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MMSET is overexpressed in cancers: link with tumor aggressiveness

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Abstract:

MMSET is expressed ubiquitously in early development and its deletion is associated with the malformation syndrome called Wolf-hirschhorn syndrome. It is involved in the t(4;14)(p16;q32) chromosomal translocation, which is the second most common translocation in multiple myeloma (MM) and is associated with the worst prognosis. MMSET expression has been shown to promote cellular adhesion, clonogenic growth and tumorigenicity in multiple myeloma. MMSET expression has been recently shown to increase with ascending tumor proliferation activity in glioblastoma multiforme. These data demonstrate that MMSET could be implicated in tumor emergence and/or progression. Therefore we compared the expression of MMSET in 40 human tumor types – brain, epithelial, lymphoid – to that of their normal tissue counterparts using publicly available gene expression data, including the Oncomine Cancer Microarray database. We found significant overexpression of *MMSET* in 15 cancers compared to their normal counterparts. Furthermore MMSET is associated with tumor aggressiveness or prognosis in many types of these aforementioned cancers.

Taken together, these data suggest that MMSET potentially acts as a pathogenic agent in many cancers. The identification of the targets of MMSET and their role in cell growth and survival will be key to understand how MMSET is associated with tumor development.

Introduction

MMSET gene is expressed ubiquitously in early development. The Wolf-hirschhorn syndrome is a malformation syndrome associated with a homozygous deletion of the distal short arm of chromosome 4 containing MMSET gene[1].

The *MMSET* gene is involved in the t(4;14)(p16;q32) chromosomal translocation, which is the most common translocation in multiple myeloma (MM) – occurring in 15% of newly-diagnosed patients – and is associated with poor prognosis[1; 2; 3]. The t(4;14) translocation dysregulates both *MMSET* and *FGFR3* genes that are closely located on chromosome 4p16. *FGFR3* has oncogenic activity in vitro and in vivo, but approximately one-third of MM tumors harboring t(4;14) translocation lacks *FGFR3* expression, whereas an overexpression of *MMSET* is a universal characteristic of t(4;14) cases[3; 4; 5]. Furthermore, the poor prognosis of t(4;14) is independent of *FGFR3* expression. These data suggest that activation of *MMSET*, not *FGFR3*, may be the critical transforming event of this recurrent translocation[1; 3; 5].

MMSET gene encodes for three isoforms including MMSET type I (647 aa) and type II (1365 aa) as a result of alternative splicing, and a 584 aa protein, known as RE-IIB (response element II-binding protein) translated from a second transcription initiation site. *MMSET* isoforms share various conserved protein domains suggesting a role in DNA-binding and chromatin modification, including PWWP domains, an HMG domain, PHD zinc fingers, and a C-terminal SET domain characteristic of histone methyltransferases[1].

The biological role of *MMSET* in MM disease is still poorly understood. A direct evidence shows that *MMSET* expression contributes to cellular adhesion, clonogenic

growth and tumorigenicity in multiple myeloma [1]. MMSET contains a SET domain that is found in many histone methyltransferases and determines their enzymatic activity. Histone lysine methylation promotes or prevents binding of proteins and protein complexes that drive particular regions of the genome into active transcription or repression[6]. MMSET has a transcriptional repressor activity, with increased H4K20 methylation gene and loss of histone acetylation. Consistent with this repressive activity, MMSET could form a complex with HDAC1 and HDAC2, mSin3a and the histone demethylase LSD1 suggesting that it is a component of transcription co-repressor complexes[7]. Moreover, RE-IIB (IL5 response element II-binding protein) has been recently demonstrated to repress IL-5 expression, through the histone H3-K27 hyper-methylation around promoter region and H3 hypo-acetylation[8].

Collectively, these data suggest that by acting directly as a modifier of chromatin as well as through binding of other chromatin modifying enzymes, MMSET may influence gene expression and potentially acts as a pathogenic agent in MM. The identification of the targets of MMSET and their role in cell growth and survival will be key to understand how MMSET is associated with tumor development[7].

