# Research outlines how sex differences have evolved

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Researchers at the Francis Crick Institute and Heidelberg University in Germany have shown that sex differences in animals vary dramatically across species, organs and developmental stages, and evolve quickly at

the gene level but slowly at the cell type level.

Mammals have different traits depending on sex, like antlers in male deer. These are known as "sexually dimorphic" traits, and include differences which aren't visible, such as in internal organs. However, researchers didn't know when and where sex differences emerge, and which genes and cells are responsible for them.

In this study, published today (Nov. 2) in *Science*, the researchers analyzed the activity of genes in males and females over time in humans and four species (mice, rats, rabbits, opossums and chickens), covering the development of five organs (brain, cerebellum, heart, kidney and liver), into adulthood in the animals and up to birth in humans.

A different approach was used for humans, as the available data only goes up to shortly after birth. The researchers looked at sex-biased genes until shortly after birth, and then checked if these same genes continued to show sex differences in adults using a public resource (the GTEx resource). This means the list of sex-biased genes in humans only included genes showing differences before or just after birth, whereas in the animals, it included sex-biased genes at any stage of development.

The researchers discovered that the organs that are different between the sexes vary across species. For example, the liver and the kidney were the most sexually dimorphic in rats and mice, whereas in rabbits, the heart was the most sexually dimorphic and liver and kidney not at all.

The researchers also found that, in all animals and humans, few sex differences occurred while organs were developing. Instead, they increased sharply around sexual maturity.

The researchers then investigated the genes responsible for sex differences, finding that different genes are "sex-biased" (expressed

differently depending on sex) across species. Only a very small number of sex-biased genes were shared across species, suggesting that sex differences have evolved quickly. The few genes that were shared were usually located on the sex (X and Y) chromosomes.

Although sex-biased genes differed between species, the study showed that the types of cells that are sexually dimorphic are the same across species. For example, in mice and rats, different genes were sex biased in the liver, but, in both cases, the sex-biased genes were active in the hepatocytes, the main type of cell in the liver. This may explain why there are sex differences in drug processing in the liver.

Leticia Rodríguez-Montes, Ph.D. student at Heidelberg University, and first author, said, "It was interesting to see that despite the fast evolution of sex differences, a few genes located on the X and Y sex chromosomes showed differences between the sexes in all mammalian species. These probably serve as basic genetic triggers for the development of traits specific to each sex in all mammals."

Margarida Cardoso Moreira, Group Leader of the Evolutionary Developmental Biology Laboratory at the Crick, and co-leader of the study with Henrik Kaessmann at Heidelberg University, said, "By taking an evolutionary approach, we've observed that sex differences evolve fast at the gene level but slowly at the cell level. This has implications for how we use animal models to understand sex differences in humans, as it's helpful to know that a particular cell type is sexually dimorphic across species, even if there are other differences.

"It was also surprising to us that there are so few sex differences until sexual maturity. We were expecting most differences to occur in adults because this is when sex differences are most visible, but we also expected to see a gradual increase in sex differences during organ development, instead of an abrupt rise around sexual maturity. This

research is another piece in the puzzle of understanding why we are sexually dimorphic and how this impacts us."

**More information:** Leticia Rodríguez-Montes et al, Sex-biased gene expression across mammalian organ development and evolution, *Science* (2023). DOI: 10.1126/science.adf1046. www.science.org/doi/10.1126/science.adf1046

Marie Sémon, Sex-biased gene expression in mammals, *Science* (2023). DOI: 10.1126/science.adk9990 , www.science.org/doi/10.1126/science.adk9990

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