

## **Supplementary data:**

### **Suppl. Figure 1: Spontaneous motor activity of DM at ages of 3 to 18 months.**

Documentation of spontaneous open-field behaviour as the most sensitive and reliable measure of abnormal movements in PD mouse models revealed highly significant marked reductions of horizontal activity, vertical activity, and stereotype movements for the DM mice relative to their appropriate WT controls, already at the age of 3 months (columns at the left side). While this early onset low exploration activity of DM animals remained quite constant across their lifespan, the corresponding F1-hybrid controls showed later age-progressive reduction in spontaneous motor activity.

### **Suppl. Figure 2: pSer129-SNCA immunohistochemistry of DM mice at ages 15-17 months.**

Bright field immunohistochemical stainings of pSer129-SNCA-immunoreactivity were performed in old DM mice with paralysis (A-C) or without paralysis (D/E). In paralytic DM animals, (A) thoracic / cervical levels of the spinal cord showed milder stages of inclusion formation (black arrows), (B) motor cortex showed discrete aggregation pathology (black arrows), while (C) striatum remained free of detectable pathology. In non-paralytic old DM mice, (D) the lumbar spinal cord showed mild inclusion pathology with only few immunopositive neurites (black arrow), and (E) the ventral tegmental area of the midbrain also showed only discrete aggregation (black arrow).

### **Suppl. Figure 3: Immunohistochemistry of *Pink1*<sup>-/-</sup> mice at ages 15-17 months.**

Bright field immunohistochemical stainings were performed in age-matched *Pink1*<sup>-/-</sup> spinal cord as a control for Figure 4 spinal cord (upper panels) and for Figure 5 midbrain (lower panels). Protein aggregation was not detected by antibodies against pSer129-SNCA, p62 or ubiquitin.

### **Suppl. Figure 4: Double immunofluorescence in DM midbrain beyond age 1 year demonstrates aggregates in non-dopaminergic cells.**

The colocalization with TH as a marker of midbrain dopaminergic (DAergic) neurons in the substantia nigra pars compacta (SNc) and the ventral tegmental area (VTA) was assessed. The 4B12 antibody detects human

alpha-synuclein selectively and demonstrates transgenic overexpression with nuclear staining throughout the midbrain DAergic neurons (A-C, white arrows). However, the pSer129-SNCA staining shows the protein aggregation to occur preferentially in proximity rather than in DAergic SN / VTA neurons (D-F). The p62 staining shows also protein aggregates again in neurons adjacent to DAergic cells (G-I). Similarly, ubiquitin staining in spite of high background immunoreactivity localizes the protein aggregates mostly outside the DAergic neurons (J-L). In low magnifications of all three stainings, the aggregates formed in a band of neurons and neurites just dorsal to the SN / VTA line of DAergic nerve cells.

**Suppl. Figure 5: Double immunofluorescence in DM midbrain beyond age 1 year demonstrates aggregates to occur not in astrocytes, but in neurons.**

The pSer129-SNCA staining in the VTA of aged DM mice was assessed by double immunofluorescence for colocalization with markers of glial and neuronal differentiation. GFAP (glial fibrillary acidic protein) as a marker of astrocytes clearly was not present in the cells affected by aggregates (A-C), while NeuN (neuronal nuclear antigen Rbfox3) as a general marker of neurons did colocalize with these cells (D-F, white arrows). Parvalbumin staining as a marker of interneurons produced immunoreactivity in multiple affected cells (G-I, white arrows), while GAD65 (glutamate decarboxylase encoded by *GAD2*) as a marker of GABAergic neurons were not present in the cells with aggregates (J-L), and VGLUT2 (vesicular glutamate transporter 2) as a marker of subcortical glutamatergic neurons was observed only in individual aggregate-containing cells (M-O, white arrows).

**Suppl. Figure 6: Global transcriptome GSEA downregulation for DM cerebellum at age 6 weeks.**

Details for the NOUSHMEHR\_GBM\_SILENCED\_BY\_METHYLATION gene set.

**Suppl. Figure 7: Global transcriptome GSEA upregulation for DM cerebellum at age 6 weeks.** Details for the NAGASHIMA\_EGF\_SIGNALING\_UP gene set.

**Suppl. Figure 8: Global transcriptome GSEA upregulation for DM cerebellum at age 6 months.**

Details for the NAGASHIMA\_EGF\_SIGNALING\_UP gene set.

**Suppl. Figure 9: Global transcriptome GSEA downregulation for DM cerebellum at age 6 months.**

Details for the MITOCHONDRIAL\_MATRIX gene set.

**Suppl. Figure 10: Global transcriptome GSEA downregulation for DM midbrain at age 6 months.**

Details for the QI\_HYPOXIA\_TARGETS\_OF\_HIF1A\_AND\_FOXA2 gene set.

**Suppl. Figure 11: Global transcriptome GSEA upregulation for DM midbrain at age 6 months.** Details

for the PID\_ATM\_PATHWAY gene set.

**Suppl. Movie 1: Progressive paralysis of DM mice beyond age 1 year.**

The progressive phenotype of locomotor deficits was documented by video for several DM mice at ages beyond 1 year, before they had to be sacrificed to avoid animal suffering. Later their tissue was found to exhibit alpha-synuclein- / p62- / ubiquitin- positive aggregates in immunohistochemistry.

**Suppl. Table 1: Global ubiquitination changes of DM brain hemispheres at age 18 months.**

(A) Primary UbiScan® results are represented. The average fold change is provided in column “-/- TgA : Control”, while the fold change for each of the 3 DM:WT-F1-hybrid pairs is shown in the subsequent columns. Dysregulation of ubiquitination sites with increase above 2.0-fold were illustrated in green, while sites with decrease below -2.0-fold were highlighted in red (see a list in Excel Tab: Fold Change by Protein Type). Fold changes should be more accurate with higher maximal intensity values. Peak measurements reflect either area or height. An index number from the Details tab is used for easy lookup of peptides between tabs. Blue letters in Gene Names indicate siRNA products commercially available; in Protein Names they indicate site-specific antibodies commercially available. Within sequences in the peptide column, the ubiquitination site is indicated by \*, while oxidized methionine is indicated by #. Count in Details refers to the number of MS/MS identifications in the Details tab for each protein/site. Average RT refers to average retention time for each peptide. In the Raw Intensity column, bold letters indicate intensities manually reviewed, while red letters indicate multiple identifications for 1 m/z measurement due

to ambiguous methylation site localization. The Normalized Log 2 Ratios were calculated by subtracting the median Log2 fold change for each comparison. The Details tab contains the MS/MS (blue box) and MS (red box) scan numbers, the Retention Time, the Xcorr values, the measured peptide mass accuracy, the DeltaCN value, the Rsp value, and the Peptide Prophet Probability (PP Probability) as a reference and measure of confidence to each peptide assignment. (B) Bioinformatics information is provided on the UbiScan® primary data.

**Suppl. Table 2: Global transcriptome changes of DM brain hemispheres at ages 6 weeks and 6 months.**

The columns from left show the microarray spot identifier, the transcript symbol, the transcript name, the average expression level, the adjusted p-value and then significant down-regulations (-1, green) and up-regulations (+1, red) for different organs and ages: This decision matrix assesses cerebellum (Cbll), midbrain+brainstem (MidB), striatum (Str), at the ages 6 weeks and 6 months, comparing in each column 4 DM versus 4 WT-F1-hybrid tissues, with a cutoff value of at least logarithmic fold changes of  $\pm 0.6$ .

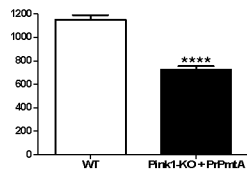
**Suppl. Table 3: Global transcriptome bioinformatics by Gene Set Enrichment Analysis.**

The automatized output from the GSEA software for each of the three brain tissues (midbrain/brainstem = MB, striatum = ST, cerebellum = CB) at two ages (6 months = 6M, 6 weeks = 6W), separated for upregulation and for downregulation, is shown in twelve datasheets of this file, in parameters defined by the Guide To Interpret Results at the GSEA internet page.

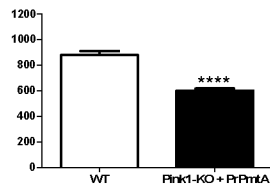
Fig 5

Horizontal Activity

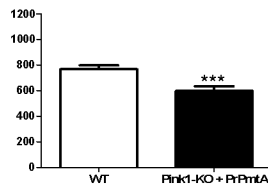
3 months



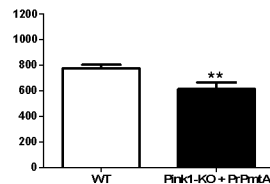
6 months



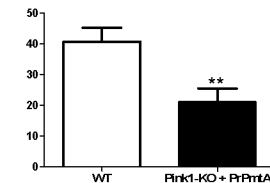
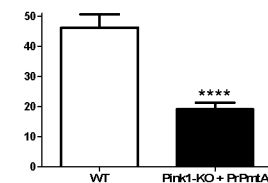
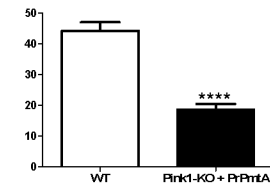
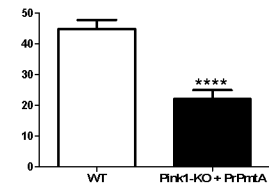
12 months



18 months



Vertical Activity



Stereotype Movements

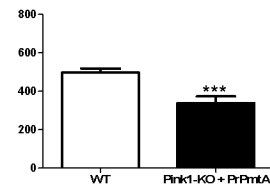
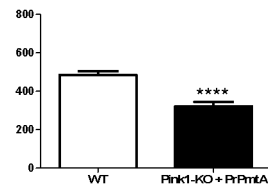
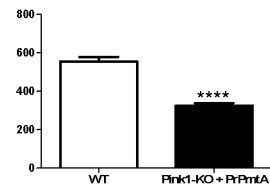
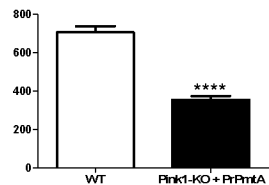


Fig S2

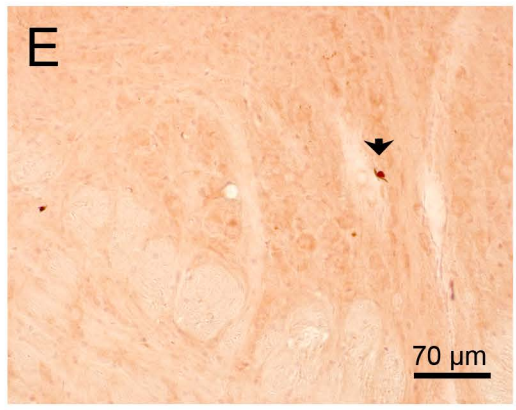
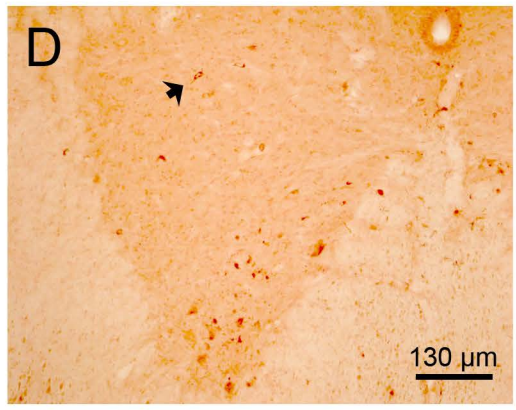
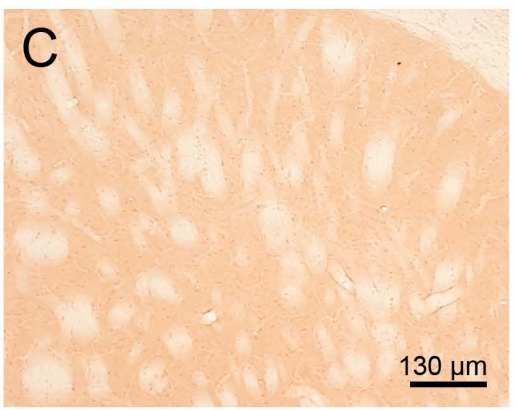
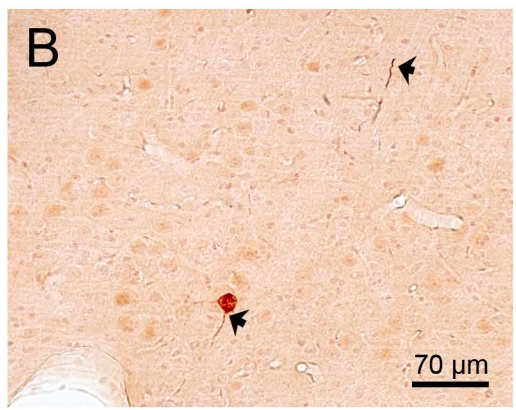
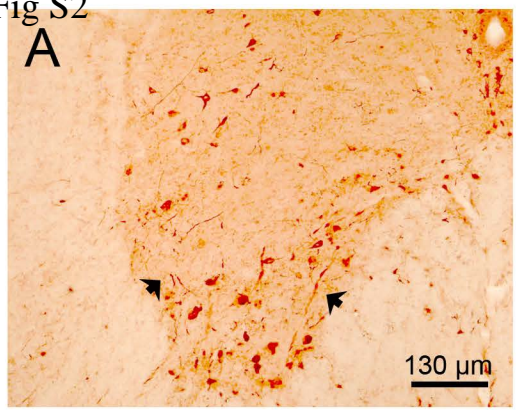
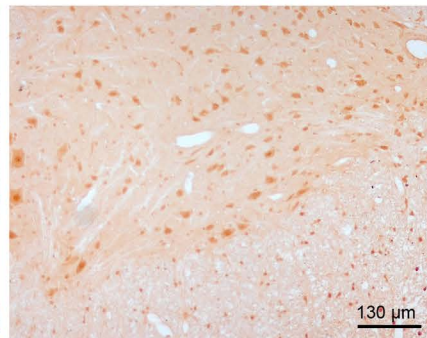
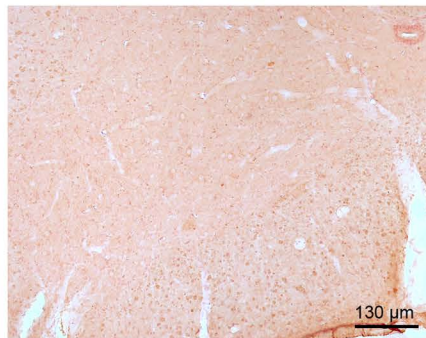
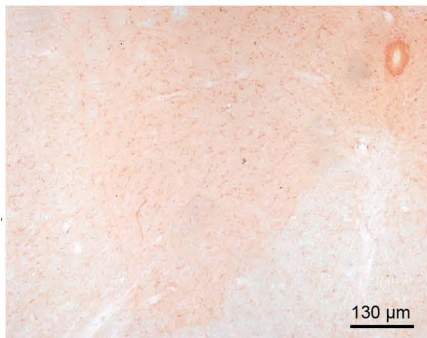


