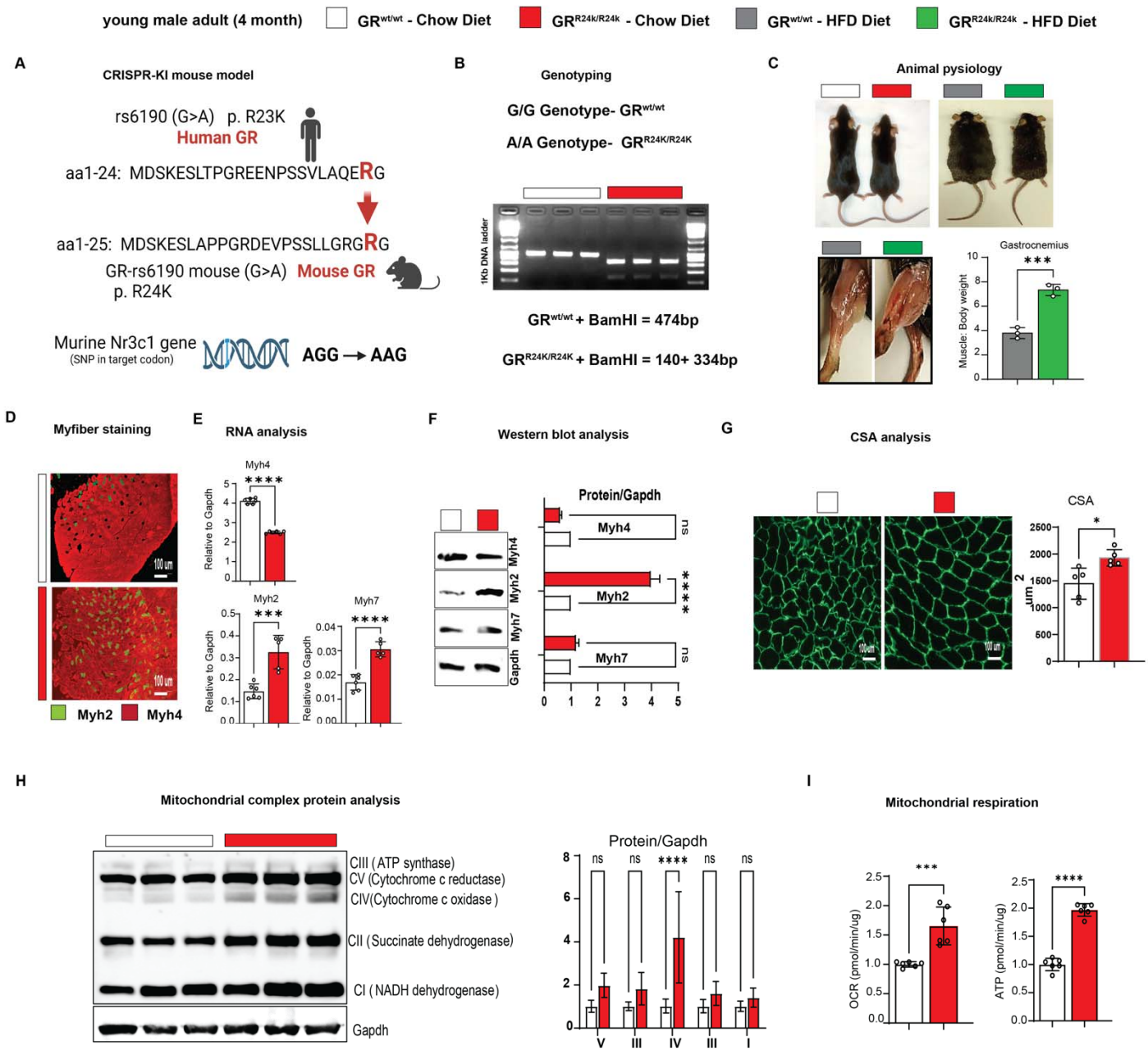
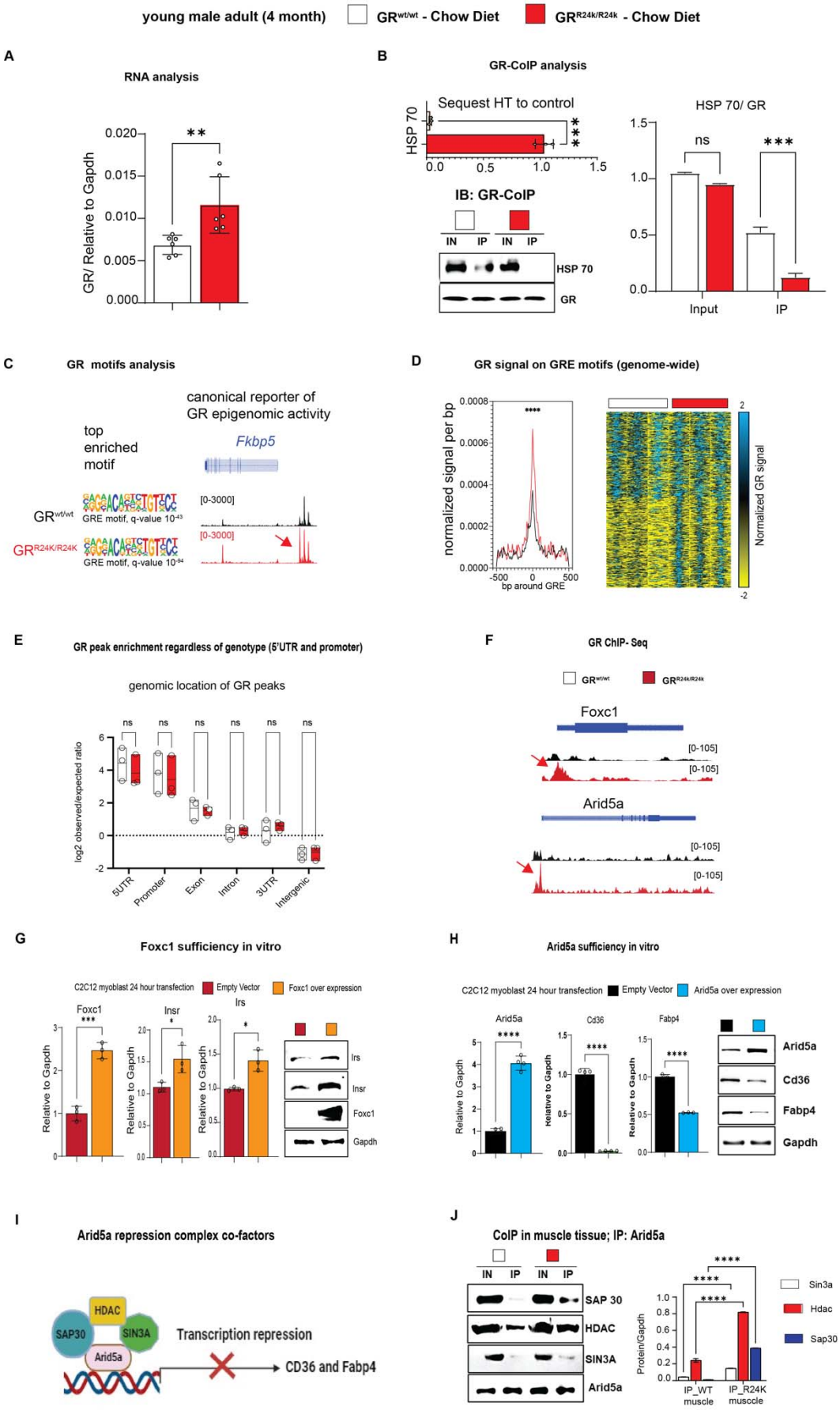


