

Table S1. Clinical characteristics of study participants

Volunteer		Age (Gender)	CERAD-K	Body mass index ¹⁾	Medicines within 3 months ²⁾
healthy	Mean±SD	60.0±6.6 ³⁾	75.3±1.5	23.9±1.4	
	Each	53 (F)	75	25.4	No
		61 (F)	74	23.6	No
		66 (M)	77	22.7	No
MCI	Mean±SD	65.3±4.2	59.3±6.4	26.0±3.3	
	Each	70 (M)	52	22.2	No
		64 (F)	63	27.3	No
		62 (F)	63	28.5	No

¹⁾ Body mass index (BMI) BMI is defined as the body mass divided by the square of the body height, and is universally expressed in units of kg/m², resulting from mass in kilograms and height in metres.

²⁾ medications that can affect the gut microbiota, such as painkillers, anti-inflammatory drugs, and antibiotics for > 3 months. Acute gastrointestinal symptoms such as diarrhea and abdominal pain within the last week.

³⁾ Indicated as mean ± SD.

Table S2. Primers for NK109 and 16S rRNA gene

	Primer	
	Forward	Reverse
NK109 gene	AGCGAGCTTGCCTAGATGAATTTG	TCT TTT AAA CTC TAG ACA TGC GTC
16S rRNA gene	TCGTCGGCAGCGTCAGATGTGTATAAG AGACAGGTGCCAGCMGCCGCGGTAA	GTCTCGTGGGCTCGGAGATGTGTATAAG AGACAGGGACTACHVGGGTWTCTAAT

Table S3. Effects of NK109 and NS on the fecal microbiota composition at the phylum level in Ag mice

Taxon Name	mean ± SD ¹⁾				
	Yg	YgS	Ag	AgN	AgS
Bacteroidetes	51.7±12.3	50.9±7.0	48.6±5.0	54.0±49.9	49.9±3.7
Firmicutes	43.4±12.0	42.6±6.9	46.6±5.3	40.9±42.9	42.9±4.5
Proteobacteria	2.7±1.7	2.0±0.2	3.4±0.8	2.7±2.9	2.9±1.3
Tenericutes	1.7±2.0	1.6±0.9	0.4±0.2	1.1±1.1	1.1±0.9
Actinobacteria	0.3±0.1	0.1±0.1	0.9±0.5*	0.4±0.5	0.5±0.3
Cyanobacteria	0.1±0.2	1.0±0.6	0.2±0.1	0.7±1.1	1.1±1.4
Deferribacteres	0.1±0.1	0.2±0.2	0.0±0.0	0.2±0.1	0.1±0.2
Saccharibacteria TM7	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0
Verrucomicrobia	0.0±0.0	1.5±1.3	0.0±0.0	0.0±1.4	1.4±1.9
Fusobacteria	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0

¹⁾Mean ± SD

Table S4. Effects of NK109 and NS on the fecal microbiota composition at the family level in Ag mice