Recent study has identified an aberrant expression of *MMSET* mRNA and protein in glioblastoma multiform compared to normal brain cortex samples using proteomic approach[9]. They demonstrated that MMSET expression increased with ascending tumor proliferation activity. Furthermore, RNA interference blocking *MMSET* expression suppresses glioma cells growth[9].

These data demonstrate that MMSET could be implicated in tumor emergence and/or progression. Therefore, we focussed on *MMSET* expression in various cancers compared to their normal counterparts and in association with staging.

Methods

Databases

We used oncomine cancer microarray database (<http://www.oncomine.org>)[10] to study gene expression of *MMSET* in 40 human tumor types and their normal tissue counterpart as indicated in table 1. To compare the gene expression of a tumor type to its normal counterpart, we used gene expression data from a same study with the same methodology. All data were log transformed, median centered per array, and the standard deviation was normalized to one per array[10].

Statistical analysis

Statistical comparisons were done with Mann Whitney or student t-test.

Results and discussion

We investigated the expression of *MMSET* in cancer using publicly available gene expression data. The 40 tumor types investigated corresponded to 4 hematological malignancies and 36 solid tumors (Table 1). We found *MMSET* overexpression in all hematological cancers and in 12/36 solid tumors (Table 1 and Supplementary figure S1). Overexpression of *MMSET* was found in glioblastoma compared to normal brain ($P = 1.7E-14$, $P = .009$, $P = .002$)[11; 12; 13]; in hepatocellular carcinoma compared to normal liver ($P = 2.9E-7$, $1.3E-6$) [14; 15]; in head and neck cancer compared to the normal ($P = .008$, $P = 2.7E-5$)[16; 17]; in bladder carcinoma compared to normal bladder ($P = 4.1E-11$, $P = 1.8E-7$)[18; 19]; in primary colon cancer compared to normal adjacent mucosa ($P = 9.5E-6$)[20]; in esophagus adenocarcinoma compared to normal esophagus ($P = .004$)[21]; in breast carcinoma compared to normal breast ($P = 3.8E-$

8)[22]; in T-cell acute lymphoblastic leukemia compared to normal bone marrow ($P = 5.1E-7$)[23]; in B-cell acute lymphoblastic leukaemia compared to normal bone marrow ($P = .001$)[23]; in lung adenocarcinoma compared to normal lung ($P = .009$, $P = 8.4E-4$, $1.7E-6$)[24; 25; 26]; in lymphoma compared to normal B-cell ($P = 3.5E-5$, $7.3E-5$)[27]; in cutaneous melanoma compared to normal melanocyte ($P = 6.46E-13$, $P = .01$, $P = .009$)[28; 29; 30]; in smoldering multiple myeloma compared to normal bone marrow ($P = 7.3E-4$)[31]; in prostate cancer compared to normal prostate ($P = 1.8E-6$, $P = .039$, $P = 5.1E-8$, $P = .002$, $P = .009$, $P = .006$, $P = .009$)[32; 33; 34; 35; 36; 37; 38]; in yolk sac tumor compared to normal testis ($P = .003$)[39]; in ovarian carcinoma compared to normal ovary ($P = .002$, $P = 1.1E-4$)[40; 41] and in clear cell carcinoma compared to normal kidney tissue ($P = .006$)[42].

MMSET has been shown to be highly overexpressed in MM with t(4;14), in association with poor prognosis. Thus, we looked for whether *MMSET* expression could be associated with tumor progression and prognosis. *MMSET* was significantly overexpressed in oligodendroglioma grade III compared to grade II ($P = .009$)[11] (Figure 1) in agreement with previous data[9]; in patients presenting advanced bladder carcinoma (grade II and III) compared to grade I in four independent studies ($P = 4E-6$, $P = .0001$, $P = .004$, $P = .008$)[19; 43; 44; 45]; in breast carcinoma grades II and III compared to grade I in four independent studies ($P = 2.2E-6$, $P = 9.1E-4$, $P = .014$, $P = .017$)[46; 47; 48; 49]; in advanced prostate carcinoma grades VII, VIII and IX compared to grade VI ($P = 1.4E-4$)[50]; in no differentiated hepatocellular carcinoma compared to differentiated hepatocellular carcinoma ($P = 7.2E-5$)[15]; in undifferentiated compared to differentiated head and neck cancer ($P = .002$)[17]; in undifferentiated compared to

differentiated cervical carcinoma[51]; in advanced papillary renal cell carcinoma stages III and IV compared to stages I and II ($P = .0039$)[52](Figure 1).

