



Supplemental Figure 1. Molecular network of genes from study. This network analysis shows that all twenty six genes measured in this study (see Figure 3, heatmap) are connected directly (solid line) or indirectly (dashed line). This map illustrates connections among genes involved in lipid metabolism, inflammation, fibrosis, and various mitochondrial regulators. This map was generated by Dr. David Crossman, Department of Genetics, University of Alabama at Birmingham, using Ingenuity Pathway Analysis (Qiagen, Redwood City, CA – www.ingenuity.com). The icon legend is included at the bottom of the figure below the network.

Supplemental Table 1. Results from three-way ANOVA on the effect of diet, genotype, and haplotype on body parameters, liver measurements, serum chemistries, and mitochondrial measurements.

	Table or Figure	Factor			Interaction			
		Diet (D)	Genotype (G)	Haplotype (H)	D x G	D x H	G x H	D x G x H
Body weight (g)	Table 1	<0.001	<0.001	0.332	<0.001	0.554	0.686	0.485
Liver weight (g)	Table 1	<0.001	<0.001	0.672	<0.001	0.968	0.356	0.044
Liver weight/body weight	Table 1	<0.0001	0.677	0.074	0.020	0.725	0.232	0.004
Liver TAG (mg/mg prot)	Table 1	0.0460	0.679	0.778	0.555	0.344	0.033	0.689
Serum TAG (mg/dL)	Table 1	<0.001	<0.001	0.009	0.009	0.212	0.271	0.167
Serum ALT (IU/L)	Table 1	<0.001	0.472	0.869	0.367	0.326	<0.001	0.006
Total serum Chol (mg/dL)	Table 1	<0.001	<0.001	0.003	0.230	0.038	0.014	0.112
Free serum Chol (mg/dL)	Table 1	<0.001	<0.001	0.388	<0.001	0.714	0.439	0.521
Serum Adiponectin (µg/mL)	Table 1	0.263	<0.001	0.781	0.038	0.519	0.040	0.004
Fibrosis	Fig. 2B	<0.001	<0.001	0.123	<0.001	0.256	0.762	0.128
Respiration - State 3	Fig. 4A	<0.001	0.605	0.205	0.388	0.314	0.015	0.003
Respiration - State 4	Fig. 4B	0.218	0.037	0.491	0.002	0.892	0.067	0.871
Respiration – RCR	Fig. 4C	0.001	0.104	0.892	0.015	0.777	0.296	0.002
Complex I activity	Fig. 5A	<0.001	0.006	0.340	0.338	0.103	0.728	0.196
Complex II-III activity	Fig. 5B	0.211	0.140	0.165	<0.001	<0.001	<0.001	<0.001
Complex IV activity	Fig. 5C	0.002	0.782	0.215	0.006	0.003	<0.001	0.248
Complex V activity	Fig. 5D	0.027	0.432	0.700	0.749	0.405	0.487	0.122
CS activity	Fig. 5E	<0.001	0.086	0.003	0.646	0.040	0.739	0.223

Values in the table represent p-values from 3-way ANOVA. P-values for diet, genotype, and haplotype indicate their independent (main) effect on the outcome. P-values for interaction indicate interdependency of diet X genotype; diet X haplotype; genotype X haplotype; and diet X genotype X haplotype. “Diet” refers to the comparison of control diet and atherogenic diet. “Genotype” refers to the comparison of nuclear DNA (C57ⁿ and C3Hⁿ). “Haplotype” refers to the comparison of mitochondrial DNA (C57^{mt} and C3H^{mt}). Abbreviations: TAG, triacylglycerol; Chol, cholesterol; ALT, alanine aminotransferase; CS, citrate synthase.

Supplemental Table 2. Results from three-way ANOVA on the effect of diet, genotype, and haplotype on gene expression.

