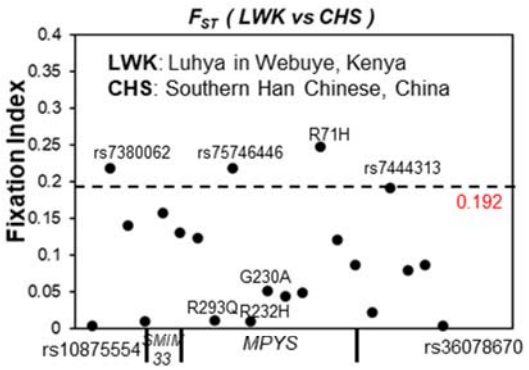
A

SNP ID	F_{ST}
rs10875554	0.0039
rs7380062	0.2188
rs73257323	0.1406
rs13181561	0.0098
rs13153461	0.1573
rs55792153	0.131
rs73257329	0.1231
rs7380824	0.0114
rs75746446	0.2188
rs1131769	0.0106
rs78233829	0.0517
rs552338116	0.0441
rs7380272	0.0495
rs11554776	0.2474
rs7447927	0.1214
rs13166214	0.0874
rs34703538	0.0223
rs7444313	0.1918
rs7448031	0.0796
rs6874798	0.0866
rs36078670	0.0041



B R232H - CHS

SNP ID	LD (r^2)
rs10875554	0.6041
rs7380062	0.0738
rs73257323	0.1079
rs13181561	0.0958
rs13153461	0.0958
rs55792153	0.1148
rs73257329	0.1429
rs7380824	0.1429
rs75746446	0.1106
rs1131769	
rs78233829	0.1478
rs552338116	0.1401
rs7380272	0.1401
rs11554776	0.1401
rs7447927	0.0958
rs13166214	0.0958
rs34703538	0.1457
rs7444313	0.1222
rs7448031	0.1429
rs6874798	0.1429
rs36078670	0

C G230A – CHS vs LWK

SNP ID	LD (r^2)	
	CHS	LWK
rs10875554	0.1987	0.0994
rs7380062	0.7004	0
rs73257323	0.9427	0.425
rs13181561	0.4235	0
rs13153461	0.4235	0
rs55792153	0.4427	0
rs73257329	1	0.4913
rs7380824	1	0.5321
rs75746446	0.7371	0
rs1131769	0.1429	0
rs78233829		
rs552338116	0.9809	0.8649
rs7380272	0.9809	1
rs11554776	0.9809	0.0701
rs7447927	0.4235	0
rs13166214	0.4235	0
rs34703538	0.9809	0.1822
rs7444313	0.5405	0
rs7448031	0.9616	0.5413
rs6874798	0.9616	0.5947
rs36078670	0.0777	0.2768

2.68kb

D R293Q – CHS vs LWK

SNP ID	LD (r^2)	
	CHS	LWK
rs10875554	0.1987	0.1439
rs7380062	0.7004	0
rs73257323	0.9427	0.2444
rs13181561	0.4235	0.0834
rs13153461	0.4235	0
rs55792153	0.4427	0.0705
rs73257329	1	0.2825
rs7380824		
rs75746446	0.7371	0
rs1131769	0.1429	0
rs78233829	1	0.5321
rs552338116	0.9809	0.499
rs7380272	0.9809	0.5321
rs11554776	0.9809	0
rs7447927	0.4235	0
rs13166214	0.4235	0.0575
rs34703538	0.9809	0.5594
rs7444313	0.5405	0
rs7448031	0.9616	0.2772
rs6874798	0.9616	0.3231
rs36078670	0.0777	0.1398

Figure S1. Natural selection of *HAQ* and *AQ-MPYS* during the Out-of-Africa migration. A. F_{ST} scores of the 21 SNPs covering 18.5kb genomic regions were calculated in the LWK and CHS populations. The three SNPs with a higher F_{ST} score and carried by the positively selected *HAQ-1* haplotype are highlighted in red. The *MPYS* gene and its nearby *SMIM33* gene were marked. **B-D**. 1000Genome LD r^2 score of indicated SNPs from LWK and CHS populations. The r^2 scores >0.8, which indicates a strong LD, are highlighted.

