Sex Differences in Fatty Acid and Mitochondrial Metabolism are Associated with Diastolic Dysfunction in Heart Failure

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Figure 1. Female predisposition to diastolic dysfunction in HFpEF

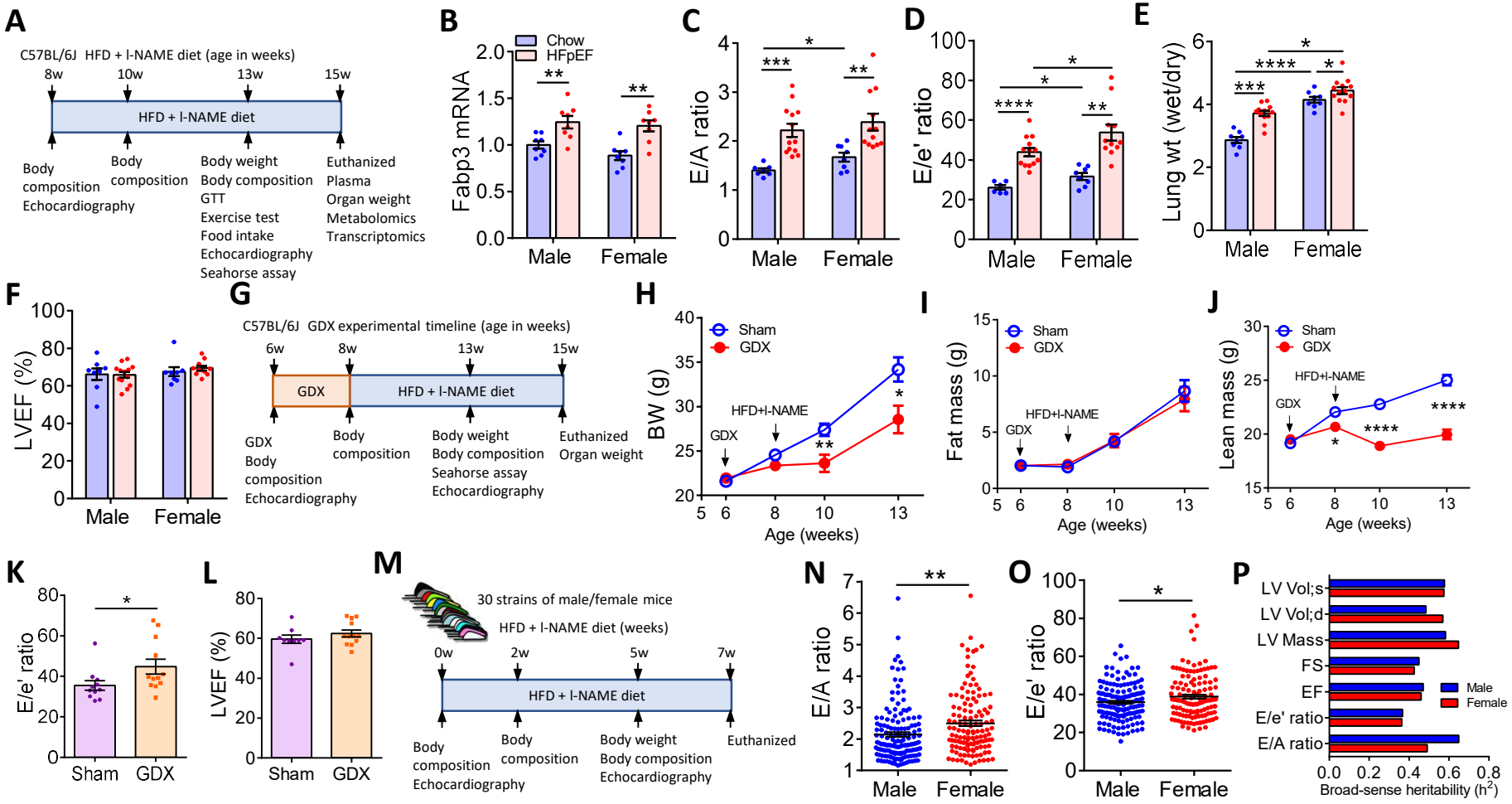


Figure 2. Molecular and pathway analysis of sex differences in HFpEF.

