# Supplementary Material: Phenotype-Genotype Association Analysis of ACTH-Secreting Pituitary Adenoma and Its Molecular Link to Patient Osteoporosis

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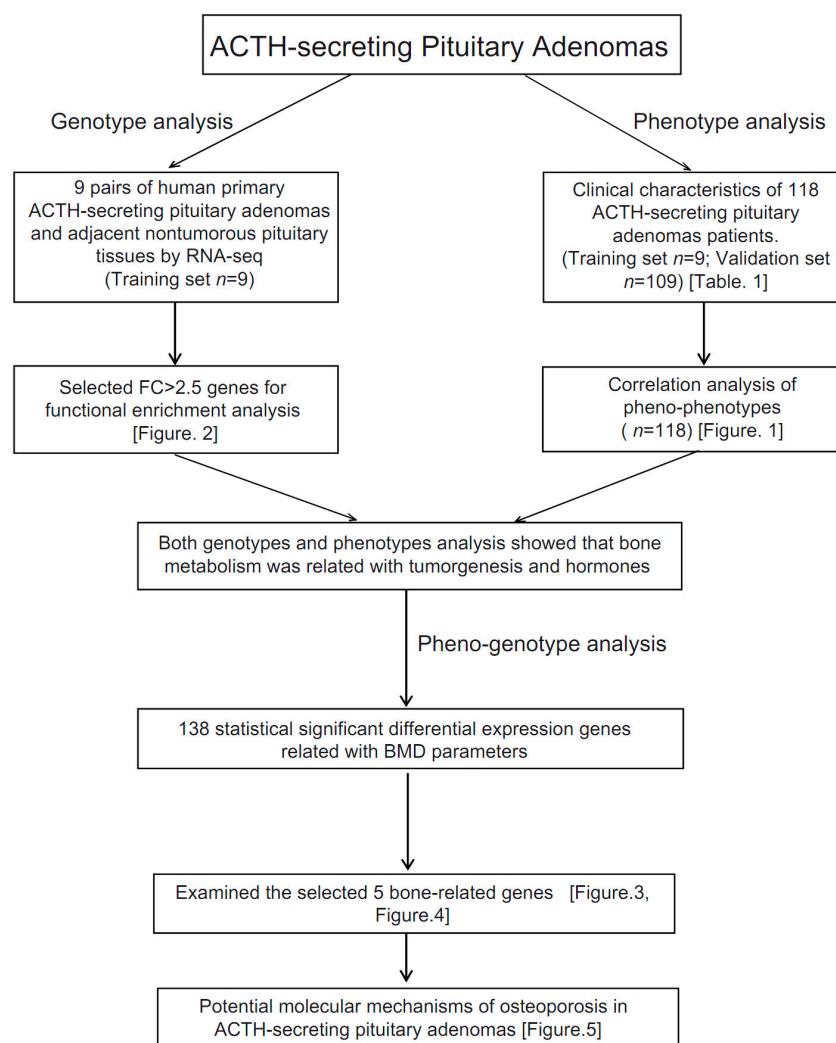
Figure S1. A framework of ACTH-secreting pituitary adenoma pheno-genotype analysis.
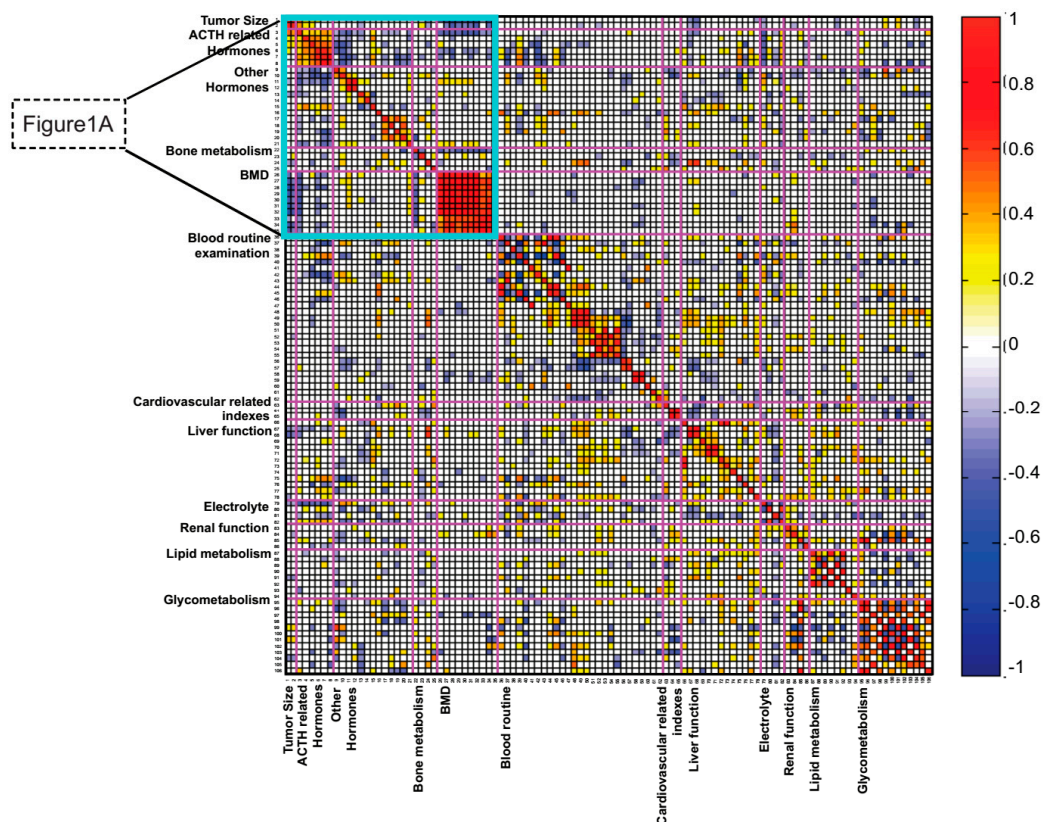
Figure S2. Spearman's rank correlation coefficient analysis of 106 clinical characteristics indices. A total of 106 clinical characteristics indices were processed for SRCC analysis. These phenotypes were shown in Table S1. The heat map of the SRCC results (*p* value < 0.05, FDR < 0.05) was generated using Matlab 7.0 software. Warm colours represent positive correlations, and cold colours represent negative correlations. White indicates no association.
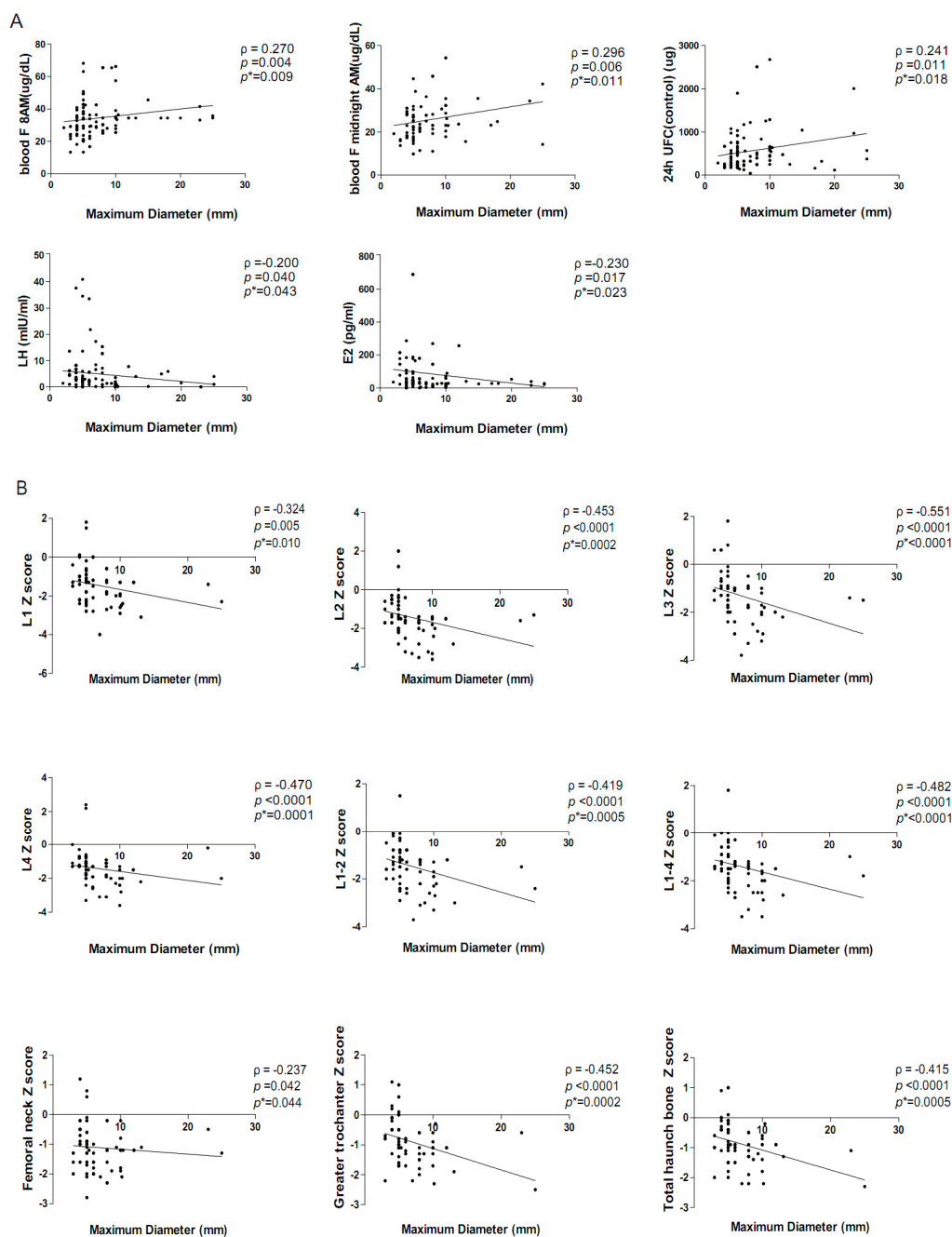
Figure S3. The maximum tumor diameter correlated with ACTH-secreting pituitary adenoma-related hormones, LH, E2 and age-matched bone mineral density (BMD) indices in ACTH-secreting pituitary adenomas. (**A**) The maximum tumor diameter was positively correlated with ACTH-secreting Pituitary Adenoma Related Hormones: 8 AM cortisol, midnight AM cortisol, 24 h UFC and was negatively correlated with LH and E2 levels; (**B**) The maximum tumor diameter negatively correlated with the age-matched BMD indices: L1, L2, L3, L4, L1-2, L1-4, the neck of the femur, the greater trochanter and the total haunch bone. Spearman's rank correlation analysis (Rho), *p* value and the Benjamini & Hochberg multiple testing correction (*p* *) were used to control for false discovery rate (FDR) and were provided in each graph.
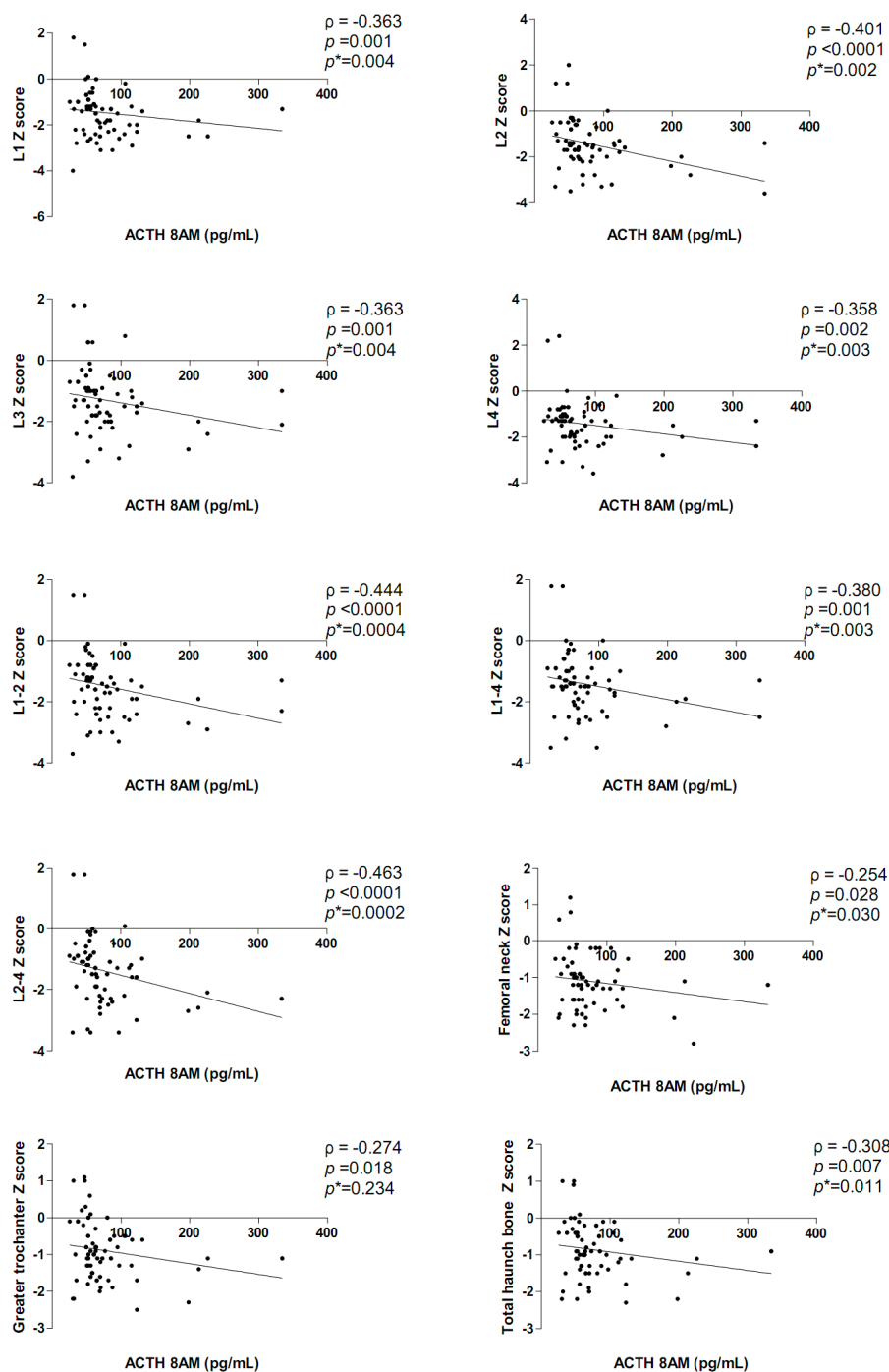
Figure S4. The 8 AM plasma ACTH Levels was inversely correlated with age-matched bone mineral density (BMD) indices in ACTH-secreting pituitary adenoma patients. The 8 AM plasma ACTH was negatively correlated with the age-matched BMD indices: L1, L2, L3, L4, L1-2, L1-4, L2-4, the neck of the femur, the greater trochanter and the total haunch bone. Spearman's rank correlation analysis (Rho), *p* value and the Benjamini & Hochberg multiple testing correction (*p* *) were used to control for false discovery rate (FDR) and were provided in each graph.
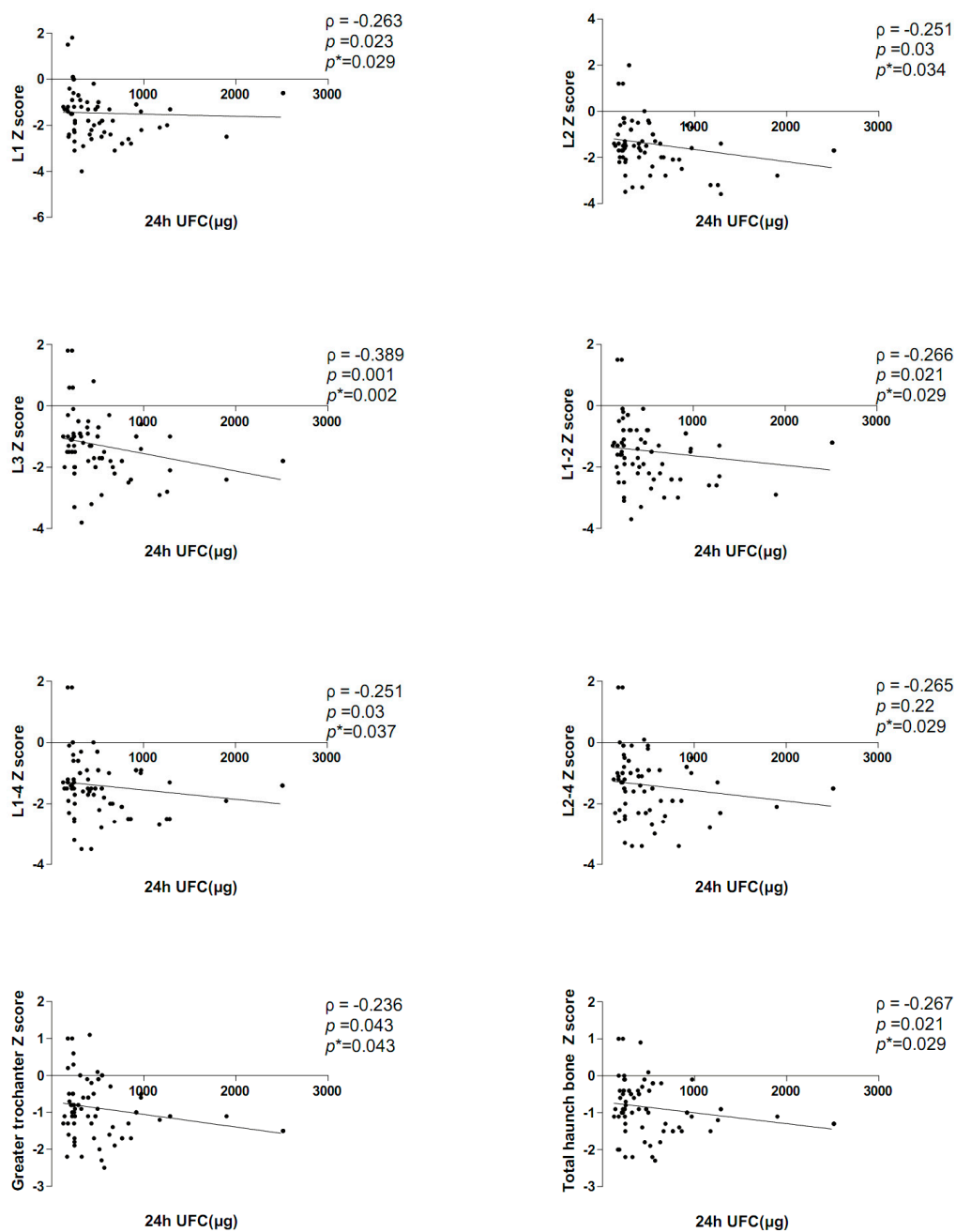
Figure S5. 24 h urinary-free cortisol level was inversely correlated with age-matched bone mineral density (BMD) indices in ACTH-secreting pituitary adenoma patients. The 24-h urinary-free cortisol level was correlated inversely with the age-matched BMD indices: L1, L2, L3, L1-2, L1-4, the greater trochanter and the total haunch bone. Spearman's rank correlation analysis (Rho), the *p* value and the Benjamini & Hochberg multiple testing correction (*p* *) were used to control for false discovery rate (FDR) and were provided in each graph.
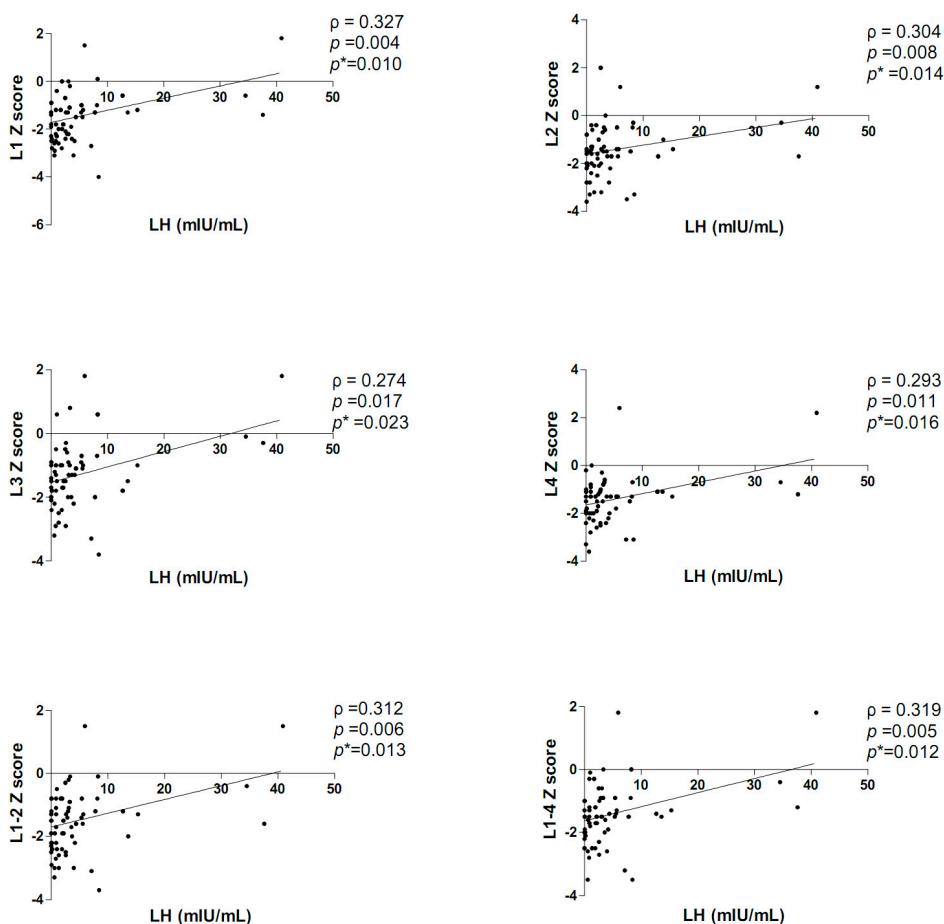
Figure S6. The LH level was positively correlated with age-matched bone mineral density (BMD) indices in ACTH-secreting pituitary adenoma patients. LH level was positively correlated with the age-matched BMD indices: L1, L2, L3, L4, L1-2 and L1-4. Spearman's rank correlation analysis (Rho), the *p* value and the Benjamini & Hochberg multiple testing correction (*p* *) were used to control for false discovery rate (FDR) and were provided in each graph.