Furthermore, as it has been demonstrated in MM, *MMSET* expression is associated with bad prognostic in others cancers (Figure 2). *MMSET* is overexpressed in patients with head and neck squamous cell carcinoma dead at 5 years compared to patients alive at 5 years ($P = 1.2E-4$)[53]; in 1 year relapsing MM patient compared to patients with no relapse ($P = 3.2E-4$)[54]; in MM patients alive compared to dead MM patient at one year ($P = .001$)[54]; in prostate carcinoma patients presenting recurrence compared to prostate carcinoma patients with no recurrence ($P = 1.5E-4$) at 5 years [50] and in dead glioma patients compared to alive glioma patients at 3 years ($P = .009$) [55].

Correlations between *MMSET* and HDAC expression in tumor cells

In patients with MM, it was recently demonstrated that *MMSET* could form a complex with HDAC1 and HDAC2, mSin3a and the histone demethylase LSD1 suggesting that *MMSET* is a component of transcription co-repressor complexes. Interestingly, the genes of at least one of these four *MMSET* partners are overexpressed in cancers presenting a *MMSET* overexpression compared to their normal counterpart (Supplementary Table 1). Furthermore, *HDAC1*, *HDAC2* and *LSD1* overexpression are associated with tumor aggressiveness, as *MMSET*, in brain and liver cancers (Supplementary Table 2). Furthermore a high expression of the *MMSET* partners is associated with prognosis in brain cancer (Supplementary Table 3). *HDAC2* and *LSD1* overexpression is also associated with breast and lung progression; and they are associated with prognosis in breast cancer (Supplementary Table 3).

Conclusions:

The analysis reported here demonstrates that *MMSET* mRNA is overexpressed in at least in 15 cancers compared to their normal counterparts, and within a given tumor categories is associated with tumor progression or bad prognosis. The properties of transcriptional co-factor of MMSET appear to be associated with tumorigenesis. The identification of the targets of MMSET and their role in cell growth and survival will be key to understanding how MMSET is associated with tumor development.

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Figure legends

Figure 1: Association between MMSET expression and progression in various cancers

MMSET gene expression in oligodendroglioma [9], bladder[19; 43; 44; 45], breast carcinoma [46; 47; 48; 49], prostate carcinoma[50], in hepatocellular carcinoma [15], head and neck cancer[17], cervical carcinoma[51], papillary renal cell carcinoma[52].

Figure 2: Association of MMSET expression with prognosis

MMSET expression in alive patients with head and neck carcinoma, in dead patients with head and neck carcinoma [53], in MM patients with no relapse, in MM patients with relapse[54], in alive and dead patients with MM [54], in prostate carcinoma patients with no recurrence, prostate carcinoma patients with recurrence [50], in alive and dead patients with glioma [55].

