DNA language models are powerful zero-shot predictors of genome-wide variant effects

Gonzalo Benegas[1], Sanjit Singh Batra[2], and Yun S. Song[2,3,*]

[1] Graduate Group in Computational Biology, University of California, Berkeley
[2] Computer Science Division, University of California, Berkeley
[3] Department of Statistics, University of California, Berkeley

Abstract

The expanding catalog of genome-wide association studies (GWAS) provides biological insights across a variety of species, but identifying the causal variants behind these associations remains a significant challenge. Experimental validation is both labor-intensive and costly, highlighting the need for accurate, scalable computational methods to predict the effects of genetic variants across the entire genome. Inspired by recent progress in natural language processing, unsupervised pre-training on extensive protein sequence databases has proven successful in extracting complex information related to proteins. These models showcase their ability to learn variant effects in coding regions using a zero-shot approach. Expanding on this idea, we here introduce the **G**enomic **P**re-trained **N**etwork (**GPN**), a model designed to learn genome-wide variant effects through unsupervised pre-training on genomic DNA sequences. Our model also successfully learns gene structure and DNA motifs without any supervision. To demonstrate its utility, we train GPN on *unaligned* reference genomes of *Arabidopsis thaliana* and seven related species within the Brassicales order, and test its ability to predict the functional impact of genetic variants in *Arabidopsis thaliana* by utilizing allele frequencies from the 1001 Genomes Project and a comprehensive database of GWAS. Notably, GPN outperforms predictors based on popular conservation scores such as phyloP and phastCons. Our predictions for *Arabidopsis thaliana* can be visualized as sequence logos in the UCSC Genome Browser (https://genome.ucsc.edu/s/gbenegas/gpn-arabidopsis). We provide code (https://github.com/songlab-cal/gpn) to train GPN for any given species using its DNA sequence alone, enabling the zero-shot prediction of variant effects across the entire genome.

Introduction

The emergence of genome-wide association studies (GWAS) has significantly enhanced our ability to examine the genetic basis of complex traits and diseases in both humans and plants. In humans, GWAS have played a crucial role in identifying genetic variants associated with a range of traits, including schizophrenia and obesity [1]. Similarly, in plants, GWAS have shed light on the genetic factors influencing traits such as drought tolerance, disease resistance, and yield [2]. A central challenge in GWAS is pinpointing causal variants for a trait, as linkage disequilibrium (LD) can lead to spurious associations [3]. This process, known as fine-mapping, serves as a foundation for constructing accurate, portable polygenic risk scores and understanding the underlying

*To whom correspondence should be address: yss@berkeley.edu

mechanisms. Although experimental validation of causal variants is the gold standard, it is not scalable. Instead, a scalable fine-mapping strategy involves utilizing computational variant effect predictors [4], which vary from conservation scores to deep learning models trained on functional genomics data. Accurate variant effect prediction is also vital for diagnosing rare diseases and interpreting rare variants that lie beyond the scope of traditional GWAS [5].

Recently, state-of-the-art performance in predicting the effects of missense (coding) variants has been achieved by training unsupervised models on extensive protein sequence databases [6] or their corresponding multiple sequence alignments [7]. These large language models can predict missense variant effects in a zero-shot manner, without the need for additional training on labeled data. This progress has been driven by advancements in natural language processing, where significant strides have been made by pre-training language models on vast text corpora. Pre-trained models such as BERT can be fine-tuned for downstream tasks such as sentiment analysis [8]. More recently, language models like GPT-4 have demonstrated impressive leaps in test performance across various disciplines, from law to computer science [9].

A widely-used approach to interpreting non-coding variant effects involves training a supervised model to predict functional genomics data — such as chromatin accessibility, transcription factor binding, or gene expression — and then evaluating variants based on how they disrupt these predictions. This approach was first introduced by DeepSEA [10], which utilized 919 functional genomics tracks, and has since been refined by Enformer [11] with 6,956 tracks and Sei [12] with 21,907 tracks. However, this approach's success depends on the availability of high-quality functional genomics data from a diverse array of cell types, which can be prohibitively expensive to generate for most species. Certain models focus on specific classes of non-coding variants. For instance, classifiers trained solely on sequence data can successfully predict cryptic splicing [13, 14]. To evaluate the effects of regulatory variants, Lee *et al.* [15] developed a support vector machine that distinguishes putative regulatory sequences from random genomic sequences. More recently, a deep learning model capable of predicting Hi-C signal from sequence data demonstrated its potential to predict the impact of regulatory variants on DNA folding within the nucleus [16]. Additionally, a deep learning model [17] was effectively trained to predict DNA methylation levels of CpG sites from sequence data, enabling the prediction of non-coding variant effects on DNA methylation.

However, variant-specific models are inherently not well-suited for diagnosing rare diseases, fine-mapping, or calculating polygenic risk scores, as these tasks necessitate the comparison of genome-wide variants on a uniform scale. An important class of genome-wide scores includes conservation scores phyloP [18] and phastCons [19], which are computed from genome-wide alignment of multiple species. Since these do not require functional genomics data, they have been widely applied, including to non-model organisms [20]. In humans, CADD is another important genome-wide variant effect predictor that combines conservation and functional genomics annotations and is trained to distinguish between an inferred set of putative benign and putative pathogenic variants [21, 22].

