Table S1. Clinical and histopathological characteristics of gastric cancer samples from Caucasian patient dataset

	Code (Paired Normal Tissue)	Code (Gastric Cancer)	Sex	age	Date of Dx	Location	Histology	Pattern	Precursor	Depth	LV Invasion	Metastasis	stage
1	GN1	GT1	M	65	2001	Distal	poorly	vvariegated	NA	T3	yes	2,7	IIB
2	GN2	GT2	F	63	2004	Distal	moderate	intestinal	adenoma, metaplasia	T2	no	0,15	IB
3	GN3	GT4	F	72	2004	body	moderate	intestinal	metaplasia	T3	yes	5,28	IIIA
4	GN4	GT4	M	71	2005	Distal	moderate	intestinal	metaplasia	T3	yes	0,24	IIA
5	GN5	GT5	M	54	2003	Distal	moderate to poorly	lymphoepithelioma -like, intestinal	adenoma, metaplasia	T2	yes	0,11	IB
6	GN6	GT6	F	75	2003	Proximal	poorly	intestinal	NA	T3	yes	16,41	IIIC
7	GN7	GT7	F	76	2003	Antrum	poorly	NA	NA	T4	yes	6,25	IIIB
8	GN8	GT8	F	68	2003	Body	poorly	signet ring cell	NA	T4	yes	13,16	IIIC
9	GN9	GT9	M	69	2003	Distal	moderate	intestinal	adenoma	T3	no	0,13	IIA
10	GN10	GT10	M	73	2003	Proximal	poorly	mucinous component	NA	T3	yes	8,21	IIIB
11	GN11	GT11	M	74	2004	GE junction	moderate to poorly	NA	NA	T4	yes	5,9	IIIB
12	GN12	GT12	M	53	2003	Body	moderate	NA	adenoma	T1	no	0,9	IA
13	GN13	GT13	F	74	2004	Distal	poorly	signet ring cell	NA	T4	yes	8,26	IIIC
14	GN14	GT14	M	68	2004	Body	poorly	signet ring cell	NA	T3	yes	1,28	IIB
15	GN15	GT15	F	66	2004	Body	moderate	intestinal	metaplasia	T4	yes	5,31	IIIB
16	GN16	GT16	F	79	2004	Body	moderate to poorly	NA	NA	T3	yes	5,23	IIIA
17	GN17	GT17	M	74	2005	Proximal	poorly	NA	NA	T2	yes	15,37	IIIA
18	GN18	GT18	M	68	2005	Body	moderate to poorly	mucinous component	metaplasia	T3	yes	0,13	IIA
19	GN19	GT19	M	60	2003	GE junction	moderate to poorly	signet ring cell	NA	T2	yes	2,3	IIB
20	GN20	GT20	F	61	2006	Body	poorly	signet ring cell	NA	T1	no	0,12	IA
21	GN21	GT21	F	68	2007	Body	poorly	signet ring cell	NA	T4	yes	14,18	IIIC
22	GN22	GT22	F	64	2007	Body	moderate to poorly	mucinous component	NA	T3	no	2,28	IIB

Table S2. Characteristics of expression datasets of Asian Pacific patients reported in published studies including the Caucasian patients in this study.

Dataset	Ethnic Group	Comparison Group	Measurement Platform	Gene No.
TCGA (*22*)	Caucasian	29 paired tumor and non-tumor	Illumina Hiseq	27,608
Cho et al. (*21*)	Korean	65 tumor *vs.* 19 non-tumor	Illumina Human WG-6 v3.0	25,235
Kim et al. (*20*)	Korean	24 tumor *vs.* 6 non-tumor	SOLiD Single-read RNA-seq	18,890
This study	Caucasian	22 paired tumor and non-tumor	SOLiD Paired-end RNA-seq	15,987

Table S3. Clinical and pathological characteristics of tumor cases in the tissue microarray**.**

Total cases	**251 (Discovery set 2006)**	**251 (Validation set 2005)**
Sex		
Male : Female	2.73 : 1 (71%:29%)	1.89 : 1 (65%:35%)
Age	59 ± 12 yrs (26-82)	58 ± 12 yrs (28-84)
Lauren type		
Intestinal	42%	50.60%
Diffuse	51.20%	47.80%
Mixed	6.40%	1.20%
Indeterminate	0.40%	0.40%
Depth		
pT2	26.80%	32.30%
pT3	40.00%	37.50%
pT4a	29.20%	28.30%
pT4b	4.00%	2%
Nodal involvement		
pN0	30.40%	31.10%
pN1	24.80%	16.30%
pN2	19.60%	23.90%
pN3a	16.40%	17.10%
pN3b	8.80%	11.60%
Lymphovascular invasion		
absent	46.40%	37.50%
present	53.60%	62.50%
UICC stage		
Ib	15.20%	16.70%
IIa	18.00%	16.30%
IIb	18.80%	19.50%
IIIa	17.20%	13.50%
IIIb	14.00%	16.30%
IIIc	16.80%	17.50%
Recurrence		
absent	76.80%	69.30%
present	23.20%	30.70%
Death		
no	75.20%	64.50%
yes	24.80%	35.50%

The total number of cases was 251 (discovery data set) and 251 (validation data se)t. Inclusion criteria: advanced gastricadenocarcinoma cases underwent gastrectomy and lymphadenectomy from Jan. 2006 to Dec. 2006 (discovery data set) and from Jan. 2005 to Dec. 2005) validation data set) at the National Cancer Center, Korean.
Exclusion criteria: noncurative resection, developed in remnant stomach, follow-up was incomplete.

Table S4. Relationships of WNT5A intensity and positivity with pathological and clinical variables.

