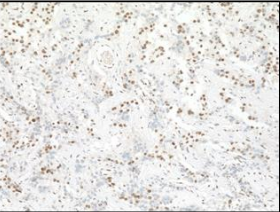


# Supplemental Figure1

## Quantitative immunohistochemistry analysis of MSH6.

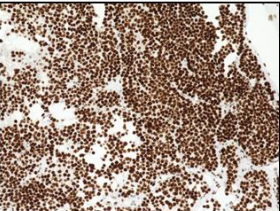


Low protein expression of MSH6

intensity : 159



**Protein expression level : 13**

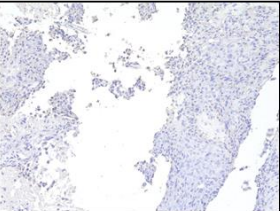


High protein expression of MSH6

intensity : 95



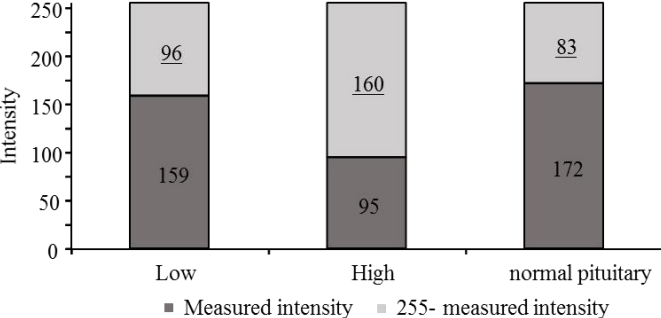
**Protein expression level : 77**



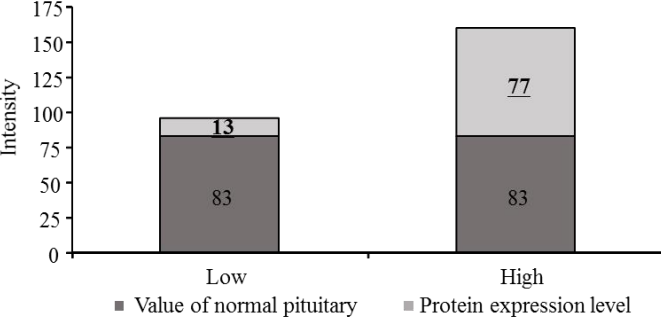
Normal pituitary (unstained)

intensity : 172

**Quantitative analysis of MSH6 protein**



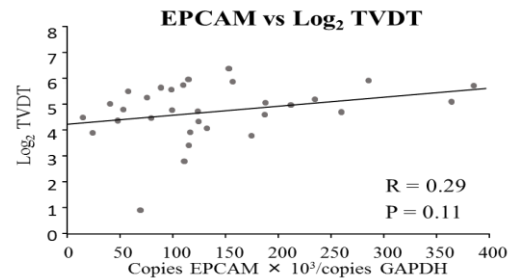
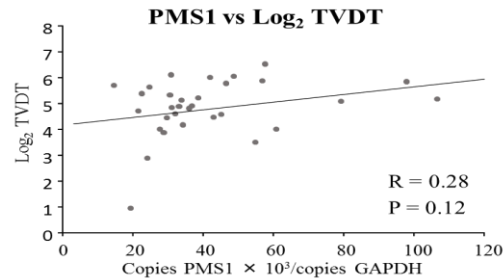
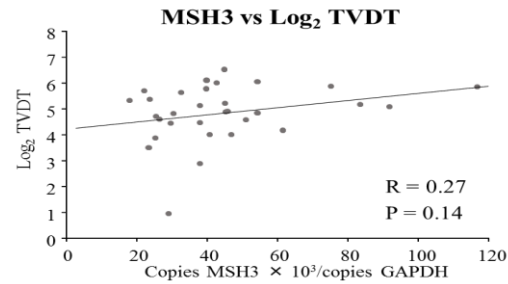
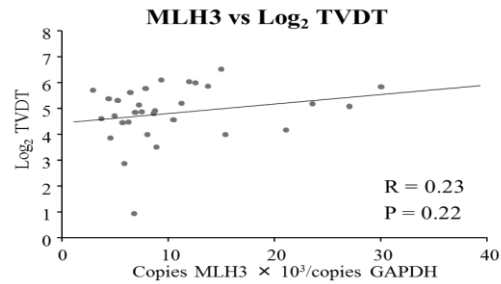
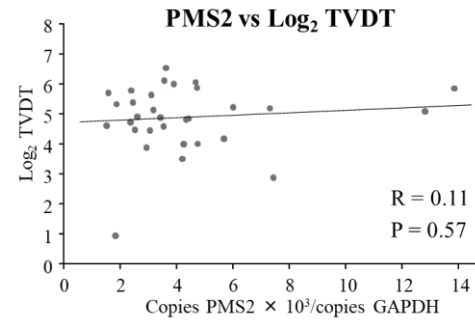
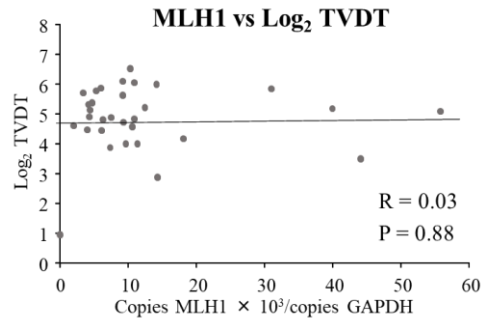
Corrected by the value of normal pituitary gland