In this paper, we introduce the **G**enomic **P**re-trained **N**etwork (**GPN**), a multi-species DNA language model trained using self-supervision. While existing DNA language models [23, 24, 25, 26, 27, 28, 29] have not yet demonstrated the ability to make accurate zero-shot variant effect predictions, GPN presents a unified approach capable of accurate zero-shot prediction of genome-wide variant effects. We demonstrate its utility by achieving state-of-the-art performance in *Arabidopsis thaliana*, a model organism for plant biology and a source of insight into human diseases [30]. Moreover, GPN outperforms genome-wide conservation scores such as phyloP and PhastCons, which rely on whole-genome alignments of 18 closely related species [20]. GPN's internal representation of DNA sequences can distinguish genomic regions like introns, untranslated regions, and coding sequences. Additionally, the confidence of GPN's predictions can help reveal regulatory grammar,

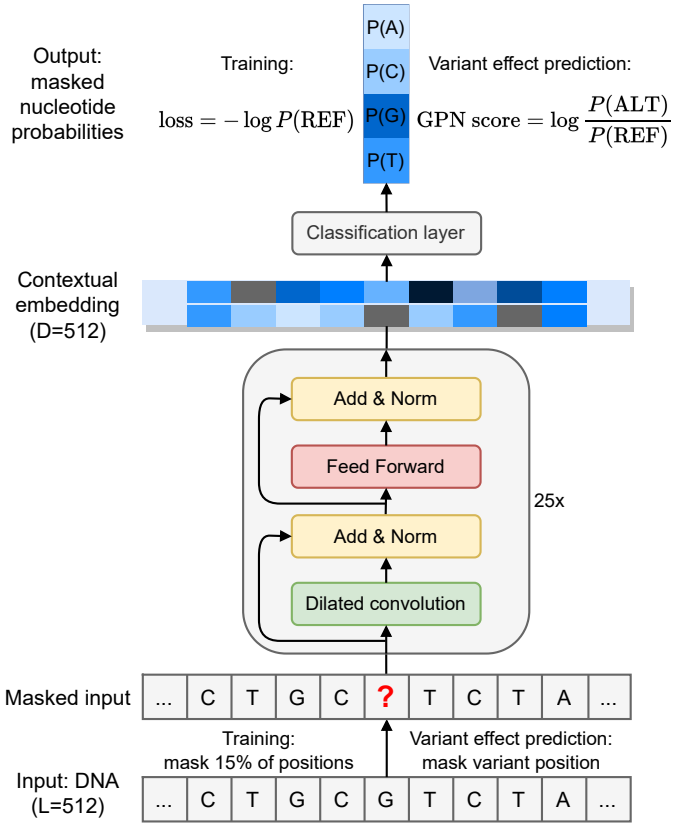


Figure 1: Overview of GPN (Genomic Pre-trained Network). The input is a 512-bp DNA sequence where certain positions have been masked, and the goal is to predict the nucleotides at the masked positions. During training, 15% of the positions are masked. During variant effect prediction, only the variant position is masked. The sequence is processed through a convolutional neural network resulting in a high-dimensional contextual embedding of each position. Then, a final layer outputs four nucleotide probabilities at each masked position. The model is trained on the reference sequence with the cross-entropy loss. The GPN variant effect prediction score is defined as the log-likelihood ratio between the alternate and reference allele. L: window length in base pairs. D: embedding dimension. REF: reference allele. ALT: alternate allele.

such as transcription factor binding motifs. Our results lay the foundation for developing state-of-the-art genome-wide variant effect predictors for any species using genomic sequence alone, which can be readily integrated into GWAS fine-mapping and polygenic risk scores.

Results

Training a multi-species DNA language model. We used *unaligned* reference genomes from *Arabidopsis thaliana* and seven related species within the Brassicales order to pre-train a language model based on a convolutional neural network (Supplementary Table S1). This model was designed to predict masked nucleotides conditioned on their local genomic context (Figure 1, Materials and Methods). During the training process, we encountered challenges with repetitive elements, which can be functionally significant but are heavily overrepresented in the genomes [31]. We found that reducing the weight of prediction loss for repetitive regions led to improved test perplexity in

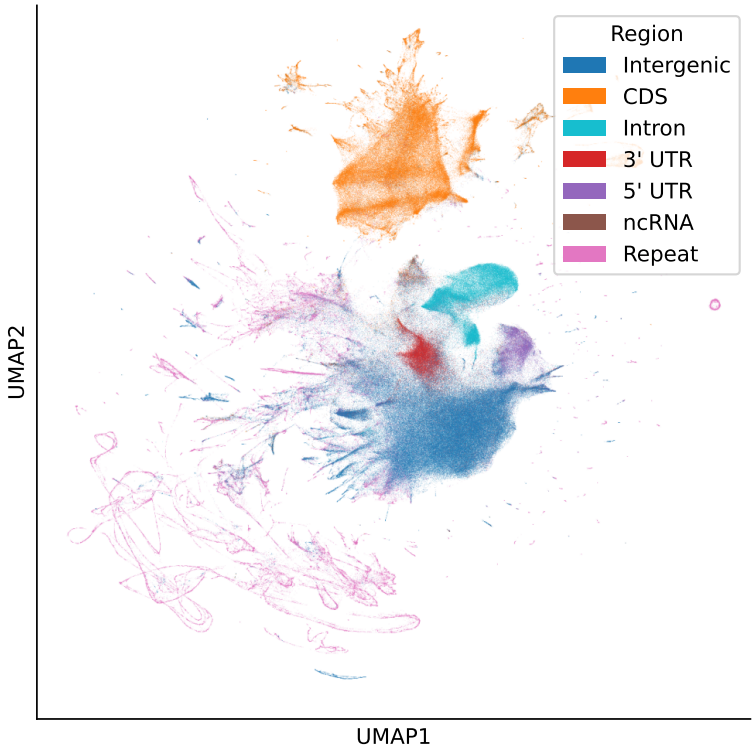


Figure 2: Unsupervised clustering of genomic windows. UMAP visualization of GPN embeddings averaged over non-overlapping 100-bp windows along the genome, annotated with gene region.

non-repetitive regions, which are often of greater interest (Supplementary Table S2). Our findings suggest that moderately down-weighting the prediction loss on repetitive elements yields superior results compared to no down-weighting or complete exclusion of repeat regions. Consequently, we use this model throughout the remainder of the paper unless otherwise specified.

Unsupervised clustering of genomic regions. To understand how well the model has learned the structure of the genome, we averaged GPN's contextual embeddings (512 dimensions) of nucleotides over 100 base pair (bp) windows from the reference genome and visualized them using UMAP [32] (Figure 2). Notably, GPN, trained without any supervision, has learned to distinguish genomic regions such as intergenic, introns, coding sequences (CDS), untranslated regions (UTR) and non-coding RNA (ncRNA). This level of separation cannot be achieved merely through k-mer frequencies (Supplementary Figure S1). To some extent, the model embeddings can also distinguish different repeat families (Supplementary Figure S2).

