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Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our [Editorial Policies](#) and the [Editorial Policy Checklist](#).

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

- ☐ ☒ The exact sample size (n) for each experimental group/condition, given as a discrete number and unit of measurement
- ☐ ☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
- ☐ ☒ The statistical test(s) used AND whether they are one- or two-sided
Only common tests should be described solely by name; describe more complex techniques in the Methods section.
- ☒ ☐ A description of all covariates tested
- ☐ ☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
- ☐ ☒ 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)
- ☐ ☒ For null hypothesis testing, the test statistic (e.g. F , t , r) with confidence intervals, effect sizes, degrees of freedom and P value noted
Give P values as exact values whenever suitable.
- ☒ ☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
- ☒ ☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
- ☒ ☐ Estimates of effect sizes (e.g. Cohen's d , Pearson's r), 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 commercial, open source or custom software was used for data collection.

Data analysis

Statistical analyses were performed using GraphPad Prism (v10.2.0). Data were first assessed for normality using the Shapiro–Wilk test, after which parametric or non-parametric tests were applied accordingly. Statistical methods included Student's t -test, Mann–Whitney test, Fisher's exact test, Chi-square test, and one- or two-way ANOVA with appropriate post hoc corrections (e.g., Sidak's multiple comparisons test). A significance threshold of $p < 0.05$ was used throughout. For RNA sequencing data, reads were aligned to the mouse genome M27 using STAR (v2.7.10b), quantified with RSEM (v1.3.1) or Salmon (v1.10.3), and analyzed for differential expression using DESeq2 (v1.44). Gene ontology enrichment analysis was performed using the ClusterProfiler package (v4.12.6). Spatial transcriptomic data were analyzed using region-based approaches and validated across multiple biological replicates. Downstream analyses and visualisation were performed in R (v4.4.1) using Seurat (v4.4.0 or v5.4.0) and Nebulosa (v1.14.0). Live calcium measurements were performed with NIS software (v5.42.17) and analysed using Igor Pro v6 (WaveMetrics).

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](#)

All data supporting the findings of this study are available from the corresponding authors upon reasonable request. RNA sequencing data generated in this study will be deposited in the Gene Expression Omnibus (GEO) repository, with accession numbers provided upon publication. Publicly available datasets used in this study are cited in the Methods section. Source data underlying all figures are provided with the manuscript.

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

Human placental samples were collected without stratification based on sex or gender of the pregnant individuals. Fetal sex was recorded where available but was not used as a primary variable in study design or analysis, and no sex-based analyses were performed. The focus of the study was on placental tissue biology, and therefore potential sex-specific effects were not specifically addressed.

Reporting on race, ethnicity, or other socially relevant groupings

Race, ethnicity, and other socially constructed groupings were not collected or considered in this study. Human samples were used to assess general biological properties of placental tissue, and no analyses were performed based on such variables.

Population characteristics

Human placental samples were obtained from pregnancies classified as either appropriate for gestational age (AGA) or early-onset fetal growth restriction (FGR), including both term and preterm deliveries. Clinical information collected included gestational age at delivery, birth weight, and other relevant obstetric parameters. Maternal characteristics such as age, body mass index, and fetal sex distribution were comparable between groups as described in the manuscript. Exclusion criteria included multiple pregnancies, maternal age <18 years, fetal structural or chromosomal abnormalities, preterm prelabour rupture of membranes or maternal bacterial or viral infection

Recruitment

Participants were recruited prospectively at University College London Hospital as part of the EVERREST study, as well as through clinical sampling at UZ Leuven. Inclusion criteria for FGR pregnancies were based on ultrasound-estimated fetal weight and gestational age, while control pregnancies included appropriately grown fetuses. Exclusion criteria included multiple pregnancies, fetal abnormalities, and maternal infections. Recruitment was based on clinical presentation, which may introduce some degree of selection bias inherent to clinical cohort studies.

Ethics oversight

Human placental samples were collected following written informed consent from all participants. The study was approved by the institutional ethics committees of the University Hospital Gasthuisberg Leuven (Belgium; approval number S60993) and University College London Hospital (United Kingdom; REC references 15/LO/1488 and 13/LO/1254). All procedures were conducted in accordance with relevant guidelines and regulations

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

Sample sizes were determined based on field standards and practical considerations related to animal breeding and sample availability. No statistical methods were used to predetermine sample size. For bulk RNA sequencing, six placentas per genotype were analyzed. For histological and stereological analyses, samples were typically derived from multiple litters per condition. In vitro experiments were conducted using multiple independent clones or biological replicates depending on the assay

Data exclusions

No data points were excluded from the analyses unless technical failure occurred or predefined quality control criteria were not met. ROUT test for outliers was applied when data had high variability, and data were excluded when identified as outlier. For electrophysiological recordings, experiments with excessive voltage clamp errors were excluded. For RNA-based analyses, samples failing quality thresholds were not included.