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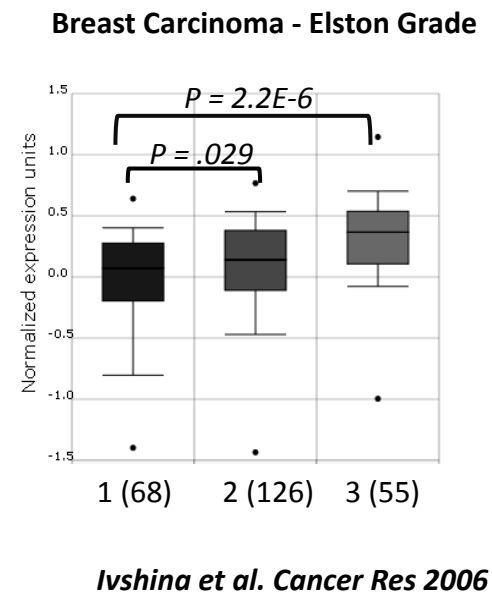
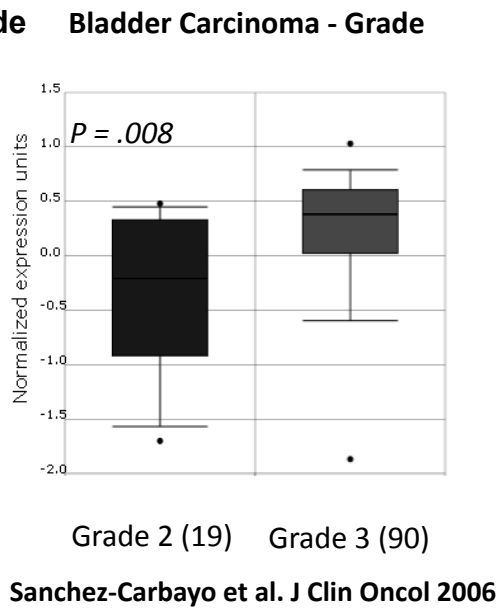
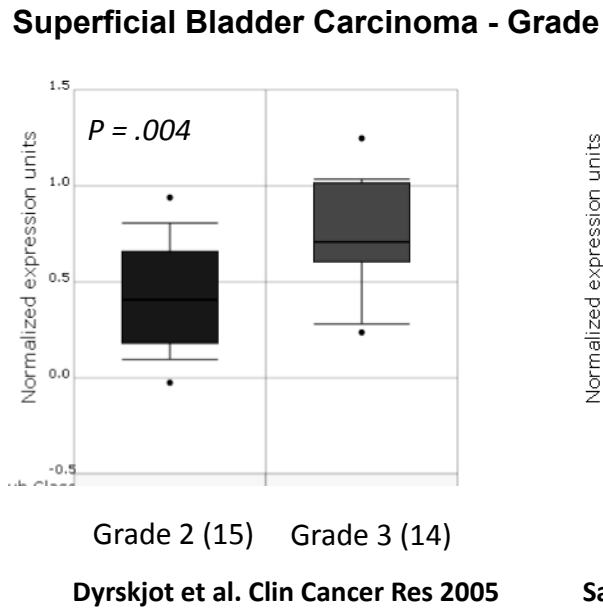
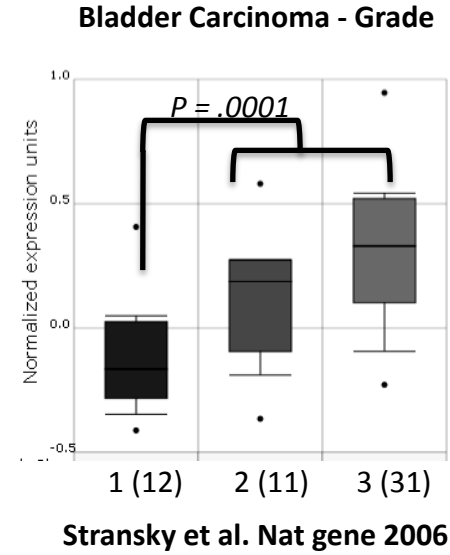
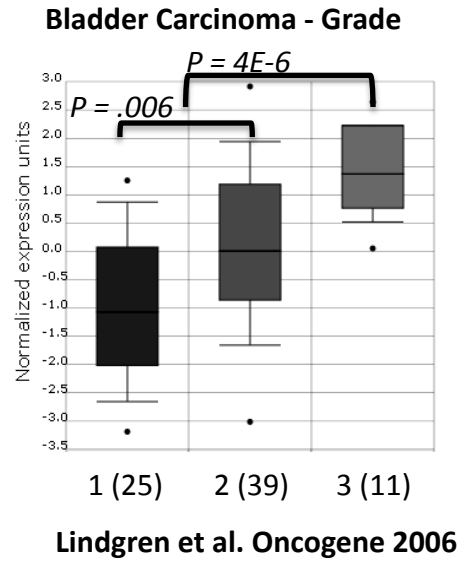
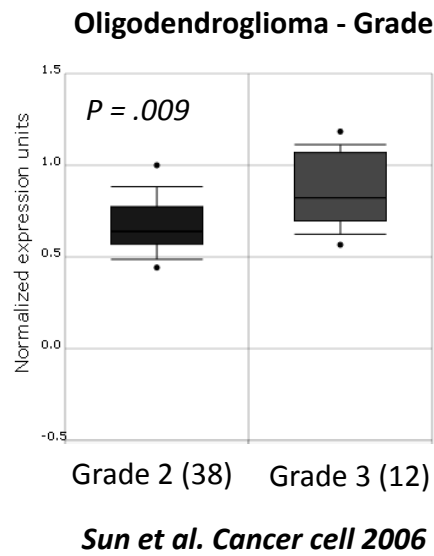
Table 1