Fig S3 Phospho Ser129 SNCA

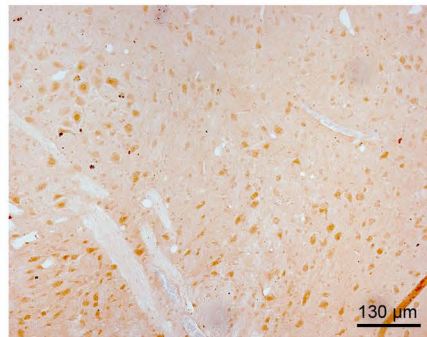
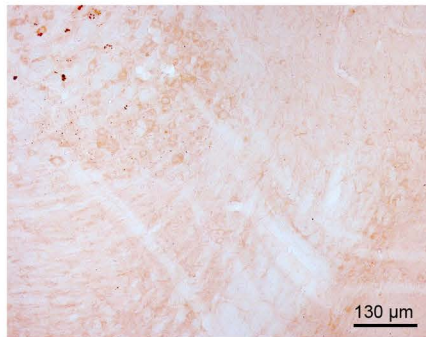
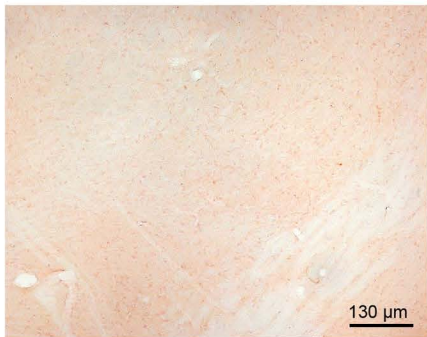
p62/SQSTM1

Ubiquitin

Spinal cord



Midbrain



A Fig S4

4B12



B

TH



C

Merge



D

pSer129-SNCA



E

TH



F

Merge



G

P62/SQSTM1



H

TH



I

Merge



J

Ubiquitin



K

TH



L

Merge





**A Fig S5**

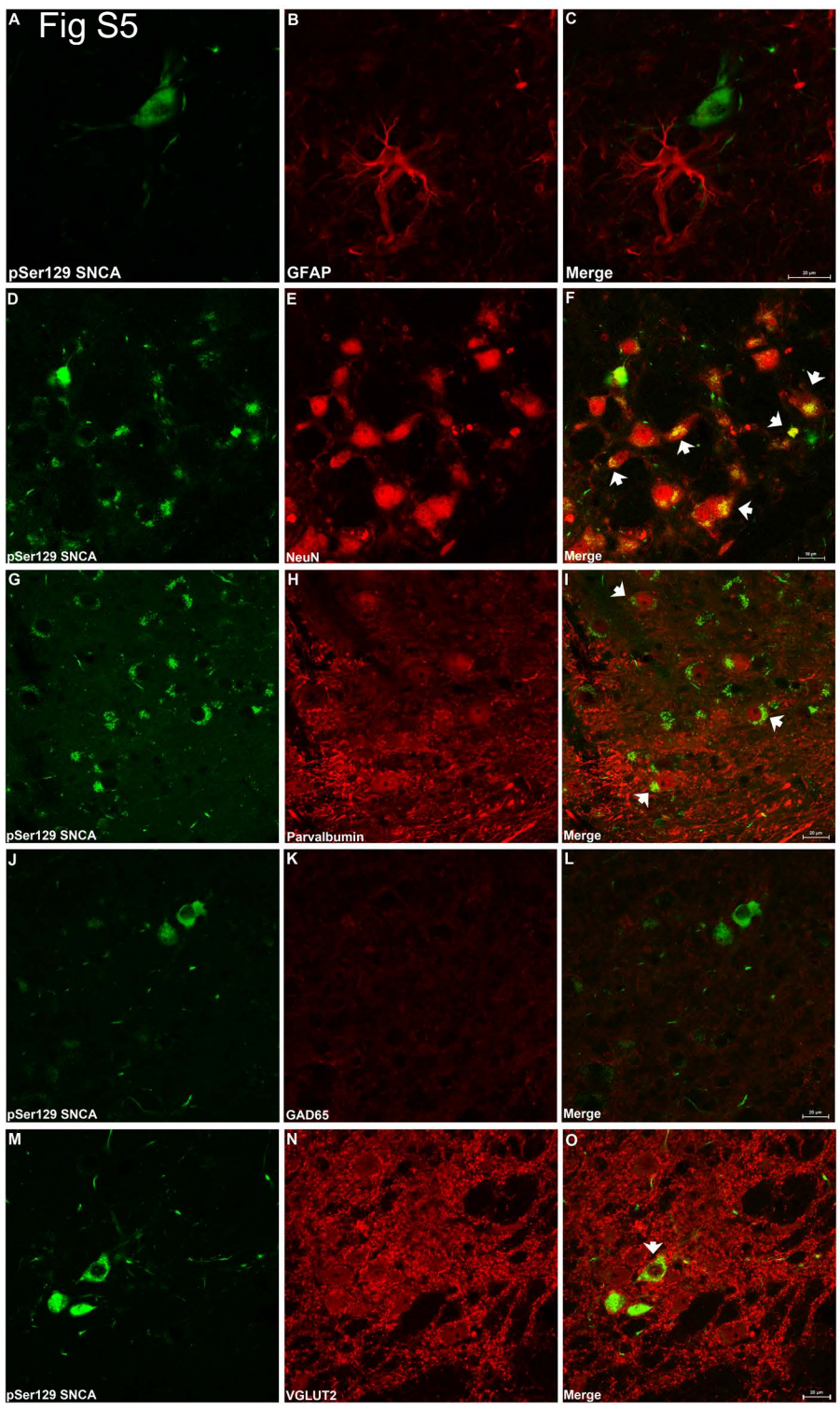
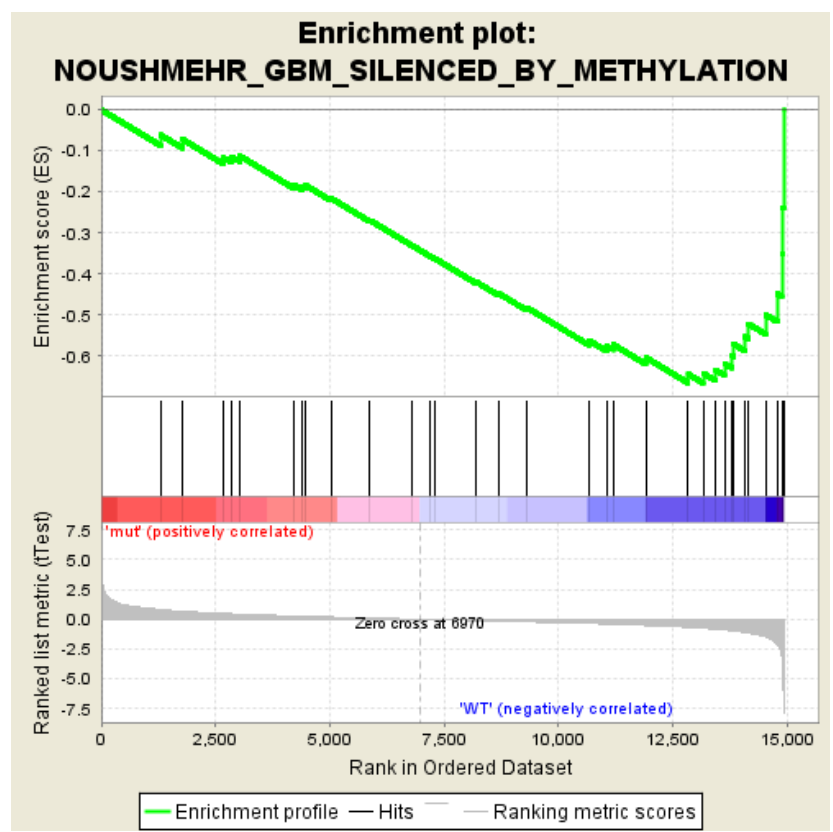


Fig S6

**Table: GSEA Results Summary**

Dataset	CB_6W_collapsed_to_symbols.general.cls#mut_versus_WT
Phenotype	general.cls#mut_versus_WT
Upregulated in class	WT
GeneSet	NOUSHMEHR_GBM_SILENCED_BY_METHYLATION
Enrichment Score (ES)	-0.6654536
Normalized Enrichment Score (NES)	-2.131186
Nominal p-value	0.0
FDR q-value	0.016506651
FWER p-Value	0.034



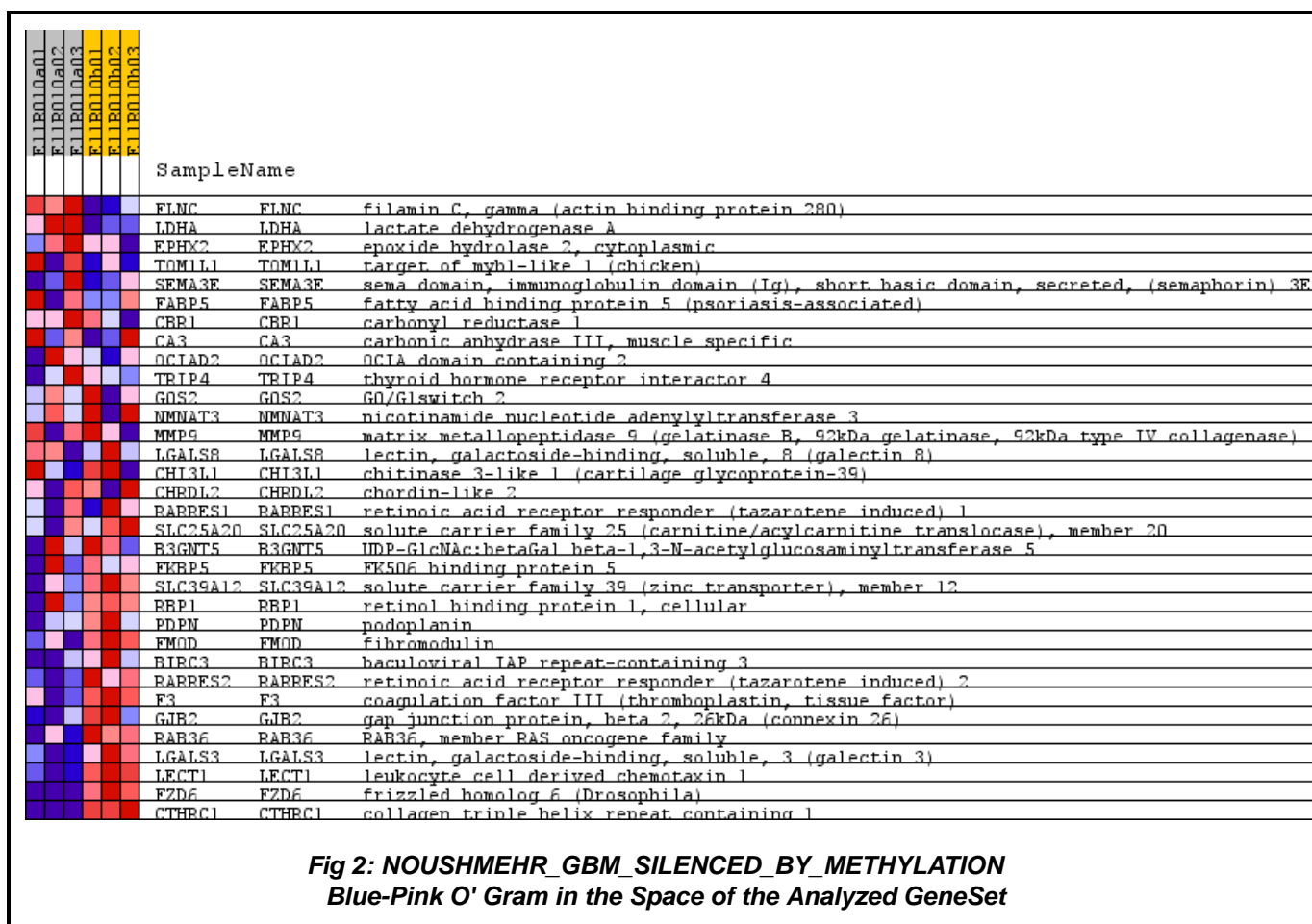
**Fig 1: Enrichment plot: NOUSHMEHR\_GBM\_SILENCED\_BY\_METHYLATION**  
 Profile of the Running ES Score & Positions of GeneSet Members on the Rank Ordered List

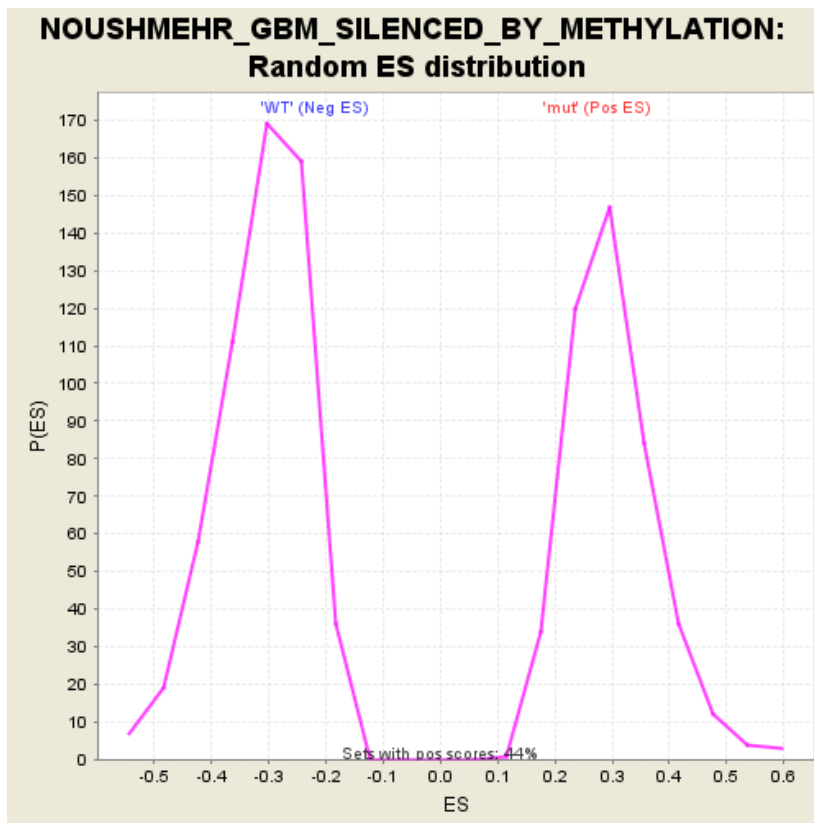
**Table: GSEA details [plain text format]**

