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Data in Brief

Transcriptional profiling of MEF2-regulated genes in human neural progenitor cells derived from embryonic stem cells

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ABSTRACT

The myocyte enhancer factor 2 (MEF2) family of transcription factors is highly expressed in the brain and constitutes a key determinant of neuronal survival, differentiation, and synaptic plasticity. However, genome-wide transcriptional profiling of MEF2-regulated genes has not yet been fully elucidated, particularly at the neural stem cell stage. Here we report the results of microarray analysis comparing mRNAs isolated from human neural progenitor/stem cells (hNPCs) derived from embryonic stem cells expressing a control vector versus progenitors expressing a constitutively-active form of MEF2 (MEF2CA), which increases MEF2 activity. Microarray experiments were performed using the Illumina Human HT-12 V4.0 expression beadchip (GEO#: GSE57184). By comparing vector-control cells to MEF2CA cells, microarray analysis identified 1880 unique genes that were differentially expressed. Among these genes, 1121 genes were up-regulated and 759 genes were down-regulated. Our results provide a valuable resource for identifying transcriptional targets of MEF2 in hNPCs.

Specifications	
Organism/cell line/tissue	Homo sapiens/ human neural progenitor cells derived from embryonic stem cells (hNPCs)
Sex	N/A
Sequencer or array type	Microarray: Illumina HumanHT-12 V4.0 expression beadchip
Data format	Raw and processed
Experimental factors	hNPCs expressing control vector versus constitutively-active MEF2 (MEF2CA)
Experimental features	We performed a microarray analysis to identify genes differentially expressed in hNPCs expressing MEF2CA versus control vector
Consent	N/A
Sample source location	La Jolla, CA, USA

Direct link to deposited data

Deposited data can be found in the Gene Expression Omnibus (GEO) database: http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE57184

Experimental design, materials and methods

Culture and transfection of human neural progenitor cells (hNPCs) derived from embryonic stem cells

We cultured H9 human embryonic stem cells (WiCell Research Institute) and then induced neural differentiation into neural progenitor cells (hNPCs), as previously described [1]. We transfected the hNPCs with control vector- or constitutively active MEF2 (MEF2CA)-tdTomato mammalian expression constructs by electroporation using the human stem cell Nucleofector® kit, according to the manufacturer's instructions (Lonza/Amaxa Biosystem). On the third day after transfection, the cells were incubated with Annexin V-FITC, according to manufacturer's instructions (BD Pharmingen). Next, tdTomato-positive cells and Annexin V-FITC-negative cells were sorted and selected on a FACSVantageSE DiVa (BD Biosciences) with a 100 μm nozzle at 13 psi.

tdTomato and Annexin V-FITC were excited at 488 nm and detected with standard PE and FITC emission filters, respectively.

RNA extraction, purification, and quality verification

We extracted total RNA from transfected hNPCs using Trizol Reagent and the PureLink™ RNA Mini Kit, according to the manufacturer's

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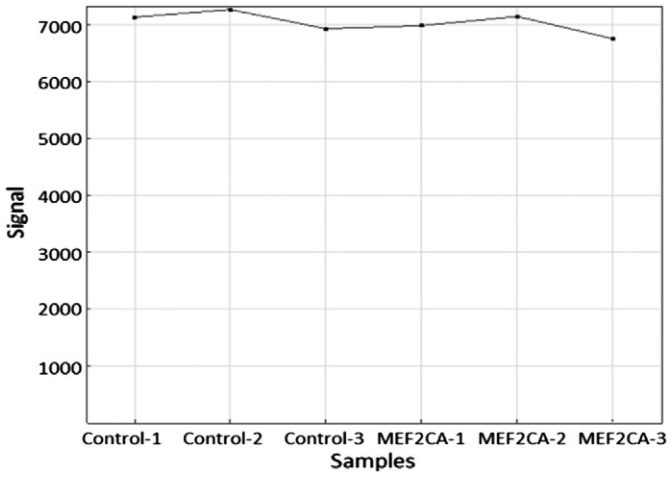

Fig. 1. GenomeStudio control summary plot. Signal intensity values (*y*-axis) of hybridization controls are consistently high across all six samples of control-1, -2, -3 and MEF2CA-1, -2, -3 (*x*-axis).

