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REPA: Applying Pathway Analysis to Genome-wide Transcription Factor Binding Data

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Abstract—Pathway analysis has been extensively applied to aid in the interpretation of the results of genome-wide transcription profiling studies, and has been shown to successfully find associations between the biological phenomena under study and biological pathways. There are two widely used approaches of pathway analysis: over-representation analysis, and gene set analysis. Recently genome-wide transcription factor binding data has become widely available allowing for the application of pathway analysis to this type of data. In this work, we developed REPA (Regulatory Enrichment Pathway Analysis) to apply gene set analysis to genome-wide transcription factor binding data to infer associations between transcription factors and biological pathways. We used the transcription factor binding data generated by the ENCODE project, and gene sets from the Molecular Signatures and KEGG databases. Our results showed that 54% of the predictions examined have literature support and that REPA's recall is roughly 54%. This level of precision is promising as several of REPA's predictions are expected to be novel and can be used to guide new research avenues. In addition, the results of our case studies showed that REPA enhances the interpretation of genome-wide transcription profiling studies by suggesting putative regulators behind the observed transcriptional responses.

Index Terms—Transcription factor binding data, pathway analysis, gene set analysis.

1 Introduction

Pathway analysis identifies pathways or functions related to biological phenomena under study by associating gene functional annotations in at least one biological knowledge base, such as the KEGG [1] or the Gene Ontology (GO) [2], with gene expression patterns observed in a genome-wide transcriptional profiling study [3]. The result of pathway analysis is a list of biological pathways or functions (generally referred to as gene sets) which provides an insight into the biology underlying the phenomena under study. There are two widely used approaches for pathway analysis: Over-representation analysis (ORA) and functional class scoring (FCS) also called gene set analysis (GSA). In the ORA approach, a list of genes of interest (for example, those genes deemed differentially expressed in a study) is created, and a statistical test is applied to determine whether the fraction of genes in the list associated with a given gene set (e.g., pathway or function) is larger than expected by chance; that is, whether genes associated to a given gene set are over-represented among the genes in the input list. In the FCS or GSA approach, all genes in the experiment are first grouped in gene sets (a gene set consists of a group of genes sharing a functional annotation); then the expression measurements for all genes in the experiment are used to calculate a summary statistic per gene set; and the statistical significance of each gene set statistic is assessed. Pathway analysis (either the ORA or the GSA approach) has become an intrinsic part of most gene expression data analysis workflows [3] and there is a plethora of tools for pathway analysis of gene expression data [4].

Most of the focus of pathway analysis has been the analysis of gene expression data; however, genome-wide transcription factor binding data obtained from Chip-Seq or Chip-ChIP experiments has become increasingly available. Transcription factor binding data (TFBD) provides genome-wide measurements of the strength of binding of a transcription factor (TF) to genomic locations. These genomic locations are likely transcription factor binding sites that can then be associated to genes based on their proximity to coding regions. TFBD needs to be further analyzed to be used for further biological investigations. Applying pathway analysis to TFBD is a logical step to associate transcription factors to gene sets. Lachmann *et al.* [5] developed the system Chip Enrichment Analysis (ChEA) to apply ORA to TFBD. ChEA links a transcription factor to a user-generated list of genes by statistically assessing whether targets of the transcription factor are over-represented among the genes in the input list [5].

To the best of our knowledge, ChEA has been the only application of pathway analysis to TFBD. In this work, we investigated the use of GSA to associate transcription factors to gene sets based on genome-wide TFBD. To do this, we collected TFBD from the ENCODE project [6], developed REPA (Regulatory Enrichment Pathway Analysis) to apply GSA to this data, estimated REPA's precision and recall, and demonstrated the utility of REPA in two cases studies.

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2 Materials and Methods

2.1 Transcription factor binding data (TFBD)

Under the ENCODE project [6], numerous Chip-Seq and Chip-ChIP experiments were performed, and genome-wide TFBD for 160 transcription factors in 44 cell lines was produced for a total of approximately 1.4 million transcription factor - target-gene interactions [7]. This data was processed and made freely available for download on the ChEA2 web site by Kou *et al.* [7]. We downloaded the ENCODE TFBD in BED format from ChEA2. This TFBD contained the start and end genomic coordinates of the transcription factor binding sites, score and signal. The score and signal values represent the strength of the binding between the transcription factor and the DNA.

