A DNA methylation signature discriminates between excellent and non-response to lithium in patients with bipolar disorder type 1

Running title: DNA methylation and response to lithium in BD

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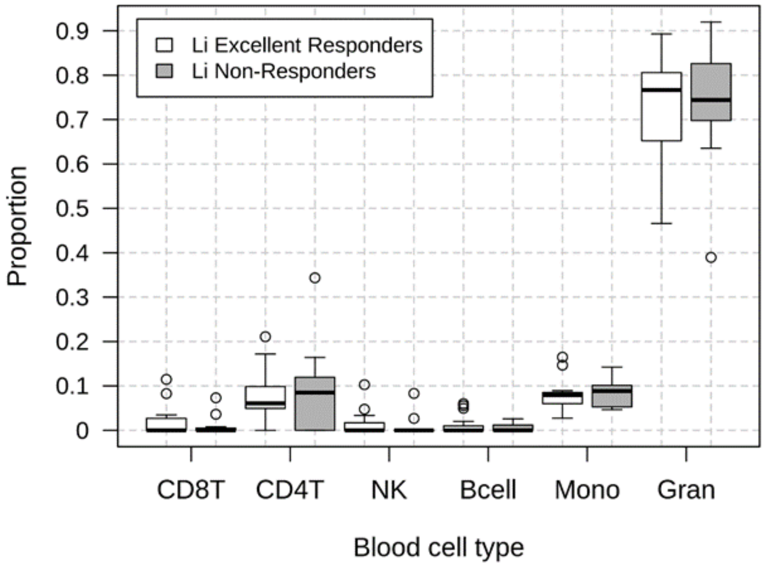
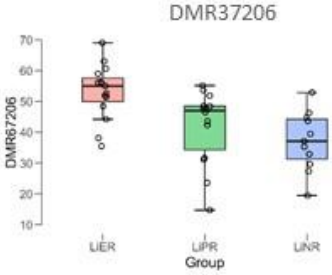
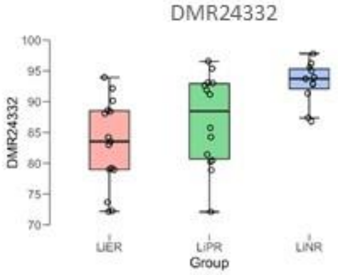
Supplementary Figure 1: Predicted proportions of T lymphocytes (CD8T and CD4T), Natural killer cells (NK), B Lymphocytes (Bcell), Monocytes (Mono) and granulocytes (Gran) in periphal blood samples from Li excellent responders and non responders.



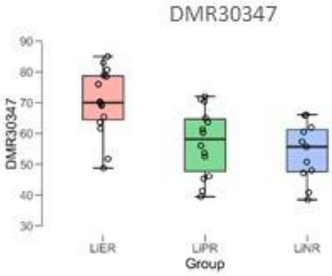
Supplementary Figure 2: Box plots of the individual methylation levels of the 7 DMRs in the 15 LiER and 11 LiNR included in the initial analysis and additional 14 LiPR. Results of the one way ANOVA (Welch's) are presented for each DMR.



F=9.99 p<0.001



F=12.12 p<0.001



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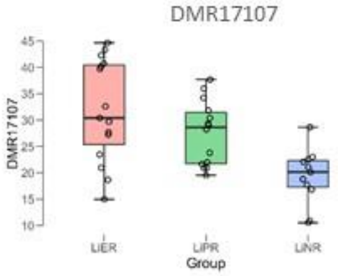

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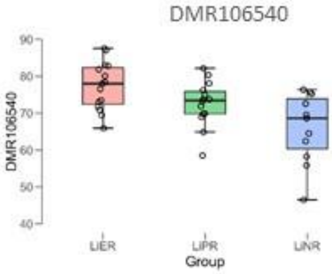
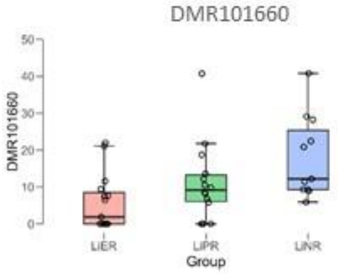
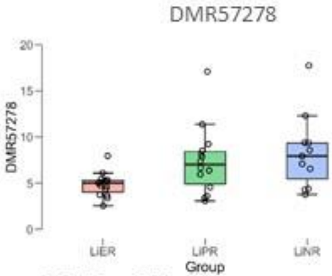