	Factor			Interaction			
	Diet (D)	Genotype (G)	Haplotype (H)	D x G	D x H	G x H	D x G x H
<i>ACADM</i>	<0.001	0.323	0.463	0.621	0.998	0.043	0.110
<i>CPT1A</i>	<0.001	0.646	0.275	0.044	0.980	0.546	0.550
<i>PPARA</i>	<0.001	0.316	0.255	0.820	0.033	0.335	0.057
<i>FABP1</i>	0.626	<0.001	0.304	0.585	0.425	0.245	0.473
<i>PPARG</i>	0.102	<0.001	0.838	0.207	0.645	0.930	0.700
<i>DGAT1</i>	<0.001	0.600	0.300	0.200	0.063	0.152	0.451
<i>SREBP1</i>	<0.001	0.065	0.498	0.119	0.233	0.919	0.279
<i>FASN</i>	<0.001	0.111	0.280	0.524	0.062	0.118	<0.001
<i>PNPLA3</i>	<0.001	0.073	0.001	0.005	0.802	0.452	<0.001
<i>TNFA</i>	<0.001	<0.001	0.074	<0.001	0.072	0.039	0.057
<i>NFkB</i>	<0.001	<0.001	0.884	<0.001	0.588	0.729	0.535
<i>HMOX1</i>	<0.001	0.002	0.433	0.005	0.435	0.195	0.111
<i>NOS2</i>	<0.001	<0.001	0.002	<0.001	0.001	0.002	0.003
<i>TLR2</i>	<0.001	<0.001	0.202	<0.001	0.166	0.098	0.167
<i>TLR4</i>	<0.001	<0.001	0.210	<0.001	0.152	0.138	0.221
<i>TLR9</i>	0.002	0.003	0.003	0.017	<0.001	0.005	0.003
<i>MYD88</i>	<0.001	<0.001	0.071	0.002	0.295	0.656	0.543
<i>COL 1A1</i>	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
<i>COL 4A1</i>	<0.001	0.002	0.468	0.002	0.534	0.641	0.440
<i>TGFB1</i>	<0.001	<0.001	0.765	0.001	0.969	0.465	0.950
<i>SIRT1</i>	<0.001	0.048	0.913	0.063	0.541	0.929	0.235
<i>PPARGC1A</i>	<0.001	0.033	0.897	<0.001	0.348	0.327	0.210
<i>PPARGC1B</i>	0.002	0.460	0.173	0.011	0.119	0.173	0.127
<i>HIF1A</i>	<0.001	<0.001	0.994	0.007	0.990	0.901	0.995
<i>NRF1</i>	<0.001	<0.001	0.462	<0.001	0.330	0.362	0.625
<i>TFB1M</i>	0.002	<0.001	0.255	0.463	0.266	0.700	0.413

Values in the table represent p-values from 3-way ANOVA. P-values for diet, genotype, and haplotype indicate their independent (main) effect on gene expression (Figure 3 of the main text). P-values for interaction indicate interdependency of diet X genotype; diet X haplotype; genotype X haplotype; and diet X genotype X haplotype. “Diet” refers to the comparison of control diet and atherogenic diet. “Genotype” refers to the comparison of nuclear DNA (C57ⁿ and C3Hⁿ). “Haplotype” refers to the comparison of mitochondrial DNA (C57^{mt} and C3H^{mt}).

Supplemental Table 3. Results represent statistically significant p-values for select pair-wise comparisons between treatment groups.