To link the transcription factor binding sites to the genes that the transcription factor likely regulates, we intersected the genomic coordinates in the TFBD with the promoter regions of all human genes coding for lincRNA, miRNA and proteins using the BEDtools' command intersectBed [8]. The promoter region of a gene was defined as 3000 bp upstream of the transcription start site (TSS). Genomic coordinates of the promoter regions of all human genes were downloaded from Ensembl's BioMart [9] (Ensembl release 71, human genome GRCh37.p10). At the end of this step we have a linked-TFBD containing data for 131 transcription factors.

2.2 Gene sets

We obtained gene sets from the KEGG database (downloaded in March 2014) [1], [10] and from the Molecular Signatures Database version 5 (MSigDB) [11]. MSigDB consists of eight collections: 50 hallmark gene sets, 326 positional gene sets (C1), 4725 curated gene sets (C2), 836 motif gene sets (C3), 858 computational gene sets (C4), 1454 GO gene sets (C5), 189 oncogenic signatures (C6) and 1910 immunologic signatures (C7). Collection C2 of the MSigDB contains 1330 canonical pathways derived from the BioCarta, KEGG, and Reactome [12] pathway databases. Since we noticed a discrepancy between MSigDB KEGG-derived gene sets and those gene sets obtained directly from KEGG, we used the KEGG database (instead of MSigDB) to define the KEGG gene sets. We excluded all gene sets with more than 350 genes as they are usually too general to be informative to guide further biological research. There were 484 such gene sets.

2.3 Description of REPA

We developed REPA (Regulatory Enrichment Pathway Analysis) to apply GSA to linked-TFBD with the aim of inferring associations between transcription factors and gene sets. These associations are based on how strongly a transcription factor (TF) binds to the promoter regions of the genes in a gene set. As measurement of the binding strength of a transcription factor with a specific genomic location, we used the signal value provided in the TFBD from the ENCODE project. To test whether a transcription factor binds preferentially to genes in a given gene set, a competitive test [13] was used. That is, the transcription factor binding signal values for the genes in a gene set were compared against that transcription factor binding signal values for genes randomly selected to form gene sets of the same size as the original gene set. The null hypothesis is that the transcription factor binds with the same strength to the promoter regions of the genes in a gene set as to those promoter regions of the genes in the random gene sets.

For each transcription factor, REPA first gets the transcription factor binding signal values for the genes in each gene set using the linked-TFBD. If the linked-TFBD contains more than one binding signal value for a given gene (i.e., more than one transcription binding site in the promoter region of that gene or signal values corresponding to different cell lines), REPA takes the maximum binding signal value available for that gene. For those gene sets with at least 5 genes with a binding signal value, a competitive permutation test is performed where the binding signal values of the genes in the gene set are compared against permuted gene sets of the same size as the real gene set. Permuted gene sets are formed by randomly selecting genes. The binding signal values of the genes in a permuted gene set are obtained in the same way as the signal values of the genes in the real gene set. Then the Mann-Whitney U test [14], a non-parametric test, is used to test whether the median signal value of the real gene set is statistically significantly higher than the median signal value of the permuted gene set, based on a given threshold of significance. One thousand permutations are performed for each gene set - transcription factor combination. At the end of the permutations, REPA reports the number of statistically significant tests nst. The permutation based p-value is then calculated as $max(1 - \frac{nst}{numberofpermutation}, \frac{1}{numberofpermutations})$. Signal values from different cell lines are combined to maximize the amount of binding data available per TF.

2.4 Pathway analysis of gene expression data

To illustrate the use of REPA to enhance the interpretation of transcriptional profiling studies, we combined REPA's predictions with the results of performing GSA on gene expression data. To perform GSA on expression data, we used the Bioconductor package GAGE (version 2.14.4) [15] and set the q-value for statistical significance to 0.0001. As for gene sets, we used canonical pathways and hallmark gene sets.

For the first case study, we used gene expression data from a study comparing gene expression of patient-matched histologically normal (HN) and ductal carcinoma in situ (DCIS) tissue from patients with estrogen receptor positive sporadic breast cancer (GEO accession number GSE16873) [16]. The normalized version of this data was obtained from the Bioconductor package gageData (version 2.2.0). To perform GSA on this data, the gage function was executed with default parameters.