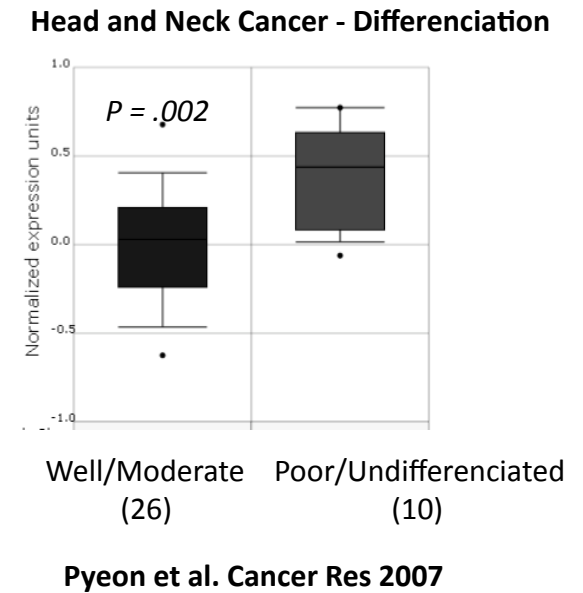
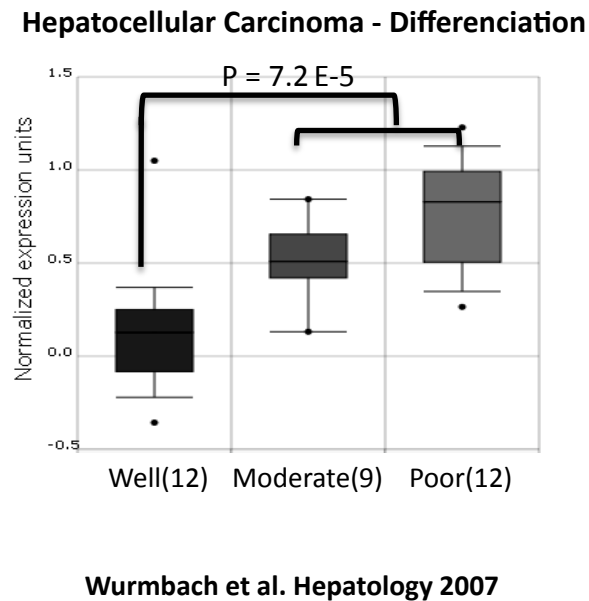
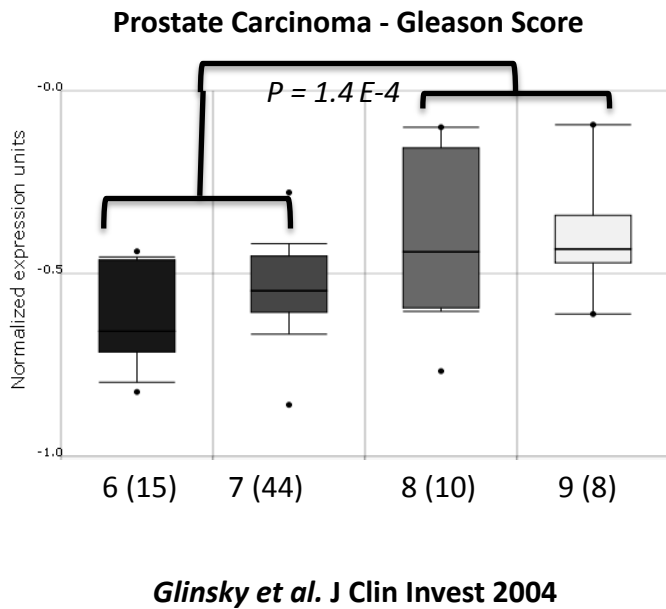
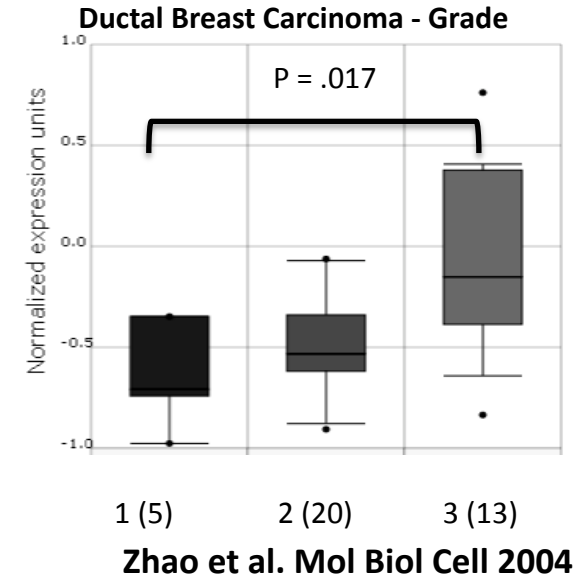
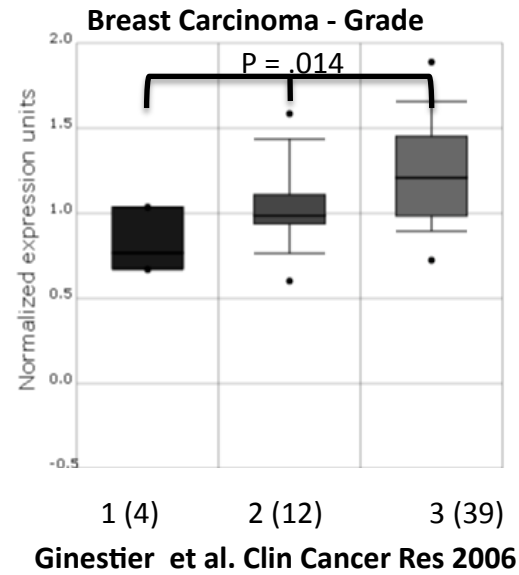
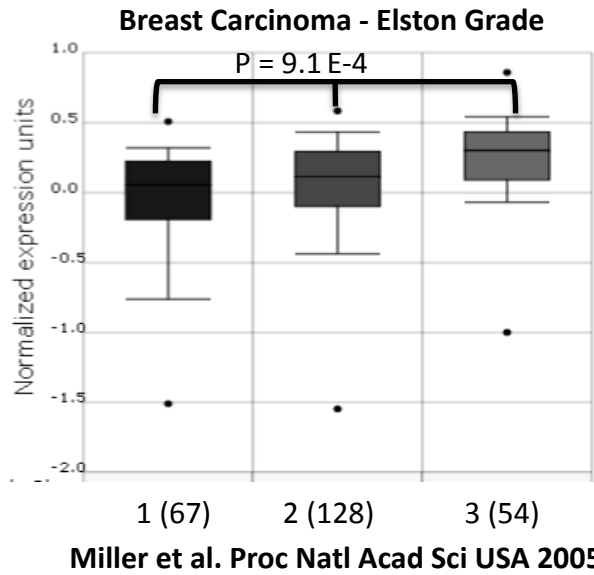
Tissue	Datasets	Gene overexpression compared to normal tissue counterpart				
		<i>MMSET</i>	<i>HDAC1</i>	<i>HDAC2</i>	<i>LSD1</i>	<i>SIN3A</i>
Myeloma	8	<u>Yes</u>	No	<u>Yes</u>	No	Yes
Leukemia	33	<u>Yes</u>	Yes	Yes	Yes	No
Lymphoma	16	<u>Yes</u>	<u>Yes</u>	Yes	Yes	No
Bladder	8	<u>Yes</u>	<u>Yes</u>	Yes	Yes	No
Blood	2	No	No	No	No	No
Brain	23	<u>Yes</u>	<u>Yes</u>	Yes	Yes	No
Breast	44	<u>Yes</u>	No	Yes	No	No
Cervix	1	No	No	No	No	No
Chondrosarcoma	1	No	No	No	No	No
Colon	12	<u>Yes</u>	No	Yes	No	No
Endocrine	1	No	No	No	No	No
