

Reporting Summary

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Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

|                                     |                                                                                                                                                                                                                                                                                                |
|-------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| n/a                                 | Confirmed                                                                                                                                                                                                                                                                                      |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> The exact sample size ( <i>n</i> ) for each experimental group/condition, given as a discrete number and unit of measurement                                                                                                                               |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly                                                                                                                                               |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> The statistical test(s) used AND whether they are one- or two-sided<br><i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i>                                                               |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> A description of all covariates tested                                                                                                                                                                                                                     |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons                                                                                                                                        |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals) |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> For null hypothesis testing, the test statistic (e.g. <i>F</i> , <i>t</i> , <i>r</i> ) with confidence intervals, effect sizes, degrees of freedom and <i>P</i> value noted<br><i>Give P values as exact values whenever suitable.</i>                     |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings                                                                                                                                                                      |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes                                                                                                                                                |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> Estimates of effect sizes (e.g. Cohen's <i>d</i> , Pearson's <i>r</i> ), indicating how they were calculated                                                                                                                                               |

Our web collection on [statistics for biologists](#) contains articles on many of the points above.

Software and code

Policy information about [availability of computer code](#)

|                 |                                                                                                                                                                                                                                                                                                                                                         |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Data collection | No code was used in the collection of data other than the standard wget command.                                                                                                                                                                                                                                                                        |
| Data analysis   | The code written for data analysis is available on GitHub at <a href="https://github.com/AlberAqil/Switch_like_gene_expression_modulates_disease_risk_2025">https://github.com/AlberAqil/Switch_like_gene_expression_modulates_disease_risk_2025</a> ( <a href="https://doi.org/10.5281/zenodo.15270596">https://doi.org/10.5281/zenodo.15270596</a> ). |

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio [guidelines for submitting code & software](#) for further information.

Data

Policy information about [availability of data](#)

All manuscripts must include a [data availability statement](#). This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our [policy](#)

The transcriptomic data supporting this study's findings were obtained from the Genotype-Tissue Expression (GTEx) project. The data are available through the GTEx portal (<https://www.gtexportal.org/home/downloads/adult-gtex/overview>). The data regarding the samples' age and confounders were obtained from dbGaP accession number phs000424.v10.p2. All data analyses described in the Methods section and the resulting data are deposited on Figshare (<https://doi.org/10.6084/>

m9.figshare.28848356) as supplementary data.

## Research involving human participants, their data, or biological material

Policy information about studies with [human participants or human data](#). See also policy information about [sex, gender \(identity/presentation\), and sexual orientation](#) and [race, ethnicity and racism](#).

### Reporting on sex and gender

The study specifically analyzed biological sex differences in gene expression, particularly in tissues such as the breast. Of the 943 individuals analyzed for RNA-seq, 312 were females, and 631 were males. Sex-based gene expression differences were identified, with certain genes showing either female- or male-biased expression. However, the study did not analyze or account for gender identity or gender expression, as only biological sex data were available and relevant to the gene expression patterns being studied. Therefore, the analysis strictly focused on the impact of biological sex on switch-like gene expression and its disease associations.

### Reporting on race, ethnicity, or other socially relevant groupings

Socially relevant categorization variables were not employed in this study. Specific demographic details regarding race or ethnicity were not analyzed in this study, because the focus was on the gene expression patterns across tissues and the identification of switch-like genes. The study does not aim to make conclusions based on race, ethnicity, or other socially relevant groupings.

### Population characteristics

The population used in this study consists of 943 human individuals whose transcriptomic data were obtained from the GTEx project. These individuals vary in age, sex, and tissue samples, but detailed individual-level information such as race, ethnicity, and other demographic characteristics were not analyzed. The study primarily focused on gene expression patterns across 27 tissues, with sex as a biological variable included in the analysis. No other covariates, such as medical history or lifestyle factors, were incorporated into the analysis, as the study's goal was to identify switch-like gene expression patterns and their associations with disease susceptibility.

### Recruitment

The individuals whose data were used in this study were recruited as part of the Genotype-Tissue Expression (GTEx) project. Participants were recruited postmortem, with informed consent obtained from their next of kin. No additional recruitment biases or self-selection issues are relevant to this study, as the dataset was pre-existing and anonymized.

### Ethics oversight

The data utilized in this study are from the GTEx project, which obtained institutional review board (IRB) approval for all collected samples. Informed consent was provided by all individuals/next-of-kin from whom data were collected. The study followed ethical guidelines for biomedical research involving human participants. Vaginal tissue sections reused in this work were collected and stained under approval from the Regional Ethical Review Board, Uppsala, Sweden (record-/diary-number 2008/076).

Note that full information on the approval of the study protocol must also be provided in the manuscript.

## Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see [nature.com/documents/nr-reporting-summary-flat.pdf](https://www.nature.com/documents/nr-reporting-summary-flat.pdf)

## Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

### Sample size

The study analyzed 943 individual transcriptomes from the GTEx database across 27 tissues.

### Data exclusions

14 surgical samples were excluded such that we only included either postmortem or organ donor samples.

### Replication

The entire analysis was performed twice. The same results were obtained.

### Randomization

Randomization was not applicable due to the nature of the study.

### Blinding

Blinding was not applicable due to the nature of the study's design, which relies on pre-existing datasets.

## Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

## Materials &amp; experimental systems

|                                     |                                                        |
|-------------------------------------|--------------------------------------------------------|
| n/a                                 | Involved in the study                                  |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> Antibodies         |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Eukaryotic cell lines         |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Palaeontology and archaeology |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Animals and other organisms   |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Clinical data                 |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Dual use research of concern  |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Plants                        |

## Methods

|                                     |                                                 |
|-------------------------------------|-------------------------------------------------|
| n/a                                 | Involved in the study                           |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> ChIP-seq               |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Flow cytometry         |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> MRI-based neuroimaging |

## Antibodies

|                 |                                                                                                                                                                                                                                                                                                                           |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Antibodies used | A polyclonal rabbit anti-ALOX12 antibody (catalog no. HPA010691; Prestige Antibodies® powered by Atlas Antibodies, Sigma-Aldrich) was diluted 1:50 in 0.1 % bovine serum albumin. Sections were incubated overnight at 4 °C. Negative controls, prepared by omitting the primary antibody, were included for all samples. |
| Validation      | The antibody is tested with IHC tissue array of 44 normal human tissues and 20 of the most common cancer type tissues.                                                                                                                                                                                                    |

## Plants

|                       |                                                                          |
|-----------------------|--------------------------------------------------------------------------|
| Seed stocks           | This study did not involve the use of plants or plant-derived materials. |
| Novel plant genotypes | This study did not involve the use of plants or plant-derived materials. |
| Authentication        | This study did not involve the use of plants or plant-derived materials. |