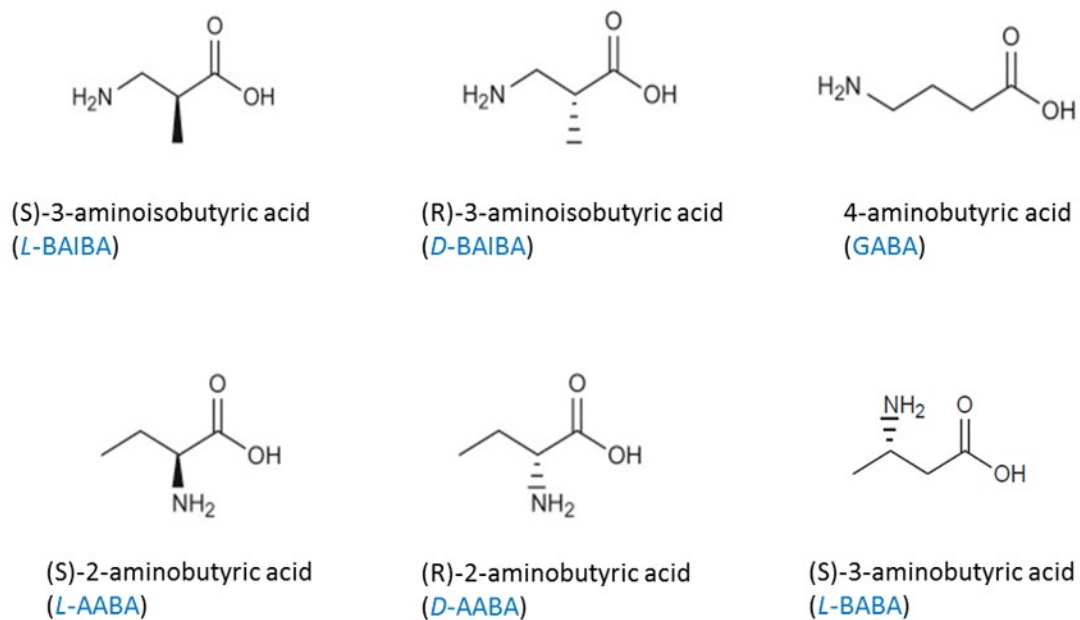


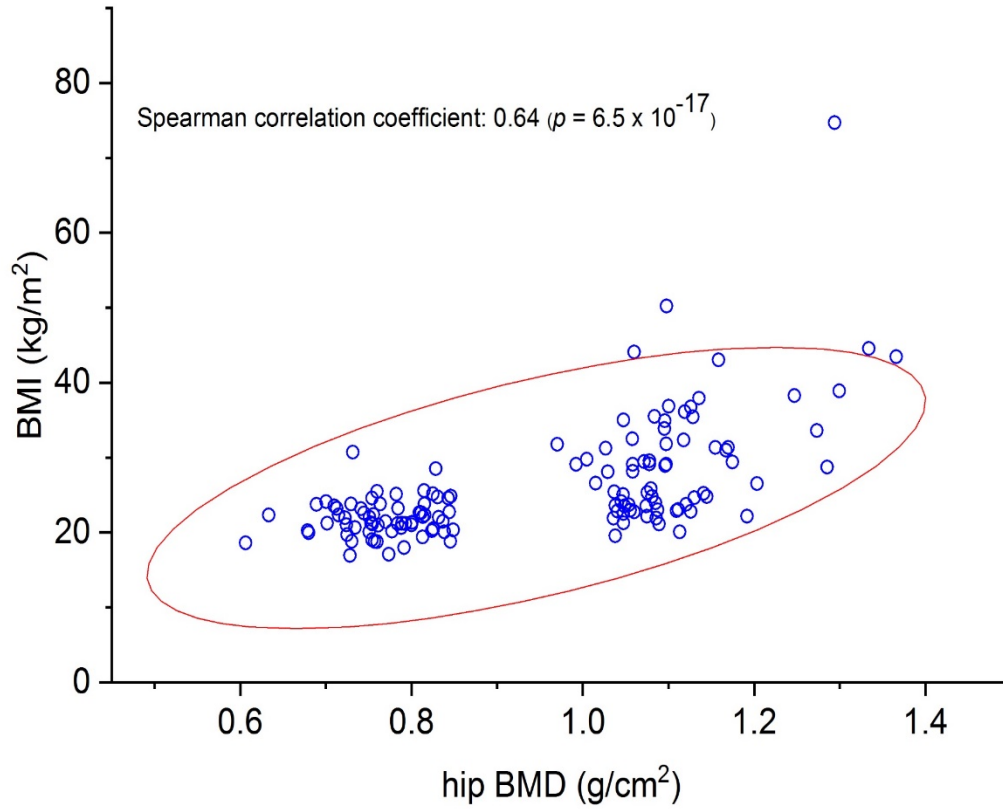
Supplementary Data:

Supplementary Figure 1



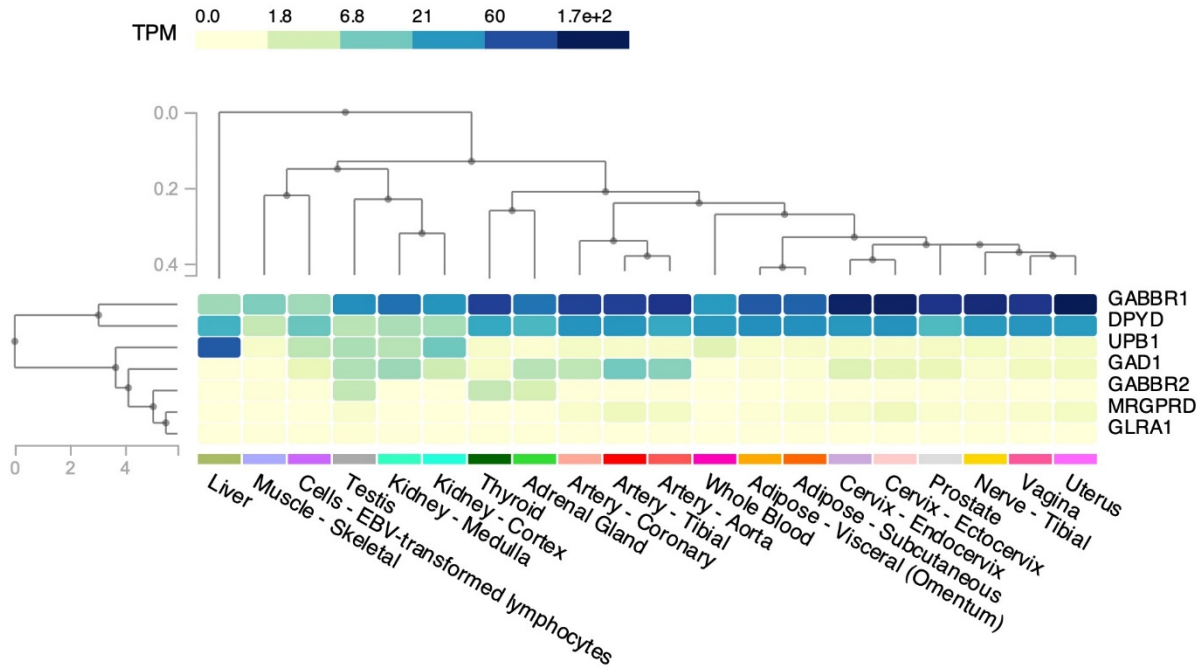
**Supplementary Fig. 1.** Structures of the six major isomeric aminobutyric acids identified and chromatographically separated using our new LC-MS/MS method.

**Supplementary Figure 2**



**Supplementary Fig. 2.** Association analysis between BMD and BMI in young Caucasian women subjects. n=136.

**Supplementary Figure 3**



**Supplementary Fig. 3.** A heatmap for reference panel of the median TPM gene expression levels for the aminobutyric acids related genes. The tissues were selected by either potential bone-related, sex-related tissues, or relatively high expressed of the genes. The reference expression profiles for the tissues were obtained from GTXs Portal (<https://www.gtexportal.org/home/>) on October 30, 2019.

TPM: Transcripts per million.