## Supplemental Figure 2

### Correlation between expression of MMR genes other than *MSH6* and *MSH2* and $\text{Log}_2$ TVDT.

Expression of other MMR genes (*MLH1*, *PMS2*, *MLH3*, *MSH3*, *PMS1*, and *EPCAM*) was not associated with  $\text{Log}_2$  TVDT.



# Supplemental Table1A

## Clinical, imageological, and histopathological characteristics of 47 patients with PA at Wakayama Medical University Hospital.

Case Number	sex	age (years)	Clinical phenotype	Pathological phenotype	micro/macro	preoperative TV(cm <sup>3</sup> )	TVDT (month)	Time Interval of MRI (month)	follow-up period (month)	MIB-1 LI (%)	recurrence
1	male	43	Nonfunctioning adenoma	Gonadotroph adenoma	macro	11.67	54.4	48.5	49.8	1.7	-
2	male	55	Nonfunctioning adenoma	Gonadotroph adenoma	macro	6.99	24.1	49.5	51.0	1.1	+
3	male	70	Nonfunctioning adenoma	Gonadotroph adenoma	macro	5.77	22.0	44.2	46.0	1.0	+
4	male	71	Nonfunctioning adenoma	Gonadotroph adenoma	macro	5.86	34.7	50.2	53.6	1.5	-
5	female	69	Nonfunctioning adenoma	Gonadotroph adenoma	macro	5.73	29.8	42.6	44.1	2.3	-
6	female	54	Nonfunctioning adenoma	Gonadotroph adenoma	macro	2.25	15.8	32.4	35.8	1.2	-
7	male	67	Nonfunctioning adenoma	Gonadotroph adenoma	macro	7.07	57.8	41.9	43.4	1.6	-
8	male	49	Nonfunctioning adenoma	Gonadotroph adenoma	macro	8.62	23.6	29.2	31.6	1.2	-
9*	male	57	Plurihormonal adenoma (PRL, ACTH)	Plurihormonal adenoma (PRL, ACTH)	macro	9.46	N.A	N.A	N.A	1.1	-
10	female	43	Thyrotroph adenoma	Thyrotroph adenoma	macro	0.50	36.0	20.3	23.9	0.3	-
11	female	42	Nonfunctioning adenoma	Gonadotroph adenoma	macro	12.17	68.3	18.6	21.3	1.9	+
12**	male	37	Somatotroph adenoma	Somatotroph adenoma	macro	1.15	N.A	N.A	N.A	2.5	-
13	male	53	Nonfunctioning adenoma	Silent thyrotroph adenoma	macro	24.08	65.6	19.0	21.3	0.6	-
14	female	24	Lactotroph adenoma	Lactotroph adenoma	micro	0.95	N.A	N.A	N.A	4.6	-
15***	female	49	Somatotroph adenoma	Somatotroph adenoma	macro	3.60	N.A	N.A	N.A	2.5	-
16	female	70	Nonfunctioning adenoma	Gonadotroph adenoma	macro	12.89	36.8	24.8	26.8	3.3	+
17	female	76	Nonfunctioning adenoma	Gonadotroph adenoma	macro	9.70	57.1	17.7	21.1	1.6	-
18	male	22	Lactotroph adenoma	Lactotroph adenoma	macro	1.61	33.6	12.2	14.7	3.2	-
19	female	42	Nonfunctioning adenoma	Silent thyrotroph adenoma	macro	39.91	21.6	4.8	6.7	6.2	+
20	male	32	Lactotroph adenoma	Lactotroph adenoma	macro	12.66	N.A	N.A	N.A	2.2	-
21	female	61	Nonfunctioning adenoma	Silent lactotroph adenoma	macro	8.37	14.5	18.0	20.0	1.2	-
