GenNet Framework: Interpretable Neural Networks for Predicting Phenotype from Genotype

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Introduction

Neural networks are currently the state of the art in many areas of scientific research and applications but are seldom applied in population genomics and **predictive genetics** due to the computational burden and lack of **interpretability**. Here, we propose a novel **open-source** deep learning framework, **GenNet**, for interpretable predictions of phenotypes from genotypes. In this framework, public prior **biological knowledge** (e.g. DNA and pathway annotations) is used to define a sparse, **memory-efficient networks**.

Methods

In the framework, **prior knowledge** is used to create groups of connected nodes to reduce the number of learnable parameters in comparison to a fully connected neural network. For example in the first layer, where **millions** of single nucleotide polymorphisms (**SNPs**) inputs are only connected to their corresponding **genes**, creating **meaningful** and **interpretable connections** while significantly **reducing** the total number of **parameters**.
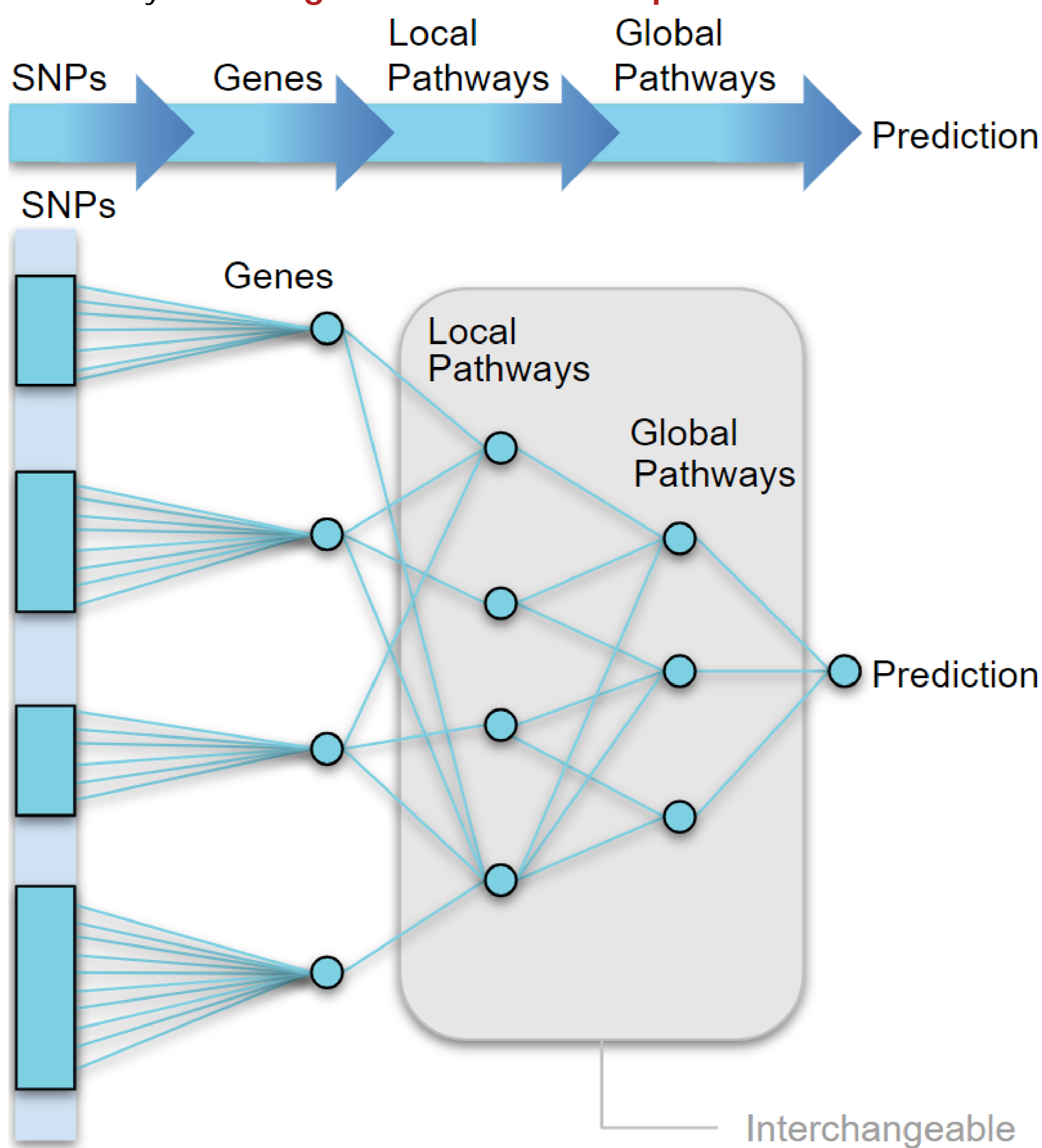

