Supplementary figure legends

Figure S1 Effects of early-life microbiota disruption on skeletal development.

(A) Experimental design: SPF C57BL/6 breeders received vancomycin or autoclaved water; pups were weaned at 3 weeks and maintained on vancomycin (Vanc) or autoclaved water (Ctrl) until 4 weeks of age. (B-J) Bone parameters including femur length (B), cortical area (Ct. Ar) (C), cortical thickness (Ct. Th) (D), trabecular bone volume fraction (BV/TV) (E), trabecular number (Tb. N) (F), trabecular thickness (Tb. Th) (G), and trabecular spacing (Tb. Sp) (H) are shown. Data are presented as mean ± SEM. Statistical significance was determined by unpaired *t* test or Mann–Whitney *U* test, as appropriate. ns, not statistically significant, **, $p<0.01$

Figure S2 Trabecular bone phenotypes in 4-week-old WT and CF mice under SPF and GF conditions.

Trabecular number (Tb. N), trabecular thickness (Tb. Th), trabecular spacing (Tb. Sp), cortical area (Ct. Ar), representative 3D reconstruction of femur cortical and trabecular bone, serum IGFBP3, serum P1NP, serum CTX-1, growth plate resting zone (RZ), proliferative zone (PZ), hypertrophic zone (HZ) are shown for SPF mice (A-K) and GF mice (L-V) at 4 weeks of age. Two WT GF CTX-1 measurements were missing due to insufficient serum collected. Data are represented as mean ± SEM. Statistical significance was determined by unpaired *t* test or Mann–Whitney *U* test, as appropriate. ns, not statistically significant.

Figure S3 Effects of dietary SCFA supplementation on growth and skeletal phenotypes in WT and CF mice.

(A) Experimental design: 4-week-old WT and CF mice were treated with dietary SCFA supplementation for 4 weeks under SPF conditions. Effect of SCFA on body length (B) and bone parameters including femur length (C), cortical area (Ct. Ar) (D), cortical thickness (Ct. Th) (E), trabecular bone volume fraction (BV/TV) (F), trabecular number (Tb. N) (G), trabecular thickness (Tb. Th) (H), trabecular spacing (Tb. Sp) (I) is shown. Effect of SCFA on serum measurements of P1NP (J), CTX1 (K) and IGF-1 (L) is shown. Data are represented as mean ± SEM. Statistical significance was determined by Two-way ANOVA with Benjamini and Hochberg post hoc or Mann–Whitney *U* test, as appropriate. ns, not statistically significant, *, $p<0.05$, ***, $p<0.001$

Figure S4 Body weight growth and growth rates in WT and CF mice under SPF and GF conditions.

(A) Body weight growth curves of WT and CF from 1-week-old to 14-week-old under SPF and GF are shown. (B) Body weight growth curves from 1 to 4 weeks, from 4 to 8 weeks, and from 8 to 14 weeks of age were calculated by linear regression. Differences in difference (DID) analysis was performed using a linear mixed-effects model. Data are presented as mean (95%CI). ns, not statistically significant.

Figure S5 Trabecular bone parameters in WT and CF mice at 14 weeks of age under SPF and GF conditions.

Trabecular number (Tb. N), trabecular thickness (Tb. Th), trabecular spacing (Tb. Sp), trabecular tissue mineral density (Tb. TMD), cortical area (Ct. Ar), representative 3D reconstruction of femur cortical and trabecular bone, serum P1NP, and serum CTX-1 are shown for SPF mice (A-G) and GF mice (H-N) at 14 weeks of age. Data are represented

as mean ± SEM. Statistical significance was determined by unpaired *t* test or Mann–Whitney *U* test, as appropriate. ns, not statistically significant, *, $p<0.05$, **, $p<0.01$.

Figure S6 Cecal microbiome of WT and CF mice at 4-week-old and 14-week-old

(A) Filtered read depth of post adapter trimming and the host the mouse genome (GRCm39) decontamination. (B) Rarefaction curve. The red dotted line indicates the sequencing depth used for rarefaction. (C) NMDS plots (NMDS1 vs. NMDS2 and NMDS1 vs. NMDS3 projections) depict β-diversity based on unweighted UniFrac distance. (D-E) Bar plots depict relative abundance of taxa at phylum (D) and species level (E).

Figure S7 Increased microbial nucleoside and nucleotide biosynthesis and amino acid biosynthesis in CF mice.

(A, B) Forest plots showing pathways significantly differentially abundant between WT and CF mice in nucleoside and nucleotide biosynthesis (A) and amino acid biosynthesis (B). The x-axis indicates mean differences in CPM, with 95% CI. Negative values indicate enrichment in the WT group, whereas positive values indicate enrichment in the CF group.

Fig. S1

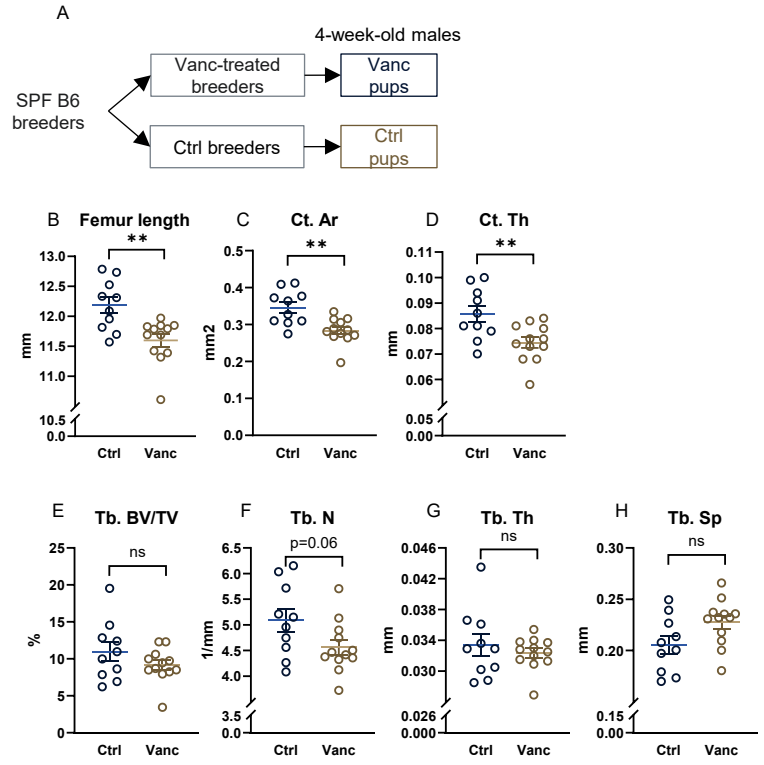

A
4-week-old males
SPF B6 breeders
Vanc-treated breeders
Vanc pups
Ctrl breeders
Ctrl pups
B
Femur length
mm
C
Ct. Ar
mm2
D
Ct. Th
mm
**
Ctrl
Vanc
E
Tb. BV/TV
%
F
Tb. N
1/mm
p=0.06
G
Tb. Th
mm
H
Tb. Sp
mm
ns

Fig. S2

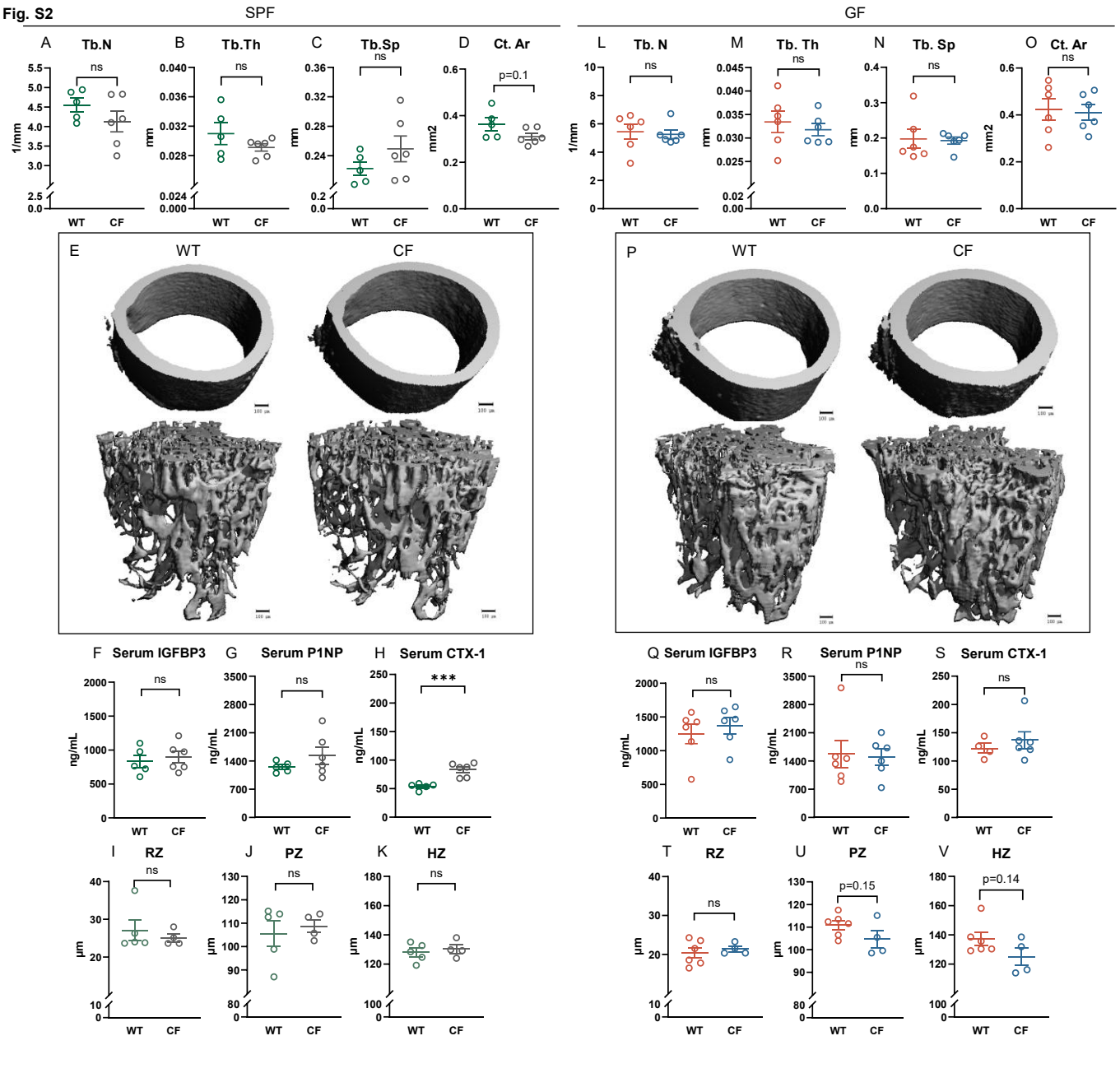

SPF
GF
A Tb.N
B Tb.Th
C Tb.Sp
D Ct. Ar
L Tb. N
M Tb. Th
N Tb. Sp
O Ct. Ar
1/mm
mm
mm2
ns
p=0.1
WT
CF
E
P
F Serum IGFBP3
G Serum P1NP
H Serum CTX-1
Q Serum IGFBP3
R Serum P1NP
S Serum CTX-1
ng/mL
***
I RZ
J PZ
K HZ
T RZ
U PZ
V HZ
µm
p=0.15
p=0.14

Fig. S3

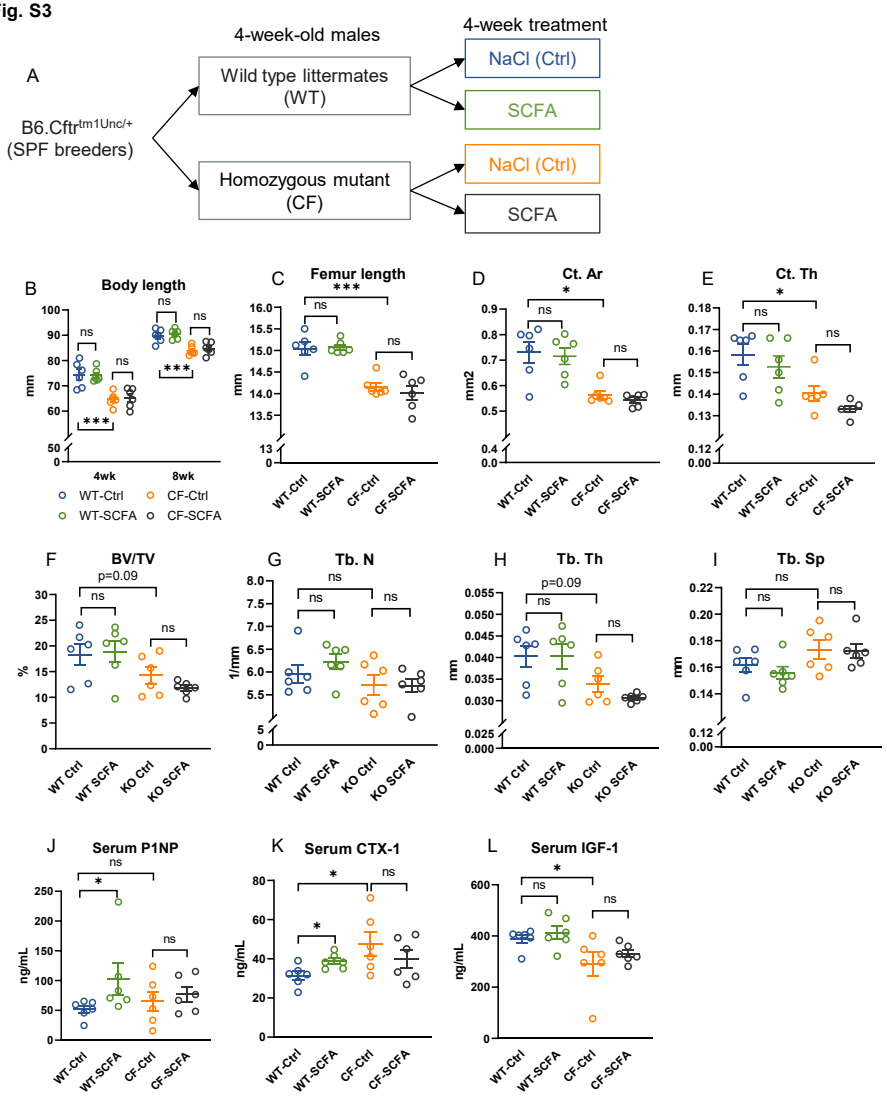
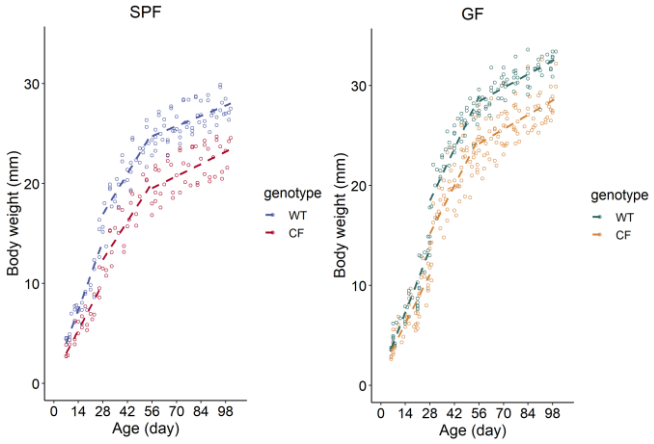