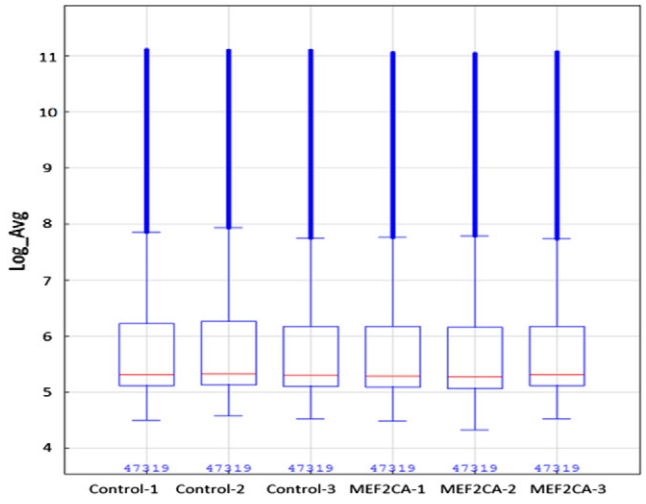

Fig. 2. Logarithmic box plot of mean signal across all samples. Mean signal intensity of all assays is plotted for each of six samples (control-1, -2, -3 and MEF2CA-1, -2, -3) (*x*-axis). A complete view of median values, percentile and the outlier points (thick vertical blue lines) of all samples is illustrated with a log Avg signal plot.

instructions (Invitrogen). After checking RNA concentration and purity on a NanoDrop 2000c (Thermo Fisher Scientific), RNA quality and quantity were further validated using an Experion Automated Electrophoresis Station and Experion RNA Analysis Kits (BioRAD Laboratories).

mRNA profiling by microarray analysis and data processing

We prepared labeled cRNA from 500 ng of RNA using the Illumina® RNA amplification kit (Ambion/ Life Technologies). We then hybridized the labeled cRNA (750 ng) overnight, at 58 °C, to HumanHT-12 Expression BeadChips (>46,000 gene transcripts; Illumina), following the manufacturer's instructions. We subsequently washed and developed BeadChips with fluorolink streptavidin-Cy3 (GE Healthcare) and used an Illumina BeadArray Reader to scan the BeadChips. We then collected and analyzed the microarray data as follows: we used the software tool GenomeStudio V2011.1 (Illumina) for gene expression quantification and its in-built plotting features for data quality control (QC), including Control Summary Plot (Fig. 1) and Box Plot (Fig. 2). We found that all 6 samples (control-1,-2, -3 and MEF2CA-1, -2, -3) were of good quality according to GenomeStudio QC guidelines [2]. The sample probe text file generated from GenomeStudio was processed using Genespring GX 11.5 (Agilent Technologies) and probes with detection *p*-values ≤0.05 were used for further statistical analysis. Log2 transformation was applied to probe level intensities of all 6 samples in order to generate identical distributions for comparison, which was then followed by quantile normalization [3]. Statistical significance of the differential expression of genes between control and MEF2CA samples was determined by Student's unpaired *t test*. The *p*-values were corrected via application of the Benjamini and Hochberg false discovery rate (FDR) algorithm [4]. The extent and direction of differential expression between the groups were determined by calculating a fold change value (Fig. 3). A fold change of ≥1.5 and an FDR-adjusted *p*-value of ≤0.05 were used as criteria to indicate differential expression between the two groups. We list the identified 1121 up-regulated and 759 down-regulated differentially expressed genes in Table 1.