Figure 1: *Overview of neural networks in the **GenNet framework**. Different types of prior biological knowledge can be used to **define** the **connections**. In the shown network **gene annotations** were used to define the connections to the first layer and **pathway annotations** to group the genes from the first layer. Aside from gene and pathway annotations, our framework provides layers built from exon annotations, chromosome annotations and cell and tissue type expressions.*

GenNet is an open-source framework written in **Keras and Tensorflow**, code and tutorials are available on `https://github.com/arnovanhilten/GenNet/`.

Conclusion

- We developed a framework with **memory-efficient** and **interpretable neural networks** by using publicly available **biological** knowledge.
- These networks obtain **good predictive performance** even while only using **exomic variants**.
- We anticipate this approach as having the potential for uncovering **novel insights** into the genetic architecture of complex diseases

Results

The framework is validated in linear and non-linear simulations (see figure 2) and applied to **the Rotterdam study** (exonic variants) the **UK Biobank** and the **Schizophrenia WES Data** (see table 1). Identifying commonly associated genes for identifying hair and eye color such as *OCA2* and *HERC2*, validating the interpretabilty of the network.

Trait	Dataset (type)	Subjects & Phenotype Class I	Class II	Heritability	AUC Lasso	AUC GenNet	GenNet: top 3 genes
Eye color	Rotterdam genotype array	4041 Blue	2250 Other	0.80-0.98	0.68	0.75	*HERC2, OCA2, LAMC1*
Hair color	UK Biobank WES data	1648 Blond	1656 Red	0.70-0.97	0.78	0.83	*MC1R*, OCA2, TC2N*
	UK Biobank WES data	1672 Dark brown	1664 Red	0.70-0.97	0.79	0.88	*MC1R*, OCA2, ZCCHC4*
	UK Biobank WES data	4352 Blond	4343 Dark brown	0.70-0.97	0.64	0.75	*OCA2, TC2N, EXOC2*
Male baldness	UK Biobank WES data	3454 No balding	3454 Severe balding	0.60-0.70	0.57	0.57	*NGEF, NKRD18B, SYNJ2*
Bipolar	UK Biobank WES data	343 Cases	347 Controls	0.73-0.93	0.59	0.60	*LINC00266-1, CSMD1, TCERG1L*
Schizophrenia	Sweden WES data	4969 Cases	6245 Controls	0.80-0.85	0.65	0.74	*ZNF773, PCNT, DYSF*