A
B6.Cftr tm1Unc/+
(SPF breeders)
4-week-old males
Wild type littermates
(WT)
Homozygous mutant
(CF)
4-week treatment
NaCl (Ctrl)
SCFA
NaCl (Ctrl)
SCFA
B
Body length
mm
4wk
8wk
WT-Ctrl
WT-SCFA
CF-Ctrl
CF-SCFA
C
Femur length
mm
D
Ct. Ar
mm2
E
Ct. Th
mm
F
BV/TV
%
G
Tb. N
1/mm
H
Tb. Th
mm
I
Tb. Sp
mm
J
Serum P1NP
ng/mL
K
Serum CTX-1
ng/mL
L
Serum IGF-1
ng/mL
WT Ctrl
WT SCFA
KO Ctrl
KO SCFA
ns
p=0.09

Fig. S4

A



B

Body weight growth slope and 95%CI during different growth stages

	SPF		GF		DID significance
	WT	CF	WT	CF	
1-4wk	0.49 (0.41, 0.57)	0.34 (0.27, 0.4)###	0.45 (0.39, 0.51)	0.35 (0.29, 0.41)##	ns
4-8wk	0.29 (0.22, 0.36)	0.27 (0.18, 0.36)	0.37 (0.31, 0.43)	0.34 (0.28, 0.4)	ns
8-14wk	0.07 (0.05, 0.1)	0.09 (0.05, 0.12)	0.1 (0.07, 0.12)	0.1 (0.07, 0.13)	ns

Fig. S5

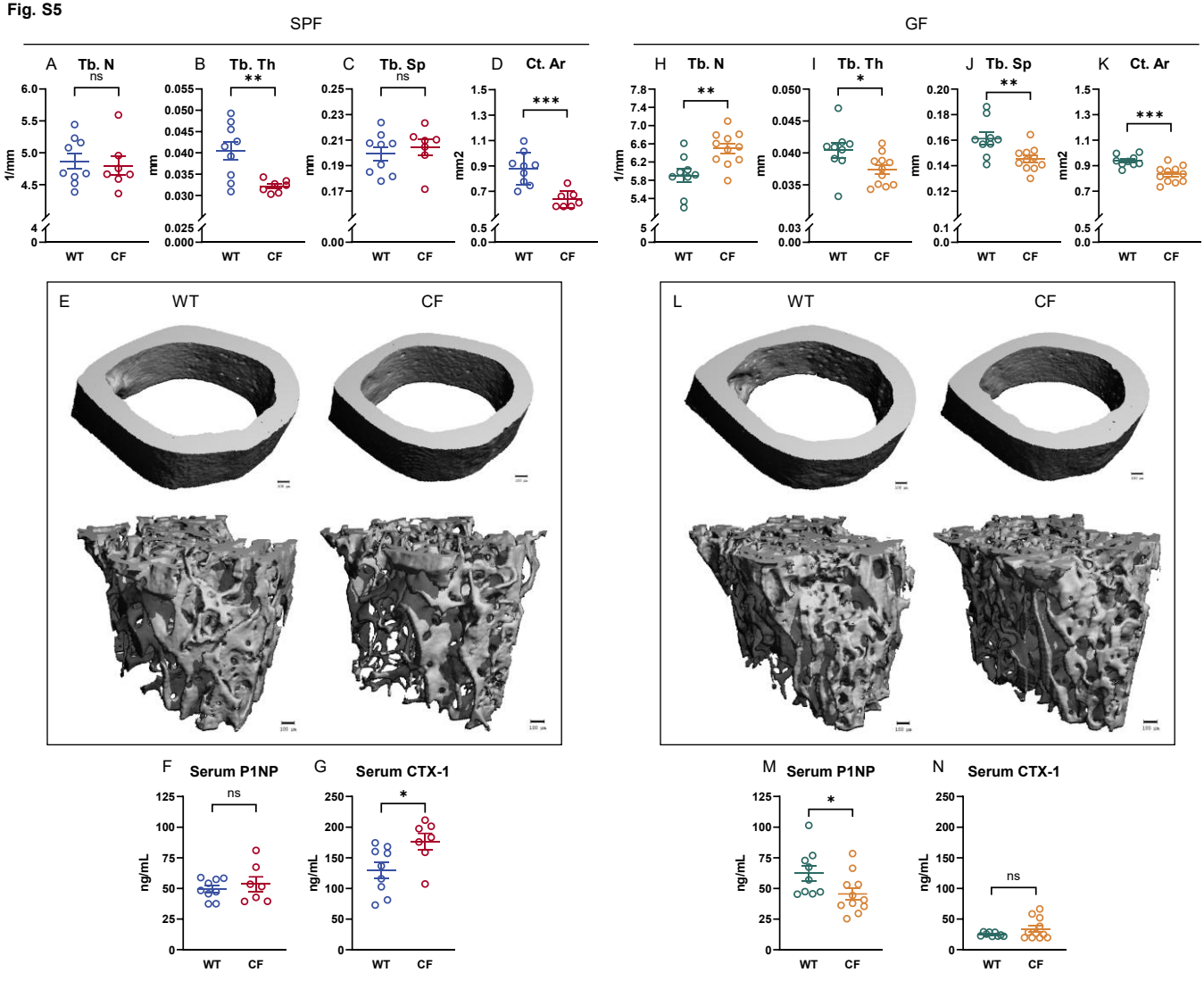
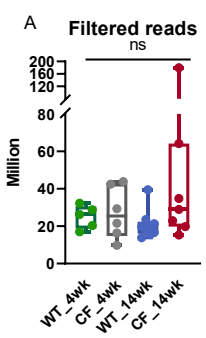
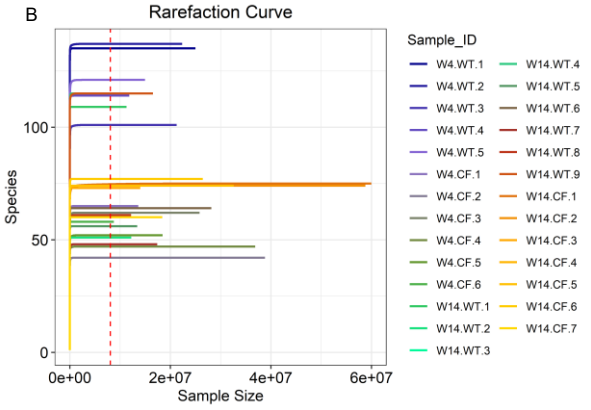
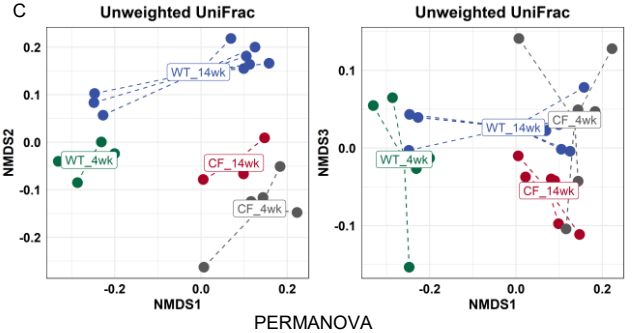

SPF
GF
A Tb. N
B Tb. Th
C Tb. Sp
D Ct. Ar
H Tb. N
I Tb. Th
J Tb. Sp
K Ct. Ar
1/mm
mm
mm2
ns
**
***
*
WT
CF
E
L
F Serum P1NP
G Serum CTX-1
M Serum P1NP
N Serum CTX-1
ng/mL

Fig. S6







PERMANOVA

WT vs CF	p-val
4wk	0.245
14wk	0.515

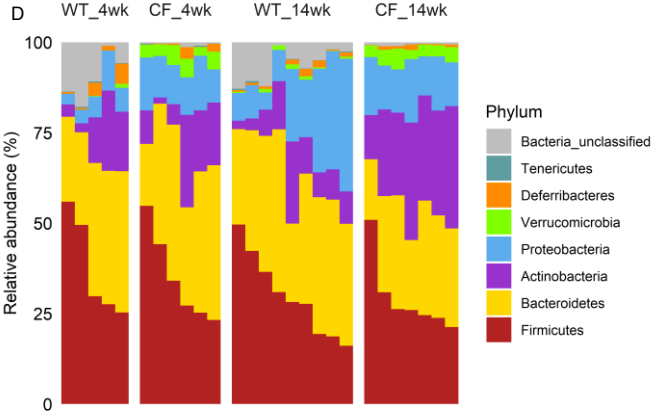
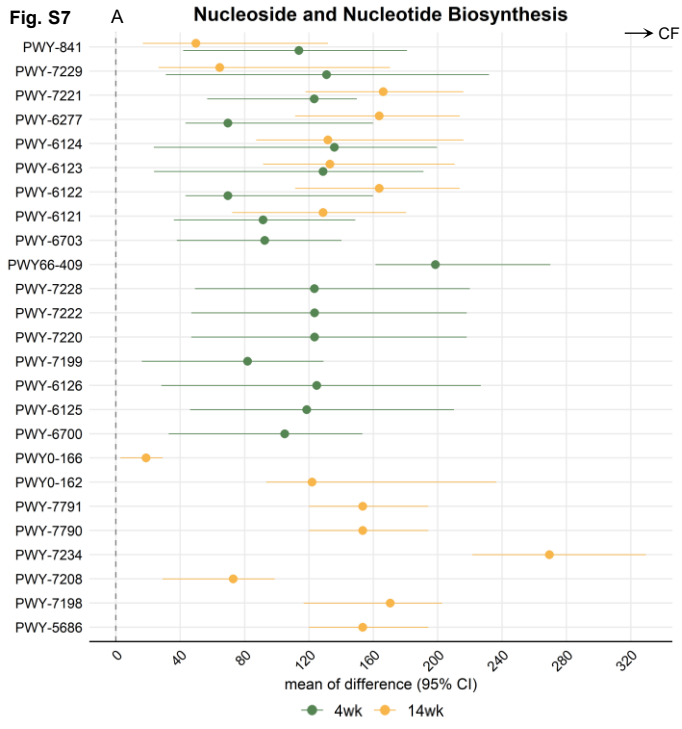




Fig. S7


A
Nucleoside and Nucleotide Biosynthesis
CF
PWY-841
PWY-7229
PWY-7221
PWY-6277
PWY-6124
PWY-6123
PWY-6122
PWY-6121
PWY-6703
PWY66-409
PWY-7228
PWY-7222
PWY-7220
PWY-7199
PWY-6126
PWY-6125
PWY-6700
PWY0-166
PWY0-162
PWY-7791
PWY-7790
PWY-7234
PWY-7208
PWY-7198
PWY-5686
0
40
80
120
160
200
240
280
320
mean of difference (95% CI)
4wk
14wk

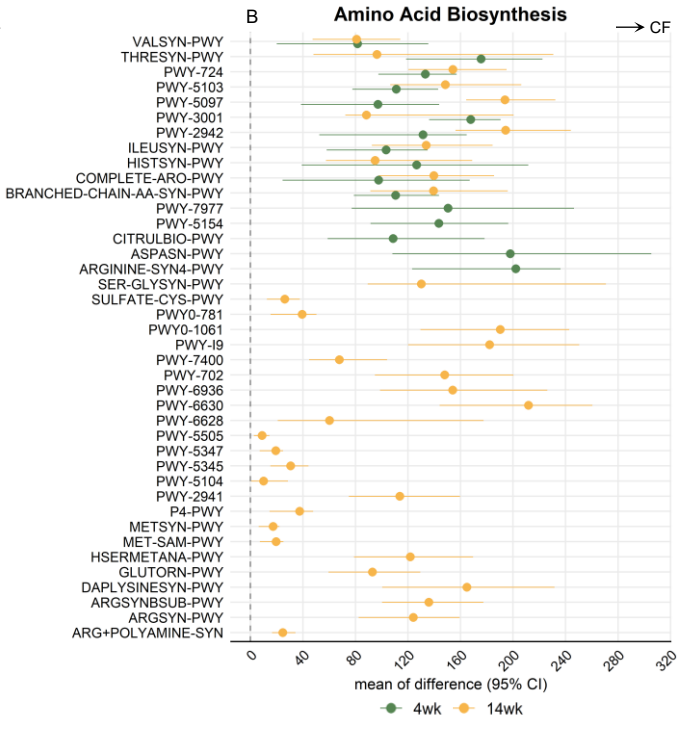

B
Amino Acid Biosynthesis
CF
VALSYN-PWY
THRESYN-PWY
PWY-724
PWY-5103
PWY-5097
PWY-3001
PWY-2942
ILEUSYN-PWY
HISTSYN-PWY
COMPLETE-ARO-PWY
BRANCHED-CHAIN-AA-SYN-PWY
PWY-7977
PWY-5154
CITRULBIO-PWY
ASPASN-PWY
ARGININE-SYN4-PWY
SER-GLYSYN-PWY
SULFATE-CYS-PWY
PWY0-781
PWY0-1061
PWY-I9
PWY-7400
PWY-702
PWY-6936
PWY-6630
PWY-6628
PWY-5505
PWY-5347
PWY-5345
PWY-5104
PWY-2941
P4-PWY
METSYN-PWY
MET-SAM-PWY
HSERMETANA-PWY
GLUTORN-PWY
DAPLYSINESYN-PWY
ARGSYNBSUB-PWY
ARGSYN-PWY
ARG+POLYAMINE-SYN
0
40
80
120
160
200
240
280
320
mean of difference (95% CI)
4wk
14wk

Table S1 Differentially abundant phylum between WT and CF mice

Phylum	WT.mean±sem	CF.mean±sem	Mean of difference (95% CI)	adj.p	Significant	Age
Actinobacteria	11.423±3.781	12.726±3.595	1.709 (-12.915,14.397)	0.784	not significant	4wk
Verrucomicrobia	0.241±0.21	4.114±0.507	3.743 (2.374,5.382)	0.055	not significant	4wk
Bacteroidetes	32.381±3.245	34.69±4.237	3.582 (-11.915,17.203)	0.548	not significant	4wk
Tenericutes	0.199±0.064	0.114±0.059	-0.105 (-0.316,0.148)	0.548	not significant	4wk
Deferribacteres	2.281±1.005	1.007±0.545	-0.723 (-5.181,1.728)	0.241	not significant	4wk
Firmicutes	37.625±6.289	34.792±5.07	-2.14 (-26.316,18.867)	0.598	not significant	4wk
Proteobacteria	6.042±1.423	11.927±0.98	6.089 (0.397,10.873)	0.095	not significant	4wk
Bacteria_unclassified	9.809±2.952	0.631±0.175	-10.429 (-17.491,-0.641)	0.055	not significant	4wk
Actinobacteria	9.229±2.011	26.188±2.788	19.234 (9.58,25.258)	0.006	increased in CF	14wk
Verrucomicrobia	0.649±0.16	3.741±0.409	2.919 (2.094,4.077)	0.006	increased in CF	14wk
Bacteroidetes	34.382±2.291	25.916±2.175	-7.708 (-16.718,-2.096)	0.042	increased in WT	14wk
Tenericutes	0.167±0.056	0.012±0.006	-0.102 (-0.309,-0.005)	0.016	increased in WT	14wk
Deferribacteres	0.972±0.238	0.664±0.184	-0.282 (-1.104,0.372)	0.612	not significant	14wk
Firmicutes	29.935±3.772	29.102±3.799	-1.684 (-12.724,8.59)	0.916	not significant	14wk
Proteobacteria	18.243±3.967	13.662±0.951	-2.522 (-17.688,6.852)	0.916	not significant	14wk
Bacteria_unclassified	6.422±1.512	0.714±0.101	-4.342 (-11.112,-1.441)	0.006	increased in WT	14wk