For the second case study, we used gene expression data from a study profiling host transcriptional responses of well-differentiated, primary human bronchial epithelial cells during infection of influenza A viruses (GEO accession number GSE48466) [17]. The normalized version of this data was obtained from GEO using the Bioconductor package GEOquery (version 2.30) [18]. We identified gene sets differentially expressed between uninfected cells and cells infected with H1N1pdm isolates from a nonfatal case

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(A/KY/136/09). For this case study, the parameter *compare* of the gage function was set to *unpaired*, and all other parameters were set to default values.

To reduce the amount of redundancy in GAGE results, we compared every pair of differentially expressed gene sets. We obtained the number of genes in common between each pair and removed those gene sets with a significant overlap with another gene set (p-value < 0.0001 using the hypergeometric distribution) and at least 50% of their genes lying on the intersection between both gene sets. This filtering reduced the number of gene sets by 70%; however, the number of associated TFs decreased by only 7%. This indicates that REPAs predictions are replicated in different annotation scheme.

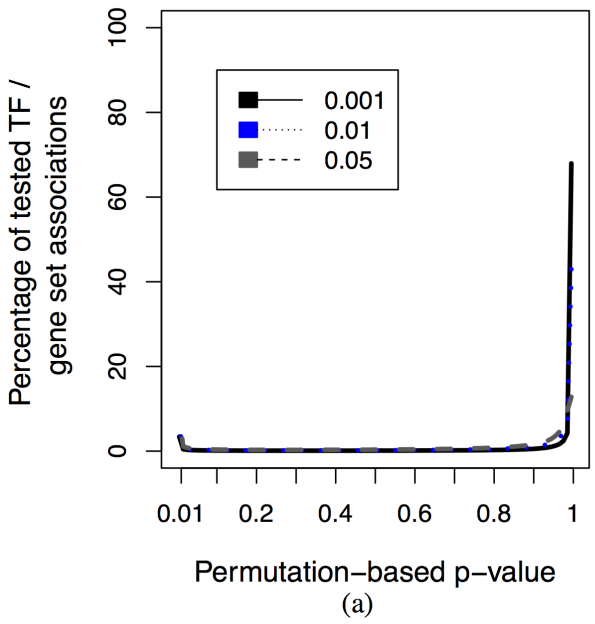
To obtain a list of statistically differentially expressed genes in each case study, we used the R/Bioconductor package limma [19] (version 3.20.8). For the breast cancer study we performed a moderated paired t-test, and for the influenza case study we performed a simple two sample comparison. Both of these approaches are described step by step in limma's user's guide.

3 Results and Discussion

3.1 Inferring associations between transcription factors and gene sets

REPA tested 803,711 transcription factor - gene set pairs and predicted 68,008 (or 8.5%) of these pairs to be true associations. REPA's predictions contained associations for 88 TFs and 8,277 gene sets. To explore the effect of the significance threshold used in the Mann-Whitney U test in the distribution of permutation-based p-values, we set the significance threshold at 0.001, 0.01 and 0.05. Figure 1 shows the distribution of permutation-based p-values corresponding to each of these significance thresholds. The distribution of permutation-based p-values has features that indicate a successful differentiation between non-associated TF - gene set pairs and TF - gene set associations with strong binding signal. The peaks on the left side (Figure 1b) contain TF - gene set associations with strong signal for which the null hypothesis was rejected. TF - gene set pairs with a p-value of less than 0.015 were predicted by REPA to be true associations. The TF -gene set pairs concentrated in the peaks on the right side or uniformly distributed in the interval $[0.015, 1)$ correspond to TF - gene set pairs for which the null hypothesis was accepted; i.e., these TF - gene set pairs did not have a strong binding signal.

The number of REPA's predictions varied from 68,008 to 29,317 depending on the significance threshold used for the Mann-Whitney U test. Since the permutation-based p-value distribution remained stable at the different significance threshold for the Mann-Whitney U test, we set the significance threshold for the Mann-Whitney U test to 0.05 and predicted as true associations those 68,008 TF - gene set pairs with a permutation-based p-value of less than 0.015. Out of the 68,008 REPA's predictions, 8,948 (13.2%) involved either a canonical pathway, a GO gene set or a hallmark gene set. All REPA's predictions are available as supplementary material.