Figure S7. The estradiol level was positively correlated with the age-matched bone mineral density (BMD) indices in ACTH-secreting pituitary adenoma patients. Estradiol level was positively correlated with the age-matched BMD indices: L1 and L1-2. Spearman's rank correlation analysis (Rho), the *p* value and the Benjamini & Hochberg multiple testing correction (*p* *) were used to control for false discovery rate (FDR) and were provided in each graph.
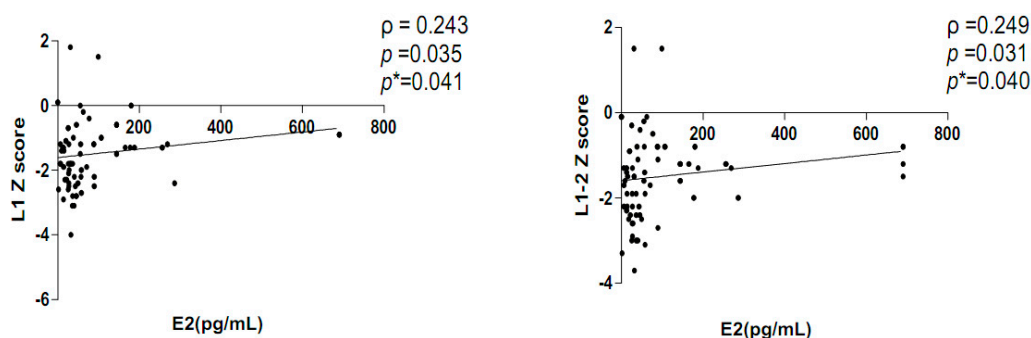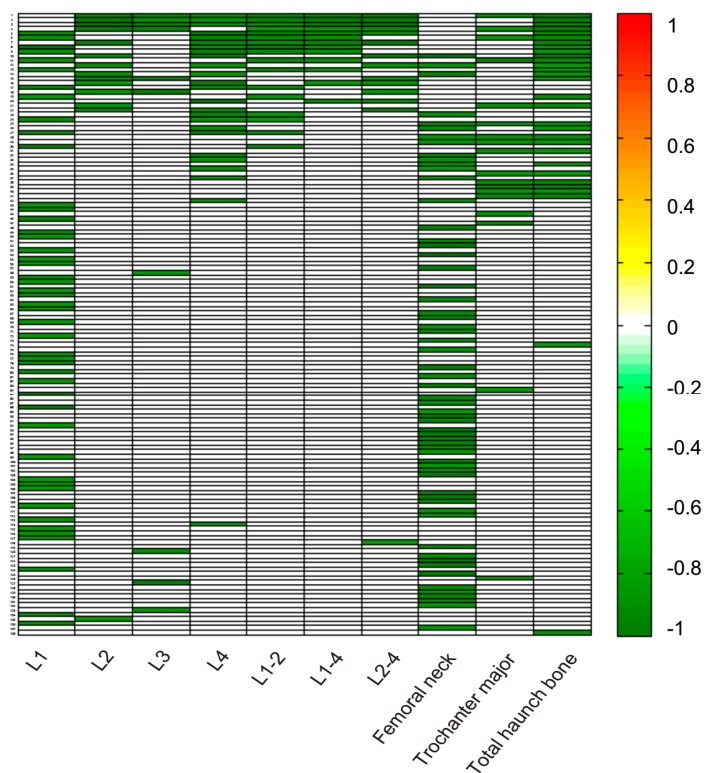
Figure S8. Spearman's Rank Correlation Coefficient (SRCC) analysis of age-matched bone mineral density (BMD) phenotypes and genotypes.The 10 clinical age-matched BMD phenotypes and 423 differentially expressed encoding genes in the ACTH-secreting pituitary adenomas were processed for SRCC analysis. There were 138 genes that were highly related with BMD indices (Tables S8 and S9). The heat map of the SRCC results (p value < 0.05, FDR < 0.05) was generated using Matlab 7.0 software. Warm colours represent positive correlations, cold colours represent negative correlations and white indicates no association.
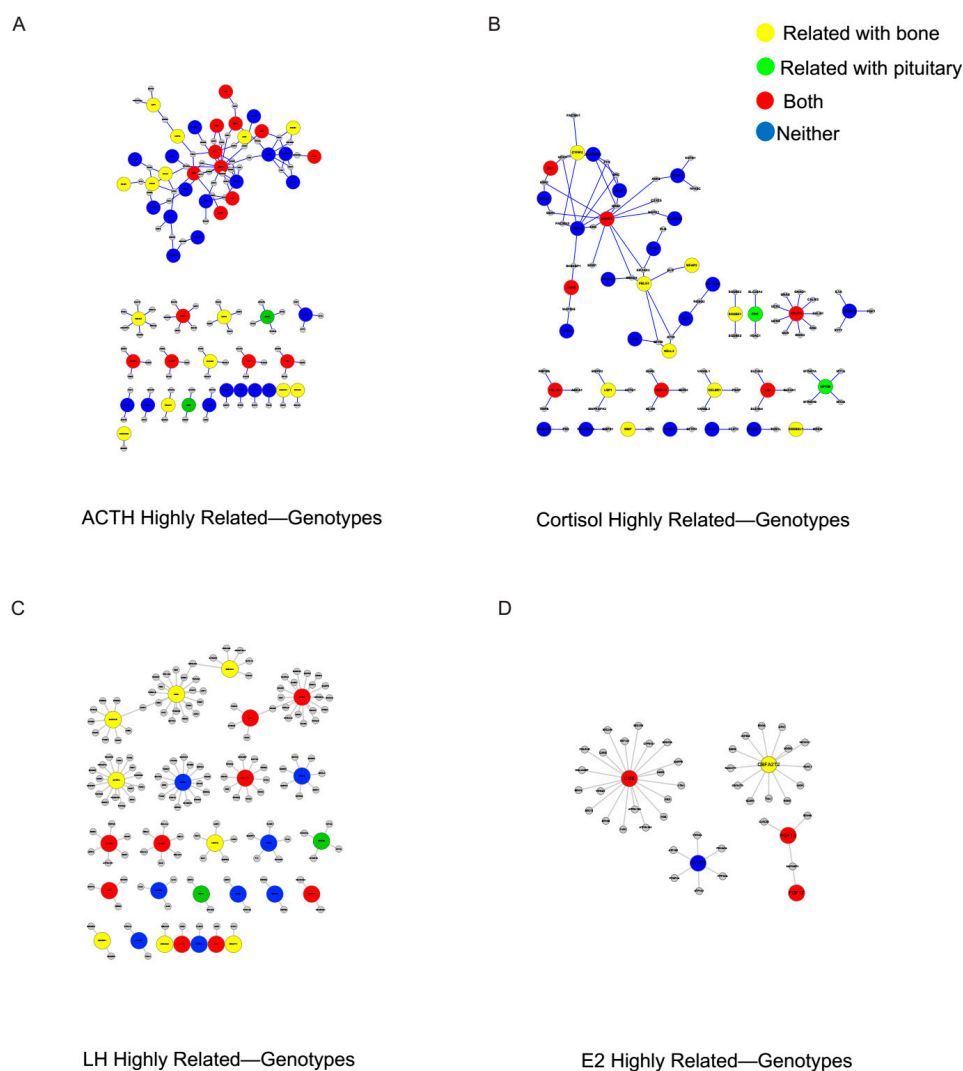
Figure S9. Gene expression profile of ACTH-related hormones in the PPI connection. Literature mining of the genes highly related to ACTH (**A**), genes highly related to cortisol (**B**), genes related to LH (**C**) and genes related to E2 (**D**) assessed for PPI connection. Red represents genes reported for bone and pituitary adenoma fields. Yellow and green represent genes reported for the bone or pituitary adenomas field, respectively. Blue represents genes not reported for bone or pituitary adenomas.
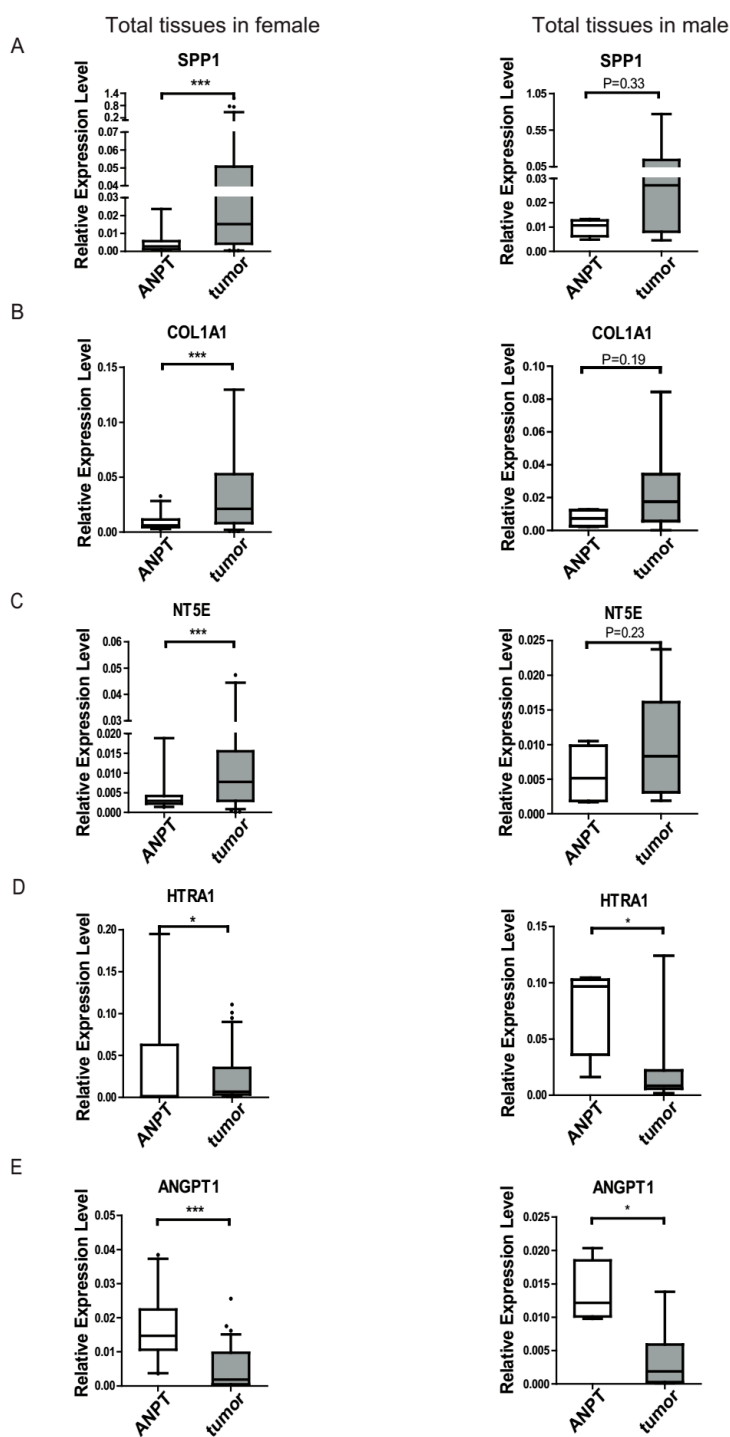
Figure S10. Signature profile of BMD Z score-related gene expression in ACTH-secreting pituitary adenomas. Comparison of expression levels of *SPP1* (**A**), *COL1A1* (**B**), *NT5E* (**C**), *HTRA1* (**D**) and *ANGPT1* (**E**) between ANPT and ACTH-secreting pituitary adenomas via qRT-PCR, including 92 female tissues (29 female paired tissues and 63 female unpaired tissues) and 17 male tissues (ANPT, $n = 4$; tumor, $n = 13$). The data are representative of three technical repeats with the median (quartiles). (Mann-Whitney test, p * < 0.05, p *** < 0.001. ANPT versus tumors).
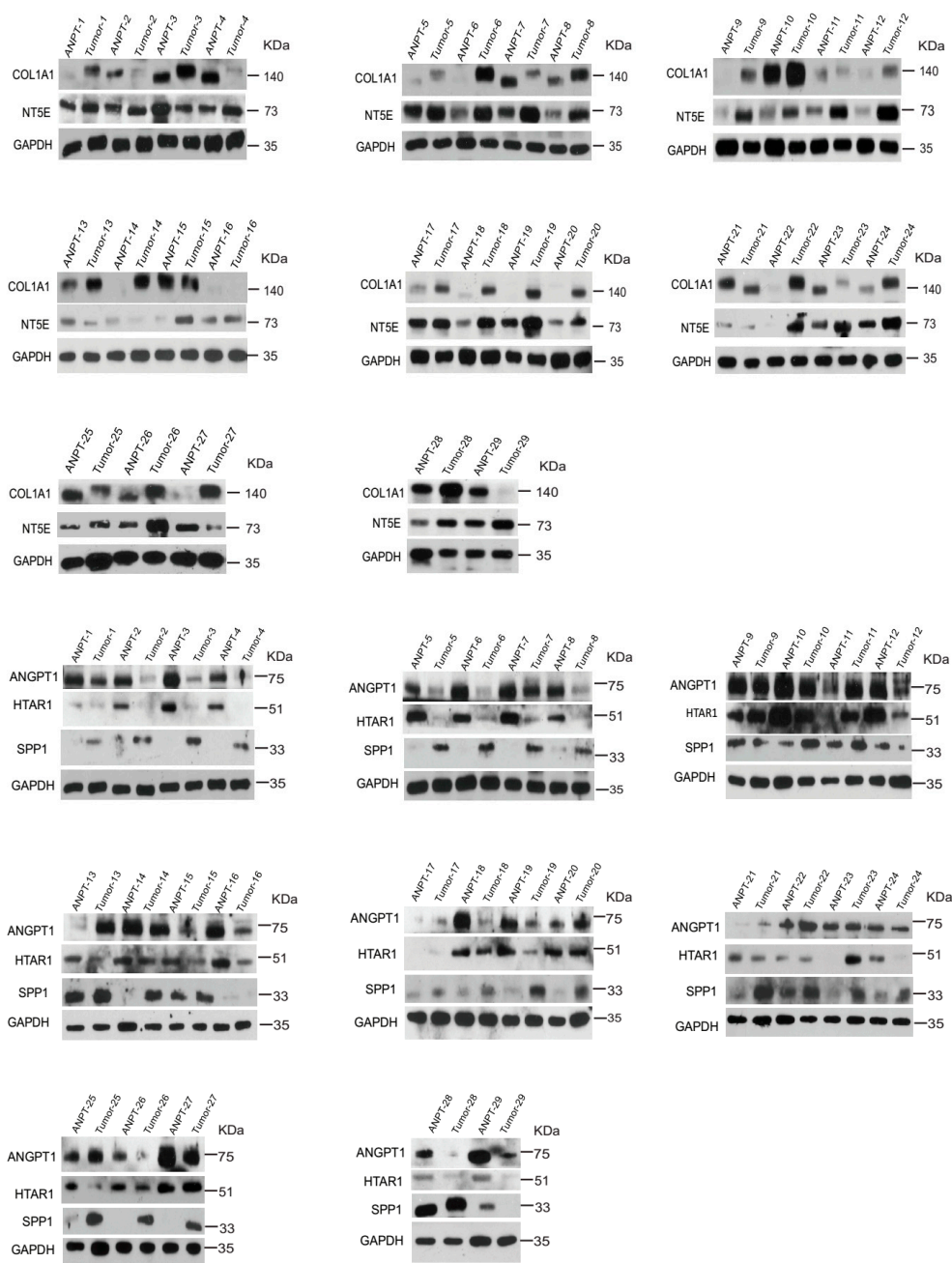
Figure S11. Full-length blots of Figure 4. Western blot assessedthe expression levels of SPP1, COL1A1, NT5E, HTRA1 and ANGPT1 protein between 29 female pairs of ANPT and ACTH-secreting pituitary adenomas.

