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Subtype specific promoter methylation in glioblastoma

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Abstract: Glioblastoma is known to be the most lethal glioma and five year survival rate is only 10 %. Thus, it is urgent to identify critical genes for glioblastoma therapy. In this paper, we have analysed promoter methylation profiles downloaded from The Cancer Genome Atlas using recently proposed principal component analysis based unsupervised feature extraction. New set of genes with aberrant promoter methylation associated with previously identified subtypes was identified.

1. Introduction

Glioblastoma is the most lethal glioma wish very little five year survival rate[1]. Thus, identification of critical genes for therapy purpose of glioblastoma is urgent. In this paper, we applied recently proposed [2], [3], [4], [5] principal component analysis (PCA) based unsupervised feature extraction (FE) to promoter methylation profiles of glioblastoma downloaded from The Cancer Genome Atlas (TCGA)[6]. We have identified genes with aberrant promoter methylation associated with previously identified subtypes [7].

2. Results

By applying PCA based unsupervised FE, we have identified that the second principal component (PC2) exhibits distinction between subtypes. Fig. 1 shows the contribution to PC2 from samples (see Table 1 for *P*-values).

Table 1 *P*-values computed by *t* test that rejects null hypothesis (row and column have same mean) in favour of the hypothesis that column has larger mean than row.

	Classical	Neural	Mesenchymal
Proneural	0.0004	0.0001	0.000015
Classical		0.058	0.000019
Neural			0.052

Since PC2 turned out to exhibit distinction between samples, we have selected probes with larger absolute PC2 scores. Fig. 2 shows promoter methylation profiles of top ranked 12 outlier probes along PC2 in negative or positive direction. For most probes, only Proneural subtypes are significantly larger or less than other subtypes. Thus, PC2 possibly indicates the aberrant hyper/hypomethylation associated with Proneural subtype. Although Verhaak et al[7] identified subtype with gene expression, in this study proneual subtype has also associated aberrant promoter meythylation.

Next, in order to confirm if genes associated with identified probes are related to cancers, we have used gendoo[8] and DisGeNet[9] (Table 2). Among 42 genes listed, 31 genes (74 %) were reported to be related to cancer related genes by either gendoo or DisGeNet. Two genes (ERBB2 and LRRC4) were reported to be related to glioblastoma, additional five genes (TTC12, LGALS3, WFDC2, BCAT2, ANK3) were related to other neuronal tumor. Thus, PCA based unsupervised FE seemed to work pretty well.

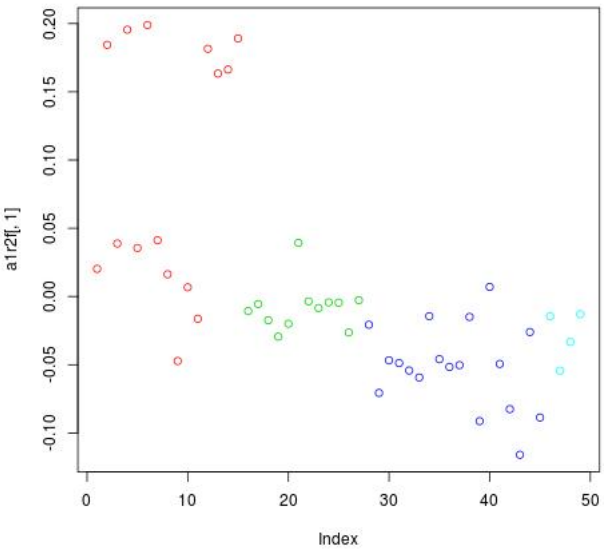

Fig. 1 Contribution to the second principal component from samples. Red: Proneural, green: Classical, blue: Mesenchymal, cyan: Neural.

3. Conclusion

In this paper, PCA based unsupervised FE was applied to promoter methylation of glioblastoma. Many subtype specific aberrant promoter methylayion was identified.