DNA motifs revealed by high-confidence model predictions. To further understand GPN, we individually masked each position in the genome and obtained the model output distribution over nucleotides, given its context. To facilitate utilizing these predicted distributions, we created sequence logos that can be visualized in the UCSC Genome Browser [33, 34] (`https://genome.ucsc.edu/s/gbenegas/gpn-arabidopsis`), where the height of each letter is proportional to its probability, and the overall height is given by the information content, measured in bits [35] (see Figure 3a for an example). The model's prediction confidence correlates with the expected functionality of the sites. For example, exonic positions are predicted with higher confi-

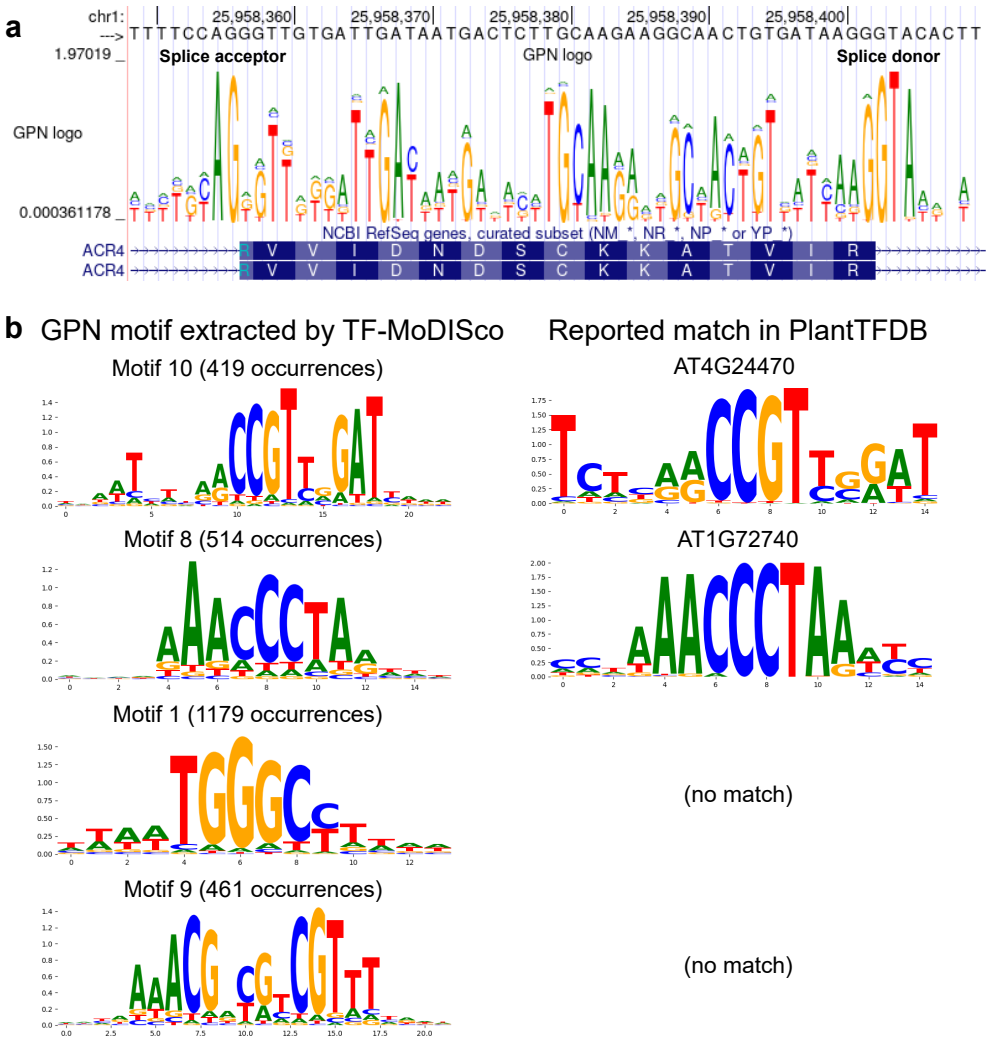


Figure 3: Sequence logos derived from model predictions. Each position in the genome was independently masked and the model distribution over the four nucleotides was computed. (a) Sequence logo visualized in the UCSC Genome Browser (https://genome.ucsc.edu/s/gbenegas/gpn-arabidopsis). The height of each letter is proportional to its probability, while the overall height at each position is equal to 2 minus the entropy of the distribution. (b) Example GPN motifs in promoter regions, extracted by TF-MoDISco, with significant matches in PlantTFDB.

dence than the surrounding introns, except for the canonical splice acceptor and donor dinucleotide motifs. Similarly, the third nucleotide position within codons, which usually does not affect amino acid identity, is generally predicted with lower confidence than the first two positions. Start and stop codon motifs are similarly well predicted (Supplementary Figure S3).

We hypothesized that scanning promoters for small regions of high-confidence GPN predictions could help identify transcription factor binding sites. To achieve this, we adapted TF-MoDISco [36], a tool for *de novo* discovery of transcription factor binding sites using supervised models. This tool clusters high-scoring regions into motifs and compares them to databases of known motifs. Applying the adapted TF-MoDISco to GPN scores in promoter regions, we discovered approximately a hundred motifs (Supplementary Figure S4), with four examples shown in Figure 3b, the first two

