

Supplementary Table 1: Genomes that were sequenced and used in this study.

Mouse-derived 20 strains

Strain ID	Total assembly length (bp)	Number of contigs	Top hit species or strain in NCBI database	Similarity (%)
18E8	3,244,486	2	<i>Muribaculum gordoncarteri</i>	89.9
19E12	2,674,659	1	<i>Akkermansia muciniphila</i>	99.7
1A11	2,456,117	2	<i>Ligilactobacillus murinus</i>	99.9
1A1	2,384,728	2	<i>Bifidobacterium pseudolongum</i>	99.5
1A3	2,873,390	3	<i>Parasutterella excrementihominis</i>	96.4
1A6	1,938,521	1	<i>Lactobacillus gasseri</i>	99.6
1B6	2,383,513	1	<i>Parvibacter caecicola</i>	99.9
1C4	2,674,875	2	<i>Faecalibaculum rodentium</i>	99.9
1H8	2,876,382	1	<i>Adlercreutzia hattorii</i>	95.6
21A7	5,673,957	2	<i>Sporofaciens muscoli</i>	97.1
21B5	2,971,061	1	<i>Paramuribaculum intestinale</i>	99.6
27G3	4,018,501	6	<i>Blautia pseudococcoides</i>	93.1
4A1	5,230,926	1	<i>Klebsiella pneumoniae</i>	99.7
4B7	2,712,920	1	<i>Corynebacterium casei</i>	98.7
4D1	2,271,672	1	<i>Jeotgalicoccus halotolerans</i>	99.2
4D3	3,344,465	1	<i>Glutamicibacter arilaitensis</i>	97.1
4H5	2,726,222	1	<i>Mammaliicoccus stepanovicii</i>	99.0
4H6	3,017,345	1	<i>Trichococcus pasteurii</i>	95.4
80E1	2,368,189	1	<i>Turicibacter sanguinis</i>	97.5
8H4	2,166,690	1	<i>Taurinivorans muris</i>	100.0

Human (T19)-derived 33 strains

Strain ID	Total assembly length (bp)	Number of contigs	Top hit species or strain in NCBI database	Similarity (%)
T19_1	2,974,661	1	<i>Thomasclavelia spiroformis</i>	99.4
T19_2	5,024,545	9	<i>Clostridium transplantifaeale</i>	98.1
T19_3	3,163,535	1	<i>Adlercreutzia equolifaciens subsp.celatus</i>	100.0
T19_4	2,163,167	1	<i>Anaerofustis stercorihominis</i>	97.5
T19_5	3,427,503	2	<i>Anaerostipes caccae</i>	99.8
T19_6	3,802,024	2	<i>Anaerotruncus colihominis</i>	99.4
T19_7	5,139,677	2	<i>Bacteroides fragilis</i>	99.9
T19_8	7,296,942	3	<i>Bacteroides ovatus</i>	99.8
T19_9	5,349,103	3	<i>Bacteroides uniformis</i>	99.9
T19_10	5,266,042	3	<i>Phocaeicola dorei</i>	99.8
T19_11	4,729,031	8	<i>Bacteroides stercoris</i>	99.7
T19_12	3,337,322	17	<i>Bacteroides thetaiotaomicron</i>	97.9
T19_13	5,612,250	6	<i>Phocaeicola vulgatus</i>	100.0
T19_14	4,292,219	2	<i>Bilophila</i> sp. 4_1_30	99.2
T19_15	3,395,750	4	<i>Agathobaculum desmolans</i>	96.8
T19_16	4,884,259	19	<i>Clostridium phoceensis</i>	95.3
T19_18	4,756,915	2	<i>[Clostridium] innocuum</i>	98.7
T19_19	4,142,374	5	<i>Coprobacillus cateniformis</i>	99.2
T19_20	6,521,274	1	<i>Eisenbergiella massiliensis</i>	99.6
T19_21	3,183,812	2	<i>Enterococcus hirae</i>	99.5
T19_22	3,066,490	2	<i>Enterococcus gallinarum</i>	99.8
T19_23	3,762,316	2	<i>Thomasclavelia ramosa</i>	99.4
T19_24	3,795,284	1	<i>Extibacter muris</i>	100.0
T19_25	4,970,176	2	<i>Flavonifractor plautii</i>	100.0
T19_26	3,848,062	2	<i>Fournierella massiliensis</i>	98.8
T19_27	7,860,147	2	<i>Hungatella hathewayi</i>	98.7
T19_28	6,234,800	1	<i>Hungatella hathewayi</i>	99.4
T19_29	2,497,425	2	<i>Parasutterella excrementihominis</i>	99.3
T19_30	3,783,283	2	<i>Coprococcus phoceensis</i>	98.3
T19_31	3,066,495	4	<i>Romboutsia timonensis</i>	99.8
T19_32	4,162,312	2	<i>Ruthenibacterium lactatiformans</i>	99.9
T19_34	6,248,809	2	<i>Bacteroides xylanisolvens</i>	99.5
T19_35	6,350,693	1	<i>Blautia coccoides</i>	99.9