	WNT5A Intensity (Discovery data set 2006)			p-value	WNT5A Intensity (Validation data set 205)			p-value
	0	**1**	**2**		**0**	**1**	**2**	
Sex								
Male	35 (62.5%)	98 (71.0%)	45 (78.9%)	0.157	22(59.5%)	95(65.1%)	47(69.1%)	0.607
Female	21 (37.5%)	40 (29.0%)	12 (21.1%)		15(40.5%)	51(34.9%)	21(30.9%)	
Total	56	138	57		37	146	68	
Age (mean±SD)	57.0±12.1	57.7±12.6	63.5±8.4	<0.001	55.7±10.7	57.6±13.0	60.9±11.7	0.078
Lauren								
Intestinal	15 (26.8%)	57 (43.5%)	34 (73.9%)	<0.001	9(24.3%)	70(49.0%)	48(71.6%)	<0.001
Diffuse	41 (73.2%)	74 (56.5%)	12 (26.1%)		28(75.7%)	73(51.0%)	19(28.4%)	
Depth								
pT2	16 (28.6%)	37 (26.8%)	16 (28.1%)	0.062	10(27.0%)	48(32.9%)	23(33.8%)	0.381
pT3	31 (55.4%)	47 (34.1%)	22 (38.6%)		13(35.1%)	52(35.6%)	29(42.6%)	
pT4a	9 (16.1%)	47 (34.1%)	16 (28.1%)		14(37.8%)	46(31.5%)	16(23.5%)	
pT4b	0 (0.0%)	7 (5.1%)	3 (5.3%)		0(0.0%)	5(3.4%)	0(0.0%)	
Nodal involvement								
pN0	23 (41.1%)	35 (25.4%)	20 (35.1%)	0.005	12(32.4%)	48(32.9%)	18(26.5%)	0.632
pN1	10 (17.9%)	39 (28.3%)	13 (22.8%)		6(16.2%)	20(13.7%)	15(22.1%)	
pN2	12 (21.4%)	27 (19.6%)	9 (15.8%)		6(16.2%)	34(23.3%)	20(29.4%)	
pN3a	11 (19.6%)	26 (18.8%)	4 (7.0%)		8(21.6%)	26(17.8%)	9(13.2%)	
pN3b	0 (0%)	11 (8.0%)	11 (19.3%)		5(13.5%)	18(12.3%)	6(8.8%)	
UICC stage								
IB	11 (19.6%)	18 (13.0%)	11 (19.3%)	0.122	6(16.2%)	26(17.8%)	10(14.7%)	0.904
IIA	11 (19.6%)	22 (15.9%)	12 (21.1%)		5(13.5%)	23(15.8%)	13(19.1%)	
IIB	11 (19.6%)	28 (20.3%)	8 (14.0%)		8(21.6%)	27(18.5%)	14(20.6%)	
IIIA	13 (23.2%)	26 (18.8%)	4 (7.0%)		4(10.8%)	18(12.3%)	12(17.6%)	
IIIB	6 (10.7%)	16 (11.6%)	12 (21.1%)		5(13.5%)	25(17.1%)	11(16.2%)	
IIIC	4 (7.1%)	28 (20.3%)	10 (17.5%)		9(24.3%)	27(18.5%)	8(11.8%)	

Table S5. Clinical relevance of WNT5A in diffuse type. Beta is an estimate of logarithm of hazard ratio, so exp(beta) implies hazard ratio compared with baseline hazard rate. (Df: degrees of freedom; Coxph: cox proportional hazard model)

	WNT5A intensity (diffuse type case)		Discovery data set (2006)				Validation data set (2005)				Merged: Discovery and Validation data set (2006 and 2005)			
Test	**Model specification**		**Beta (exp(beta))**	**se**	**z**	**P-value**	**Beta (exp(beta))**	**se**	**z**	**P-value**	**Beta (exp(beta))**	**se**	**z**	**P-value**
Log-rank	0 vs. (1 and 2) df1					2.51E-02				0.115				5.70E-03
	0 vs. 1 vs. 2 df2					7.79E-05				0.269				5.10E-03
Coxph	No covariates 0 vs. (1 and 2) df1		0.967 (2.63)	0.449	2.16	3.10E-02	0.637 (1.89)	0.411	1.55	0.120	0.814 (2.26)	0.303	2.69	7.20E-03
	Sex, age 0 vs. (1 and 2) df1		0.962 (2.62)	0.451	2.14	3.30E-02	0.608 (1.84)	0.413	1.48	0.140	0.751 (2.12)	0.305	2.46	1.40E-02
	No covariates 0 vs. 1 vs. 2 df2	0 *vs.* 1	0.747 (2.11)	0.463	1.61	1.10E-01	0.666 (1.95)	0.419	1.59	0.110	0.729 (2.07)	0.310	2.35	1.90E-02
		0 *vs.* 2	2.041 (7.70)	0.543	3.76	1.70E-04	0.517 (1.68)	0.535	0.97	0.330	1.184 (3.27)	0.379	3.12	1.80E-03
		0 *vs.* 1 *vs.* 2				1.27E-03				0.236				4.57E-03
	Sex, age 0 vs. 1 vs. 2 df2	0 *vs.* 1	0.760 (2.22)	0.465	1.63	1.00E-01	0.636 (1.89)	0.420	1.51	0.130	0.720 (2.05)	0.310	2.32	2.00E-02
		0 *vs.* 2	1.778 (5.92)	0.550	3.23	1.20E-03	0.495 (1.64)	0.535	0.92	0.360	1.102 (3.01)	0.381	2.89	3.80E-03
		0 *vs.* 1 *vs.* 2				5.93E-03				0.274				8.15E-03