Taxon Name	mean \pm SD ¹⁾				
	Yg	YgS	Ag	AgN	AgS
Muribaculaceae	35.7 \pm 10.8	37.7 \pm 7.0	36.2 \pm 3.1	31.2 \pm 7.2	31.5 \pm 4.7
Lachnospiraceae	26.8 \pm 12.4	28.1 \pm 5.0	20.2 \pm 6.8	21.5 \pm 5.2	23.6 \pm 4.0
Lactobacillaceae	8.0 \pm 6.0	1.1 \pm 0.5	13.8 \pm 5.2	8.1 \pm 2.4	8.9 \pm 4.3
Rikenellaceae	6.3 \pm 2.3	3.0 \pm 1.3	2.0 \pm 0.3	2.6 \pm 1.3	4.7 \pm 1.2
Ruminococcaceae	6.0 \pm 2.4	9.5 \pm 2.3	6.2 \pm 2.3	7.1 \pm 1.9	7.3 \pm 2.6
Prevotellaceae	4.8 \pm 3.0	4.7 \pm 3.3	2.8 \pm 1.6	12.5 \pm 5.2	6.3 \pm 4.3
Bacteroidaceae	2.8 \pm 1.5	2.7 \pm 1.1	5.4 \pm 1.9	5.7 \pm 1.1	4.9 \pm 1.5
Christensenellaceae	1.9 \pm 0.5	2.7 \pm 0.5	2.4 \pm 0.7	1.9 \pm 1.2	1.5 \pm 1.3
Odoribacteraceae	1.6 \pm 1.3	1.7 \pm 0.6	1.2 \pm 0.4	0.6 \pm 0.3	1.9 \pm 1.3
Acholeplasmataceae	1.5 \pm 2.1	1.4 \pm 1.0	0.2 \pm 0.1	0.9 \pm 0.8	0.7 \pm 0.8
Helicobacteraceae	1.0 \pm 1.7	0.1 \pm 0.1	1.2 \pm 0.9	0.3 \pm 0.2	1.3 \pm 1.6
Sutterellaceae	1.0 \pm 1.3	0.8 \pm 0.3	1.3 \pm 0.7	1.3 \pm 0.7	0.6 \pm 0.4
Desulfovibrionaceae	0.5 \pm 0.1	0.8 \pm 0.3	0.7 \pm 0.4	0.7 \pm 0.3	0.6 \pm 0.3
Erysipelotrichaceae	0.4 \pm 0.5	0.8 \pm 0.3	1.9 \pm 1.1	1.3 \pm 1.0	1.1 \pm 1.1
AC160630 f	0.3 \pm 0.1	0.7 \pm 0.4	0.6 \pm 0.3	0.7 \pm 0.8	0.5 \pm 0.3
Porphyromonadaceae	0.3 \pm 0.2	0.5 \pm 0.2	0.3 \pm 0.1	0.7 \pm 0.3	0.2 \pm 0.2
Coriobacteriaceae	0.2 \pm 0.1	0.1 \pm 0.1	0.3 \pm 0.1	0.2 \pm 0.1	0.5 \pm 0.3
Rhodospirillaceae	0.2 \pm 0.1	0.3 \pm 0.2	0.2 \pm 0.1	0.3 \pm 0.3	0.3 \pm 0.3
Dehalobacterium f	0.2 \pm 0.1	0.3 \pm 0.1	0.2 \pm 0.1	0.2 \pm 0.1	0.2 \pm 0.1
PAC000197 f	0.1 \pm 0.3	0.2 \pm 0.2	0.1 \pm 0.1	0.2 \pm 0.1	0.4 \pm 0.4
FR888536 f	0.1 \pm 0.2	1.0 \pm 0.6	0.2 \pm 0.1	0.7 \pm 0.4	1.1 \pm 1.4
Deferribacteraceae	0.1 \pm 1	0.2 \pm 0.2	0.0 \pm 0.0	0.2 \pm 0.1	0.1 \pm 0.2
Mogibacterium f	0.1 \pm 0.0	0.1 \pm 0.0	0.1 \pm 0.0	0.1 \pm 0.0	0.1 \pm 0.0
Peptococcaceae	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0
Bifidobacteriaceae	0.0 \pm 0.0	0.0 \pm 0.0	0.6 \pm 0.4*	0.2 \pm 0.2	0.0 \pm 0.0 [#]

¹⁾Mean \pm SD

Table S5. Effects of NK109 and NS on the fecal microbiota composition at the phylum level in Ag mice

Taxon Name	mean \pm SD ¹⁾				
	Yg	YgS	Ag	AgN	AgS
Lactobacillus murinus group	7.8 \pm 5.9	0.4 \pm 0.2	12.9 \pm 5.0	5.8 \pm 2.9	7.4 \pm 3.7
PAC001077 s	6.2 \pm 3.8	1.0 \pm 0.8	0.8 \pm 0.6	2.4 \pm 1.6	8.3 \pm 6.4
PAC001070 s group	6.1 \pm 5.7	5.9 \pm 1.5	8.6 \pm 2.2	5.8 \pm 4.3	4.2 \pm 3.8
PAC001093 s	3.5 \pm 5.4	0.3 \pm 0.7	0.5 \pm 1.0	0.1 \pm 0.2	2.6 \pm 3.9
PAC002450 s	3.0 \pm 4.1	10.4 \pm 1.8	5.6 \pm 3.1	4.4 \pm 3.6	1.1 \pm 2.5
PAC001060 s	2.5 \pm 1.4	0.1 \pm 0.2	0.4 \pm 0.3	0.4 \pm 0.7	1.4 \pm 0.8
PAC001383 s	2.4 \pm 2.8	0.1 \pm 0.1	0.1 \pm 0.1	0.7 \pm 0.9	0.7 \pm 1.1
KE159538 s	2.0 \pm 2.2	1.5 \pm 1.7	0.4 \pm 0.5	1.0 \pm 0.9	0.4 \pm 0.7
PAC001071 s	1.8 \pm 1.6	0.0 \pm 0.0	0.1 \pm 0.0	0.2 \pm 0.2	1.7 \pm 1.6
PAC002443 s	1.8 \pm 1.5	0.4 \pm 0.3	0.3 \pm 0.6	0.8 \pm 0.7	0.3 \pm 0.2
PAC002399 s	1.8 \pm 0.5	0.6 \pm 0.5	0.6 \pm 0.7	0.4 \pm 0.2	0.6 \pm 0.3
PAC002444 s	1.7 \pm 0.9	1.3 \pm 1.1	0.4 \pm 0.2	0.2 \pm 0.3	0.6 \pm 0.5
Muribaculum intestinale	1.6 \pm 1.6	1.0 \pm 0.9	2.8 \pm 0.6	2.3 \pm 1.4	0.4 \pm 0.2
PAC001080 s	1.5 \pm 2.1	1.4 \pm 1.0	0.2 \pm 0.2	0.9 \pm 0.8	0.6 \pm 0.8
PAC002400 s	1.4 \pm 1.1	1.2 \pm 0.4	0.7 \pm 0.2	0.6 \pm 0.3	1.0 \pm 0.6