**Supplementary Table 1.** Analytes and deuterated standards and their MRM transition conditions

#	Compounds	Retention time (min)	MRM (+/-)	MRM Transition ( <i>m/z</i> )	MS parameters			Compound type
					Q1(V)	CE(V)	Q3(V)	
1	<i>L</i> -AABA	4.8	MRM(+)	104.1>58.0	-31	-19	-26	Analyte
2	<i>D</i> -AABA	7.4	MRM(+)	104.1>58.0	-31	-19	-26	Analyte
3	<i>L</i> -BABA	8.4	MRM(+)	104.1>86.0	-30	-18	-25	Analyte
4	<i>D</i> -BAIBA	10.2	MRM(+)	104.1>86.0	-30	-18	-28	Analyte
5	<i>L</i> -BAIBA	11.3	MRM(+)	104.1>86.0	-30	-17	-28	Analyte
6	GABA	15.8	MRM(+)	104.1>69.0	-29	-12	-16	Analyte
7*	<i>L</i> -AABA- <i>d</i> <sub>6</sub>	4.8	MRM(+)	110.1>64.0	-11	-24	-25	IS
8*	<i>D</i> -AABA- <i>d</i> <sub>6</sub>	7.4	MRM(+)	110.1>64.0	-11	-24	-25	IS
9*	<i>D</i> -BAIBA- <i>d</i> <sub>3</sub>	10.2	MRM(+)	107.1>89.0	-30	-15	-18	IS
10*	<i>L</i> -BAIBA- <i>d</i> <sub>3</sub>	11.3	MRM(+)	107.1>89.0	-30	-15	-18	IS
11*	GABA- <i>d</i> <sub>6</sub>	15.8	MRM(+)	110.1>92.0	-28	-12	-19	IS

\*deuterated standards. IS, internal standard.

**Supplementary Table 2.** Slopes and coefficients ( $R^2$ ) of linear regression analysis for aminobutyric acid isomers spiked in 5% BSA in PBS (w/v) versus in plasma, serum and CSF (0.02 – 163.84  $\mu\text{M}$ ) to assess the parallelism of their matrix effects.

	Human Serum			Mouse Serum			Mouse Plasma			Human CSF		
	Linear range ( $\mu\text{M}$ )	Slope	$R^2$	Linear range ( $\mu\text{M}$ )	Slope	$R^2$	Linear range ( $\mu\text{M}$ )	Slope	$R^2$	Linear range ( $\mu\text{M}$ )	Slope	$R^2$
<b><i>L</i>-BAIBA</b>	0.02 - 40.96	0.90	0.9986	0.02 - 40.96	0.88	0.9957	0.02 - 40.96	0.93	0.9995	0.02 - 20.48	0.98	0.9995
<b><i>D</i>-BAIBA</b>	0.02 - 40.96	0.94	0.9952	0.02 - 40.96	0.92	0.9957	0.02 - 40.96	0.93	0.9996	0.02 - 20.48	0.96	0.9997
<b>GABA</b>	0.02 - 40.96	0.91	0.9905	0.02 - 40.96	0.94	0.9976	0.02 - 40.96	0.90	0.9995	0.02 - 20.48	0.96	0.9991
<b><i>L</i>-AABA</b>	0.16 - 163.84	0.96	0.9977	0.16 - 163.84	0.87	0.9869	0.16 - 163.84	0.99	0.9942	0.16 - 163.84	1.04	0.9914
<b><i>D</i>-AABA</b>	0.16 - 163.84	1.07	0.9960	0.16 - 163.84	1.12	0.9915	0.16 - 163.84	1.10	0.9963	0.16 - 163.84	1.06	0.9979

CSF, cerebrospinal fluid.

**Supplementary Table 3.** Background and demographics of the studied women without (Control) or with (CASE) osteoporotic fractures (48-80 years old) and measured serum concentrations of isomeric aminobutyric acids.

