Opening 'the X-files' helped researchers to understand why women and men differ in height

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Given its unique nature, the X chromosome has often been neglected when performing large-scale genetic studies. Because women have two copies of this

chromosome and men only one, identifying genetic associations with X chromosomal genes can be particularly valuable in helping us to understand why some characteristics differ between sexes. Credit: Taru Tukiainen

Researchers from the University of Helsinki analyzed thoroughly the commonly occurring genetic variation in chromosome X, one of the two sex-determining chromosomes, in almost 25,000 Northern European individuals with diverse health-related information available. The aim of the study was to find genetic factors that could explain individual differences in several traits, including BMI, height, blood pressure and lipid levels. In addition, the researchers also investigated whether the X chromosome would contribute to some of the well-known differences between men and women in certain traits, such as height. Hundreds of genetic variants having an effect on these traits have already been identified, but, given its unique nature, the X chromosome has been neglected in most of these previous studies.

The results were published in *PLOS Genetics* journal today, February 6th.

"Studying the X chromosome has some particular challenges. The fact that women have two copies of this chromosome and men only one has to be taken into account in the analysis. We nevertheless wanted to take up the challenge since we had a strong belief that opening 'the X files' for research would reveal new, interesting biological insights", says Dr. Taru Tukiainen who is currently working at the Massachusetts General Hospital in Boston.

The study showed that a genetic variant close to ITM2A, a gene that has a role in cartilage development, is frequent among the people being shorter than average. The identified variant, which is present in more than a third of Europeans, was also shown to increase the expression of

ITM2A, suggesting that the more the gene is expressed the shorter the person will be. Interestingly, the effect of this variant on height was shown to be much stronger in women.

"The double dose of X-chromosomal genes in women could cause problems during the development. To prevent this, there is a process by which one of the two copies of the X chromosome present in the cell is silenced. When we realized that the height associated variant we identified was nearby a gene that is able to escape the silencing we were particularly excited", explains Professor Samuli Ripatti, the principal investigator behind the study.

"Because both copies of ITM2A remain active, the gene is expressed in higher levels in women. Identifying associations in regions like this where X-chromosomal gene doses are not balanced between men and women can be particularly valuable in helping us to understand why some characteristics differ between sexes", he continues.

"Based on our calculations, this variant accounts for a significant, though small proportion, 1-2% of the current difference in mean height between men and women in the Finnish population.

Also two other new X-chromosomal regions, one associating with fasting insulin levels and the other with height, were identified in this study. Neither of these showed any evidence of sex difference in the strength of the genetic effect.

More information: Chromosome X-wide association study identifies loci for fasting insulin and height and evidence for incomplete dosage compensation. Taru Tukiainen, Matti Pirinen, Antti-Pekka Sarin, Claes Ladenvall, Johannes Kettunen, Terho Lehtimäki, Marja-Liisa Lokki, Markus Perola, Juha Sinisalo, Efthymia Vlachopoulou, Johan G. Eriksson, Leif Groop, Antti Jula, Marjo-Riitta Järvelin, Olli T.

Raitakari, Veikko Salomaa, Samuli Ripatti.
www.plosgenetics.org/doi/pgen.1004127