Discussion

Here we describe the genome-wide transcriptional profiling of MEF2-regulated genes in hNPCs derived from human embryonic stem cells. This data set is the first microarray analysis to identify target genes that are differentially expressed and regulated by MEF2 in hNPCs. MEF2 transcription factors are known to be neurogenic and anti-apoptotic; thus, their transcriptional targets in neural

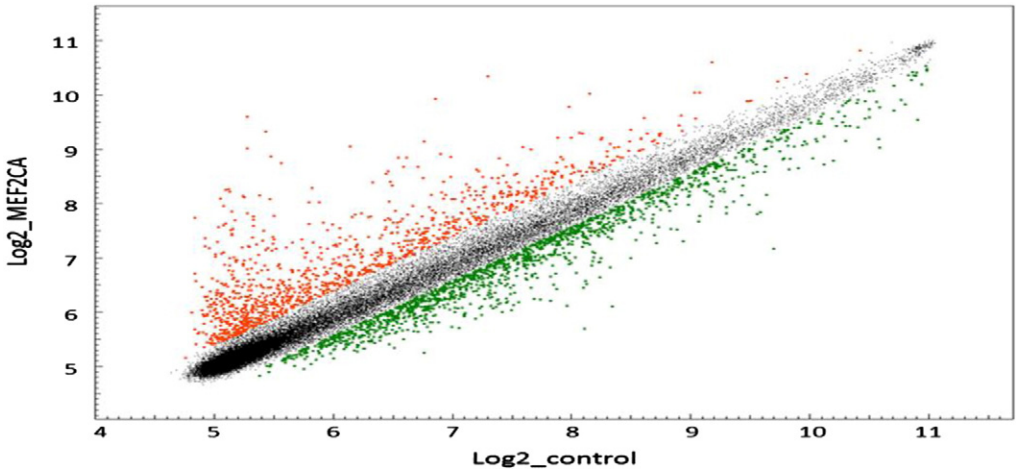

Fig. 3. Scatter plot of relative gene expression between control and MEF2CA samples. The red dots and green dots represent 1.5 fold up-regulated and down-regulated genes (adjusted $p \leq 0.05$), respectively.

Table 1
A list of differentially expressed genes in cells expressing MEF2CA compared with control.