	PROBE	GENE SYMBOL	GENE_TITLE	RANK IN GENE LIST	RANK METRIC SCORE	RUNNING ES	CORE ENRICHMENT
1	<a href="#">FLNC</a>	FLNC <a href="#">Entrez</a> , <a href="#">Source</a>	filamin C, gamma (actin binding protein 280)	1296	0.809	-0.0611	No
2	<a href="#">LDHA</a>	LDHA <a href="#">Entrez</a> , <a href="#">Source</a>	lactate dehydrogenase A	1780	0.665	-0.0722	No
3	<a href="#">EPHX2</a>	EPHX2 <a href="#">Entrez</a> , <a href="#">Source</a>	epoxide hydrolase 2, cytoplasmic	2676	0.482	-0.1168	No

4	<a href="#">TOM1L1</a>	<a href="#">TOM1L1</a> <a href="#">Entrez</a> , <a href="#">Source</a>	target of myb1-like 1 (chicken)	2843	0.457	-0.1133	No
5	<a href="#">SEMA3E</a>	<a href="#">SEMA3E</a> <a href="#">Entrez</a> , <a href="#">Source</a>	sema domain, immunoglobulin domain (Ig), short basic domain, secreted, (semaphorin) 3E	3037	0.427	-0.1126	No
6	<a href="#">FABP5</a>	<a href="#">FABP5</a> <a href="#">Entrez</a> , <a href="#">Source</a>	fatty acid binding protein 5 (psoriasis-associated)	4221	0.271	-0.1833	No
7	<a href="#">CBR1</a>	<a href="#">CBR1</a> <a href="#">Entrez</a> , <a href="#">Source</a>	carbonyl reductase 1	4389	0.253	-0.1864	No
8	<a href="#">CA3</a>	<a href="#">CA3</a> <a href="#">Entrez</a> , <a href="#">Source</a>	carbonic anhydrase III, muscle specific	4473	0.245	-0.1841	No
9	<a href="#">OCIAD2</a>	<a href="#">OCIAD2</a> <a href="#">Entrez</a> , <a href="#">Source</a>	OCIA domain containing 2	5023	0.187	-0.2150	No
10	<a href="#">TRIP4</a>	<a href="#">TRIP4</a> <a href="#">Entrez</a> , <a href="#">Source</a>	thyroid hormone receptor interactor 4	5877	0.100	-0.2690	No
11	<a href="#">G0S2</a>	<a href="#">G0S2</a> <a href="#">Entrez</a> , <a href="#">Source</a>	G0/G1switch 2	6786	0.017	-0.3294	No
12	<a href="#">NMNAT3</a>	<a href="#">NMNAT3</a> <a href="#">Entrez</a> , <a href="#">Source</a>	nicotinamide nucleotide adenyltransferase 3	7199	-0.020	-0.3564	No
13	<a href="#">MMP9</a>	<a href="#">MMP9</a> <a href="#">Entrez</a> , <a href="#">Source</a>	matrix metalloproteinase 9 (gelatinase B, 92kDa gelatinase, 92kDa type IV collagenase)	7309	-0.032	-0.3627	No
14	<a href="#">LGALS8</a>	<a href="#">LGALS8</a> <a href="#">Entrez</a> , <a href="#">Source</a>	lectin, galactoside-binding, soluble, 8 (galectin 8)	8196	-0.111	-0.4187	No
15	<a href="#">CHI3L1</a>	<a href="#">CHI3L1</a> <a href="#">Entrez</a> , <a href="#">Source</a>	chitinase 3-like 1 (cartilage glycoprotein-39)	8699	-0.156	-0.4474	No
16	<a href="#">CHRD2</a>	<a href="#">CHRD2</a> <a href="#">Entrez</a> , <a href="#">Source</a>	chordin-like 2	9310	-0.211	-0.4815	No
17	<a href="#">RARRES1</a>	<a href="#">RARRES1</a> <a href="#">Entrez</a> , <a href="#">Source</a>	retinoic acid receptor responder (tazarotene induced) 1	10670	-0.348	-0.5616	No
18	<a href="#">SLC25A20</a>	<a href="#">SLC25A20</a> <a href="#">Entrez</a> , <a href="#">Source</a>	solute carrier family 25 (carnitine/acylcarnitine translocase), member 20	11064	-0.391	-0.5755	No
19	<a href="#">B3GNT5</a>	<a href="#">B3GNT5</a> <a href="#">Entrez</a> , <a href="#">Source</a>	UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 5	11199	-0.407	-0.5714	No
20	<a href="#">FKBP5</a>	<a href="#">FKBP5</a> <a href="#">Entrez</a> , <a href="#">Source</a>	FK506 binding protein 5	11914	-0.508	-0.6030	No
21	<a href="#">SLC39A12</a>	<a href="#">SLC39A12</a> <a href="#">Entrez</a> , <a href="#">Source</a>	solute carrier family 39 (zinc transporter), member 12	12843	-0.677	-0.6436	Yes
22	<a href="#">RBP1</a>	<a href="#">RBP1</a> <a href="#">Entrez</a> , <a href="#">Source</a>	retinol binding protein 1, cellular	13169	-0.747	-0.6415	Yes
23	<a href="#">PDPN</a>	<a href="#">PDPN</a> <a href="#">Entrez</a> , <a href="#">Source</a>	podoplanin	13435	-0.822	-0.6330	Yes
24	<a href="#">FMOD</a>	<a href="#">FMOD</a> <a href="#">Entrez</a> , <a href="#">Source</a>	fibromodulin	13637	-0.882	-0.6182	Yes

25	<a href="#">BIRC3</a>	<a href="#">BIRC3</a> <a href="#">Entrez</a> , <a href="#">Source</a>	baculoviral IAP repeat-containing 3	13793	-0.938	-0.5986	Yes
26	<a href="#">RARRES2</a>	<a href="#">RARRES2</a> <a href="#">Entrez</a> , <a href="#">Source</a>	retinoic acid receptor responder (tazarotene induced) 2	13836	-0.961	-0.5706	Yes
27	<a href="#">F3</a>	<a href="#">F3</a> <a href="#">Entrez</a> , <a href="#">Source</a>	coagulation factor III (thromboplastin, tissue factor)	14082	-1.086	-0.5522	Yes
28	<a href="#">GJB2</a>	<a href="#">GJB2</a> <a href="#">Entrez</a> , <a href="#">Source</a>	gap junction protein, beta 2, 26kDa (connexin 26)	14161	-1.129	-0.5213	Yes
29	<a href="#">RAB36</a>	<a href="#">RAB36</a> <a href="#">Entrez</a> , <a href="#">Source</a>	RAB36, member RAS oncogene family	14537	-1.478	-0.4991	Yes
30	<a href="#">LGALS3</a>	<a href="#">LGALS3</a> <a href="#">Entrez</a> , <a href="#">Source</a>	lectin, galactoside-binding, soluble, 3 (galectin 3)	14797	-2.145	-0.4478	Yes
31	<a href="#">LECT1</a>	<a href="#">LECT1</a> <a href="#">Entrez</a> , <a href="#">Source</a>	leukocyte cell derived chemotaxin 1	14893	-3.196	-0.3518	Yes
32	<a href="#">FZD6</a>	<a href="#">FZD6</a> <a href="#">Entrez</a> , <a href="#">Source</a>	frizzled homolog 6 (Drosophila)	14903	-3.540	-0.2390	Yes
33	<a href="#">CTHRC1</a>	<a href="#">CTHRC1</a> <a href="#">Entrez</a> , <a href="#">Source</a>	collagen triple helix repeat containing 1	14930	-7.518	0.0001	Yes



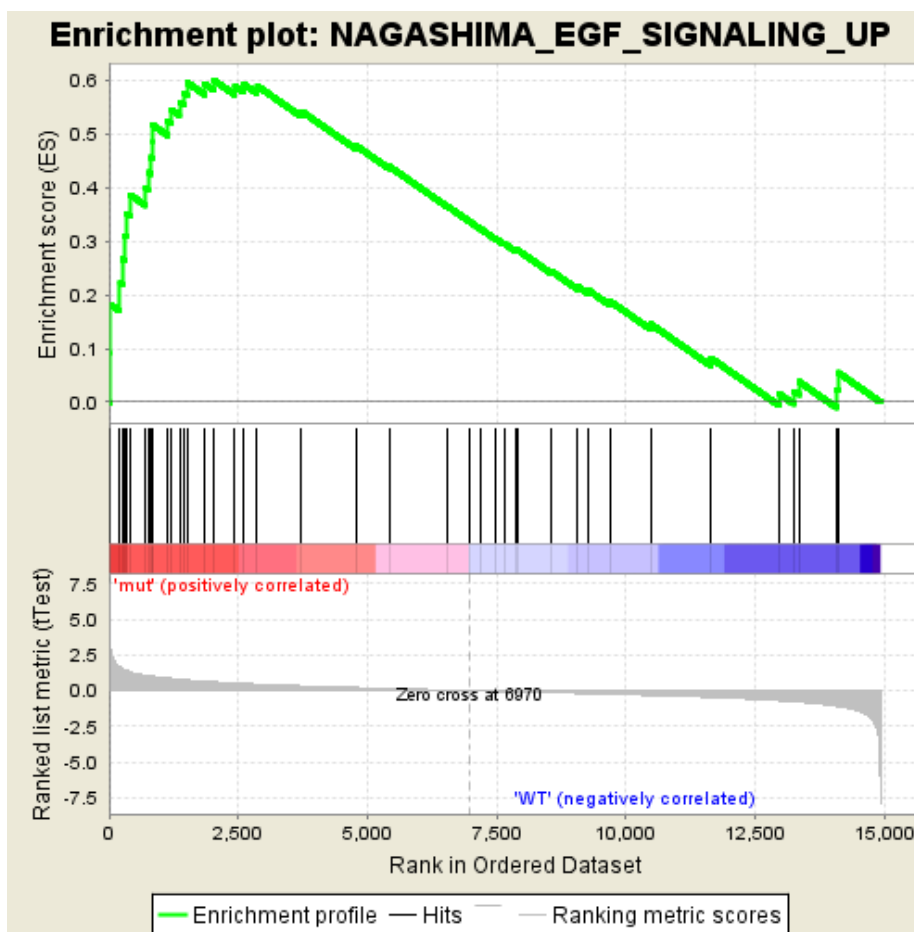


**Fig 3: NOUSHMEHR\_GBM\_SILENCED\_BY\_METHYLATION: Random ES distribution**  
**Gene set null distribution of ES for NOUSHMEHR\_GBM\_SILENCED\_BY\_METHYLATION**

Fig S7

**Table: GSEA Results Summary**

Dataset	CB_6W_collapsed_to_symbols.general.cls#mut_versus_WT
Phenotype	general.cls#mut_versus_WT
Upregulated in class	mut
GeneSet	NAGASHIMA_EGF_SIGNALING_UP
Enrichment Score (ES)	0.6003276
Normalized Enrichment Score (NES)	2.117522
Nominal p-value	0.0
FDR q-value	0.0585707
FWER p-Value	0.054



**Fig 1: Enrichment plot: NAGASHIMA\_EGF\_SIGNALING\_UP**  
**Profile of the Running ES Score & Positions of GeneSet Members on the Rank Ordered List**

**Table: GSEA details [plain text format]**

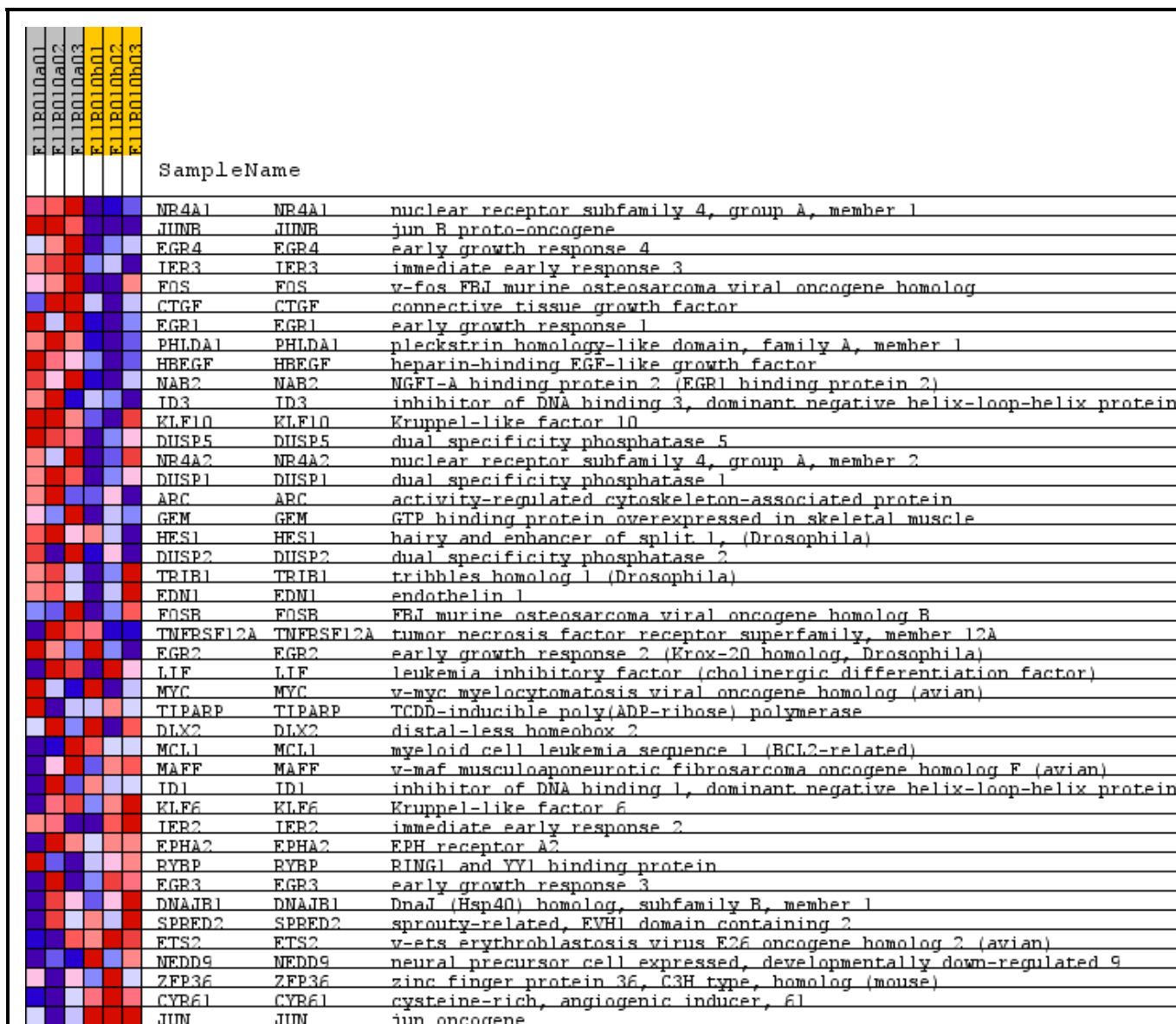
	PROBE	GENE SYMBOL	GENE_TITLE	RANK IN GENE LIST	RANK METRIC SCORE	RUNNING ES	CORE ENRICHMENT
1	<a href="#">NR4A1</a>	NR4A1 <a href="#">Entrez</a> , <a href="#">Source</a>	nuclear receptor subfamily 4, group A, member 1	24	3.032	0.0923	Yes