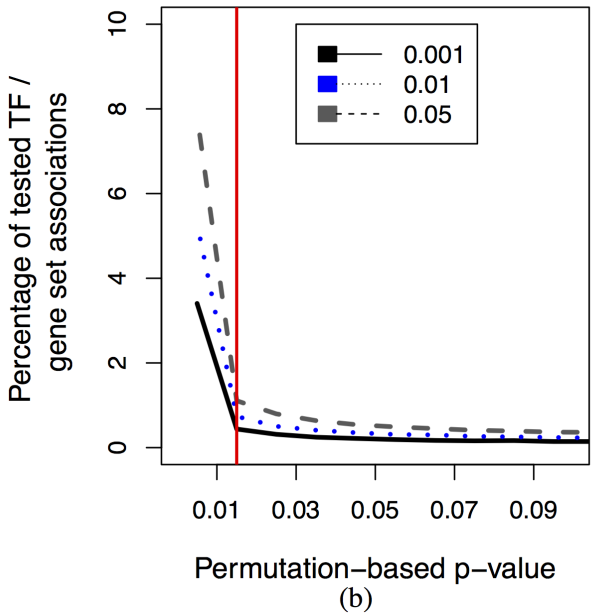


Fig. 1. Distribution of permutation-based p-values. (a) Percentage of TF - gene set pairs tested is shown as a function of REPA permutation-based p-value with different thresholds of significance used for the Mann-Whitney U test. The peak on the left side corresponds to REPA's predictions. That is, the TF - gene set pairs for which the null hypothesis was rejected (permutation-based p-value < 0.015). (b) Same as (a) but zooming in the peak on the left. REPA's predictions are those associations to the left of the vertical red line.

3.2 Number of REPA's predictions per transcription factor

We looked at the number of REPA's predictions per TF. For this analysis, we only considered predictions associating a TF with a canonical pathway, a GO gene set or a hallmark gene set, as these gene sets represent curated metabolic pathways or gene product functions. The number of REPA's predictions per TF is shown in Figure 2. There

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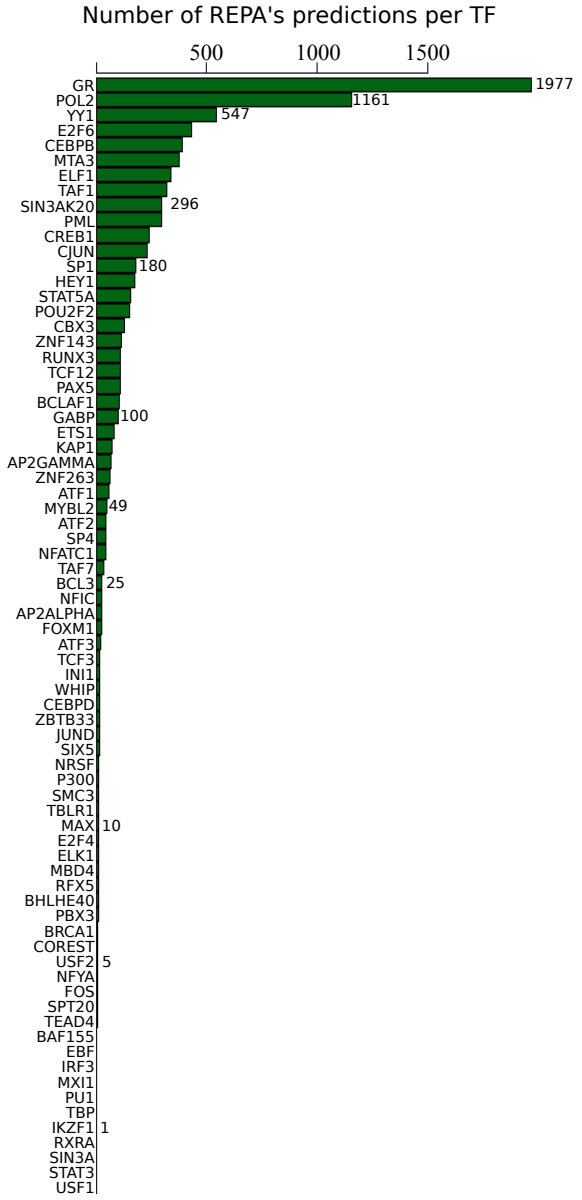

Fig. 2. Number of REPA's predictions per TF. Out of 88 TFs found among REPA's predictions, 74 (or 84%) are associated to at least one canonical pathway, GO gene set or hallmark gene set; 28 (or 37.8%) are associated to more than 50 canonical pathways, hallmark gene sets or GO gene sets; and three (3.4%), namely GR, POL2 and YY1, are associated to more than 500 of these gene sets.