Table S1. Spearman results of pheno-phenotypes.

ID	Phenotypes	0.8–1	0.5–0.8	(−0.5)–0.5	(−0.8)–(−0.5)	(−1)–(−0.8)	Total
	Tumor size						
1	Maximum diameter	2	1	22	2	0	27
2	Gross tumor volume	2	0	24	0	0	26
	ACTH-secreting pituitary adenoma related hormones						
3	ACTH 8AM	1	1	39	0	0	41
4	8AM F	1	0	23	0	0	24
5	0AM F	1	1	31	0	0	33
6	24 h UFC (control)	1	2	38	0	0	41
7	24 h UFC (low-dose DST)	1	3	37	0	0	41
8	24 h UFC (high-dose DST)	1	2	35	0	0	38
	Other pituitary related hormones						
9	GH	1	1	30	0	0	32
10	IGF-1	1	0	44	1	0	46
11	LH	1	1	31	0	0	33
12	FSH	1	1	14	0	0	16
13	E2	1	0	22	0	0	23
14	PRL	1	0	16	0	0	17
15	TSTO	1	0	33	0	0	34
16	PROG	1	1	29	0	0	31
17	FT3	1	1	29	0	0	31
18	FT4	1	1	23	0	0	25
19	T3	1	1	25	0	0	27
20	T4	1	1	20	0	0	22
21	TSH	1	0	25	0	0	26
	Bone metabolism						
22	PTH	1	0	17	0	0	18
23	P	1	0	25	0	0	26
24	Ca	1	3	28	0	0	32
25	ALP	1	0	25	0	0	26
	Age-matched bone mineral density (BMD)						
26	L1	3	4	19	0	0	26
27	L2	5	5	16	0	0	26
28	L3	4	6	11	1	0	22
29	L4	3	7	9	0	0	19
30	L1-2	5	5	14	0	0	24
31	L1-4	7	3	13	0	0	23
32	L2-4	6	4	7	1	0	18
33	Neck of femur	1	8	9	0	0	18
34	Greater trochanter	2	7	21	0	0	30
35	Total haunch bone	1	7	11	0	0	19
	Routine blood chemistry						
36	WAC	2	2	27	0	0	31
37	LY%	1	2	37	1	1	42
38	MONO%	0	0	16	0	0	16
39	NEUT%	1	1	41	3	1	47
40	EOS	2	0	31	2	0	35
41	BASO	1	0	12	0	0	13
42	LUC	1	1	28	2	0	32
43	LY#	1	1	33	1	0	36
44	MONO#	1	4	28	0	0	33
45	NEUT#	2	2	27	3	0	34
46	EOS#	2	0	29	0	0	31
47	BASO#	2	0	19	0	0	21
48	RBC	1	3	29	0	0	33
49	HGB	2	2	35	0	0	39
50	HCT	2	3	30	1	0	36
51	MCV	3	0	16	0	0	19
52	MCHC	2	1	28	0	0	31
53	MCH	3	1	20	0	0	24
54	CHCM	2	0	23	0	0	25
55	CH	3	0	16	0	0	19

Table S1. *Cont.*

ID	Phenotypes	0.8–1	0.5–0.8	(−0.5)–0.5	(−0.8)–(−0.5)	(−1)–(−0.8)	Total
56	RDW-C	1	1	30	0	0	32
57	HDW	1	1	21	1	0	24
58	PLT	1	1	18	0	0	20
59	PCT	1	1	23	0	0	25
60	PDW	1	0	16	0	0	17
61	MPV	1	0	13	0	0	14
62	ESR	1	0	26	0	0	27
	Cardiovascular related indexes						
63	hsCRP	1	0	31	0	0	32
64	SBP	1	1	22	0	0	24
65	DBP	1	1	24	0	0	26
	Liver function						
66	ALT	1	2	25	0	0	28
67	TP	2	1	37	0	0	40
68	Alb	2	1	36	0	0	39
69	A/G	1	0	28	0	0	29
70	Tbil	2	0	29	0	0	31
71	Dbil	2	0	28	0	0	30
72	GGT	1	1	40	0	0	42
73	AST	1	1	16	0	0	18
74	TBA	1	0	19	0	0	20
75	LD	1	0	42	1	0	44
76	ChE	1	0	32	0	0	33
77	ADA	1	0	32	0	0	33
78	PA	1	0	40	0	0	41
	Electrolyte						
79	K	1	0	37	0	0	38
80	Na	1	1	29	0	0	31
81	Cl	1	0	43	0	0	44
82	TCO_2	1	1	36	0	0	38
	Renal function						
83	Cr(E)	1	0	20	0	0	21
84	Urea	1	0	30	2	0	33
85	Glu	3	4	40	0	0	47
86	UA	1	0	16	0	0	17
	Lipid metabolism						
87	TC	3	0	30	0	0	33
88	TG	1	1	24	0	0	26
89	HDL-C	2	0	29	0	0	31
90	LDL-C	3	0	17	0	0	20
91	ApoA1	2	0	20	0	0	22
92	ApoB	3	1	22	0	0	26
93	Lp(a)	1	0	15	0	0	16
94	FFA	1	0	27	0	0	28
	Glycometabolism						
95	blood gloucose	2	3	40	0	0	45
96	GLU 0 min	2	5	17	0	0	24
97	INS 0 min	1	2	25	0	0	28
98	GLU 30 min	1	6	21	0	0	28
99	INS 30 min	1	3	28	1	0	33
100	GLU 60 min	1	5	27	0	0	33
101	INS 60 min	1	2	23	2	0	28
102	GLU 120 min	1	5	31	1	0	38
103	INS 120 min	1	4	21	0	0	26
104	GLU 180 min	1	3	25	0	0	29
105	INS 180 min	1	4	14	0	0	19
106	HbAlc	1	4	19	0	0	24

Table S2. Maximum diameter highly related-clinical indexes.

Clinical Indexes	n	Spearman	p Value	FDR
Gross tumor volume	110	0.941	<0.001	<0.001
ACTH 8 AM	110	0.501	<0.001	<0.001
0 AM F	84	0.296	0.006	0.011
8 AM F	110	0.270	0.004	0.009
24 h UFC (control)	110	0.241	0.011	0.018
LH	107	−0.199	0.040	0.043
Ca	109	−0.221	0.021	0.027
E2	107	−0.230	0.017	0.023
Neck of femur	75	−0.237	0.042	0.044
L1	75	−0.324	0.005	0.010
Total haunch bone	75	−0.415	<0.001	0.001
L1-2	75	−0.419	<0.001	0.001
Greater trochanter	75	−0.452	<0.001	<0.001
L2	75	−0.453	<0.001	<0.001
L4	75	−0.470	<0.001	<0.001
L1-4	75	−0.482	<0.001	<0.001
L3	75	−0.551	<0.001	<0.001
L2-4	75	−0.581	<0.001	<0.001

Table S3. ACTH 8AM highly related-osteo indexes.