Table S2 Differentially abundant genus between WT and CF mice at 4-week-old

Genus	WT.mean±sem	CF.mean±sem	Mean of difference (95% CI)	adj.p	Significant
Verrucomicrobia ; Akkermansia	0.241±0.21	4.114±0.507	3.743 (2.374,5.382)	0.026	increased in CF
Firmicutes ; Anaerostipes	0.059±0.014	0.941±0.26	0.894 (0.053,1.652)	0.026	increased in CF
Firmicutes ; Blautia	0.145±0.118	11.647±1.257	10.753 (7.853,16.724)	0.026	increased in CF
Proteobacteria ; Escherichia	0±0	0.897±0.387	1.147 (0.019,2.149)	0.026	increased in CF
Actinobacteria ; Adlercreutzia	1.723±0.163	0.023±0.013	-1.75 (-2.216,-1.24)	0.026	increased in WT
Bacteria_unclassified ; Bacteria_unclassified	4.077±1.475	0.629±0.175	-3.136 (-7.679,-0.11)	0.047	increased in WT
Firmicutes ; Clostridiaceae_unclassified	0.115±0.054	0±0	-0.07 (-0.257,0)	0.036	increased in WT
Actinobacteria ; Eggerthellaceae_unclassified	0.108±0.029	0±0	-0.078 (-0.207,-0.048)	0.024	increased in WT
Actinobacteria ; Enterorhabdus	0.08±0.015	0.004±0.004	-0.071 (-0.136,-0.049)	0.025	increased in WT
Firmicutes ; GGB28330	0.438±0.189	0±0	-0.372 (-1.085,-0.017)	0.024	increased in WT
Firmicutes ; GGB28948	0.44±0.191	0±0	-0.336 (-1.094,-0.003)	0.024	increased in WT
Bacteria_unclassified ; GGB28955	0.194±0.106	0±0	-0.105 (-0.578,-0.004)	0.024	increased in WT
Bacteria_unclassified ; GGB28963	0.05±0.025	0±0	-0.032 (-0.131,0)	0.036	increased in WT
Firmicutes ; GGB28988	2.649±0.683	0±0	-3.205 (-4.353,-0.363)	0.024	increased in WT
Firmicutes ; GGB28989	4.568±1.105	0±0	-4.407 (-6.803,-0.787)	0.024	increased in WT
Firmicutes ; GGB79989	0.378±0.187	0±0	-0.269 (-1.036,-0.024)	0.024	increased in WT
Firmicutes ; Lachnospiraceae_unclassified	1.094±0.494	0.106±0.094	-0.75 (-2.329,-0.021)	0.047	increased in WT
Bacteroidetes ; Bacteroides	1.729±0.427	15.302±2.633	13.885 (5.717,20.745)	0.026	increased in CF
Firmicutes ; Enterocloster	0.003±0.001	3.195±0.688	2.203 (1.893,5.889)	0.026	increased in CF
Firmicutes ; Enterococcus	0.001±0.001	0.335±0.079	0.311 (0.155,0.653)	0.026	increased in CF
Proteobacteria ; Helicobacter	2.676±0.869	7.691±1.263	5.426 (0.792,9.309)	0.047	increased in CF
Firmicutes ; Lachnoclostridium	0.042±0.011	1.223±0.113	1.262 (0.721,1.48)	0.026	increased in CF
Bacteroidetes ; Phocaeicola	1.887±0.713	15.467±2.404	15.191 (6.336,19.743)	0.026	increased in CF
Bacteroidetes ; Barnesiella	3.866±0.657	0.905±0.554	-2.62 (-5.303,-0.662)	0.047	increased in WT
Bacteroidetes ; Duncaniella	7.133±1.899	0.46±0.333	-7.098 (-12.684,-1.551)	0.036	increased in WT
Bacteria_unclassified ; GGB14001	0.022±0.009	0±0	-0.016 (-0.056,-0.002)	0.024	increased in WT
Bacteria_unclassified ; GGB20145	0.599±0.214	0±0	-0.731 (-1.244,-0.076)	0.024	increased in WT
Bacteroidetes ; GGB24102	1.518±0.918	0.002±0.002	-0.323 (-4.736,-0.025)	0.025	increased in WT
Bacteroidetes ; GGB27872	0.719±0.053	0.011±0.011	-0.747 (-0.882,-0.568)	0.025	increased in WT
Firmicutes ; GGB27876	1.001±0.301	0.002±0.002	-0.993 (-1.832,-0.284)	0.025	increased in WT
Firmicutes ; GGB27890	0.043±0.025	0±0	-0.008 (-0.111,0)	0.024	increased in WT
Bacteroidetes ; GGB28265	1.268±0.337	0±0	-1.036 (-2.095,-0.34)	0.024	increased in WT

Proteobacteria ; GGB28310	0.334±0.119	0±0	-0.398 (-0.581,-0.021)	0.024	increased in WT
Proteobacteria ; GGB28317	0.048±0.016	0.005±0.003	-0.029 (-0.091,-0.011)	0.036	increased in WT
Firmicutes ; GGB28403	0.128±0.073	0±0	-0.028 (-0.389,-0.013)	0.024	increased in WT
Firmicutes ; GGB28766	0.785±0.377	0±0	-0.596 (-2.087,-0.007)	0.024	increased in WT
Firmicutes ; GGB28769	0.181±0.095	0±0	-0.042 (-0.443,-0.005)	0.024	increased in WT
Firmicutes ; GGB28778	1.452±0.469	0.018±0.007	-1.282 (-2.685,-0.041)	0.026	increased in WT
Actinobacteria ; GGB28839	0.438±0.176	0±0	-0.445 (-1.008,-0.022)	0.024	increased in WT
Firmicutes ; GGB28849	0.176±0.102	0±0	-0.034 (-0.488,0)	0.036	increased in WT
Bacteria_unclassified ; GGB28888	1.004±0.339	0.001±0.001	-1.015 (-2.127,-0.023)	0.025	increased in WT
Bacteria_unclassified ; GGB28901	0.912±0.454	0±0	-0.409 (-2.323,0)	0.036	increased in WT
Bacteria_unclassified ; GGB28904	1.63±0.724	0±0	-1.21 (-3.557,-0.064)	0.024	increased in WT
Bacteria_unclassified ; GGB28927	1.269±0.35	0±0	-1.595 (-1.959,-0.001)	0.024	increased in WT
Firmicutes ; GGB28949	0.815±0.387	0.012±0.009	-0.486 (-1.839,-0.011)	0.045	increased in WT
Firmicutes ; GGB28950	0.118±0.079	0±0	-0.019 (-0.413,0)	0.036	increased in WT
Firmicutes ; GGB28956	0.902±0.537	0±0	-0.248 (-2.872,-0.011)	0.024	increased in WT
Firmicutes ; GGB29002	0.023±0.011	0±0	-0.017 (-0.062,0)	0.036	increased in WT
Firmicutes ; GGB29003	0.033±0.018	0±0	-0.026 (-0.099,0)	0.036	increased in WT
Actinobacteria ; GGB30301	0.023±0.009	0±0	-0.018 (-0.057,0)	0.036	increased in WT
Firmicutes ; GGB30466	0.073±0.041	0±0	-0.046 (-0.232,0)	0.036	increased in WT
Firmicutes ; GGB45514	0.276±0.104	0.039±0.022	-0.181 (-0.653,-0.039)	0.047	increased in WT
Firmicutes ; GGB45650	0.194±0.043	0.004±0.004	-0.167 (-0.336,-0.08)	0.025	increased in WT
Firmicutes ; GGB74395	0.395±0.217	0±0	-0.153 (-1.058,0)	0.036	increased in WT
Bacteroidetes ; Muribaculaceae_unclassified	10.017±1.235	0.79±0.347	-10.002 (-12.107,-5.257)	0.026	increased in WT
Bacteroidetes ; Muribaculum	2.33±0.7	0.179±0.106	-3.021 (-3.673,-0.33)	0.036	increased in WT
Firmicutes ; Oscillibacter	0.317±0.135	0.008±0.005	-0.314 (-0.728,-0.005)	0.045	increased in WT
Firmicutes ; Oscillospiraceae_unclassified	0.896±0.335	0±0	-1.312 (-1.628,-0.008)	0.025	increased in WT
Proteobacteria ; Parasutterella	1.452±0.209	0.738±0.058	-0.749 (-1.226,-0.102)	0.047	increased in WT
Proteobacteria ; Piscinibacter	0.093±0.015	0±0	-0.095 (-0.127,-0.038)	0.024	increased in WT

Taxa in yellow color indicates differentially abundant taxa between WT and CF mice in both ages

Table S3 Differentially abundant genus between WT and CF mice at 14-week-old

Genus	WT.mean±sem	CF.mean±sem	Mean of difference (95% CI)	adj.p	Significant
Actinobacteria ; Adlercreutzia	0.895±0.101	0.306±0.008	-0.557 (-0.69,-0.361)	0.012	increased in WT
Verrucomicrobia ; Akkermansia	0.649±0.16	3.741±0.409	2.919 (2.094,4.077)	0.012	increased in CF
Firmicutes ; Anaerostipes	0.378±0.097	1.002±0.132	0.655 (0.185,0.992)	0.026	increased in CF
Bacteria_unclassified ; Bacteria_unclassified	3.569±0.606	0.536±0.058	-3.427 (-4.966,-1.167)	0.026	increased in WT
Firmicutes ; Blautia	2.566±0.705	6.069±0.665	3.901 (0.936,5.083)	0.027	increased in CF
Firmicutes ; Clostridiaceae_unclassified	0.002±0.002	0.062±0.034	0.016 (0.006,0.163)	0.026	increased in CF
Actinobacteria ; Eggerthellaceae_unclassified	0.086±0.028	0.014±0.003	-0.048 (-0.08,-0.032)	0.027	increased in WT
Actinobacteria ; Enterorhabdus	0.109±0.019	0.03±0.009	-0.066 (-0.132,-0.033)	0.021	increased in WT
Proteobacteria ; Escherichia	0±0	0.181±0.034	0.204 (0.071,0.251)	0.012	increased in CF
Firmicutes ; GGB28330	0.577±0.156	0±0	-0.601 (-1.311,-0.17)	0.012	increased in WT
Firmicutes ; GGB28948	0.209±0.124	0.001±0.001	-0.082 (-0.235,-0.025)	0.012	increased in WT
Bacteria_unclassified ; GGB28955	0.389±0.134	0.005±0.003	-0.226 (-0.822,-0.059)	0.012	increased in WT
Bacteria_unclassified ; GGB28963	0.563±0.104	0±0	-0.457 (-0.922,-0.239)	0.012	increased in WT
Firmicutes ; GGB28988	2.2±0.37	0.001±0.001	-2.273 (-3.326,-1.349)	0.012	increased in WT
Firmicutes ; GGB28989	1.698±0.5	0±0	-2.006 (-3.339,0)	0.026	increased in WT
Firmicutes ; GGB79989	0.486±0.104	0±0	-0.378 (-0.883,-0.318)	0.012	increased in WT
Firmicutes ; Lachnospiraceae_unclassified	1.286±0.44	0±0	-0.577 (-2.906,-0.04)	0.012	increased in WT
Actinobacteria ; Bifidobacterium	5.292±1.733	23.263±2.409	19.446 (10.702,25.389)	0.013	increased in CF
Firmicutes ; Clostridium	0.023±0.02	0.085±0.024	0.049 (0.026,0.149)	0.027	increased in CF
Firmicutes ; GGB18827	0±0	0.068±0.022	0.087 (0,0.121)	0.026	increased in CF
Firmicutes ; GGB28422	0±0	0.145±0.034	0.154 (0.102,0.184)	0.012	increased in CF
Firmicutes ; GGB28763	0.831±0.25	0±0	-0.654 (-1.779,-0.147)	0.021	increased in WT
Tenericutes ; GGB31870	0.167±0.056	0.012±0.006	-0.102 (-0.309,-0.005)	0.035	increased in WT
Proteobacteria ; GGB42900	0±0	0.053±0.022	0.039 (0,0.122)	0.026	increased in CF
Firmicutes ; Ligilactobacillus	1.212±0.307	12.57±4.222	7.369 (4.891,12.596)	0.012	increased in CF
Bacteroidetes ; Prevotella	0.079±0.079	3.525±0.784	3.287 (2.441,5.158)	0.02	increased in CF

Taxa in yellow color indicates differentially abundant taxa between WT and CF mice in both ages

Table S4 Differentially abundant species between WT and CF mice at 4-week-old

Species	WT.mean±sem	CF.mean±sem	Mean of difference (95% CI)	adj.p	Significant
Akkermansia_muciniphila	0.241±0.21	4.114±0.507	3.743 (2.374,5.382)	0.026	increased in CF
Anaerostipes_hominis	0.059±0.014	0.941±0.26	0.894 (0.053,1.652)	0.026	increased in CF
Blautia_pseudococcoides	0.145±0.118	11.647±1.257	10.753 (7.853,16.724)	0.026	increased in CF
Escherichia_coli	0±0	0.897±0.387	1.147 (0.019,2.149)	0.026	increased in CF
Adlercreutzia_caecimuris	0.767±0.072	0.012±0.012	-0.716 (-1.027,-0.591)	0.023	increased in WT
Clostridiaceae_bacterium	0.115±0.054	0±0	-0.07 (-0.257,0)	0.035	increased in WT
Eggerthellaceae_bacterium	0.108±0.029	0±0	-0.078 (-0.207,-0.048)	0.023	increased in WT
Enterorhabdus_sp_P55	0.08±0.015	0.004±0.004	-0.071 (-0.136,-0.049)	0.023	increased in WT
GGB28330_SGB40904	0.438±0.189	0±0	-0.372 (-1.085,-0.017)	0.023	increased in WT
GGB28948_SGB41654	0.44±0.191	0±0	-0.336 (-1.094,-0.003)	0.023	increased in WT
GGB28955_SGB41663	0.194±0.106	0±0	-0.105 (-0.578,-0.004)	0.023	increased in WT
GGB28963_SGB41672	0.05±0.025	0±0	-0.032 (-0.131,0)	0.035	increased in WT
GGB28988_SGB41701	2.649±0.683	0±0	-3.205 (-4.353,-0.363)	0.023	increased in WT
GGB28989_SGB41703	4.568±1.105	0±0	-4.407 (-6.803,-0.787)	0.023	increased in WT
GGB79989_SGB41645	0.378±0.187	0±0	-0.269 (-1.036,-0.024)	0.023	increased in WT
Lachnospiraceae_unclassified_SGB41402	0.184±0.078	0±0	-0.152 (-0.399,0)	0.035	increased in WT
Muribaculaceae_bacterium_Isolate_013_NCI	0.586±0.066	0.015±0.01	-0.537 (-0.795,-0.432)	0.026	increased in WT
Bacteroides_acidifaciens	1.336±0.358	13.694±2.614	11.286 (4.957,19.922)	0.026	increased in CF
Bacteroides_caecimuris	0.069±0.04	0.696±0.233	0.438 (0.136,1.652)	0.035	increased in CF
Bacteroides_sp_L10_4	0.324±0.103	0.913±0.154	0.533 (0.135,1.2)	0.046	increased in CF
Clostridium_symbiosum	0.042±0.011	1.223±0.113	1.262 (0.721,1.48)	0.026	increased in CF
Enterocloster_aldenensis	0.003±0.001	3.195±0.688	2.203 (1.893,5.889)	0.026	increased in CF
Enterococcus_gallinarum	0.001±0.001	0.308±0.079	0.207 (0.155,0.653)	0.026	increased in CF
Helicobacter_typhlonius	1.649±0.746	6.245±1.2	4.489 (0.85,8.621)	0.035	increased in CF
Phocaeicola_vulgatus	0.326±0.17	12.131±2.541	10.972 (4.772,17.981)	0.026	increased in CF
Adlercreutzia_mucosicola	0.255±0.035	0.001±0.001	-0.259 (-0.372,-0.166)	0.023	increased in WT
Adlercreutzia_muris	0.702±0.117	0.01±0.008	-0.629 (-1.128,-0.483)	0.026	increased in WT
Bacteria_unclassified_SGB63107	0.464±0.087	0.021±0.021	-0.497 (-0.667,-0.184)	0.023	increased in WT
bacterium_0_1xD8_82	0.445±0.111	0±0	-0.448 (-0.675,-0.051)	0.023	increased in WT
bacterium_1XD42_1	0.112±0.05	0±0	-0.097 (-0.249,-0.004)	0.023	increased in WT
bacterium_D16_29	0.078±0.027	0±0	-0.107 (-0.136,0)	0.035	increased in WT
bacterium_D16_76	0.106±0.032	0.002±0.002	-0.09 (-0.225,-0.049)	0.023	increased in WT