22	female	74	Nonfunctioning adenoma	Silent thyrotroph adenoma	macro	4.12	29.3	17.9	19.5	1.7	-
23	female	65	Nonfunctioning adenoma	Gonadotroph adenoma	macro	22.25	91.3	10.1	10.2	3.3	+
24	female	65	Nonfunctioning adenoma	Silent somatotroph adenoma	macro	6.03	N.A	N.A	N.A	3.4	-
25	female	68	Corticotroph adenoma	Corticotroph adenoma	macro	2.72	1.9	1.8	3.5	20.0	-
26	male	68	Nonfunctioning adenoma	Gonadotroph adenoma	macro	16.50	63.5	11.0	15.7	4.5	+
27	female	50	Nonfunctioning adenoma	Silent somatotroph adenoma	macro	5.72	7.3	5.5	8.9	1.6	-
28	male	65	Nonfunctioning adenoma	Silent somatotroph adenoma	macro	22.19	51.6	12.2	14.2	0.4	+
29	female	56	Somatotroph adenoma	Somatotroph adenoma	micro	0.36	N.A	N.A	N.A	0.6	-
30	male	77	Nonfunctioning adenoma	Silent somatotroph adenoma	macro	3.82	15.9	12.4	14.3	0.9	-
31	female	60	Nonfunctioning adenoma	Gonadotroph adenoma	macro	7.87	26.1	12.9	15.3	1.4	+
32	female	63	Nonfunctioning adenoma	Gonadotroph adenoma	macro	3.66	49.0	6.7	8.4	0.3	-
33	male	61	Somatotroph adenoma	Somatotroph adenoma	macro	1.59	N.A	N.A	N.A	0.2	-
34	male	47	Nonfunctioning adenoma	Gonadotroph adenoma	macro	10.59	41.3	12.2	14.1	5.9	-
35	female	71	Somatotroph adenoma	Somatotroph adenoma	macro	4.49	N.A	N.A	N.A	1.2	-
36	female	55	Somatotroph adenoma	Somatotroph adenoma	macro	1.82	N.A	N.A	N.A	1.5	-
37	female	42	Nonfunctioning adenoma	Gonadotroph adenoma	macro	41.31	N.A	N.A	N.A	4.2	+
38	female	71	Nonfunctioning adenoma	Gonadotroph adenoma	macro	9.82	N.A	N.A	N.A	1.2	-
39	male	47	Nonfunctioning adenoma	Gonadotroph adenoma	macro	7.45	39.7	6.3	7.9	1.1	+
40	female	63	Nonfunctioning adenoma	Silent somatotroph adenoma	macro	49.23	28.4	4.6	4.9	2.4	+
41	female	54	Nonfunctioning adenoma	Gonadotroph adenoma	macro	9.00	27.8	6.1	7.7	1.9	-
42	male	72	Nonfunctioning adenoma	Silent lactotroph adenoma	macro	3.54	N.A	N.A	N.A	1.0	-
43	female	63	Nonfunctioning adenoma	Gonadotroph adenoma	macro	2.96	17.9	4.1	5.5	3.4	-
44	male	40	Nonfunctioning adenoma	Gonadotroph adenoma	macro	3.15	N.A	N.A	N.A	6.6	-
45	female	51	Nonfunctioning adenoma	Gonadotroph adenoma	macro	8.40	N.A	N.A	N.A	2.3	+
46	female	33	Corticotroph adenoma	Corticotroph adenoma	macro	10.72	11.2	3.6	3.8	10.7	+
47	male	59	Nonfunctioning adenoma	Gonadotroph adenoma	macro	7.48	N.A	N.A	N.A	0.8	-

N.A.; not available \*; *MEN1* Gly156Arg(germline and somatic mutation)

\*\*; *GNAS* Gln227His (somatic mutation) \*\*\*; *GNAS* Arg201Cys (somatic mutation)