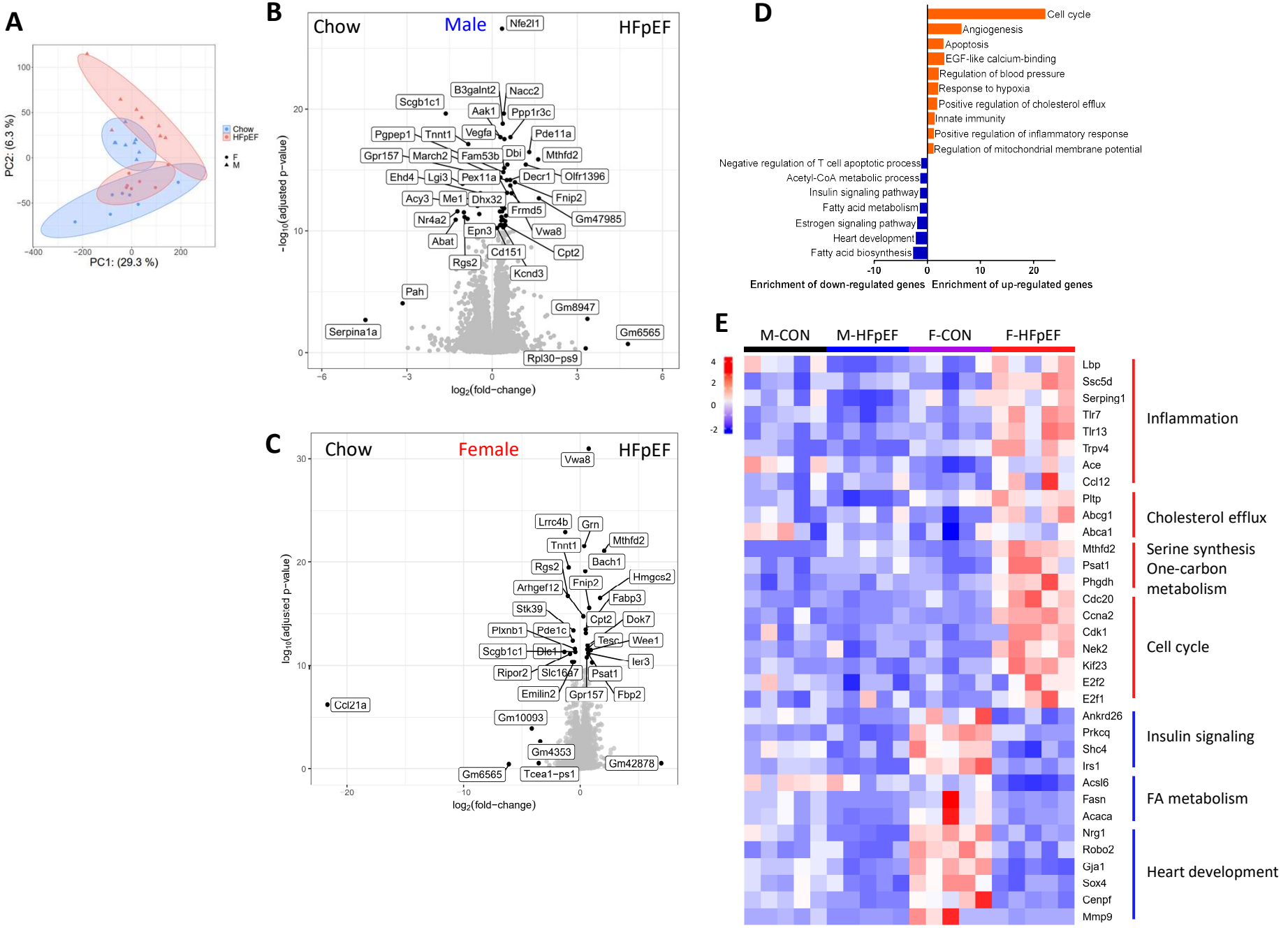


Figure 3. Diastolic function associated with mtDNA and female mice exhibited reduced mtDNA and mitochondrial function