Table 1: Summary of the experiments and results in this study for the simplest network in our framework that contains the input SNPs, the gene layer and the output layer. *MC1R was not present in gene annotations but identified by linkage disequilibrium.
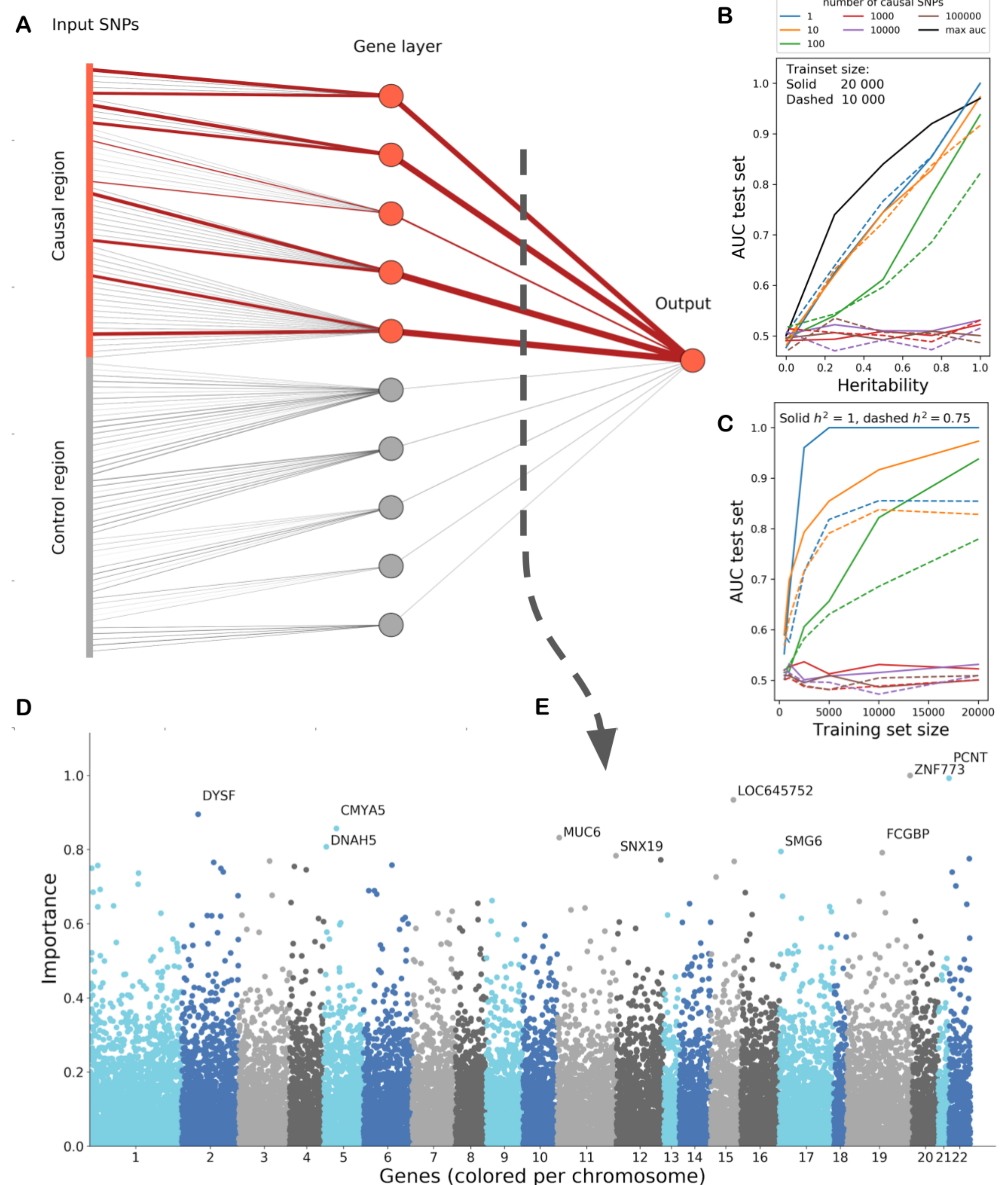

Figure 2: A) *Non-linear simulation showing the basic principle of the network, thickness of the connections represents the learned weight (causal in red).* **Run online** `https://tinyurl.com/y8hh8rul`. **B)** *Simulations with synthetic data showing the performance of GenNet expressed in the area under the curve for increasing levels of heritability and training set size* **(C)**. *In black the theoretical maximum of the AUC versus heritability.* **D)** *Manhattan plot of the importance of the genes according to the network for distinguishing between* **schizophrenia** *cases and controls.* **E)** *This manhattan plot is a cross section of the trained network between the gene layer and the outcome.*