List of differentially expressed genes (adjusted $p \leq 0.05$) with fold change ≥ 1.5 identified from microarray analysis	
1121 up-regulated genes	759 down-regulated genes
A2M, AADACL1, ABCA12, ABCA13, ABCA6, ABHD3, ABI1, ABI2, ABLIM1, ACAD11, ACADM, ACHE, ACSL1, ACTA1, ACTA2, ACTC1, ACTG2, ACTN2, ACTR3B, ACYP2, ADAM10, ADAM23, ADAMTS8, ADAMTSL2, ADAP2, ADARB1, ADCY6, ADIG, ADK, AFAP1L1, AFAP1L2, AGL, AGPAT5, AGT, AGTPBP1, AHNAK, AKAP7, AKNAD1, AKR1B1, AKR1B10, ALCAM, ALDH1A1, ALDH3B2, ALDH4A1, AMBN, AMY1B, AMY2A, AMY2B, ANGPT1, ANGPTL6, ANK1, ANK3, ANKMY1, ANKMY2, ANKRD13A, ANKRD17, ANKRD34A, ANKRD35, ANKRD46, ANKRD55, ANKS1B, ANTXR2, AOX1, AP1S2, APCDD1, APLNR, APLP2, APOBEC2, AQP1, ARHGAP15, ARHGAP24, ARHGAP25, ARHGDIB, ARHGEF17, ARID3A, ARID5B, ART3, ASB3, ASB5, ASB7, ASGR2, ASPH, ATF3, ATP1B1, ATP1B2, ATP1B3, ATP2A2, ATP5I, ATP5J, ATP6V1A, ATP8B4, ATXN2, AVPI1, B3GALNT2, B3GALT2, B3GNT2, B4GALT4, BACH2, BAI3, BARD1, BAX, BBS7, BCAS4, BMP2K, BOLL, BPNT1, BRD8, BRE, BRP44L, BSN, BTG1, BVES, C10orf10, C10orf11, C10orf76, C10orf96, C12orf26, C12orf51, C12orf59, C12orf60, C14orf37, C1orf112, C1orf117, C1orf198, C1orf218, C1orf71, C21orf34, C21orf7, C2orf40, C2orf71, C2orf86, C3orf32, C3orf38, C3orf39, C3orf45, C3orf52, C3orf70, C4orf22, C4orf34, C4orf37, C5orf13, C5orf23, C5orf24, C5orf32, C5orf51, C6orf124, C6orf167, C6orf94, C7orf41, C7orf53, C8orf34, C8orf45, C9orf5, CABC1, CACNG6, CALD1, CAMK2A, CAND2, CAPS2, CASC1, CASC3, CASP3, CASQ1, CASQ2, CASZ1, CCDC123, CCDC148, CCDC150, CCDC88A, CCDC91, CCL3, CCL3L1, CCL3L3, CCNB1IP1, CCNC, CCNDBP1, CCNYL1, CD109, CD1D, CD302, CD36, CD55, CD79A, CD97, CDC14B, CDH17, CDH5, CDNF, CDS1, CDS2, CENTA1, CEP290, CEP350, CEPT1, CFHR5, CHCHD10, CHIC2, CHST12, CHST7, CITED2, CKAP5, CKB, CKMT2, CLCNKA, CLSTN1, CLUL1, CLYBL, CNNM2, CNOT4, CNOT6L, CNTN1, COBL, COBLL1, COL10A1, COL11A2, COL13A1, COL24A1, COL4A6, COL9A1, COL9A2, COMMD6, CORO6, COX6A2, CPE, CPEB3, CPEB4, CPNE3, CPNE8, CRIM1, CRISPLD1, CRMP1, CRY1, CRYAB, CSDC2, CSRNP3, CSRP3, CTAGE5, CTGF, CUTL1, CX3CR1, CXCL13, CYBASC3, CYP20A1, CYP26B1, CYP46A1, CYP4X1, CYR61, CYSLTR1, CYTH3, DAAM2, DACH1, DACT1, DACT3, DAG1, DBNDD2, DCAF16, DCDC5, DCLK1, DDAH1, DDIT4L, DDN, DDX50, DENND1B, DENND2C, DENND3, DENND5B, DET1, DGKB, DGKD, DGKI, DHRS7C, DHX29, DIP2B, DIRC2, DKFZP586I1420, DKFZP781G0119, DLG2, DMC1, DMD, DNAI1, DNAJA4, DNAJB2, DNAJC12, DNAJC27, DNHD1, DNHD2, DNM3, DTWD2, DUSP13, DUSP14, DUSP28, DYNC1I1, DYNC2H1, DYRK3, DYRK4, DYSF, EAF2, EBI2, ECHDC2, EEF1A2, EEPD1, EFCAB7, EFCBP1, EFHB, EFHD1, EFR3A, EGF, EGFL6, EGFR, ELA1, ELK4, EMCN, ENAH, ENAM, ENDOD1, ENG, ENO3, ENPEP, ENPP3, ENPP4, ENTHD1, ENTPD4, EPDR1, EPHA4, EPHA5, EPHX1, EPS15, ERBB3, ERO1L, ESRRG, ETNK1, ETS2, EXOC6, EYA1, FABP3, FABP4, FAM108B1, FAM124B, FAM134B, FAM135A, FAM13A, FAM162B, FAM184A, FAM188A, FAM3C, FAM46B, FAM59A, FAM62B, FAM65B, FAM69A, FBXO15, FBXO3, FBXO33, FBXO38, FBXW7, FER, FGD6, FGF1, FGF20, FHL5, FHOD3, FIG4, FILIP1, FLJ11795, FLJ21986, FLJ22184, FLJ32310, FLJ45244, FLJ90650, FLRT3, FMN2, FNBP1L, FNDC1, FNDC3A, FOS, FOSB, FOXA1, FOXA2, FRAS1, FRMD3, FRY, FRYL, FRZB, FSD2, FSIP1, FUCA1, FXR1, FZD4, FZD7, GAD1, GADD45A, GALNT11, GAMT, 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IRAK2, IRF1, IRF7, IRF9, IRX3, ISG15, ISG20, ISLR2, JUN, KBTBD9, KCNG1, KCNIP3, KCNJ6, KCNK2, KCNQ2, KCTD12, KDELR3, KIAA0101, KIAA0247, KIAA1217, KIAA1324, KIF11, KIF18A, KIF20A, KIF22, KIF26B, KIF2C, KIF4A, KLHL14, KLHL29, KLRC2, KNTC1, LAMA1, LAMA4, LAMC2, LAP3, LDB2, LEF1, LGALS3BP, LHFPL2, LIF, LIFR, LIMK2, LIN28B, LINGO2, LIPG, LMCD1, LOC100129076, LOC100129681, LOC100132535, LOC100133012, LOC100133171, LOC100133489, LOC100134304, LOC100134361, LOC100134424, LOC201725, LOC387934, LOC392437, LOC399959, LOC401720, LOC439949, LOC441019, LOC642956, LOC643296, LOC645166, LOC649025, LOC649095, LOC652608, LOC652683, LOC652968, LOC654096, LOC728473, LOC729009, LOC729964, LOC730101, LOC730413, LOC731895, LPAR1, LRFN5, LRIG3, LRRC17, LSAMP, LTBP2, LUM, LXN, LY6E, LY96,MAD2L1, MAFB, MAFF, MAGEH1, MAP3K12, MATN2, MCM10, MCM2, MCM3, MCM4, MCM7, MEOX1, MGC16121, MGC24103, MGC87042, MGP, MICAL2, MIR155HG, MIR185, MIR302C, MME, MMP1, MMP10, MMP13, MMP14, MMP25, MMP9, MN1, MOCOS, MT1A, MT1G, MT2A, MTE, MX1, MX2, MXRA5, MYB, MYC, MYO19, NAMPT, NBL1, NCAM2, NCAPG, NCOA7, NDE1, NEK2, NELL2, NFE2L3, NFIX, NFKBIE, NINJ2, NKD2, NKX3-1, NLGN4X, NOVA1, NPL, NPTX2, NT5E, NTM, NTNG1, NUF2, NUPR1, OAF, OAS1, OAS2, OAS3, ODZ4, OGN, OIP5, OKL38, OLFML2B, OMD, ORC6L, OSR2, P4HA2, P8, PALMD, PANX2, PAPPA, PARP10, PARP12, PARP14, PARP2, PARP9, PAWR, PBK, PDE4B, PDGFD, PDGFRA, PDGFRL, PDIA5, PDLIM3, PDXK, PECAM1, PEG10, PFKFB3, PGF, PGM2L1, PHLDA1, PKMYT1, PKNOX2, PLAU, PLAUR, PLCH1, PLD1, PLEKHA4, PLEKHF1, PLEKHH2, PLSCR1, PLXNC1, PNMA2, PODXL, POLA2, POLQ, POSTN, POU3F2, PPAP2B, PPEF1, PPFIBP1, PPIL5, PRC1, PRDM8, PRG4, PRIC285, PRIM1, PROS1, PRR11, PRRX2, PSCD1, PSMB8, PSMB9, PSME2, PTGER4, PTGES,

