***eLife’s* transparent reporting form**

We encourage authors to provide detailed information *within their submission* to facilitate the interpretation and replication of experiments. Authors can upload supporting documentation to indicate the use of appropriate reporting guidelines for health-related research (see [EQUATOR Network](http://www.equator-network.org/%20)), life science research (see the [BioSharing Information Resource](https://biosharing.org/)), or the [ARRIVE guidelines](http://www.plosbiology.org/article/info%3Adoi/10.1371/journal.pbio.1000412) for reporting work involving animal research. Where applicable, authors should refer to any relevant reporting standards documents in this form.

If you have any questions, please consult our Journal Policies and/or contact us: editorial@elifesciences.org.

**Sample-size estimation**

* You should state whether an appropriate sample size was computed when the study was being designed
* You should state the statistical method of sample size computation and any required assumptions
* If no explicit power analysis was used, you should describe how you decided what sample (replicate) size (number) to use

Please outline where this information can be found within the submission (e.g., sections or figure legends), or explain why this information doesn’t apply to your submission:

We utilized existing GWAS data which are cited in the “Variant-to-gene mapping pipeline” sub-section of the “Methods” section.

**Replicates**

* You should report how often each experiment was performed
* You should include a definition of biological versus technical replication
* The data obtained should be provided and sufficient information should be provided to indicate the number of independent biological and/or technical replicates
* If you encountered any outliers, you should describe how these were handled
* Criteria for exclusion/inclusion of data should be clearly stated
* High-throughput sequence data should be uploaded before submission, with a private link for reviewers provided (these are available from both GEO and ArrayExpress)

Please outline where this information can be found within the submission (e.g., sections or figure legends), or explain why this information doesn’t apply to your submission:

We used three MSC-derived adipocyte biological replicates for both ATAC-seq and promoter-focused Capture-C libraries. We used six ESC-derived hypothalamic neuron biological replicates for ATAC-seq libraries and three biological replicates for promoter-focused Capture-C libraries.

Adipose data will be uploaded to GEO upon acceptance, and the overall hypothalamus data is the subject of another atlas-based manuscript currently under peer review and through that process that dataset will be made available once the paper is published– the corresponding hypothalamus preprint can be found at: https://www.biorxiv.org/content/10.1101/2020.07.06.146951v1.full

**Statistical reporting**

* Statistical analysis methods should be described and justified
* Raw data should be presented in figures whenever informative to do so (typically when N per group is less than 10)
* For each experiment, you should identify the statistical tests used, exact values of N, definitions of center, methods of multiple test correction, and dispersion and precision measures (e.g., mean, median, SD, SEM, confidence intervals; and, for the major substantive results, a measure of effect size (e.g., Pearson's r, Cohen's d)
* Report exact p-values wherever possible alongside the summary statistics and 95% confidence intervals. These should be reported for all key questions and not only when the p-value is less than 0.05.

Please outline where this information can be found within the submission (e.g., sections or figure legends), or explain why this information doesn’t apply to your submission:

This information may be found in the “Retrospective analysis” sub-section of the “Methods” section on pages 18-19.

(For large datasets, or papers with a very large number of statistical tests, you may upload a single table file with tests, Ns, etc., with reference to sections in the manuscript.)

**Group allocation**

* Indicate how samples were allocated into experimental groups (in the case of clinical studies, please specify allocation to treatment method); if randomization was used, please also state if restricted randomization was applied
* Indicate if masking was used during group allocation, data collection and/or data analysis

Please outline where this information can be found within the submission (e.g., sections or figure legends), or explain why this information doesn’t apply to your submission:

Groups were allocated based upon the cell type from which the data was derived. Additionally, GWAS data was separated based upon its trait of study and source year.

**Additional data files (“source data”)**

* We encourage you to upload relevant additional data files, such as numerical data that are represented as a graph in a figure, or as a summary table
* Where provided, these should be in the most useful format, and they can be uploaded as “Source data” files linked to a main figure or table
* Include model definition files including the full list of parameters used
* Include code used for data analysis (e.g., R, MatLab)
* Avoid stating that data files are “available upon request”

Please indicate the figures or tables for which source data files have been provided:

The SNPs surviving our biological constraints are identified in tables 1 & 2, as well as supplemental tables 1-4.
The number of SNPs surviving our constraints are identified in YYYY-TRAIT\_ConstrainedCounts, where YYYY indicates the GWAS start year and trait indicates either BMI or WHRadjBMI.
The variant-to-gene mapping results showing the surviving SNP ID, the future GWAS proxy (r2>0.8) of that surviving SNP, and the interacting gene of that SNP are identified in InteractingGenes-Merged.xlsx.

We’ve used the scripts in the linked github repository directory to create all images in the paper. createManhattanPlots.R creates the base Manhattan plot used in Figure 1 using the 2015 BMI summary statistics downloaded from GIANT

Figure 4 and Supplementary Figures 4 are created with their respective source data files using createEmpiricalDistributionOfPPVs.py

The remaining figures (figure 2, 3, 5 and supplementary figures 1, 2, 3, 5, 6) are created using createBarGraphs.R

Repository link: https://github.com/rkweku/SubThresholdProjectScripts