Barnesiella_sp_CU968	3.866±0.657	0.905±0.554	-2.62 (-5.303,-0.662)	0.046	increased in WT
Duncaniella_dubosii	4.507±1.058	0±0	-4.841 (-6.802,-1.186)	0.023	increased in WT
GGB14001_SGB21428	0.022±0.009	0±0	-0.016 (-0.056,-0.002)	0.023	increased in WT
GGB20145_SGB41586	0.599±0.214	0±0	-0.731 (-1.244,-0.076)	0.023	increased in WT
GGB24102_SGB40204	1.518±0.918	0.002±0.002	-0.323 (-4.736,-0.025)	0.023	increased in WT
GGB27872_SGB40306	0.719±0.053	0.011±0.011	-0.747 (-0.882,-0.568)	0.023	increased in WT
GGB27873_SGB41457	0.286±0.184	0±0	-0.114 (-0.981,0)	0.038	increased in WT
GGB27876_SGB40310	1.001±0.301	0.002±0.002	-0.993 (-1.832,-0.284)	0.023	increased in WT
GGB27890_SGB40324	0.043±0.025	0±0	-0.008 (-0.111,0)	0.023	increased in WT
GGB27929_SGB41624	0.216±0.119	0.002±0.002	-0.058 (-0.507,-0.002)	0.038	increased in WT
GGB28265_SGB40817	1.268±0.337	0±0	-1.036 (-2.095,-0.34)	0.023	increased in WT
GGB28310_SGB40880	0.334±0.119	0±0	-0.398 (-0.581,-0.021)	0.023	increased in WT
GGB28317_SGB40889	0.048±0.016	0.005±0.003	-0.029 (-0.091,-0.011)	0.035	increased in WT
GGB28403_SGB40190	0.128±0.073	0±0	-0.028 (-0.389,-0.013)	0.023	increased in WT
GGB28766_SGB41418	0.785±0.377	0±0	-0.596 (-2.087,-0.007)	0.023	increased in WT
GGB28769_SGB41421	0.181±0.095	0±0	-0.042 (-0.443,-0.005)	0.023	increased in WT
GGB28778_SGB41431	1.452±0.469	0.018±0.007	-1.282 (-2.685,-0.041)	0.026	increased in WT
GGB28839_SGB41503	0.438±0.176	0±0	-0.445 (-1.008,-0.022)	0.023	increased in WT
GGB28849_SGB41516	0.176±0.102	0±0	-0.034 (-0.488,0)	0.035	increased in WT
GGB28888_SGB41569	1.004±0.339	0.001±0.001	-1.015 (-2.127,-0.023)	0.023	increased in WT
GGB28901_SGB41592	0.912±0.454	0±0	-0.409 (-2.323,0)	0.035	increased in WT
GGB28904_SGB41597	1.63±0.724	0±0	-1.21 (-3.557,-0.064)	0.023	increased in WT
GGB28927_SGB41625	1.269±0.35	0±0	-1.595 (-1.959,-0.001)	0.023	increased in WT
GGB28949_SGB41655	0.815±0.387	0.012±0.009	-0.486 (-1.839,-0.011)	0.042	increased in WT
GGB28950_SGB41657	0.118±0.079	0±0	-0.019 (-0.413,0)	0.035	increased in WT
GGB28956_SGB41665	0.902±0.537	0±0	-0.248 (-2.872,-0.011)	0.023	increased in WT
GGB29002_SGB41718	0.023±0.011	0±0	-0.017 (-0.062,0)	0.035	increased in WT
GGB29003_SGB41719	0.033±0.018	0±0	-0.026 (-0.099,0)	0.035	increased in WT
GGB30301_SGB43265	0.023±0.009	0±0	-0.018 (-0.057,0)	0.035	increased in WT
GGB30466_SGB43544	0.073±0.041	0±0	-0.046 (-0.232,0)	0.035	increased in WT
GGB45514_SGB63186	0.276±0.104	0.039±0.022	-0.181 (-0.653,-0.039)	0.046	increased in WT
GGB45650_SGB63364	0.194±0.043	0.004±0.004	-0.167 (-0.336,-0.08)	0.023	increased in WT
GGB74395_SGB43523	0.395±0.217	0±0	-0.153 (-1.058,0)	0.035	increased in WT
Hungateiclostridiaceae_bacterium_KB18	0.896±0.335	0±0	-1.312 (-1.628,-0.008)	0.023	increased in WT

Lachnospiraceae_bacterium	0.195±0.121	0±0	-0.093 (-0.651,-0.002)	0.023	increased in WT
Lachnospiraceae_bacterium_A2	0.424±0.27	0±0	-0.031 (-1.336,0)	0.035	increased in WT
Lactobacillus_SGB5158	3.049±1.354	0±0	-2.097 (-8.289,-0.463)	0.023	increased in WT
Muribaculaceae_bacterium	4.456±0.836	0.298±0.292	-4.907 (-5.813,-1.339)	0.035	increased in WT
Muribaculaceae_bacterium_Isolate_104_HZI	4.257±0.409	0±0	-4.539 (-5.184,-2.809)	0.023	increased in WT
Muribaculum_intestinale	2.33±0.7	0.179±0.106	-3.021 (-3.673,-0.33)	0.035	increased in WT
Oscillibacter_sp_CU971	0.317±0.135	0.008±0.005	-0.314 (-0.728,-0.005)	0.042	increased in WT
Parasutterella_sp_NM82_D38	1.452±0.209	0.738±0.058	-0.749 (-1.226,-0.102)	0.046	increased in WT
Piscinibacter_SGB44477	0.093±0.015	0±0	-0.095 (-0.127,-0.038)	0.023	increased in WT
Streptococcus_SGB45231	0.245±0.209	0.009±0.006	-0.035 (-1.055,-0.011)	0.042	increased in WT

Taxa in yellow color indicates differentially abundant taxa between WT and CF mice in both ages

Table S5 Differentially abundant species between WT and CF mice at 14-week-old

Species	WT.mean±sem	CF.mean±sem	Mean of difference (95% CI)	adj.p	Significant
Akkermansia_muciniphila	0.649±0.16	3.741±0.409	2.919 (2.094,4.077)	0.016	increased in CF
Anaerostipes_hominis	0.378±0.097	1.002±0.132	0.655 (0.185,0.992)	0.031	increased in CF
Blautia_pseudococcoides	2.566±0.705	6.069±0.665	3.901 (0.936,5.083)	0.032	increased in CF
Clostridiaceae_bacterium	0.002±0.002	0.062±0.034	0.016 (0.006,0.163)	0.031	increased in CF
Escherichia_coli	0±0	0.181±0.034	0.204 (0.071,0.251)	0.016	increased in CF
Muribaculaceae_bacterium_Isolate_013_NCI	0.235±0.132	0.644±0.045	0.546 (0.08,0.731)	0.046	increased in CF
Adlercreutzia_caecimuris	0.611±0.073	0.156±0.008	-0.418 (-0.574,-0.265)	0.016	increased in WT
Eggerthellaceae_bacterium	0.086±0.028	0.014±0.003	-0.048 (-0.08,-0.032)	0.032	increased in WT
Enterorhabdus_sp_P55	0.109±0.019	0.03±0.009	-0.066 (-0.132,-0.033)	0.024	increased in WT
GGB28330_SGB40904	0.577±0.156	0±0	-0.601 (-1.311,-0.17)	0.016	increased in WT
GGB28948_SGB41654	0.209±0.124	0.001±0.001	-0.082 (-0.235,-0.025)	0.016	increased in WT
GGB28955_SGB41663	0.389±0.134	0.005±0.003	-0.226 (-0.822,-0.059)	0.016	increased in WT
GGB28963_SGB41672	0.563±0.104	0±0	-0.457 (-0.922,-0.239)	0.016	increased in WT
GGB28988_SGB41701	2.2±0.37	0.001±0.001	-2.273 (-3.326,-1.349)	0.016	increased in WT
GGB28989_SGB41703	1.698±0.5	0±0	-2.006 (-3.339,0)	0.031	increased in WT
GGB79989_SGB41645	0.486±0.104	0±0	-0.378 (-0.883,-0.318)	0.016	increased in WT
Lachnospiraceae_unclassified_SGB41402	0.277±0.085	0±0	-0.164 (-0.579,-0.029)	0.019	increased in WT
Bifidobacterium_animalis	4.739±1.767	22.908±2.349	20.486 (10.749,25.181)	0.017	increased in CF
Clostridium_SGB40327	0.023±0.02	0.085±0.024	0.049 (0.026,0.149)	0.032	increased in CF
GGB18827_SGB27766	0±0	0.068±0.022	0.087 (0,0.121)	0.031	increased in CF
GGB27873_SGB40307	0.001±0.001	0.064±0.02	0.054 (0.026,0.104)	0.021	increased in CF
GGB28422_SGB41005	0±0	0.145±0.034	0.154 (0.102,0.184)	0.016	increased in CF
GGB42900_SGB60120	0±0	0.053±0.022	0.039 (0,0.122)	0.031	increased in CF
Ligilactobacillus_murinus	1.212±0.307	12.57±4.222	7.369 (4.891,12.596)	0.016	increased in CF
Prevotella_sp_PCJ2	0.079±0.079	3.525±0.784	3.287 (2.441,5.158)	0.021	increased in CF
bacterium_1xD42_87	2.257±0.527	0±0	-1.779 (-3.41,-0.734)	0.019	increased in WT
GGB28763_SGB41411	0.831±0.25	0±0	-0.654 (-1.779,-0.147)	0.024	increased in WT
GGB31870_SGB45255	0.167±0.056	0.012±0.006	-0.102 (-0.309,-0.005)	0.042	increased in WT

Taxa in yellow color indicates differentially abundant taxa between WT and CF mice in both ages

Table S6 Differentially abundant functional pathway between WT and CF mice at 4-week-old