Fig. S1A

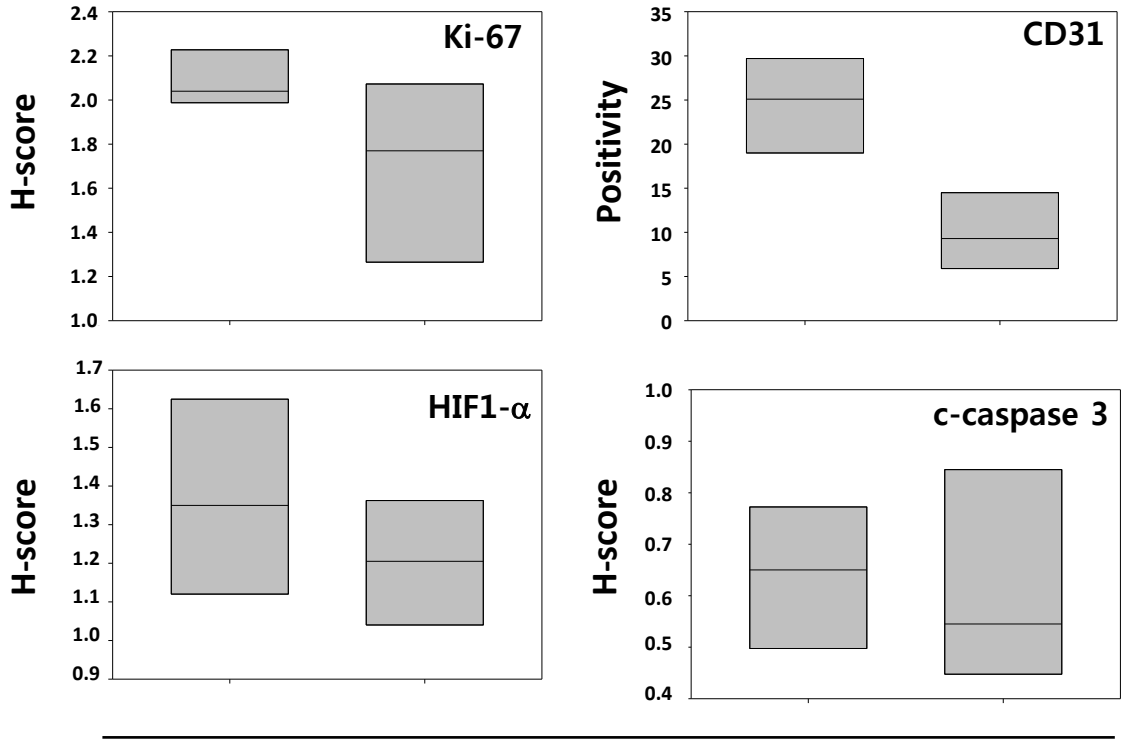

Fig. S1B

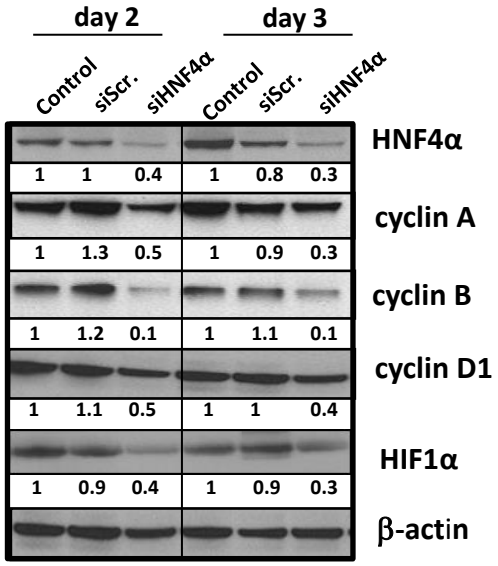

Fig. S1. HNF4α inhibition shows antiprolifeative activity. (A) IHC analysis on xenograft tumor samples silenced with shRNA-mediated HNF4α showing inhibited growth , angiogenesis and HIF-1α,in the NCI-N87 cell line . (B) Immunoblotting analysis on NCI-N87 cell line knowckdown with siRNA mediated HNF4α showed decreased cell cycle regulators and HIF-1α.

Fig. S2A

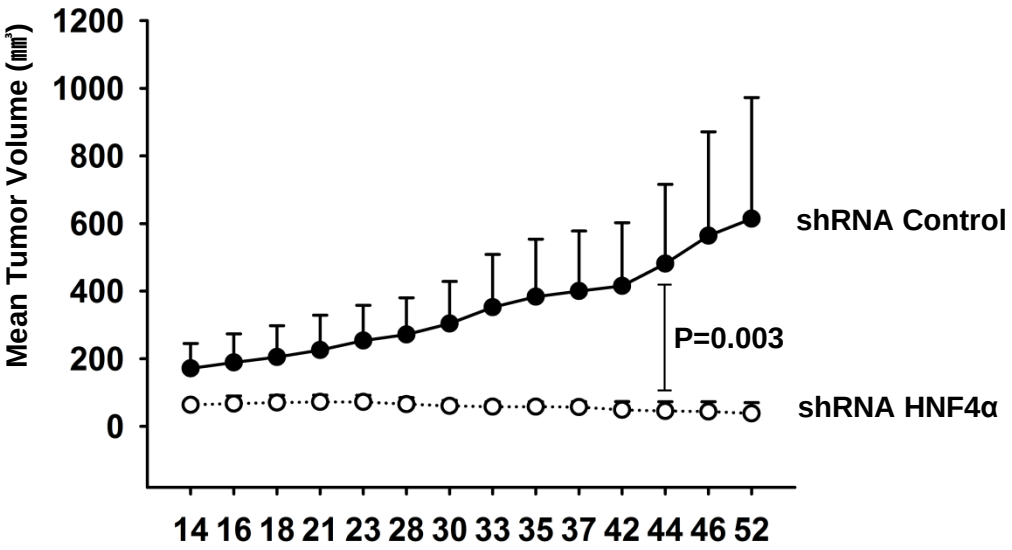

Fig. S2B

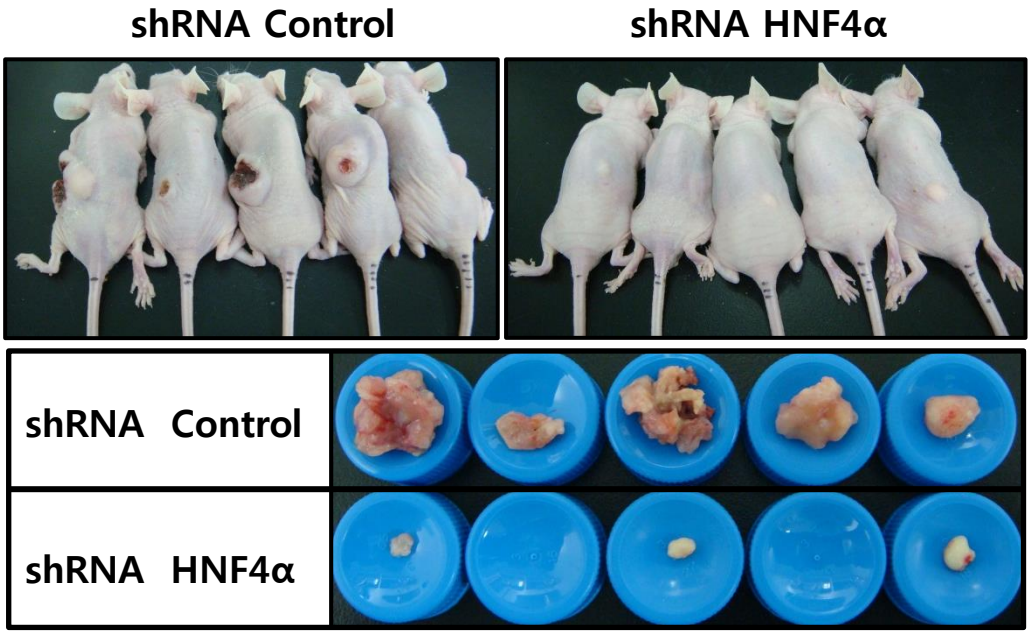

Fig. S2. HNF4α inhibition shows anti-tumor activity. (A) and (B) shRNA lentiviral particles targeting different regions of HNF4α mRNA or shRNA empty vectors were infected into MKN45 cells. Stably transfected cells were selected by puromycin. Ten, 5-week-old female BALB/C nude mice were randomly divided into two groups (5 for shRNA control, and 5 for shRNA HNF4α). Approximately 10^7 shRNA control (CTRL) cells and shRNA HNF4αcells in 100μL phosphate-buffered saline were inoculated subcutaneously.