F=6.01 p=0.008

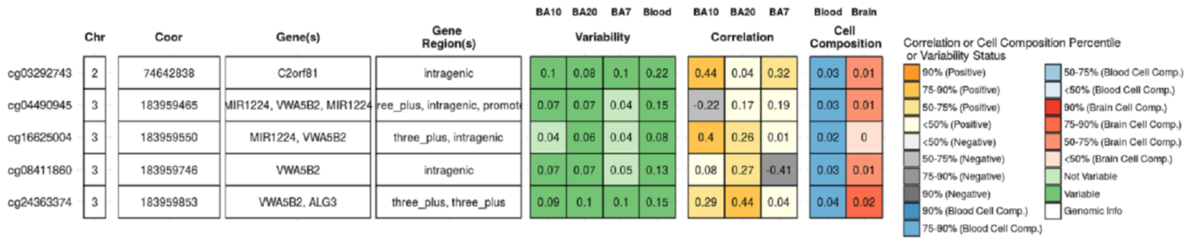


F=5.03 p=0.016



F=6.05 p=0.01

Supplementary Figure 3: Correlation (Spearman correlation value) of blood and three brain regions methylation for the five CpG present in the Blood-Brain Epigenetic Concordance (BECon) database. Values were generated from the Blood-Brain Epigenetic Concordance database ([https://redgar598.shinyapps.io /BECon/](https://redgar598.shinyapps.io/BECon/)). BA10 (Broadmann area 10, prefrontal cortex; BA7 (Broadmann area 7, parietal cortex), BA20 (Broadmann area 20, temporal cortex).



	Chr	Coor	Gene(s)	Gene Region(s)	Variability				Correlation			Cell Composition	
					BA10	BA20	BA7	Blood	BA10	BA20	BA7	Blood	Brain
cg03292743	2	74642838	C2orf81	intragenic	0.1	0.08	0.1	0.22	0.44	0.04	0.32	0.03	0.01
cg04490945	3	183959465	MIR1224, VWA5B2, MIR1224	ree_plus, intragenic, promot	0.07	0.07	0.04	0.15	-0.22	0.17	0.19	0.03	0.01
cg16625004	3	183959550	MIR1224, VWA5B2	three_plus, intragenic	0.04	0.06	0.04	0.08	0.4	0.26	0.01	0.02	0
cg08411860	3	183959746	VWA5B2	intragenic	0.07	0.07	0.05	0.13	0.08	0.27	-0.41	0.03	0.01
cg24363374	3	183959853	VWA5B2, ALG3	three_plus, three_plus	0.09	0.1	0.1	0.15	0.29	0.44	0.04	0.04	0.02

Supplementary Table 1: List of the cell type specific CpGs used for blood cell types determination

List of 600 cell type specific CpGs (Jaffe & Irizarry, Genome Biol. 2014)	CpGs used in BD methylation analysis
cg00058449	TRUE
cg00091349	TRUE
cg00103299	TRUE
cg00149213	TRUE
cg00159243	TRUE
cg00208012	TRUE
cg00219921	FALSE
cg00221794	TRUE
cg00287915	TRUE
cg00288598	TRUE
cg00366435	TRUE
cg00369058	TRUE
cg00439981	TRUE
cg00440980	TRUE
cg00445959	FALSE
cg00458681	TRUE
cg00619207	TRUE
cg00629585	TRUE
cg00644351	TRUE
cg00660167	TRUE
cg00661777	TRUE
cg00701951	TRUE
cg00702872	TRUE
cg00705730	TRUE
cg00719568	TRUE
cg00760938	TRUE
cg00782811	TRUE
cg00795812	TRUE
cg00813999	TRUE
cg00970435	TRUE
cg00984060	FALSE
cg01002223	TRUE
cg01024458	TRUE
cg01040649	TRUE
cg01154505	FALSE
cg01156249	TRUE
cg01367627	TRUE

cg01383401	TRUE
cg01447281	FALSE
cg01525879	TRUE
cg01582066	TRUE
cg01692842	TRUE
cg01710351	TRUE
cg01874152	TRUE
cg01881899	TRUE
cg01940139	TRUE
cg01987702	TRUE
cg02016178	TRUE
cg02021288	FALSE
cg02150910	TRUE
cg02212339	TRUE
cg02212836	TRUE
cg02237342	TRUE
cg02256631	FALSE
cg02321062	TRUE
cg02331830	TRUE
cg02366988	TRUE
cg02384859	TRUE
cg02402946	FALSE
cg02573468	TRUE
cg02598071	TRUE
cg02606840	TRUE
cg02661764	TRUE
cg02665297	TRUE
cg02720566	TRUE
cg02734358	TRUE
cg02821342	TRUE
cg02861441	TRUE
cg02861504	TRUE
cg02964396	FALSE
cg03055671	FALSE
cg03077671	TRUE
cg03146219	TRUE
cg03196485	TRUE
cg03209642	FALSE
cg03268893	TRUE
cg03278514	TRUE
cg03313271	TRUE
cg03318654	TRUE
cg03340036	TRUE
cg03347559	TRUE
cg03379131	TRUE
cg03419136	TRUE