Endometrium	4	No	Yes	No	No	No
Esophagus	4	<u>Yes</u>	<u>No</u>	Yes	No	No
Gastric	5	No	No	Yes	No	No
Head & Neck	5	<u>Yes</u>	<u>Yes</u>	Yes	Yes	Yes
Liver	4	<u>Yes</u>	Yes	Yes	Yes	No
Lung	16	<u>Yes</u>	Yes	Yes	Yes	No
Melanoma	10	<u>Yes</u>	Yes	Yes	Yes	No
Mesothelioma	3	No	No	No	No	No
Muscle	2	No	No	No	No	No
Neuroblastoma	2	No	No	No	No	No
Oral	1	No	<u>No</u>	Yes	No	No
Ovarian	14	<u>Yes</u>	Yes	No	No	No
Pancreas	6	No	<u>Yes</u>	No	No	No
Parathyroid	1	No	No	No	No	No
Prostate	20	Yes	Yes	Yes	Yes	No
Rectum	2	No	No	No	No	No
Renal	11	<u>Yes</u>	No	No	Yes	No
Salivary Gland	1	No	No	Yes	No	No
Sarcoma	11	No	No	No	No	No
Seminoma	1	No	yes	No	No	No
Skin	1	No	No	No	No	No
Testis	1	<u>Yes</u>	<u>No</u>	No	No	Yes
Thyroid	1	No	No	<u>No</u>	No	No
Uterus	1	No	No	No	No	No