Replication

All key findings were independently replicated. In vivo experiments included multiple biological replicates across independent litters. In vitro experiments were repeated across independent cultures or clones. Spatial transcriptomic and imaging analyses were validated across multiple biological samples. Where applicable, representative data shown are consistent with observations across replicates. RT-qPCR was performed

using technical duplicates. Structural analysis of the placental labyrinth zone was performed in 16-20 randomly selected areas (depending on analysis).

Randomization No randomization was performed. Experimental groups were defined by genotype, and littermate controls were used where appropriate to minimize variability.

Blinding All mice were assigned a non-explicit ID, which was used for all measurements.

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 & experimental systems

n/a	Involved in the study
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☐	☒ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used

Primary antibodies:

Rabbit anti-pan cytokeratin (Dako/Agilent, cat. no. Z0622), dilution 1:500, used for lectin-cytokeratin double staining.
Chicken anti-MCT1 (Millipore, cat. no. AB1286I), dilution 1:500, used for SynTI detection.
Rabbit anti-MCT4 (Millipore, cat. no. AB3314P), dilution 1:100, used for SynTII detection.

Secondary antibodies:

Goat anti-rabbit alkaline phosphatase-conjugated antibody (Jackson ImmunoResearch, cat. no. 111-055-144), dilution 1:100.
Donkey anti-chicken Cy5-conjugated antibody (Jackson ImmunoResearch), dilution 1:150.
Donkey anti-rabbit Cy3-conjugated antibody (Jackson ImmunoResearch), dilution 1:150.

Additional detection reagents:

Biotinylated isolectin B4 (Vector Laboratories, cat. no. B-1205), dilution 1:250.
HRP-conjugated streptavidin (Agilent, cat. no. P0397), dilution 1:800.

Validation

All antibodies used in this study were validated by the manufacturers. Antibody specificity is documented in the respective product data sheets provided by the commercial suppliers. Specific staining patterns corresponded to the expected localization of SynTI (MCT1) and SynTII (MCT4) cells. Omission of primary antibodies served as a negative control.

Eukaryotic cell lines

Policy information about [cell lines and Sex and Gender in Research](#)

Cell line source(s)

Mouse trophoblast stem cells (mTSC; TS-Rs26) were obtained from the Janet Rossant laboratory (Toronto, Canada). Human trophoblast stem cells (hTSCs) were obtained from the Vincent Pasque laboratory (KU Leuven, Belgium) and were derived from hPSC (Pham, Cell Stem Cell, 2022)

Authentication

Cell lines were not independently authenticated after receipt but were obtained from established and well-characterized sources and maintained under standard culture conditions.

Mycoplasma contamination

All cell lines were regularly tested using qRT-PCR and confirmed to be free of mycoplasma contamination.

Commonly misidentified lines
(See [ICLAC](#) register)

No commonly misidentified cell lines (as listed by the ICLAC register) were used in this study.

Animals and other research organisms

Policy information about [studies involving animals](#); [ARRIVE guidelines](#) recommended for reporting animal research, and [Sex and Gender in Research](#)

Laboratory animals

All mice were housed at the Animal Facility Center at KU Leuven, Gasthuisberg. Housing rooms were maintained at a controlled

temperature of 23±2°C, relative humidity of 45–70%, and a 14 h light / 10 h dark cycle. Food and water were provided ad libitum. In-house 8-12 weeks old mice were used for the study. Mice were sacrificed by cervical dislocation, whereas fetuses were culled by decapitation.

Wild animals

The study did not involve wild animals.

Reporting on sex

Both male and female animals were used in this study. Where applicable, placental samples were collected from fetuses of both sexes; however, sex was not used as an experimental variable and no sex-specific analyses were performed. Litter averages were used for analysis where appropriate.

Field-collected samples

This study did not involve samples collected in the field.

Ethics oversight

All animal experiments were conducted in accordance with institutional guidelines and were approved by the Ethical Review Committee for Animal Experiments of KU Leuven (Belgium). The study was performed under an approved project license in compliance with applicable regulations.

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

Plants

Seed stocks

na

Novel plant genotypes

na

Authentication

na