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cg03538296	TRUE
cg03605454	TRUE
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cg03708221	TRUE
cg03722295	TRUE
cg03795574	TRUE
cg03861966	TRUE
cg03887528	TRUE
cg03889044	TRUE
cg03984502	TRUE
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cg04050463	FALSE
cg04153882	TRUE
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cg04453471	TRUE
cg04468741	TRUE
cg04606170	TRUE
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cg04855678	FALSE
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cg04859102	TRUE
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cg05298628	TRUE
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cg05517541	TRUE
cg05579731	TRUE
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cg08549335	TRUE
cg08560387	FALSE
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cg08635931	TRUE
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cg08698943	TRUE
cg08769189	TRUE
cg08777095	FALSE
cg08817540	TRUE
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cg09221159	TRUE
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cg09318840	TRUE
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cg09543427	TRUE
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cg27506442	TRUE
cg27507284	TRUE
cg27582527	TRUE
ch.17.480931F	FALSE

Supplementary Table 2: List of the 74 genes associated with the 111 identified DMRs (FDR 0.05)

Official gene symbol	Name	Chromosome
ACAT2	acetyl-CoA acetyltransferase 2(ACAT2)	6
ACKR3	atypical chemokine receptor 3(ACKR3)	2
ADGB	androglobin(ADGB)	6
ANKRD20A7P	ankyrin repeat domain 20 family member A7, pseudogene(ANKRD20A7P)	9
ARMC10	armadillo repeat containing 10(ARMC10)	7
ARRB2	arrestin beta 2(ARRB2)	17
ARSE	arylsulfatase E (chondrodysplasia punctata 1)(ARSE)	X
BLACE	B-cell acute lymphoblastic leukemia expressed(BLACE)	7
C2orf81	chromosome 2 open reading frame 81(C2orf81)	2
C5orf17	chromosome 5 open reading frame 17(C5orf17)	5
C6orf25	chromosome 6 open reading frame 25(C6orf25)	6
CCDC144NL	coiled-coil domain containing 144 family, N-terminal like(CCDC144NL)	17
CFDP1	craniofacial development protein 1(CFDP1)	16
CRYGEP	crystallin gamma E, pseudogene(CRYGEP)	2
CUZD1	CUB and zona pellucida like domains 1(CUZD1)	10
DLGAP2||ERICH1-AS1	DLG associated protein 2(DLGAP2)	8
DPYS	dihydropyrimidinase(DPYS)	8
DUSP22	dual specificity phosphatase 22(DUSP22)	6
EBF3	early B-cell factor 3(EBF3)	10
EEPD1	endonuclease/exonuclease/phosphatase family domain containing 1(EEPD1)	7
EIF1AXP1	eukaryotic translation initiation factor 1A, X-linked pseudogene 1(EIF1AXP1)	1
EIF2B5	eukaryotic translation initiation factor 2B subunit epsilon(EIF2B5)	3
EPHA6	EPH receptor A6(EPHA6)	3
ESPNP	espin pseudogene(ESPNP)	1
FAAP20||C1orf86	Fanconi anemia core complex associated protein 20(FAAP20)	1
FAM24B	family with sequence similarity 24 member B(FAM24B)	10
FBXL13	F-box and leucine rich repeat protein 13(FBXL13)	7
FIP1L1	factor interacting with PAPOLA and CPSF1(FIP1L1)	4
FN3K	fructosamine 3 kinase(FN3K)	17
GFPT2	glutamine-fructose-6-phosphate transaminase 2(GFPT2)	5
HLA-DRB9	major histocompatibility complex, class II, DR beta 9 (pseudogene)(HLA-DRB9)	6
HOOK2	hook microtubule tethering protein 2(HOOK2)	19
HOXA3	homeobox A3(HOXA3)	7
HOXA4	homeobox A4(HOXA4)	7
HOXA-AS2	HOXA cluster antisense RNA 2(HOXA-AS2)	7
HOXA-AS3	HOXA cluster antisense RNA 3(HOXA-AS3)	7
HOXB3	homeobox B3(HOXB3)	17
HOXB6	homeobox B6(HOXB6)	17
HOXB-AS3	HOXB cluster antisense RNA 3(HOXB-AS3)	17
IGF2BP1	insulin like growth factor 2 mRNA binding protein 1(IGF2BP1)	17
KATNBL1P6	katanin regulatory subunit B1 like 1 pseudogene 6(KATNBL1P6)	6
LINC01237	long intergenic non-protein coding RNA 1237(LINC01237)	2
LRCOL1	leucine rich colipase like 1(LRCOL1)	12
LZTS3	leucine zipper tumor suppressor family member 3(LZTS3)	20