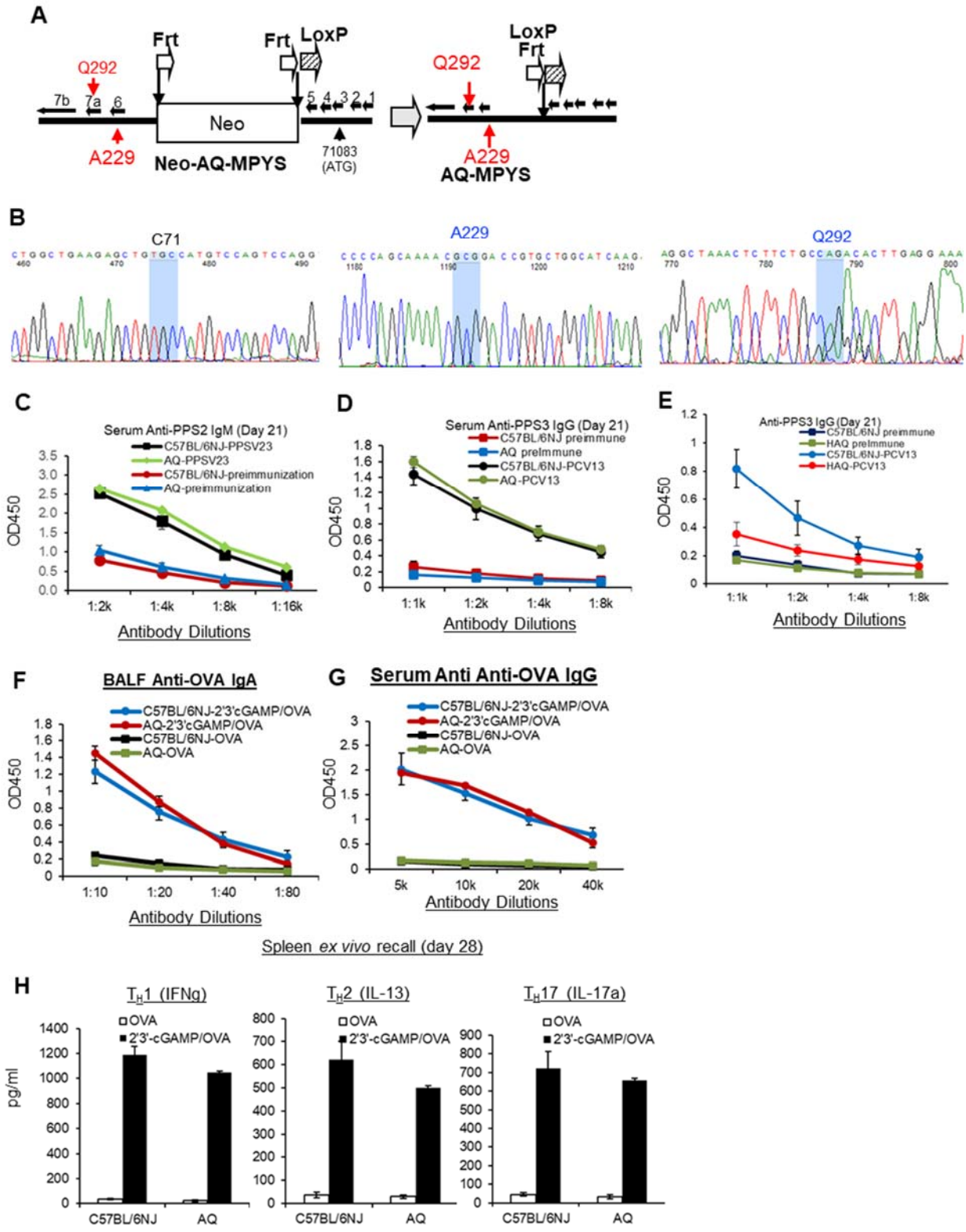


Figure S2. Generating and testing an AQ-MPYS knock-in mouse. A. A diagram illustrating the generation of an AQ knock-in mouse. Amino acids 71, 229, and 292 in mouse MPYS/STING are equivalent to human MPYS/STING amino acids 71, 230, and 293. **B.** PCR sequencing of the amino acid 71, 229, and 292 in the AQ knock-in mouse. **C.** HAQ and their WT littermates were