Supplementary Figure 1 – Additional data regarding R24K effects on muscle metabolism. Related to Figure 1 – (A-B) Diagram and genotyping PCR for R24K genocopying strategy in mice of human R23K variant. **(C)** Muscle/body mass was increased by the R24K genotype in obese mice. **(D-F)** R24K muscles showed increased expression of Myh2 (type 2A) and Myh7 (type 1) myosins, with decreased Myh4 (type 2B) expression. **(G)** Cross-sectional area (CSA) analysis confirmed increased muscle mass. **(H)** Mitochondrial complex protein levels in muscle showed non-significant upward trends, with complex IV bing significantly upregulated by the R24K homozygosity. **(I)** Glucose-fueled respiration was increased in muscle tissue of R24K vs WT mice. n=3-6♂/group; diet exposures for 12 weeks from 4mo to 7mo; Welch's t-tests: ns, non significant; *, P<0.05; **, P<0.01; ***, P<0.001; ****, P<0.0001.



Supplementary Figure 2 – Additional analyses related to the mutant GR in muscle – (A) Validation of lower Hsp70 binding by the mutant vs WT GR through CoIP. **(B)** qPCR analysis of *Nr3c1* (GR gene)

expression in muscle. **(C)** Validation of ChIP-seq datasets through unbiased motif analysis and visualization of canonical GR peaks in the *Fkbp5* promoter region. **(D-E)** Mutant GR epigenomic activity was increased on the GR-binding elements (GREs) genome-wide, despite no significant shifts in overall genomic location (GR peaks enriched for both genotypes in the promoter-5'UTR regions). **(F)** Mutant vs WT GR peaks on Foxc1 and Arid5a proximal promoters. **(G-H)** Validation of Foxc1 and Arid5a sufficiency for target gene programs in vitro in C2C12 myoblasts. **(I-J)** Diagram and CoIP for Arid5a repression complex partners in R24k vs WT muscle. n=3-4♂/group; Welch's t-tests and 2w ANOVA + Sidak (J): ns, non significant; *, P<0.05; **, P<0.01; ***, P<0.001; ****, P<0.0001.