MEI1	meiotic double-stranded break formation protein 1(MEI1)	22
MYT1L	myelin transcription factor 1 like(MYT1L)	2
NBPF13P	neuroblastoma breakpoint family member 13, pseudogene(NBPF13P)	1
NLRP1	NLR family pyrin domain containing 1(NLRP1)	17
OR2L13	olfactory receptor family 2 subfamily L member 13(OR2L13)	1
P4HA2	prolyl 4-hydroxylase subunit alpha 2(P4HA2)	5
PACRG	PARK2 coregulated(PACRG)	6
PDLIM4	PDZ and LIM domain 4(PDLIM4)	5
PKP3	plakophilin 3(PKP3)	11
PM20D1	peptidase M20 domain containing 1(PM20D1)	1
POU6F2	POU class 6 homeobox 2(POU6F2)	7
PRDM16	PR/SET domain 16(PRDM16)	1
PRRT3	proline rich transmembrane protein 3(PRRT3)	3
PRRT3-AS1	PRRT3 antisense RNA 1(PRRT3-AS1)	3
PTPRN2	protein tyrosine phosphatase, receptor type N2(PTPRN2)	7
RAD51B	RAD51 paralog B(RAD51B)	14
RALGAPA1	Ral GTPase activating protein catalytic alpha subunit 1(RALGAPA1)	14
SCRIB	scribbled planar cell polarity protein(SCRIB)	8
SOD2	superoxide dismutase 2, mitochondrial(SOD2)	6
STK32C	serine/threonine kinase 32C(STK32C)	10
TCP10L2	t-complex 10-like 2(TCP10L2)	6
TENM2	teneurin transmembrane protein 2(TENM2)	5
TMEM131	transmembrane protein 131(TMEM131)	2
TPGS1	tubulin polyglutamylase complex subunit 1(TPGS1)	19
VIPR2	vasoactive intestinal peptide receptor 2(VIPR2)	7
VWA5B2	von Willebrand factor A domain containing 5B2(VWA5B2)	3
WSCD1	WSC domain containing 1(WSCD1)	17
ZNF331	zinc finger protein 331(ZNF331)	19
ZNF714	zinc finger protein 714(ZNF714)	19
ZPBP	zona pellucida binding protein(ZPBP)	7

Supplementary Table 3: Clinical characteristics of all the patients with bipolar disorder included in the global methylation study

	LiER	**LiPR**	**LiNR**
N	15	14	11
Alda range	7-10	4-6	0-3
Ratio Male/Female	8/7	4/10	6/5
Age	49.85 +/- 11.24	46.67 +/- 9.63	46.58 +/- 6.54
BD type 1	100%	100%	100%
BMI	24.48 +/- 3.26	25.88 +/- 5.43	25.71 +/- 3.16
Smokers yes/no	6/9	8/6	6/5
Current medication			
Li yes/no	14/1	12/0	5/6
Anticonvulsants yes/no	3/12	6/8	5/6
Atypical antipsychotic yes/no	0/15	6/8	7/4
Antidepressants yes/no	3/12	4/10	4/7
Number of psychotropic drugs 1/2/3	11/3/1	0/11/3	3/4/4

Supplementary Table 4: Number of CpGs captured and average read depth of each of the CpGs per sample.

sample	nb_CpGs	mean_coverage
GAN-001-620	3686657	17.89
GAN-001-621	3684864	15.81
GAN-001-628	3686607	18.34
GAN-007-013	3686703	17.53
GAN-007-018	3685961	15.37
GAN-007-020	3686832	18.19
GAN-007-022	3679576	14.65
GAN-007-040	3685557	16.65
GAN-007-047	3686785	18.71
GAN-007-048	3686755	18.26
GAN-007-055	3685091	20.62
GAN-007-057	3686682	19.26
BP-440	3686649	18.2
BP-516	3678799	11.62
BB-204	3686560	17.94
BB-205	3686367	17.11
GAN-001-627	3686135	17.57
GAN-007-017	3686940	18.67
GAN-007-024	3682032	16.37
GAN-007-027	3686195	17.15
GAN-007-035	3686793	18.6
GAN-007-036	3686476	17.04
GAN-007-043	3683749	18.65
GAN-007-044	3674526	9.7
GAN-007-054	3686457	17.75
GAN-007-058	3684267	14.15
GAN-007-062	3687031	20.18
BP-231	3686061	17.54