Table 1 *(continued)*

List of differentially expressed genes (adjusted $p \leq 0.05$) with fold change ≥ 1.5 identified from microarray analysis	
1121 up-regulated genes	759 down-regulated genes
RAB3GAP1, RAB4A, RAD23B, RALGAPA1, RAP2A, RAPGEF2, RARB, RASA2, RASGRP2, RASGRP3, RASL12, RBM20, RBM46, RBM9, RBMS3, RDH12, RDH5, REEP1, RELN, RERG, RERGL, REV1, RFPL1S, RFTN1, RFTN2, RGS20, RHCE, RHEB, RHOBTB1, RHOBTB3, RHOQ, RHPN2, RICH2, RIOK1, RIOK3, RN5S9, RN7SK, RNASEN, RNF103, RNF11, RNF115, RNF141, RNF17, RNPC3, RPA4, RPS29, RRAGD, RRAS2, RSRC1, RTN2, RTN4, RTTN, RUNDC3B, RYR1, S100A10, SAMD4A, SBK1, SCAMP1, SCARNA11, SCARNA13, SCARNA14, SCARNA21, SCARNA8, SCHIP1, SDC2, SDCBP, SDHC, SECISBP2L, SEH1L, SEMA4D, SEMA5A, SEMA6C, SEPP1, SEPSECS, SEPT4, SEPT5, SEPT7, SEPW1, SERPINB7, SERPINH1, SERTAD2, SETBP1, SFRS2IP, SFTA2, SGCG, SH2D3C, SH3RF3, SHISA2, SHRM, SHROOM3, SIPA1L2, SLC12A2, SLC16A3, SLC16A7, SLC17A2, SLC20A2, SLC22A11, SLC22A2, SLC23A2, SLC25A14, SLC25A34, SLC25A4, SLC26A3, SLC26A6, SLC29A1, SLC2A11, SLC2A12, SLC35F5, SLC40A1, SLC41A1, SLC7A8, SLC9A9, SLIT2, SLITRK5, SLMO1, SLU7, SMCHD1, SMEK2, SMG1, SMOC1, SMYD1, SNAP25, SNAPC1, SNORA12, SNORA79, SNORD3A, SNORD3C, SNORD3D, SNTB2, SNTG1, SNX25, SNX27, SOCS2, SOD3, SORBS2, SORT1, SOS1, SOSTDC1, SPAG16, SPAG6, SPATA17, SPATA5, SPATA9, SPC25, SPHAR, SPIB, SPINT2, SPOCK1, SPPL2A, SRFBP1, SRRM4, SSFA2, ST3GAL6, ST6GAL1, ST7, STARD7, STIM1, STK3, STK38, STK38L, STOM, SUMF1, SUMO3, SUPT3H, SUSD1, SYNC1, SYNM, SYNPO2, SYNPO2L, SYPL2, SYT1, SYT17, SYT4, SYTL2, SYTL4, TACC2, TACSTD2, TAF1B, TAF7L, TAGLN, TAPT1, TBC1D15, TBXAS1, TCAP, TDRD5, TDRD9, TESK2, TG, THADA, TIAF1, TIAM2, TIGD4, TJP2, TMC6, TMC7, TMEM117, TMEM119, TMEM144, TMEM173, TMEM2, TMEM30B, TMEM35, TMEM38B, TMEM47, TMOD1, TMPRSS11A, TMTC1, TNFAIP6, TNFRSF11B, TNMD, TNNC1, TNNI3K, TOB1, TOP2B, TOR1AIP2, TOX3, TPD52L1, TRAK1, TRAPPC9, TRIM29, TRIM33, TRPC1, TRPC6, TRPM4, TSC22D2, TSGA10, TSPAN13, TSPAN3, TSPAN7, TUBB6, TUSC3, TWSG1, TXNDC11, TXNDC12, TXNDC16, TYRP1, UACA, UBA6, UBE2E1, UBE2H, UBE2J1, UBR3, ULK4, USP13, USP6NL, UTP11L, VBP1, VCL, VCX, VCX2, VCX3A, VCX-C, VCY, VEZT, VGLL2, VNN2, VOPP1, VPS26B, VTCN1, WDFY3, WDR17, WDR37, WDR62, WEE2, WFDC1, WFS1, WIPF3, WNT5B, WWC1, XIRP1, XKR6, YIPF7, YPEL5, ZAK, ZBTB20, ZC3H12C, ZCCHC11, ZDHHC17, ZFC3H1, ZFP36, ZNF280C, ZNF30, ZNF330, ZNF364, ZNF385B, ZNF533, ZNF650, ZNF81, ZNRF2, ZRANB1, ZSWIM6	