Pathway_ID	Pathway_description	Pathway_superclass	WT.mean±sem	CF.mean±sem	Mean of difference (95% CI)	adj.p	Significant
PWY-7111	pyruvate fermentation to isobutanol (engineered)	Alcohol fermentation: Isobutanol	163.963±41.186	352.071±22.177	192.578 (49.305,302.048)	0.034	increased in CF
BRANCHED-CHAIN-AA-SYN-PWY	superpathway of branched chain amino acid biosynthesis	Amino Acid Biosynthesis	364.153±9.933	474.574±7.647	110.561 (78.764,143.613)	0.023	increased in CF
COMPLETE-ARO-PWY	superpathway of aromatic amino acid biosynthesis	Amino Acid Biosynthesis	286.255±22.754	383.83±18.935	97.659 (24.466,167.019)	0.049	increased in CF
HISTSYN-PWY	L-histidine biosynthesis	Amino Acid Biosynthesis	267.611±26.474	390.962±19.256	126.604 (39.068,211.65)	0.049	increased in CF
ILEUSYN-PWY	L-isoleucine biosynthesis I (from threonine)	Amino Acid Biosynthesis	384.439±12.822	485.359±7.867	103.295 (58.032,134.964)	0.023	increased in CF
PWY-2942	L-lysine biosynthesis III	Amino Acid Biosynthesis	298.991±18.673	420.368±12.216	131.439 (52.519,164.731)	0.023	increased in CF
PWY-3001	superpathway of L-isoleucine biosynthesis I	Amino Acid Biosynthesis	193.499±9.946	362.423±4.176	167.822 (136.071,190.487)	0.023	increased in CF
PWY-5097	L-lysine biosynthesis VI	Amino Acid Biosynthesis	322.515±15.644	422.242±12.914	97.037 (38.436,143.794)	0.023	increased in CF
PWY-5103	L-isoleucine biosynthesis III	Amino Acid Biosynthesis	340.289±9.136	450.631±8.455	111.102 (77.684,142.952)	0.023	increased in CF
PWY-724	superpathway of L-lysine, L-threonine and L-methionine biosynthesis II	Amino Acid Biosynthesis	245.506±10.266	376.712±6.355	133.147 (97.54,157.124)	0.023	increased in CF
THRESYN-PWY	superpathway of L-threonine biosynthesis	Amino Acid Biosynthesis	184.791±16.642	353.75±13.699	175.654 (118.529,222.449)	0.023	increased in CF
VALSYN-PWY	L-valine biosynthesis	Amino Acid Biosynthesis	464.889±20.284	538.109±9.434	81.598 (19.993,135.461)	0.049	increased in CF
CALVIN-PWY	Calvin-Benson-Bassham cycle	Carbohydrate Biosynthesis	180.678±24.997	361.767±20.242	184.252 (87.02,278.793)	0.023	increased in CF
COLANSYN-PWY	colanic acid building blocks biosynthesis	Carbohydrate Biosynthesis	91.738±21.098	195.93±5.935	119.664 (38.593,152.39)	0.023	increased in CF
DTDPRHAMSYN-PWY	dTDP-β-L-rhamnose biosynthesis	Carbohydrate Biosynthesis	395.106±7.547	555.215±30.083	173.951 (36.328,223.64)	0.023	increased in CF
PWY-6143	CMP-pseudaminate biosynthesis	Carbohydrate Biosynthesis	27.306±11.334	0±0	-20.812 (-62.014,0)	0.037	increased in WT
PWY66-399	gluconeogenesis III	Carbohydrate Biosynthesis	42.639±12.034	128.126±8.821	82.044 (38.942,127.095)	0.023	increased in CF
FUCCAT-PWY	fucose degradation	Carbohydrate Degradation	5.938±2.16	40.406±5.154	32.989 (18.87,49.273)	0.023	increased in CF
GLUCOSE1PMETAB-PWY	glucose and glucose-1-phosphate degradation	Carbohydrate Degradation	0±0	206.213±12.877	205.34 (158.51,252.171)	0.023	increased in CF
NONOXIPENT-PWY	pentose phosphate pathway (non-oxidative branch) I	Carbohydrate Degradation	91.022±15.088	249.107±22.31	156.965 (93.17,239.54)	0.023	increased in CF
PENTOSE-P-PWY	pentose phosphate pathway	Carbohydrate Degradation	90.278±8.131	261.295±17.059	162.236 (126.331,224.313)	0.023	increased in CF
PWY-5941	glycogen degradation II	Carbohydrate Degradation	176.084±19.847	306.471±11.306	135.826 (67.631,186.203)	0.023	increased in CF
PWY-6317	D-galactose degradation I (Leloir pathway)	Carbohydrate Degradation	188.352±13.543	273.267±3.858	90.11 (51.413,123.094)	0.023	increased in CF
PWY-6901	superpathway of glucose and xylose degradation	Carbohydrate Degradation	122.236±8.037	273.983±13.486	148.668 (114.738,213.367)	0.023	increased in CF
PWY-8178	pentose phosphate pathway (non-oxidative branch) II	Carbohydrate Degradation	110.204±19.704	259.904±19.001	154.688 (72.992,243.274)	0.023	increased in CF
ARO-PWY	chorismate biosynthesis I	Carboxylic Acid Biosynthesis	306.405±22.604	400.153±20.847	97.982 (10.545,161.217)	0.049	increased in CF
PWY-6163	chorismate biosynthesis from 3-dehydroquinate	Carboxylic Acid Biosynthesis	320.473±24.087	420.112±16.54	100.405 (22.981,172.461)	0.049	increased in CF
GALACTARDEG-PWY	D-galactarate degradation I	Carboxylic Acid Degradation	1.441±0.894	54.017±9.485	54.533 (24.661,82.19)	0.023	increased in CF
GLUCARDEG-PWY	D-glucarate degradation I	Carboxylic Acid Degradation	1.352±0.853	49.276±8.055	52.788 (24.896,74.601)	0.023	increased in CF
GLUCARGALACTSUPER-PWY	superpathway of D-glucarate and D-galactarate degradation	Carboxylic Acid Degradation	1.441±0.894	54.017±9.485	54.533 (24.661,82.19)	0.023	increased in CF
P441-PWY	superpathway of N-acetylneuraminate degradation	Carboxylic Acid Degradation	87.433±26.231	174.002±11.018	88.158 (20.163,163.701)	0.049	increased in CF
PWY-6385	peptidoglycan biosynthesis III (mycobacteria)	Cell Structure Biosynthesis	334.663±22.152	471.363±11.866	144.514 (59.669,193.749)	0.023	increased in CF
PWY-6386	UDP-N-acetylmuramoyl-pentapeptide biosynthesis II (lysine-containing)	Cell Structure Biosynthesis	332.018±23.035	492.941±14.838	160.057 (69.068,230.242)	0.023	increased in CF
PWY-6387	UDP-N-acetylmuramoyl-pentapeptide biosynthesis I (meso-diaminopimelate containing)	Cell Structure Biosynthesis	375.164±25.091	492.024±13.685	119.572 (17.988,182.64)	0.049	increased in CF
PWY-7953	UDP-N-acetylmuramoyl-pentapeptide biosynthesis III (meso-diaminopimelate containing)	Cell Structure Biosynthesis	315.093±21.952	462.926±12.945	154.555 (67.204,204.751)	0.023	increased in CF
BIOTIN-BIOSYNTHESIS-PWY	biotin biosynthesis I	Cofactor Carrier and Vitamin Biosynthesis	68.505±26.629	204.775±22.202	138.818 (59.402,249.627)	0.023	increased in CF
FOLSYN-PWY	superpathway of tetrahydrofolate biosynthesis and salvage	Cofactor Carrier and Vitamin Biosynthesis	52.327±20.03	150.144±11.494	95.579 (37.066,152.656)	0.049	increased in CF
PANTO-PWY	phosphopantothenate biosynthesis I	Cofactor Carrier and Vitamin Biosynthesis	258.171±8.801	379.316±5.973	124.013 (89.771,150.065)	0.023	increased in CF
PANTOSYN-PWY	superpathway of coenzyme A biosynthesis I (bacteria)	Cofactor Carrier and Vitamin Biosynthesis	262.698±12.229	337.594±9.708	77.237 (32.442,120.855)	0.034	increased in CF
PWY-4041	γ-glutamyl cycle	Cofactor Carrier and Vitamin Biosynthesis	35.371±5.495	159.123±11.23	126.892 (89.744,158.868)	0.023	increased in CF
PWY-5121	superpathway of geranylgeranyl diphosphate biosynthesis II (via MEP)	Cofactor Carrier and Vitamin Biosynthesis	148.43±39.889	290.938±14.442	142.223 (33.517,262.56)	0.049	increased in CF
PWY-5188	tetrapyrrole biosynthesis I (from glutamate)	Cofactor Carrier and Vitamin Biosynthesis	104.372±11.993	178.075±21.206	66.453 (24.487,166.189)	0.049	increased in CF
PWY-6519	8-amino-7-oxononanoate biosynthesis I	Cofactor Carrier and Vitamin Biosynthesis	68.331±26.99	201.283±23.799	132.369 (42.353,252.122)	0.034	increased in CF
PWY-6612	superpathway of tetrahydrofolate biosynthesis	Cofactor Carrier and Vitamin Biosynthesis	38.479±15.488	115.04±10.01	72.818 (26.912,119.477)	0.049	increased in CF
PWY-6895	superpathway of thiamine diphosphate biosynthesis II	Cofactor Carrier and Vitamin Biosynthesis	0±0	92.835±32.974	91.908 (8.506,175.309)	0.023	increased in CF
PWY-6897	thiamine diphosphate salvage II	Cofactor Carrier and Vitamin Biosynthesis	91.968±9.82	173.187±11.193	78.493 (39.869,119.803)	0.023	increased in CF
PWY-7282	4-amino-2-methyl-5-diphosphomethylpyrimidine biosynthesis II	Cofactor Carrier and Vitamin Biosynthesis	20.641±5.806	108.544±9.798	90.807 (56.081,120.941)	0.023	increased in CF
PWY-7357	thiamine phosphate formation from pyrithiamine and oxythiamine (yeast)	Cofactor Carrier and Vitamin Biosynthesis	92.026±10.82	165.759±15.636	65.919 (25.419,127.061)	0.023	increased in CF
PWY0-845	superpathway of pyridoxal 5'-phosphate biosynthesis and salvage	Cofactor Carrier and Vitamin Biosynthesis	10.902±3.502	89.484±9.8	84.029 (36.403,106.094)	0.023	increased in CF
PYRIDOXSYN-PWY	pyridoxal 5'-phosphate biosynthesis I	Cofactor Carrier and Vitamin Biosynthesis	8.844±2.875	74.882±8.372	69.995 (30.249,90.006)	0.023	increased in CF
THISYNARA-PWY	superpathway of thiamine diphosphate biosynthesis III (eukaryotes)	Cofactor Carrier and Vitamin Biosynthesis	66.652±8.632	121.671±13.248	50.331 (13.61,100.306)	0.023	increased in CF
PHOSLIPSYN-PWY	superpathway of phospholipid biosynthesis I (bacteria)	Fatty Acid and Lipid Biosynthesis	87.417±15.534	185.876±11.758	102.418 (52.195,137.309)	0.023	increased in CF
PWY-5667	CDP-diacylglycerol biosynthesis I	Fatty Acid and Lipid Biosynthesis	269.682±4.765	470.825±27.647	200.053 (132.271,283.075)	0.023	increased in CF
PWY0-1319	CDP-diacylglycerol biosynthesis II	Fatty Acid and Lipid Biosynthesis	269.682±4.765	470.825±27.647	200.053 (132.271,283.075)	0.023	increased in CF
PWY-7117	C4 photosynthetic carbon assimilation cycle, PEPCK type	Generation of Precursor Metabolites and Energy	85.239±30.058	177.862±16.516	93.165 (9.541,193.207)	0.049	increased in CF
PWY-7383	anaerobic energy metabolism (invertebrates, cytosol)	Generation of Precursor Metabolites and Energy	27.18±9.196	78.768±9.395	49.65 (19.925,87.678)	0.034	increased in CF
POLYISOPRENSYN-PWY	polyisoprenoid biosynthesis (E. coli)	Lipid carrier for LPS biosnthesis	82.566±22.864	219.161±7.309	146.261 (71.584,193.88)	0.023	increased in CF
PWY-6121	5-aminoimidazole ribonucleotide biosynthesis I	Nucleoside and Nucleotide Biosynthesis	373.273±20.935	464.101±10.254	91.388 (36.042,148.772)	0.034	increased in CF
PWY-6122	5-aminoimidazole ribonucleotide biosynthesis II	Nucleoside and Nucleotide Biosynthesis	415.181±24.007	507.09±3.999	69.561 (43.262,159.77)	0.023	increased in CF
PWY-6123	inosine-5'-phosphate biosynthesis I	Nucleoside and Nucleotide Biosynthesis	306.226±28.47	422.943±12.651	128.718 (23.644,191.172)	0.049	increased in CF
PWY-6124	inosine-5'-phosphate biosynthesis II	Nucleoside and Nucleotide Biosynthesis	289.968±30.188	412.413±13.399	135.798 (23.571,199.598)	0.049	increased in CF
PWY-6277	superpathway of 5-aminoimidazole ribonucleotide biosynthesis	Nucleoside and Nucleotide Biosynthesis	415.181±24.007	507.09±3.999	69.561 (43.262,159.77)	0.023	increased in CF
PWY-7221	guanosine ribonucleotides de novo biosynthesis	Nucleoside and Nucleotide Biosynthesis	393.234±16.594	507.902±7.166	123.271 (56.743,149.717)	0.023	increased in CF
PWY-7229	superpathway of adenosine nucleotides de novo biosynthesis I	Nucleoside and Nucleotide Biosynthesis	336.582±36.997	483.537±4.556	130.936 (31.026,231.921)	0.023	increased in CF
PWY-841	superpathway of purine nucleotides de novo biosynthesis I	Nucleoside and Nucleotide Biosynthesis	276.653±25.398	399.904±5.073	113.661 (41.843,180.942)	0.023	increased in CF
PWY-6353	purine nucleotides degradation II (aerobic)	Nucleoside and Nucleotide Degradation	13.884±5.424	108.984±17.234	96.033 (46.005,147.556)	0.023	increased in CF
PWY-6595	superpathway of guanosine nucleotides degradation (plants)	Nucleoside and Nucleotide Degradation	3.748±1.671	59.293±9.327	61.713 (26.433,83.184)	0.023	increased in CF
PWY-6606	guanosine nucleotides degradation II	Nucleoside and Nucleotide Degradation	13.093±2.254	81.194±9.993	74.013 (37.068,94.841)	0.023	increased in CF
PWY-6607	guanosine nucleotides degradation I	Nucleoside and Nucleotide Degradation	3.372±1.582	63.167±11.974	63.07 (23.718,90.843)	0.023	increased in CF
PWY0-1298	superpathway of pyrimidine deoxyribonucleosides degradation	Nucleoside and Nucleotide Degradation	2.911±1.601	69.462±7.959	69.275 (39.61,93.089)	0.023	increased in CF
SALVADEHYPOX-PWY	adenosine nucleotides degradation II	Nucleoside and Nucleotide Degradation	12.337±5.851	73.718±13.698	64.312 (12.35,95.23)	0.023	increased in CF
ANAEROFRUCAT-PWY	homolactic fermentation	SCFA fermentation: Acetate Lactate Formate and Ethanol	135.996±21.271	255.829±13.618	125.294 (34.77,187.907)	0.023	increased in CF
P461-PWY	hexitol fermentation to lactate, formate, ethanol and acetate	SCFA fermentation: Acetate Lactate Formate and Ethanol	22.502±7.328	83.656±12.14	55.849 (23.135,100.528)	0.023	increased in CF
PWY-6270	isoprene biosynthesis I	Secondary Metabolite Biosynthesis	208.005±19.774	333.318±4.256	130.587 (57.312,167.847)	0.023	increased in CF
PWY-7392	taxadiene biosynthesis (engineered)	Secondary Metabolite Biosynthesis	110.607±30.423	256.075±7.836	140.251 (44.357,220.373)	0.023	increased in CF
PWY-7560	methylerythritol phosphate pathway II	Secondary Metabolite Biosynthesis	197.125±19.967	324.396±4.356	133.167 (55.684,173.629)	0.023	increased in CF