Fig. S3A

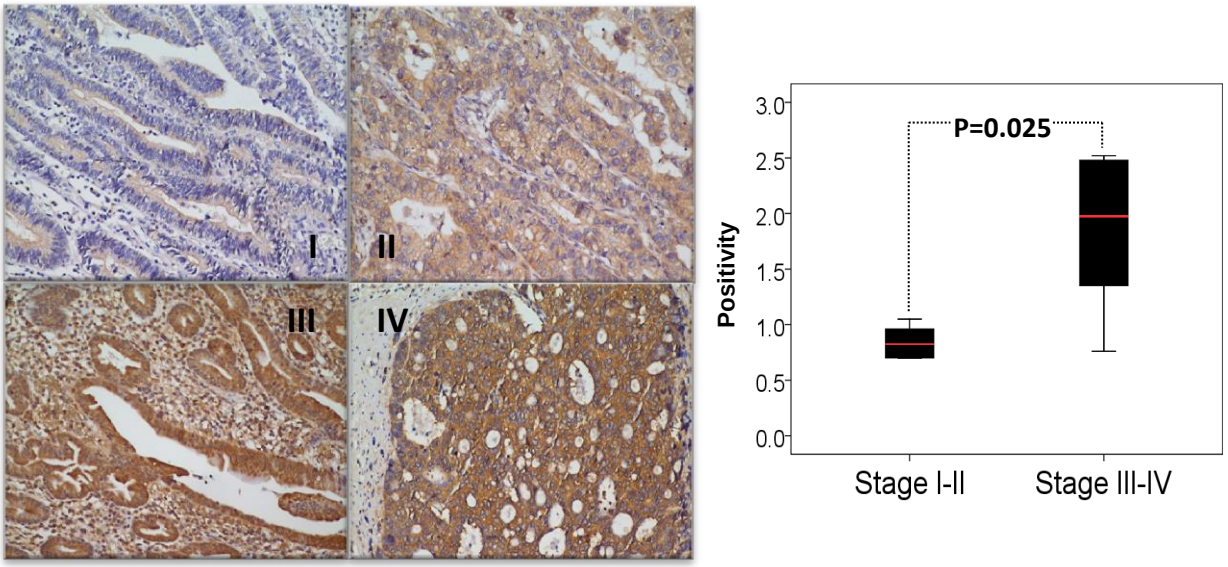

Fig. S3B

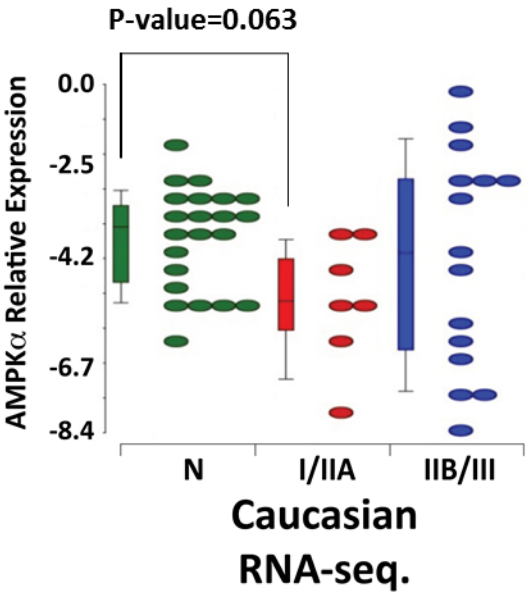

Fig. S3C

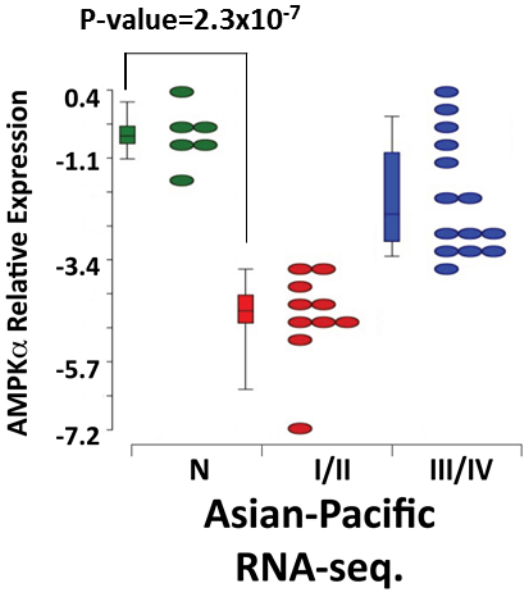

Fig. S3. Expression of AMPKα2 in both Caucasian and Pacific-Asian GC patients tumors. **(A)** AMPKα2 expression on Asian gastric cancer, and immunohistochemistry was done on 10 patient tissue samples per tumor stage. **(B)-(C)** The expression of AMPKα2 based on RNA-seq data.

Fig. S4A

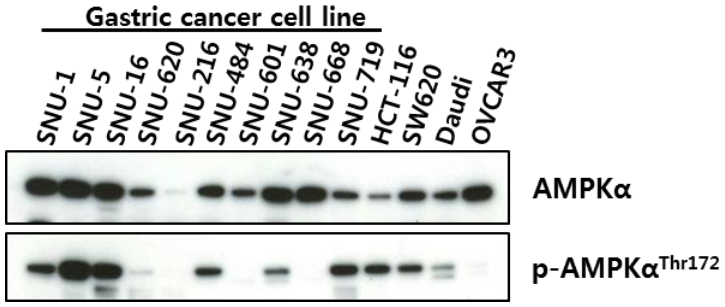

Fig. S4B

Xenograft	AMPKα2
SNU 5	2
SNU 16	2.3
SNU 484	1.2
SNU 601	2.4
SNU 638	2.6
SNU 668	3
SNU 719	2.3
SNU 1967	1.8
NCC19	2.2
NCC 59	1.9
MKN 1	2.3
MKN 28	1.6
MKN 45	2.7
NUGC3	2.5
NUGC4	1.9
NCI-N87	1.9