2	<a href="#">JUNB</a>	JUNB <a href="#">Entrez</a> , <a href="#">Source</a>	jun B proto-oncogene	28	2.903	0.1821	Yes
3	<a href="#">EGR4</a>	EGR4 <a href="#">Entrez</a> , <a href="#">Source</a>	early growth response 4	211	1.682	0.2220	Yes
4	<a href="#">IER3</a>	IER3 <a href="#">Entrez</a> , <a href="#">Source</a>	immediate early response 3	256	1.566	0.2676	Yes
5	<a href="#">FOS</a>	FOS <a href="#">Entrez</a> , <a href="#">Source</a>	v-fos FBJ murine osteosarcoma viral oncogene homolog	300	1.459	0.3099	Yes
6	<a href="#">CTGF</a>	CTGF <a href="#">Entrez</a> , <a href="#">Source</a>	connective tissue growth factor	328	1.415	0.3519	Yes
7	<a href="#">EGR1</a>	EGR1 <a href="#">Entrez</a> , <a href="#">Source</a>	early growth response 1	412	1.296	0.3865	Yes
8	<a href="#">PHLDA1</a>	PHLDA1 <a href="#">Entrez</a> , <a href="#">Source</a>	pleckstrin homology-like domain, family A, member 1	709	1.069	0.3998	Yes
9	<a href="#">HBEGF</a>	HBEGF <a href="#">Entrez</a> , <a href="#">Source</a>	heparin-binding EGF-like growth factor	756	1.044	0.4291	Yes
10	<a href="#">NAB2</a>	NAB2 <a href="#">Entrez</a> , <a href="#">Source</a>	NGFI-A binding protein 2 (EGR1 binding protein 2)	813	1.015	0.4568	Yes
11	<a href="#">ID3</a>	ID3 <a href="#">Entrez</a> , <a href="#">Source</a>	inhibitor of DNA binding 3, dominant negative helix-loop-helix protein	835	1.005	0.4865	Yes
12	<a href="#">KLF10</a>	KLF10 <a href="#">Entrez</a> , <a href="#">Source</a>	Kruppel-like factor 10	839	1.002	0.5173	Yes
13	<a href="#">DUSP5</a>	DUSP5 <a href="#">Entrez</a> , <a href="#">Source</a>	dual specificity phosphatase 5	1136	0.875	0.5246	Yes
14	<a href="#">NR4A2</a>	NR4A2 <a href="#">Entrez</a> , <a href="#">Source</a>	nuclear receptor subfamily 4, group A, member 2	1210	0.845	0.5459	Yes
15	<a href="#">DUSP1</a>	DUSP1 <a href="#">Entrez</a> , <a href="#">Source</a>	dual specificity phosphatase 1	1362	0.784	0.5600	Yes
16	<a href="#">ARC</a>	ARC <a href="#">Entrez</a> , <a href="#">Source</a>	activity-regulated cytoskeleton-associated protein	1455	0.755	0.5772	Yes
17	<a href="#">GEM</a>	GEM <a href="#">Entrez</a> , <a href="#">Source</a>	GTP binding protein overexpressed in skeletal muscle	1510	0.739	0.5965	Yes
18	<a href="#">HES1</a>	HES1 <a href="#">Entrez</a> , <a href="#">Source</a>	hairy and enhancer of split 1, (Drosophila)	1852	0.647	0.5936	Yes
19	<a href="#">DUSP2</a>	DUSP2 <a href="#">Entrez</a> , <a href="#">Source</a>	dual specificity phosphatase 2	2033	0.606	0.6003	Yes

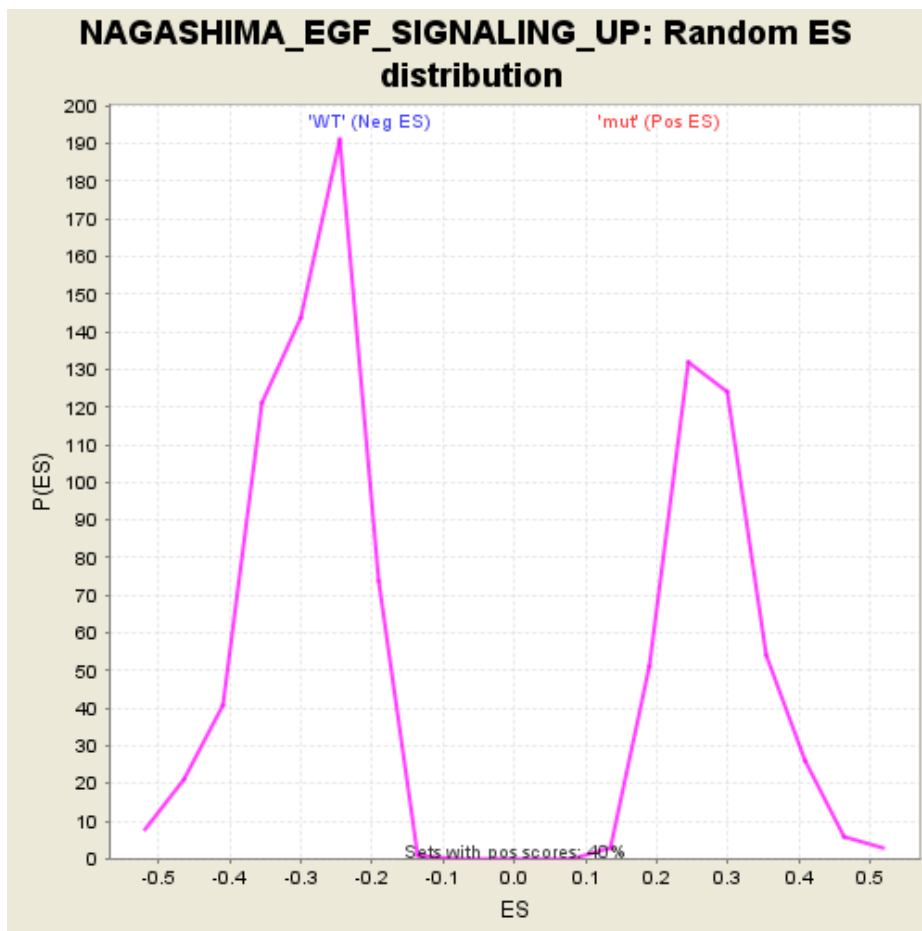
20	<a href="#">TRIB1</a>	<a href="#">TRIB1</a> <a href="#">Entrez</a> , <a href="#">Source</a>	tribbles homolog 1 (Drosophila)	2435	0.525	0.5897	No
21	<a href="#">EDN1</a>	<a href="#">EDN1</a> <a href="#">Entrez</a> , <a href="#">Source</a>	endothelin 1	2611	0.492	0.5932	No
22	<a href="#">FOSB</a>	<a href="#">FOSB</a> <a href="#">Entrez</a> , <a href="#">Source</a>	FBJ murine osteosarcoma viral oncogene homolog B	2867	0.454	0.5901	No
23	<a href="#">TNFRSF12A</a>	<a href="#">TNFRSF12A</a> <a href="#">Entrez</a> , <a href="#">Source</a>	tumor necrosis factor receptor superfamily, member 12A	3720	0.329	0.5431	No
24	<a href="#">EGR2</a>	<a href="#">EGR2</a> <a href="#">Entrez</a> , <a href="#">Source</a>	early growth response 2 (Krox-20 homolog, Drosophila)	4783	0.212	0.4783	No
25	<a href="#">LIF</a>	<a href="#">LIF</a> <a href="#">Entrez</a> , <a href="#">Source</a>	leukemia inhibitory factor (cholinergic differentiation factor)	5421	0.146	0.4401	No
26	<a href="#">MYC</a>	<a href="#">MYC</a> <a href="#">Entrez</a> , <a href="#">Source</a>	v-myc myelocytomatosis viral oncogene homolog (avian)	6559	0.039	0.3649	No
27	<a href="#">TIPARP</a>	<a href="#">TIPARP</a> <a href="#">Entrez</a> , <a href="#">Source</a>	TCDD-inducible poly(ADP-ribose) polymerase	6968	0.000	0.3375	No
28	<a href="#">DLX2</a>	<a href="#">DLX2</a> <a href="#">Entrez</a> , <a href="#">Source</a>	distal-less homeobox 2	7206	-0.021	0.3222	No
29	<a href="#">MCL1</a>	<a href="#">MCL1</a> <a href="#">Entrez</a> , <a href="#">Source</a>	myeloid cell leukemia sequence 1 (BCL2-related)	7478	-0.046	0.3055	No
30	<a href="#">MAFF</a>	<a href="#">MAFF</a> <a href="#">Entrez</a> , <a href="#">Source</a>	v-maf musculoaponeurotic fibrosarcoma oncogene homolog F (avian)	7644	-0.062	0.2963	No
31	<a href="#">ID1</a>	<a href="#">ID1</a> <a href="#">Entrez</a> , <a href="#">Source</a>	inhibitor of DNA binding 1, dominant negative helix-loop-helix protein	7860	-0.081	0.2844	No
32	<a href="#">KLF6</a>	<a href="#">KLF6</a> <a href="#">Entrez</a> , <a href="#">Source</a>	Kruppel-like factor 6	7906	-0.085	0.2840	No
33	<a href="#">IER2</a>	<a href="#">IER2</a> <a href="#">Entrez</a> , <a href="#">Source</a>	immediate early response 2	8546	-0.141	0.2455	No
34	<a href="#">EPHA2</a>	<a href="#">EPHA2</a> <a href="#">Entrez</a> , <a href="#">Source</a>	EPH receptor A2	9067	-0.189	0.2164	No
35	<a href="#">RYBP</a>	<a href="#">RYBP</a> <a href="#">Entrez</a> , <a href="#">Source</a>	RING1 and YY1 binding protein	9274	-0.207	0.2090	No
36	<a href="#">EGR3</a>	<a href="#">EGR3</a> <a href="#">Entrez</a> , <a href="#">Source</a>	early growth response 3	9709	-0.248	0.1875	No
37	<a href="#">DNAJB1</a>	<a href="#">DNAJB1</a> <a href="#">Entrez</a> , <a href="#">Source</a>	DnaJ (Hsp40) homolog, subfamily B, member 1	10485	-0.330	0.1457	No



38	<a href="#">SPRED2</a>	SPRED2 <a href="#">Entrez</a> , <a href="#">Source</a>	sprouty-related, EVH1 domain containing 2	11647	-0.469	0.0823	No
39	<a href="#">ETS2</a>	ETS2 <a href="#">Entrez</a> , <a href="#">Source</a>	v-ets erythroblastosis virus E26 oncogene homolog 2 (avian)	12973	-0.704	0.0151	No
40	<a href="#">NEDD9</a>	NEDD9 <a href="#">Entrez</a> , <a href="#">Source</a>	neural precursor cell expressed, developmentally down-regulated 9	13252	-0.769	0.0202	No
41	<a href="#">ZFP36</a>	ZFP36 <a href="#">Entrez</a> , <a href="#">Source</a>	zinc finger protein 36, C3H type, homolog (mouse)	13351	-0.797	0.0383	No
42	<a href="#">CYR61</a>	CYR61 <a href="#">Entrez</a> , <a href="#">Source</a>	cysteine-rich, angiogenic inducer, 61	14080	-1.086	0.0231	No
43	<a href="#">JUN</a>	JUN <a href="#">Entrez</a> , <a href="#">Source</a>	jun oncogene	14109	-1.099	0.0553	No



**Fig 2: NAGASHIMA\_EGF\_SIGNALING\_UP**  
**Blue-Pink O' Gram in the Space of the Analyzed GeneSet**

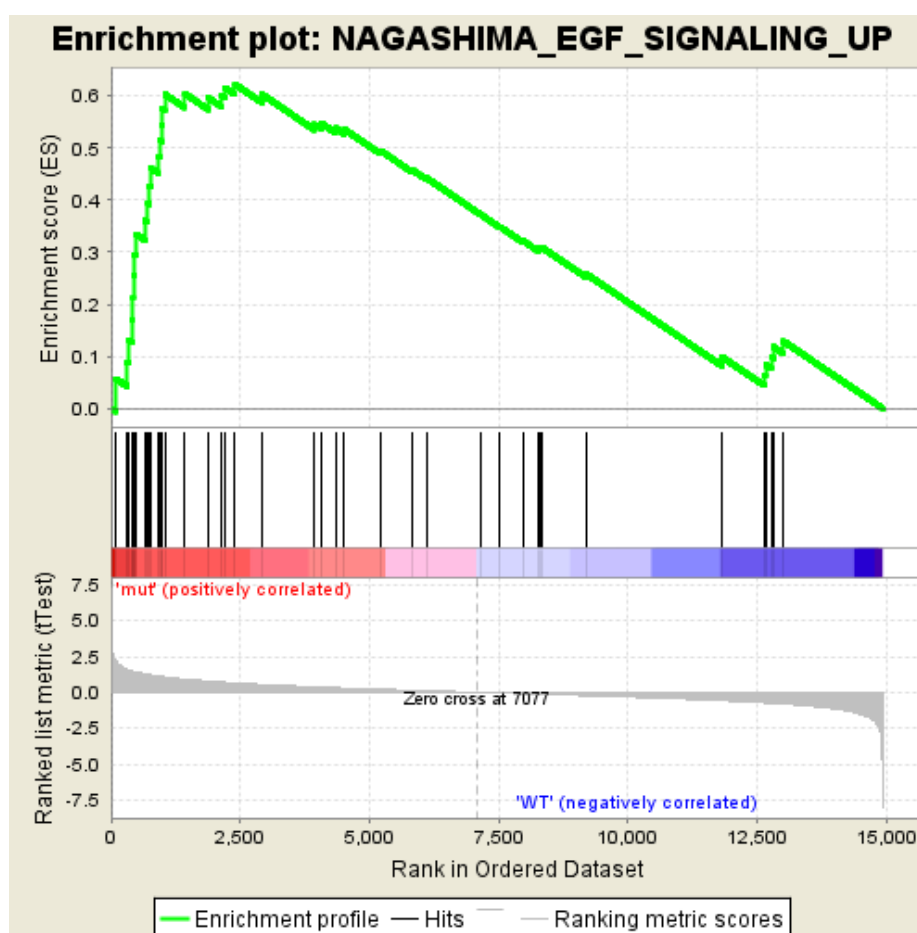


**Fig 3: NAGASHIMA\_EGF\_SIGNALING\_UP: Random ES distribution**  
**Gene set null distribution of ES for NAGASHIMA\_EGF\_SIGNALING\_UP**