PAC000198 s	1.4±1.2	0.6±0.7	0.4±0.8	0.2±0.1	0.4±0.3
PAC001065 s group	1.2±0.9	0.1±0.0	0.4±0.3	0.1±0.1	0.4±0.4
AB606328 s	1.1±1.3	0.9±0.3	0.4±0.2	0.4±0.2	1.1±0.8
KE159571 s	1.1±1.5	0.0±0.0	0.0±0.0	0.0±0.1	0.0±0.0
PAC002481 s	1.1±0.6	1.4±0.4	0.9±0.4	0.7±0.3	1.2±1.0
PAC001696 s	1.0±2.1	4.3±2.8	0.5±1.3	0.0±0.0	1.7±4.0
PAC001128 s	1.0±0.4	0.3±0.1	0.7±0.3	0.3±0.2	0.5±0.5
PAC001066 s	1.0±0.3	0.6±0.2	0.2±0.2	1.1±0.4	0.5±0.2
PAC001515 s	1.0±0.9	1.0±1.2	0.2±0.3	0.1±0.2	0.6±1.3
PAC002441 s group	0.9±0.6	0.6±0.3	0.5±0.1	0.6±0.2	0.5±0.2

¹⁾Mean ± SD

Table S6. The relationship between differentially enriched gut microbiota composition and spontaneous alteration score in YMT in Ag mice (in the network analysis)

	Spontaneous alteration score in Y-maze task	R	R ²	P-value		Spontaneous alteration score in Y-maze task	R	R ²	P-value
Phylum	Bacteroidetes	0.1061	0.0113	0.5769	species	Lactobacillus murinus group	-0.5401	0.2917	0.0021
	Firmicutes	-0.1032	0.0107	0.5874		PAC002443 s	0.497	0.2470	0.0052
	Actinobacteria	-0.5982	0.3578	0.0005		PAC002444 s	0.3888	0.1512	0.0337
Family	Muribaculaceae	-0.1368	0.0187	0.4712		PAC001066 s	0.5784	0.3345	0.0008
	Lachnospiraceae	0.3368	0.1134	0.0688		PAC002447 s	-0.4414	0.1948	0.0146
	Lactobacillaceae	-0.5606	0.3143	0.0013		PAC001119 s	0.4182	0.1749	0.0215
	Rikenellaceae	0.4272	0.1825	0.0186		PAC001688_s group	0.4202	0.1766	0.0208
	Ruminococcaceae	0.3850	0.1482	0.0356		PAC001382 s	0.4007	0.1606	0.0282
	Bacteroidaceae	-0.3446	0.1187	0.0622		PAC001684 s	0.4827	0.2330	0.0069
	Odoribacteraceae	0.0286	0.0008	0.8807		PAC001666 s	0.4276	0.1828	0.0184
	Erysipelotrichaceae	-0.4636	0.2149	0.0099		PAC001558 s	-0.5133	0.2635	0.0037
	Coriobacteriaceae	-0.2678	0.0717	0.1525		PAC001668 s	0.3931	0.1545	0.0316
	Bifidobacteriaceae	-0.5992	0.3590	0.0005		PAC001267 s	-0.4165	0.1735	0.022
	Peptostreptococcaceae	-0.0633	0.0040	0.7399		KE159714_s group	-0.4344	0.1887	0.0164
Genus	Lactobacillus	-0.5609	0.3146	0.0013		Lactobacillus uc	-0.6899	0.4760	<0.0001
	Alistipes	0.4534	0.2056	0.0119		AB599946 s	-0.5511	0.3037	0.0016
	LLKB_g	0.3416	0.1167	0.0647		PAC001199 s	0.3943	0.1555	0.0311
	PAC000186_g	-0.5416	0.2933	0.002		KB822463 s	-0.7004	0.4906	<0.0001
	Bacteroides	-0.3446	0.1187	0.0622		Bifidobacterium pseudolongum group	-0.6015	0.3618	0.0004
	Oscillibacter	0.4118	0.1696	0.0237		PAC001589 s	-0.5161	0.2664	0.0035
	PAC000664_g	-0.0399	0.0016	0.8343		PAC001266 s	-0.6567	0.4313	<0.0001
	KE159571_g	0.255	0.0650	0.1738		PAC001043_g uc	-0.5801	0.3365	0.0008
	Odoribacter	0.02849	0.0008	0.8812		Lactobacillus intestinalis	-0.5801	0.3365	0.0008
	PAC001092_g	0.2355	0.0555	0.2104		PAC001396_s	-0.6622	0.4385	<0.0001
	PAC001112_g	-0.2443	0.0597	0.1933		PAC001294_s	-0.3945	0.1556	0.031
	PAC001066_g	0.5794	0.3357	0.0008		HQ740432_s	-0.4342	0.1885	0.0165
	PAC000692_g	0.1377	0.0190	0.4682		PAC001528_s	-0.4147	0.1720	0.0227
	Agathobaculum	0.1754	0.0308	0.3539		PAC002299_s	-0.4755	0.2261	0.0079
	Eubacterium_g17	0.3643	0.1327	0.0478		PAC001488_s group	-0.5447	0.2967	0.0019