P42-PWY	incomplete reductive TCA cycle	TCA cycle	67.777±9.222	159.337±17.346	88.991 (41.692,162.819)	0.034	increased in CF
PWY-6969	TCA cycle V (2-oxoglutarate synthase)	TCA cycle	94.768±16.148	189.634±16.649	99.552 (28.199,158.034)	0.034	increased in CF
ARGININE-SYN4-PWY	L-ornithine biosynthesis II	Amino Acid Biosynthesis	61.166±9.114	252.613±16.779	202.105 (123.19,236.226)	0.023	increased in CF
ASPASN-PWY	superpathway of L-aspartate and L-asparagine biosynthesis	Amino Acid Biosynthesis	133.786±26.743	331.573±21.741	197.954 (108.166,305.328)	0.023	increased in CF
CITRULBIO-PWY	L-citrulline biosynthesis	Amino Acid Biosynthesis	88.981±12.601	205.626±21.414	108.65 (58.804,178.388)	0.023	increased in CF
PWY-5154	L-arginine biosynthesis III (via N-acetyl-L-citrulline)	Amino Acid Biosynthesis	68.429±14.537	211.703±15.891	143.496 (91.539,196.458)	0.023	increased in CF
PWY-7977	L-methionine biosynthesis IV	Amino Acid Biosynthesis	169.534±24.703	321.441±21.267	150.458 (77.176,246.526)	0.023	increased in CF
HISDEG-PWY	L-histidine degradation I	Amino Acid Degradation	117.499±7.482	284.993±9.386	165.695 (133.468,198.311)	0.023	increased in CF
PWY-5030	L-histidine degradation III	Amino Acid Degradation	48.734±10.971	196.575±15.466	152.652 (95.985,198.404)	0.023	increased in CF
FUC-RHAMCAT-PWY	superpathway of fucose and rhamnose degradation	Carbohydrate Degradation	10.614±3.592	67.594±7.593	55.364 (33.394,78.498)	0.023	increased in CF
GLCMANNANAUT-PWY	superpathway of N-acetylglucosamine, N-acetylmannosamine and N-acetylneuraminate degradation	Carbohydrate Degradation	103.007±8.878	194.87±19.973	79.397 (34.681,156.631)	0.023	increased in CF
HEXITOLDEGSUPER-PWY	superpathway of hexitol degradation (bacteria)	Carbohydrate Degradation	0.804±0.804	27.189±10.826	28.793 (0.833,54.083)	0.047	increased in CF
PWY-1042	glycolysis IV	Carbohydrate Degradation	356.516±27.087	468.372±5.507	116.746 (22.44,176.677)	0.023	increased in CF
PWY-621	sucrose degradation III (sucrose invertase)	Carbohydrate Degradation	21.384±9.088	105.175±10.232	88.417 (51.983,122.652)	0.023	increased in CF
PWY-6531	mannitol cycle	Carbohydrate Degradation	0±0	20.673±8.032	20.646 (1.406,39.886)	0.023	increased in CF
PWY-6731	starch degradation III	Carbohydrate Degradation	20.589±3.376	59.747±9.575	45.494 (7.329,66.666)	0.023	increased in CF
PWY-6902	chitin degradation II (Vibrio)	Carbohydrate Degradation	91.714±24.55	308.014±29.168	236.371 (105.336,299.646)	0.034	increased in CF
PWY-7237	myo-, chiro- and scyllo-inositol degradation	Carbohydrate Degradation	46.036±9.652	174.225±18.697	119.881 (77.271,191.15)	0.023	increased in CF
RHAMCAT-PWY	L-rhamnose degradation I	Carbohydrate Degradation	67.227±12.156	206.035±6.185	136.221 (103.039,172.05)	0.023	increased in CF
PWY0-1586	peptidoglycan maturation (meso-diaminopimelate containing)	Cell Structure Biosynthesis	84.305±19.774	280.927±32.573	198.452 (83.657,295.604)	0.023	increased in CF
1CMET2-PWY	folate transformations III (E. coli)	Cofactor Carrier and Vitamin Biosynthesis	208.022±20.408	344.811±12.541	131.38 (81.756,210.731)	0.023	increased in CF
COBALSYN-PWY	superpathway of adenosylcobalamin salvage from cobinamide I	Cofactor Carrier and Vitamin Biosynthesis	4.825±1.312	20.598±3.904	15.738 (4.657,26.651)	0.034	increased in CF
HEME-BIOSYNTHESIS-II-1	heme b biosynthesis V (aerobic)	Cofactor Carrier and Vitamin Biosynthesis	0.31±0.31	20.976±5.879	21.958 (6.496,36.595)	0.023	increased in CF
PWY-5189	tetrapyrrole biosynthesis II (from glycine)	Cofactor Carrier and Vitamin Biosynthesis	24.737±5.792	62.832±10.117	41.173 (4.717,75.259)	0.034	increased in CF
PWY-6147	6-hydroxymethyl-dihydropterin diphosphate biosynthesis I	Cofactor Carrier and Vitamin Biosynthesis	83.28±10.639	267.042±18.595	193.455 (114.995,235.531)	0.023	increased in CF
PWY-6823	molybdopterin biosynthesis	Cofactor Carrier and Vitamin Biosynthesis	67.202±5.06	132.457±17.648	54.524 (33.059,142.83)	0.023	increased in CF
PWY0-1415	superpathway of heme b biosynthesis from uroporphyrinogen-III	Cofactor Carrier and Vitamin Biosynthesis	0.311±0.311	20.778±5.789	21.548 (6.539,35.754)	0.023	increased in CF
PYRIDNUCSAL-PWY	NAD salvage pathway I (PNC VI cycle)	Cofactor Carrier and Vitamin Biosynthesis	0±0	19.104±7.103	23.541 (2.226,44.856)	0.023	increased in CF
PYRIDNUCSYN-PWY	NAD de novo biosynthesis I (from aspartate)	Cofactor Carrier and Vitamin Biosynthesis	198.697±12.442	299.008±10.686	101.359 (63.294,140.695)	0.023	increased in CF
RIBOSYN2-PWY	flavin biosynthesis I (bacteria and plants)	Cofactor Carrier and Vitamin Biosynthesis	142.964±4.803	281.363±11.602	147.371 (93.765,169.863)	0.023	increased in CF
PWY-5973	cis-vaccenate biosynthesis	Fatty Acid and Lipid Biosynthesis	222.325±17.782	391.153±17.562	172.34 (99.773,235.562)	0.023	increased in CF
PWY-7663	gondoate biosynthesis (anaerobic)	Fatty Acid and Lipid Biosynthesis	202.789±20.83	370.102±17.272	176.054 (101.46,239.065)	0.023	increased in CF
PWY66-429	fatty acid biosynthesis initiation (mitochondria)	Fatty Acid and Lipid Biosynthesis	287.679±27.214	457.968±14.568	168.899 (81.456,255.044)	0.023	increased in CF
PWY-561	superpathway of glyoxylate cycle and fatty acid degradation	Fatty Acid and Lipid Degradation	0±0	22.679±9.501	25.162 (0,50.324)	0.041	increased in CF
PWY-1269	CMP-3-deoxy-D-manno-octulosonate biosynthesis	LPS biosynthesis	41.427±4.312	136.441±11.667	99.614 (52.079,124.601)	0.023	increased in CF
PWY-7316	dTDP-N-acetylviosamine biosynthesis	LPS biosynthesis	0.504±0.309	33.266±6.616	27.35 (17.061,57.702)	0.023	increased in CF
PWY-7323	superpathway of GDP-mannose-derived O-antigen building blocks biosynthesis	LPS biosynthesis	48.282±5.889	150.85±13.549	99.688 (61.803,149.359)	0.023	increased in CF
PWY-7328	superpathway of UDP-glucose-derived O-antigen building blocks biosynthesis	LPS biosynthesis	72.875±9.628	173.608±17.985	97.988 (43.39,159.724)	0.023	increased in CF
PWY0-1241	ADP-L-glycero-β-D-manno-heptose biosynthesis	LPS biosynthesis	41.223±7.946	81.586±4.937	41.424 (16.844,69.917)	0.023	increased in CF
PWY-4984	urea cycle	Nitrogen Compound Metabolism	73.32±10.278	184.152±20.37	110.401 (51.266,176.871)	0.023	increased in CF
PWY-6125	superpathway of guanosine nucleotides de novo biosynthesis II	Nucleoside and Nucleotide Biosynthesis	225.678±29.482	352.458±10.09	118.618 (46.121,210.186)	0.023	increased in CF
PWY-6126	superpathway of adenosine nucleotides de novo biosynthesis II	Nucleoside and Nucleotide Biosynthesis	282.65±34.514	418.414±7.327	124.769 (28.223,226.852)	0.023	increased in CF
PWY-6700	queuosine biosynthesis I (de novo)	Nucleoside and Nucleotide Biosynthesis	281.803±18.553	378.855±16.83	104.892 (32.804,153.205)	0.034	increased in CF
PWY-6703	preQ0 biosynthesis	Nucleoside and Nucleotide Biosynthesis	146.449±12.431	236.194±13.268	92.423 (37.876,140.202)	0.023	increased in CF
PWY-7199	pyrimidine deoxyribonucleosides salvage	Nucleoside and Nucleotide Biosynthesis	155.138±19.97	233.276±10.767	81.786 (16.181,129.063)	0.034	increased in CF
PWY-7220	adenosine deoxyribonucleotides de novo biosynthesis II	Nucleoside and Nucleotide Biosynthesis	180.856±29.344	305.588±12.165	123.422 (46.872,218.005)	0.023	increased in CF
PWY-7222	guanosine deoxyribonucleotides de novo biosynthesis II	Nucleoside and Nucleotide Biosynthesis	180.856±29.344	305.588±12.165	123.422 (46.872,218.005)	0.023	increased in CF
PWY-7228	superpathway of guanosine nucleotides de novo biosynthesis I	Nucleoside and Nucleotide Biosynthesis	248.753±30.88	385.67±9.111	123.36 (49.155,219.983)	0.023	increased in CF
PWY66-409	superpathway of purine nucleotide salvage	Nucleoside and Nucleotide Biosynthesis	6.808±3.653	213.823±18.309	198.586 (161.405,270.024)	0.023	increased in CF
P164-PWY	purine nucleobases degradation I (anaerobic)	Nucleoside and Nucleotide Degradation	12.942±1.981	76.295±11.884	67.082 (27.124,94.044)	0.023	increased in CF
PWY-5497	purine nucleobases degradation II (anaerobic)	Nucleoside and Nucleotide Degradation	8.2±2.495	64.615±9.767	57.027 (28.553,83.548)	0.023	increased in CF
PWY-5695	inosine 5'-phosphate degradation	Nucleoside and Nucleotide Degradation	244.614±27.454	392.494±16.444	129.877 (97.193,236.505)	0.023	increased in CF
PWY-6608	guanosine nucleotides degradation III	Nucleoside and Nucleotide Degradation	22.3±4.623	122.274±11.155	108.484 (58.541,128.12)	0.023	increased in CF
PWY-8131	5'-deoxyadenosine degradation II	Nucleoside and Nucleotide Degradation	2.894±1.378	21.455±3.745	17.579 (8.604,31.56)	0.023	increased in CF
CENTFERM-PWY	pyruvate fermentation to butanoate	SCFA fermentation: Butyrate	26.832±7.55	0.477±0.477	-19.706 (-48.712,-8.72)	0.023	increased in WT
PWY-5676	acetyl-CoA fermentation to butanoate II	SCFA fermentation: Butyrate	2.634±1.613	15.945±3.319	12.911 (1.482,23.938)	0.023	increased in CF
PWY-6590	superpathway of Clostridium acetobutylicum acidogenic fermentation	SCFA fermentation: Butyrate and Acetate	33.551±9.026	0.633±0.633	-25.515 (-60.002,-11.534)	0.023	increased in WT
PWY-6859	all-trans-farnesol biosynthesis	Secondary Metabolite Biosynthesis	58.153±17.776	169.773±6.552	119.216 (56.583,154.509)	0.023	increased in CF
TCA-GLYOX-BYPASS	superpathway of glyoxylate bypass and TCA	TCA cycle	0±0	20.887±8.854	24.052 (0,48.104)	0.041	increased in CF

Pathway in yellow color indicates differentially abundant pathway between WT and CF mice in both ages

Table S7 Differentially abundant functional pathway between WT and CF mice at 14-week-old