Fig S8

**Table: GSEA Results Summary**

Dataset	CB_6M_collapsed_to_symbols.general.cls#mut_versus_WT
Phenotype	general.cls#mut_versus_WT
Upregulated in class	mut
GeneSet	NAGASHIMA_EGF_SIGNALING_UP
Enrichment Score (ES)	0.62230736
Normalized Enrichment Score (NES)	2.2834282
Nominal p-value	0.0
FDR q-value	0.0018626772
FWER p-Value	0.0030



**Fig 1: Enrichment plot: NAGASHIMA\_EGF\_SIGNALING\_UP**  
**Profile of the Running ES Score & Positions of GeneSet Members on the Rank Ordered List**

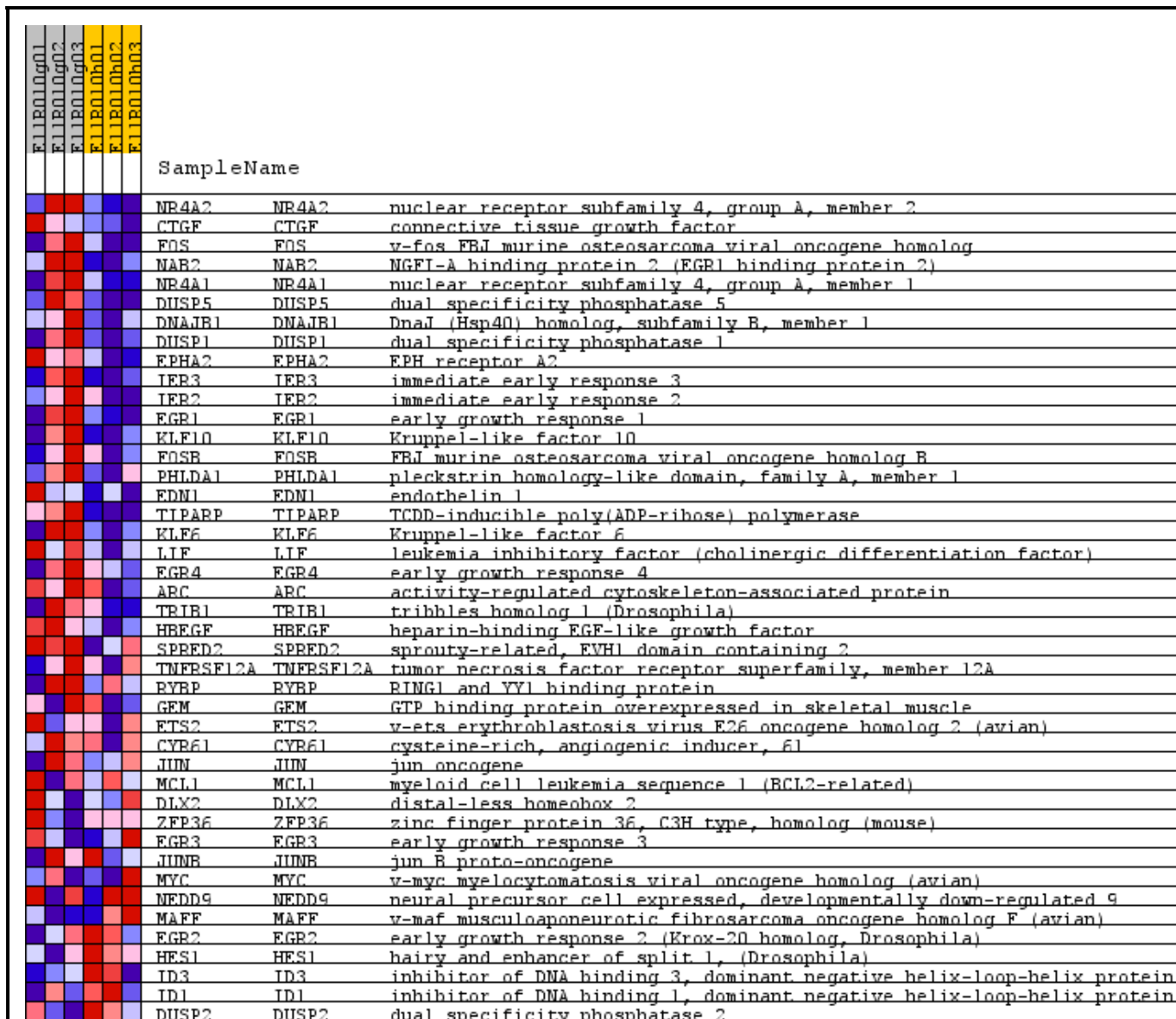
**Table: GSEA details [plain text format]**

	PROBE	GENE SYMBOL	GENE_TITLE	RANK IN GENE LIST	RANK METRIC SCORE	RUNNING ES	CORE ENRICHMENT
1	<a href="#">NR4A2</a>	NR4A2 <a href="#">Entrez</a> , <a href="#">Source</a>	nuclear receptor subfamily 4, group A, member 2	99	2.157	0.0564	Yes

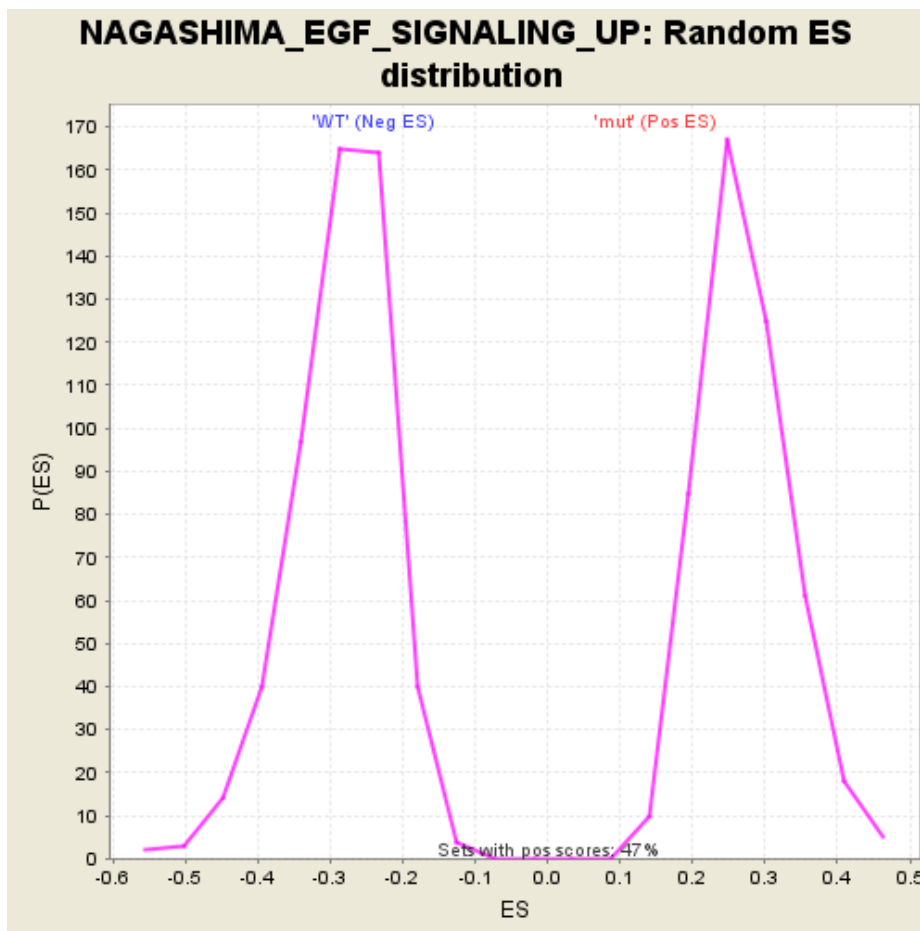
2	<a href="#">CTGF</a>	CTGF <a href="#">Entrez</a> , <a href="#">Source</a>	connective tissue growth factor	304	1.598	0.0893	Yes
3	<a href="#">FOS</a>	FOS <a href="#">Entrez</a> , <a href="#">Source</a>	v-fos FBJ murine osteosarcoma viral oncogene homolog	347	1.544	0.1316	Yes
4	<a href="#">NAB2</a>	NAB2 <a href="#">Entrez</a> , <a href="#">Source</a>	NGFI-A binding protein 2 (EGR1 binding protein 2)	414	1.480	0.1704	Yes
5	<a href="#">NR4A1</a>	NR4A1 <a href="#">Entrez</a> , <a href="#">Source</a>	nuclear receptor subfamily 4, group A, member 1	424	1.467	0.2126	Yes
6	<a href="#">DUSP5</a>	DUSP5 <a href="#">Entrez</a> , <a href="#">Source</a>	dual specificity phosphatase 5	430	1.461	0.2550	Yes
7	<a href="#">DNAJB1</a>	DNAJB1 <a href="#">Entrez</a> , <a href="#">Source</a>	DnaJ (Hsp40) homolog, subfamily B, member 1	448	1.446	0.2961	Yes
8	<a href="#">DUSP1</a>	DUSP1 <a href="#">Entrez</a> , <a href="#">Source</a>	dual specificity phosphatase 1	489	1.408	0.3345	Yes
9	<a href="#">EPHA2</a>	EPHA2 <a href="#">Entrez</a> , <a href="#">Source</a>	EPH receptor A2	654	1.289	0.3611	Yes
10	<a href="#">IER3</a>	IER3 <a href="#">Entrez</a> , <a href="#">Source</a>	immediate early response 3	710	1.249	0.3939	Yes
11	<a href="#">IER2</a>	IER2 <a href="#">Entrez</a> , <a href="#">Source</a>	immediate early response 2	742	1.230	0.4277	Yes
12	<a href="#">EGR1</a>	EGR1 <a href="#">Entrez</a> , <a href="#">Source</a>	early growth response 1	770	1.213	0.4614	Yes
13	<a href="#">KLF10</a>	KLF10 <a href="#">Entrez</a> , <a href="#">Source</a>	Kruppel-like factor 10	923	1.122	0.4839	Yes
14	<a href="#">FOSB</a>	FOSB <a href="#">Entrez</a> , <a href="#">Source</a>	FBJ murine osteosarcoma viral oncogene homolog B	944	1.113	0.5151	Yes
15	<a href="#">PHLDA1</a>	PHLDA1 <a href="#">Entrez</a> , <a href="#">Source</a>	pleckstrin homology-like domain, family A, member 1	977	1.093	0.5448	Yes
16	<a href="#">EDN1</a>	EDN1 <a href="#">Entrez</a> , <a href="#">Source</a>	endothelin 1	990	1.090	0.5759	Yes
17	<a href="#">TIPARP</a>	TIPARP <a href="#">Entrez</a> , <a href="#">Source</a>	TCDD-inducible poly(ADP-ribose) polymerase	1041	1.066	0.6037	Yes
18	<a href="#">KLF6</a>	KLF6 <a href="#">Entrez</a> , <a href="#">Source</a>	Kruppel-like factor 6	1430	0.912	0.6042	Yes
19	<a href="#">LIF</a>	LIF <a href="#">Entrez</a> , <a href="#">Source</a>	leukemia inhibitory factor (cholinergic differentiation factor)	1883	0.778	0.5966	Yes

20	<a href="#">EGR4</a>	EGR4 <a href="#">Entrez</a> , <a href="#">Source</a>	early growth response 4	2142	0.708	0.6000	Yes
21	<a href="#">ARC</a>	ARC <a href="#">Entrez</a> , <a href="#">Source</a>	activity-regulated cytoskeleton-associated protein	2197	0.695	0.6166	Yes
22	<a href="#">TRIB1</a>	TRIB1 <a href="#">Entrez</a> , <a href="#">Source</a>	tribbles homolog 1 (Drosophila)	2398	0.654	0.6223	Yes
23	<a href="#">HBEGF</a>	HBEGF <a href="#">Entrez</a> , <a href="#">Source</a>	heparin-binding EGF-like growth factor	2915	0.546	0.6036	No
24	<a href="#">SPRED2</a>	SPRED2 <a href="#">Entrez</a> , <a href="#">Source</a>	sprouty-related, EVH1 domain containing 2	3941	0.376	0.5457	No
25	<a href="#">TNFRSF12A</a>	TNFRSF12A <a href="#">Entrez</a> , <a href="#">Source</a>	tumor necrosis factor receptor superfamily, member 12A	4064	0.358	0.5480	No
26	<a href="#">RYBP</a>	RYBP <a href="#">Entrez</a> , <a href="#">Source</a>	RING1 and YY1 binding protein	4342	0.319	0.5387	No
27	<a href="#">GEM</a>	GEM <a href="#">Entrez</a> , <a href="#">Source</a>	GTP binding protein overexpressed in skeletal muscle	4516	0.296	0.5357	No
28	<a href="#">ETS2</a>	ETS2 <a href="#">Entrez</a> , <a href="#">Source</a>	v-ets erythroblastosis virus E26 oncogene homolog 2 (avian)	5212	0.211	0.4952	No
29	<a href="#">CYR61</a>	CYR61 <a href="#">Entrez</a> , <a href="#">Source</a>	cysteine-rich, angiogenic inducer, 61	5829	0.138	0.4579	No
30	<a href="#">JUN</a>	JUN <a href="#">Entrez</a> , <a href="#">Source</a>	jun oncogene	6104	0.107	0.4426	No
31	<a href="#">MCL1</a>	MCL1 <a href="#">Entrez</a> , <a href="#">Source</a>	myeloid cell leukemia sequence 1 (BCL2-related)	7147	-0.008	0.3729	No
32	<a href="#">DLX2</a>	DLX2 <a href="#">Entrez</a> , <a href="#">Source</a>	distal-less homeobox 2	7529	-0.049	0.3487	No
33	<a href="#">ZFP36</a>	ZFP36 <a href="#">Entrez</a> , <a href="#">Source</a>	zinc finger protein 36, C3H type, homolog (mouse)	7970	-0.099	0.3221	No
34	<a href="#">EGR3</a>	EGR3 <a href="#">Entrez</a> , <a href="#">Source</a>	early growth response 3	8269	-0.127	0.3058	No
35	<a href="#">JUNB</a>	JUNB <a href="#">Entrez</a> , <a href="#">Source</a>	jun B proto-oncogene	8290	-0.130	0.3082	No
36	<a href="#">MYC</a>	MYC <a href="#">Entrez</a> , <a href="#">Source</a>	v-myc myelocytomatosis viral oncogene homolog (avian)	8331	-0.134	0.3094	No
37	<a href="#">NEDD9</a>	NEDD9 <a href="#">Entrez</a> , <a href="#">Source</a>	neural precursor cell expressed, developmentally down-regulated 9	9193	-0.228	0.2583	No