	Acetatifactor	-0.0252	0.0006	0.895		Clostridium celatum group	-0.7739	0.5989	<0.0001
	PAC001043_g	0.3676	0.1351	0.0457		PAC001271_s	-0.493	0.2430	0.0056
	PAC001199_g	0.3059	0.0936	0.1002		Clostridium uc	-0.7017	0.4924	<0.0001
	Clostridium g21	-0.1248	0.0156	0.5111		DQ815552_s	-0.5526	0.3054	0.0015
	PAC000661_g	-0.0656	0.0043	0.7307		DQ815878_s	-0.6489	0.4211	0.0001
	Dubosiella	-0.06	0.0036	0.7527		FJ881246_s	-0.5212	0.2716	0.0031
	PAC001091_g	-0.3485	0.1215	0.0591		Lactococcus garvieae group	-0.7121	0.5071	<0.0001
	PAC001516_g	-0.0998	0.0100	0.6		PAC000686_s	-0.5168	0.2671	0.0035
	KE159605_g	-0.2771	0.0768	0.1383		PAC001090_s	-0.489	0.2391	0.0061
	PAC001266_g	-0.6565	0.4310	<0.0001		PAC001092_g uc	-0.4146	0.1719	0.0227
	Bifidobacterium	-0.5992	0.3590	0.0005		PAC001553_s group	-0.5539	0.3068	0.0015
	PAC001116_g	-0.493	0.2430	0.0056		PAC001588_s	-0.6109	0.3732	0.0003
	Roseburia	-0.4205	0.1768	0.0207		PAC001665_s	-0.6387	0.4079	0.0001
	PAC001588_g	0.01566	0.0002	0.9345		PAC001902_s	-0.5875	0.3452	0.0006
	Lactococcus	-0.7439	0.5534	<0.0001					
	PAC001090_g	-0.489	0.2391	0.0061					

Table S7. The relationship between differentially enriched gut microbiota composition and exploration score in NORT in Ag mice (in the network analysis)

	Exploration score in NORT	R	R^2	P-value		Exploration score in NORT	R	R^2	P-value
Phylum	Bacteroidetes	0.1673	0.0280	0.3768	species	KE159538_s	0.4289	0.1840	0.018
	Firmicutes	-0.1879	0.0353	0.3202		PAC002443_s	0.4004	0.1603	0.0283
	Actinobacteria	-0.3981	0.1585	0.0293		PAC002399_s	0.4285	0.1836	0.0181
Family	Muribaculaceae	0.1490	0.0222	0.4319		PAC002444_s	0.4092	0.1674	0.0248
	Lachnospiraceae	0.1952	0.0381	0.3012		PAC002447_s	-0.3614	0.1306	0.0498
	Lactobacillaceae	-0.3830	0.1467	0.0367		PAC001119_s	0.3675	0.1351	0.0457
	Rikenellaceae	0.3502	0.1226	0.0578		PAC001688_s group	0.3897	0.1519	0.0333
	Ruminococcaceae	0.0721	0.0052	0.7052		PAC001382_s	0.3819	0.1458	0.0373
	Bacteroidaceae	-0.3706	0.1373	0.0438		PAC001684_s	0.4219	0.1780	0.0202
	Odoribacteraceae	0.0099	0.0001	0.9587		PAC001666_s	0.5377	0.2891	0.0022
	Erysipelotrichaceae	-0.2478	0.0614	0.1868		PAC001558_s	-0.4757	0.2263	0.0079
	Coriobacteriaceae	-0.2111	0.0446	0.2627		PAC001668_s	0.4798	0.2302	0.0073
	Bifidobacteriaceae	-0.3735	0.1395	0.0421		PAC001267_s	-0.3882	0.1507	0.034
	Peptostreptococcaceae	-0.2606	0.0679	0.1642		KE159714_s group	-0.5576	0.3109	0.0014
Genus	KE159538_g	0.348	0.1211	0.0595		Lactobacillus uc	-0.4997	0.2497	0.0049
	Alistipes	0.3974	0.1579	0.0296		AB599946_s	-0.5164	0.2667	0.0035
	LLKB_g	0.3031	0.0919	0.1035		PAC001199_s	0.3779	0.1428	0.0395
	PAC000186_g	-0.3553	0.1262	0.054		KB822463_s	-0.6891	0.4749	<0.0001
	Bacteroides	-0.3706	0.1373	0.0438		Bifidobacterium pseudolongum group	-0.3713	0.1379	0.0434
	Oscillibacter	0.09756	0.0095	0.608		PAC001589_s	-0.4845	0.2347	0.0067
	PAC000664_g	-0.2359	0.0556	0.2095		PAC001266_s	-0.5561	0.3092	0.0014
	PAC001127_g	0.4285	0.1836	0.0181		PAC001043_g uc	-0.5835	0.3405	0.0007
	KE159571_g	0.3751	0.1407	0.0411		Lactobacillus intestinalis	-0.4075	0.1661	0.0254
	Odoribacter	0.009914	0.0001	0.9585		PAC001396_s	-0.5827	0.3395	0.0007