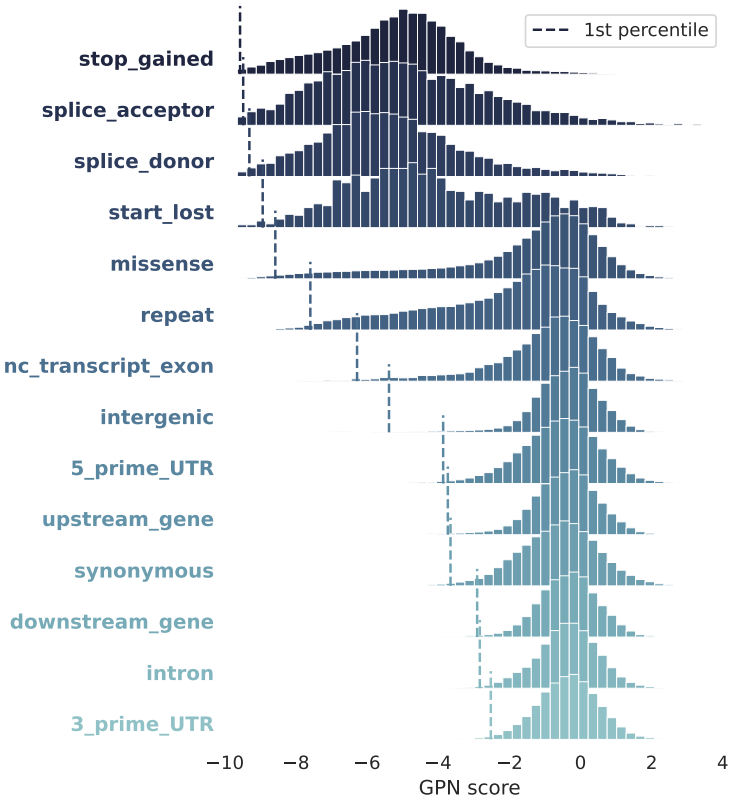
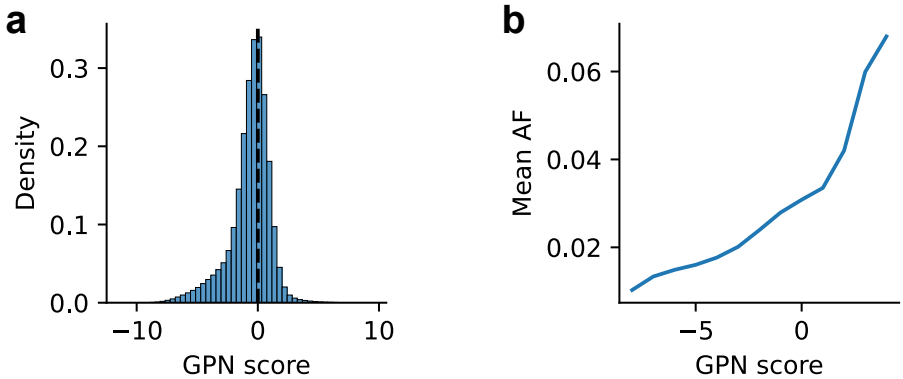


Figure 4: Variant effect prediction: *in silico* mutagenesis. Distribution of GPN scores computed for all possible single-nucleotide polymorphisms (SNPs) in a 1 Mb region, across categories, sorted by 1st percentile.

having a significant match in PlantTFDB [20]. Some of the discovered motifs are well-documented in the literature but do not have a significant match in this database, such as the third motif [37] in Figure 3b. Some motifs could represent novel promoter elements, like the fourth motif, which is palindromic with symmetrical entropies, suggesting that it could form RNA or DNA alternative secondary structure [38].

Zero-shot variant effect prediction. GPN can be employed to calculate a pathogenicity or functionality score for any single-nucleotide polymorphism (SNP) in the genome using the log-likelihood ratio between the alternate and reference allele (GPN score, Figure 1). Visually, this involves comparing the heights of the letters in the logo plot (Figure 3a).

In silico mutagenesis. We first computed GPN scores for *in silico* mutagenesis of SNPs within a 1 Mb region and aggregated the results across variant types (Figure 4). The ranking of variant types based on the lowest percentile of GPN scores is generally consistent with established notions of deleteriousness. For example, the four lowest scored variant types are splice donor, splice acceptor, stop gained and start lost variants, which significantly disrupt the open reading frame. As expected, missense variants are ranked before synonymous variants. However, we observed that variants within repetitive elements were assigned unusually low GPN scores, ranking close to missense variants. Reducing the training loss weight on repeats does somewhat improve this situation, but even with a weight of zero, there is a heavy tail of pathogenic scores on repeats (Supplementary Figure S5a).



c

GPN score	Rare (AC = 1)	Common (AF ≥ 5%)
Putative functional (lower 0.1%)	3 920	342
Putative non-functional (upper 90%)	2 668 533	1 166 703

Odds ratio: 5.01, p-value: 3.47e−279

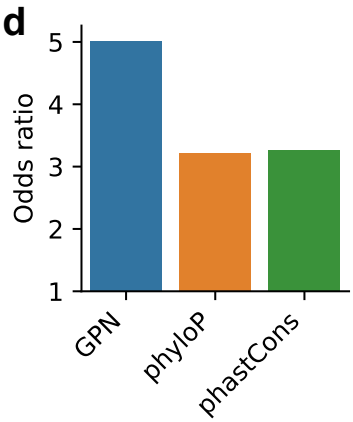
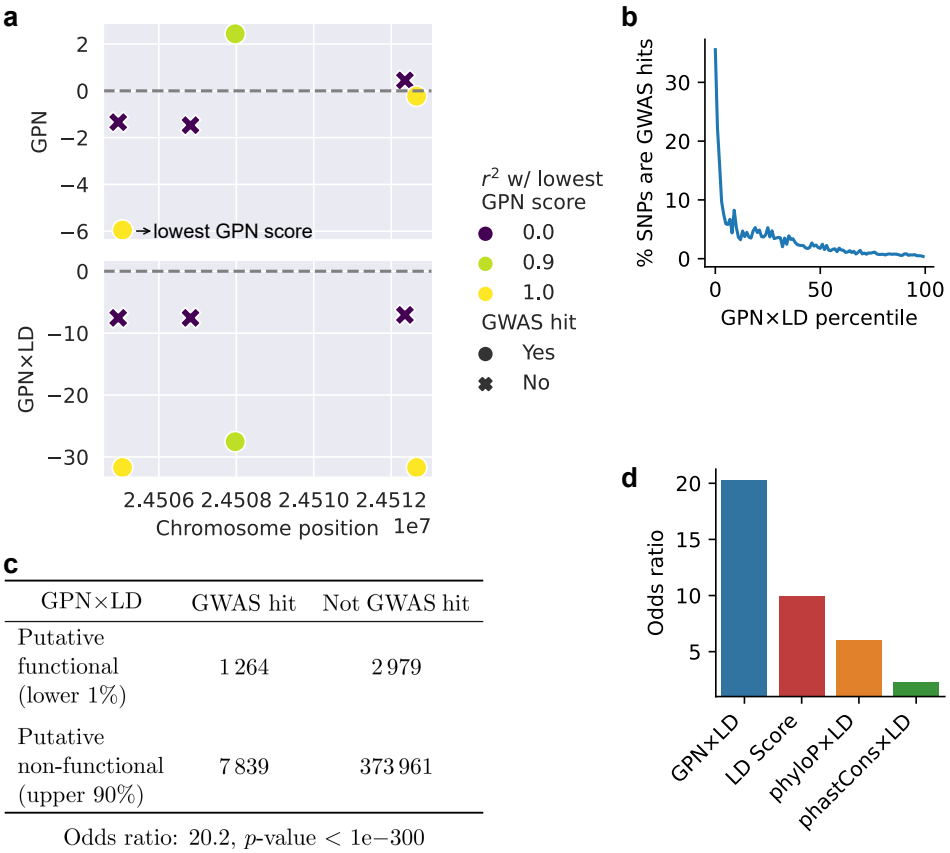


