

GENETICS

Genetic analysis reveals role of testosterone levels in human disease



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Many studies have reported associations between testosterone levels and the risk of several diseases, including type 2 diabetes mellitus. However, whether these associations are causal or correlative has been unclear. A new study that analysed data from the UK Biobank study demonstrates that many genetic variations influence testosterone levels and that levels of testosterone are causally related to the risk of several diseases.

“The randomized controlled trials conducted to date have been too small to understand how testosterone levels might directly influence risk of disease,” says corresponding author John Perry (University of Cambridge, UK). “Due to the growing interest in the use of testosterone supplementation, we thought it was important to begin to understand the full impact testosterone might have on disease risk.” In many countries, testosterone supplements are used for a wide range of indications, including bone health, sexual function and muscle mass, in both men and women.

The researchers used a dataset of >425,000 women and men of European ancestry from the UK Biobank study, for whom genetic

variation and levels of sex hormones had recently been measured. Using genetic association testing implemented in a linear mixed model, the researchers identified 2,571 genetic variants that influenced the levels of testosterone or related sex hormones.

Next, the researchers used Mendelian Randomization to assess whether the effects of testosterone were causal or correlative. “The benefit here is that genetic effects are randomly allocated and fixed at conception so cannot be modified by disease processes,” explains Perry. “An association between genetically higher levels of testosterone and disease is therefore more likely to represent causality rather than just a correlation.”

The analyses revealed that levels of testosterone do have a causal role in the development of certain diseases. Indeed, each 1 s.d. increase in testosterone levels in men led to a 15% reduction in risk of type 2 diabetes mellitus but a 23% increase in the risk of prostate cancer. In women, each 1 s.d. increase in testosterone levels led to a 37% increased risk of type 2 diabetes mellitus. In addition, each 1 s.d. increase in testosterone levels increased the risk of polycystic ovary syndrome with an OR of 1.51 (95% CI, 1.33–1.72).

“We have shown that testosterone levels in men and women are heritable (~20%) and influenced by the combined effect of many genetic variants and genes,” says Perry. Notably, the genetic determinants of testosterone levels were different between men and women. Furthermore, high levels of testosterone were detrimental

in women, increasing the risk of hormone-sensitive cancers, such as breast and endometrial cancers, and metabolic disorders, such as polycystic ovary syndrome and type 2 diabetes mellitus. By contrast, high levels of testosterone were largely beneficial in men, reducing the risk of type 2 diabetes mellitus and other aspects of metabolic health (such as fasting levels of glucose and body fat levels) but increasing the risk of prostate cancer. “We were surprised to see that testosterone appeared to increase the risk of women developing polycystic ovary syndrome,” says Perry. “The prevailing thought has been that increased testosterone was solely the consequence of the disease, but our research suggests that testosterone may also play a direct role in disease susceptibility.”

“It is important to state that we do not recommend anyone to take medication to alter testosterone levels on the basis of our findings,” states Perry. “However, our findings should inform those already taking, or considering use of, such medications.” The researchers hope that future work will continue to explore the broader implications of testosterone levels on human health, as well as the use of testosterone supplements in healthy people. “Mechanistically, it would also be very interesting to understand the biological steps between altered testosterone levels and type 2 diabetes mellitus and how this is different between men and women,” concludes Perry.

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ORIGINAL ARTICLE Ruth, K. S. et al. Using human genetics to understand the disease impacts of testosterone in men and women. *Nat. Med.* **26**, 252–258 (2020)



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