Characteristics		All	CASE	Control
<b>Age (years), mean ± SD</b>		60.59 ± 6.55	61.00 ± 6.77	60.51 ± 6.46
48-59, n (%)		26 (48.1)	13 (48.1)	13 (48.1)
60-80, n (%)		28 (51.9)	14 (51.9)	14 (51.9)
<b>Gender</b>				
Female, n (%)		54 (100)	27 (100)	27 (100)
Male, n (%)		0 (0)	0 (0)	0 (0)
<b>T-score</b>				
TSpine, mean ± SD		-1.15 ± 0.83	-1.24 ± 0.86	-1.07 ± 0.80
THIP, mean ± SD		-0.92 ± 0.70	-0.92 ± 0.68	-0.92 ± 0.73
<b>Location of fractures</b>				
= 0, n (%)		27 (50)	0 (0)	27 (100)
= 1, n (%)		8 (14.8)	8 (29.6)	0 (0)
= 2, n (%)		10 (18.5)	10 (37.0)	0 (0)
≥ 3, n (%)		9 (16.7)	9 (33.3)	0 (0)
Axial fractures		9 (16.7)	9 (33.3)	0 (0)
Appendicular fractures		18 (33.3)	18 (66.7)	0 (0)
<b>Serum concentrations (μM)</b>				
<i>L</i> -BAIBA	mean ± SD	N.D.	N.D.	N.D.
	Range	-	-	-
<i>D</i> -BAIBA	mean ± SD	1.13 ± 0.46	1.07 ± 0.45	1.20 ± 0.46
	Range	0.38–2.24	0.38–1.97	0.71–2.24
GABA	mean ± SD	0.13 ± 0.03	0.12 ± 0.02	0.13 ± 0.03
	Range	0.08–0.20	0.08–0.16	0.09–0.20
<i>L</i> -AABA	mean ± SD	4.78 ± 1.44	4.82 ± 1.43	4.75 ± 1.46
	Range	2.31–7.86	2.31–7.78	2.36–7.86
<i>D</i> -AABA	mean ± SD	N.D.	N.D.	N.D.
	Range	-	-	-

N.D., not determined.

**Supplementary Table 4.** Background and demographics of the younger women group (21 - 41 years old) with various bone mineral density (BMD) and measured serum concentrations of isomeric aminobutyric acids.

<b>Characteristics</b>	<b>Mean ± SD</b>	<b>Minimum</b>	<b>Maximum</b>	<b>Sample size</b>
<b>Age</b> (years)	31.5 ± 5.1	21	40.6	136
<b>Gender</b>				
Female, n (%)	136 (100)			
Male, n (%)	0 (0)			
<b>Weight</b> (kg)	70.3 ± 21.4	44.5	220	136
<b>Height</b> (cm)	164.6 ± 6.4	150	182.6	136
<b>BMI</b> (kg m <sup>-2</sup> )	26.0 ± 7.5	17	74.7	136
<b>Waist Circumference</b> (cm)	78.1 ± 16.1	41.5	132	136
<b>T-score</b> (hip)	0.03 ± 1.49	-2.75	3.48	136
<b>HTOT_BMD</b> (cm <sup>-2</sup> )	0.95 ± 0.18	0.606	1.366	136
<b>Smoke</b> , n (%)	48 (35)			
<b>Drinking</b> , n (%)	104 (76)			
<b>Pure Alcohol Intake</b> (ml)	36.5 ± 52.4	0	336	136
<b>Physical Activity</b> (times/week)	3.1 ± 2.2	0	7	136
<b>Dairy Intake</b> (cups per day)*	1.6 ± 1.3	0	8	136
<b>Serum concentrations</b> (µM)				
<i>L</i> -BAIBA	0.115 ± 0.030	0.076	0.157	6
<i>D</i> -BAIBA	1.98 ± 0.93	0.58	6.20	135
GABA	0.42 ± 0.12	0.21	0.74	135
<i>L</i> -AABA	31.82 ± 13.53	4.48	79.72	135
<i>D</i> -AABA	N.D.	N.D.	N.D.	136

\*Diary Intake (cups per day): three different types of the dairy intake have been converted to the same unit. 1) The milk was measured by cup unit; 2) Yogurt: 8 ounces = 1 cup; 3) Cheese: 1.5 ounces = 1 cup.

Therefore, Total Dairy Intake = cheese cups per day + yogurt cups per day + milk cups per day.

N.D., not determined.

**Supplementary Table 5.** The list of GWAS summary statistics for VEGAS gene-based analysis

<b>Short Study</b>	<b>Traits</b>	<b>Data Usage</b>	<b>Ref</b>
GEFOS2	FN-BMD LS-BMD	Provided both pooled and gender-stratified summary statistics.	1
GEFOS ALLFX	Fracture		2
GEFOS LIFE COURSE	Total body BMD	Provided both pooled and age-stratified summary statistics. Five age strata, each spanning 15 years, including “less 15”, “15 to 30”, “30 to 45”, “45 to 60”, and “60 more”.	3
UKBB 2017	eBMD		4
UKBB 2018	eBMD Fracture	The p-values from infinitesimal model were used for fracture data, and the p-values from non-infinitesimal model were used for eBMD data.	5

BMD: bone mineral density; eBMD: Bone mineral density estimated from quantitative heel ultrasounds,

FB BMD: Femoral Neck BMD, LS-BMD: Lumbar Spine BMD.