Figure 5: Variant effect prediction: rare vs. common. The GPN score was computed for over 10 million variants in the 1001 Genomes. (a) Distribution of GPN scores. (b) Mean allele frequency for different GPN score bins. (c) Contingency table and odds ratio showing enrichment of putative functional GPN scores in rare variants. AC: allele count. AF: allele frequency. (d) Comparison of odds ratios as in (c) obtained with different models.

Benchmarking using allele frequencies in 1001 Genomes. Following our *in silico* mutagenesis experiments, we analyzed over 10 million SNPs from naturally occurring accessions of the 1001 Genomes Project [39]. While most variants have a neutral GPN score, there is a heavy tail of putative functional variants with negative GPN scores (Figure 5a). Notably, variants with lower GPN scores are, on average, less frequent in the population, suggesting they could be under purifying selection (Figure 5b, full distribution in Supplementary Figure S6). To evaluate the capability of identifying putative functional variants, we assessed the enrichment of rare versus common variants in the tail of genome-wide score distributions. Putative functional SNPs, defined as the lowest 0.1% of GPN scores, exhibit a five-fold enrichment in rare variants (Figure 5c); see Supplementary Figure S7 for different allele frequency thresholds. GPN outperforms other genome-wide variant effect predictors for *Arabidopsis*, specifically phyloP and phastCons, which are conservation scores derived from a broader set of 18 Brassicales species (Figure 5d). In fact, GPN scores are only weakly correlated with phyloP ($r = 0.23, p < 10^{-300}$) and phastCons ($r = 0.13, p < 10^{-300}$). A notable advantage of GPN is that it is able to score variants that could not be scored by phyloP and phastCons due to unsuccessful whole-genome alignment (14.3% of all variants). GPN performs comparably to phyloP and phastCons when using less stringent thresholds for defining putative functional SNPs (Supplementary Figure S8), indicating its particular strength in detecting deleterious variants at the extreme tail. GPN also achieves significant odds ratios when computed only within particular



c

GPN×LD	GWAS hit	Not GWAS hit
Putative functional (lower 1%)	1 264	2 979
Putative non-functional (upper 90%)	7 839	373 961

Odds ratio: 20.2, p-value $<$ 1e−300

Figure 6: Variant effect prediction: GWAS. GPN scores were analyzed for around half a million variants tested in AraGWAS. (a) Example region of the genome with six variants tested for association with maximum temperature in January. GPN×LD successfully separates GWAS hits and non-hits. (b) Percentage of GWAS hits (for any trait) in each percentile bin of GPN×LD scores. (c) Contingency table and odds ratio showing enrichment of GWAS hits (for any trait) in putative functional (associated) GPN×LD scores. (d) Comparison of odds ratios obtained with different models.

variant classes, but its performance relative to phyloP and phastCons varies (Supplementary Figure S8). On a separate note, the highest odds ratio is achieved by the GPN model trained with an intermediate loss weight on repeats (Supplementary Figure S5b).

Enrichment of GWAS hits in regions with low GPN scores. In our pursuit to further evaluate the efficacy of GPN, we examined the AraGWAS Catalog [40], a comprehensive database of genome-wide association studies (GWAS) in *Arabidopsis thaliana*. We hypothesized that GWAS hits may be enriched in regions with low GPN scores. An advantage of GPN is that it can give substantially different scores to variants in strong linkage disequilibrium (LD) with each other, if their surrounding contexts are different (e.g., see Figure 6a, top). In contrast, the standard GWAS would give similar scores to such variants; in particular, neutral variants in strong LD with a functional variant would also be associated with a trait. To account for this difference, we devised a new score, GPN×LD, which weighs GPN scores by LD (Materials and Methods). With this approach, GPN×LD effectively distinguishes GWAS hits from non-hits (Figure 6a, bottom). We also discovered that the tail of GPN×LD scores is enriched in GWAS hits (Figure 6b). In particular, by studying odds ratios (Figure 6c), we found that SNPs with the lower 1% of GPN×LD scores are 20-fold enriched

in GWAS hits compared to the upper 90% of GPN×LD scores, while less than 10-fold enrichment was observed for other methods (Figure 6d); see Supplementary Figure S9 for different thresholds. Interestingly, the GPN model trained with an intermediate loss weight on repeats achieves the best performance (Supplementary Figure S5c).

Discussion

Here we present the first zero-shot genome-wide variant effect predictor based on unsupervised pre-training of DNA language models. We demonstrate that GPN outperforms other genome-wide variant effect predictors in *Arabidopsis thaliana*, a model species for plant biology. Since GPN is trained only on DNA sequence, it can be readily applied to understudied non-model organisms even in the absence of extensive functional genomics data, while still providing state-of-the-art zero-shot variant effect prediction genome-wide.