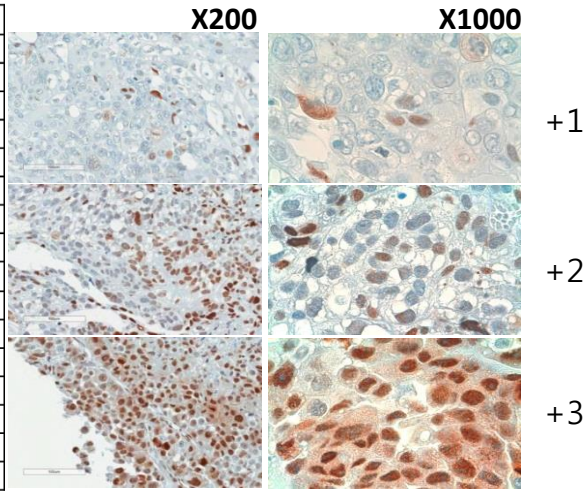

Fig. S4C

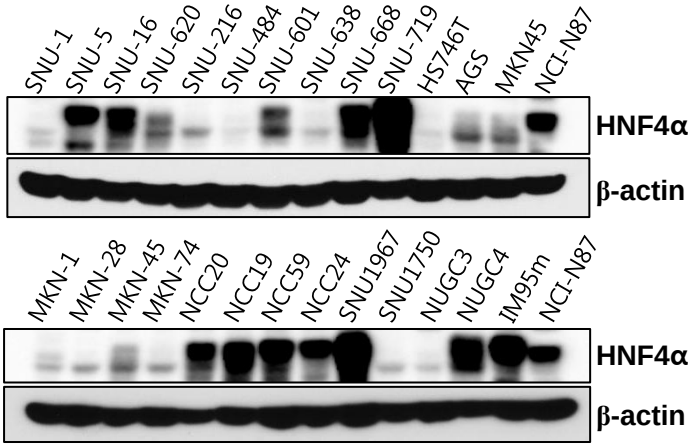

Fig. S4. The protein expression of AMPKα. **(A)** in a panel of gastric cell lines and **(B)** xenograft models from various GC cell lines **(C)** Protein expression of HNF4α in a panel of gastric cell lines.

Fig. S5

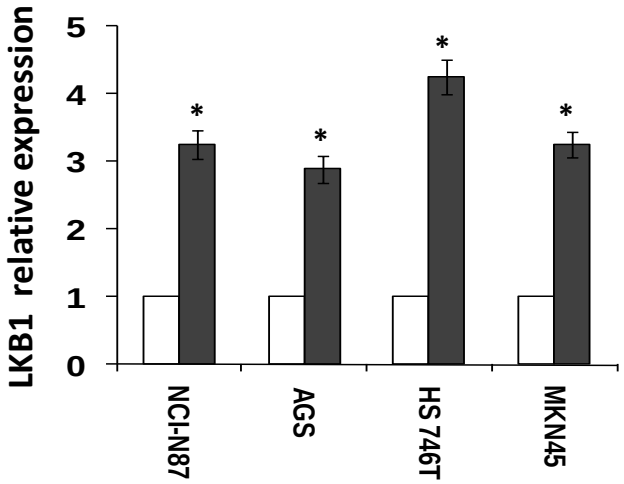

Fig S5. Effect of metformin treatment on the expression of liver kinase B1 (LKB1). Measurement of LKB1 gene expression levels at day 2 with metformin treatment. (white bars= NT, black bar= MET (10 mM) treatment. RNA expression was determined using qRT-PCR, **P* < 0.05.

Fig. S6

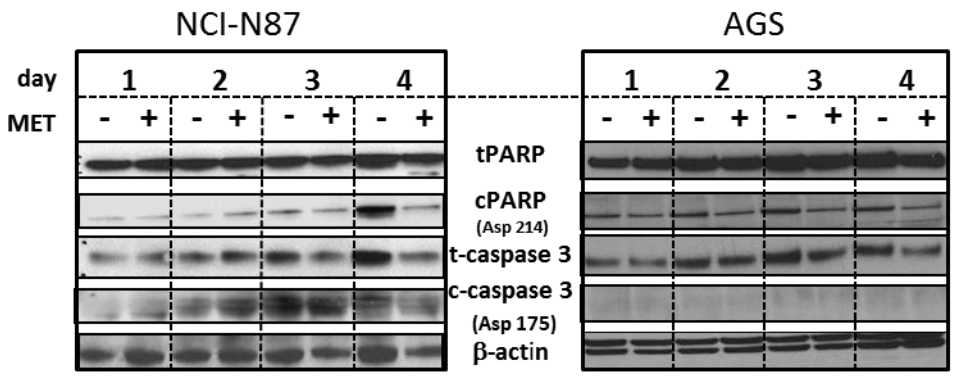

Fig. S6. Metformin antiproliferation activity against NCI-N87 and AGS GC cells. Decreased levels of cleaved caspase 3 and poly ADP-ribose polymerase upon metformin treatments, as determined by immuno-blotting.

