

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) 66 (M)	74 77	23.6 22.7	No 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) 62 (F)	63 63	27.3 28.5	No 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	AGCGAGCTGCCTAGATGAATTTG	TCT TTT AAA CTC TAG ACA TGC GTC
16S rRNA gene	TCGTCGGCAGCGTCAGATGTGTATAAG AGACAGGTGCCAGCMGCCGCGTAA	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 1.1	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
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		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	species	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
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	0.0v0.1	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	
Saccharimonas f	-0.4306	0.1854	0.0222	PAC001154 s	-0.6334	0.4012	0.0003		
Genus	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
	Genus	Bacteroides	0.1844	0.0340		0.3476	EU505164_s	-	0.4099	0.1680
PAC002400_g		0.6348	0.4030	0.0003		PAC001781_s	0.6781	0.4598	<0.0001	
Prevotellaceae_uc		0.0283	0.0008	0.8864		Frisingicoccus_uc	-	0.5330	0.2841	0.0035
Parasutterella		0.6831	0.4666	<0.0001	PAC001099_s	-	0.4086	0.1670	0.0309	
PAC001456_g		0.4389	0.1926	0.0194	PAC002420_s	-	0.4114	0.1692	0.0296	
PAC000692_g		0.1672	0.0280	0.3952	Gemella_haemolysans_group	-	0.4055	0.1644	0.0323	
PAC001141_g		-0.1723	0.0297	0.3805	PAC001192_s_group	-	0.4133	0.1708	0.0288	
PAC000661_g		-0.1553	0.0241	0.4299	PAC001653_s	-	0.4578	0.2096	0.0143	
Frisingicoccus		-0.0678	0.0046	0.7316	PAC001787_s	-	0.3904	0.1524	0.0400	
PAC001043_g		-0.3756	0.1411	0.0489	PAC002153_s	-	0.4814	0.2317	0.0095	
PAC000197_g		0.3158	0.0997	0.1016	PAC002422_s	-	0.3816	0.1456	0.0451	
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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