We can think of GPN as a generalized conservation score. Similar to phyloP and phastCons, GPN is genome-wide, can be trained on genomic sequence alone, and is cell-type and mechanism agnostic [41]. The key distinction is that while phyloP and phastCons only consider nucleotide frequencies at a specific site, GPN can learn from joint nucleotide distributions across all similar contexts appearing in the genome. Furthermore, GPN does not rely on whole-genome alignments, which can often have a lower quality in non-coding regions.

The capability of GPN to score genome-wide variants on a unified scale renders it ideal for integration into rare disease diagnosis, fine-mapping, and polygenic risk scores, including burden tests. The separation of genomic regions based on GPN embeddings suggests that it could be further fine-tuned for *de novo* genome annotation. Combining GPN predictions with TF-MoDISco offers a promising strategy for discovering functional motifs. Although in this study we focused on transcription factor binding sites, we believe that GPN predictions around splice junctions could also facilitate the identification of splicing factor binding sites.

Repetitive elements, which are inherent components of eukaryotic genomes, pose several challenges that have been underexplored in DNA language modeling studies. First, these elements are significantly over-represented [31]. The improved perplexity in non-repetitive regions upon down-weighting repeats can be attributed to the model allocating fewer parameters exclusively to repetitive elements. Second, repetitive elements display reduced sequence variation compared to other regions, in particular younger repeats with little time to accumulate mutations [42]. We believe that these reasons together cause the model to be overconfident, leading to the assignment of more deleterious scores than expected. Our proposed down-weighting of repeats only partially mitigates these issues, and we encourage further investigation by the scientific community. Potential research directions include examining the effects of down-weighting repeats based on their respective families or inferred age.

While the current implementation of GPN achieves state-of-the-art variant effect prediction for *Arabidopsis thaliana*, there is room for improving its training scheme. Mounting evidence suggests that larger models and more extensive training data can enhance performance [43]. Our current proof-of-concept model is considerably smaller — by 200 times — than the largest published protein language model [44]. One strategy to improve GPN, inspired by protein modeling, involves explicitly incorporating multiple sequence alignments [45, 46]. However, this enhancement will be bottle-necked by the quality of alignment in non-coding genome regions. Other promising avenues for DNA language modeling include incorporating DNA-specific inductive biases, such as reverse-complement equivariance [47], as opposed to our current method of averaging model outputs for both strands during testing. Additionally, integrating long-range information using recent advances

in state space models [48] may further boost performance. In conclusion, DNA language models represent a powerful framework for genome-wide variant effect prediction, and we believe that exploring the above avenues to further improve GPN would be worthwhile.

Materials and Methods

Pre-training. We obtained a list of Brassicales reference genome assemblies from NCBI Genome (https://www.ncbi.nlm.nih.gov/data-hub/genome/), filtered for RefSeq-annotated and kept only one per genus, resulting in a total of 8 reference genomes (Supplementary Table S1). We held out *Arabidopsis* chromosomes 4 and 5 for validation and testing, respectively. For each genome, we subsampled genomic windows of size 512 bp, with a step of 256 bp and augmented with the reverse complement. However, we did not draw genomic windows uniformly from the whole genome, but emphasized certain regions. In particular, we took the union of exons (with a small intronic flank), promoters (1000 bp upstream of transcription start sites) as well as an equivalent amount of random windows from the whole genome. We think this decision may improve performance, but leave experimentation for further studies. Additionally, we subset the number of windows from each genome to the number of windows from *Arabidopsis*, given its unusually small genome.

We set up a masked language modeling task [8], in which 15% of the tokens in a nucleotide sequence were masked and had to be predicted from their context. In contrast to most DNA language models that tokenize sequences into overlapping k-mers [24, 26, 28] or use byte-pair encoding [23], we used bare nucleotides as tokens. While a thorough benchmark of different tokenization strategies is lacking, using single-nucleotide tokens makes interpretation easier, in particular for zero-shot variant effect prediction.

While language model pre-training successes were first showcased by transformer architectures, convolutional models have shown similarly good performance in natural language [49] and protein modeling [50]. In our initial experiments, we noticed that convolutional models converged faster than transformer models. The locality of convolutions may be a good inductive bias for modeling DNA sequences at this scale. The linear complexity of convolution also simplifies inference or fine-tuning on longer sequences such as entire chromosomes, which in the case of transformers might require chunking (with some overlap) and aggregating the results.

We implemented GPN, a convolutional neural network, using the Hugging Face library [51]. The masked DNA sequence was one-hot encoded and then consecutively processed by 25 convolutional blocks. Each convolutional block consisted of a dilated convolutional layer followed by a feed-forward layer, with intermediate residual connections and layer normalization (Figure 1). Throughout the layers, the embedding dimension (number of convolutional filters) was kept fixed at 512. The dilation was increased exponentially up to a certain value and then cycled. A list of hyperparameters is displayed in Supplementary Table S3. We trained three models varying only in the loss weight on repetitive elements (marked lowercase in the fasta file). We trained each model for 150 K steps, taking approximately 4 days with 4 NVIDIA A100 80GB GPUs. Test perplexity is displayed in Supplementary Table S2.

Analysis of model embeddings. Model embeddings were averaged over non-overlapping 100-bp windows. Embeddings from the forward and reverse strand were averaged, and then standardized. The gene annotation was downloaded from EnsemblPlants. The annotation of repetitive elements was downloaded from http://ucsc.gao-lab.org/cgi-bin/hgTables?hgsid=167291_E9nY5UIAQRUOAR01xJAsum4vDukw. We considered intergenic regions with 100% overlap with repeats as a separate "Repeat" class. Windows with ambiguous annotation (e.g. 50% CDS and 50% intron) were excluded from the analysis.

Motif analysis. Each position in the genome was independently masked and the model distribution over nucleotides was extracted. The distribution was averaged between the results from the forward and reverse strands.

An adaptation of TF-MoDISco was run with model predictions in regions 500 bp upstream of transcription start sites, after filtering repeats and exons. The exact score fed into Modisco was the nucleotide probability minus 0.25, so it would be roughly centered at 0. Since TF-MoDISco expects genomic windows of equal length, we concatenated our variable-length windows into one large window, interspersed with 20 undefined 'N' nucleotides.