38	<a href="#">MAFF</a>	<a href="#">MAFF</a> <a href="#">Entrez</a> , <a href="#">Source</a>	v-maf musculoaponeurotic fibrosarcoma oncogene homolog F (avian)	11825	-0.575	0.0984	No
39	<a href="#">EGR2</a>	<a href="#">EGR2</a> <a href="#">Entrez</a> , <a href="#">Source</a>	early growth response 2 (Krox-20 homolog, Drosophila)	12645	-0.724	0.0645	No
40	<a href="#">HES1</a>	<a href="#">HES1</a> <a href="#">Entrez</a> , <a href="#">Source</a>	hairy and enhancer of split 1, (Drosophila)	12668	-0.729	0.0843	No
41	<a href="#">ID3</a>	<a href="#">ID3</a> <a href="#">Entrez</a> , <a href="#">Source</a>	inhibitor of DNA binding 3, dominant negative helix-loop-helix protein	12777	-0.750	0.0990	No
42	<a href="#">ID1</a>	<a href="#">ID1</a> <a href="#">Entrez</a> , <a href="#">Source</a>	inhibitor of DNA binding 1, dominant negative helix-loop-helix protein	12818	-0.758	0.1185	No
43	<a href="#">DUSP2</a>	<a href="#">DUSP2</a> <a href="#">Entrez</a> , <a href="#">Source</a>	dual specificity phosphatase 2	13012	-0.803	0.1289	No



**Fig 2: NAGASHIMA\_EGF\_SIGNALING\_UP**  
**Blue-Pink O' Gram in the Space of the Analyzed GeneSet**

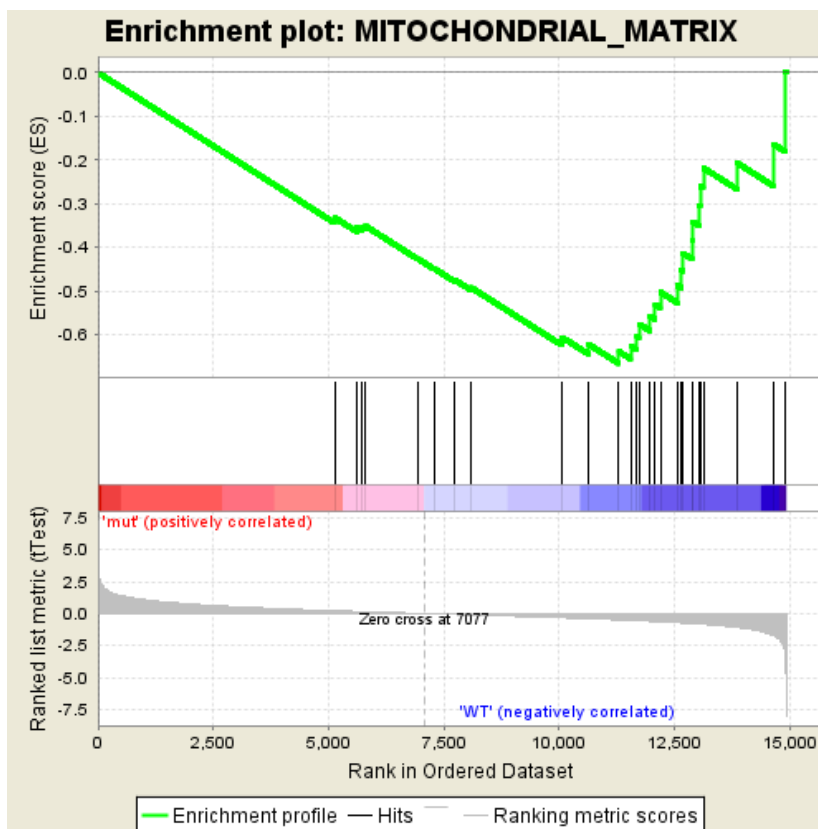


**Fig 3: NAGASHIMA\_EGF\_SIGNALING\_UP: Random ES distribution**  
**Gene set null distribution of ES for NAGASHIMA\_EGF\_SIGNALING\_UP**

Fig S9

**Table: GSEA Results Summary**

Dataset	CB_6M_collapsed_to_symbols.general.cls#mut_versus_WT
Phenotype	general.cls#mut_versus_WT
Upregulated in class	WT
GeneSet	MITOCHONDRIAL_MATRIX
Enrichment Score (ES)	-0.66644275
Normalized Enrichment Score (NES)	-2.174532
Nominal p-value	0.0
FDR q-value	0.014642635
FWER p-Value	0.018



**Fig 1: Enrichment plot: MITOCHONDRIAL\_MATRIX**  
 Profile of the Running ES Score & Positions of GeneSet Members on the Rank Ordered List

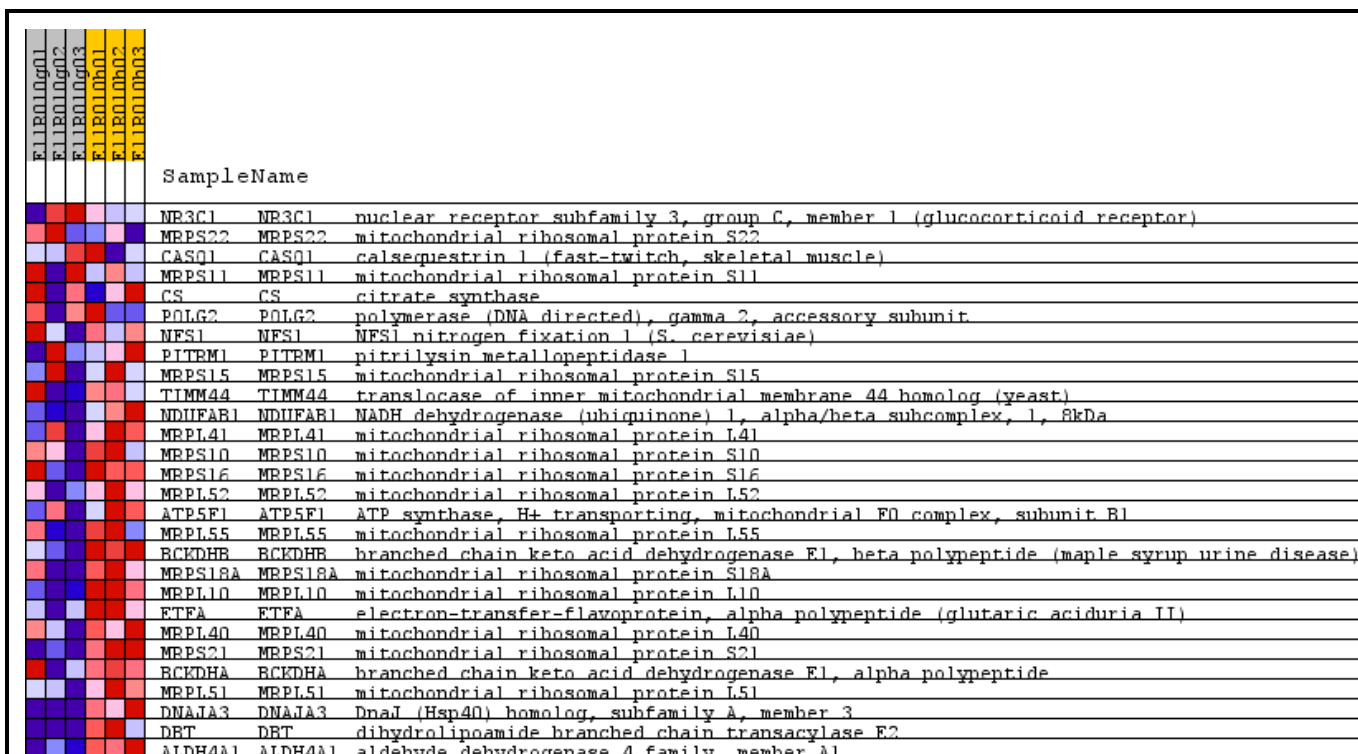
**Table: GSEA details [plain text format]**

	PROBE	GENE SYMBOL	GENE_TITLE	RANK IN GENE LIST	RANK METRIC SCORE	RUNNING ES	CORE ENRICHMENT
1	<a href="#">NR3C1</a>	NR3C1 <a href="#">Entrez</a> , <a href="#">Source</a>	nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor)	5133	0.219	-0.3321	No
2	<a href="#">MRPS22</a>	MRPS22 <a href="#">Entrez</a> , <a href="#">Source</a>	mitochondrial ribosomal protein S22	5613	0.164	-0.3550	No
3	<a href="#">CASQ1</a>	CASQ1 <a href="#">Entrez</a> , <a href="#">Source</a>	calsequestrin 1 (fast-twitch, skeletal muscle)	5732	0.150	-0.3545	No

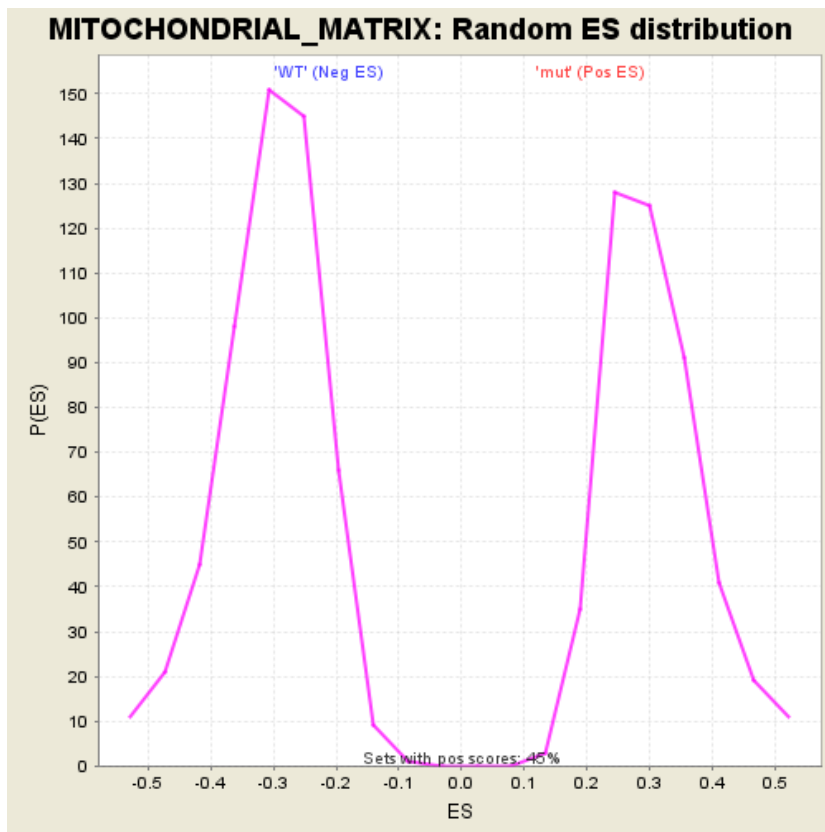


4	<a href="#">MRPS11</a>	MRPS11 <a href="#">Entrez</a> , <a href="#">Source</a>	mitochondrial ribosomal protein S11	5807	0.141	-0.3516	No
5	<a href="#">CS</a>	CS <a href="#">Entrez</a> , <a href="#">Source</a>	citrate synthase	6927	0.018	-0.4257	No
6	<a href="#">POLG2</a>	POLG2 <a href="#">Entrez</a> , <a href="#">Source</a>	polymerase (DNA directed), gamma 2, accessory subunit	7290	-0.023	-0.4487	No
7	<a href="#">NFS1</a>	NFS1 <a href="#">Entrez</a> , <a href="#">Source</a>	NFS1 nitrogen fixation 1 (S. cerevisiae)	7731	-0.071	-0.4742	No
8	<a href="#">PITRM1</a>	PITRM1 <a href="#">Entrez</a> , <a href="#">Source</a>	pitriysin metallopeptidase 1	8090	-0.110	-0.4921	No
9	<a href="#">MRPS15</a>	MRPS15 <a href="#">Entrez</a> , <a href="#">Source</a>	mitochondrial ribosomal protein S15	10064	-0.327	-0.6061	No
10	<a href="#">TIMM44</a>	TIMM44 <a href="#">Entrez</a> , <a href="#">Source</a>	translocase of inner mitochondrial membrane 44 homolog (yeast)	10635	-0.401	-0.6219	No
11	<a href="#">NDUFAB1</a>	NDUFAB1 <a href="#">Entrez</a> , <a href="#">Source</a>	NADH dehydrogenase (ubiquinone) 1, alpha/beta subcomplex, 1, 8kDa	11300	-0.492	-0.6389	Yes
12	<a href="#">MRPL41</a>	MRPL41 <a href="#">Entrez</a> , <a href="#">Source</a>	mitochondrial ribosomal protein L41	11553	-0.530	-0.6260	Yes
13	<a href="#">MRPS10</a>	MRPS10 <a href="#">Entrez</a> , <a href="#">Source</a>	mitochondrial ribosomal protein S10	11689	-0.553	-0.6041	Yes
14	<a href="#">MRPS16</a>	MRPS16 <a href="#">Entrez</a> , <a href="#">Source</a>	mitochondrial ribosomal protein S16	11735	-0.561	-0.5756	Yes
15	<a href="#">MRPL52</a>	MRPL52 <a href="#">Entrez</a> , <a href="#">Source</a>	mitochondrial ribosomal protein L52	11972	-0.598	-0.5579	Yes
16	<a href="#">ATP5F1</a>	ATP5F1 <a href="#">Entrez</a> , <a href="#">Source</a>	ATP synthase, H+ transporting, mitochondrial F0 complex, subunit B1	12087	-0.617	-0.5309	Yes
17	<a href="#">MRPL55</a>	MRPL55 <a href="#">Entrez</a> , <a href="#">Source</a>	mitochondrial ribosomal protein L55	12199	-0.638	-0.5026	Yes
18	<a href="#">BCKDHB</a>	BCKDHB <a href="#">Entrez</a> , <a href="#">Source</a>	branched chain keto acid dehydrogenase E1, beta polypeptide (maple syrup urine disease)	12567	-0.709	-0.4875	Yes
19	<a href="#">MRPS18A</a>	MRPS18A <a href="#">Entrez</a> , <a href="#">Source</a>	mitochondrial ribosomal protein S18A	12653	-0.726	-0.4525	Yes
20	<a href="#">MRPL10</a>	MRPL10 <a href="#">Entrez</a> , <a href="#">Source</a>	mitochondrial ribosomal protein L10	12687	-0.732	-0.4136	Yes
21	<a href="#">ETF A</a>	ETF A <a href="#">Entrez</a> , <a href="#">Source</a>	electron-transfer-flavoprotein, alpha polypeptide (glutaric aciduria II)	12887	-0.773	-0.3836	Yes
22	<a href="#">MRPL40</a>	MRPL40 <a href="#">Entrez</a> , <a href="#">Source</a>	mitochondrial ribosomal protein L40	12903	-0.778	-0.3410	Yes
23	<a href="#">MRPS21</a>	MRPS21 <a href="#">Entrez</a> , <a href="#">Source</a>	mitochondrial ribosomal protein S21	13040	-0.810	-0.3047	Yes