**Supplementary Table 6.** Genes coding for enzymes and receptors associated with BAIBA and GABA metabolism.

<b>Aminobutyric Acids</b>	<b>Symbol</b>	<b>Description</b>	<b>Ref.</b>
BAIBA	<i>AGXT2</i>	Alanine--Glyoxylate Aminotransferase 2	6
	<i>FFAR3</i> *	G protein-coupled receptor 41	7,8
	<i>MRGPRD</i> %	MAS Related GPR Family Member D	9
	<i>DPYD</i> #	Dihydropyrimidine Dehydrogenase	10,11
	<i>DPYS</i>	Dihydropyrimidinase	12
	<i>UPBI</i>	Beta-Ureidopropionase 1	13
	<i>ALDH6A1</i>	Methylmalonate-Semialdehyde Dehydrogenase	14
<i>L</i> -BAIBA	<i>ABAT</i>	4-Aminobutyrate Aminotransferase	15
<i>D</i> -BAIBA	<i>AGXT2</i>	Alanine--Glyoxylate Aminotransferase 2	16
GABA	<i>GABBR1</i>	Gamma-Aminobutyric Acid Type B Receptor Subunit 1	17
	<i>GABBR2</i>	Gamma-Aminobutyric Acid Type B Receptor Subunit 2	17
	<i>GLRA1</i>	Glycine receptor subunit alpha-1	18
	<i>GLRA2</i> *	Glycine receptor subunit alpha-2	19
	<i>GLRA3</i>	Glycine receptor subunit alpha-3	20
	<i>GLRA4</i> *	Glycine receptor subunit alpha-4	21
	<i>GAD1</i>	Glutamate Decarboxylase 1	22
	<i>ABAT</i>	4-Aminobutyrate Aminotransferase	23

\* No summary statistics from all GWAS studies, % No summary statistics in GEFOS ALLFX and GEFOS2 studies, # No summary statistics in UKBB2017 and UKBB2018 studies.

**Supplementary Table 7.** Background and demographics of the 122 younger women group (21 - 41 years old) for which blood was used for transcriptomics analysis.

<b>Characteristics</b>	<b>Mean ± SD</b>	<b>Minimum</b>	<b>Maximum</b>	<b>Sample size</b>
<b>Age</b> (years)	31.5 ± 5.1	21	40.6	122
<b>Gender</b>				
Female, n (%)	122 (100)			
Male, n (%)	0 (0)			
<b>Weight</b> (kg)	70.8 ± 22.0	44.5	220	122
<b>Height</b> (cm)	164.6 ± 6.5	150	182.6	122
<b>BMI</b> (kg m <sup>-2</sup> )	25.8 ± 6.4	17	50.2	122
<b>Waist Circumference</b> (cm)	78.8 ± 16.2	48.5	132	122
<b>T-score</b> (hip)	0.01 ± 1.5	-2.75	3.48	122
<b>HTOT_BMD</b> (cm <sup>-2</sup> )	0.9 ± 0.20	0.6065	1.366	122
<b>Smoke</b> , n (%)	46 (38)			
<b>Drinking</b> , n (%)	93 (76)			
<b>Pure Alcohol Intake</b> (ml)	37.0 ± 54.7	0	336	122
<b>Physical Activity</b> (times/week)	3.1 ± 2.2	0	7	122
<b>Dairy Intake</b> (cups per day)*	1.55 ± 1.3	0	8	122
<b>Serum concentrations</b> (µM)				
<i>L</i> -BAIBA	0.115 ± 0.030	0.076	0.157	6
<i>D</i> -BAIBA	1.98 ± 0.9	0.64	6.20	122
GABA	0.42 ± 0.12	0.21	0.74	122
<i>L</i> -AABA	32.33 ± 13.92	4.48	79.72	122
<i>D</i> -AABA	N.D.	N.D.	N.D.	122

\*Diary Intake (cups per day): three different types of the dairy intake have been converted to the same unit.

1) The milk was measured by cup unit; 2) Yogurt: 8 ounces = 1 cup; 3) Cheese: 1.5 ounces = 1 cup.

Therefore, Total Dairy Intake = cheese cups per day + yogurt cups per day + milk cups per day.

N.D., not determined.

**Supplementary Table 8.** Measured expression levels of aminobutyric acids-related genes in human peripheral blood monocytes.