Variant effect prediction. We scored variants by masking the position and calculating the log-likelihood ratio between the alternate and reference allele. Scores computed from the forward and reverse strands were averaged. We calculated odds ratio and p-value with Fisher's exact test. When comparing to phyloP and phastCons, we excluded variants where these scores are undefined.

All possible SNPs in the region `Chr5:3,500,000-4,500,000` were generated and their consequences annotated with Ensembl Variant Effect Predictor [52] web interface https://plants.ensembl.org/Arabidopsis_thaliana/Tools/VEP, with the `upstream/downstream` argument set to 500, used to call variants as upstream/downstream instead of intergenic. We compared scores for variant types with at least 1000 variants, and we excluded variants with different consequences in different transcripts.

The 1001 Genomes genotype matrix was downloaded from https://aragwas.1001genomes.org/api/genotypes/download and combined with metadata from https://1001genomes.org/data/GMI-MPI/releases/v3.1/1001genomes_snp-short-indel_only_ACGTN.vcf.gz. This genotype matrix is binary, since all the accessions are homozygous, as *Arabidopsis* is predominantly selfing. Variants with alternate allele frequency greater than 50% were excluded. Variant consequences produced by Ensembl Variant Effect Predictor were downloaded from Ensembl Plants. Conservation scores were downloaded from http://plantregmap.gao-lab.org/download.php#alignment-conservation. For conservation scores phyloP and phastCons, we simply flipped the sign to obtain a variant score, i.e., variants at conserved sites should be considered more pathogenic. We defined rare variants as those with allele count equal to 1 (to be precise, it is two alleles in the same homozygous accession), and common variants as those with allele frequency above 5%. Model scores were defined as pathogenic or benign based on a quantile threshold that we varied from 0.1% to 10%.

GWAS summary statistics were downloaded through the AraGWAS API, with their default threshold of minimum allele count of 6 (to be precise, at least 6 homozygous accesions having the allele). The LD matrix of squared Pearson correlations (r^2) was calculated within a radius of 100 kb around each variant, using `sgkit` (https://pystatgen.github.io/). We define a weighted sum of GPN scores according to LD (i and j index SNPs):

$$\text{GPN} \times \text{LD}_i = -\sum_j |\text{GPN}_j| \cdot r_{ij}^2$$

This is an unsigned version of the Signed LD Profile [53] and can also be interpreted as the multiplication between the LD matrix and the vector of GPN scores. We similarly defined phyloP×LD and phastCons×LD. We considered the baseline LD Score [54], the unweighted sum of LD with a given variant:

$$\text{LD Score}_i = -\sum_j r_{ij}^2$$

Code availability. Code to reproduce all results, including instructions to load the pre-trained model, is available at https://github.com/songlab-cal/gpn.

Competing interest statement

The authors declare no competing interests.

Acknowledgments

We would like to thank Carlos Albors, Jesús Martínez-Gómez, Eyes Robson, Nilah Ioannidis and Allison Gaudinier for helpful discussions. This research is supported in part by an NIH grant R35-GM134922 and a grant from the Koret-UC Berkeley-Tel Aviv University Initiative in Computational Biology and Bioinformatics.

References

[1] Visscher PM, et al. (2017) 10 years of GWAS discovery: biology, function, and translation. *The American Journal of Human Genetics* 101(1):5–22.

[2] Tibbs Cortes L, Zhang Z, Yu J (2021) Status and prospects of genome-wide association studies in plants. *The Plant Genome* 14(1):e20077.

[3] Brandes N, Weissbrod O, Linial M (2022) Open problems in human trait genetics. *Genome Biology* 23(1):131.

[4] Weissbrod O, et al. (2020) Functionally informed fine-mapping and polygenic localization of complex trait heritability. *Nature Genetics* 52(12):1355–1363.

[5] Marwaha S, Knowles JW, Ashley EA (2022) A guide for the diagnosis of rare and undiagnosed disease: beyond the exome. *Genome Medicine* 14(1):1–22.

[6] Meier J, et al. (2021) Language models enable zero-shot prediction of the effects of mutations on protein function. *Advances in Neural Information Processing Systems* 34.

[7] Frazer J, et al. (2021) Disease variant prediction with deep generative models of evolutionary data. *Nature* 599(7883):91–95.

[8] Devlin J, Chang MW, Lee K, Toutanova K (2018) BERT: Pre-training of deep bidirectional transformers for language understanding. *arXiv preprint arXiv:1810.04805*.

[9] Bubeck S, et al. (2023) Sparks of artificial general intelligence: Early experiments with GPT-4. *arXiv preprint arXiv:2303.12712*.

[10] Zhou J, Troyanskaya OG (2015) Predicting effects of noncoding variants with deep learning–based sequence model. *Nature Methods* 12(10):931–934.

[11] Avsec Ž, et al. (2021) Effective gene expression prediction from sequence by integrating long-range interactions. *Nature Methods* 18(10):1196–1203.

[12] Chen KM, Wong AK, Troyanskaya OG, Zhou J (2022) A sequence-based global map of regulatory activity for deciphering human genetics. *Nature Genetics* 54(7):940–949.

[13] Jaganathan K, et al. (2019) Predicting splicing from primary sequence with deep learning. *Cell* 176(3):535–548.

[14] Cheng J, et al. (2019) MMSplice: modular modeling improves the predictions of genetic variant effects on splicing. *Genome Biology* 20(1):1–15.

[15] Lee D, et al. (2015) A method to predict the impact of regulatory variants from DNA sequence. *Nature Genetics* 47(8):955–961.

[16] Fudenberg G, Kelley DR, Pollard KS (2020) Predicting 3D genome folding from DNA sequence with Akita. *Nature Methods* 17(11):1111–1117.

[17] Zeng H, Gifford DK (2017) Predicting the impact of non-coding variants on DNA methylation. *Nucleic Acids Research* 45(11):e99–e99.

[18] Pollard KS, Hubisz MJ, Rosenbloom KR, Siepel A (2010) Detection of nonneutral substitution rates on mammalian phylogenies. *Genome Research* 20(1):110–121.

[19] Siepel A, et al. (2005) Evolutionarily conserved elements in vertebrate, insect, worm, and yeast genomes. *Genome Research* 15(8):1034–1050.