Supplementary Table 2: A search across all representative microbial genomes found in the human gut for the NrfA signal peptide.

The percentages of taxa possessing the indicated signal sequence are shown.

	Actinobacteriota	Bacteroidota	Bdellovibrionota	Campylobacterota	Cyanobacteria	Desulfobacterota	Elusimicrobiota	Eremiobacterota	Fibrobacterota
LSP ★	3.571428571	0	0	0	0	82.14285714	0	0	0
OTHER	3.921568627	72.54901961	0	13.07189542	0	3.267973856	0	0	0
SP	0	2.352941176	0	2.352941176	0	0	0	0	0

	Firmicutes	Firmicutes_A	Firmicutes_B	Firmicutes_C	Firmicutes_G	Fusobacteriota	Myxococcota	Patescibacteria	Proteobacteria	Spirochaetota	Synergistota	Verrucomicrobiota
LSP	7.142857143	0	3.571428571	0	0	0	0	0	3.571428571	0	0	0
OTHER	0	0	0	5.882352941	0	0	0	0	1.307189542	0	0	0
SP	0	1.176470588	0	3.529411765	0	0	0	0	90.58823529	0	0	0

SP: Sec/SPI (the “standard” secretory signal peptide putatively transported by the Sec translocon and cleaved by Signal Peptidase I)

LSP: Sec/SPII (lipoprotein signal peptide known to be transported by the Sec translocon and cleaved by Signal Peptidase II)

★; Exact species which were predicted to carry NrfA with LSP signal peptide are
Adlercreutzia equolifaciens (in Phylum Actinobacteriota),
Bilophila wadsworthia, *Bilophila* sp902373525, *Desulfovibrio piger*, *Desulfovibrio legallii*, *Desulfovibrio fairfieldensis*, *Mailhella* sp900555975 (in Desulfobacterota),
Neobacillus jeddahensis and *Neobacillus* sp000821085 (Firmucutes), *Desulfitobacterium hafniense* (Firmcutes_B) and *Plesiomonas shigelloides* (Proteobacteria).

Supplementary Table 3: A breakdown of the ingredients and caloric content in the diets used in the left panel of Figure 1a.

Diet	Control		Low protein & High carbo.		Low protein		High protein	
	gram%	kcal%	gram%	kcal%	gram%	kcal%	gram%	kcal%
Protein	20	20	7	7.5	7	7	42	41
Carbohydrate	64	64	80.7	85.3	77	77	41	42
Fat	7	16	2.3	7.2	7	16	7	17
Total		100		100		100		100
kcal/gram	4.0		3.8		4.0		4.0	
Ingredient	gram	kcal	gram	kcal	gram	kcal	gram	kcal
Casein	200	800	71	284	71	284	420	1680
L-Cystine	3	12	1.07	4	1.07	4	6	24
Corn Starch	397.486	1590	573.2	2293	528.5	2114	177.5	710
Maltodextrin 10	132	528	132	528	132	528	132	528
Sucrose	100	400	100	400	100	400	100	400
Cellulose, BW200	50	0	50	0	50	0	50	0
Soybean Oil	70	630	23.3	210	70	630	70	630
t-Butylhydroquinone	0.014	0	0.014		0.014	0	0.014	0
Mineral Mix S10022G	35	0	35	0	35	0	35	0
Vitamin Mix V10037	10	40	10	40	10	40	10	40
Choline Bitartrate	2.5	0	2.5	0	2.5	0	2.5	0
Total	1000	4000	998.07	3786.724	1000.084	4000	1003	4040