Subject ID	Expression levels (TPM)						
	<i>DPYD</i>	<i>GABBR1</i>	<i>GABBR2</i>	<i>GAD1</i>	<i>GLRA1</i>	<i>MRGPRD</i>	<i>UPBI</i>
DNAM01700	98.18	83.17	0	0	0.44	0	0.35
DNAM01701	173.85	67.85	0	0	0	0	0
DNAM01702	169.45	69.26	0	0	0	0	0
DNAM01703	165.22	42.33	0	0.05	0	0	0.28
DNAM01704	283.61	101.49	0	0	0.34	0	0.27
DNAM01705	149.44	38.44	0	0.07	0	0	0.38
DNAM01706	280.39	29.74	0.02	0	0.08	0	0.33
DNAM01707	244.34	34.6	0	0.75	0.28	0	0.33
DNAM01708	114.03	132.82	0	0	0	0.28	0.12
DNAM01709	48.6	56.85	0	0	0	0	0
DNAM01710	285.6	36.87	0	0	0	0.31	0
DNAM01711	21.94	55.87	0	0	0	0	0
DNAM01712	215.7	53.14	0	0	0	0	0.25
DNAM01714	134.12	73.62	0	0	0.13	0.27	0.69
DNAM01715	93.19	41.21	0	0	0	0	0.41
DNAM01716	61.72	55.07	0	0	0	0	0
DNAM01719	90.95	64.24	0	0	0	0	1.04
DNAM01720	110.44	67.4	0	0	0	0	1.44
DNAM01722	302.85	43.39	0	0	0.23	0	0.61
DNAM01723	190.08	87.22	0	0.08	0.17	0.31	0.14
DNAM11001	29.55	5.04	0	0	0	0	0
DNAM11002	24.07	6.63	0	0	0	0	0
DNAM11005	48.91	9.94	0	0	0	0	0.24
DNAM11006	98.34	28.53	0	0	0	0	0.28
DNAM11007	202.35	31.04	0	0	0	0	0.19
DNAM11008	55.37	19.86	0	0	0.19	0	0.31
DNAM11009	94.47	41.4	0	0	0.22	0	0.18
DNAM11010	98.01	31.44	0	0	0	0	0
DNAM11012	127.74	18.44	0	0	0	0	0.37
DNAM11013	5.74	1.69	0	0	0	0	0
DNAM11014	97.44	30.69	0	0	0	0	0.16
DNAM11015	85.56	28	0	0	0	0	0.86
DNAM11016	124.06	39.83	0	0	0	0	0.29
DNAM11017	100.2	68.2	0	0	0	0	0

DNAM11018	28.84	10.79	0	0.3	0	0	0
DNAM11019	23.72	9.78	0	0.24	0	0	0.56
DNAM11020	188.3	13.31	0	0	0.39	0	0.21
DNAM11021	140.48	38.74	0	0	0.44	0	0.57
DNAM11027	5.16	3.62	0	0	0	0	0.13
DNAM11030	70.56	27.27	0	0	0.32	0.23	0.3
DNAM11031	230.42	34.34	0	0	0.17	0	0.42
DNAM11032	242.07	15.19	0	0	0	0	0.5
DNAM11033	178.49	44.89	0	0	0	0	0.08
DNAM11037	231.04	14.95	0	0	0.12	0	0.86
DNAM11038	203.74	2.94	0	0	0.12	0	0.49
DNAM11039	223.48	10.34	0	0	0	0	0.08
DNAM11040	187.47	13.75	0	0.04	0	0	0.08
DNAM11041	151.03	63.1	0	0	0.18	0	0.14
DNAM11042	135.09	20.78	0	0.07	0.16	0.29	0.75
DNAM11045	233.18	41.52	0	0	0	0.14	0.06
DNAM11046	332.31	79.02	0	0	0	0	0.76
DNAM11047	203.91	58.95	0	0	0	0	0.35
DNAM11048	269.18	56.96	0	0	0	0	0.15
DNAM11049	183.39	10.55	0	0	0	0	0.46
DNAM11050	176.87	10.16	0.11	0	0	0	0
DNAM11051	241.72	24.19	0	0	0	0	0.59
DNAM11054	337.63	135.96	0	0.12	0	0	0.61
DNAM11055	104.26	43.92	0	0	0	0	0.53
DNAM11056	245.97	75.44	0	0.17	0.23	0	0.2
DNAM11057	234.58	31.31	0	0.09	0	0	0.31
DNAM11058	39.02	18.3	0	0	0	0	0
DNAM11060	151.99	16.51	0	0	0.11	0	0
DNAM11061	176.96	26.61	0	0	0.16	0	0.32
DNAM11064	1.7	12.83	0	0	0	0	0.3
DNAM11065	234.57	23.85	0	0	0	0	0
DNAM11066	163.18	26	0	0	0.11	0	0.09
DNAM11068	195.49	32.4	0.03	0	0	0.18	0.85
DNAM11069	22	145.85	0.17	0	0	0	0
DNAM11071	96.53	41.18	0	0	0	0	0.13
DNAM11072	102.17	13.73	0	0	0.09	0	0.15
DNAM11074	229.48	54.19	0	0	0	1.02	1.03
DNAM11075	0.12	19.97	0	0	0	0	0
DNAM11076	205.28	56.64	0	0.49	0.12	0	0.38
DNAM11077	113.48	22.22	0	0	0	0	0

