Genetic etiologies of the sex hormone testosterone differ between female late pre-menopause and post-menopause stages

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BACKGROUND

The steroid sex hormones testosterone and estradiol regulate many aspects of physiology(1). These hormones exhibit distinct bioactivities based on sex and vary across different stages of life(2,3), particularly before and after the menopause transition in females. These sex hormone levels differ by sex as found in many previous studies(4,5). We hypothesized that genetic effects regulating sex hormone levels also vary across the lifespan, especially before and after the female menopause transition, and designed this study to describe and compare the genetic etiologies of the sex hormone testosterone.

For this study we used data from UK Biobank(7), a large-scale biomedical database and research resource containing de-identified genetic, lifestyle and health information, and biological samples from half a million UK participants (Table 1). For each participants testosterone levels were calculated from blood samples and then genotyped. We used Genome-Wide Association Study (GWAS) that identified genomic variants statistically associated with testosterone level by surveying the genomes of individuals in the sample. The large sample size available makes this study promising for a significant finding.

METHODS

Using data from unrelated persons of "White British" ancestry(6) in the UK Biobank(7), we stratified by sex and by approximate stage of life: menopause stages (pre, peri, post) in females and age tertiles in males (Table 1). GWAS were performed for estimated total levels of testosterone within stratified cohorts, adjusting for: technical covariates of genotype array and top 10 principal components. From these GWAS summary statistics containing 90+ million SNPs we filtered out SNPs that are not in the "HapMap 3" consensus list(8) to only include SNPs that are common across variety of populations. The QC criteria used for these SNPs are Hardy-Weinberg p>0.000001 (per population), missingness <0.05 (per population), <3 Mendel errors (per population), and SNP must have a rsID and map to unique genomic location. Then we compared the BETA values associated with each SNPs between the stratified groups (female pre-post menopause; male high-low age) and calculated Z scores and associated P-values(12). Then we used this calculated p-value to identify Lead SNPs and conduct Gene Set Enrichment Analysis (GSEA) based on genes associated with the identified Lead SNPs. The Lead SNPs and their BETA values for females were plotted using scatterplots (Fig: 3).

RESULTS

- The genetic correlation for female pre-menopause vs post-menopause was less than 1 (rg: 0.65 se: 0.08; Fig: 1).
- 38 Lead SNPs were identified based on BETA difference p-values for female pre-menopause vs post-menopause (Fig: 2 & Fig: 1 black dots).
- The differences in GWAS effects between pre-menopause and post-menopause relate to immune functional gene sets (Fig: 7).
- The genetic correlation for male age low vs age high was almost 1 (rg: 0.94; se: 0.08).
- 150 Lead SNPs were identified based on BETA difference for male age low vs age high.
- High correlation (close to 1) and high number of identified lead SNPs are conflicting results for male dataset and further investigation needed before further gene set enrichment analysis.

DISCUSSION

We observed broad, autosome-wide differences in different stages of life for females in the genetic etiologies of testosterone. The 0.65 genetic correlation between pre-menopausal and post-menopausal females suggests a lot of the differences in testosterone level are not explained just by differences in alleles. The Gene Set Enrichment Analysis (GSEA) identified gene sets associated with immune disorders(13) and inflammation(14) suggesting inflammatory functional pathways could describe some of the remaining differences in genetic regulation of testosterone levels between pre-menopausal and post-menopausal females. Some differences between the two groups could be due to age differences as many of the genes identified are linked with diseases that are prevalent in older individuals(15).

LIMITATIONS & FUTURE WORK

The overall advanced stage of life (female avg: 58; male avg: 59) of the participants in UK Biobank(9) data (Table 1) limits the generalizability of our findings. Large sample size difference between pre-menopausal (24,920) and post-menopausal (157,020) women could have driven some of the differences we observed in BETA values for females. Future study should include similar size samples that are representative of the population. And redo gene-set enrichment analysis after adjusting for age.

Despite strong genetic correlation between male age-low and age-high we observed many individual SNPs with significant BETA differences. Further investigation into the conflicting results and the dataset is needed before conducting any gene-set enrichment analysis.