Osteo Indexes	n	Spearman	p Value	FDR
Neck of femur	75	−0.254	0.028	0.030
Greater trochanter	75	−0.274	0.018	0.023
Total haunch bone	75	−0.308	0.007	0.011
L4	75	−0.358	0.002	0.003
L1	75	−0.363	0.001	0.004
L3	75	−0.363	0.001	0.004
L1-4	75	−0.379	0.001	0.003
L2	75	−0.401	<0.001	0.002
L1-2	75	−0.444	<0.001	<0.001
L2-4	75	−0.463	<0.001	<0.001

Table S4. 24 h UFC (control) highly related-osteo.

Osteo Indexes	n	Spearman	p Value	FDR
Greater trochanter	75	−0.236	0.043	0.043
L2	75	−0.251	0.030	0.034
L1-4	75	−0.251	0.030	0.037
L1	75	−0.263	0.023	0.029
L2-4	75	−0.265	0.022	0.029
L1-2	75	−0.266	0.021	0.029
Total haunch bone	75	−0.267	0.021	0.029
L3	75	−0.389	0.001	0.002

Table S5. LH highly related-osteo indexes.

Osteo Indexes	n	Spearman	p Value	FDR
L1	75	0.327	0.004	<0.001
L1-4	75	0.319	0.005	<0.001
L1-2	75	0.312	0.006	0.001
L2	75	0.304	0.008	0.010
L4	75	0.293	0.011	0.011
L3	75	0.274	0.017	0.013

Table S6. E2 highly related-osteo indexes.

Osteo Indexes	n	Spearman	p Value	FDR
L1	75	0.243	0.035	0.041
L1-2	75	0.249	0.031	0.040

Table S7. Information of sequencing quality control.

ID	Tissue	Library Size (bp)	Strand Specific	Sequencing Type	Library Size (bp)	Read Length (nt)	Total Reads	Total Basepairs	Reads Mapped to Genome	Mapping Ratio
N1	tumor	300	NO	Pair-end	300	100	73,614,480	7,361,448,000	60,612,808	82.34%
	ANPTs	300	NO	Pair-end	300	100	78,173,560	7,817,356,000	62,375,857	79.79%
N2	tumor	300	NO	Pair-end	300	100	78,173,560	7,817,356,000	56,070,088	71.73%
	ANPTs	300	NO	Pair-end	300	100	89,010,912	8,901,091,200	73,630,521	82.72%
N3	tumor	300	NO	Pair-end	300	100	79,580,300	7,958,030,000	64,790,623	81.42%
	ANPTs	300	NO	Pair-end	300	100	76,619,924	7,661,992,400	64,033,275	83.57%
N4	tumor	300	NO	Pair-end	300	100	76,996,314	7,699,631,400	62,752,759	81.50%
	ANPTs	300	NO	Pair-end	300	100	90,919,768	9,091,976,800	46,035,736	50.63%
N5	tumor	300	YES	Pair-end	300	100	124,465,980	12,446,598,000	101,145,421	81.26%
	ANPTs	300	YES	Pair-end	300	100	64,252,872	6,425,287,200	52,554,201	81.79%
N6	tumor	300	YES	Pair-end	300	100	48,795,594	4,879,559,400	41,181,643	84.40%
	ANPTs	300	YES	Pair-end	300	100	47,704,480	4,770,448,000	40,219,630	84.31%
N7	tumor	300	YES	Pair-end	300	100	68,686,500	6,868,650,000	57,919,244	84.32%
	ANPTs	300	YES	Pair-end	300	100	75,849,422	7,584,942,200	63,327,495	83.49%
N8	tumor	300	YES	Pair-end	300	100	90,908,180	9,090,818,000	75,853,891	83.44%
	ANPTs	300	YES	Pair-end	300	100	87,935,006	8,793,500,600	53,538,621	60.88%
N9	tumor	300	YES	Pair-end	300	100	73,968,232	7,396,823,200	62,944,377	85.10%
	ANPTs	300	YES	Pair-end	300	100	78,229,188	7,822,918,800	63,552,258	81.24%

Table S8. Age-matched bone mineral density (BMD) highly related-genotypes.

Gene	Count of Highly Related BMD	FC	L1	L2	L3	L4	L1–2	L1–4	L2–4	Neck of Femur	Greater Trochanter	Total Haunch Bone
COL1A1	8	3.01	—	0.93	0.89	0.86	0.88	0.93	0.96	—	0.82	0.91
RAB3B	7	4.79	—	0.98	0.85	0.87	0.92	0.96	0.97	—	—	0.97
INSR	7	3.36	—	0.98	0.91	0.84	0.84	0.91	0.98	—	—	0.89
RFX4	7	3.13	—	0.94	0.92	—	0.82	0.85	0.90	—	0.82	0.98
LYPD1	6	3.32	0.87	—	—	0.97	0.92	0.89	0.83	—	—	0.86
PITX1	6	2.88	0.85	—	—	0.92	0.90	0.87	—	—	0.82	0.90
CNGA4	6	2.57	—	0.95	—	0.93	0.89	0.94	0.97	—	—	0.91
STK17B	5	3.46	0.98	—	—	0.85	0.91	0.84	—	—	—	0.82
NT5E	5	3.00	0.86	—	—	0.92	0.90	0.86	—	—	—	0.84
PPAPDC1A	5	2.82	—	0.86	—	1.00	—	—	0.91	0.99	—	0.99
ACOT7	5	2.66	0.86	—	—	—	0.89	0.86	—	—	0.95	0.90
GADD45B	5	2.60	—	0.90	—	0.86	—	—	0.87	0.86	—	0.83
ATP2B2	4	3.41	0.84	—	—	—	0.87	0.81	—	—	—	0.81
BAMBI	4	3.08	—	0.85	—	0.84	—	—	—	0.92	—	0.87
SIX2	4	2.79	—	0.87	0.93	—	—	—	0.82	—	—	0.84
CYFIP2	4	2.69	—	0.82	—	0.96	—	0.81	0.86	—	—	—
MYH6	3	5.97	0.88	—	—	0.85	0.83	—	—	—	—	—
KIAA1024	3	5.94	—	0.85	0.94	—	—	—	0.85	—	—	—
HFM1	3	4.70	0.84	—	—	—	0.86	—	—	—	—	0.89
RASEF	3	4.52	—	—	—	0.94	—	0.81	0.83	—	—	—
ZBTB49	3	3.17	—	0.86	—	—	—	—	—	—	0.84	0.90
C1orf95	3	2.97	—	0.86	—	0.83	—	—	0.90	—	—	—
IGFBP3	3	2.78	—	—	—	0.93	0.81	—	—	0.87	—	—
ATP6V1C2	3	2.68	0.90	—	—	0.85	0.84	—	—	—	—	—
PDE7A	3	2.68	—	—	—	—	—	—	—	0.87	0.83	0.84
OLFM2	3	2.66	—	—	—	0.89	—	—	—	0.90	—	0.81
PITPNM2	3	2.59	0.83	—	—	0.88	0.81	—	—	—	—	—
CHGA	3	2.57	—	—	—	—	—	—	—	0.87	0.86	0.90
TCF7L2	3	2.53	—	—	—	—	—	—	—	0.87	0.81	0.83
HIGD1B	2	6.64	0.93	—	—	—	0.84	—	—	—	—	—
FABP7	2	3.50	—	—	—	—	—	—	—	—	0.85	0.84
LHX3	2	3.45	—	—	—	0.88	—	—	—	0.87	—	—
COL11A2	2	3.23	—	—	—	0.84	—	—	—	0.87	—	—
PI16	2	3.10	—	—	—	—	—	—	—	0.86	—	0.83

Table S8. *Cont.*

Gene	Count of Highly Related BMD	FC	L1	L2	L3	L4	L1–2	L1–4	L2–4	Neck of Femur	Greater Trochanter	Total Haunch Bone
SOCS2	2	3.00	—	—	—	0.85	—	—	—	0.83	—	—
MYCL1	2	2.99	—	—	—	—	—	—	—	—	0.83	0.83
SLC38A3	2	2.96	—	—	—	0.85	—	—	—	0.86	—	—
SCD5	2	2.93	—	—	—	—	—	—	—	—	0.88	0.91
THBD	2	2.88	—	—	—	—	—	—	—	—	0.90	0.89
KIAA1211	2	2.82	—	—	—	—	—	—	—	—	0.83	0.87
PPARGC1A	2	2.82	—	—	—	—	—	—	—	—	0.90	0.92
PPIF	2	2.58	—	—	—	0.84	—	—	—	0.87	—	—
CRHR1	1	7.47	0.83	—	—	—	—	—	—	—	—	—
CHRNE	1	5.16	0.88	—	—	—	—	—	—	—	—	—
DPP6	1	4.99	—	—	—	—	—	—	—	—	0.85	—
TMEM100	1	4.90	0.93	—	—	—	—	—	—	—	—	—
FOXL2	1	4.79	—	—	—	—	—	—	—	—	0.82	—
MSX1	1	4.50	—	—	—	—	—	—	—	0.94	—	—
NELL2	1	4.45	0.83	—	—	—	—	—	—	—	—	—
PTGDR2	1	4.26	0.83	—	—	—	—	—	—	—	—	—
C14orf180	1	4.20	—	—	—	—	—	—	—	0.89	—	—
GPR149	1	4.17	—	—	—	—	—	—	—	0.97	—	—
MEIS2	1	4.16	0.83	—	—	—	—	—	—	—	—	—
CACNG2	1	4.11	—	—	—	—	—	—	—	0.95	—	—
GPC3	1	4.11	0.83	—	—	—	—	—	—	—	—	—
HSD11B1	1	4.00	0.83	—	—	—	—	—	—	—	—	—
NTNG1	1	3.92	—	—	—	—	—	—	—	0.96	—	—
TRIM2	1	3.77	—	—	0.82	—	—	—	—	—	—	—
GNAL	1	3.77	0.82	—	—	—	—	—	—	—	—	—
TLE3	1	3.75	0.83	—	—	—	—	—	—	—	—	—
ALDH1A2	1	3.74	—	—	—	—	—	—	—	0.92	—	—
MYT1L	1	3.74	0.82	—	—	—	—	—	—	—	—	—
SALL1	1	3.73	0.83	—	—	—	—	—	—	—	—	—
FMOD	1	3.71	—	—	—	—	—	—	—	0.90	—	—
S100A13	1	3.69	0.83	—	—	—	—	—	—	—	—	—
RSPO3	1	3.61	0.85	—	—	—	—	—	—	—	—	—
TSPAN12	1	3.54	—	—	—	—	—	—	—	0.89	—	—
TSPAN8	1	3.52	—	—	—	—	—	—	—	0.88	—	—

Table S8. *Cont.*

Gene	Count of Highly Related BMD	FC	L1	L2	L3	L4	L1–2	L1–4	L2–4	Neck of Femur	Greater Trochanter	Total Haunch Bone
SCGN	1	3.46	0.82	—	—	—	—	—	—	—	—	—
S100A1	1	3.42	—	—	—	—	—	—	—	0.85	—	—
KCNH8	1	3.39	—	—	—	—	—	—	—	0.87	—	—
PLEKHG5	1	3.37	0.83	—	—	—	—	—	—	—	—	—
ARMC4	1	3.36	—	—	—	—	—	—	—	0.82	—	—
HTRA1	1	3.35	—	—	—	—	—	—	—	—	—	0.82
PLCD3	1	3.33	—	—	—	—	—	—	—	0.87	—	—
FAM163A	1	3.28	0.81	—	—	—	—	—	—	—	—	—
PPP1R13L	1	3.26	0.83	—	—	—	—	—	—	—	—	—
ANGPT1	1	3.25	0.83	—	—	—	—	—	—	—	—	—
VSTM1	1	3.25	—	—	—	—	—	—	—	0.96	—	—
GNRHR	1	3.21	0.83	—	—	—	—	—	—	—	—	—
ZNF521	1	3.20	—	—	—	—	—	—	—	0.85	—	—
PITX2	1	3.11	0.83	—	—	—	—	—	—	—	—	—
SLC16A2	1	3.10	—	—	—	—	—	—	—	0.93	—	—
ESR1	1	3.09	—	—	—	—	—	—	—	—	0.82	—
USH1C	1	3.08	0.82	—	—	—	—	—	—	—	—	—
IGFBP5	1	3.08	—	—	—	—	—	—	—	0.91	—	—
PCP4	1	3.07	—	—	—	—	—	—	—	0.85	—	—
ATG9B	1	3.06	0.91	—	—	—	—	—	—	—	—	—
SCN1B	1	3.06	—	—	—	—	—	—	—	0.82	—	—
DHRS3	1	3.05	—	—	—	—	—	—	—	0.95	—	—
CPVL	1	3.03	—	—	—	—	—	—	—	0.91	—	—
COL4A6	1	3.01	0.83	—	—	—	—	—	—	—	—	—
MATN2	1	3.00	—	—	—	—	—	—	—	0.96	—	—
LGR5	1	2.98	—	—	—	—	—	—	—	0.95	—	—
F3	1	2.97	—	—	—	—	—	—	—	0.86	—	—
APOL4	1	2.97	—	—	—	—	—	—	—	0.92	—	—
RNASE1	1	2.95	—	—	—	—	—	—	—	0.88	—	—
C19orf33	1	2.95	—	—	—	—	—	—	—	0.84	—	—
NEUROD4	1	2.95	0.83	—	—	—	—	—	—	—	—	—
GPX3	1	2.94	—	—	—	—	—	—	—	0.91	—	—
C7	1	2.92	—	—	—	—	—	—	—	0.82	—	—
CPNE4	1	2.88	—	—	—	—	—	—	—	0.84	—	—

Table S8. *Cont.*

Gene	Count of Highly Related BMD	FC	L1	L2	L3	L4	L1–2	L1–4	L2–4	Neck of Femur	Greater Trochanter	Total Haunch Bone
PHGDH	1	2.88	—	—	—	—	—	—	—	0.98	—	—
AMPD3	1	2.86	0.83	—	—	—	—	—	—	—	—	—
PLTP	1	2.86	0.82	—	—	—	—	—	—	—	—	—
SPP1	1	2.86	0.83	—	—	—	—	—	—	—	—	—
PKD1L1	1	2.85	—	—	—	—	—	—	—	0.90	—	—
AMOT	1	2.85	—	—	—	—	—	—	—	0.98	—	—
CYS1	1	2.83	—	—	—	—	—	—	—	0.86	—	—
C17orf72	1	2.83	0.83	—	—	—	—	—	—	—	—	—
AGR3	1	2.83	—	—	—	—	—	—	—	0.87	—	—
FLRT1	1	2.83	—	—	—	—	—	—	—	0.84	—	—
ZNF516	1	2.81	0.84	—	—	—	—	—	—	—	—	—
UCK2	1	2.81	—	—	—	0.83	—	—	—	—	—	—
IGSF1	1	2.80	0.83	—	—	—	—	—	—	—	—	—
FZD7	1	2.79	0.87	—	—	—	—	—	—	—	—	—
FGF1	1	2.77	0.83	—	—	—	—	—	—	—	—	—
MFAP2	1	2.77	—	—	—	—	—	—	0.82	—	—	—
GDPD2	1	2.75	—	—	—	—	—	—	—	0.85	—	—
SYNE2	1	2.70	—	—	0.89	—	—	—	—	—	—	—
ADAM28	1	2.70	—	—	—	—	—	—	—	0.88	—	—
EXOC3L2	1	2.68	—	—	—	—	—	—	—	0.97	—	—
NTRK2	1	2.66	—	—	—	—	—	—	—	0.94	—	—
EPHX1	1	2.66	0.82	—	—	—	—	—	—	—	—	—
FBXO31	1	2.64	—	—	—	—	—	—	—	0.98	—	—
CDH20	1	2.64	—	—	—	—	—	—	—	—	0.81	—
RAB40C	1	2.64	—	—	0.94	—	—	—	—	—	—	—
NFIX	1	2.63	—	—	—	—	—	—	—	0.89	—	—
KIAA1462	1	2.63	—	—	—	—	—	—	—	0.83	—	—
OXT	1	2.61	—	—	—	—	—	—	—	0.91	—	—
CDH22	1	2.60	—	—	—	—	—	—	—	0.85	—	—
SYT12	1	2.60	—	—	—	—	—	—	—	0.84	—	—
PRRG4	1	2.56	—	—	0.84	—	—	—	—	—	—	—
TIMP4	1	2.55	0.84	—	—	—	—	—	—	—	—	—
ADCY2	1	2.54	—	0.83	—	—	—	—	—	—	—	—
GALNT14	1	2.53	0.83	—	—	—	—	—	—	—	—	—
CCL14	1	2.51	—	—	—	—	—	—	—	0.87	—	—
FILIP1	1	2.51	—	—	—	—	—	—	—	—	—	0.85

—: *p* value > 0.05.