Pathway_ID	Pathway_description	Pathway_superclass	WT.mean±sem	CF.mean±sem	Mean of difference (95% CI)	adj.p	Significant
PWY-7111	pyruvate fermentation to isobutanol (engineered)	Alcohol fermentation: Isobutanol	235.594±21.135	423.649±16.09	180.488 (121.076,260.681)	0.003	increased in CF
BRANCHED-CHAIN-AA-SYN-PWY	superpathway of branched chain amino acid biosynthesis	Amino Acid Biosynthesis	378.323±15.999	525.055±8.716	139.474 (91.423,196.043)	0.003	increased in CF
COMPLETE-ARO-PWY	superpathway of aromatic amino acid biosynthesis	Amino Acid Biosynthesis	315.872±14.113	457.13±16.401	139.64 (97.718,185.627)	0.003	increased in CF
HISTSYN-PWY	L-histidine biosynthesis	Amino Acid Biosynthesis	340.457±17.796	442.914±15.612	94.972 (57.554,168.931)	0.008	increased in CF
ILEUSYN-PWY	L-isoleucine biosynthesis I (from threonine)	Amino Acid Biosynthesis	396.34±14.23	536.105±9.646	133.892 (92.5,184.396)	0.003	increased in CF
PWY-2942	L-lysine biosynthesis III	Amino Acid Biosynthesis	311.125±17.466	506.609±12.234	194.385 (156.214,244.087)	0.003	increased in CF
PWY-3001	superpathway of L-isoleucine biosynthesis I	Amino Acid Biosynthesis	272.888±21.217	393.456±3.433	88.266 (72.262,200.418)	0.003	increased in CF
PWY-5097	L-lysine biosynthesis VI	Amino Acid Biosynthesis	318.045±10.774	513.323±11.352	193.793 (164.393,232.302)	0.003	increased in CF
PWY-5103	L-isoleucine biosynthesis III	Amino Acid Biosynthesis	346.97±15.719	504.734±10.175	148.485 (106.472,206.298)	0.003	increased in CF
PWY-724	superpathway of L-lysine, L-threonine and L-methionine biosynthesis II	Amino Acid Biosynthesis	271.346±12.502	429.499±8.402	154.145 (120.4,195.15)	0.003	increased in CF
THRESYN-PWY	superpathway of L-threonine biosynthesis	Amino Acid Biosynthesis	268.726±28.524	390.543±8.89	96.298 (47.992,230.702)	0.003	increased in CF
VALSYN-PWY	L-valine biosynthesis	Amino Acid Biosynthesis	503.226±9.16	584.169±9.977	80.829 (47.38,114.078)	0.004	increased in CF
CALVIN-PWY	Calvin-Benson-Bassham cycle	Carbohydrate Biosynthesis	235.98±11.471	311.154±5.733	76.531 (43.912,109.512)	0.003	increased in CF
COLANSYN-PWY	colanic acid building blocks biosynthesis	Carbohydrate Biosynthesis	145.893±17.113	214.449±12.715	62.56 (16.534,114.82)	0.023	increased in CF
DTDPRHAMSYN-PWY	dTDP-β-L-rhamnose biosynthesis	Carbohydrate Biosynthesis	398.231±28.106	569.639±11.574	186.021 (87.362,241.686)	0.013	increased in CF
PWY-6143	CMP-pseudaminate biosynthesis	Carbohydrate Biosynthesis	19.111±4.502	0.063±0.063	-16.496 (-29.34,-4.699)	0.006	increased in WT
PWY66-399	gluconeogenesis III	Carbohydrate Biosynthesis	41.688±6.668	158.674±9.537	117.942 (86.699,140.595)	0.003	increased in CF
FUCCAT-PWY	fucose degradation	Carbohydrate Degradation	13.756±4.656	26.244±2.864	15.331 (4.526,25.352)	0.039	increased in CF
GLUCOSE1PMETAB-PWY	glucose and glucose-1-phosphate degradation	Carbohydrate Degradation	0±0	131.559±14.558	117.733 (105.426,151.422)	0.003	increased in CF
NONOXIPENT-PWY	pentose phosphate pathway (non-oxidative branch) I	Carbohydrate Degradation	133.53±11.825	219.567±6.645	86.095 (47.964,124.089)	0.003	increased in CF
PENTOSE-P-PWY	pentose phosphate pathway	Carbohydrate Degradation	127.512±12.071	239.089±5.072	99.244 (82.127,155.89)	0.003	increased in CF
PWY-5941	glycogen degradation II	Carbohydrate Degradation	209.796±11.764	312.933±11.354	107.971 (67.513,137.275)	0.003	increased in CF
PWY-6317	D-galactose degradation I (Leloir pathway)	Carbohydrate Degradation	158.993±11.919	238.886±12.984	78.311 (36.829,114.555)	0.003	increased in CF
PWY-6901	superpathway of glucose and xylose degradation	Carbohydrate Degradation	156.343±9.97	268.804±3.052	103.078 (86.373,150.184)	0.003	increased in CF
PWY-8178	pentose phosphate pathway (non-oxidative branch) II	Carbohydrate Degradation	149.916±10.167	215.077±5.475	70.909 (37.236,97.821)	0.003	increased in CF
ARO-PWY	chorismate biosynthesis I	Carboxylic Acid Biosynthesis	326.001±13.956	460.054±17.088	140.99 (82.165,179.719)	0.003	increased in CF
PWY-6163	chorismate biosynthesis from 3-dehydroquinate	Carboxylic Acid Biosynthesis	345.551±12.942	444.937±15.54	106.666 (49.769,137.271)	0.006	increased in CF
GALACTARDEG-PWY	D-galactarate degradation I	Carboxylic Acid Degradation	5.1±2.065	20.597±2.811	15.943 (7.852,23.766)	0.006	increased in CF
GLUCARDEG-PWY	D-glucarate degradation I	Carboxylic Acid Degradation	4.43±1.814	18.281±2.475	14.501 (6.868,20.707)	0.006	increased in CF
GLUCARGALACTSUPER-PWY	superpathway of D-glucarate and D-galactarate degradation	Carboxylic Acid Degradation	5.1±2.065	20.597±2.811	15.943 (7.852,23.766)	0.006	increased in CF
P441-PWY	superpathway of N-acetylneuraminate degradation	Carboxylic Acid Degradation	91.534±17.384	210.504±4.075	117.36 (67.525,169.557)	0.003	increased in CF
PWY-6385	peptidoglycan biosynthesis III (mycobacteria)	Cell Structure Biosynthesis	342.738±18.124	547.361±9.018	210.089 (160.136,260.111)	0.003	increased in CF
PWY-6386	UDP-N-acetylmuramoyl-pentapeptide biosynthesis II (lysine-containing)	Cell Structure Biosynthesis	339.237±20.15	554.362±14.419	212.43 (164.151,280.058)	0.003	increased in CF
PWY-6387	UDP-N-acetylmuramoyl-pentapeptide biosynthesis I (meso-diaminopimelate containing)	Cell Structure Biosynthesis	360.911±13.946	568.354±11.407	210.259 (175.589,255.98)	0.003	increased in CF
PWY-7953	UDP-N-acetylmuramoyl-pentapeptide biosynthesis III (meso-diaminopimelate containing)	Cell Structure Biosynthesis	325.514±22.56	557.14±9.46	224.194 (171.141,290.787)	0.003	increased in CF
BIOTIN-BIOSYNTHESIS-PWY	biotin biosynthesis I	Cofactor Carrier and Vitamin Biosynthesis	121.426±27.857	205.224±8.057	62.84 (12.663,191.081)	0.039	increased in CF
FOLSYN-PWY	superpathway of tetrahydrofolate biosynthesis and salvage	Cofactor Carrier and Vitamin Biosynthesis	141.244±18.131	209.577±8.893	51.567 (20.536,132.662)	0.013	increased in CF
PANTO-PWY	phosphopantothenate biosynthesis I	Cofactor Carrier and Vitamin Biosynthesis	293.287±14.701	357.709±6.5	71.636 (22.106,101.793)	0.018	increased in CF
PANTOSYN-PWY	superpathway of coenzyme A biosynthesis I (bacteria)	Cofactor Carrier and Vitamin Biosynthesis	292.629±13.629	346.748±4.34	65.016 (10.981,83.833)	0.039	increased in CF
PWY-4041	γ-glutamyl cycle	Cofactor Carrier and Vitamin Biosynthesis	64.275±9.728	109.934±8.787	50.893 (13.534,79.013)	0.013	increased in CF
PWY-5121	superpathway of geranylgeranyl diphosphate biosynthesis II (via MEP)	Cofactor Carrier and Vitamin Biosynthesis	259.555±29.083	373.141±12.939	77.931 (38.044,219.81)	0.006	increased in CF
PWY-5188	tetrapyrrole biosynthesis I (from glutamate)	Cofactor Carrier and Vitamin Biosynthesis	120.733±12.891	174.522±5.206	50.284 (17.285,92.589)	0.013	increased in CF
PWY-6519	8-amino-7-oxononanoate biosynthesis I	Cofactor Carrier and Vitamin Biosynthesis	115.292±27.263	208.488±9.189	79.161 (20.382,198.468)	0.023	increased in CF
PWY-6612	superpathway of tetrahydrofolate biosynthesis	Cofactor Carrier and Vitamin Biosynthesis	112.225±15.917	166.764±7.605	40.611 (11.162,112.599)	0.023	increased in CF
PWY-6895	superpathway of thiamine diphosphate biosynthesis II	Cofactor Carrier and Vitamin Biosynthesis	0±0	71.508±11.976	80.818 (49.995,86.901)	0.003	increased in CF
PWY-6897	thiamine diphosphate salvage II	Cofactor Carrier and Vitamin Biosynthesis	125.111±7.265	168.626±4.709	44.318 (20.887,64.684)	0.004	increased in CF
PWY-7282	4-amino-2-methyl-5-diphosphomethylpyrimidine biosynthesis II	Cofactor Carrier and Vitamin Biosynthesis	28.562±4.9	118.974±5.368	90.124 (72.61,106.165)	0.003	increased in CF
PWY-7357	thiamine phosphate formation from pyrithiamine and oxythiamine (yeast)	Cofactor Carrier and Vitamin Biosynthesis	106.023±3.958	169.945±5.821	66.894 (45.304,81.482)	0.003	increased in CF
PWY0-845	superpathway of pyridoxal 5'-phosphate biosynthesis and salvage	Cofactor Carrier and Vitamin Biosynthesis	15.146±3.168	98.14±8.734	78.24 (61.078,108.972)	0.003	increased in CF
PYRIDOXSYN-PWY	pyridoxal 5'-phosphate biosynthesis I	Cofactor Carrier and Vitamin Biosynthesis	12.417±2.618	82.242±7.761	63.53 (51.017,93.418)	0.003	increased in CF
THISYNARA-PWY	superpathway of thiamine diphosphate biosynthesis III (eukaryotes)	Cofactor Carrier and Vitamin Biosynthesis	98.949±8.086	132.103±6.082	31.192 (9.457,55.798)	0.018	increased in CF
PHOSLIPSYN-PWY	superpathway of phospholipid biosynthesis I (bacteria)	Fatty Acid and Lipid Biosynthesis	162.806±13.054	233.107±8.518	70.688 (28.383,108.519)	0.004	increased in CF
PWY-5667	CDP-diacylglycerol biosynthesis I	Fatty Acid and Lipid Biosynthesis	349.204±22.151	418.186±6.879	66.136 (11.779,132.573)	0.05	increased in CF
PWY0-1319	CDP-diacylglycerol biosynthesis II	Fatty Acid and Lipid Biosynthesis	349.204±22.151	418.186±6.879	66.136 (11.779,132.573)	0.05	increased in CF
PWY-7117	C4 photosynthetic carbon assimilation cycle, PEPCK type	Generation of Precursor Metabolites and Energy	150.307±23.504	252.436±5.878	82.969 (35.894,184.898)	0.003	increased in CF
PWY-7383	anaerobic energy metabolism (invertebrates, cytosol)	Generation of Precursor Metabolites and Energy	21.912±4.256	108.267±8.373	83.373 (63.884,109.331)	0.003	increased in CF
POLYISOPRENSYN-PWY	polyisoprenoid biosynthesis (E. coli)	Lipid carrier for LPS biosnthesis	136.274±19.152	220.554±15.581	85.549 (28.297,142.84)	0.018	increased in CF
PWY-6121	5-aminoimidazole ribonucleotide biosynthesis I	Nucleoside and Nucleotide Biosynthesis	386.459±15.652	512.526±19.237	128.712 (72.266,180.417)	0.003	increased in CF
PWY-6122	5-aminoimidazole ribonucleotide biosynthesis II	Nucleoside and Nucleotide Biosynthesis	413.512±15.114	579.175±18.111	163.655 (111.382,213.702)	0.003	increased in CF
PWY-6123	inosine-5'-phosphate biosynthesis I	Nucleoside and Nucleotide Biosynthesis	360.167±21.065	502.584±10.614	133.019 (91.554,210.562)	0.003	increased in CF
PWY-6124	inosine-5'-phosphate biosynthesis II	Nucleoside and Nucleotide Biosynthesis	348.479±21.804	490.003±10.888	131.7 (87.222,215.955)	0.003	increased in CF
PWY-6277	superpathway of 5-aminoimidazole ribonucleotide biosynthesis	Nucleoside and Nucleotide Biosynthesis	413.512±15.114	579.175±18.111	163.655 (111.382,213.702)	0.003	increased in CF
PWY-7221	guanosine ribonucleotides de novo biosynthesis	Nucleoside and Nucleotide Biosynthesis	403.115±17.274	566.467±12.249	166.092 (117.837,215.921)	0.003	increased in CF
PWY-7229	superpathway of adenosine nucleotides de novo biosynthesis I	Nucleoside and Nucleotide Biosynthesis	396.19±23.679	484.745±8.717	64.474 (26.532,170.353)	0.006	increased in CF
PWY-841	superpathway of purine nucleotides de novo biosynthesis I	Nucleoside and Nucleotide Biosynthesis	334.113±18.409	401.223±8.144	49.74 (16.722,131.834)	0.008	increased in CF
PWY-6353	purine nucleotides degradation II (aerobic)	Nucleoside and Nucleotide Degradation	31.976±4.852	51.03±3.415	18.07 (4.274,35.774)	0.023	increased in CF
PWY-6595	superpathway of guanosine nucleotides degradation (plants)	Nucleoside and Nucleotide Degradation	10.92±2.717	28.759±2.013	16.676 (9.592,27.358)	0.003	increased in CF
PWY-6606	guanosine nucleotides degradation II	Nucleoside and Nucleotide Degradation	21.796±3.38	35.669±3.473	14.367 (3.292,23.928)	0.03	increased in CF
PWY-6607	guanosine nucleotides degradation I	Nucleoside and Nucleotide Degradation	9.752±2.438	29.163±1.912	18.839 (12.196,26.699)	0.003	increased in CF
PWY0-1298	superpathway of pyrimidine deoxyribonucleosides degradation	Nucleoside and Nucleotide Degradation	18.765±3.932	49.876±4.649	30.858 (15.728,45.077)	0.003	increased in CF
SALVADEHYPOX-PWY	adenosine nucleotides degradation II	Nucleoside and Nucleotide Degradation	16.984±2.806	31.906±2.452	15.499 (5.875,24.543)	0.01	increased in CF

ANAEROFRUCAT-PWY	homolactic fermentation	SCFA fermentation: Acetate Lactate Formate and Ethanol	193.144±12.647	276.202±9.391	78.665 (42.568,116.18)	0.003	increased in CF
P461-PWY	hexitol fermentation to lactate, formate, ethanol and acetate	SCFA fermentation: Acetate Lactate Formate and Ethanol	16.787±5.419	129.648±18.359	106.67 (73.572,145.352)	0.003	increased in CF
PWY-6270	isoprene biosynthesis I	Secondary Metabolite Biosynthesis	218.392±22.615	320.31±9.015	116.308 (27.635,156.598)	0.01	increased in CF
PWY-7392	taxadiene biosynthesis (engineered)	Secondary Metabolite Biosynthesis	172.937±21.493	265.787±11.098	98.22 (29.194,158.775)	0.013	increased in CF
PWY-7560	methylerythritol phosphate pathway II	Secondary Metabolite Biosynthesis	206.935±22.46	307.538±10.193	112.652 (30.324,158.802)	0.01	increased in CF
P42-PWY	incomplete reductive TCA cycle	TCA cycle	105.965±14.319	210.172±11.884	96.424 (63.237,145.645)	0.003	increased in CF
PWY-6969	TCA cycle V (2-oxoglutarate synthase)	TCA cycle	121.815±14.495	251.993±8.054	131.003 (93.28,171.198)	0.003	increased in CF
PWY0-1477	ethanolamine utilization	Amine Degradation	42.195±10.19	200.894±17.999	164.644 (114.5,210.872)	0.003	increased in CF
ARG+POLYAMINE-SYN	superpathway of arginine and polyamine biosynthesis	Amino Acid Biosynthesis	7.162±2.368	32.632±2.894	24.6 (16.51,34.35)	0.003	increased in CF
ARGSYN-PWY	L-arginine biosynthesis I (via L-ornithine)	Amino Acid Biosynthesis	283.524±11.905	406.967±9.836	123.988 (82.449,159.456)	0.003	increased in CF
ARGSYNBSUB-PWY	L-arginine biosynthesis II (acetyl cycle)	Amino Acid Biosynthesis	299.19±10.347	440.187±10.87	135.908 (100.317,177.437)	0.003	increased in CF
DAPLYSINESYN-PWY	L-lysine biosynthesis I	Amino Acid Biosynthesis	172.003±20.64	343.487±15.319	164.9 (100.34,231.608)	0.003	increased in CF
GLUTORN-PWY	L-ornithine biosynthesis I	Amino Acid Biosynthesis	250.054±8.444	344.123±12.9	92.865 (59.463,129.353)	0.003	increased in CF
HSERMETANA-PWY	L-methionine biosynthesis III	Amino Acid Biosynthesis	213.307±11.541	338.666±16.546	121.731 (78.855,169.622)	0.003	increased in CF
MET-SAM-PWY	superpathway of S-adenosyl-L-methionine biosynthesis	Amino Acid Biosynthesis	1.839±0.776	18.327±3.27	19.554 (7.147,25.125)	0.005	increased in CF
METSYN-PWY	superpathway of L-homoserine and L-methionine biosynthesis	Amino Acid Biosynthesis	1.618±0.683	16.155±2.889	17.221 (6.293,22.122)	0.005	increased in CF
P4-PWY	superpathway of L-lysine, L-threonine and L-methionine biosynthesis I	Amino Acid Biosynthesis	3.613±1.503	35.477±6.06	37.432 (14.54,47.818)	0.003	increased in CF
PWY-2941	L-lysine biosynthesis II	Amino Acid Biosynthesis	84.565±9.234	215.461±31.328	113.747 (74.988,159.651)	0.003	increased in CF
PWY-5104	L-isoleucine biosynthesis IV	Amino Acid Biosynthesis	11.2±1.982	24.547±5.404	10.035 (0.569,28.532)	0.03	increased in CF
PWY-5345	superpathway of L-methionine biosynthesis (by sulfhydrylation)	Amino Acid Biosynthesis	7.151±2.789	37.61±6.162	30.631 (15.182,44.215)	0.007	increased in CF
PWY-5347	superpathway of L-methionine biosynthesis (transsulfuration)	Amino Acid Biosynthesis	1.839±0.776	18.18±3.236	19.324 (7.112,24.881)	0.005	increased in CF
PWY-5505	L-glutamate and L-glutamine biosynthesis	Amino Acid Biosynthesis	6.671±1.833	15.174±1.271	8.841 (2.569,14.482)	0.023	increased in CF
PWY-6628	superpathway of L-phenylalanine biosynthesis	Amino Acid Biosynthesis	176.385±24.945	267.3±7.001	60.166 (20.764,177.527)	0.003	increased in CF
PWY-6630	superpathway of L-tyrosine biosynthesis	Amino Acid Biosynthesis	116.247±16.441	320.264±20.2	211.719 (144.172,260.453)	0.003	increased in CF
PWY-6936	seleno-amino acid biosynthesis (plants)	Amino Acid Biosynthesis	138.618±19.698	292.494±16.271	154.12 (98.794,226.158)	0.003	increased in CF
PWY-702	L-methionine biosynthesis II	Amino Acid Biosynthesis	93.512±15.603	241.83±16.009	147.995 (94.861,200.341)	0.003	increased in CF
PWY-7400	L-arginine biosynthesis IV (archaebacteria)	Amino Acid Biosynthesis	175.401±15.215	244.977±4.514	67.713 (44.655,104.047)	0.018	increased in CF
PWY-I9	L-cysteine biosynthesis VI (from L-methionine)	Amino Acid Biosynthesis	144.894±20.448	330.136±15.092	182.096 (120.146,250.495)	0.003	increased in CF
PWY0-1061	superpathway of L-alanine biosynthesis	Amino Acid Biosynthesis	42.504±11.838	228.446±19.786	190.277 (129.455,242.749)	0.003	increased in CF
PWY0-781	aspartate superpathway	Amino Acid Biosynthesis	3.806±1.583	37.315±6.361	39.405 (15.301,50.349)	0.003	increased in CF
SER-GLYSYN-PWY	superpathway of L-serine and glycine biosynthesis I	Amino Acid Biosynthesis	252.155±30.042	415.095±5.98	130.168 (89.283,270.745)	0.003	increased in CF
SULFATE-CYS-PWY	superpathway of sulfate assimilation and cysteine biosynthesis	Amino Acid Biosynthesis	5.793±2.25	31.615±5.23	26.153 (12.577,37.584)	0.006	increased in CF
GLUDEG-I-PWY	GABA shunt	Amino Acid Degradation	6.253±3.24	17.421±2.78	11.83 (4.965,19.286)	0.048	increased in CF
PWY-8187	L-arginine degradation XIII (reductive Stickland reaction)	Amino Acid Degradation	101.142±10.587	54.938±9.894	-56.598 (-72.006,-10.917)	0.008	increased in WT
GLUCONEO-PWY	gluconeogenesis I	Carbohydrate Biosynthesis	240.158±10.502	292.292±4.497	46.316 (25.859,80.125)	0.003	increased in CF
PWY-5659	GDP-mannose biosynthesis	Carbohydrate Biosynthesis	152.113±19.062	267.688±17.842	113.496 (41.971,172.856)	0.003	increased in CF
PWY-622	starch biosynthesis	Carbohydrate Biosynthesis	83.15±16.952	213.823±5.696	132.635 (78.973,182.176)	0.003	increased in CF
PWY-7238	sucrose biosynthesis II	Carbohydrate Biosynthesis	296.204±31.598	454.228±20.026	141.334 (75.442,272.515)	0.006	increased in CF
PWY-7315	dTDP-N-acetylthomosamine biosynthesis	Carbohydrate Biosynthesis	52.966±9.668	9.152±1.593	-38.387 (-76.288,-16.022)	0.003	increased in WT
UDPNAGSYN-PWY	UDP-N-acetyl-D-glucosamine biosynthesis I	Carbohydrate Biosynthesis	251.954±18.86	467.869±29.743	218.922 (118.213,290.179)	0.003	increased in CF
ANAGLYCOLYSIS-PWY	glycolysis III (from glucose)	Carbohydrate Degradation	311.649±9.624	428.301±4.255	114.346 (94.237,145.132)	0.003	increased in CF
GLYCOCAT-PWY	glycogen degradation I	Carbohydrate Degradation	56.231±13.229	117.096±7.352	66.018 (20.943,100.401)	0.01	increased in CF
GLYCOLYSIS	glycolysis I (from glucose 6-phosphate)	Carbohydrate Degradation	258.724±11.021	399.935±8.926	139.329 (103.494,171.719)	0.003	increased in CF
GLYCOLYSIS-E-D	superpathway of glycolysis and the Entner-Doudoroff pathway	Carbohydrate Degradation	105.452±8.051	190.484±7.787	90.296 (58.255,112.469)	0.003	increased in CF
LACTOSECAT-PWY	lactose and galactose degradation I	Carbohydrate Degradation	17.299±1.524	35.358±2.231	18.145 (11.769,24.456)	0.003	increased in CF
PWY-5384	sucrose degradation IV (sucrose phosphorylase)	Carbohydrate Degradation	70.28±13.637	243.845±10.641	172.153 (133.747,207.938)	0.003	increased in CF
PWY-5484	glycolysis II (from fructose 6-phosphate)	Carbohydrate Degradation	237.287±12.193	375.987±6.491	134.116 (108.488,169.552)	0.003	increased in CF
PWY-5723	Rubisco shunt	Carbohydrate Degradation	0±0	29.647±14.557	15.978 (14.51,23.646)	0.003	increased in CF
PWY-6527	stachyose degradation	Carbohydrate Degradation	122.302±16.424	292.791±26.33	160.289 (104.46,220.239)	0.003	increased in CF
PWY-7345	superpathway of anaerobic sucrose degradation	Carbohydrate Degradation	132.563±23.718	282.442±7.188	119.983 (90.592,229.862)	0.003	increased in CF
PWY-8004	Entner-Doudoroff pathway I	Carbohydrate Degradation	90.244±8.962	184.738±10.364	101.547 (61.571,126.418)	0.003	increased in CF
PWY-5130	2-oxobutanoate degradation I	Carboxylic Acid Degradation	7.204±1.376	16.344±1.589	9.194 (3.917,15.003)	0.008	increased in CF
PEPTIDOGLYCANSYN-PWY	peptidoglycan biosynthesis I (meso-diaminopimelate containing)	Cell Structure Biosynthesis	367.9±13.871	569.016±11.124	202.32 (166.469,245.837)	0.003	increased in CF
COA-PWY	coenzyme A biosynthesis I (prokaryotic)	Cofactor Carrier and Vitamin Biosynthesis	305.268±14.086	404.294±18.753	96.595 (46.462,138.157)	0.003	increased in CF
COA-PWY-1	superpathway of coenzyme A biosynthesis III (mammals)	Cofactor Carrier and Vitamin Biosynthesis	310.741±14.211	405.823±21.595	88.622 (37.998,130.302)	0.008	increased in CF
HEME-BIOSYNTHESIS-II	heme b biosynthesis I (aerobic)	Cofactor Carrier and Vitamin Biosynthesis	29.28±6.633	97.501±8.026	70.539 (44.098,96.872)	0.003	increased in CF
PWY-3841	folate transformations II (plants)	Cofactor Carrier and Vitamin Biosynthesis	313.019±13.109	457.772±8.727	152.244 (105.372,175.542)	0.003	increased in CF
PWY-5838	superpathway of menaquinol-8 biosynthesis I	Cofactor Carrier and Vitamin Biosynthesis	0±0	24.443±5.298	19.03 (14.767,36.868)	0.003	increased in CF
PWY-5840	superpathway of menaquinol-7 biosynthesis	Cofactor Carrier and Vitamin Biosynthesis	0±0	16.79±3.303	16.4 (12.525,18.325)	0.003	increased in CF
PWY-5861	superpathway of demethylmenaquinol-8 biosynthesis I	Cofactor Carrier and Vitamin Biosynthesis	0±0	17.029±3.793	13.042 (10.043,26.059)	0.003	increased in CF
PWY-5897	superpathway of menaquinol-11 biosynthesis	Cofactor Carrier and Vitamin Biosynthesis	0±0	21.761±4.763	16.847 (13.024,32.941)	0.003	increased in CF
PWY-5898	superpathway of menaquinol-12 biosynthesis	Cofactor Carrier and Vitamin Biosynthesis	0±0	21.761±4.763	16.847 (13.024,32.941)	0.003	increased in CF
PWY-5899	superpathway of menaquinol-13 biosynthesis	Cofactor Carrier and Vitamin Biosynthesis	0±0	21.761±4.763	16.847 (13.024,32.941)	0.003	increased in CF
PWY-5918	superpathway of heme b biosynthesis from glutamate	Cofactor Carrier and Vitamin Biosynthesis	47.516±8.843	116.506±7.984	73.818 (35.107,95.111)	0.003	increased in CF
PWY-6151	S-adenosyl-L-methionine salvage I	Cofactor Carrier and Vitamin Biosynthesis	303.957±16.799	508.921±15.527	194.248 (151.158,258.296)	0.003	increased in CF
PWY-6168	flavin biosynthesis III (fungi)	Cofactor Carrier and Vitamin Biosynthesis	0±0	33.983±8.175	34.4 (10.594,51.325)	0.003	increased in CF
PWY-7356	thiamine diphosphate salvage IV (yeast)	Cofactor Carrier and Vitamin Biosynthesis	42.846±5.018	114.341±6.638	79.858 (46.29,89.675)	0.003	increased in CF
PWY-7761	NAD salvage pathway II (PNC IV cycle)	Cofactor Carrier and Vitamin Biosynthesis	76.601±12.201	220.664±13.35	148.197 (100.121,182.642)	0.003	increased in CF
PWY-7851	coenzyme A biosynthesis II (eukaryotic)	Cofactor Carrier and Vitamin Biosynthesis	296.676±14.702	376.896±21.481	68.534 (20.194,123.086)	0.018	increased in CF
FASYN-ELONG-PWY	fatty acid elongation -- saturated	Fatty Acid and Lipid Biosynthesis	135.527±32.886	359.972±13.048	216.352 (131.746,337.85)	0.003	increased in CF
PWY-5367	petroselinate biosynthesis	Fatty Acid and Lipid Biosynthesis	37.722±14.021	213.481±17.508	191.093 (127.238,230.983)	0.003	increased in CF
PWY-5971	palmitate biosynthesis (type II fatty acid synthase)	Fatty Acid and Lipid Biosynthesis	136.895±37.019	362.262±11.742	206.065 (123.68,355.489)	0.003	increased in CF
PWY-5981	CDP-diacylglycerol biosynthesis III	Fatty Acid and Lipid Biosynthesis	42.107±9.118	144.647±11.136	103.3 (73.17,135.529)	0.003	increased in CF

