

## 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  |
|-------------------------------------|--|
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> The exact sample size ( $n$ ) for each experimental group/condition, given as a discrete number and unit of measurement  |
| <input type="checkbox"/>            | <input checked="" 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 checked="" type="checkbox"/> | <input 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. $F$ , $t$ , $r$ ) with confidence intervals, effect sizes, degrees of freedom and $P$ value noted<br><i>Give <math>P</math> 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 checked="" type="checkbox"/> | <input type="checkbox"/> 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

Data analysis

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 RNA-Seq dataset generated during the sequencing procedure is deposited in the Gene Expression Omnibus database (access number GSE247670), the mass spectrometry proteomics and peptidomics datasets have been deposited to the ProteomeXchange Consortium via the PRIDE partner repository (access numbers PXD046940, PXD046506) and available from the corresponding author upon request.

## 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	We studied 19 biopsy specimens of male and female patients undergoing a liver biopsy for medical reasons. Due to the low frequency of suitable donors analyses on sex or gender differences were not performed.
Reporting on race, ethnicity, or other socially relevant groupings	Due to the low frequency of suitable donors analyses on race, ethnicity and other grouping were not performed.
Population characteristics	The sex and detailed clinical characteristics of these patients are shown in Supplementary Table 1.
Recruitment	We studied biopsy specimens of patients undergoing a liver biopsy for medical reasons. Written informed consent was obtained from each participant.
Ethics oversight	Biopsies were collected after approval of the Hôpital Erasme Ethics Committee (Brussels, Belgium).

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	We have estimated the number of samples to ensure a power of 80% with a statistical significance level of 5% using GraphPad StatMate. In addition, we designed our experiments based on previous experience (Gurzov EN, et al. Cell Metabolism 2014, Litwak SA, et al. Diabetes 2017).
Data exclusions	No data has been excluded in the analysis with the exception of sick mice (due to injury, infection, etc.) or inappropriate values provided by the equipment.
Replication	Results have been replicated in at least 2 independent experiments.
Randomization	By breeding P <sub>trk</sub> <sup>+/-</sup> mice we obtained P <sub>trk</sub> <sup>-/-</sup> and P <sub>trk</sub> <sup>+/+</sup> males and females littermates. P <sub>trk</sub> <sup>+/+</sup> and P <sub>trk</sub> <sup>-/-</sup> mice aged 8 weeks, were randomly assigned to experimental diet-induced obesity feeding with unrestricted access to the specific diets: a HFD (60 kcal% fat D12492), a HFHFCD (40 kcal% Fat, 20 kcal% Fructose, and 2% Cholesterol, D09100310i), or a control diet (10 kcal% Fat, D09100304i) from Research Diets (New Brunswick, NJ, USA). For the maintenance of the mice and for experiments that did not involve diet-induced obesity, a standard chow diet was employed (RM1 (P) 801151, Special Diets Services, UK).
Blinding	Blinding in cell culture and animal model experiments was not practically feasible. Further data output was quantitative and not subject to bias.

## 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
<input type="checkbox"/>	<input checked="" type="checkbox"/> Antibodies
<input type="checkbox"/>	<input checked="" type="checkbox"/> Eukaryotic cell lines
<input checked="" type="checkbox"/>	<input type="checkbox"/> Palaeontology and archaeology
<input type="checkbox"/>	<input checked="" 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	The detailed full list of antibodies, use and dilutions are included as Supplementary Table 3.
Validation	<p>The validation includes examination of several cell lines and/or tissues of known expression levels allows accurate determination of species cross-reactivity and verifies specificity.</p> <p>Treatment of cell lines with growth factors, chemical activators or inhibitors, which induce or inhibit target expression, verifies specificity. Phosphatase treatment confirms phospho-specificity.</p> <p>The use of siRNA transfection or knockout cell lines verifies target specificity. Side-by-side comparison of lots to ensures lot-to-lot consistency.</p> <p>Optimal dilutions and buffers are predetermined, positive and negative cell extracts are specified, and detailed protocols are already optimized.</p> <p>Cell Signaling Technology provide a validation procedure and statement. Antibody validations can also be found at the company website in the data sheet for each antibody online (<a href="https://www.cellsignal.com/">https://www.cellsignal.com/</a>).</p> <p>Santa Cruz Biotechnology antibody validations can be found at the company website in the data sheet for each antibody (<a href="https://www.scbt.com/home">https://www.scbt.com/home</a>).</p> <p>BD Biosciences antibody validations can be found at the company website in the data sheet for each antibody (<a href="https://www.bdbiosciences.com/en-us">https://www.bdbiosciences.com/en-us</a>).</p> <p>Bio-Rad provide a validation procedure and statement. Antibody validations can also be found at the company website in the data sheet for each antibody online (<a href="https://www.bio-rad-antibodies.com/primary-antibodies-monoclonal-polyclonal.html">https://www.bio-rad-antibodies.com/primary-antibodies-monoclonal-polyclonal.html</a>).</p> <p>Thermo Fisher Scientific validations can be found at the company website in the data sheet for each antibody (<a href="https://www.thermofisher.com/us/en/home.html">https://www.thermofisher.com/us/en/home.html</a>).</p> <p>Sigma-Aldrich provide a validation statement. Antibody validations can also be found at the company website in the data sheet for each antibody online (<a href="https://www.sigmaaldrich.com/US/en/products">https://www.sigmaaldrich.com/US/en/products</a>).</p> <p>R&amp;D Systems validations can be found at the company website in the data sheet for each antibody (<a href="https://www.rndsystems.com/products/antibodies#quality">https://www.rndsystems.com/products/antibodies#quality</a>).</p>

## Eukaryotic cell lines

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

Cell line source(s)	HepG2 cell line (# HB-8065; ATCC), Cellosaurus HLE (CVCL_1281), Cellosaurus HuH-6 (CVCL_4381), hESC H1 (WiCell).
Authentication	As per company authentication description. The authentication was not performed in our laboratory.
Mycoplasma contamination	We have performed rutin mycoplasma tests in our cell lines. No contaminations have been detected.
Commonly misidentified lines (See <a href="#">ICLAC</a> register)	None.

## 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	Ptprk knockout mice were generated at The Jackson Laboratory (Ptprk-8356J-M669 project) by CRISPR/Cas9 technology and were bred on a pure C57BL/6N background. The duration for which the animals were subjected to the experimental diets ranged from 4 to 40 weeks.
Wild animals	No wild animals were used in our studies.
Reporting on sex	Both male and female mice have been used in our studies. The information is provided in the figure legends.
Field-collected samples	No field collected samples were used in our study.
Ethics oversight	Liver samples were collected after approval of the Hôpital Erasme Ethics Committee (Brussels, Belgium). Written informed consent was obtained from each participant. The study was conducted with the approved human ethics by the Comité d'Éthique hospitalo-facultaire Erasme Université libre de Bruxelles (PI Gurzov approval Ref P2019/498). Mice were housed and managed in compliance with the Belgian Regulations for Animal Care, and the animal protocols underwent approval from the Commission d'Éthique du Bien-Être Animal (CEBEA), Faculté de Médecine, Université libre de Bruxelles (dossier No. 732).

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

## Plants

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Seed stocks

No seed stocks were used in our studies.

Novel plant genotypes

No plants were used in our studies.

Authentication

No authentication was required in our studies.