immunized (*i.m.*) with Pneumovax® 23 (0.125 µg in 50 µl saline). Anti-PPS2 IgM was determined on day 21 post-immunization and pre-immunization. Data are representative of three independent experiments. **D-E**. HAQ, AQ, and their WT littermates were immunized (*i.m.*) with Prevnar13® (0.125µg in 50µl saline). Anti-PPS3 IgG was determined on day 21 post-immunization. (n=4 mice/group). Data are representative of three independent experiments. **F-G.** WT and AQ mice were immunized (*i.n.*) with two doses (14 days apart) of OVA or OVA plus 2'3'-cGAMP (5µg). IgA in bronchoalveolar lavage fluid (BALF) (**F**) and serum (**G**) was determined by ELISA 28 days post-immunization. (n=4mice/group). Data are representative of three independent experiments. **H.** Splenocytes from immunized WT and AQ mice in **E** were recalled with 5µg/ml OVA for 4 days in culture. Cytokines were measured in the supernatant by ELISA. Data are representative of three independent experiments. Graphs represent the mean with error bars indication s.e.m.

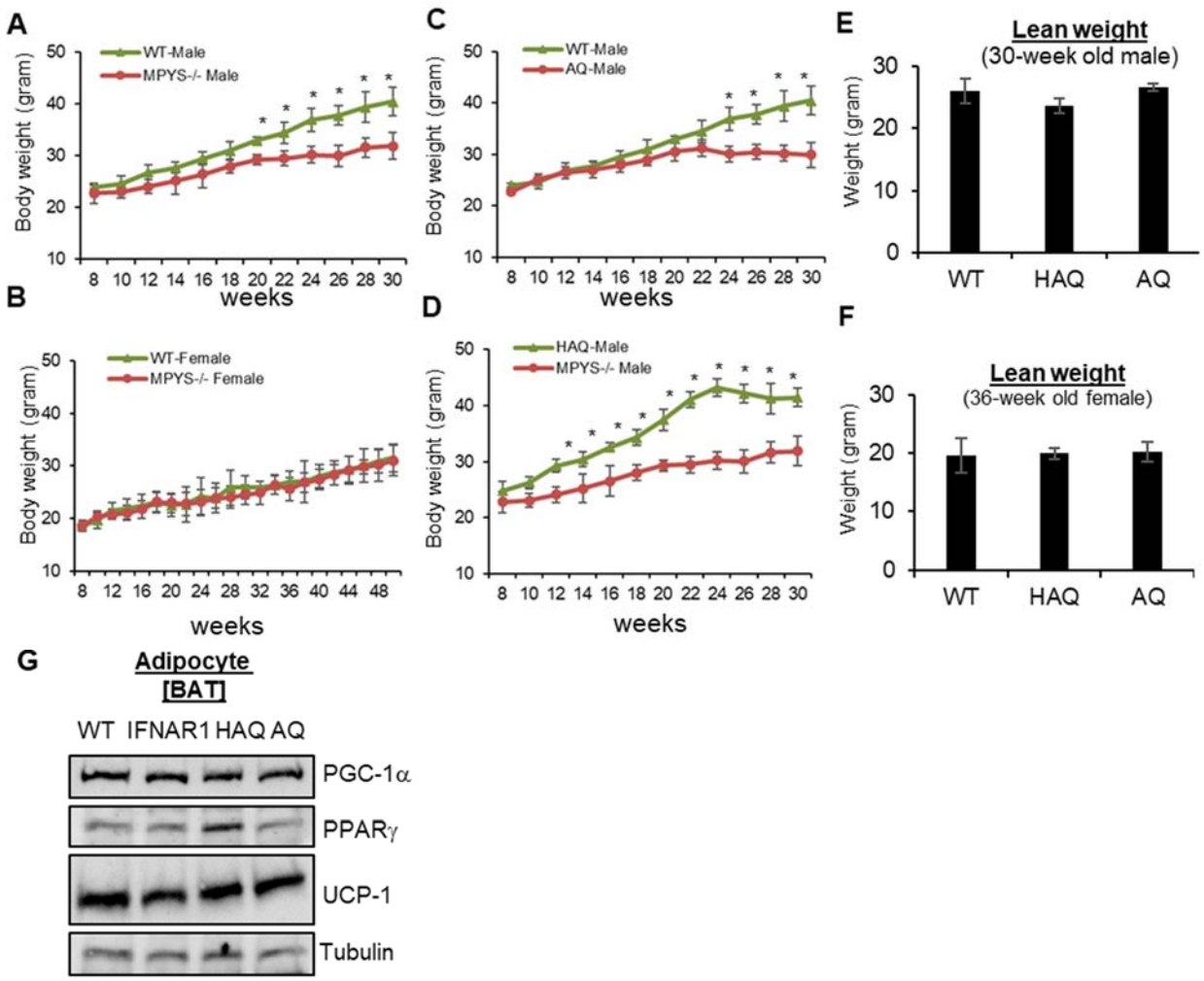


Figure S3. HAQ mice have more body and fat weight than the AQ mice on a chow diet. A-D. Mouse body weight was determined weekly in the indicated mice. (n=5-8 mice/group). Data are representative of three independent experiments. **E-F.