Table S9. Osteo-related genes.

ID	N1 Tumor	N1 ANPTs	N2 Tumor	N2 ANPTs	N3 Tumor	N3 ANPTs	N4 Tumor	N4 ANPTs	N5 Tumor	N5 ANPTs	N6 Tumor	N6 ANPTs	N7 Tumor	N7 ANPTs	N8 Tumor	N8 ANPTs	N9 Tumor	N9 ANPTs	Differentail Recurrence	DI	Avg (Tumor)	Avg (ANPTs)	Gene Symbol	Chr	FC
NM_000088	40.10	5.07	43.31	9.33	77.52	7.59	5.41	7.36	16.26	6.24	21.30	3.31	12.44	3.88	24.57	4.79	24.26	5.71	8	0.668	29.4626	5.92063	COL1A1	chr17	3.01
NM_002867	78.90	2.25	68.27	2.84	54.60	3.54	2.25	3.76	33.42	1.99	55.90	1.62	16.51	1.43	35.83	1.39	42.35	5.40	8	0.791	43.1134	2.69056	RAB3B	chr1	4.79
NM_001079817	88.35	9.62	53.97	9.41	94.81	10.07	7.92	8.51	19.79	6.86	38.24	5.50	10.85	4.89	34.87	5.96	73.20	12.84	8	0.703	46.8891	8.18416	INSR	chr19	3.36
NM_213594	0.27	6.65	0.30	4.41	0.36	5.74	3.71	2.80	1.05	3.80	0.00	4.76	4.91	3.03	0.28	5.56	0.00	6.03	7	−0.680	1.20784	4.75336	RFX4	chr12	3.13
NM_001077427	1.71	24.28	2.00	16.03	1.94	19.78	11.34	18.63	23.78	58.97	1.51	30.08	33.97	41.80	19.45	36.92	0.58	39.67	6	−0.699	10.6968	31.7958	LYPD1	chr2	3.32
NM_002653	21.85	143.56	32.03	158.57	22.98	111.75	101.51	113.15	49.20	100.13	7.88	79.51	47.24	80.58	25.41	81.52	9.77	53.11	7	−0.652	35.3185	102.432	PITX1	chr5	2.88
NM_001037329	7.27	0.39	3.94	0.39	4.95	0.19	0.39	0.41	0.26	0.47	2.52	0.16	0.32	0.44	9.48	1.29	1.66	0.17	6	0.612	3.42163	0.436548	CNGA4	chr11	2.57
NM_004226	9.69	1.58	7.61	2.07	18.04	1.64	1.77	2.16	7.63	2.11	13.05	1.57	6.68	1.63	6.17	1.71	26.00	3.98	8	0.711	10.7378	2.05126	STK17B	chr2	3.46
NM_002526	15.62	1.62	18.26	2.64	13.47	1.33	3.39	1.73	8.57	2.10	31.88	2.07	3.84	5.18	4.71	1.69	17.51	3.64	7	0.667	13.0272	2.44483	NT5E	chr6	3.00
NM_001030059	12.02	0.00	7.35	0.08	6.05	0.44	0.05	0.04	1.21	0.05	0.48	0.00	1.70	0.09	0.08	0.00	6.82	0.07	8	0.646	3.97368	0.0855755	PPAPDC1A	chr10	2.82
NM_181864	0.84	6.64	1.02	2.80	0.41	3.78	2.36	2.82	3.89	4.71	0.29	2.60	0.55	2.25	0.69	3.52	1.17	5.07	7	−0.624	1.24907	3.80045	ACOT7	chr1	2.66
NM_015675	198.82	34.59	169.21	30.85	131.76	32.65	23.16	25.69	138.46	70.46	133.77	23.91	45.20	27.65	184.90	47.83	557.12	110.95	6	0.616	175.822	44.9527	GADD45B	chr19	2.60
NM_001001331	9.80	1.39	10.98	2.10	10.23	1.83	1.27	1.48	7.81	1.25	6.86	0.66	5.23	2.17	12.62	2.41	9.43	2.53	8	0.706	8.24858	1.7587	ATP2B2	chr3	3.41
NM_012342	1.52	18.37	0.92	11.82	0.44	6.96	6.91	6.29	3.28	6.33	0.48	7.67	2.20	2.59	0.70	6.25	0.04	4.55	6	−0.675	1.83169	7.8706	BAMBI	chr10	3.08
NM_016932	3.47	29.58	2.72	11.29	2.20	26.19	38.42	32.44	9.62	25.34	1.12	7.35	4.39	6.23	1.27	10.81	1.38	5.13	7	−0.642	7.1763	17.1509	SIX2	chr2	2.79
NM_001037332	18.28	4.45	23.61	3.90	17.16	3.47	4.67	5.18	5.97	2.52	32.45	1.34	10.38	3.42	18.65	3.03	15.00	3.43	8	0.689	16.2413	3.41592	CYFIP2	chr5	3.22
NM_002471	49.39	0.60	50.54	0.84	157.14	5.49	0.81	0.77	179.89	5.40	268.46	1.39	29.61	2.19	7.48	2.12	138.85	7.02	8	0.833	98.0186	2.86987	MYH6	chr14	5.97
NM_015206	13.75	0.35	6.13	0.32	15.69	0.40	0.18	0.32	8.20	0.60	5.12	0.32	3.30	0.52	9.14	0.40	12.08	0.90	8	0.832	8.17541	0.45839	KIAA1024	chr15	5.94
NM_001017975	15.89	0.92	10.66	0.89	17.65	0.89	0.73	0.75	17.69	1.56	42.83	1.23	4.30	1.88	13.73	0.87	26.54	2.74	8	0.787	16.6687	1.30376	HFM1	chr1	4.70
NM_152573	23.53	1.49	15.81	1.36	14.93	1.62	1.21	1.87	23.55	4.60	23.17	1.65	27.75	3.07	12.04	1.61	77.62	17.12	8	0.779	24.4024	3.82164	RASEF	chr9	4.52
NM_145291	52.97	4.42	57.15	5.20	96.54	5.63	2.14	3.33	9.49	5.04	32.52	2.32	9.07	3.83	38.92	3.33	86.81	11.75	7	0.685	42.8454	4.98444	ZBTB49	chr4	3.17
NM_001003665	0.55	4.60	1.01	5.35	1.23	6.07	4.63	4.59	0.99	2.73	0.58	2.60	2.07	3.69	1.26	3.76	0.12	3.82	7	−0.664	1.38323	4.13486	C1orf95	chr1	2.97
NM_000598	11.78	122.91	10.50	107.23	4.65	44.56	79.69	70.19	95.49	243.65	17.44	291.84	77.73	90.03	84.99	208.53	21.12	222.18	7	−0.641	44.8201	155.679	IGFBP3	chr7	2.78
NM_144583	31.05	2.67	18.26	2.55	50.70	3.55	1.99	2.25	11.61	2.89	17.77	0.67	4.22	2.07	0.00	0.98	28.79	8.09	7	0.627	18.2676	2.85882	ATP6V1C2	chr2	2.68
NM_001242318	5.08	1.30	6.05	1.25	5.43	1.19	1.37	1.08	3.28	1.61	4.05	0.59	2.52	1.27	6.39	1.29	6.89	2.30	7	0.627	4.56203	1.31953	PDE7A	chr8	2.68
NM_058164	1.63	12.78	1.18	10.43	0.59	12.95	11.70	11.23	2.03	2.74	0.49	7.03	5.26	7.55	1.74	5.72	0.17	6.27	6	−0.624	2.755	8.52246	OLFM2	chr19	2.66
NM_020845	21.92	4.85	31.06	7.41	42.19	6.81	5.98	5.87	11.10	5.14	43.14	5.28	13.83	7.21	10.18	6.21	46.83	6.68	6	0.613	25.1373	6.16246	PITPNM2	chr12	2.59
NM_001275	89.71	611.70	92.86	670.13	130.97	950.83	400.64	320.79	168.27	325.94	39.17	506.93	383.19	463.42	56.71	392.91	88.14	283.09	6	−0.611	161.074	502.859	CHGA	chr14	2.57
NM_001198531	5.88	0.82	7.09	0.75	9.14	0.99	0.51	1.15	1.72	1.27	7.19	0.37	2.32	2.11	2.80	0.41	10.85	0.00	7	0.605	5.27676	0.875456	TCF7L2	chr10	2.53
NM_016438	9.98	0.40	11.65	1.13	10.15	5.20	1.77	0.46	38.93	3.73	19.08	0.27	4.02	0.88	10.18	1.05	9.85	0.15	8	0.849	12.8466	1.47395	HIGD1B	chr17	6.64
NM_001446	1.39	11.38	1.40	8.69	1.26	23.24	13.41	15.00	4.44	13.54	0.72	17.72	10.59	12.60	0.99	16.92	0.65	8.85	7	−0.714	3.87308	14.2158	FABP7	chr6	3.50
NM_014564	1.66	20.07	1.25	15.83	0.90	20.13	15.20	13.21	3.39	11.34	0.00	10.73	6.40	8.51	1.82	8.20	0.00	10.70	7	−0.710	3.40104	13.1909	LHX3	chr9	3.45
NM_080681	0.00	3.40	0.00	5.09	0.00	9.38	3.76	2.84	4.64	29.95	0.00	13.49	8.96	5.71	1.59	5.98	0.00	13.69	7	−0.691	2.1043	9.94793	COL11A2	chr6	3.23
NM_001199159	1.33	12.95	0.59	6.77	0.24	7.11	5.58	5.48	1.77	3.81	0.18	4.65	2.26	1.70	0.27	1.73	0.06	3.71	7	−0.678	1.36572	5.32201	PI16	chr6	3.10
NM_003877	2.75	20.84	1.86	16.28	1.86	15.68	15.90	18.15	7.10	17.16	0.82	15.05	10.68	15.92	10.44	18.19	0.77	17.83	6	−0.667	5.79905	17.2336	SOCS2	chr12	3.00
NM_001033082	8.92	1.16	7.58	0.92	14.06	1.43	1.07	1.43	2.71	1.07	8.34	0.31	1.55	1.05	7.36	0.78	23.27	2.77	7	0.665	8.32031	1.21319	MYCL1	chr1	2.99
NM_006841	20.59	2.19	21.70	1.60	25.40	1.94	1.91	1.13	1.84	0.67	16.39	0.92	4.10	1.28	0.43	1.06	23.56	1.08	8	0.663	12.8806	1.3204	SLC38A3	chr3	2.96
NM_001037582	6.56	42.00	6.95	30.13	5.05	37.69	40.99	39.93	5.42	13.60	1.28	15.28	14.52	18.54	2.07	18.75	2.59	16.91	7	−0.658	9.49237	25.871	SCD5	chr4	2.93
NM_000361	70.88	7.48	41.53	6.03	67.34	5.93	5.11	5.24	3.05	3.18	28.90	1.78	3.43	1.84	33.92	2.29	52.58	6.26	6	0.653	34.0825	4.44683	THBD	chr20	2.88
NM_020722	3.34	0.60	3.91	0.65	8.09	0.72	0.36	0.36	1.68	0.57	4.96	0.53	1.37	0.73	6.24	0.83	11.06	1.89	7	0.646	4.55588	0.765442	KIAA1211	chr4	2.82
NM_013261	3.46	0.71	2.76	0.63	3.43	0.62	0.74	0.92	2.41	1.34	5.69	0.82	2.13	1.11	7.49	1.27	7.25	1.40	6	0.645	3.92915	0.979337	PPARGC1A	chr4	2.82
NM_005729	93.19	5.88	124.40	6.18	35.79	5.58	5.43	8.45	15.05	2.25	19.32	1.07	2.91	1.98	3.01	1.74	22.90	1.92	6	0.612	35.7797	3.89561	PPIF	chr10	2.58
NM_004382	95.23	0.79	124.65	2.63	53.82	1.02	0.26	0.51	10.72	0.71	13.26	0.00	1.08	0.00	39.62	0.00	18.91	1.70	8	0.866	39.7285	0.816888	CRHR1	chr17	7.47
NM_000080	67.86	3.26	70.49	4.61	110.94	5.37	2.07	1.77	54.12	3.08	27.24	0.51	5.06	0.95	7.56	1.45	46.61	5.96	8	0.806	43.5513	2.9954	CHRNE	chr17	5.16
NM_001039350	22.08	1.32	27.77	2.70	44.13	1.72	2.53	2.37	5.94	2.03	27.72	1.89	3.80	0.46	14.69	0.79	48.81	1.05	8	0.800	21.9404	1.59285	DPP6	chr7	4.99
NM_018286	12.71	1.29	12.28	1.84	17.89	1.84	1.26	1.98	13.33	1.74	27.46	1.73	9.18	1.02	9.84	1.17	70.61	4.14	8	0.796	19.3954	1.86047	TMEM100	chr17	4.90
NM_023067	0.38	11.47	0.42	9.54	0.26	12.40	5.75	4.91	1.96	6.56	0.03	9.09	4.77	10.19	0.10	9.62	0.01	7.46	8	−0.791	1.51981	9.02789	FOXL2	chr3	4.79