[20] Tian F, Yang DC, Meng YQ, Jin J, Gao G (2020) PlantRegMap: charting functional regulatory maps in plants. *Nucleic Acids Research* 48(D1):D1104–D1113.

[21] Rentzsch P, Witten D, Cooper GM, Shendure J, Kircher M (2019) CADD: predicting the deleteriousness of variants throughout the human genome. *Nucleic Acids Research* 47(D1):D886–D894.

[22] Quang D, Chen Y, Xie X (2015) DANN: a deep learning approach for annotating the pathogenicity of genetic variants. *Bioinformatics* 31(5):761–763.

[23] Zaheer M, et al. (2020) Big Bird: Transformers for longer sequences. *Advances in Neural Information Processing Systems* 33:17283–17297.

[24] Ji Y, Zhou Z, Liu H, Davuluri RV (2021) DNABERT: pre-trained bidirectional encoder representations from Transformers model for DNA-language in genome. *Bioinformatics* 37(15):2112–2120.

[25] Mo S, et al. (2021) Multi-modal self-supervised pre-training for large-scale genome data in *NeurIPS 2021 AI for Science Workshop*.

[26] Yang M, et al. (2022) Integrating convolution and self-attention improves language model of human genome for interpreting non-coding regions at base-resolution. *Nucleic Acids Research* 50(14):e81–e81.

[27] Hoarfrost A, Aptekmann A, Farfañuk G, Bromberg Y (2022) Deep learning of a bacterial and archaeal universal language of life enables transfer learning and illuminates microbial dark matter. *Nature Communications* 13(1):1–12.

[28] Gwak HJ, Rho M (2022) Vibe: a hierarchical bert model to identify eukaryotic viruses using metagenome sequencing data. *Briefings in Bioinformatics* 23(4). bbac204.

[29] Bai Z, et al. (2022) Identification of bacteriophage genome sequences with representation learning. *Bioinformatics*. btac509.

[30] Jones AM, et al. (2008) The impact of Arabidopsis on human health: diversifying our portfolio. *Cell* 133(6):939–943.

[31] Bourque G, et al. (2018) Ten things you should know about transposable elements. *Genome Biology* 19:1–12.

[32] McInnes L, Healy J, Melville J (2018) UMAP: Uniform manifold approximation and projection for dimension reduction. *arXiv preprint arXiv:1802.03426*.

[33] Kent WJ, et al. (2002) The human genome browser at UCSC. *Genome Research* 12(6):996–1006.

[34] Nair S, et al. (2022) The dynseq browser track shows context-specific features at nucleotide resolution. *Nature Genetics* 54(11):1581–1583.

[35] Schneider TD, Stephens RM (1990) Sequence logos: a new way to display consensus sequences. *Nucleic Acids Research* 18(20):6097–6100.

[36] Shrikumar A, et al. (2018) Technical note on transcription factor motif discovery from importance scores (TF-MoDISco) version 0.5. 6.5. *arXiv preprint arXiv:1811.00416*.

[37] Evrard A, Ndatimana T, Eulgem T (2009) FORCA, a promoter element that responds to crosstalk between defense and light signaling. *BMC Plant Biology* 9:1–13.

[38] Szlachta K, et al. (2018) Alternative DNA secondary structure formation affects RNA polymerase II promoter-proximal pausing in human. *Genome Biology* 19:1–19.

[39] Alonso-Blanco C, et al. (2016) 1,135 genomes reveal the global pattern of polymorphism in *Arabidopsis thaliana*. *Cell* 166(2):481–491.

[40] Togninalli M, et al. (2020) AraPheno and the AraGWAS catalog 2020: a major database update including RNA-seq and knockout mutation data for *Arabidopsis thaliana*. *Nucleic Acids Research* 48(D1):D1063–D1068.

[41] Sullivan PF, et al. (2023) Leveraging base pair mammalian constraint to understand genetic variation and human disease. *bioRxiv* pp. 2023–03.

[42] Zhou W, Liang G, Molloy PL, Jones PA (2020) DNA methylation enables transposable element-driven genome expansion. *Proceedings of the National Academy of Sciences* 117(32):19359–19366.

[43] Kaplan J, et al. (2020) Scaling laws for neural language models. *arXiv preprint arXiv:2001.08361*.

[44] Lin Z, et al. (2023) Evolutionary-scale prediction of atomic-level protein structure with a language model. *Science* 379(6637):1123–1130.

[45] Rao RM, et al. (2021) MSA Transformer in *International Conference on Machine Learning*. (PMLR), pp. 8844–8856.

[46] Jumper J, et al. (2021) Highly accurate protein structure prediction with AlphaFold. *Nature* 596(7873):583–589.

[47] Zhou H, Shrikumar A, Kundaje A (2022) Towards a better understanding of reverse-complement equivariance for deep learning models in genomics in *Machine Learning in Computational Biology*. (PMLR), pp. 1–33.

[48] Gu A, Goel K, Re C (2021) Efficiently modeling long sequences with structured state spaces in *International Conference on Learning Representations*.

[49] Tay Y, et al. (2021) Are pretrained convolutions better than pretrained transformers? in *Proceedings of the 59th Annual Meeting of the Association for Computational Linguistics and the 11th International Joint Conference on Natural Language Processing (Volume 1: Long Papers)*. (Association for Computational Linguistics, Online), pp. 4349–4359.

[50] Yang KK, Lu AX, Fusi N (2022) Convolutions are competitive with transformers for protein sequence pretraining in *ICLR2022 Machine Learning for Drug Discovery*.

[51] Wolf T, et al. (2019) HuggingFace's Transformers: State-of-the-art Natural Language Processing. *arXiv preprint arXiv:1910.03771*.

[52] McLaren W, et al. (2016) The Ensembl Variant Effect Predictor. *Genome Biology* 17(1):1–14.

[53] Reshef YA, et al. (2018) Detecting genome-wide directional effects of transcription factor binding on polygenic disease risk. *Nature Genetics* 50(10):1483–1493.

[54] Bulik-Sullivan BK, et al. (2015) LD score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nature Genetics* 47(3):291–295.