Fig. S7

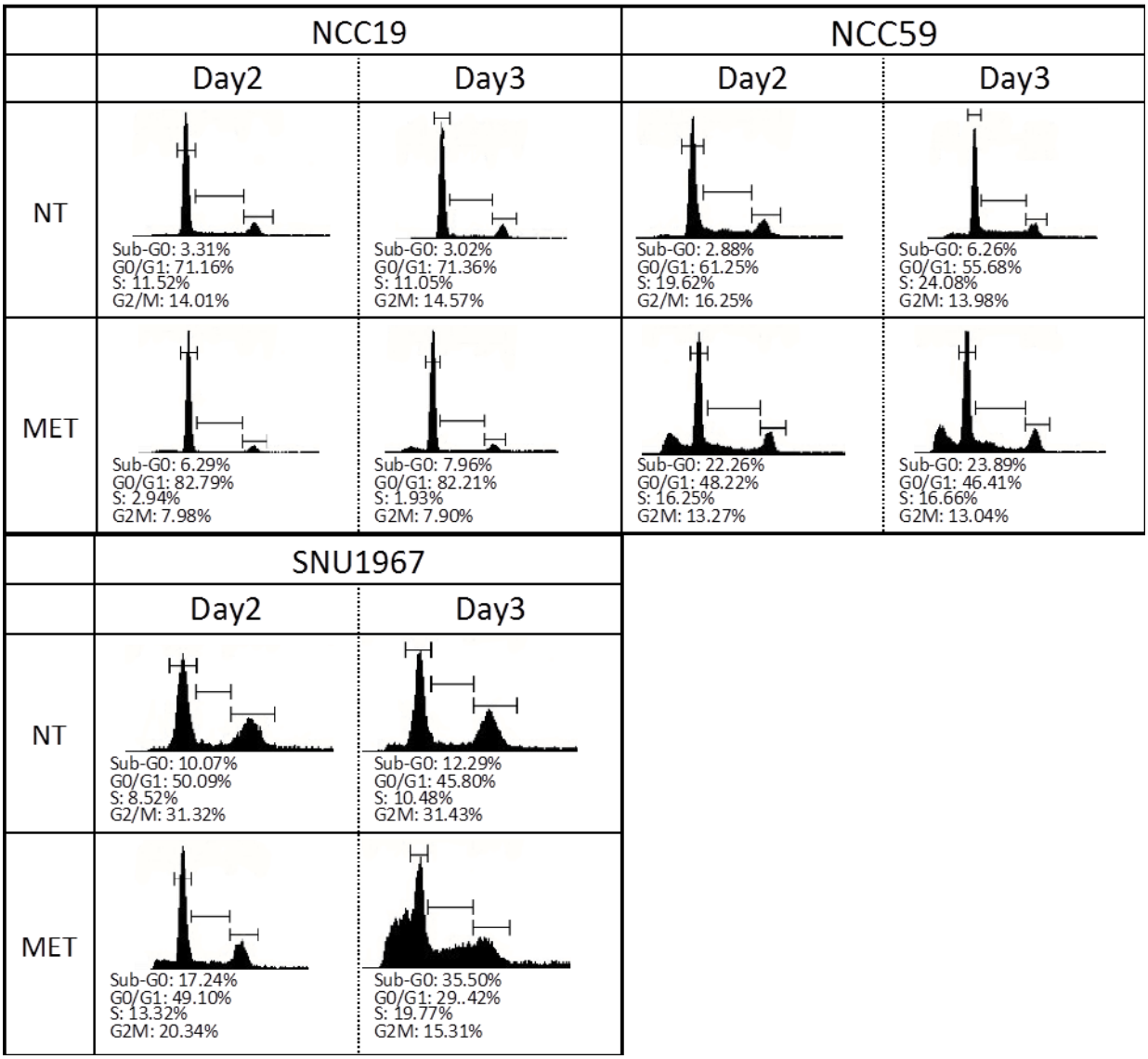

Fig S7 Cell cycle effects following metformin treatment. Measurement of cell cycle distribution at days 2 and 3 after metformin treatment.

Fig. S8

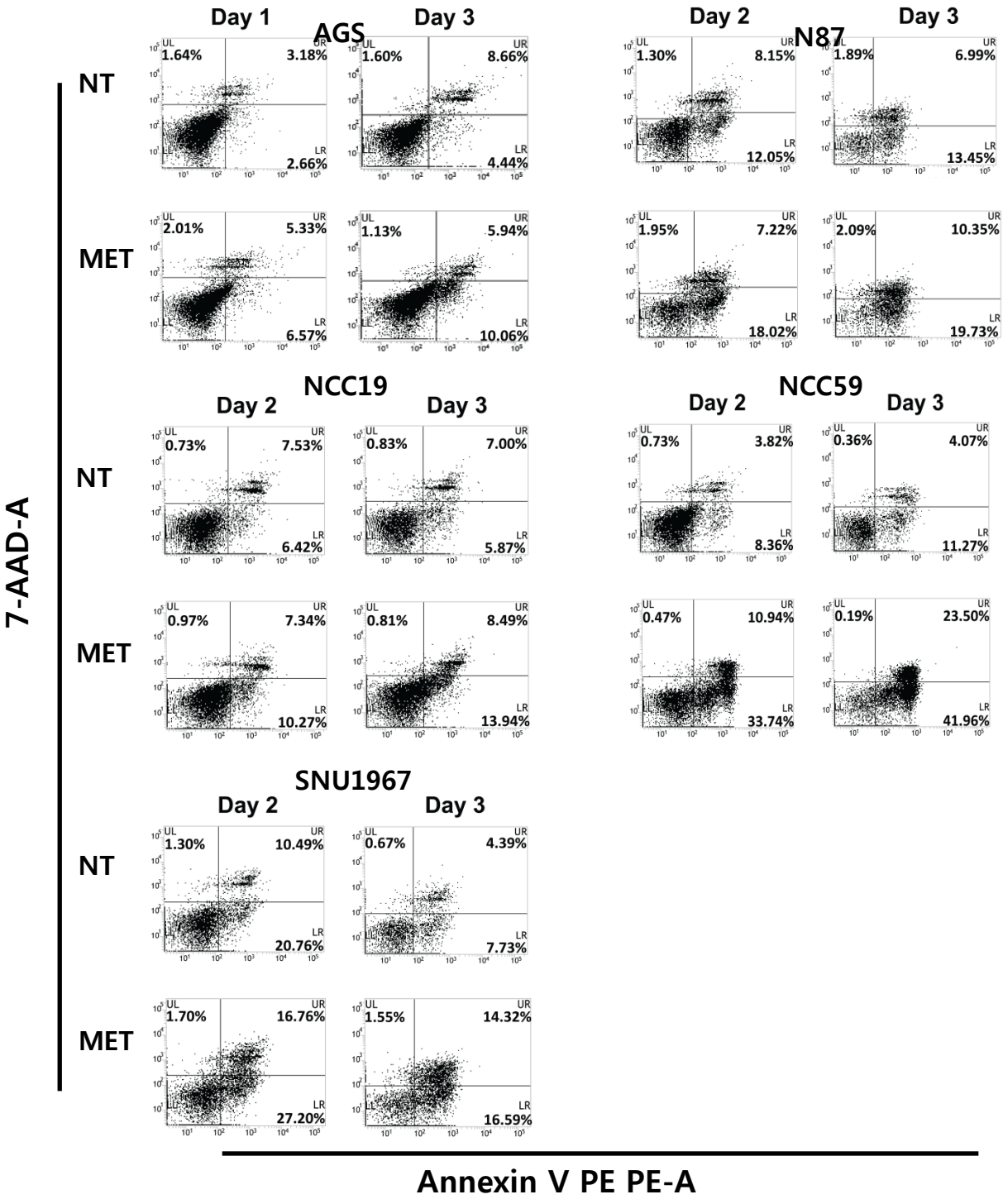

Fig. S8. Apoptotic activity of metformin treatment of five GC cell lines
Apoptosis and necrosis were analyzed by flow cytometry. Annexin V PE apoptosis detection Kit I (BD Biosciences) was used for staining the cells.