FIGURE 1: Manhattan Plot Testosterone Pre vs Post Menopause (Correlation: rg: 0.65; se: 0.08)

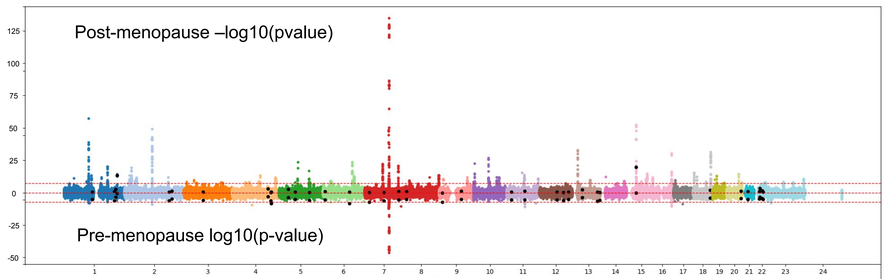


FIGURE 2: Manhattan Plot of pre vs post menopause BETA difference and associated p-values.

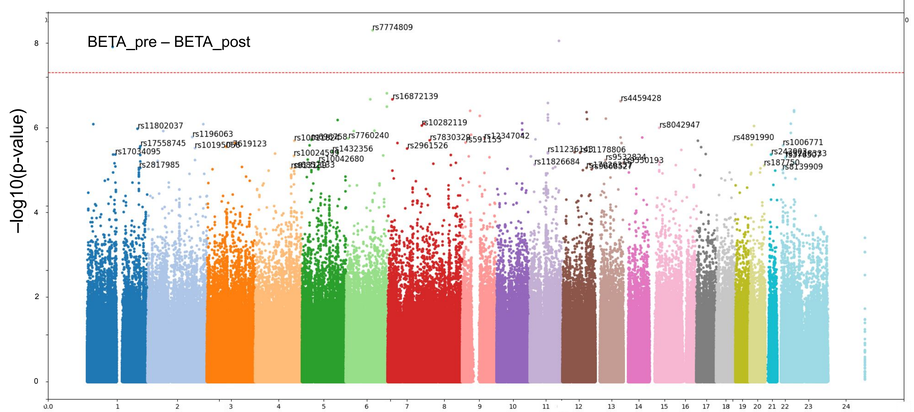


FIGURE 3: Scatterplot: Lead SNPs based on P-value associated with pre-post menopause BETA difference

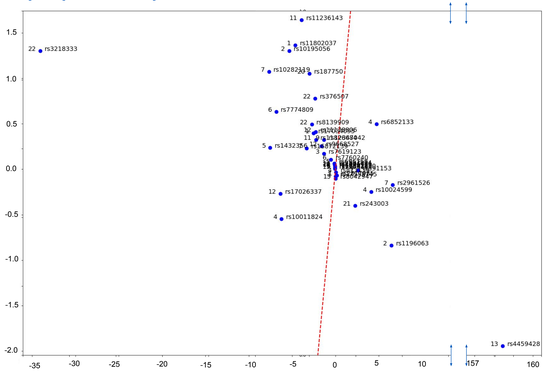
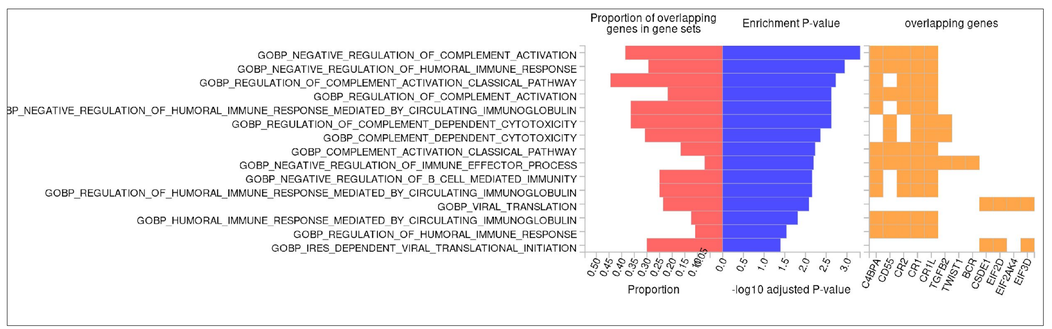


TABLE 1: UK Biobank cohorts stratified by sex and stage of life

		Age (years)	
Cohort	Records	Range	Median
Female	220,774	40-71	58
Premenopause	24,920	40-46	43
Perimenopause	30,988	47-55	50
Postmenopause	157,020	40-71	61
Male	187,847	39-73	59
Younger	61,039	39-53	47
Middle	67,831	54-62	59
Older	58,977	63-73	66

FIGURE 4: Female pre vs post: Enrichment of Gene Sets (GO biological processes: MsigDB c5)



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