Parameter	1 vs 2	3 vs 4	5 vs 6	7 vs 8	1 vs 3	1 vs 5	1 vs 7	3 vs 5	3 vs 7	5 vs 7	2 vs 4	2 vs 6	2 vs 8	4 vs 6	4 vs 8	6 vs 8
Body Weight	0.0046	<.0001	0.0007	<.0001			0.0044	0.0618		<0.0001	<.0001		<.0001	<.0001		<.0001
Liver weight	0.0080	<.0001	<.0001	<.0001				0.0505			<.0001	0.0212	<.0001	<.0001		<.0001
Liver wt/body wt	<.0001	0.0173	<.0001	<.0001					0.0886			0.0007		<.0001	0.0877	0.0248
Liver TAG	0.093			0.0004			0.054	0.063	0.023	0.006					0.032	
Serum TAG		<.0001		<.0001	<.0001		<.0001	<0.0001	0.0788	<0.0001	0.0161		0.0001	0.0042	0.0569	<.0001
Total Serum Chol	0.0009		0.0120	<.0001	0.0004		<.0001	0.0021		<.0001	0.0560		<0.0001	0.0320	0.0160	<0.0001
Free Serum Chol	<.0001		<.0001		0.0015		<.0001	0.0018		<0.0001						
Serum Adipon		0.0227	0.0105		0.0002	0.0281		<0.0001	0.0061	0.0006			0.0241			0.0246
Serum ALT	0.0381		0.0001	<.0001								0.0190	0.0069	0.0005	0.0002	
Fibrosis	<.0001		0.0013								<.0001		<.0001	<.0001		<.0001
State 3			0.0025	<.0001			0.0066	0.0306	0.0017					0.0025	0.0007	
State 4	0.0078		0.0509								0.0004		0.0319	0.0509		0.0105
RCR			<.0001	0.0273		0.0422	0.0652	0.0380	0.0571		0.0105			0.0005		0.0158
Complex I	0.0034	0.0061		0.0025	0.0291									0.0062		0.0120
Complex II-III		<.0001	0.0539	0.0017	<.0001	0.0699	0.0191	<0.0001	<0.0001		0.0025			0.0217	0.0032	
Complex IV	0.0008	0.0932	0.0129	0.0206				0.0013	0.0038		<.0001	0.0004	0.0015			
Complex V				0.0111												
CS	0.0002	0.0801		0.0014							0.0001	0.0003	0.0438		0.0531	
ACADM	0.0008	0.0005	0.0392	0.0129		0.0294	0.0379									
CPT1	<.0001	0.0018	<.0001	0.0004												
PPARA	0.0049		0.0093	<.0001									0.0710		0.0038	0.0450
FABP1					0.0021		0.0018	0.0028		0.0023	0.0499		0.0006	0.0532	0.0658	0.0006
PPARG			0.0569		0.0009		0.0009	0.0017		0.0016	<.0001		<.0001	<.0001		<.0010
DGAT1	<.0001	0.0130	0.0035	0.0007								0.0147				
SREBP1	<.0001	0.0002	<.0001	<.0001	0.0163			0.0582								
FASN	0.0979		0.0003	<.0001	0.0137		0.0853	0.0005	0.0004				0.0802		0.0924	
PNPLA3		0.0804	<0.0001	0.0013	0.0004			<0.0001	0.0001			0.0002	0.0793	0.0076		0.0350
TNFA	<.0001	0.0500	0.0085	0.0280							<.0001	0.0005	<.0001	0.0158		0.0004
NfκB	<.0001		<.0001	<.0001							0.0003		0.0003	0.0003		0.0040
HMOX1	<.0001	0.0070	0.004	0.0932							0.0003	0.0283	<.0001	0.0724		0.0161
NOS2	<.0001	0.0002	<.0001	0.0892							<.0001	<.0001	<.0001	<.0001		0.0360