24	<a href="#">BCKDHA</a>	<a href="#">BCKDHA</a> <a href="#">Entrez</a> , <a href="#">Source</a>	branched chain keto acid dehydrogenase E1, alpha polypeptide	13063	-0.815	-0.2604	Yes
25	<a href="#">MRPL51</a>	<a href="#">MRPL51</a> <a href="#">Entrez</a> , <a href="#">Source</a>	mitochondrial ribosomal protein L51	13132	-0.837	-0.2181	Yes
26	<a href="#">DNAJA3</a>	<a href="#">DNAJA3</a> <a href="#">Entrez</a> , <a href="#">Source</a>	DnaJ (Hsp40) homolog, subfamily A, member 3	13866	-1.077	-0.2068	Yes
27	<a href="#">DBT</a>	<a href="#">DBT</a> <a href="#">Entrez</a> , <a href="#">Source</a>	dihydrolipoamide branched chain transacylase E2	14644	-1.712	-0.1630	Yes
28	<a href="#">ALDH4A1</a>	<a href="#">ALDH4A1</a> <a href="#">Entrez</a> , <a href="#">Source</a>	aldehyde dehydrogenase 4 family, member A1	14903	-3.250	0.0019	Yes



**Fig 2: MITOCHONDRIAL\_MATRIX**  
**Blue-Pink O' Gram in the Space of the Analyzed GeneSet**

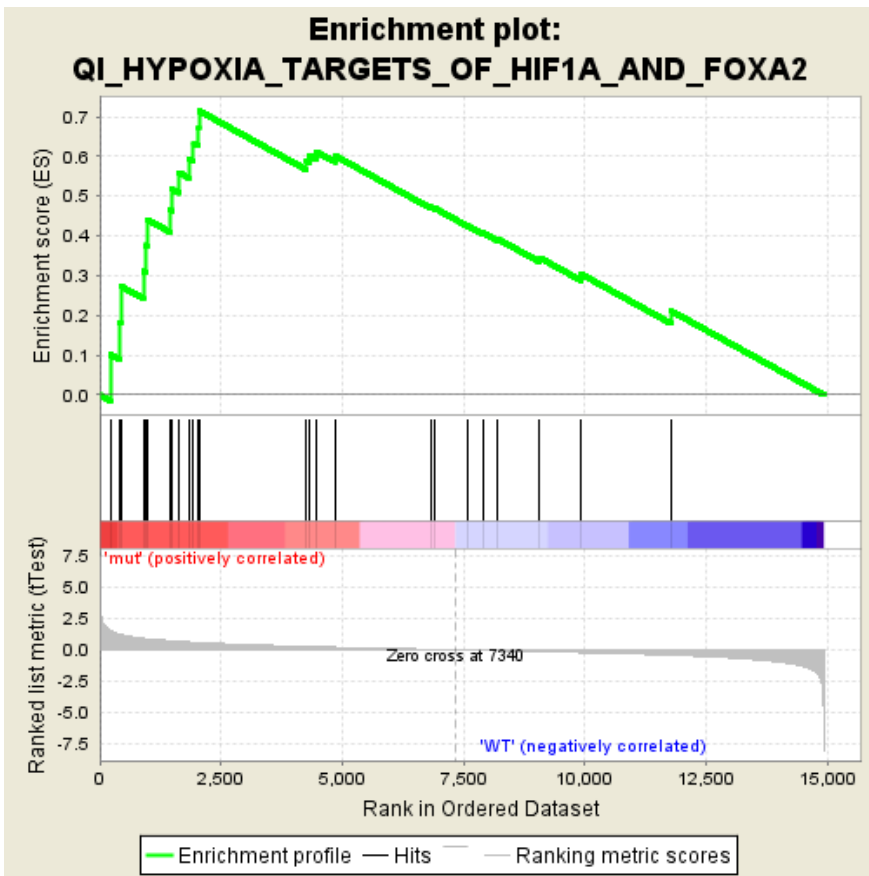


**Fig 3: MITOCHONDRIAL\_MATRIX: Random ES distribution**  
**Gene set null distribution of ES for MITOCHONDRIAL\_MATRIX**

Fig S10

**Table: GSEA Results Summary**

Dataset	MB_6M_collapsed_to_symbols.general.cls#mut_versus_WT
Phenotype	general.cls#mut_versus_WT
Upregulated in class	mut
GeneSet	QI_HYPOXIA_TARGETS_OF_HIF1A_AND_FOXA2
Enrichment Score (ES)	0.71504146
Normalized Enrichment Score (NES)	2.1899784
Nominal p-value	0.0
FDR q-value	0.014409064
FWER p-Value	0.015



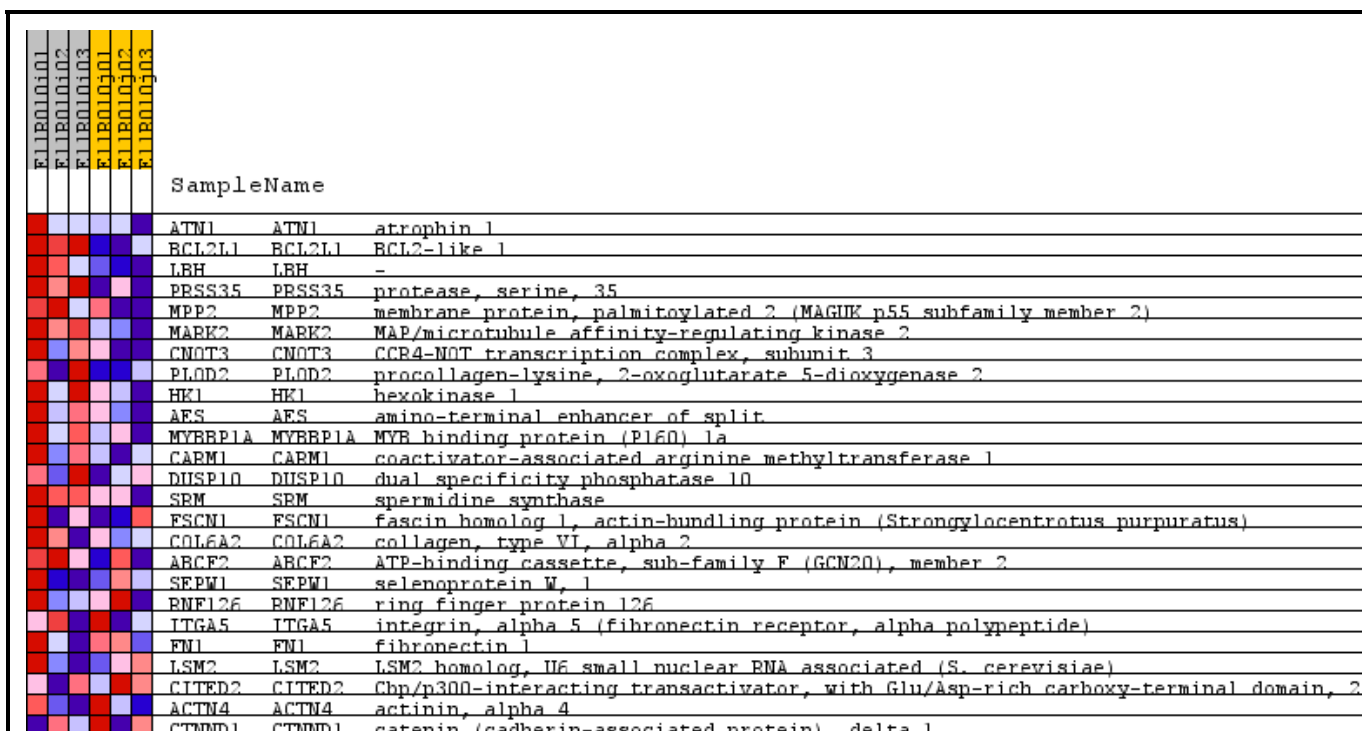
**Fig 1: Enrichment plot: QI\_HYPOXIA\_TARGETS\_OF\_HIF1A\_AND\_FOXA2**  
**Profile of the Running ES Score & Positions of GeneSet Members on the Rank Ordered List**

**Table: GSEA details [plain text format]**

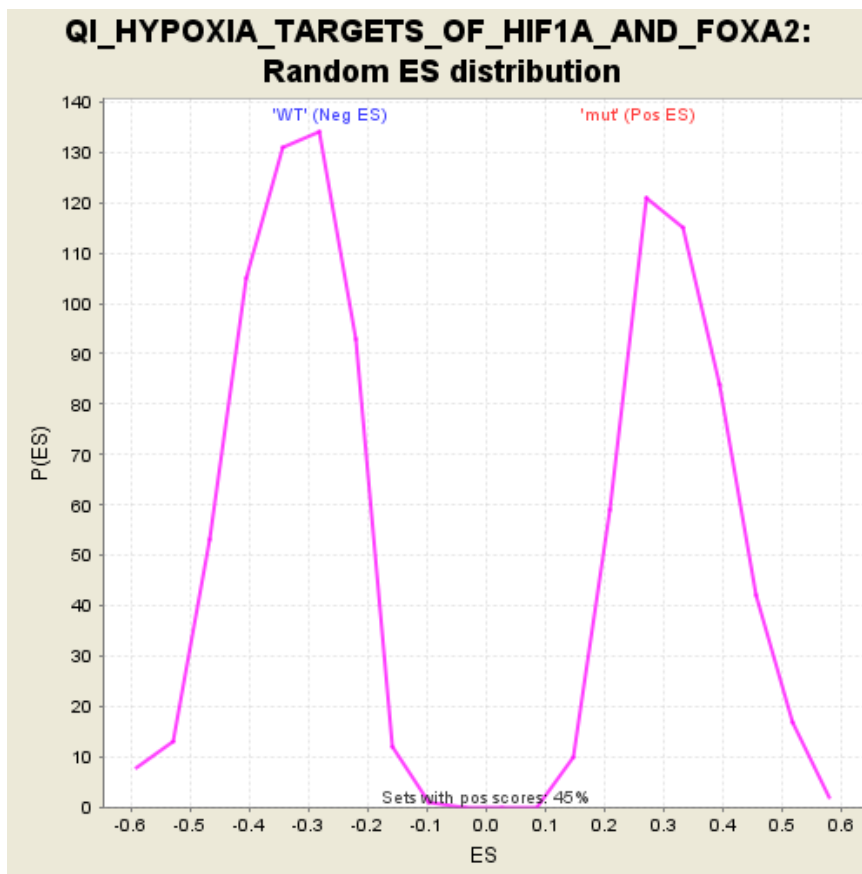
	PROBE	GENE SYMBOL	GENE_TITLE	RANK IN GENE LIST	RANK METRIC SCORE	RUNNING ES	CORE ENRICHMENT
1	<a href="#">ATN1</a>	ATN1 <a href="#">Entrez, Source</a>	atrophin 1	218	1.533	0.1012	Yes
2	<a href="#">BCL2L1</a>	BCL2L1 <a href="#">Entrez, Source</a>	BCL2-like 1	404	1.251	0.1832	Yes

3	<a href="#">LBH</a>	<a href="#">LBH</a> <a href="#">Entrez</a> , <a href="#">Source</a>	-	434	1.222	0.2735	Yes
4	<a href="#">PRSS35</a>	<a href="#">PRSS35</a> <a href="#">Entrez</a> , <a href="#">Source</a>	protease, serine, 35	900	0.917	0.3115	Yes
5	<a href="#">MPP2</a>	<a href="#">MPP2</a> <a href="#">Entrez</a> , <a href="#">Source</a>	membrane protein, palmitoylated 2 (MAGUK p55 subfamily member 2)	945	0.898	0.3764	Yes
6	<a href="#">MARK2</a>	<a href="#">MARK2</a> <a href="#">Entrez</a> , <a href="#">Source</a>	MAP/microtubule affinity-regulating kinase 2	974	0.887	0.4415	Yes
7	<a href="#">CNOT3</a>	<a href="#">CNOT3</a> <a href="#">Entrez</a> , <a href="#">Source</a>	CCR4-NOT transcription complex, subunit 3	1444	0.736	0.4656	Yes
8	<a href="#">PLOD2</a>	<a href="#">PLOD2</a> <a href="#">Entrez</a> , <a href="#">Source</a>	procollagen-lysine, 2-oxoglutarate 5-dioxygenase 2	1485	0.725	0.5176	Yes
9	<a href="#">HK1</a>	<a href="#">HK1</a> <a href="#">Entrez</a> , <a href="#">Source</a>	hexokinase 1	1636	0.685	0.5593	Yes
10	<a href="#">AES</a>	<a href="#">AES</a> <a href="#">Entrez</a> , <a href="#">Source</a>	amino-terminal enhancer of split	1835	0.633	0.5938	Yes
11	<a href="#">MYBBP1A</a>	<a href="#">MYBBP1A</a> <a href="#">Entrez</a> , <a href="#">Source</a>	MYB binding protein (P160) 1a	1934	0.611	0.6334	Yes
12	<a href="#">CARM1</a>	<a href="#">CARM1</a> <a href="#">Entrez</a> , <a href="#">Source</a>	coactivator-associated arginine methyltransferase 1	2039	0.590	0.6709	Yes
13	<a href="#">DUSP10</a>	<a href="#">DUSP10</a> <a href="#">Entrez</a> , <a href="#">Source</a>	dual specificity phosphatase 10	2045	0.589	0.7150	Yes
14	<a href="#">SRM</a>	<a href="#">SRM</a> <a href="#">Entrez</a> , <a href="#">Source</a>	spermidine synthase	4261	0.270	0.5868	No
15	<a href="#">FSCN1</a>	<a href="#">FSCN1</a> <a href="#">Entrez</a> , <a href="#">Source</a>	fascin homolog 1, actin-bundling protein ( <i>Strongylocentrotus purpuratus</i> )	4314	0.263	0.6032	No
16	<a href="#">COL6A2</a>	<a href="#">COL6A2</a> <a href="#">Entrez</a> , <a href="#">Source</a>	collagen, type VI, alpha 2	4461	0.249	0.6122	No
17	<a href="#">ABCF2</a>	<a href="#">ABCF2</a> <a href="#">Entrez</a> , <a href="#">Source</a>	ATP-binding cassette, sub-family F (GCN20), member 2	4850	0.209	0.6019	No
18	<a href="#">SEPW1</a>	<a href="#">SEPW1</a> <a href="#">Entrez</a> , <a href="#">Source</a>	selenoprotein W, 1	6823	0.042	0.4728	No
19	<a href="#">RNF126</a>	<a href="#">RNF126</a> <a href="#">Entrez</a> , <a href="#">Source</a>	ring finger protein 126	6904	0.035	0.4701	No
20	<a href="#">ITGA5</a>	<a href="#">ITGA5</a> <a href="#">Entrez</a> , <a href="#">Source</a>	integrin, alpha 5 (fibronectin receptor, alpha polypeptide)	7597	-0.018	0.4250	No
21	<a href="#">FN1</a>	<a href="#">FN1</a> <a href="#">Entrez</a> , <a href="#">Source</a>	fibronectin 1	7895	-0.042	0.4082	No

