

Description of Additional Supplementary Files

Supplementary Data 1. List of cohorts included for each phenotype where cross-cohort meta-analyses were available.

Supplementary Data 2. List of all variants predicted to induce loss of function of MSTN as detected in whole exome sequencing data from 11 cohorts (see Supplementary Table 1 for cohort list). Positions are based on the GRCh38 genome assembly.

Supplementary Data 3. Summary statistics for gene burden associations between MSTN and quantitative traits related to lean mass and fat mass, including (1) MSTN pLoF + missense (5/5), AAF<0.5%, (2) MSTN pLoF, AAF<0.5%, and (3) MSTN non-function-disrupting missense, AAF<0.5% (the latter includes all missense variants not present in the other two categories). AAF indicates alternative allele frequency. pLoF indicates putative loss-of-function. Also included are summary statistics for sex-stratified analyses.

Supplementary Data 4. Summary statistics for associations between MSTN gene burden variants and DXA-derived measures of lean and fat mass. AAF indicates alternative allele frequency. pLoF indicates putative loss-of-function.

Supplementary Data 5. Summary statistics for associations between individual MSTN missense variants and measures of fat-free and fat mass. Positions are based on the GRCh38 genome assembly.

Supplementary Data 6. Summary statistics for custom gene burden associations between MSTN missense masks and MRI-derived fat volume traits, including (1) MSTN pLoF + missense (5/5), AAF<0.5%, (2) MSTN any other missense, AAF<0.5%, and (3) MSTN any other missense, AAF<0.5% removing the Arg88Gln variant. AAF indicates alternative allele frequency. pLoF indicates putative loss-of-function. Also included are summary statistics for associations with the single Arg88Gln variant.

Supplementary Data 7. Summary statistics for associations between MSTN missense variants and cardiac wall thickness. Positions are based on the GRCh38 genome assembly.

Supplementary Data 8. Summary statistics for gene burden test associations across cardiometabolic traits. AAF indicates alternative allele frequency. pLoF indicates putative loss-of-function.

Supplementary Data 9. Summary statistics for gene burden test associations across infertility-related traits. Within the outcome column, FSHB indicates follicle stimulating hormone subunit beta levels and PCOS indicates polycystic ovary syndrome. AAF indicates alternative allele frequency. pLoF indicates putative loss-of-function.