<i>TLR2</i>	<.0001		0.0035								<.0001	0.0522	0.0002	0.0026		0.0146
<i>TLR4</i>	<.0001	0.0160	0.0011	0.0730							<.0001	0.0093	<.0001	0.0131		0.0128
<i>TLR9</i>	<.0001			0.0810							<.0001	<.0001	<.0001			
<i>MYD88</i>	<.0001		0.0006								<.0001	0.0552	0.0002	0.0026		0.0237
<i>Col 1a</i>	<.0001	0.0006	<.0001	0.0784							<.0001	<.0001	<.0001	<.0001		<.0001
<i>Col4A1</i>	0.0008	0.0485	<.0001	0.0012							0.0082		0.0072	0.0003		0.0003
<i>TGFB1</i>	0.0001		0.0004	0.0072							0.0006		0.0001	0.0011		0.0003
<i>SIRT1</i>	0.0008		0.0004								0.0665		0.0213	0.0650		
<i>PPARGC1A</i>	<.0001		0.0002						0.0883	0.0049			<.0001	0.0267		0.0006
<i>PPARGC1B</i>	0.0044		0.0048	0.0632						0.0028			0.7893	0.0030	0.0054	
<i>HIF1A</i>	0.0008		0.0007							0.0018			0.0015	0.002		0.0017
<i>NRF1</i>	<.0001	0.0170	<.0001	0.0084							<.0001		<.0001	0.0001		0.0006
<i>TFB1M</i>	0.0323		0.0509	0.0268	0.0011		0.0047	0.0002		0.0010	0.0805		0.0038	0.0110		0.0004

Results in black font are p-values ($p < 0.05$) for pair wise comparisons between treatment groups. Gray font p-values just missed statistical significance. A blank space indicate $P \geq 0.10$

1 vs. 2= WT C57 (C57ⁿ:C57^{mt})-Control vs. WT C57 (C57ⁿ:C57^{mt})-Atherogenic

3 vs. 4= WT C3H (C3Hⁿ:C3H^{mt})-Control vs. WT C3H (C3Hⁿ:C3H^{mt})-Atherogenic

5 vs. 6= MNX C57ⁿ (C57ⁿ:C3H^{mt})-Control vs. MNX C57ⁿ (C57ⁿ:C3H^{mt})-Atherogenic

7 vs. 8= MNX C3Hⁿ (C3Hⁿ:C57^{mt})-Control vs. MNX C3Hⁿ (C3Hⁿ:C57^{mt})-Atherogenic

1 vs. 3= WT C57 (C57ⁿ:C57^{mt})-Control vs. WT C3H (C3Hⁿ:C3H^{mt})-Control

1 vs. 5= WT C57 (C57ⁿ:C57^{mt})-Control vs. MNX C57ⁿ (C57ⁿ:C3H^{mt})-Control

1 vs. 7= WT C57 (C57ⁿ:C57^{mt})-Control vs. MNX C3Hⁿ (C3Hⁿ:C57^{mt})-Control

3 vs. 5= WT C3H (C3Hⁿ:C3H^{mt})-Control vs. MNX C57ⁿ (C57ⁿ:C3H^{mt})-Control

3 vs. 7= WT C3H (C3Hⁿ:C3H^{mt})-Control vs. MNX C3Hⁿ (C3Hⁿ:C57^{mt})-Control

5 vs. 7= MNX C57ⁿ (C57ⁿ:C3H^{mt})-Control vs. MNX C3Hⁿ (C3Hⁿ:C57^{mt})-Control

2 vs. 4= WT C57 (C57ⁿ:C57^{mt})-Atherogenic vs. WT C3H (C3Hⁿ:C3H^{mt})-Atherogenic

2 vs. 6= WT C57 (C57ⁿ:C57^{mt})-Atherogenic vs. MNX C57ⁿ (C57ⁿ:C3H^{mt})-Atherogenic

2 vs. 8= WT C57 (C57ⁿ:C57^{mt})-Atherogenic vs. MNX C3Hⁿ (C3Hⁿ:C57^{mt})-Atherogenic

4 vs. 6= WT C3H (C3Hⁿ:C3H^{mt})-Atherogenic vs. MNX C57ⁿ (C57ⁿ:C3H^{mt})-Atherogenic

4 vs. 8= WT C3H (C3Hⁿ:C3H^{mt})-Atherogenic vs. MNX C3Hⁿ (C3Hⁿ:C57^{mt})-Atherogenic