PWY-5989	stearate biosynthesis II (bacteria and plants)	Fatty Acid and Lipid Biosynthesis	115.154±29.671	339.607±16.878	228.45 (126.442,329.254)	0.003	increased in CF
PWY-6113	superpathway of mycolate biosynthesis	Fatty Acid and Lipid Biosynthesis	0±0	16.036±4.522	17.304 (0,27.596)	0.008	increased in CF
PWY-6282	palmitoleate biosynthesis I (from (5Z)-dodec-5-enoate)	Fatty Acid and Lipid Biosynthesis	116.697±29.759	345.123±14.382	228.722 (134.549,329.797)	0.003	increased in CF
PWY-6284	superpathway of unsaturated fatty acids biosynthesis (E. coli)	Fatty Acid and Lipid Biosynthesis	73.735±23.704	299.035±16.194	230.789 (150.152,286.86)	0.003	increased in CF
PWY-6285	superpathway of fatty acids biosynthesis (E. coli)	Fatty Acid and Lipid Biosynthesis	0±0	40.328±12.349	31.077 (17.998,79.921)	0.003	increased in CF
PWY-7388	octanoyl-[acyl-carrier protein] biosynthesis (mitochondria, yeast)	Fatty Acid and Lipid Biosynthesis	51.768±18.053	270.536±21.831	237.232 (168.447,288.228)	0.003	increased in CF
PWY-7664	oleate biosynthesis IV (anaerobic)	Fatty Acid and Lipid Biosynthesis	126.29±31.345	356.815±13.602	226.967 (137.387,338.904)	0.003	increased in CF
PWY0-862	(5Z)-dodecenoate biosynthesis I	Fatty Acid and Lipid Biosynthesis	115.936±29.548	352.747±14.328	237.528 (144.101,339.784)	0.003	increased in CF
PWY4FS-7	phosphatidylglycerol biosynthesis I (plastidic)	Fatty Acid and Lipid Biosynthesis	111.555±9.82	182.067±8.134	68.927 (42.668,103.218)	0.004	increased in CF
PWY4FS-8	phosphatidylglycerol biosynthesis II (non-plastidic)	Fatty Acid and Lipid Biosynthesis	111.555±9.82	182.067±8.134	68.927 (42.668,103.218)	0.004	increased in CF
PWY66-430	myristate biosynthesis (mitochondria)	Fatty Acid and Lipid Biosynthesis	51.112±17.837	269.077±21.988	235.816 (166.068,287.2)	0.003	increased in CF
PWY-5136	fatty acid β-oxidation II (plant peroxisome)	Fatty Acid and Lipid Degradation	4.173±2.045	21.169±2.473	19.947 (9.682,25.327)	0.004	increased in CF
PWY-241	C4 photosynthetic carbon assimilation cycle, NADP-ME type	Generation of Precursor Metabolites and Energy	126.334±17.141	196.144±6.571	60.96 (15.209,125.549)	0.008	increased in CF
PWY-7115	C4 photosynthetic carbon assimilation cycle, NAD-ME type	Generation of Precursor Metabolites and Energy	43.574±11.118	165.748±9.245	132.7 (81.789,151.395)	0.003	increased in CF
SO4ASSIM-PWY	assimilatory sulfate reduction I	Inorganic Nutrient Metabolism	2.741±1.076	14.889±2.584	12.309 (5.68,18.215)	0.007	increased in CF
OANTIGEN-PWY	O-antigen building blocks biosynthesis (E. coli)	LPS biosynthesis	269.187±15.942	453.379±23.355	169.779 (123.82,248.79)	0.003	increased in CF
PWY-5686	UMP biosynthesis I	Nucleoside and Nucleotide Biosynthesis	426.876±11.767	580.812±11.105	153.351 (119.936,194.214)	0.003	increased in CF
PWY-7198	pyrimidine deoxyribonucleotides de novo biosynthesis IV	Nucleoside and Nucleotide Biosynthesis	90.172±16.581	247.976±10.036	170.421 (116.662,202.731)	0.003	increased in CF
PWY-7208	superpathway of pyrimidine nucleobases salvage	Nucleoside and Nucleotide Biosynthesis	206.895±11.467	269.501±7.537	72.94 (28.966,98.802)	0.008	increased in CF
PWY-7234	inosine-5'-phosphate biosynthesis III	Nucleoside and Nucleotide Biosynthesis	81.145±14.278	350.415±17.952	269.412 (221.552,329.353)	0.003	increased in CF
PWY-7790	UMP biosynthesis II	Nucleoside and Nucleotide Biosynthesis	426.876±11.767	580.812±11.105	153.351 (119.936,194.214)	0.003	increased in CF
PWY-7791	UMP biosynthesis III	Nucleoside and Nucleotide Biosynthesis	426.876±11.767	580.812±11.105	153.351 (119.936,194.214)	0.003	increased in CF
PWY0-162	superpathway of pyrimidine ribonucleotides de novo biosynthesis	Nucleoside and Nucleotide Biosynthesis	206.603±23.761	358.659±7.002	121.917 (93.382,236.399)	0.003	increased in CF
PWY0-166	superpathway of pyrimidine deoxyribonucleotides de novo biosynthesis (E. coli)	Nucleoside and Nucleotide Biosynthesis	16.644±6.445	35.908±8.242	18.749 (2.742,29.054)	0.03	increased in CF
PWY0-1297	superpathway of purine deoxyribonucleosides degradation	Nucleoside and Nucleotide Degradation	54.585±11.935	145.093±9.474	93.775 (51.813,125.92)	0.004	increased in CF
POLYAMSYN-PWY	superpathway of polyamine biosynthesis I	Polyamine biosynthesis	3.725±1.235	17.487±1.641	12.973 (8.855,18.471)	0.003	increased in CF
PWY-6305	superpathway of putrescine biosynthesis	Polyamine biosynthesis	6.352±1.954	23.937±3.378	18.797 (9.257,27.701)	0.006	increased in CF
PWY0-1479	tRNA processing	rRNA metabolism	0±0	16.467±3.435	14.664 (11.989,25.886)	0.003	increased in CF
TRNA-CHARGING-PWY	tRNA charging	rRNA metabolism	371.4±13.354	498.282±13.062	124.264 (77.889,162.173)	0.003	increased in CF
PWY0-42	2-methylcitrate cycle I	SCFA degradation: Propanoate Degradation	8.773±1.644	18.567±4.217	6.682 (0.857,18.263)	0.039	increased in CF
PWY-5022	4-aminobutanoate degradation V	SCFA fermentation: Butyrate and Acetate	6.221±3.202	17.275±2.731	11.689 (4.95,18.825)	0.048	increased in CF
P161-PWY	acetylene degradation (anaerobic)	SCFA fermentation: Ethanol and Acetate	41.852±10.356	200.894±17.999	164.855 (114.5,211.334)	0.003	increased in CF
PWY4LZ-257	superpathway of fermentation (Chlamydomonas reinhardtii)	SCFA fermentation: Ethanol and Acetate	46.151±10.987	145.084±7.012	105.89 (69.363,127.179)	0.003	increased in CF
P124-PWY	Bifidobacterium shunt	SCFA fermentation: Lactate and Acetate	50.834±11.83	192.336±18.369	139.636 (97.789,194.84)	0.003	increased in CF
P41-PWY	pyruvate fermentation to acetate and (S)-lactate I	SCFA fermentation: Lactate and Acetate	183.036±8.414	367.191±22.964	192.533 (124.293,241.209)	0.003	increased in CF
PWY-5100	pyruvate fermentation to acetate and lactate II	SCFA fermentation: Lactate and Acetate	217.935±11.851	374.316±23.78	166.601 (92.309,224.183)	0.003	increased in CF
P122-PWY	heterolactic fermentation	SCFA fermentation: Lactate and Ethanol	42.403±11.439	145.188±7.409	106.941 (69.867,136.269)	0.003	increased in CF
NONMEVIPP-PWY	methylerythritol phosphate pathway I	Secondary Metabolite Biosynthesis	347.963±16.1	462.551±16.355	124.952 (56.668,164.537)	0.004	increased in CF
PWY-5913	partial TCA cycle (obligate autotrophs)	TCA cycle	101.665±16.673	180.818±13.402	82.872 (26.818,132.808)	0.013	increased in CF

Pathway in yellow color indicates differentially abundant pathway between WT and CF mice in both ages