Fig. S9

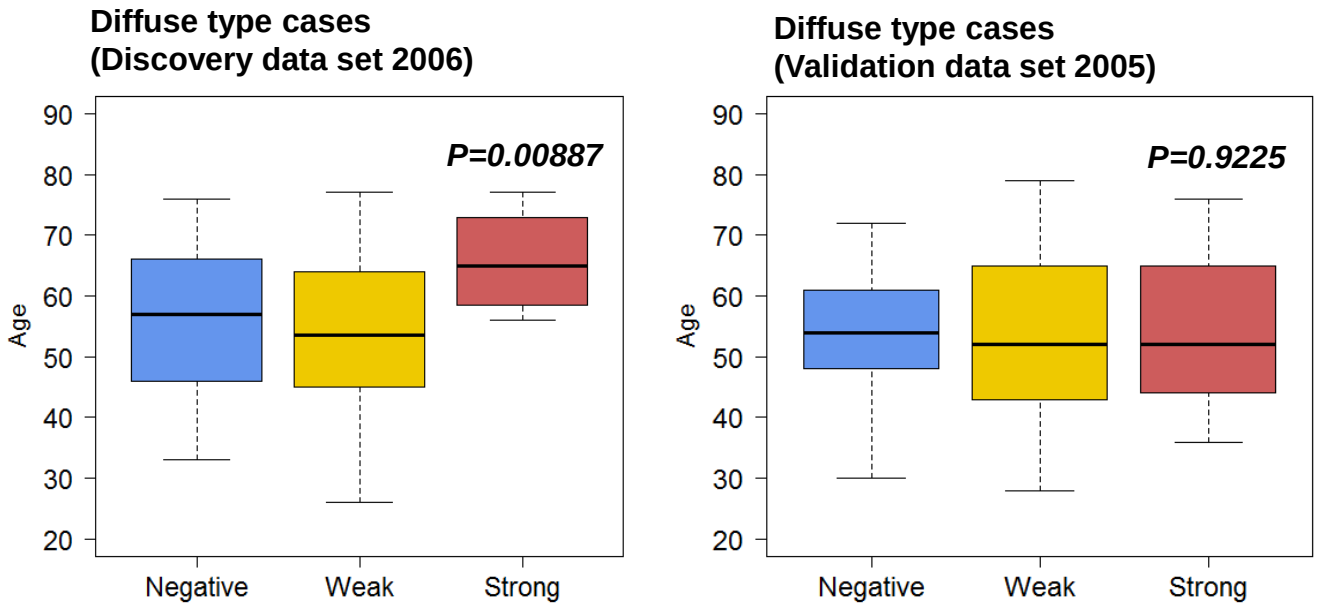

Fig. S9 Clinical relevance of WNT5A expression in diffuse type GC. Significance in aging population (left panel) in discovery data set-2006 *vs.* validation data set-2005 (right panel) .