Diet	Low fat		High fat		Low carbo	
	gram%	kcal%	gram%	kcal%	gram%	kcal%
Protein	20	20	20	14	42	45
Carbohydrate	68	72	34	25	23	28
Fat	2	8	20	61	10	27
Total		100		100		100
kcal/gram	3.8		5.5		3.6	
Ingredient	gram	kcal	gram	kcal	gram	kcal
Casein	200	800	200	800	420	1680
L-Cystine	3	12	3	12	6	24
Corn Starch	444.2	1776.7	108	432	0	0
Maltodextrin 10	132	528	132	528	132	528
Sucrose	100	400	100	400	100	400
Cellulose, BW200	50	0	50	0	200	0
Soybean Oil	23.3	109.7	200	1800	100	900
t-Butylhydroquinone	0.014	0	0.014	0	0.014	0
Mineral Mix S10022G	35	0	35	0	35	0
Vitamin Mix V10037	10	40	10	40	10	40
Choline Bitartrate	2.5	0	2.5	0	2.5	0
Total	1000	3794.44	1004.514	5496	1005.514	3600

Supplementary Table 4: A breakdown of the ingredients and caloric content in the diets used in the right panel of Figure1a.

Diet	Control		Low protein		Low Protein & High fat		Very low fat	
	gram%	kcal%	gram%	kcal%	gram%	kcal%	gram%	kcal%
Protein	20	20	7	7	8	7	19	20
Carbohydrate	64	64	77	77	64	64	72	77
Fat	7	16	7	16	14	29	1	3
Total		100		100		100		100
kcal/gram	4.0		4.0		4.3		3.7	
Ingredient	gram	kcal	gram	kcal	gram	kcal	gram	kcal
Casein	200	800	71	284	71	284	200	800
L-Cystine	3	12	1.07	4	1.07	4	3	12
Corn Starch	397.486	1590	528.5	2114	397.486	1590	525.75	2103
Maltodextrin 10	132	528	132	528	132	528	132	528
Sucrose	100	400	100	400	100	400	100	400
Cellulose, BW200	50	0	50	0	50	0	50	0
Soybean Oil	70	630	70	630	128.2	1154	13	117
t-Butylhydroquinone	0.014	0	0.014	0	0.014	0	0.014	0
Mineral Mix S10022G	35	0	35	0	35	0	35	0
Vitamin Mix V10037	10	40	10	40	10	40	10	40
Choline Bitartrate	2.5	0	2.5	0	2.5	0	2.5	0
Total	1000	4000	1000.084	4000	927.270	4000	1071.264	4000

Diet	Low fat		Ketogenic	
	gram%	kcal%	gram%	kcal%
Protein	19	20	31	20
Carbohydrate	67	70	0	0
Fat	4	10	55	80
Total		100		100
kcal/gram	3.8		6.1	
Ingredient	gram	kcal	gram	kcal
Casein	200	800	200	800
L-Cystine	3	12	3	12
Corn Starch	560.75	2243	0	0
Maltodextrin 10	150	600	0	0
Sucrose	0	0	0	0
Cellulose, BW200	50	0	50	0
Soybean Oil	25	225	25	225
Cocoa Butter	20	180	335.89	3023
Mineral Mix, S10026	10	0	10	0
Dicalcium Phosphate	13	0	13	0
Calcium Carbonate	5.5	0	5.5	0
Potassium Citrate, 1 H2	16.5	0	16.5	0
Vitamin Mix, V10001C, 10x Vitamins	1	4	1	4
Choline Bitartrate	2	0	2	0
Total	1056.75	4064	661.89	4064

Supplementary Table 5: A breakdown of the ingredients in the diets used in Figure 1c, 1d, Extended Data Figure 2a, 2b, and 6b.

Diets containing varying levels of proteins used in Figure1c.

	40% (High protein diet)	20% Protein	15% Protein	10% Protein	7% Protein	5% Protein	2.5% Protein
Ingredients	Grams	Grams	Grams	Grams	Grams	Grams	Grams
Casein	420	200	150	100	71	50	25
L-Cystine	6	3	2.25	1.5	1.07	0.75	0.375
Corn Starch	177.5	397.5	448.2	498.8	526.5	549.9	575.0
Maltodextrin 10	132	132	132	132	132	132	132
Sucrose	100	100	100	100	100	100	100
Soybean Oil	70	70	70	70	70	70	70
Cellulose	50	50	50	50	50	50	50
Choline Bitartrate	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Vitamin Mix V10037	10	10	10	10	10	10	10
Mineral Mix for AIN93G	35	35	35	35	35	35	35
t-Butylhydroquinone	0.014	0.014	0.014	0.014	0.014	0.014	0.014
Total	1003	1000	1000	1000	998.07	1000	1000
Kcal/g	4	4	4	4	4	4	4

Diets containing varying levels of defined amino acids used in Figure1d, Extended Data Figure2a, 2b and 6b.