** Body composition was measured in the unanesthetized mouse by a quantitative magnetic resonance method using an EchoMRI™ 700 Analyzer (EchoMRI LLC, Houston, TX, USA). (n=5-8 mice/group). Data are representative of three independent experiments. **G**. Western blot analysis of thermogenesis genes in the brown adipose tissue. Data are representative of three independent experiments. Graphs represent the mean with error bars indication s.e.m. *P* values were determined by one-way ANOVA Tukey's multiple comparison test. * $P<0.05$

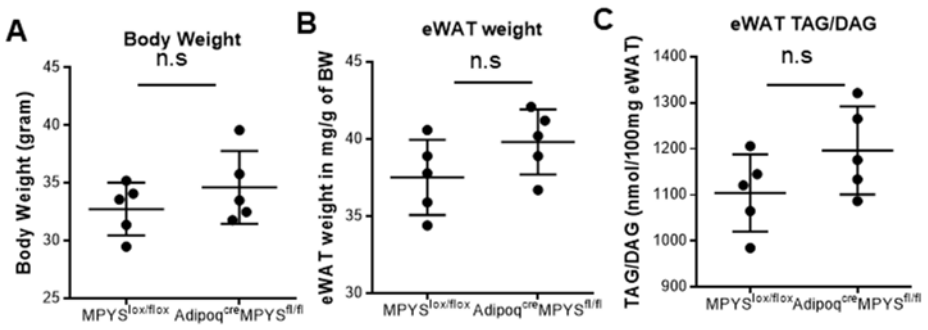


Figure S4. Adipoq^{cre}MPYS$^{fl/fl}$ have similar body weight as the MPYS$^{fl/fl}$ mice. A. Mouse's body weight was determined in the indicated 6-month-old male mice. (n=5 mice/group). Data are representative of three independent experiments. **B**. Weight of epididymal white adipose tissue (eWAT) from indicated 6-month-old male mice was recorded. (n=5 mice/group). Data are representative of three independent experiments. **C.** Total triglyceride in 100mg eWAT was quantified with BioVision triglyceride kit (cat# K622). (n=5 mice/group). Data are representative of three independent experiments. Graphs represent the mean with error bars indication s.e.m. *P* values determined by unpaired student T-test. n.s.: not significant.