PAC001092_g	0.2075	0.0431	0.2713	PAC001294_s	-0.374	0.1399	0.0417
PAC001112_g	-0.1691	0.0286	0.3717	HQ740432_s	-0.4601	0.2117	0.0105
PAC000692_g	0.08221	0.0068	0.6658	PAC002368_s	-0.4516	0.2039	0.0122
Agathobaculum	0.2001	0.0400	0.2891	PAC002299_s	-0.5816	0.3383	0.0007
Eubacterium_g17	0.4246	0.1803	0.0193	PAC001488_s group	-0.7246	0.5250	<0.0001
Acetatifactor	-0.1031	0.0106	0.5877	Clostridium celatum group	-0.5599	0.3135	0.0013
PAC001043_g	0.2268	0.0514	0.228	PAC001271_s	-0.6966	0.4853	<0.0001
PAC001199_g	0.3179	0.1011	0.0869	Clostridium_uc	-0.5086	0.2587	0.0041
Clostridium_g21	-0.1077	0.0116	0.5712	DQ815552_s	-0.5894	0.3474	0.0006
PAC000661_g	-0.2457	0.0604	0.1905	DQ815878_s	-0.5101	0.2602	0.004
Dubosiella	0.05326	0.0028	0.7798	FJ881246_s	-0.6017	0.3620	0.0004
PAC001091_g	-0.4245	0.1802	0.0194	Lactococcus garvieae group	-0.6324	0.3999	0.0002
PAC001516_g	-0.1279	0.0164	0.5005	PAC000686_s	-0.525	0.2756	0.0029
KE159605_g	-0.3407	0.1161	0.0654	PAC001090_s	-0.586	0.3434	0.0007
PAC001266_g	-0.5905	0.3487	0.0006	PAC001092_g_uc	-0.4512	0.2036	0.0123
Bifidobacterium	-0.3735	0.1395	0.0421	PAC001553_s group	-0.4201	0.1765	0.0208
PAC001116_g	-0.451	0.2034	0.0124	PAC001588_s	-0.5462	0.2983	0.0018
Roseburia	-0.6574	0.4322	<0.0001	PAC001665_s	-0.6055	0.3666	0.0004
PAC001588_g	0.03653	0.0013	0.848	PAC001902_s	-0.5269	0.2776	0.0028
Lactococcus	-0.6308	0.3979	0.0002				
PAC001090_g	-0.586	0.3434	0.0007				

Table S8. Effects of NK109 and NS on the fecal microbiota composition at the phylum level in Tg mice

Taxon Name	mean \pm SD ¹⁾			
	NC	Tg	TgN	TgS
Bacteroidetes	56.7 \pm 8.5	46.5 \pm 7.2	52.8 \pm 10.5	54.2 \pm 6.3
Firmicutes	37.9 \pm 8.3	45.0 \pm 7.4	43.4 \pm 11.3	37.0 \pm 7.2
Proteobacteria	3.8 \pm 2.0	5.1 \pm 3.7	1.7 \pm 0.4	6.8 \pm 2.6
Tenericutes	1.0 \pm 0.6	2.9 \pm 2.1	1.4 \pm 2.1	1.5 \pm 2.4
Cyanobacteria	0.3 \pm 0.1	0.4 \pm 0.7	0.4 \pm 0.6	0.2 \pm 0.4
Actinobacteria	0.2 \pm 0.2	0.1 \pm 0.0	0.2 \pm 0.1	0.2 \pm 0.2
Deferribacteres	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0
Chlamydiae	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0
Saccharibacteria_TM7	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0
Verrucomicrobia	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0

¹⁾mean \pm SD

Table S9. Effects of NK109 and NS on the fecal microbiota composition at the family level in Tg mice