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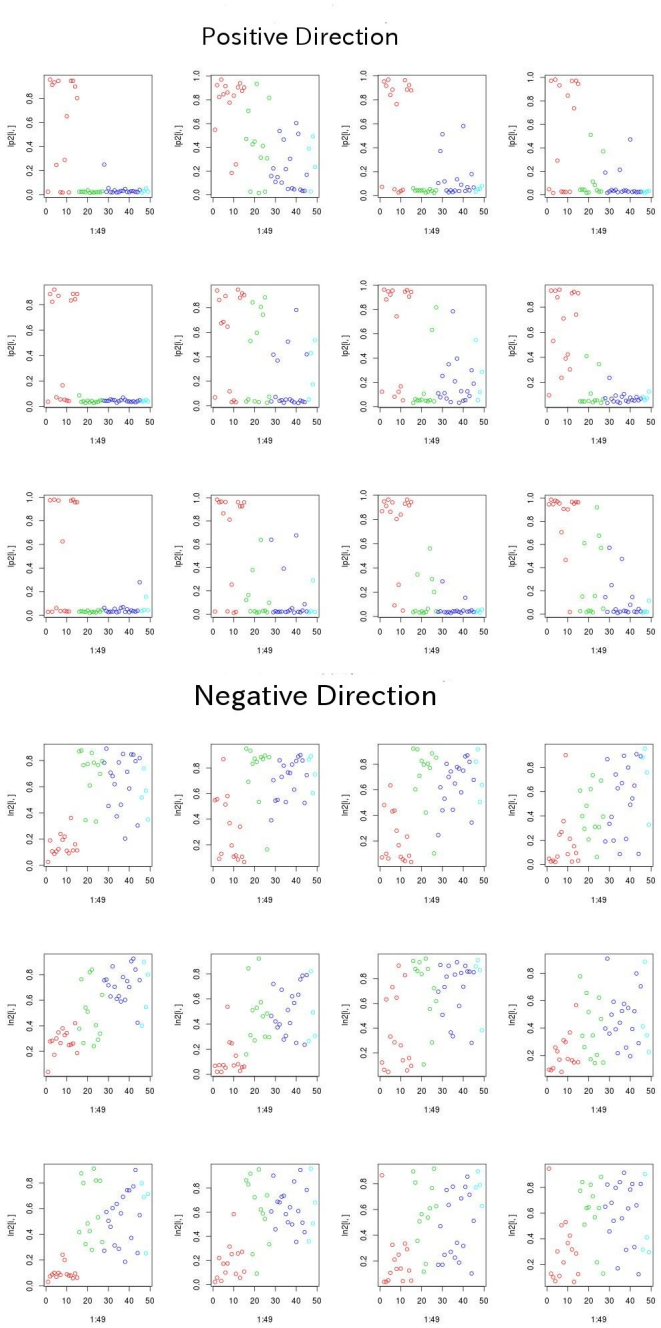

Fig. 2 Promoter methylation of individual probes. Upper panel: with larger PC2 scores. Lower panel: with smaller (negatively larger) PC2 scores. For each panel, from the bottom-left corner to bottom-right corner, middle-left to middle-right, and top-left corner to top-right corner, is the rank order of absolute PC2 scores. Color is the same as Fig. 1.

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Table 2 Cancer related diseases association of genes associated with selected probes with aberrant promoter methylation associated with glioblastoma. Outliers along PC2 with positive/nagative PC scores. Bolded: Glioblastoma, Underlined: other neuronal tumor

Positive direction	
TTC12	Leukemia-Lymphoma; Neuroblastoma; Melanoma;
SERPINB9	Lymphoma, T/b-Cell; Skin Neoplasms; Melanoma; Neoplasms
GNMT	Carcinoma, Hepatocellular; Liver Neoplasms;
VEPH1	Neoplasms
RNU5E	—
RNU5D	—
CKMT2	Leukemia, Myeloid, Acute
SEMA5A	Neoplasm Metastasis
LGALS3	Brain Neoplasms; Nerve Sheath Neoplasms
XKR8	—
ADAM12	Bone Neoplasms; Breast Neoplasms; Plasmacytoma
RSPH9	—
ERBB2	**Glioblastoma**; Breast Neoplasms; Lymphatic Metastasis
WFDC2	Neuroblastoma; Ovarian Neoplasms; Lung Neoplasms
BCAT2	Neuroblastoma;
CYB561	—
RBP1	Leiomyoma; Breast Neoplasms; Breast Neoplasms
CCDC109B	Stomach Neoplasms
HIST1H1A	Lymphoma; Kidney Neoplasms
Negative direction	
TRAPPC2	—
OFD1	Neoplasms
ACTL6B	Neoplasms
SLAIN1	—
MYT1	Oligodendroglioma; Astrocytoma
G6PC2	Insulinoma; Astrocytoma
SLC34A1	—
C22orf23	—
POLR2F	Neoplasm Metastasis;Colorectal Neoplasms
GTF2F2	Leukemia, Erythroblastic, Acute; Leukemia, Experimental
KCTD4	—
OR1G1	—
ARPP-21	—
APOD	Breast Neoplasms; Sweat Gland Neoplasms;Neurofibroma
CAPZB	Neoplasms
LRRC4	**Glioblastoma**; Brain Neoplasms; Glioma
SND1	Lymphoma, B-Cell; Neoplasms, Mesothelial; Carcinoma
LRTM1	—
CACNA2D3	Carcinoma, Renal Cell; Kidney Neoplasms; Stomach Neoplasms
JPH4	—
ANK3	Peripheral Nervous System Neoplasms; Neuroma; Neurofibroma, Plexiform
OBP2B	Neoplasms; Neurodegenerative Diseases
TAAR6	Neoplasms; Mental Disorders

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