Basic helix-loop-helix domain containing, class B2	1.68	<i>Bhlhb2</i>	Rn.81055	1369415_at	Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism	BPD [42]
Ceramide UDP-galactosyltransferase	1.54	<i>Ugt8</i>	Rn.9744	1368858_at	Metabolism; energy pathways	SCZ [43], BPD [21], MDD [44]
Cyclin D1	1.68	<i>Ccnd1</i>	Rn.22279	1371150_at	Cell communication; signal transduction	SCZ [45]
Discoidin domain receptor [neurotrophic tyrosine kinase, receptor, type 4 (cell adhesion kinase)]	1.54	<i>Ddr1</i>	Rn.7807	1370216_at	Cell communication; signal transduction	SCZ [46]
Dopamine-1A receptor	1.60	<i>Drd1a</i>	Rn.24039	1368478_at	Cell communication; signal transduction	AUT [47], SCZ [48], BPD [49], MDD [50]
Fatty acid binding protein 7, brain	1.46	<i>Fabp7</i>	Rn.10014	1370024_at	Transport	SCZ [51], MDD (animal model) [52]
FBJ murine osteosarcoma viral oncogene homologue	1.9	<i>c-fos</i>	Rn.103750	1375043_at	Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism	Altered expression following lithium treatment [53,54]
Gap junction protein, α 1, 43 kDa (connexin43)	1.74	<i>Gja1</i>	Rn.10346	1369639_at	Transport	AUT [54]
Gastrin-releasing peptide	1.74	<i>Grp</i>	Rn.10930	1368611_at	Signal Transduction	MDD [55]
High mobility group box 2	1.57	<i>Hmgb2</i>	Rn.2874	1367676_at	Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism	SCZ [56]
JunB proto-oncogene	1.75	<i>Junb</i>	Rn.15806	1387788_at	Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism	SCZ (animal model) [57]
Neurofibromatosis type 1	1.64	<i>Nf1</i>	Rn.10686	1369014_at	Cell communication; signal transduction	AUT [58]
Paired box homoeotic gene 6	1.54	<i>Pax6</i>	Rn.89724	1369242_at	Regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism	AUT [59]
Phosphodiesterase 10A	1.58	<i>Pde10a</i>	Rn.44869	1370669_a_at	Cell communication; signal transduction	SCZ [60]

Table S2 | Continued

Gene product	Fold change	Symbol	UniGene	Gene name	Function	Disease
Rat platelet factor 4 (PF4) gene	2.29	<i>Pf4</i>	Rn.6800	1371250_at	Immune Response	MDD [61]
Solute carrier family 5 (choline transporter), member 7	1.66	<i>Slc5a7</i>	Rn.44872	1387543_at	Transport	MDD [62]
Tachykinin 1	2.62	<i>Tac1</i>	Rn.1920	1369309_a_at	Regulation of Immune Response; Signal Transduction	AUT [63], SCZ [16], BPD [64], MDD (animal model) [65]
Wingless-related MMTV integration site 2	1.61	<i>Wnt2</i>	Rn.12718	1386807_at	Cell communication; signal transduction	AUT [66]

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