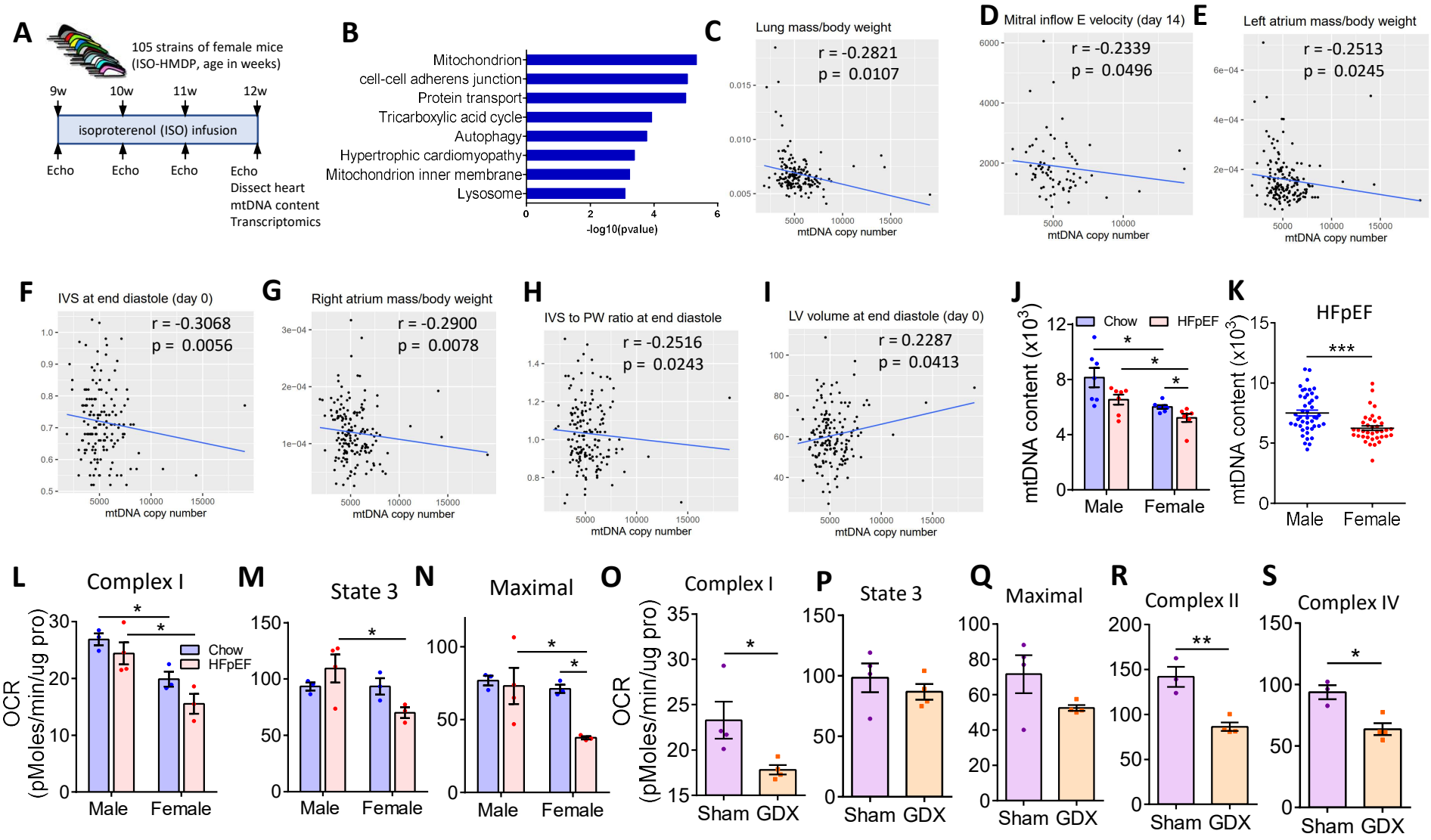
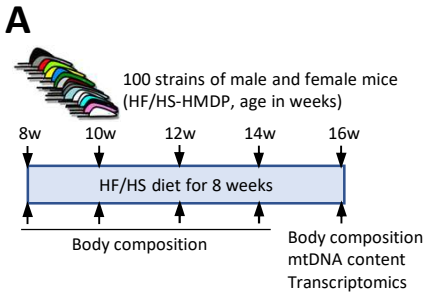
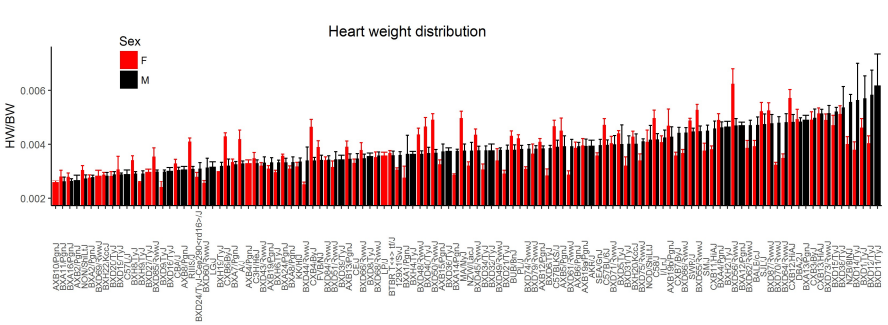