Table S9. *Cont.*

ID	N1 Tumor	N1 ANPTs	N2 Tumor	N2 ANPTs	N3 Tumor	N3 ANPTs	N4 Tumor	N4 ANPTs	N5 Tumor	N5 ANPTs	N6 Tumor	N6 ANPTs	N7 Tumor	N7 ANPTs	N8 Tumor	N8 ANPTs	N9 Tumor	N9 ANPTs	Differentail Recurrence	DI	Avg (Tumor)	Avg (ANPTs)	Gene Symbol	Chr	FC
NM_002448	1.69	18.25	0.70	10.44	0.42	8.86	5.81	7.02	2.77	9.25	0.47	7.02	3.26	7.53	0.63	7.12	0.40	5.21	8	−0.778	1.79492	8.96657	MSX1	chr4	4.50
NM_001145108	0.28	8.92	0.54	9.19	1.57	13.18	8.96	11.20	1.08	2.40	0.00	5.43	3.06	6.97	0.39	5.62	0.46	8.70	8	−0.775	1.81558	7.9582	NELL2	chr12	4.45
NM_004778	3.22	0.41	2.82	0.30	2.90	0.82	0.48	0.23	20.65	2.66	11.64	0.14	3.60	0.81	3.69	0.65	5.06	0.28	9	0.765	6.00721	0.69912	PTGDR2	chr11	4.26
NM_001008404	7.11	0.16	31.40	0.22	29.96	0.48	0.15	0.30	26.24	0.70	7.57	0.06	1.74	0.11	0.02	0.07	6.71	0.02	9	0.762	12.3204	0.234088	C14orf180	chr14	4.20
NM_001038705	0.24	1.81	0.10	2.43	0.12	1.95	2.46	5.19	1.70	3.72	0.00	4.40	4.97	5.54	0.00	4.06	0.00	2.17	8	−0.760	1.06384	3.4763	GPR149	chr3	4.17
NM_170676	0.26	3.64	0.01	3.21	0.00	3.06	3.49	2.82	2.50	6.66	0.00	8.69	2.89	4.12	0.08	6.47	0.00	8.53	7	−0.760	1.02438	5.24318	MEIS2	chr15	4.16
NM_006078	4.39	0.85	9.58	0.59	5.34	0.43	0.14	0.39	8.34	1.62	9.24	0.63	2.54	0.83	4.90	0.77	16.42	1.79	9	0.757	6.76393	0.877184	CACNG2	chr22	4.11
NM_004484	12.01	36.08	1.26	54.51	2.13	40.00	38.78	35.28	2.87	25.13	0.00	13.86	21.86	48.00	1.35	11.07	0.00	24.15	8	−0.757	8.91792	32.0085	GPC3	chrX	4.11
NM_181755	0.83	5.24	0.26	4.03	0.00	4.58	3.84	4.85	6.80	11.67	0.00	13.74	8.99	14.64	0.33	9.23	0.00	16.98	6	−0.750	2.33964	9.4395	HSD11B1	chr1	4.00
NM_014917	0.47	5.37	0.08	2.47	0.31	2.62	2.09	2.11	1.22	4.59	0.12	3.07	2.85	5.05	0.82	4.36	0.01	3.75	7	−0.745	0.8861	3.70967	NTNG1	chr1	3.92
NM_001130067	1.76	0.00	4.18	0.97	2.31	0.35	0.40	0.62	6.35	0.00	4.59	0.00	4.59	0.00	4.51	0.00	1.24	1.14	7	0.735	3.3256	0.34232	TRIM2	chr4	3.77
NM_002071	0.31	3.39	0.00	2.90	0.10	3.13	3.07	3.49	2.63	10.66	0.04	11.62	10.80	14.83	0.35	16.98	0.00	16.78	7	−0.764	1.92189	9.30976	GNAL	chr18	4.24
NM_001105192	1.40	4.22	0.81	7.33	0.58	3.36	5.57	7.39	2.18	3.82	0.00	4.54	1.92	4.42	0.08	2.94	0.00	2.53	7	−0.733	1.39317	4.50438	TLE3	chr15	3.75
NM_003888	1.78	19.75	0.58	12.23	0.78	12.51	9.46	10.64	3.45	10.03	0.38	13.55	5.73	7.03	0.93	7.31	0.00	16.53	7	−0.733	2.56637	12.176	ALDH1A2	chr15	3.74
NM_015025	0.98	6.69	0.42	5.21	0.17	4.28	5.53	5.24	3.45	9.64	0.01	11.01	7.37	9.75	0.29	12.10	0.00	12.14	7	−0.733	2.0259	8.44953	MYT1L	chr2	3.74
NM_002968	0.75	7.53	0.42	5.00	0.27	5.05	5.38	4.65	2.89	8.83	0.01	8.69	4.19	6.33	1.44	7.84	0.04	8.87	7	−0.732	1.70952	6.97682	SALL1	chr16	3.73
NM_002023	3.01	16.71	1.24	15.73	0.85	15.34	11.97	17.15	2.92	7.77	0.73	6.62	4.14	5.15	0.58	4.94	0.02	4.37	7	−0.731	2.82848	10.4193	FMOD	chr1	3.71
NM_005979	0.81	4.45	1.25	6.13	0.33	8.14	0.99	2.95	0.60	2.14	0.00	5.58	0.86	2.87	0.38	4.10	0.74	1.11	8	−0.729	0.663753	4.15109	S100A13	chr1	3.69
NM_032784	38.68	1.35	42.10	1.58	70.49	1.70	0.48	1.51	84.49	7.52	242.13	2.32	22.11	2.39	2.32	1.11	256.55	7.53	9	0.723	84.3726	3.00139	RSPO3	chr6	3.61
NM_012338	0.69	6.66	0.35	4.96	0.41	6.46	6.91	8.63	5.22	10.97	0.97	8.83	8.07	10.81	1.75	11.22	0.19	9.70	7	−0.717	2.7284	8.69409	TSPAN12	chr7	3.54
NM_004616	9.86	1.02	12.36	0.81	15.24	0.58	0.38	0.80	5.16	0.75	22.81	0.79	0.31	0.16	2.59	0.29	16.59	0.92	8	0.716	9.47787	0.679506	TSPAN8	chr12	3.52
NM_006998	10.29	71.01	3.98	48.36	1.76	41.69	70.28	82.44	21.44	53.92	0.23	44.79	13.10	20.95	11.04	28.91	2.72	40.21	7	−0.711	14.9832	48.03	SCGN	chr6	3.46
NM_006271	10.28	59.33	7.93	83.21	3.98	87.06	21.85	26.85	12.82	20.11	4.41	25.70	4.25	9.26	1.38	5.93	0.00	22.10	7	−0.708	7.43308	37.7261	S100A1	chr1	3.42
NM_144633	0.88	7.08	0.17	5.38	0.25	5.33	5.20	7.09	1.94	6.01	0.12	7.16	6.71	7.24	2.70	7.16	0.01	7.87	7	−0.705	1.99743	6.70115	KCNH8	chr3	3.39
NM_198681	0.47	3.32	0.49	5.04	0.31	2.89	5.65	4.17	1.10	5.16	0.00	3.74	3.48	4.51	0.05	3.66	0.16	2.48	7	−0.703	1.30106	3.88714	PLEKHG5	chr1	3.37
NM_018076	0.45	3.37	0.44	3.73	0.36	2.28	2.73	4.45	2.30	5.03	0.52	10.66	6.57	8.29	2.61	10.14	0.75	7.32	7	−0.702	1.85839	6.14156	ARMC4	chr10	3.36
NM_002775	19.77	134.27	11.63	98.22	9.45	70.44	87.43	111.71	38.47	79.78	8.71	108.97	68.77	97.49	10.90	121.24	9.96	68.46	7	−0.702	29.4542	98.9555	HTRA1	chr10	3.35
NM_133373	1.26	5.06	0.55	4.10	0.35	3.62	3.47	2.91	1.69	6.27	0.40	1.99	1.07	2.33	0.68	3.14	0.17	2.51	8	−0.700	1.07327	3.54647	PLCD3	chr17	3.33
NM_173509	2.99	18.14	1.05	10.89	0.84	17.39	15.60	11.87	9.13	22.70	0.07	26.97	15.84	20.94	0.58	21.58	0.15	43.13	7	−0.696	5.13848	21.5127	FAM163A	chr1	3.28
NM_006663	3.16	8.00	2.79	15.23	0.13	3.61	5.13	4.17	1.19	3.07	0.00	7.98	1.73	3.99	0.42	4.79	0.97	4.12	8	−0.694	1.72402	6.10631	PPP1R13L	chr19	3.26
NM_001146	0.66	2.88	0.00	2.37	0.01	3.50	2.69	2.01	2.22	6.27	0.00	10.09	5.94	5.73	1.33	7.52	0.02	13.19	7	−0.693	1.43127	5.95102	ANGPT1	chr8	3.25
NM_198481	1.04	7.58	0.81	16.20	0.04	3.14	9.66	8.04	0.24	0.32	0.00	6.06	1.89	4.70	0.00	4.27	0.00	3.78	7	−0.692	1.52016	6.00986	VSTM1	chr19	3.25
NM_000406	2.13	31.90	1.36	23.03	0.27	3.92	10.05	11.58	0.57	1.45	0.00	13.03	3.26	4.46	0.06	8.26	0.00	10.83	7	−0.689	1.9675	12.0511	GNRHR	chr4	3.21
NM_015461	1.57	5.52	0.51	3.89	0.36	4.04	4.14	3.56	1.63	3.98	0.43	4.86	2.93	4.71	0.84	6.71	0.43	6.47	7	−0.687	1.42626	4.86103	ZNF521	chr18	3.20
NM_000325	1.02	8.10	0.45	8.99	0.33	9.44	7.77	6.26	0.91	2.06	0.00	4.86	3.51	3.78	0.22	4.32	0.00	3.83	7	−0.678	1.57751	5.73724	PITX2	chr4	3.11
NM_006517	5.41	28.10	1.62	19.35	2.02	26.37	20.36	15.83	2.82	6.80	0.47	7.20	6.33	8.99	1.05	9.68	0.27	8.56	7	−0.678	4.4832	14.5416	SLC16A2	chrX	3.10
NM_001122741	0.51	4.77	0.39	5.44	0.30	4.17	2.00	1.88	0.73	1.50	0.05	2.20	1.47	2.50	0.23	4.44	0.00	3.63	7	−0.677	0.631294	3.39299	ESR1	chr6	3.09
NM_005709	1.31	5.95	1.09	12.32	0.62	8.09	1.73	2.88	4.44	9.37	0.02	13.18	4.66	5.21	1.16	2.63	0.29	17.74	7	−0.676	1.70162	8.5971	USH1C	chr11	3.08
NM_000599	32.89	257.26	20.85	240.51	15.81	155.30	162.26	160.05	49.68	138.20	9.79	198.44	121.37	127.03	27.95	140.78	6.21	197.93	7	−0.675	49.6462	179.499	IGFBP5	chr2	3.08
NM_006198	6.46	19.65	1.36	21.72	2.54	25.32	13.11	12.07	6.47	17.78	1.32	18.25	4.49	18.08	11.77	18.18	0.32	12.19	7	−0.674	5.31696	18.1396	PCP4	chr21	3.07
NM_173681	24.82	2.02	6.45	1.73	12.35	2.08	1.69	2.17	10.29	0.99	21.80	0.52	4.23	0.57	0.61	0.50	5.82	0.95	7	0.674	9.78487	1.28148	ATG9B	chr7	3.07
NM_001037	50.63	8.16	78.49	8.23	35.80	7.67	6.04	4.71	18.38	5.18	53.92	4.84	13.04	3.18	5.07	4.11	39.94	2.61	7	0.673	33.4806	5.41018	SCN1B	chr19	3.06
NM_004753	6.20	35.05	4.24	39.33	1.88	19.61	22.76	22.77	8.57	27.15	1.92	12.98	9.95	11.91	2.38	10.54	0.67	13.60	7	−0.672	6.50672	21.438	DHRS3	chr1	3.05
NM_031311	3.12	7.60	0.50	7.53	1.62	5.39	11.72	13.35	2.51	6.10	0.46	5.35	3.68	6.53	1.51	8.88	0.58	6.89	7	−0.670	2.85666	7.51403	CPVL	chr7	3.03
NM_033641	1.97	4.70	0.28	4.23	0.20	3.73	5.54	3.82	2.15	5.49	0.00	8.26	4.50	6.38	0.35	7.51	0.00	5.42	7	−0.667	1.66589	5.50447	COL4A6	chrX	3.01
NM_030583	0.64	4.20	0.33	3.93	0.44	3.28	2.18	2.10	2.79	4.18	0.50	4.98	2.94	5.66	0.88	3.55	0.43	4.64	6	−0.667	1.23643	4.05834	MATN2	chr8	3.00
NM_003667	22.28	0.05	17.28	0.02	46.26	0.13	0.31	0.04	0.04	0.04	4.85	0.00	0.18	0.23	8.77	0.08	8.30	0.05	7	0.664	12.0301	0.0720564	LGR5	chr12	2.98