Fig. S10A

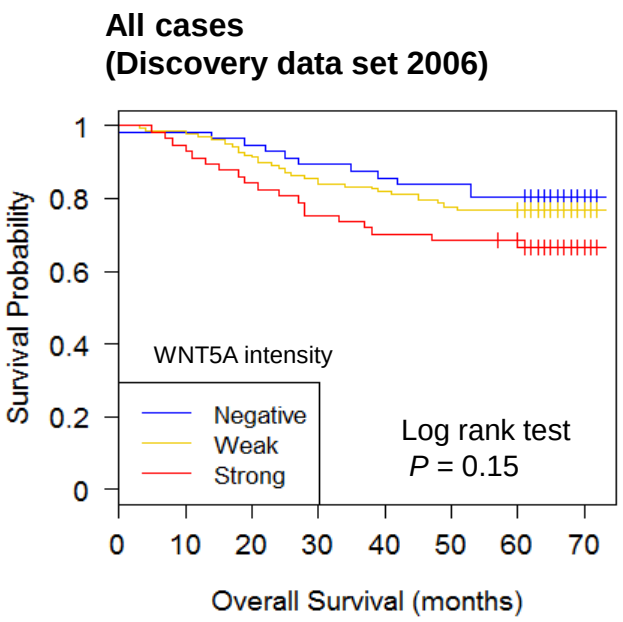

Fig. S10B

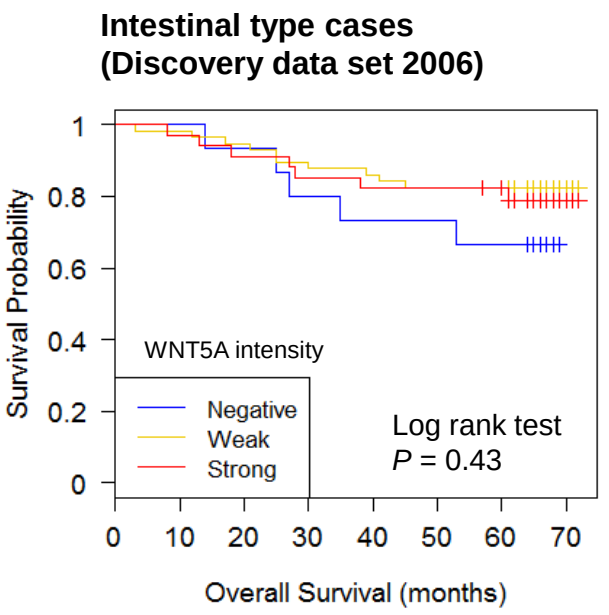

Fig. S10C

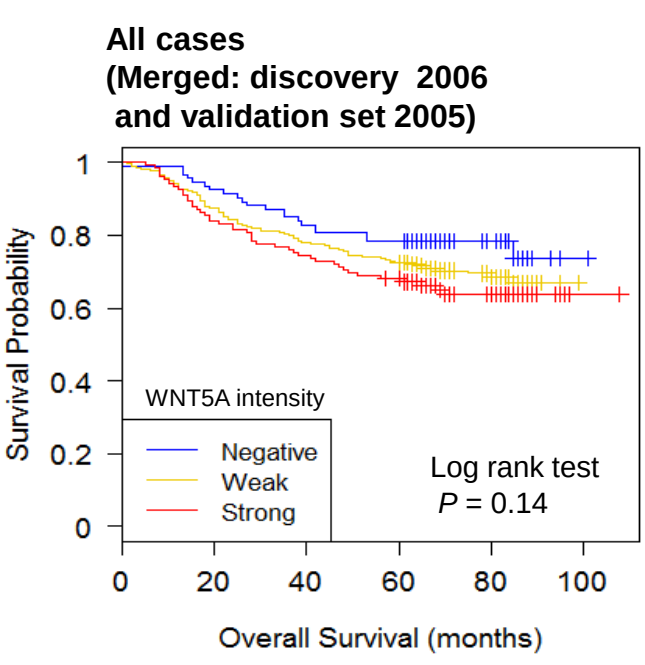

Fig. S10D

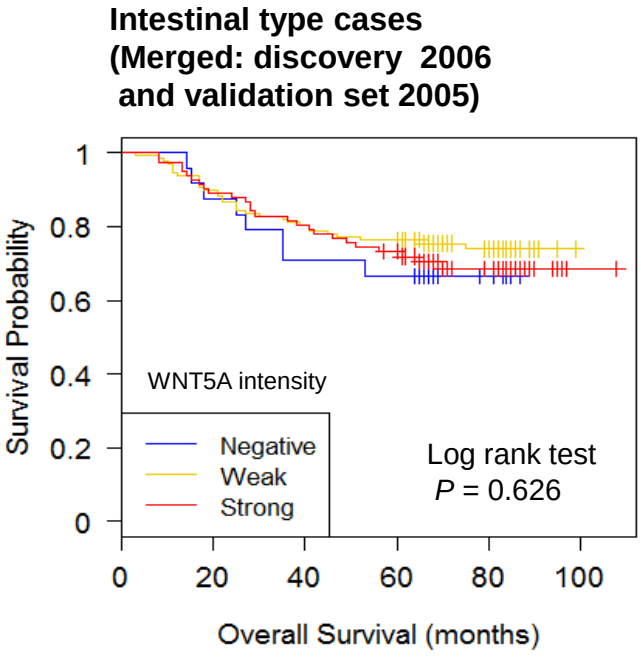

Fig. S10 Discovery data set-2006 and merged (discovery 2006 and validation data set-2005). Kaplan-Meier plots showing the correlation of WNT5A with overall patient survival (A) in all cases and (B) in intestinal type cases. (C) WNT5A expression as associated with overall survival in all GC subtypes (C) or in intestinal type GC (D) cases.

Fig. S11A

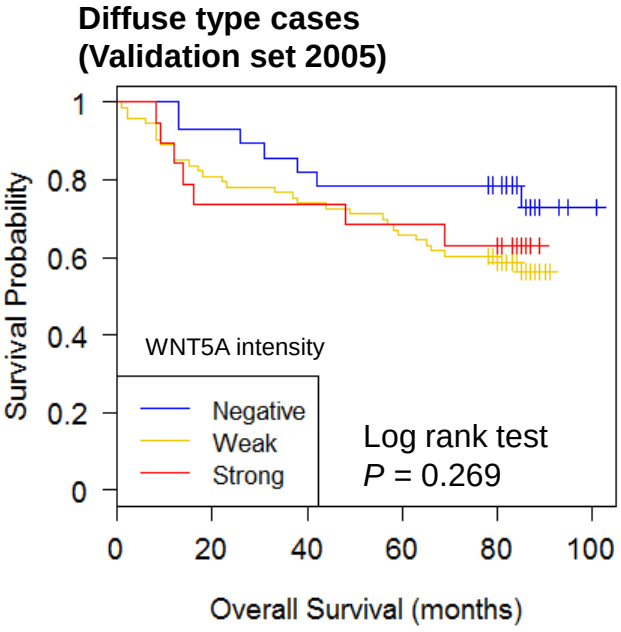

Fig. S11B

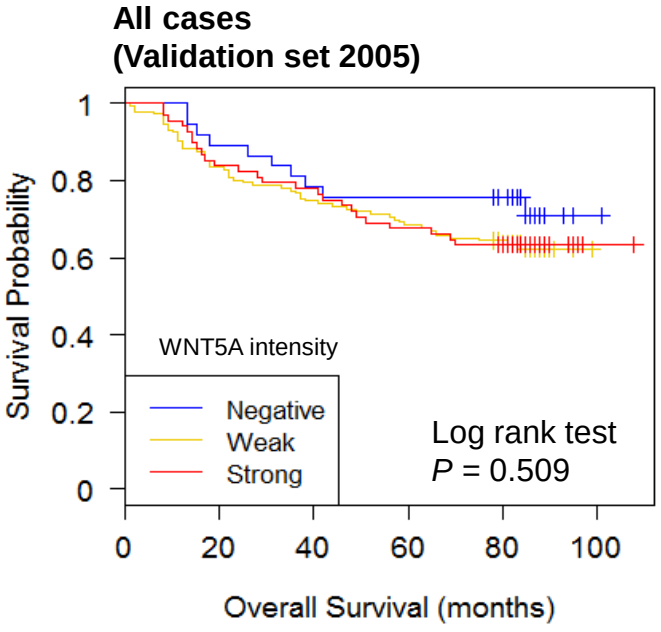

Fig. S11C

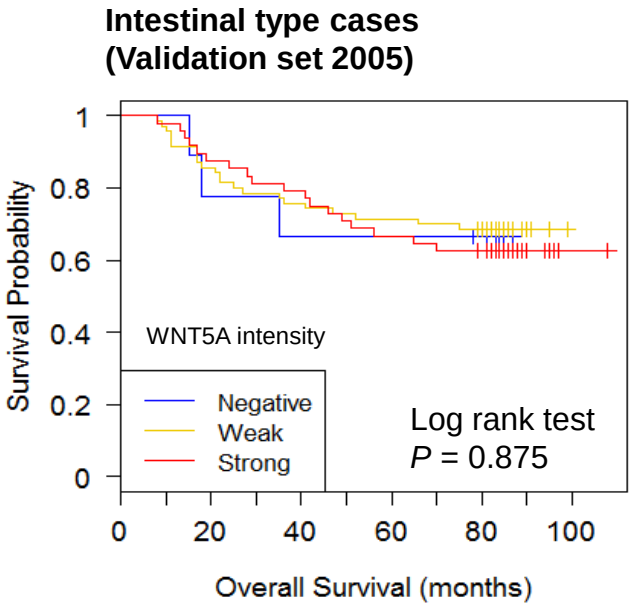

Fig. S11 Validation data set 2005, Kaplan-Meier plots showing the correlation of WNT5A with patient Survivals (A) in all cases and (B) in intestinal type cases.