Table 1

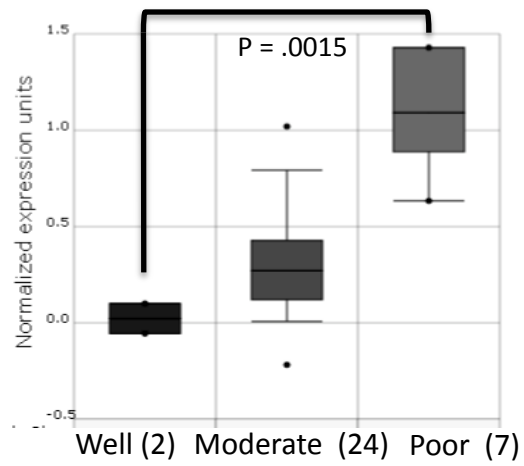
Expression of *MMSET*, *HDAC1*, *HDAC2*, *LSD1*, *Sin3A* in human tumor types to that of their normal tissue counterparts using publicly available gene expression data, including the Oncomine Cancer Microarray database.

Figure 1 : Association of MMSET expression with tumor grade



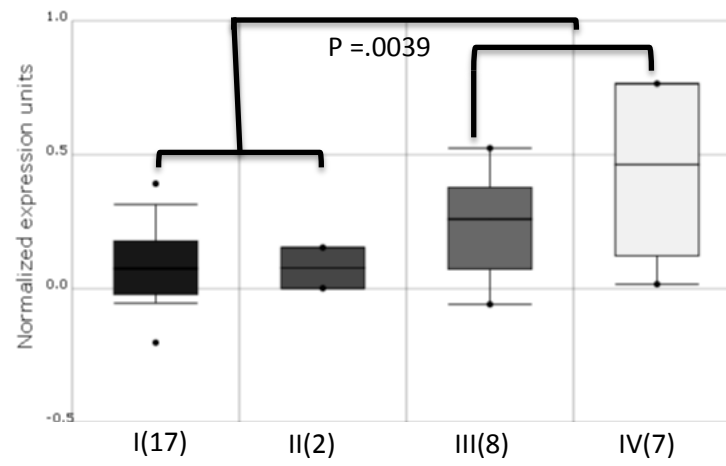


Cervical Carcinoma - Differentiation



Bachtiary et al. Clin Cancer Res 2006

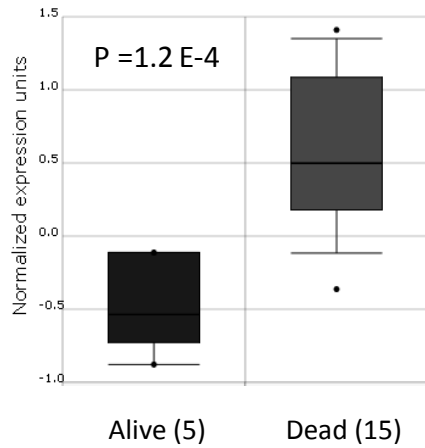
Papillary Renal Cell Carcinoma - Stage



Yang et al. Cancer Res 2005

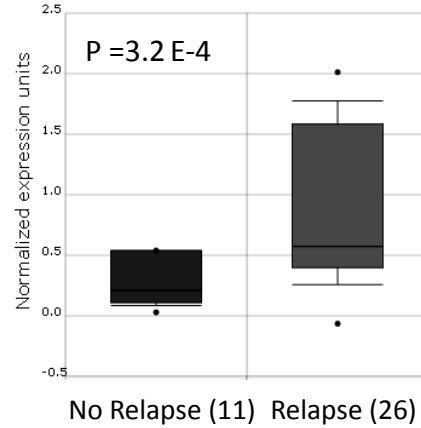