# Supplemental Table1B

## Clinical, imageological, and histopathological characteristics of 46 patients with PA at Toranomom Hospital.

Case Number	sex	age	Clinical phenotype	Pathological phenotype	micro/macro	MIB-1 LI(%)	recurrence
1	male	71	Nonfunctioning adenoma	Gonadotroph adenoma	macro	4.1	-
2	female	41	Nonfunctioning adenoma	Gonadotroph adenoma	macro	0.6	-
3	female	53	Nonfunctioning adenoma	null cell adenoma	macro	2.2	-
4	female	19	Nonfunctioning adenoma	Silent somatotroph adenoma	macro	3.6	+
5	female	21	Nonfunctioning adenoma	Gonadotroph adenoma	macro	3.2	-
6	female	72	Nonfunctioning adenoma	Silent corticotroph adenoma	macro	0.3	-
7	male	65	Nonfunctioning adenoma	Gonadotroph adenoma	macro	0.5	-
8	female	53	Nonfunctioning adenoma	Gonadotroph adenoma	macro	1.6	-
9	female	62	Nonfunctioning adenoma	Gonadotroph adenoma	macro	1.2	-
10	male	31	Nonfunctioning adenoma	Silent lactotroph adenoma	macro	3.8	-
11	male	60	Nonfunctioning adenoma	null cell adenoma	macro	0.9	-
12	male	69	Nonfunctioning adenoma	Gonadotroph adenoma	macro	1.9	-
13	male	68	Nonfunctioning adenoma	Gonadotroph adenoma	macro	1	-
14	male	41	Nonfunctioning adenoma	Gonadotroph adenoma	macro	1.4	-
15	male	36	Nonfunctioning adenoma	Gonadotroph adenoma	macro	1.1	-
16	female	40	Nonfunctioning adenoma	Silent corticotroph adenoma	macro	1.5	-
17	female	65	Nonfunctioning adenoma	Silent corticotroph adenoma	macro	2.4	-
18	male	60	Nonfunctioning adenoma	Gonadotroph adenoma	macro	2.4	-
19	male	56	Nonfunctioning adenoma	Gonadotroph adenoma	macro	1.9	-
20	female	62	Nonfunctioning adenoma	Gonadotroph adenoma	macro	2.3	-
21	male	66	Nonfunctioning adenoma	Gonadotroph adenoma	macro	2.8	-
22	male	35	Nonfunctioning adenoma	Gonadotroph adenoma	macro	2.2	-
23	female	43	Nonfunctioning adenoma	Silent corticotroph adenoma	macro	0.9	-
24	female	49	Nonfunctioning adenoma	Gonadotroph adenoma	macro	1.7	+
25	male	61	Nonfunctioning adenoma	Silent corticotroph adenoma	macro	1.9	-
26	female	71	Nonfunctioning adenoma	Gonadotroph adenoma	macro	2.8	+
27	female	53	Nonfunctioning adenoma	Silent corticotroph adenoma	macro	1.6	-
28	female	80	Nonfunctioning adenoma	Gonadotroph adenoma	macro	1.6	-
29	female	35	Nonfunctioning adenoma	Silent corticotroph adenoma	macro	0.7	+
30	female	37	Nonfunctioning adenoma	silent plurihormonal adenoma (PRL, GH)	macro	2.7	-
31	female	36	Nonfunctioning adenoma	Gonadotroph adenoma	macro	2.8	-
32	female	50	Nonfunctioning adenoma	Silent corticotroph adenoma	macro	1.8	-
33	female	21	Nonfunctioning adenoma	Silent thyrotroph adenoma	macro	3.2	-
34	male	68	Nonfunctioning adenoma	Silent corticotroph adenoma	macro	1.4	-
35	female	50	Nonfunctioning adenoma	Silent corticotroph adenoma	macro	1.8	-
36	male	84	Nonfunctioning adenoma	Gonadotroph adenoma	macro	1.6	+
37	female	39	Nonfunctioning adenoma	Silent corticotroph adenoma	macro	3.2	-
38	male	50	Nonfunctioning adenoma	Gonadotroph adenoma	macro	1.5	-
39	female	62	Nonfunctioning adenoma	Gonadotroph adenoma	macro	0.8	-
40	male	53	Nonfunctioning adenoma	Gonadotroph adenoma	macro	3.6	-
41	female	52	Nonfunctioning adenoma	Silent corticotroph adenoma	macro	0.3	-
42	female	54	Nonfunctioning adenoma	Gonadotroph adenoma	macro	2.1	-
43	male	41	Nonfunctioning adenoma	Gonadotroph adenoma	macro	1.8	-
44	female	30	Nonfunctioning adenoma	Silent corticotroph adenoma	macro	2.7	-
45	male	53	Nonfunctioning adenoma	Gonadotroph adenoma	macro	2.2	-
46	male	56	Nonfunctioning adenoma	Gonadotroph adenoma	macro	0.9	-

## Supplemental Table2A

qRT-PCR primers used to measure mRNA expression (human *MLH1*, *PMS2*, *MSH2*, *MSH6*, *MLH3*, *MSH3*, *PMS1*, *EPCAM*, *ATR*, and *GAPDH*).