DNAM11078	235.58	29.7	0	0.05	0	0	0.42
DNAM11079	199.61	26.93	0	0.15	0.3	0	0.8
DNAM11080	208.94	34.3	0	0	0	0	0.38
DNAM11081	214.22	75	0	0	0.07	0	0.58
DNAM11083	2.39	17.27	0	0	0	0	0
DNAM11084	224.84	25.03	0	0	0.1	0	0.48
DNAM11085	249.47	22.68	0	0	0	0	0.09
DNAM11086	0.52	59.51	0	0	0	0	0
DNAM11087	96.49	100.09	0	0	0	0	0
DNAM11088	210.65	37.66	0	0	0.11	0	0.5
DNAM11089	195.58	11.45	0	0	0.11	0	0.39
DNAM11090	9.5	101.17	0	0	0	0	0
DNAM11091	157.71	10.23	0	0	0	0	0.48
DNAM11092	2.16	48.17	0	0	0	0	0
DNAM11093	171.07	41.8	0	0	0	0	0.61
DNAM11094	268.26	24.28	0	0	0	0	0.36
DNAM11095	53.46	19.56	0	0	0	0	0
DNAM11096	257.85	19.8	0	0	0	0	0.59
DNAM11097	238.38	30.99	0.04	0	0	0.29	0.5
DNAM11098	174.51	21.76	0	0	0	0	0.09
DNAM11099	149.25	76.4	0	0.96	0	0	0
DNAM11100	52.09	171.45	0	0	0	0	0
DNAM11101	207.84	46.49	0	0	0	0	0.1
DNAM11102	264.03	13.66	0	0	0	0	0.55
DNAM11103	236.47	8.01	0	0	0	0	1.11
DNAM11104	152.56	32.69	0	0	0	0	0.34
DNAM11105	13.61	138.89	0	0	0	0	0
DNAM11108	150.19	8.64	0	0.16	0	0	0.21
DNAM11110	163.63	10.51	0	0	0	0	0
DNAM11111	146.24	22.72	0	0	0	0	0.1
DNAM11114	174.44	18.31	0	0.18	0	0	0.43
DNAM11116	247.33	7.87	0.02	0	0.08	0	0
DNAM11117	70.56	1.12	0	0	0	0	0
DNAM11118	91.4	9.79	0	0	0	0	0.99
DNAM11119	101.2	16.35	0	0.04	0	0	0.3
DNAM11120	226.46	12.67	0.07	0	0	0	0.32
DNAM11121	257.56	9.72	0	0	0	0	0.21
DNAM11122	229.49	16.98	0	0.07	0	0	0.51
DNAM11123	222.26	99.6	0	0	0.12	0	0.19
DNAM11124	231.74	32.53	0	0	0.16	0	0.13

DNAM11125	212.17	30.95	0	0	0	0	0.13
DNAM11126	171.08	36.09	0	0.42	0	0	0.85
DNAM11127	257.78	28.28	0	0	0	0	0.52
DNAM11128	251.12	31.57	0	0.04	0	0	0.59
DNAM11129	252.02	56.6	0	0	0	0	1.08
DNAM11130	170.66	30.16	0	0.06	0	0	0.11
DNAM11131	241.73	49.08	0	0	0	0	0.34
DNAM11132	46.2	50.16	0.04	0	0	0.76	1.33

TPM, Transcripts per million.

## References

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