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

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**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:

Sample size estimation was not applicable for this study. We used all data genome-wide for 30 different pancreatic islet epigenomic datasets, resulting in a total of 505,273 genomic intervals with any regulatory annotations, as indicated in the Methods section: CNN input sequence and feature encoding. We used training cross-validation on withheld chr1 and 2 to avoid over-fitting of the models.

**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 trained the convolutional neural networks 1000 times, and averaged their results across all the networks to achieve robust variant predictions. This information can be found in Methods sections: CNN training and Application of CNN models to variant prioritization.

The information about the experimental validation of PROX1 locus enhancer activity can be found in the Methods section: Plasmid transfection and Luciferase reporter assay. We used 3 biological replicates (wells) for each tested condition, and 3 technical replicates of the luciferase reporter assays.

**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.

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All the statistical tests are described in the relevant Methods sections. Additionally all the code used to run all the statistical tests and generate the results presented in this study is available in GitHub repository (<https://github.com/agawes/islet_CNN>)

(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

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This is not applicable for this study, as no individual-level data and experimental groups were used.

**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
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* Avoid stating that data files are “available upon request”

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

All the code used to run the analyses and generate figures presented in this study is available in GitHub repository: <https://github.com/agawes/islet_CNN>