human		Primers	length	PCR products size
MLH1	Forward	5'-AGCAGCACATCGAGAGCAA	19mer	125bp
	Reverse	5'-CGAGGTCAGACTTGTGTGG	20mer	
PMS2	Forward	5'-GCATGGAGTTGGAAGGAGTT	20mer	106bp
	Reverse	5'-CATGTGGTAGACCTCATTACAG	22mer	
MSH2	Forward	5'-ACCAGCAGCAAAGAAGTGCT	20mer	86bp
	Reverse	5'-AGGGCATTGTTCACCTTG	20mer	
MSH6	Forward	5'-CATGCGGCGACTGTCTAT	19mer	145bp
	Reverse	5'-CAGAATTACTGGCGACACA	20mer	
MLH3	Forward	5'-TGCCACTGACTGCCAGAAG	20mer	99bp
	Reverse	5'-CAATAAGCGGCAACTTTCC	20mer	
MSH3	Forward	5'-AGGAAGGAGGAAGTGATCTGG	21mer	151bp
	Reverse	5'-TGCAGAGATTCTGTCTGGACTC	22mer	
PMS1	Forward	5'-CATCACTTCGGTGGTCAATG	20mer	123bp
	Reverse	5'-CCGTATCTCGCACCTCAAT	20mer	
EPCAM	Forward	5'-ACTTTTGCCGAGCTCAG	18mer	104bp
	Reverse	5'-GCACCAACTGAAGTACACTGG	21mer	
ATR	Forward	5'-GCCAAGACAAATTCTGTGTCA	21mer	178bp
	Reverse	5'-CTCATGGCTTCCACTCACAT	20mer	
GAPDH	Forward	5'-GAAAGGTGAAGGTCGGAGTCA	20mer	226bp
	Reverse	5'-GAAAGATGGTGA TGGGATTTTC	20mer	

## Supplemental Table2B

qRT-PCR primers used to measure mRNA expression (mouse *MSH2*, *MSH6*, *ATR*, and *GAPDH*).

mouse		Primers	length	PCR products size
MSH2	Forward	5'-GTGCTGCCCTACCA GAGATG	20mer	157bp
	Reverse	5'-ACTGCTGCCATGTCCA ACTT	20mer	
MSH6	Forward	5'-CGGAGGCAA A GGATCTCAAC	20mer	166bp
	Reverse	5'-AACGTTCCATCAA A GGGATG	20mer	
ATR	Forward	5'-GGAGCTGGCGTCCATGAT	18mer	100bp
	Reverse	5'-CTGGCAGAGAA TCTGTCTTGG	21mer	
GAPDH	Forward	5'-GAAGGTGAAGGTCGGAGTCA	20mer	171bp
	Reverse	5'-GAAGATGGTGATGGGATTTTC	20mer	

### Supplemental Table3

### Correlation between MMR gene expression and preoperative TV and MIB1-LI.

MMR gene expression was not associated with TV, MIB1-LI, or Knosp grade.

	Preoperative TV (all sample) (n=47)		Preoperative TV (except recurrence) (n=33)		Preoperative TV (nonfunctioning tumor) (n=34)		Preoperative TV (nonfunctioning tumor except recurrence) (n=20)		MIB-1 LI (all sample) (n=47)	
	single correlation coefficient	P value	single correlation coefficient	P value	single correlation coefficient	P value	single correlation coefficient	P value	single correlation coefficient	P value
MSH6	-0.050	0.74	0.010	0.95	-0.11	0.52	-0.082	0.73	-0.16	0.29
MSH2	-0.10	0.50	-0.069	0.70	-0.082	0.65	-0.057	0.81	-0.19	0.19
MLH1	-0.12	0.42	-0.33	0.061	0.075	0.67	-0.10	0.67	-0.07	0.63
PMS2	-0.18	0.22	-0.21	0.24	-0.13	0.46	-0.18	0.44	0.15	0.31
MLH3	-0.21	0.16	-0.24	0.17	-0.15	0.38	-0.24	0.30	-0.15	0.31
MSH3	-0.11	0.47	-0.15	0.41	-0.053	0.76	-0.098	0.68	-0.18	0.23
PMS1	-0.17	0.26	-0.16	0.38	-0.10	0.56	-0.11	0.66	-0.19	0.21
EPCAM	0.021	0.89	0.17	0.35	-0.013	0.93	0.087	0.72	-0.13	0.39

※ simple linear regression analysis