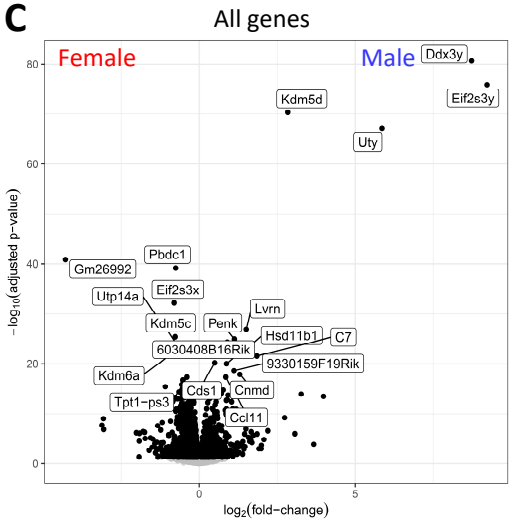
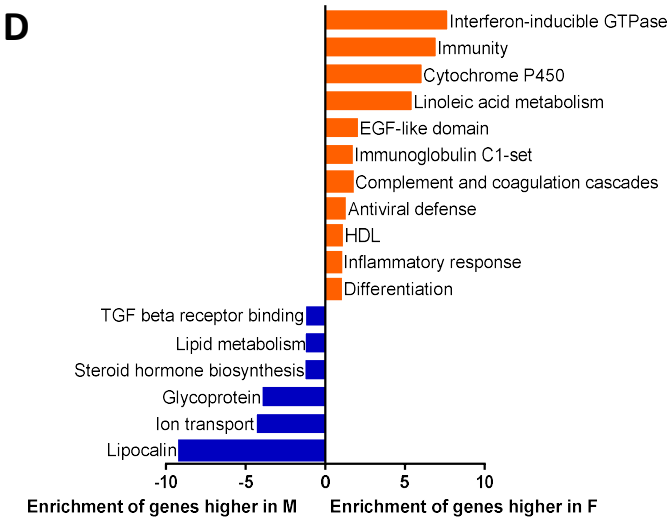