Taxon Name	mean \pm SD ¹⁾			
	NC	Tg	TgN	TgS
Muribaculaceae	41.4 \pm 6.1	29.1 \pm 6.3	39.8 \pm 8.5	39.6 \pm 8.0
Lachnospiraceae	24.6 \pm 7.6	31.9 \pm 5.8	31.5 \pm 10.7	25.9 \pm 8.8
Bacteroidaceae	8.3 \pm 3.2	6.9 \pm 2.5	3.6 \pm 3.9	4.0 \pm 1.7
Ruminococcaceae	6.2 \pm 2.9	6.8 \pm 2.4	5.9 \pm 2.4	4.7 \pm 2.4

Lactobacillaceae	3.8±6.2	1.9±1.5	1.8±1.3	1.8±1.5
Christensenellaceae	2.8±1.1	4.0±2.4	3.9±1.9	4.0±1.7
Prevotellaceae	2.8±2.5	2.7±1.0	3.0±4.0	2.3±2.4
Rikenellaceae	2.5±0.9	4.5±1.6	3.5±1.9	5.6±3.7
Sutterellaceae	1.8±1.4	0.1±0.0	0.2±0.1	0.2±0.3
Desulfovibrionaceae	1.1±0.7	1.1±0.9	0.7±0.4	0.6±0.6
AC160630 f	0.7±0.2	0.7±0.6	1.0±0.4	1.4±0.8
Acholeplasmataceae	0.7±0.6	0.4±0.7	0.2±0.2	0.6±1.0
Helicobacteraceae	0.6±0.6	3.8±3.9	0.4±0.3	5.7±2.3
Porphyromonadaceae	0.6±0.4	0.4±0.2	0.0±0.0	0.2±0.3
Odoribacteraceae	0.4±0.5	2.1±1.9	2.0±2.3	1.1±0.6
PAC000197 f	0.3±0.5	0.0±0.0	0.2±0.3	0.0±0.1
FR888536 f	0.3±0.1	0.4±0.7	0.4±0.6	0.2±.4
Erysipelotrichaceae	0.2±0.2	0.2±0.1	0.1±0.1	0.3±0.5
Rhodospirillaceae	0.2±0.3	0.1±.2	0.4±0.3	0.4±0.5
Coriobacteriaceae	0.2±0.1	0.1±0.0	0.2±.1	0.1±.1
Dehalobacterium f	0.1±0.1	0.2±.1	0.1±0.1	0.1±0.1
Bifidobacteriaceae	0.1±0.1	0.0±0.0	0.1±0.1	0.1±0.2
Mogibacterium f	0.1±0.0	0.0±0.0	0.1±0.0	0.0±0.0
Mycoplasmataceae	0.0±0.0	2.3±1.8	1.0±1.9	0.8±1.9
Deferribacteraceae	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0

¹⁾mean ± SD

Table S10. Effects of NK109 and NS on the fecal microbiota composition at the species level in Tg mice

Taxon Name	AVE ± STD			
	NC	Tg	TgN	TgS
PAC001077 s	10.9±2.2	4.5±3.7	9.5±6.3	1.1±0.8
PAC002443 s	5.1±2.5	3.9±1.5	0.7±1.0	2.8±2.1
PAC001065 s group	4.7±1.5	2.6±1.6	3.2±2.2	3.2±2.7
PAC001770 s	3.3±3.0	0.0±0.0	1.8±3.8	1.5±2.9
PAC002400 s	3.3±1.0	0.7±0.8	1.1±0.6	1.6±1.1
KE159538 s	2.8±2.9	0.1±0.0	1.5±3.8	0.7±0.8
PAC001515 s	2.7±1.6	2.9±2.5	2.4±1.7	1.7±1.6
PAC001071 s	2.6±1.4	1.3±1.9	1.0±0.8	1.4±1.4
PAC001120 s	2.3±6.0	0.2±0.3	0.0±0.1	0.1±0.2
EF097112 s	2.1±1.0	0.7±0.3	1.0±0.7	1.6±1.1
Lactobacillus murinus group	2.0±2.9	1.7±1.3	1.0±0.8	1.2±1.2
PAC001066 s	1.9±0.4	1.8±2.3	1.0±0.9	1.1±0.9
PAC001060 s	1.9±0.7	1.9±1.7	1.9±2.4	2.8±2.3
Bacteroides uc	1.8±0.9	0.2±0.1	0.1±0.1	0.1±0.2
PAC000198 s	1.7±0.6	1.0±0.7	1.8±1.2	1.9±1.4
PAC001064 s	1.6±1.0	2.3±1.8	3.8±2.7	3.1±1.1
PAC001070 s group	1.6±2.0	1.6±1.1	1.0±1.5	6.0±9.2
PAC001084 s	1.4±2.5	0.2±0.4	1.8±1.9	1.2±1.7
PAC001072 s	1.4±1.4	0.7±0.6	0.5±0.6	1.7±1.5
PAC001139 s	1.3±0.9	1.3±0.8	1.2±0.9	1.9±1.6
PAC002476 s	1.3±0.8	0.0±0.0	0.0±0.0	0.0±0.0
Bacteroides acidifaciens group	1.3±0.8	2.0±2.1	1.4±0.9	1.1±0.6
PAC002481 s	1.2±1.1	2.4±1.1	1.1±0.8	1.3±1.4
PAC001456 s	1.1±0.6	0.4±0.5	0.9±0.8	0.7±1.0