PTGIS, PTGS2, PTHLH, PTPRE, PTPRU, PTTG1, PTTG3P, RAB22A, RAB27A, RAB7B, RAD51AP1, RAD54L, RANGAP1, RARRES2, RARRES3, RASL10A, RBBP4, RBBP8, RDH10, RELB, REM1, RGMB, RGS17, RGS4, RHOJ, RHOU, RIPK2, ROR2, RPL22L1, RPL36A, RRM1, RRM2, RSAD2, RSPO3, RUNX2, S100A13, S1PR3, SAMD9, SAMD9L, SCARA3, SCG5, SCN9A, SCXA, SDC1, SEC14L2, SEL1L3, SELM, SEMA3C, SEMA7A, SEPT3, SERPINA3, SERPING1, SERTAD4, SFRP1, SFRP2, SGK, SGK1, SGPP2, SH3PXD2B, SHANK3, SHMT2, SIK1, SLAMF8,SLC12A8, SLC15A3, SLC16A9, SLC1A3, SLC20A1, SLC22A17, SLC22A4, SLC25A24, SLC2A5, SLC31A2, SLC35F2, SLC39A14, SLC43A3, SLC5A6, SLC6A9, SLC7A5, SLC7A7, SNAI2, SOD2, SOX3, SOX9, SP100, SP110, SPANXE, SPARC, SPIN4, SPON1, SPP1, SPSB1, SRGN, SRPX2, SSBP4, SSX2IP, STAT1, STAT2, STC1, STEAP1, STEAP2, STIL, STOX2, STRA6, STXBP6, SULF1, SULF2, SYT7, TAC1, TAC3, TACC3, TAP1, TAP2, TAPBP, TCEAL7, TCF21, TDO2, TFF3, TFPI2, TGFB3, TGFBR2, TGM2, THBS4, TIMP3, TJAP1, TK1, TMEM154, TMEM158, TMEM163, TMEM16A, TMEM217, TMEM4, TMEM90B, TNC, TNFAIP3, TNFRSF10B, TNFRSF19, TNFRSF8, TNFSF10, TNFSF11, TNFSF13B, TNFSF9, TNIP3, TNPO1, TOP2A, TPR, TPX2, TRAM2, TREM1, TRIB3, TRIM15, TRIM22, TRIM5, TRIM9, TRIP13, TROAP, TSHZ2, TSHZ3, TSKU, TSPAN6, TXNIP, TYMS, UAP1, UBA7, UBASH3B, UBE2C, UBE2L6, UBE2T, UPP1, USP1, USP18, VANGL2, VARS, VASH1, VAT1L, VCAM1, VCAN, VEGFA, VGF, VRK1, WARS, WEE1, WNT5A, XAF1, XRCC3, ZMIZ1, ZNF365, ZNF697, ZP4, ZSWIM4, ZWILCH

progenitors that mediate these effects are of great biological interest. Accordingly, our results reveal that MEF2 target genes are enriched in pathways involved in nervous system development and function [5]. Recently, dominant mutations in *MEF2C* (5q14.3 microdeletions) resulting in haploinsufficiency have been linked to autism spectrum disorder (ASD) in multiple human cases [6–8]. Additionally, transcriptome analyses of human ASD brains have identified *MEF2C* as a "node" connecting various genes affected in autism [9,10]. Therefore, the profiling of transcriptional targets of MEF2 at the neural stem cell stage, as studied here, may reveal potential therapeutic targets for ASD.

Conflict of interest

The authors declare no conflicts of interest.

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