Table S9. *Cont.*

ID	N1 Tumor	N1 ANPTs	N2 Tumor	N2 ANPTs	N3 Tumor	N3 ANPTs	N4 Tumor	N4 ANPTs	N5 Tumor	N5 ANPTs	N6 Tumor	N6 ANPTs	N7 Tumor	N7 ANPTs	N8 Tumor	N8 ANPTs	N9 Tumor	N9 ANPTs	Differential Recurrence	DI	Avg (Tumor)	Avg (ANPTs)	Gene Symbol	Chr	FC
NM_001993	7.41	43.40	3.49	33.56	3.08	31.12	31.80	34.17	48.25	107.95	3.69	72.62	67.31	78.30	21.46	60.62	1.24	123.24	7	−0.664	20.8595	64.9965	F3	chr1	2.97
NM_030643	1.16	8.29	0.35	9.99	0.37	5.91	12.03	21.95	2.28	5.31	0.27	5.83	7.59	10.38	5.93	5.37	0.19	4.55	6	−0.663	3.35235	8.61906	APOL4	chr22	2.97
NM_198235	0.77	2.26	0.52	3.38	0.74	4.72	0.65	5.72	0.74	1.57	0.18	1.53	2.25	2.48	0.38	2.36	0.00	1.31	8	−0.661	0.692303	2.81541	RNASE1	chr14	2.95
NM_033520	9.42	34.95	5.60	56.88	1.03	33.07	46.23	42.83	17.72	52.77	12.05	66.90	14.97	22.90	3.91	21.95	3.25	14.19	7	−0.661	12.6857	38.4917	C19orf33	chr19	2.95
NM_021191	1.38	16.68	0.74	11.69	0.71	5.98	7.25	7.38	6.47	16.08	0.42	35.10	13.88	17.83	16.00	29.80	1.32	22.12	6	−0.661	5.35256	18.0733	NEUROD4	chr12	2.95
NM_002084	119.49	590.64	51.79	492.15	39.58	293.41	281.50	274.94	280.70	681.38	60.00	605.99	342.59	377.41	54.43	459.35	31.66	534.36	7	−0.660	140.194	478.847	GPX3	chr5	2.94
NM_000587	0.69	3.53	0.19	3.40	0.17	2.52	1.79	1.93	4.23	7.79	0.47	4.19	2.62	2.71	0.24	2.53	0.06	4.78	6	−0.658	1.16174	3.71025	C7	chr5	2.92
NM_130808	45.44	3.61	59.26	3.51	65.65	4.84	2.98	3.28	16.67	1.99	30.96	1.79	4.48	2.89	1.99	2.34	58.92	5.10	6	0.653	31.8151	3.25965	CPNE4	chr3	2.88
NM_006623	6.38	29.83	3.15	23.93	3.14	21.02	20.40	17.90	13.19	34.59	3.94	27.50	20.46	26.69	6.13	29.96	0.39	22.90	7	−0.652	8.57494	26.034	PHGDH	chr1	2.88
NM_001025390	0.17	1.90	0.23	1.84	0.26	2.04	0.95	1.10	0.88	2.02	0.00	1.94	3.24	3.10	1.35	5.37	0.28	2.38	7	−0.651	0.81804	2.41119	AMPD3	chr11	2.86
NM_006227	1.85	8.78	0.66	11.28	1.03	9.76	5.52	5.67	0.00	1.68	0.00	0.80	1.05	2.06	0.27	2.41	0.31	2.04	7	−0.650	1.18709	4.94303	PLTP	chr20	2.86
NM_000582	12.85	0.00	10.11	0.15	1.92	0.00	0.62	0.46	0.25	0.77	22.29	0.00	0.82	0.00	12.40	0.44	4.60	0.46	8	0.650	7.31808	0.254295	SPP1	chr4	2.86
NM_138295	1.19	0.04	7.80	0.15	26.00	0.34	0.12	0.10	2.54	0.13	1.35	0.03	0.24	0.07	0.11	0.06	1.91	0.03	7	0.650	4.58405	0.105711	PKD1L1	chr7	2.85
NM_001113490	0.91	6.86	0.47	6.16	0.85	5.58	6.05	6.02	1.13	4.24	0.41	4.32	5.01	3.85	0.84	4.51	0.09	6.42	7	−0.650	1.7513	5.32956	AMOT	chrX	2.85
NM_001037160	0.42	4.07	0.22	3.97	0.21	3.47	3.94	5.35	1.04	1.35	0.13	1.15	2.20	1.83	0.00	1.68	0.13	1.24	6	−0.647	0.921785	2.67876	CYS1	chr2	2.83
NM_001164257	2.43	12.01	1.81	7.08	0.24	4.30	6.86	7.77	1.07	7.60	0.00	2.43	2.10	1.50	0.62	2.28	0.80	3.17	7	−0.647	1.76833	5.35072	C17orf72	chr17	2.83
NM_176813	0.96	10.55	0.57	10.19	0.00	8.48	7.16	5.94	1.09	3.65	0.00	11.01	2.46	4.38	3.99	3.47	0.00	3.70	6	−0.647	1.8038	6.81801	AGR3	chr7	2.83
NM_013280	6.97	0.21	14.89	0.27	4.66	0.23	0.25	0.11	1.40	0.07	5.78	0.04	0.96	0.22	0.32	0.00	5.05	0.16	9	0.646	4.47702	0.14489	FLRT1	chr11	2.83
NM_014643	2.19	8.24	2.18	6.77	0.40	5.77	8.28	8.26	2.96	8.45	0.28	8.46	5.56	7.28	2.72	7.07	0.08	10.32	7	−0.645	2.73999	7.84666	ZNF516	chr18	2.81
NM_012474	29.96	4.16	22.99	4.79	30.44	4.56	2.97	4.33	8.59	1.61	7.78	1.18	4.71	1.53	2.82	1.57	16.02	2.72	7	0.645	14.0308	2.93778	UCK2	chr1	2.81
NM_001170963	1.65	39.83	1.53	8.32	1.89	3.05	1.85	4.36	6.89	17.80	0.00	21.97	17.06	16.24	1.30	17.17	7.16	15.02	7	−0.643	4.37106	15.973	IGSF1	chrX	2.80
NM_003507	1.09	10.20	1.76	7.95	1.14	6.48	6.00	5.85	1.97	3.82	0.05	3.11	3.37	3.23	0.82	5.24	0.14	4.51	6	−0.642	1.81482	5.59805	FZD7	chr2	2.79
NM_000800	0.80	5.53	0.33	3.75	0.00	3.80	3.70	3.41	2.71	2.57	0.00	3.93	2.93	3.46	0.13	6.94	0.00	2.96	6	−0.639	1.17801	4.04017	FGF1	chr5	2.77
NM_002403	4.91	26.03	5.95	18.51	0.00	9.42	10.56	13.35	1.03	3.64	2.39	9.13	5.39	10.46	1.79	3.76	4.55	10.93	7	−0.639	4.06329	11.6929	MFAP2	chr1	2.77
NM_017711	0.67	5.73	0.00	3.13	0.38	4.72	3.23	3.33	0.80	0.92	0.00	1.45	0.75	1.55	0.12	1.48	0.00	2.19	7	−0.636	0.660344	2.72132	GDPD2	chrX	2.75
NM_182914	7.17	0.47	16.70	1.99	11.68	1.98	2.79	3.74	12.92	5.48	20.26	4.64	7.34	6.49	61.69	6.38	25.40	5.70	7	0.629	18.4396	4.09437	SYNE2	chr14	2.70
NM_014265	0.99	5.80	0.32	3.01	0.25	3.08	4.11	3.69	3.12	9.53	0.35	5.71	4.58	4.93	3.92	7.13	0.28	7.44	6	−0.629	1.99274	5.59059	ADAM28	chr8	2.70
NM_138568	1.61	6.24	1.00	8.24	0.52	4.33	4.73	3.77	1.57	4.01	0.48	3.10	3.38	3.24	1.25	4.23	0.06	2.71	7	−0.626	1.62213	4.43192	EXOC3L2	chr19	2.68
NM_001007097	1.91	4.88	0.31	3.59	0.61	4.25	5.84	5.59	1.30	2.70	0.42	5.29	4.96	5.14	0.38	2.35	0.20	5.39	7	−0.624	1.77023	4.3519	NTRK2	chr9	2.66
NM_000120	9.84	0.45	25.44	2.19	12.43	1.53	0.59	0.62	0.23	0.00	1.84	0.00	0.61	0.30	33.16	0.30	1.33	0.17	8	0.624	9.49584	0.616705	EPHX1	chr1	2.66
NM_024735	61.07	13.73	105.73	14.25	109.67	13.53	10.26	10.97	23.27	12.63	74.64	8.15	16.77	11.75	37.84	9.82	58.67	18.46	6	0.621	55.3231	12.5864	FBXO31	chr16	2.64
NM_031891	8.22	0.62	8.82	0.69	12.28	0.65	0.51	0.68	0.56	0.33	11.36	0.16	0.67	0.31	1.44	0.08	11.87	1.61	7	0.621	6.19342	0.569858	CDH20	chr18	2.64
NM_021168	15.71	2.25	6.52	2.22	9.00	1.47	2.86	1.00	8.99	3.29	7.51	3.10	2.97	3.02	14.77	2.89	7.49	3.31	8	0.621	8.42429	2.50629	RAB40C	chr16	2.64
NM_002501	5.22	14.86	1.57	11.02	0.84	13.40	12.84	7.77	5.96	13.77	2.08	15.85	9.25	14.48	2.00	12.13	1.37	13.95	7	−0.620	4.56958	13.0244	NFIX	chr19	2.63
NM_020848	1.11	2.67	0.47	5.85	0.37	2.25	3.72	3.17	1.56	4.88	0.95	5.86	5.12	4.39	0.86	4.08	0.39	5.48	7	−0.619	1.61734	4.29134	KIAA1462	chr10	2.63
NM_000915	11.05	29.14	1.18	58.76	0.13	1.62	35.57	24.18	1.81	2.93	0.23	8.23	1.24	0.47	0.00	3.65	0.00	2.10	7	−0.617	5.69113	14.5656	OXT	chr20	2.61
NM_021248	11.16	1.32	20.84	0.80	13.01	0.93	0.37	0.81	2.38	0.25	5.64	0.14	0.54	0.08	0.73	0.03	4.70	0.46	9	0.616	6.59668	0.537555	CDH22	chr20	2.60
NM_177963	1.05	5.32	0.29	4.14	0.22	4.16	4.19	2.45	1.96	3.20	0.22	6.38	4.59	4.34	0.40	5.73	0.04	5.35	6	−0.615	1.43936	4.56256	SYT12	chr11	2.60
NM_024081	0.55	5.05	0.64	2.75	1.12	4.51	4.00	3.53	1.67	5.12	1.30	4.35	2.98	3.77	0.31	3.27	0.69	3.32	7	−0.609	1.47354	3.9624	PRRG4	chr11	2.56
NM_003256	2.98	10.44	2.81	9.77	1.69	10.21	10.08	13.04	1.66	3.73	0.20	2.91	3.38	3.85	1.49	3.30	0.17	3.26	7	−0.607	2.71861	6.72398	TIMP4	chr3	2.55
NM_020546	22.43	3.63	22.42	4.16	21.52	3.41	3.94	3.53	4.68	2.13	11.58	2.51	3.98	3.35	27.52	4.16	18.35	3.90	7	0.607	15.1575	3.41924	ADCY2	chr5	2.54
NM_024572	1.06	5.70	0.73	2.56	0.50	4.00	3.45	1.57	2.06	5.65	0.00	3.77	1.99	2.86	0.15	3.12	0.00	4.94	8	−0.605	1.10593	3.79552	GALNT14	chr2	2.53
NM_032963	25.43	81.84	26.45	187.39	17.59	145.55	189.19	153.18	18.83	32.53	6.70	29.91	19.11	25.45	4.39	19.97	0.71	16.40	6	−0.602	34.266	76.913	CCL14	chr17	2.51
NM_015687	4.47	1.30	6.13	1.85	8.90	1.43	1.43	1.35	10.24	4.03	23.25	4.10	5.40	4.33	14.89	3.00	22.09	5.81	7	0.601	10.7563	3.02213	FILIP1	chr6	2.51

Table S10. ACTH highly related-genotypes.

Gene	FC	PCC	*p* Value	FDR
PPP1R1B	4.18	0.980	<0.001	0.001
TNFAIP8L3	3.12	0.961	<0.001	0.001
AHRR	2.65	0.950	<0.001	0.003
PNMT	3.51	0.944	<0.001	0.003
THBS2	2.52	0.939	<0.001	0.003
LRRC10B	2.73	0.938	<0.001	0.003
CREB3L1	3.82	0.931	<0.001	0.004
IER3	2.54	0.929	<0.001	0.004
GPR50	3.15	0.929	<0.001	0.003
FOSB	3.00	0.924	<0.001	0.003
TFPI2	3.27	0.922	<0.001	0.004
CELSR1	2.53	0.915	0.001	0.005
HMGN5	2.55	0.909	0.001	0.005
STRC	3.06	0.908	0.001	0.005
HHATL	3.12	0.901	0.001	0.005
AVPR1B	4.42	0.897	0.001	0.005
VSTM1	3.25	0.896	0.001	0.005
ENPP2	2.50	0.894	0.001	0.005
PDLIM4	3.25	0.893	0.001	0.005
ASAP2	3.41	0.893	0.001	0.004
PLEKHG5	3.12	0.893	0.001	0.004
UGT2A1	2.83	0.893	0.001	0.004
SOCS3	2.68	0.891	0.001	0.004
SLIT1	3.64	0.889	0.001	0.004
INMT	3.05	0.884	0.002	0.004
CHIA	2.84	0.878	0.002	0.004
MDFI	3.07	0.874	0.002	0.005
FAM92B	2.51	0.866	0.003	0.005
GHRHR	3.16	0.861	0.003	0.006
ABCB9	2.89	0.853	0.003	0.007
HTATSF1	2.99	0.853	0.003	0.007
MFAP4	3.35	0.850	0.004	0.007
C14orf132	2.58	0.849	0.004	0.007
ZNF331	2.92	0.848	0.004	0.007
PEBP4	2.54	0.847	0.004	0.007
GNAL	3.51	0.842	0.004	0.008
SHISA9	7.58	0.838	0.005	0.008
MYCL1	2.60	0.831	0.006	0.009
CACNA2D3	4.05	0.825	0.006	0.010
RASD1	3.34	0.824	0.006	0.010
GPR68	5.00	0.824	0.006	0.010
SHROOM2	2.81	0.820	0.007	0.011
ARC	2.97	0.820	0.007	0.011
B4GALNT4	2.53	0.818	0.007	0.011
VWA5B1	2.66	0.816	0.007	0.011
SCUBE1	3.25	0.790	0.011	0.016
AOC2	2.70	0.789	0.011	0.016
CA4	3.12	0.783	0.013	0.018

Table S10. *Cont.*

Gene	FC	PCC	*p* Value	FDR
COL9A3	2.78	0.782	0.013	0.018
FOLR1	3.01	0.777	0.014	0.019
ADCY5	2.62	0.768	0.016	0.021
UNC5A	4.04	0.758	0.018	0.023
CNTN2	4.19	0.757	0.018	0.023
SEP14	2.65	0.751	0.020	0.025
CCDC68	3.49	0.751	0.020	0.025
FRMD3	3.09	0.750	0.020	0.025
ASCL1	2.93	0.748	0.020	0.025
FRMD3	3.03	0.748	0.020	0.025
CNKSR1	2.51	0.736	0.024	0.028
CYR61	2.96	0.710	0.032	0.036
PRRG4	2.56	0.707	0.033	0.037
COL8A1	2.73	0.706	0.034	0.037
TBX20	3.83	0.699	0.036	0.039
GH2	4.57	0.689	0.040	0.042
RAMP1	2.53	0.678	0.045	0.047
FAM107B	2.55	0.674	0.047	0.047
LMX1A	3.94	0.674	0.047	0.047
MAMLD1	3.60	0.673	0.047	0.047
DRD2	2.64	0.670	0.048	0.048

Table S11. Cortisol highly related-genotypes.