PAC001079 s	1.0±0.6	0.8±0.9	0.5±0.5	0.3±0.3
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¹⁾mean ± SD

Table S11. The relationship between differentially enriched gut microbiota composition and spontaneous alteration score in YMT in Tg mice (in the network analysis)

	Spontaneous alteration score in Y-maze task	R	R ²	P-value		Spontaneous alteration score in Y-maze task	R	R ²	P-value
Phylum	Bacteroidetes	0.3181	0.1012	0.0990	species	PAC002400 s	0.6245	0.3900	0.0004
	Firmicutes	-0.2404	0.0578	0.2178		Bacteroides uc	0.5648	0.3190	0.0017
	Proteobacteria	-0.0182	0.0003	0.9270		PAC002476 s	0.5814	0.3380	0.0012
	Tenericutes	-0.2355	0.0555	0.2277		PAC002481 s	-0.3894	0.1516	0.0405
	Actinobacteria	0.3721	0.1385	0.0512		PAC001456 s	0.3819	0.1458	0.0449
	Saccharibacteria TM7	-0.4306	0.1854	0.0222		PAC001358 s	0.3864	0.1493	0.0423
Family	Muribaculaceae	0.4444	0.1975	0.0178		HQ793361 s	0.6093	0.3712	0.0006
	Lachnospiraceae	-0.2747	0.0755	0.1571		EF603776 s	0.4596	0.2112	0.0139
	Bacteroidaceae	0.0604	0.0036	0.7601		PAC002511_s group	-0.5051	0.2551	0.0061
	Ruminococcaceae	-0.0610	0.0037	0.7580		PAC001731 s	0.4060	0.1648	0.0321
	Christensenellaceae	-0.2935	0.0861	0.1296		PAC001768 s	0.4596	0.2112	0.0139
	Prevotellaceae	-0.1767	0.0312	0.3684		PAC002299 s	0.4519	0.2042	0.0158
	Sutterellaceae	0.5582	0.3116	0.0020		PAC001764 s	-0.3773	0.1424	0.0478
	PAC000197_f	0.2403	0.0577	0.2181		PAC001495_s group	-0.3951	0.1561	0.0374
	Coriobacteriaceae	0.2985	0.0891	0.1229		PAC000688 s	-0.3909	0.1528	0.0397
	Gemella f	-0.5184	0.2687	0.0047		Bacteroides dorei	0.5531	0.3059	0.0023
Genus	Saccharimonas f	-0.4306	0.1854	0.0222		PAC001154 s	-0.6334	0.4012	0.0003
	Bacteroides	0.0584	0.0034	0.7680		EU505164 s	-0.5057	0.2557	0.0060
	PAC002400 g	0.6329	0.4006	0.0003		PAC001781 s	0.3867	0.1495	0.0421
	Prevotellaceae uc	0.0106	0.0001	0.9573		Frisingicoccus uc	-0.5762	0.3320	0.0013
	Parasutterella	0.5820	0.3387	0.0012		PAC001099 s	-0.4754	0.2260	0.0106
	PAC001456 g	0.3831	0.1468	0.0442		PAC002420 s	-0.4537	0.2058	0.0153
	PAC000692_g	0.1520	0.0231	0.4400		Gemella haemolysans group	-0.5184	0.2687	0.0047
	PAC001141_g	-0.2329	0.0542	0.2330		PAC001192_s group	-0.3906	0.1526	0.0399
	PAC000661 g	-0.0234	0.0005	0.9061		PAC001653 s	-0.3821	0.1460	0.0448
	Frisingicoccus	-0.0266	0.0007	0.8931		PAC001787_s	-0.4440	0.1971	0.0179
	PAC001043 g	-0.1783	0.0318	0.3641		PAC002153 s	-0.5075	0.2576	0.0058
	PAC000197 g	0.2411	0.0581	0.2164		PAC002422 s	-0.5093	0.2594	0.0056
	PAC001199 g	-0.1825	0.0333	0.3525					
	PAC001402 g	-0.3866	0.1495	0.0421					
	PAC001266 g	0.1457	0.0212	0.4596					
	PAC001457 g	0.0304	0.0009	0.8780					
	PAC001468 g	0.4060	0.1648	0.0321					
	PAC001270 g	-0.4168	0.1737	0.0273					
	PAC000748 g	-0.4412	0.1947	0.0188					
	Gemella	-0.5184	0.2687	0.0047					
	PAC000677 g	-0.4306	0.1854	0.0222					
	PAC001637 g	-0.4639	0.2152	0.0129					
	PAC002153 g	-0.5075	0.2576	0.0058					