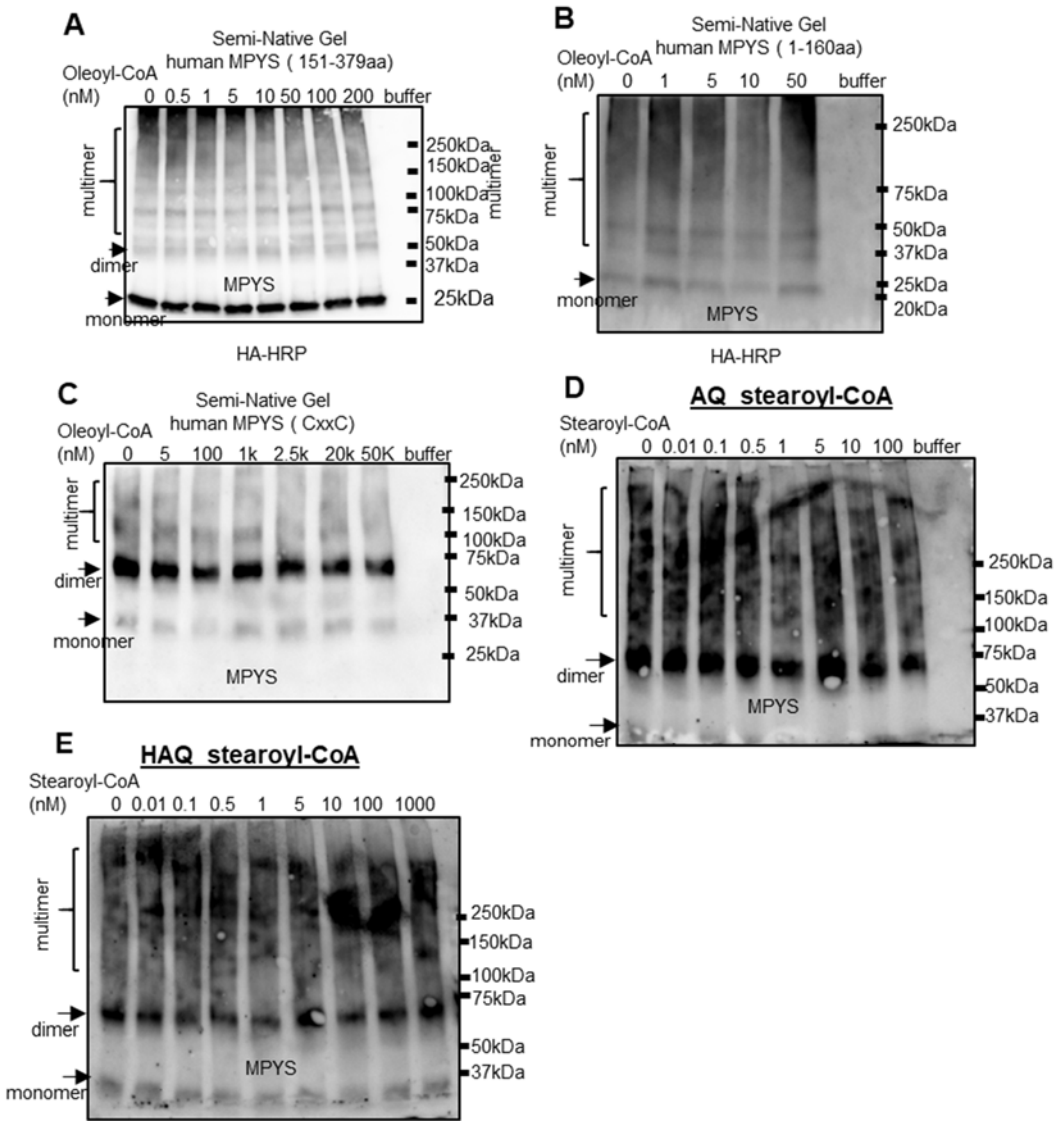


Figure S5. N-terminal of MPYS mediates multimer formation. A-C. Human MPYS (151-379aa), MPYS (1-160aa), or MPYS CxxC protein was solubilized in POPC buffer as in **Figure 8E.** Oleoyl-CoA, at the indicated concentration, was added to the MPYS-POPC solution. After 20mins, the MPYS-POPC solution was mixed with a loading buffer (0.5% SDS) and ran in a running buffer with 0.1% SDS (BioRad, cat#1610732) on a 4-20% Mini-PROTEAN TGX GEL (no SDS, BioRad, cat#4568094) for 1.5hrs. The blot was probed with HA-HRP (BioLegend, clone 16B12). Data are representative of three independent experiments. **D-E.** Human HAQ and AQ MPYS were solubilized in POPC buffer**.** Stearoyl-CoA (Avantilipids, cat#870718), at the indicated concentration, was added to the MPYS-POPC solution. After 20mins, the MPYS-POPC solution was mixed with a loading buffer (0.5% SDS) and ran in a running buffer with 0.1% SDS (BioRad, cat#1610732) on a 4-20% Mini-PROTEAN TGX GEL (no SDS, BioRad, cat#4568094) for 1.5hrs. The blot was probed with anti-MPYS/STING Ab (ProteinTech, cat#19581-1-AP). Data are representative of three independent experiments.