Gene	FC	Blood F 8 AM	Blood F 0 AM	24 h UFC (Control)	24 h UFC (Control) Small Doses of the Second Day	24 h UFC (Control) High Doses of the Second Day
SHISA9	7.58	0.75	—	—	—	—
GPR50	3.15	0.74	0.98	—	—	—
PPP1R1B	4.18	0.71	0.88	—	—	—
HHATL	3.12	0.69	0.92	—	—	—
ASAP2	3.41	0.69	0.91	—	—	—
PLEKHG5	3.12	0.69	0.91	—	—	—
PDLIM4	3.25	0.69	0.91	—	—	—
UGT2A1	2.83	0.69	0.91	—	—	—
PNMT	3.51	0.68	0.90	—	—	—
ENPP2	2.50	0.68	0.92	—	—	—
AHRR	2.65	0.67	0.91	—	—	—
CHIA	2.84	—	0.97	—	—	—
TNFAIP8L3	3.12	—	0.93	—	—	—
LRRC10B	2.73	—	0.91	—	—	—
CREB3L1	3.82	—	0.93	—	—	—
CELSR1	2.53	—	0.88	—	—	—
STRC	3.06	—	0.95	—	—	—
VSTM1	3.25	—	—	0.72	—	—
SLIT1	3.64	—	0.89	—	—	—
INMT	3.05	—	0.89	—	—	—
GHRHR	3.16	—	0.92	—	—	—
ABCB9	2.89	—	0.91	—	—	—
MFAP4	3.35	—	0.93	—	—	—
C14orf132	2.58	—	0.89	—	—	—
SHROOM2	2.81	—	0.88	—	—	—
VWA5B1	2.66	—	0.89	—	—	—
AOC2	2.70	—	0.91	—	—	—
CA4	3.12	—	0.89	—	—	—

Table S11. *Cont.*

Gene	FC	Blood F 8 AM	Blood F 0 AM	24 h UFC (Control)	24 h UFC (Control) Small Doses of the Second Day	24 h UFC (Control) High Doses of the Second Day
CCDC68	3.49	—	0.91	—	—	—
FRMD3	3.03	—	0.92	—	—	—
CNKSR1	2.51	—	0.93	—	—	—
PRRG4	2.56	—	0.90	—	—	—
TFPI2	3.27	—	0.99	—	—	—
SCUBE1	3.25	—	0.98	—	—	—
CYFIP2	2.69	—	—	0.72	—	—
KIAA1024	5.94	—	0.00	—	0.76	—
RAB40C	2.64	—	0.00	—	0.91	0.73
ELMOD1	2.74	—	0.91	—	—	—
SCOC	3.96	—	0.91	—	—	—
PPP1R27	2.71	—	0.88	—	—	—
FBLN1	2.85	—	0.90	—	—	—
DTNA	4.99	—	—	0.79	—	—
ACAN	4.24	—	-0.90	—	—	—
CRHR1	4.10	—	—	—	0.75	0.78
MAMLD1	3.31	—	0.89	—	—	—
C3orf72	4.57	—	0.98	—	—	—
TNNT2	4.04	—	—	—	0.72	0.76
DIO2	3.92	—	—	0.68	—	—
NELL2	3.73	—	—	0.74	—	—
NCOA7	3.33	—	0.90	—	0.71	0.75
SKAP1	3.24	—	—	0.79	—	—
RIIAD1	3.08	—	—	0.69	—	—
MGP	3.08	—	0.88	—	—	—
C19orf33	2.95	—	—	0.68	—	—
SMAD3	2.81	—	—	0.79	—	—
MFAP2	2.77	—	—	0.79	—	—
S100A13	2.62	—	—	0.79	—	—
LSP1	2.60	—	0.89	—	—	—
PRR5	2.52	—	0.91	—	—	—
CPNE4	2.88	−0.69	—	—	—	—
SLC38A3	2.96	−0.69	—	—	—	—
CNGA3	2.67	−0.69	—	—	—	—
PPIF	2.58	−0.70	—	—	—	—
SCN1B	3.06	−0.71	—	—	—	—
FLRT1	2.83	−0.72	—	—	—	—
APOL4	2.97	−0.73	—	—	—	—
PPAPDC1A	2.82	−0.75	—	—	—	−0.71
OXT	2.61	−0.80	—	—	—	—

—: *p* value > 0.05.

Table S12. LH highly related-genotypes.

Gene	FC	PCC	*p* Value	FDR
POU1F1	6.26	0.922	<0.001	0.017
DRD2	2.85	0.898	0.001	0.021
LHB	2.64	0.895	0.001	0.015
ALDOB	2.73	0.886	0.001	0.015
TBX20	3.83	0.874	0.002	0.017
GH2	4.57	0.870	0.002	0.016
LOC100507588	3.38	0.865	0.003	0.015
GPR50	3.15	0.862	0.003	0.014
HSPB3	5.62	0.849	0.004	0.017
SEP14	2.65	0.829	0.006	0.023
APLN	2.59	0.816	0.007	0.027
DRD2	2.64	0.805	0.009	0.030
CNTN2	4.19	0.799	0.010	0.031
DLK1	4.87	0.797	0.010	0.029
HMP19	3.37	0.796	0.010	0.028
LYVE1	3.38	0.782	0.013	0.033
MAMLD1	3.60	0.773	0.014	0.035
MARCO	2.72	0.772	0.015	0.034
COL9A3	2.78	0.769	0.015	0.033
SCUBE1	3.25	0.753	0.019	0.039
GNA14	3.88	0.752	0.019	0.038
COL8A1	2.73	0.746	0.021	0.037
SERTM1	4.45	0.746	0.021	0.036
MEGF11	3.67	0.744	0.022	0.035
TFPI2	3.27	0.743	0.022	0.034
FLRT1	2.83	0.740	0.023	0.035
LMX1A	3.94	0.738	0.023	0.034
MDK	2.98	0.736	0.024	0.034
MYCL1	2.60	0.735	0.024	0.033
CHIA	2.84	0.732	0.025	0.033
ANKS1B	2.54	0.725	0.027	0.035
ZNF331	2.92	0.719	0.029	0.036
POU1F1	3.95	0.712	0.031	0.038
FAM92B	2.51	0.701	0.035	0.041
PMAIP1	4.66	0.692	0.039	0.044
GNAL	3.51	0.687	0.041	0.045
ARC	2.97	0.683	0.043	0.046
CYFIP2	3.22	0.668	0.049	0.052
RARA	3.51	0.668	0.049	0.050
CDH20	2.64	0.668	0.049	0.049
IL20RA	2.53	−0.750	0.020	0.037

Table S13. E2 highly related-genotypes.

Gene	FC	PCC	*p* Value	FDR
FXYD1	4.53	0.952	<0.001	0.001
CBFA2T2	3.25	0.940	<0.001	0.001
FSTL5	2.84	0.939	<0.001	0.001
CBS	4.15	0.934	<0.001	0.001
B3GAT1	2.95	0.934	<0.001	0.001
SEZ6L	3.88	0.934	<0.001	<0.001
FGF13	4.07	0.933	<0.001	<0.001
PRR5	2.58	0.722	0.028	0.030
FGF12	3.12	0.705	0.034	0.034

Table S14. Information of five selected genes.

ID	N1		N2		N3		N4		N5		N6		N7		N8		N9		Differentail Recurrence	DI	Avg (Tumor)	Avg (ANPTs)	Gene Symbol	Chr
	Tumor	ANPTs	Tumor	ANPTs	Tumor	ANPTs	Tumor	ANPTs	Tumor	ANPTs	Tumor	ANPTs	Tumor	ANPTs	Tumor	ANPTs	Tumor	ANPTs						
NM_001146	0.66	2.88	0.00	2.37	0.01	3.50	2.69	2.01	2.22	6.27	0.00	10.09	5.94	5.73	1.33	7.52	0.02	13.19	7	−0.693	1.431	5.951	*ANGPT1*	chr8
NM_000088	40.10	5.07	43.31	9.33	77.52	7.59	5.41	7.36	16.26	6.24	21.30	3.31	12.44	3.88	24.57	4.79	24.26	5.71	8	0.668	29.463	5.921	*COL1A1*	chr17
NM_002526	15.62	1.62	18.26	2.64	13.47	1.33	3.39	1.73	8.57	2.10	31.88	2.07	3.84	5.18	4.71	1.69	17.51	3.64	7	0.667	13.027	2.445	*NT5E*	chr6
NM_002775	19.77	134.27	11.63	98.22	9.45	70.44	87.43	111.71	38.47	79.78	8.71	108.97	68.77	97.49	10.90	121.24	9.96	68.46	7	−0.702	29.454	98.956	*HTRA1*	chr10
NM_001040058	39.45	1.44	37.05	0.95	7.99	1.54	3.06	0.85	1.41	3.42	87.76	0.54	0.00	0.93	33.11	2.06	11.36	1.19	9	0.634	24.577	1.437	*SPP1*	chr4

Table S15. Primer sequences.

Gene Symbol	Forward (5′ to 3′)	Reverse (5′ to 3′)
SPP1	GCATTCCGATGTGATTGAT	GTCTACAACCAGCATATCTTC
COL1A1	CACGACAAAGCAGAAACA	ATCAAGACAAGAACGAGGTA
NT5E	GATGGCTCCTCTCAATCA	TGTGTCTCAGGTTGTTGT
HTRA1	ACGGTGAAGTGATTGGAA	TGAGTGACATCATTCGGATA
ANGPT1	CCGAGCCTATTCACAGTAT	AATCAGCACCGTGTAAGA
GAPDH	GGTGGTCTCCTCTGACTTCAACA	GTTGCTGTAGCCAAATTCGTTGT

Table S16. Full name and unit of clinical indexes.

ID	Clinical Indexes	Full Name	Untis
	Tumor size		
1	Maximum diameter	Maximum diameter	mm
2	Gross tumor volume	Gross tumor volume	mm³
	ACTH-secreting pituitary adenoma related hormones		
3	ACTH 8 AM	8 AM plasma adrenocorticotropic hormone level	pg/mL
4	8 AM F	8AM total serum cortisol level	ug/dL
5	0 AM F	Midnight AM total serum cortisol level	ug/dL
6	24 h UFC (control)	24-h Urinary-free cortisol test (control)	ug
7	24 h UFC (low-dose DST)	24-h Urinary cortisol level (low-dose dexamethasone suppression test)	ug
8	24 h UFC (high-dose DST)	24-h urinary cortisol level (high-dose dexamethasone suppression Test）	ug
	Other pituitary related hormones		
9	GH	Growth hormone	ng/mL
10	IGF-1	Insulinlike growth factor 1	ng/mL
11	LH	Luteinizing hormone	mIU/mL
12	FSH	Follicle-stimulating hormone	mIU/mL
13	E2	Estradiol	pg/mL
14	PRL	Prolactin	ng/mL
15	TSTO	Testosterone	ng/dL
16	PROG	Progesterone	ng/mL
17	FT3	Serum free triiodothyronine	pg/mL
18	FT4	Serum free thyroxine	ng/dL
19	T3	Triiodothyronine	ng/mL
20	T4	Thyroxine	ug/dL
21	TSH	Serum thyroid stimulating hormone	uIU/mL
	Bone metabolism		
22	PTH	Serum parathyroid hormone	pg/mL
23	P	Serum calcium	mmol/L
24	Ca	Serum phosphate	mmol/L
25	ALP	Serum alkaline phosphatase	U/L
	Age-matched bone mineral density (BMD)		
26	L1	First lumbar Z-score	score
27	L2	Second lumbar Z-score	score
28	L3	Third Lumbar Z-score	score
29	L4	Fourth Lumbar Z-score	score
30	L1-2	lumbar 1-2 Z-score	score
31	L1-4	lumbar 1-4 Z-score	score
32	L2-4	lumbar 2-4 Z-score	score
33	Neck of femur	Neck of femur Z-score	score
34	Greater trochanter	Greater trochanter Z-score	score
35	Total Haunch Bone	Total haunch bone Z-score	score
	Routine blood chemistry		
36	WAC	White blood cell	10⁹/L
37	LY% (%)	Lymphocyte	%
38	MONO% (%)	Monocyte	%
39	NEUT% (%)	Ueutrophile granulocyte	%
40	EOS (%)	Eosnophils	%
41	BASO (%)	Basophilic granulocyte	%
42	LUC (%)	Large unstained cell	%
43	LY#	Lymphocyte	10⁹/L
44	MONO#	Monocyte	10⁹/L
45	NEUT#	Neutrophile granulocyte	10⁹/L
46	EOS#	Eosnophils	10⁹/L
47	BASO#	Basophilic granulocyte	10⁹/L
48	RBC	Red blood cell	10¹²/L
49	HGB	Hemoglobin	g/L

Table S16. *Cont.*

ID	Clinical Indexes	Full Name	Untis
50	HCT	Hematocrit	%
51	MCV	Mean corpuscular volume	fl
52	MCHC	Mean corpuscular hemoglobin concentration	g/L
53	MCH	Mean corpuscular hemoglobin	pg
54	CHCM	Cellular hemoglobin concentration mean	g/L
55	CH	Cellular hemoglobin	pg
56	RDW-C	Red cell distribution width	%
57	HDW	Hemoglobin distribution width	%
58	PLT	Platelets	10^9/L
59	PCT	Plateletcrit	%
60	PDW	Platelet distribution width	%
61	MPV	Mean platelet volume	fl
62	ESR	Erythrocyte sedimentation rate	mm/h
	Cardiovascular related indexes		
63	hsCRP	High sensitivity C reactive protein	mg/L
64	SBP	Systolic blood pressure	mmHg
65	DBP	Diastolic blood pressure	mmHg
	Liver function		
66	ALT	Alanine aminotransferase	U/L
67	TP	Total protein	g/L
68	Alb	Albumin	g/L
69	A/G	Albumin/globulin	ratio
70	Tbil	Total bilirubin	umol/L
71	Dbil	Direct bilirubin	umol/L
72	GGT	γ-glutamyl transpeptidase	U/L
73	AST	Aspartic acid transaminase	U/L
74	TBA	Total bile acids	umol/L
75	LD	Lactic dehydrogenase	U/L
76	ChE	Acetylcholine esterase	kU/L
77	ADA	Adenosine deaminase	U/L
78	PA	Prealbumin	mg/L
	Electrolyte		
79	K	Kalium	mmol/L
80	Na	Sodium	mmol/L
81	Cl	Chlorine	mmol/L
82	TCO_2	Total carbon dioxide	mmol/L
	Renal function		
83	Cr(E)	Creatinine	umol/L
84	Urea	Urea	mmol/L
85	Glu	Glutamic acid	mmol/L
86	UA	Uric acid	umol/L
	Lipid metabolism		
87	TC	Total cholesterol	mmol/L
88	TG	Triglyceride	mmol/L
89	HDL-C	High-density lipoproteincholesterol	mmol/L
90	LDL-C	Low-density lipoprotein cholesterol	mmol/L
91	ApoA1	Apolipoprotein A1	g/L
92	ApoB	Apolipoprotein B	g/L
93	Lp(a)	Lipoprotein	mg/L
94	FFA	Free fatty acid	umol/L
	Glycometabolism		
95	blood gloucose	Blood glucose	mmol/L
96	GLU 0 min	Glucose 0 min	mmol/L
97	INS 0 min	Insulin 0 min	uIU/mL
98	GLU 30 min	Glucose 30 min	mmol/L
99	INS 30 min	Insulin 30 min	uIU/mL
100	GLU 60 min	Glucose 60 min	mmol/L
101	INS 60 min	Insulin 60 min	uIU/mL
102	GLU 120 min	Glucose 120 min	mmol/L
103	INS 120 min	Insulin 120 min	uIU/mL
104	GLU 180 min	Glucose 180 min	mmol/L
105	INS 180 min	Insulin 180 min	uIU/mL
106	HbAlc	Glycosylated hemoglobin	%