	20% AAs	15% AAs	10% As	7% AAs	5% AAs	2.5% AAs	2.5% NEAA	2.5% EAA	low Ile	low Leu	low Val	low Phe	low Trp	low His	low Lys	low Met	low Thr
Ingredients	Grams	Grams	Grams	Grams	Grams	Grams	Grams	Grams	Grams	Grams	Grams	Grams	Grams	Grams	Grams	Grams	Grams
L-Histidine-HCl-H2O	5.03	3.7725	2.515	1.7605	1.2575	0.63	5.03	0.63	5.03	5.03	5.03	5.03	5.03	0.63	5.03	5.03	5.03
L-Isoleucine	9.14	6.855	4.57	3.199	2.285	1.14	9.14	1.14	1.14	9.14	9.14	9.14	9.14	9.14	9.14	9.14	9.14
L-Leucine	16.03	12.0225	8.015	5.6105	4.0075	2	16.03	2	16.03	2	16.03	16.03	16.03	16.03	16.03	16.03	16.03
L-Lysine-HCl	16.97	12.7275	8.485	5.9395	4.2425	2.12	16.97	2.12	16.97	16.97	16.97	16.97	16.97	16.97	2.12	16.97	16.97
L-Methionine	5.03	3.7725	2.515	1.7605	1.2575	0.63	5.03	0.63	5.03	5.03	5.03	5.03	5.03	5.03	5.03	0.63	5.03
L-Phenylalanine	8.76	6.57	4.38	3.066	2.19	1.1	8.76	1.1	8.76	8.76	8.76	1.1	8.76	8.76	8.76	8.76	8.76
L-Threonine	7.08	5.31	3.54	2.478	1.77	0.89	7.08	0.89	7.08	7.08	7.08	7.08	7.08	7.08	7.08	7.08	0.89
L-Tryptophan	2.05	1.5375	1.025	0.7175	0.5125	0.26	2.05	0.26	2.05	2.05	2.05	2.05	0.26	2.05	2.05	2.05	2.05
L-Valine	11.56	8.67	5.78	4.046	2.89	1.44	11.56	1.44	11.56	11.56	1.44	11.56	11.56	11.56	11.56	11.56	11.56
L-Arginine	6.34	4.755	3.17	2.219	1.585	0.79	0.79	6.34	6.34	6.34	6.34	6.34	6.34	6.34	6.34	6.34	6.34
L-Alanine	5.03	3.7725	2.515	1.7605	1.2575	0.63	0.63	5.03	5.03	5.03	5.03	5.03	5.03	5.03	5.03	5.03	5.03
L-Asparagine-H2O	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
L-Aspartate	11.93	8.9475	5.965	4.1755	2.9825	1.49	1.49	11.93	11.93	11.93	11.93	11.93	11.93	11.93	11.93	11.93	11.93
L-Cystine	3.73	2.7975	1.865	1.3055	0.9325	0.47	0.47	3.73	3.73	3.73	3.73	3.73	3.73	3.73	3.73	3.73	3.73
L-Glutamic Acid	36.17	27.1275	18.085	12.6595	9.0425	4.52	4.52	36.17	36.17	36.17	36.17	36.17	36.17	36.17	36.17	36.17	36.17
L-Glutamine	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Glycine	3.17	2.3775	1.585	1.1095	0.7925	0.4	0.4	3.17	3.17	3.17	3.17	3.17	3.17	3.17	3.17	3.17	3.17
L-Proline	19.76	14.82	9.88	6.916	4.94	2.47	2.47	19.76	19.76	19.76	19.76	19.76	19.76	19.76	19.76	19.76	19.76
L-Serine	8.95	6.7125	4.475	3.1325	2.2375	1.12	1.12	8.95	8.95	8.95	8.95	8.95	8.95	8.95	8.95	8.95	8.95
L-Tyrosine	9.51	7.1325	4.755	3.3285	2.375	1.19	1.19	9.51	9.51	9.51	9.51	9.51	9.51	9.51	9.51	9.51	9.51
Total L-Amino Acids	186.24	139.68	93.12	65.184	46.56	23.29	94.73	114.8	178.24	172.21	176.12	178.58	184.45	181.84	171.39	181.84	180.05
Com Starch	404.901	451.461	498.021	525.957	544.581	567.851	496.411	476.341	412.901	418.931	415.021	412.561	406.691	409.301	419.751	409.301	411.091
Maltodextrin 10	132	132	132	132	132	132	132	132	132	132	132	132	132	132	132	132	132
Sucrose	107.0777	107.0777	107.0777	107.0777	107.0777	107.0777	107.0777	107.0777	107.0777	107.0777	107.0777	107.0777	107.0777	107.0777	107.0777	107.0777	107.0777
Cellulose	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50
Soybean Oil	70	70	70	70	70	70	70	70	70	70	70	70	70	70	70	70	70
t-Butylhydroquinone	0.014	0.014	0.014	0.014	0.014	0.014	0.014	0.014	0.014	0.014	0.014	0.014	0.014	0.014	0.014	0.014	0.014
Mineral Mix S10022C	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Calcium Carbonate	7.34	7.34	7.34	7.34	7.34	7.34	7.34	7.34	7.34	7.34	7.34	7.34	7.34	7.34	7.34	7.34	7.34
Potassium Citrate, 1 H2O	2.4773	2.4773	2.4773	2.4773	2.4773	2.4773	2.4773	2.4773	2.4773	2.4773	2.4773	2.4773	2.4773	2.4773	2.4773	2.4773	2.4773
Potassium Phosphate, Monobasic	6.86	6.86	6.86	6.86	6.86	6.86	6.86	6.86	6.86	6.86	6.86	6.86	6.86	6.86	6.86	6.86	6.86
Calcium Phosphate, dibasic	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Sodium Chloride	2.59	2.59	2.59	2.59	2.59	2.59	2.59	2.59	2.59	2.59	2.59	2.59	2.59	2.59	2.59	2.59	2.59
Sodium Bicarbonate	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Vitamin Mix V10037	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Choline Bitrarrate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000
Kcal/g	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4