Figure 2 : Association of MMSET expression with prognosis

Head and Neck Squamous Cell Carcinoma Overall Survival - 5 Years



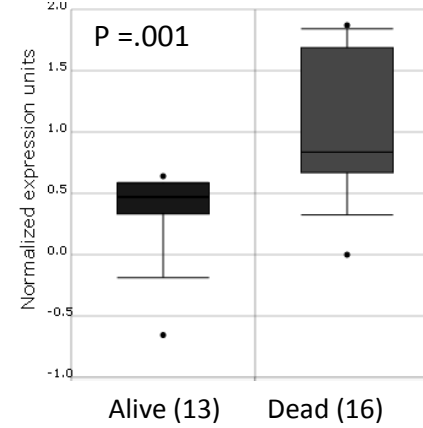
Chung et al. Cancer Cell 2004

Multiple Myeloma - Relapse Status - 1 Year



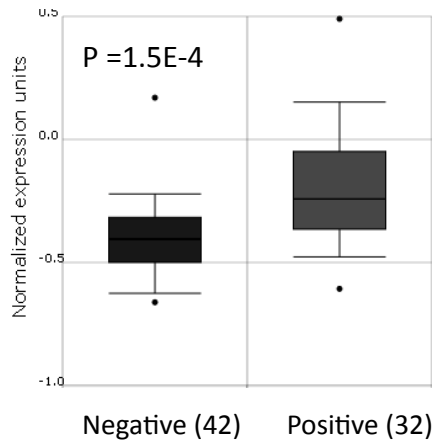
Carasco et al. Cancer Cell 2006

Multiple Myeloma - Survival - 1 Year



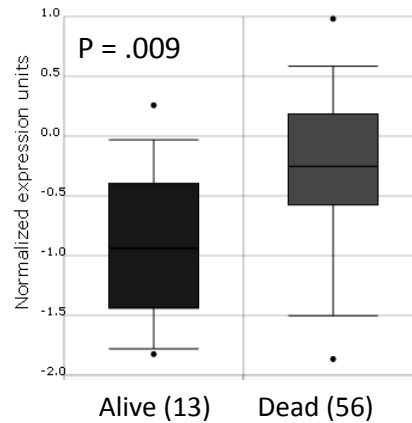
Carasco et al. Cancer Cell 2006

Prostate Carcinoma - Biochemical Recurrence - 5 Years



Glinksy et al. J Clin Invest 2004

Glioma - Survival - 3 Years



Freije et al. Cancer Res 2006