

The Lypla1 gene impacts obesity in a sex-specific manner

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Susceptibility to obesity, insulin resistance and other cardio-metabolic traits may also be dependent on a person's sex. An international research team of the University of California (UCLA), Helmholtz Zentrum München, a partner of the DZD, and Ludwig-Maximilians-Universität München studied sex differences and sex-specific interaction with the genetic background in cardio-metabolic phenotypes. The researchers

discovered, among other things, a sex-specific obesity locus of the *Lypla1* gene, which is associated with human obesity. The results of the study have now been published in *Cell Metabolism*.

Men and women may be differently susceptible to obesity, insulin resistance, and other cardio-metabolic traits. Women often have more advantageous metabolic profiles. This has been described for mice but also for humans. But how does sex interact with genes? What role does natural genetic variance play? And how does this affect the development of cardio-metabolic traits? In order to answer these questions, an international team of researchers used an [animal model](#) (hybrid mouse diversity panel) to search for sex-specific differences in 50 cardio-metabolic traits. The effect of sex on cardio-metabolic traits was investigated in terms of sex-specific correlations with specific disease phenotypes, their genetic architecture and the underlying expression networks in fat and liver. It was found that sex—depending on the genetic background—plays a role in gene expression and the development of cardio-metabolic traits. The research team discovered a sex-specific obesity locus for the *Lypla1* gene.

"In addition, we were able to show that there is sex-specific regulation for the 'beiging' of white adipose tissue and sex-specific interactions for mitochondrial function," said UCLA Professor Aldons J. Lusis, last author and head of the study. Brown adipose tissue can produce heat through the oxidation of fatty acids. This takes place in mitochondria, which are also responsible for the brownish coloration of the tissue. If the "good" brown fat is activated, the metabolism is stimulated and the "bad" white fat deposits are reduced. The occurrence of brown or beige adipocytes in white adipose tissue is called "browning" or "beiging," a phenomenon associated with increased energy consumption and, at least in the [mouse model](#), with protection against obesity.

The current study showed that females have a higher mitochondrial

activity and produce more [brown adipose tissue](#). This reduces fat mass and insulin resistance. In males, the interaction between genes and sex tends to lead to low mitochondrial activity and low beiging. Weight and insulin resistance increase.

"In the reference literature, there are already indications of major differences in adipose biology between sexes also in humans. This study provides insights into the depth and breadth of sex differences in metabolism. We believe that our results provide compelling evidence as to why males and females in [biological research](#) should be treated as distinct organisms as a whole, rather than attempting to reconcile these differences one molecule at a time," said DZD researcher Professor Susanna Hofmann, MD of the Institute for Diabetes and Regenerative Research of the Helmholtz Diabetes Center. Her group, together with Professor Axel Walch from the Core Facility Pathology & Tissue Analytics at Helmholtz Zentrum München, examined the adipose [tissue](#) and analyzed the sex differences in the browning of [white adipose tissue](#).

There are still many gaps in the understanding of the biology underlying these sex-specific differences. As a long-term goal, the researchers therefore want to develop a biological network model that describes the differences between men and women (the "sex-ome") at system level. Such a model will require identifying the primary and downstream sex-biased factors that act on the network and understanding how the sex-biased network interactions give rise to [sex differences](#) in the emergent phenotypes.

More information: Frode Norheim et al, Gene-by-Sex Interactions in Mitochondrial Functions and Cardio-Metabolic Traits, *Cell Metabolism* (2019). [DOI: 10.1016/j.cmet.2018.12.013](https://doi.org/10.1016/j.cmet.2018.12.013)

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