Table S12. The relationship between differentially enriched gut microbiota composition and exploration score in NORT in Tg mice (in the network analysis)

	Exploration score in NORT	R	R ²	P-value		Exploration score in NORT	R	R ²	P-value
Phylum	Bacteroidetes	0.2102	0.0442	0.2831	species	PAC002400_s	0.6382	0.4073	0.0003
	Firmicutes	-0.1214	0.0147	0.5384		Bacteroides_uc	0.6273	0.3935	0.0004
	Proteobacteria	0.0054	0.0000	0.9783		PAC002476_s	0.6972	0.4861	<0.0001
	Tenericutes	-0.3845	0.1478	0.0433		PAC002481_s	-0.4039	0.1631	0.0331
	Actinobacteria	0.3078	0.0947	0.1111		PAC001456_s	0.4433	0.1965	0.0181
	Saccharibacteria_TM7	-0.4154	0.1726	0.0279		PAC001358_s	0.3771	0.1422	0.0479
Family	Muribaculaceae	0.2523	0.0637	0.1953		HQ793361_s	0.6164	0.3799	0.0005
	Lachnospiraceae	-0.1743	0.0304	0.3750		EF603776_s	0.5650	0.3192	0.0017
	Bacteroidaceae	0.1836	0.0337	0.3497		PAC002511_s_group	-0.5083	0.2584	0.0058
	Ruminococcaceae	0.0451	0.0020	0.8199		PAC001731_s	0.5875	0.3452	0.0010
	Christensenellaceae	-0.2286	0.0523	0.2419		PAC001768_s	0.4882	0.2383	0.0084
	Prevotellaceae	-0.1688	0.0285	0.3906		PAC002299_s	0.5429	0.2947	0.0028
	Sutterellaceae	0.6109	0.3732	0.0006		PAC001764_s	-0.5019	0.2519	0.0065
	PAC000197_f	0.3192	0.1019	0.0978		PAC001495_s_group	-0.4497	0.2022	0.0164
	Coriobacteriaceae	0.3231	0.1044	0.0935		PAC000688_s	-0.4541	0.2062	0.0152
	Gemella_f	-0.4055	0.1644	0.0323		Bacteroides_dorei	0.5664	0.3208	0.0017
	Saccharimonas_f	-0.4154	0.1726	0.0279		PAC001154_s	-0.4262	0.1816	0.0237
						EU505164_s	-0.4099	0.1680	0.0303
Genus	Bacteroides	0.1844	0.0340	0.3476		PAC001781_s	0.6781	0.4598	<0.0001
	PAC002400_g	0.6348	0.4030	0.0003		Frisingicoccus_uc	-0.5330	0.2841	0.0035
	Prevotellaceae_uc	0.0283	0.0008	0.8864		PAC001099_s	-0.4086	0.1670	0.0309
	Parasutterella	0.6831	0.4666	<0.0001		PAC002420_s	-0.4114	0.1692	0.0296
	PAC001456_g	0.4389	0.1926	0.0194		Gemella_haemolysans_group	-0.4055	0.1644	0.0323
	PAC000692_g	0.1672	0.0280	0.3952		PAC001192_s_group	-0.4133	0.1708	0.0288
	PAC001141_g	-0.1723	0.0297	0.3805		PAC001653_s	-0.4578	0.2096	0.0143
	PAC000661_g	-0.1553	0.0241	0.4299		PAC001787_s	-0.3904	0.1524	0.0400
	Frisingicoccus	-0.0678	0.0046	0.7316		PAC002153_s	-0.4814	0.2317	0.0095
	PAC001043_g	-0.3756	0.1411	0.0489		PAC002422_s	-0.3816	0.1456	0.0451
	PAC000197_g	0.3158	0.0997	0.1016					
	PAC001199_g	-0.2385	0.0569	0.2216					
	PAC001402_g	-0.3639	0.1324	0.0570					
	PAC001266_g	0.1598	0.0255	0.4167					
	PAC001457_g	0.1120	0.0125	0.5704					

	PAC001468 g	0.5875	0.3452	0.0010
	PAC001270 g	-0.4642	0.2155	0.0128
	PAC000748 g	-0.4298	0.1847	0.0224
	Gemella	-0.4055	0.1644	0.0323
	PAC000677 g	-0.4154	0.1726	0.0279
	PAC001637 g	-0.4554	0.2074	0.0149
	PAC002153 g	-0.4814	0.2317	0.0095

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