Supplementary Table 6: The primer sets used for *Bilophila* sp. 4_1_30 (St.14) mutagenesis.

	Primer name	Sequence(5' - 3')
For Δupp mutant	upp_upstream_Fw	TACCGGGCCCCCCTCGAGGCCGGGAT CTTTGAGGAAATCCTTCCCCGCCACCG
	upp_upstream_Rv	TTTTATTCTGCGGCAGGCGGCGGGGCGC
	upp_downstream_Fw	CCGCCTGCCGCAGAATAAAAGGATTCCCGAAACGC
	upp_downstream_Rv	AGTGGATCCCCCGGGCTGCACGTCATGAAGGCCTGGCAG
	upp_check#1_Fw	TGCCGTGCGCCGAGCATGGTG
	upp_check#2_Rv	ATGGTGCTGCCGATGTAACG
For $\Delta nrfA$ mutant	pBluescriptbackbone_Fw	GAACCCCTTTCCCCGGGCTGCAGGAATT
	pBluescriptbackbone_Rv	AAACGAACCGAGCTCCAGCTTTTGTTCCTTTAG
	nrfA_upstream_Fw	AGCTGGAGCTCGGTTTCGTTTGTCTTTAC
	nrfA_upstream_Rv	CGGGGCGTAAGCGTATGATGAAGGGGGAAG
	cat_catprom_PaphII_upp_Fw	CATCATACGCTTACGCCCCGCCCTGCCA
	cat_catprom_PaphII_upp_Rv	ATGGTGCGCGCTACCGCGTGCCGAAAATGCG
	nrfA_downstream_Fw	CACGCGGTAGCGGCCACCATCCTTGTGC
	nrfA_downstream_Rv	CAGCCCGGGGAAAGGGGTTCGGCGGAGATG
	nrfA_check#3_Fw	GCAGATGGTTGGTTCCCTCG
	nrfA_check#4(cat)_Rv	AGTACTGCGATGAGTGGCAG
	nrfA_check#5(cat)_Fw	GAAAGTTGGAACCTCTTACG
	nrfA_check#6_Rv	ATGCCGATGATCCCGAATGC
	nrfA_check#7_Fw	CTACTGGATCTTCTTGTTGC
	nrfA_check#8_Rv	GAATAGCCGTGTATTCTGCA