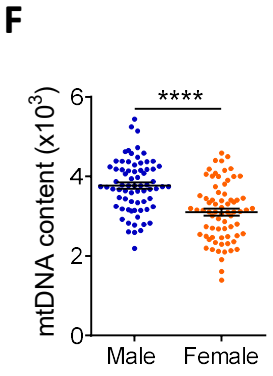
Figure 4. Genetic dissection of sex differences in mice

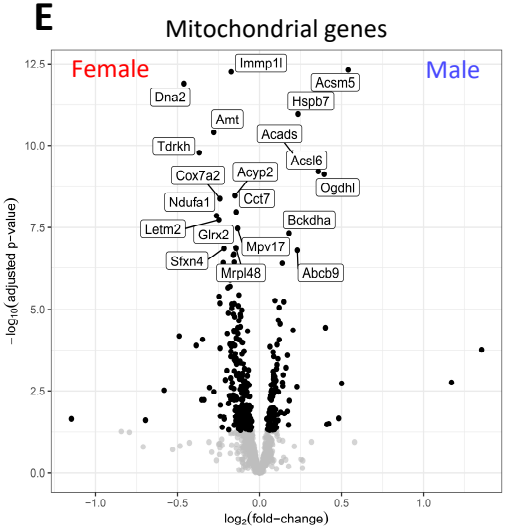


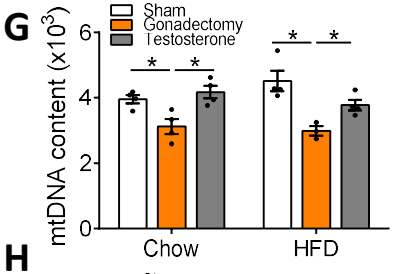












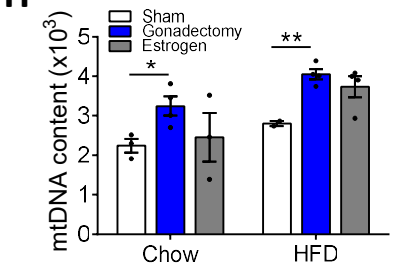


Figure 5. Identification of Acsl6 as a sex-specific cis-regulator of diastolic dysfunction