22	<a href="#">LSM2</a>	<a href="#">LSM2</a> <a href="#">Entrez</a> , <a href="#">Source</a>	LSM2 homolog, U6 small nuclear RNA associated ( <i>S. cerevisiae</i> )	8210	-0.067	0.3922	No
23	<a href="#">CITED2</a>	<a href="#">CITED2</a> <a href="#">Entrez</a> , <a href="#">Source</a>	Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain, 2	9073	-0.139	0.3449	No
24	<a href="#">ACTN4</a>	<a href="#">ACTN4</a> <a href="#">Entrez</a> , <a href="#">Source</a>	actinin, alpha 4	9929	-0.215	0.3038	No
25	<a href="#">CTNND1</a>	<a href="#">CTNND1</a> <a href="#">Entrez</a> , <a href="#">Source</a>	catenin (cadherin-associated protein), delta 1	11781	-0.420	0.2114	No



**Fig 2: QI\_HYPOXIA\_TARGETS\_OF\_HIF1A\_AND\_FOXA2**  
**Blue-Pink O' Gram in the Space of the Analyzed GeneSet**



**Fig 3: QI\_HYPOXIA\_TARGETS\_OF\_HIF1A\_AND\_FOXA2: Random ES distribution**  
**Gene set null distribution of ES for QI\_HYPOXIA\_TARGETS\_OF\_HIF1A\_AND\_FOXA2**

Fig S11

Table: GSEA Results Summary

Dataset	MB_6M_collapsed_to_symbols.general.cls#mut_versus_WT
Phenotype	general.cls#mut_versus_WT
Upregulated in class	mut
GeneSet	PID_ATM_PATHWAY
Enrichment Score (ES)	0.5320049
Normalized Enrichment Score (NES)	1.6343192
Nominal p-value	0.006342495
FDR q-value	1.0
FWER p-Value	1.0

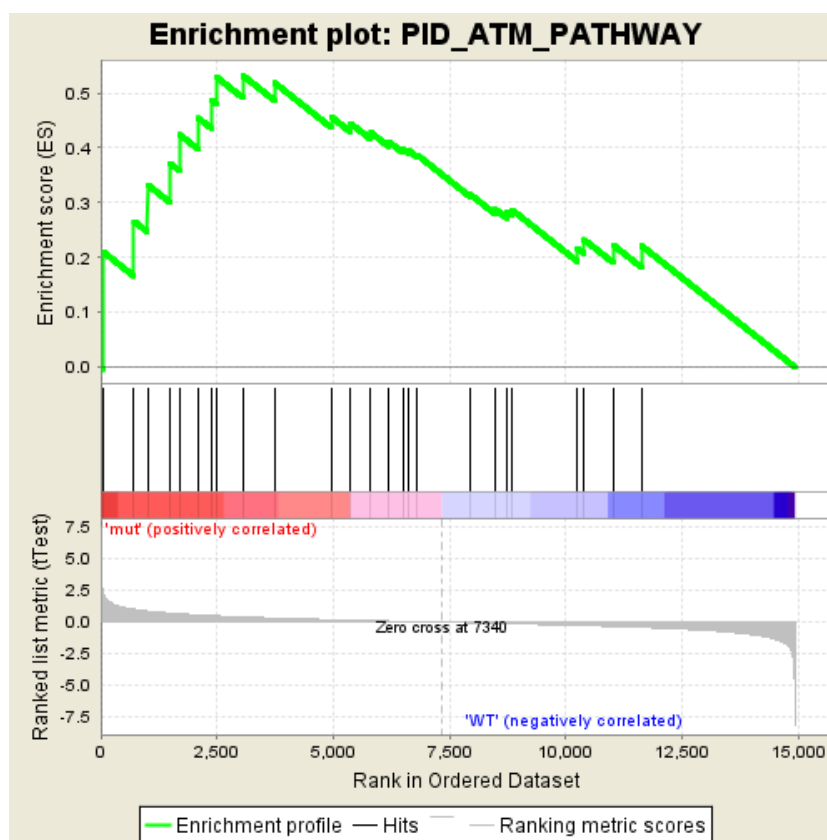


Fig 1: Enrichment plot: PID\_ATM\_PATHWAY  
Profile of the Running ES Score & Positions of GeneSet Members on the Rank Ordered List

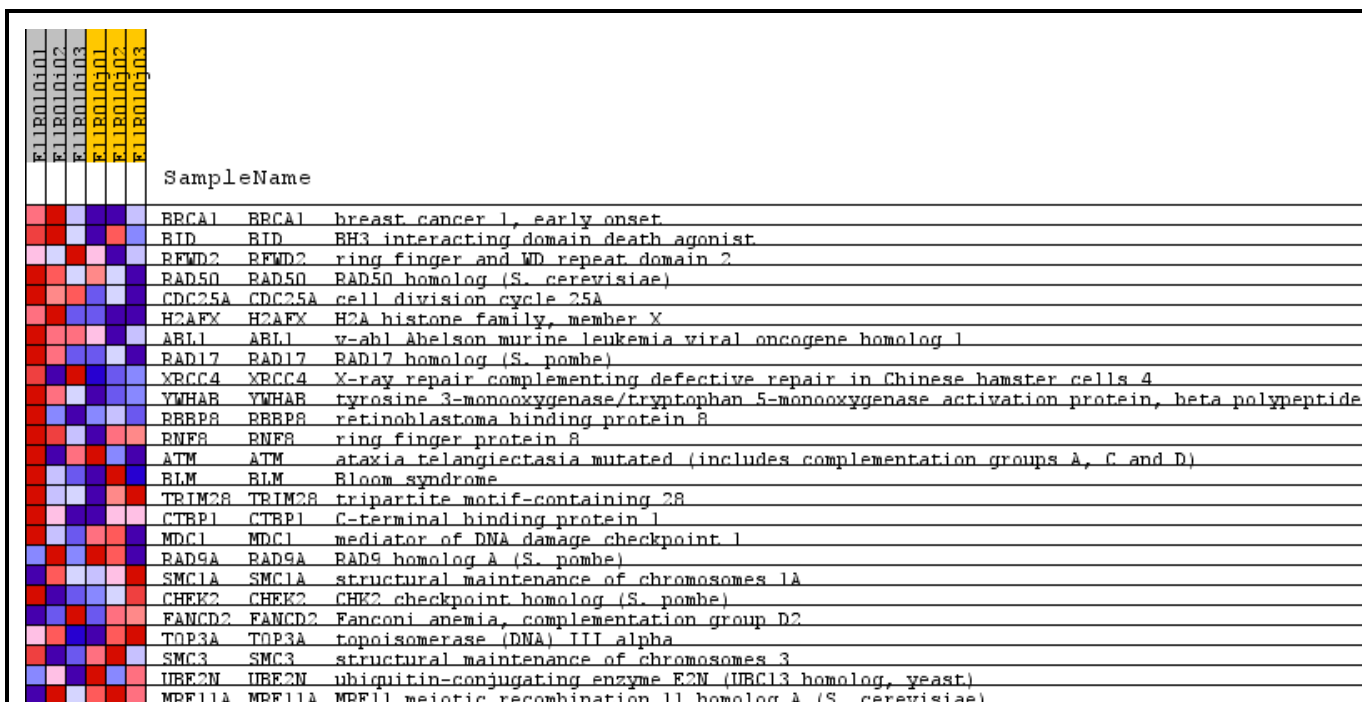
Table: GSEA details [plain text format]

	PROBE	GENE SYMBOL	GENE_TITLE	RANK IN GENE LIST	RANK METRIC SCORE	RUNNING ES	CORE ENRICHMENT
1	<a href="#">BRCA1</a>	BRCA1 <a href="#">Entrez</a> , <a href="#">Source</a>	breast cancer 1, early onset	66	2.166	0.2090	Yes
2	<a href="#">BID</a>	BID <a href="#">Entrez</a> , <a href="#">Source</a>	BH3 interacting domain death agonist	713	1.018	0.2660	Yes
3	<a href="#">RFWD2</a>	RFWD2 <a href="#">Entrez</a> , <a href="#">Source</a>	ring finger and WD repeat domain 2	1002	0.874	0.3328	Yes

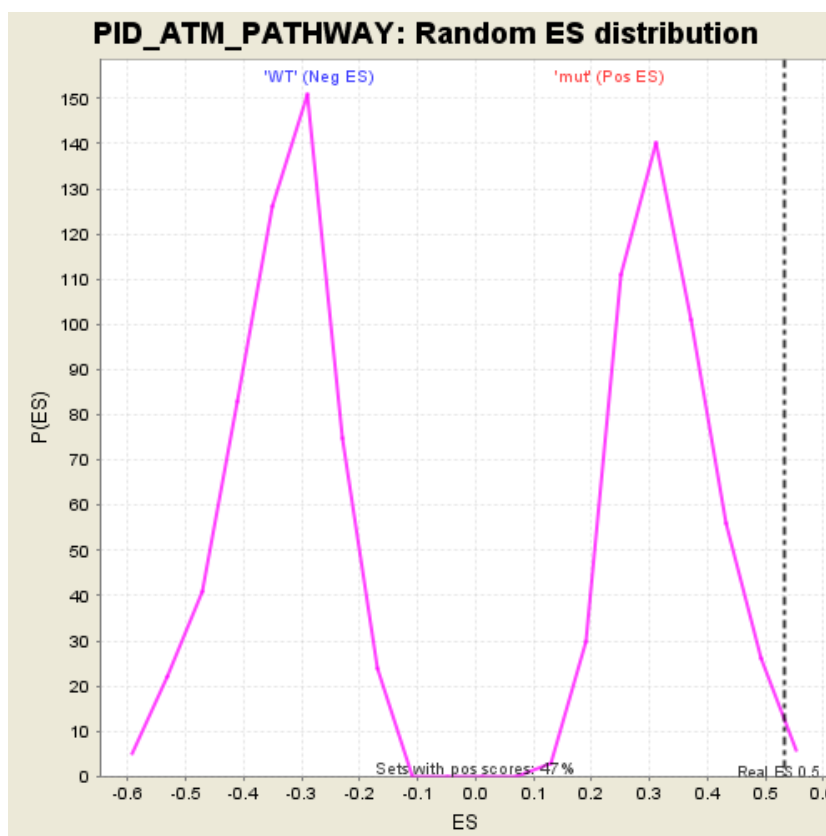


4	<a href="#">RAD50</a>	<a href="#">RAD50</a> <a href="#">Entrez</a> , <a href="#">Source</a>	RAD50 homolog (S. cerevisiae)	1495	0.723	0.3711	Yes
5	<a href="#">CDC25A</a>	<a href="#">CDC25A</a> <a href="#">Entrez</a> , <a href="#">Source</a>	cell division cycle 25A	1692	0.673	0.4242	Yes
6	<a href="#">H2AFX</a>	<a href="#">H2AFX</a> <a href="#">Entrez</a> , <a href="#">Source</a>	H2A histone family, member X	2094	0.580	0.4545	Yes
7	<a href="#">ABL1</a>	<a href="#">ABL1</a> <a href="#">Entrez</a> , <a href="#">Source</a>	v-abl Abelson murine leukemia viral oncogene homolog 1	2374	0.523	0.4873	Yes
8	<a href="#">RAD17</a>	<a href="#">RAD17</a> <a href="#">Entrez</a> , <a href="#">Source</a>	RAD17 homolog (S. pombe)	2498	0.501	0.5284	Yes
9	<a href="#">XRCC4</a>	<a href="#">XRCC4</a> <a href="#">Entrez</a> , <a href="#">Source</a>	X-ray repair complementing defective repair in Chinese hamster cells 4	3053	0.414	0.5320	Yes
10	<a href="#">YWHAB</a>	<a href="#">YWHAB</a> <a href="#">Entrez</a> , <a href="#">Source</a>	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, beta polypeptide	3739	0.329	0.5185	No
11	<a href="#">RBBP8</a>	<a href="#">RBBP8</a> <a href="#">Entrez</a> , <a href="#">Source</a>	retinoblastoma binding protein 8	4954	0.199	0.4567	No
12	<a href="#">RNF8</a>	<a href="#">RNF8</a> <a href="#">Entrez</a> , <a href="#">Source</a>	ring finger protein 8	5376	0.161	0.4443	No
13	<a href="#">ATM</a>	<a href="#">ATM</a> <a href="#">Entrez</a> , <a href="#">Source</a>	ataxia telangiectasia mutated (includes complementation groups A, C and D)	5809	0.126	0.4277	No
14	<a href="#">BLM</a>	<a href="#">BLM</a> <a href="#">Entrez</a> , <a href="#">Source</a>	Bloom syndrome	6187	0.093	0.4116	No
15	<a href="#">TRIM28</a>	<a href="#">TRIM28</a> <a href="#">Entrez</a> , <a href="#">Source</a>	tripartite motif-containing 28	6499	0.068	0.3974	No
16	<a href="#">CTBP1</a>	<a href="#">CTBP1</a> <a href="#">Entrez</a> , <a href="#">Source</a>	C-terminal binding protein 1	6630	0.058	0.3944	No
17	<a href="#">MDC1</a>	<a href="#">MDC1</a> <a href="#">Entrez</a> , <a href="#">Source</a>	mediator of DNA damage checkpoint 1	6807	0.043	0.3869	No
18	<a href="#">RAD9A</a>	<a href="#">RAD9A</a> <a href="#">Entrez</a> , <a href="#">Source</a>	RAD9 homolog A (S. pombe)	7948	-0.046	0.3150	No
19	<a href="#">SMC1A</a>	<a href="#">SMC1A</a> <a href="#">Entrez</a> , <a href="#">Source</a>	structural maintenance of chromosomes 1A	8491	-0.091	0.2877	No
20	<a href="#">CHEK2</a>	<a href="#">CHEK2</a> <a href="#">Entrez</a> , <a href="#">Source</a>	CHK2 checkpoint homolog (S. pombe)	8729	-0.112	0.2828	No
21	<a href="#">FANCD2</a>	<a href="#">FANCD2</a> <a href="#">Entrez</a> , <a href="#">Source</a>	Fanconi anemia, complementation group D2	8839	-0.120	0.2873	No
22	<a href="#">TOP3A</a>	<a href="#">TOP3A</a> <a href="#">Entrez</a> , <a href="#">Source</a>	topoisomerase (DNA) III alpha	10252	-0.244	0.2166	No
23	<a href="#">SMC3</a>	<a href="#">SMC3</a> <a href="#">Entrez</a> , <a href="#">Source</a>	structural maintenance of chromosomes 3	10393	-0.258	0.2326	No

24	<a href="#">UBE2N</a>	<a href="#">Entrez</a> , <a href="#">Source</a>	ubiquitin-conjugating enzyme E2N (UBC13 homolog, yeast)	11028	-0.327	0.2223	No
25	<a href="#">MRE11A</a>	<a href="#">Entrez</a> , <a href="#">Source</a>	MRE11 meiotic recombination 11 homolog A (S. cerevisiae)	11632	-0.401	0.2214	No



**Fig 2: PID\_ATM\_PATHWAY**  
*Blue-Pink O' Gram in the Space of the Analyzed GeneSet*



**Fig 3: PID\_ATM\_PATHWAY: Random ES distribution**  
*Gene set null distribution of ES for PID\_ATM\_PATHWAY*