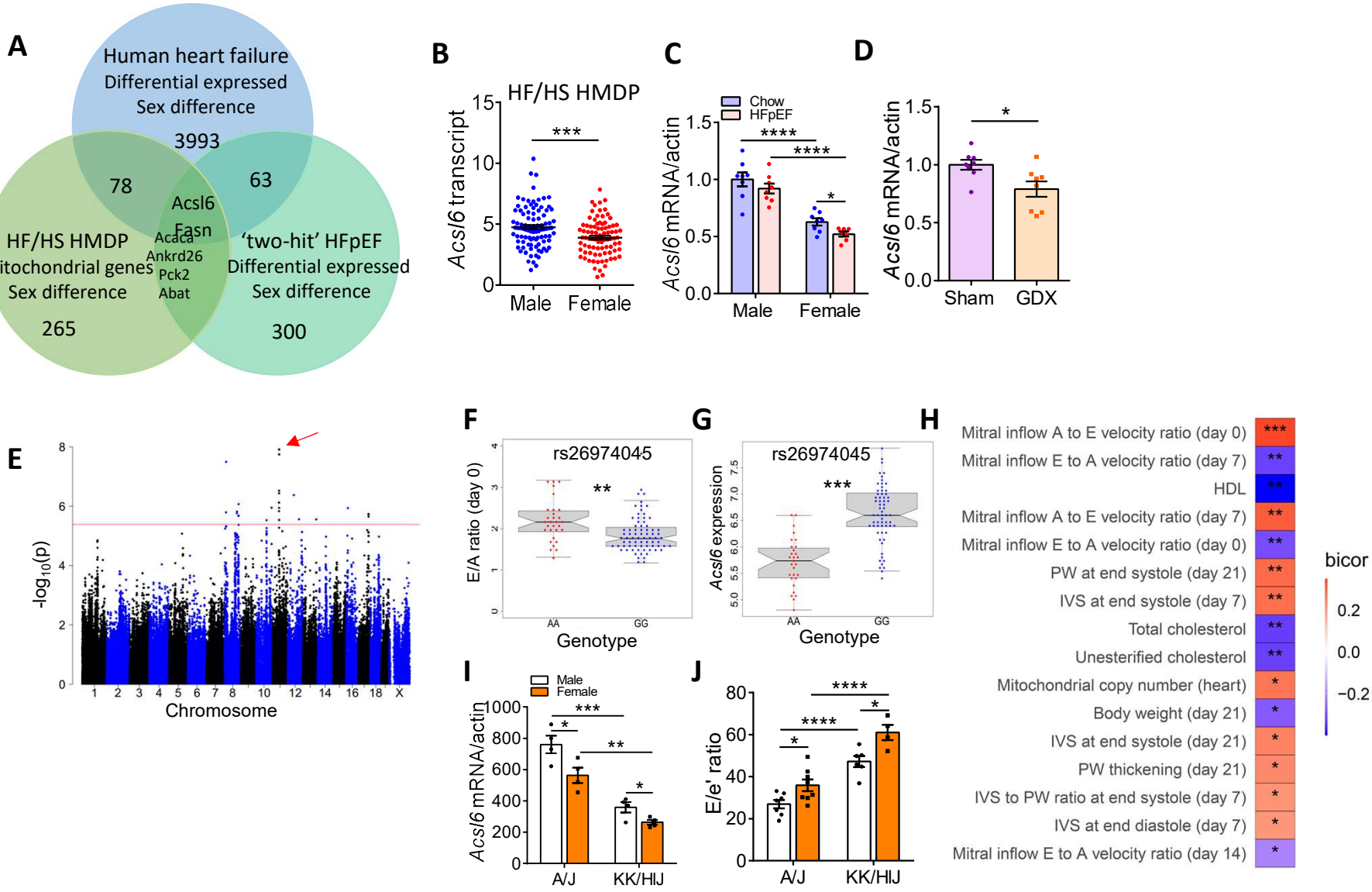
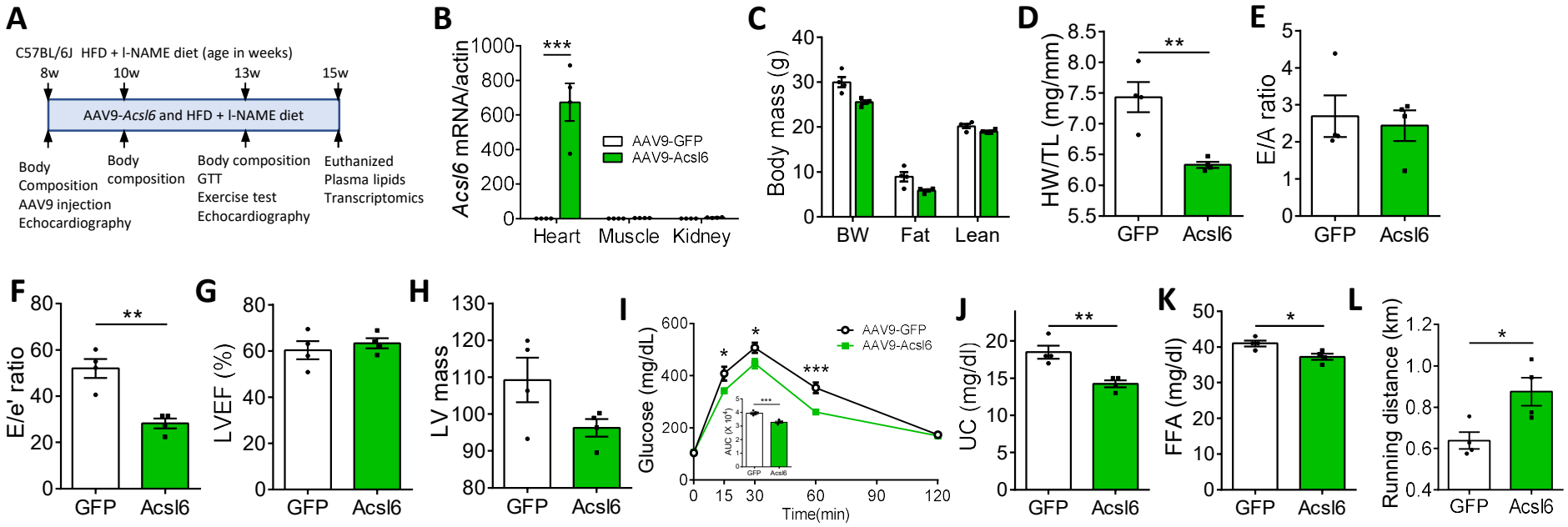


Figure 6. Acsl6 is a key regulator of diastolic dysfunction



Summary

- The genetic control of HFpEF traits was examined using inbred mouse strains from the Hybrid Mouse Diversity Panel (HMDP) subjected to either a two-hit model, isoproterenol infusion, or an obesifying diet. Diastolic dysfunction and other HFpEF traits exhibited high heritability.
- Females were significantly more susceptible to diastolic dysfunction than males and tended to have reduced fatty acid oxidation and mitochondrial function as compared to males.
- Mitochondrial DNA levels were regulated by gonadal hormones and were inversely correlated with diastolic dysfunction.
- Integrative genetic analyses of the heart transcriptome identified *Acsl6* is a sex-specific *cis*-regulator of diastolic dysfunction.