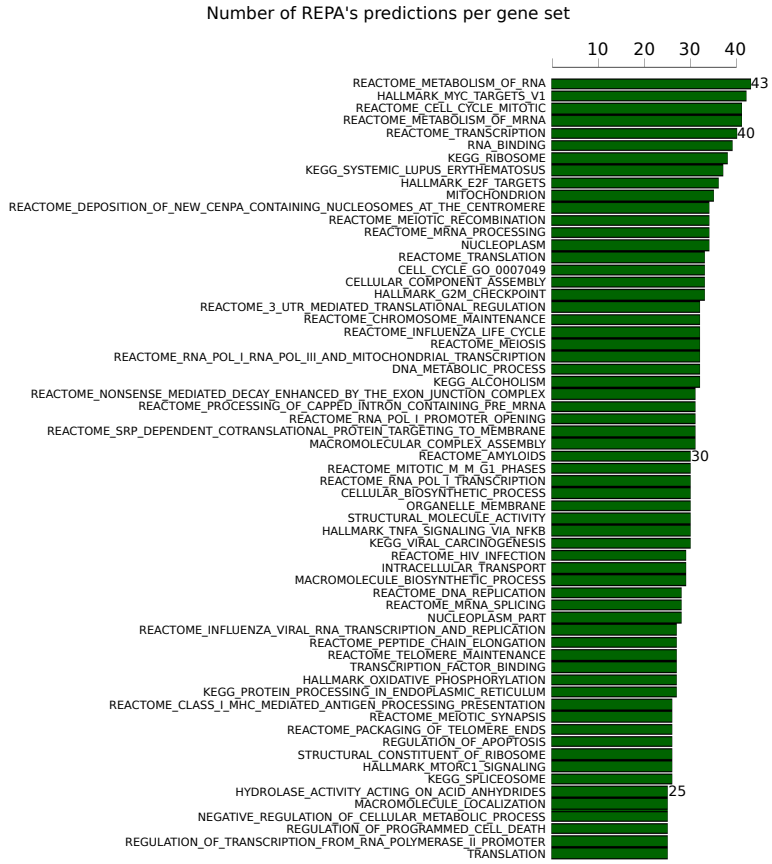

Fig. 3. Number of REPA's predictions per gene set (canonical pathways, GO gene sets and hallmark gene sets). The barplot shows the 63 genes sets predicted to be regulated by at least 25 TFs. 1,980 canonical pathways, GO gene sets and hallmark gene sets were predicted to be regulated by at least one TF, 30 (or 1.5%) were associated to more than 30 TFs and 240 (or 7.6%) were associated to more than 10 TFs.

are three TFs associated to more than 500 gene sets. These DNA-binding proteins are the glucocorticoid receptor (GR), the polymerase (RNA) II (DNA directed) polypeptide A (POL2), and the YY1 transcription factor. It is known that GR regulates diverse cellular functions (such as mitosis and apoptosis) and essential biological processes (such as growth, development, metabolism, and behaviour), and is expressed in most cell types [20], [21]. To explain how a single TF can regulate such a variety of processes, it has been proposed that different GR isoforms allow for regulation of genes in a cell type specific manner, and that each GR isoform regulates both a common and a unique group of genes in each cell type [20], [21]. The *POL2* gene encodes for the largest subunit of RNA polymerase II, the polymerase that synthesize mRNA in eukaryotes. POL2 is a general transcription factor that initiates transcription and is responsible for transcriptional regulation [22]. YY1 is an ubiquitously expressed transcription factor that regulates cell proliferation and differentiation, and is a multifunctional mediator of different signalling pathways that modulates an impressive and increasing list of genes [23]. Thus, one would expect that these three TFs regulate many different gene sets and REPA's results reflect this.

3.3 Number of REPA's predictions per gene set

We also looked at the number of REPA's predictions per gene set. There were 1,980 canonical pathways, GO gene sets and hallmark gene sets predicted to be regulated by at least one TF. Out of these 1,980, 30 (or 1.5%) were associated to more than 30 TFs. Figure 3 shows gene sets associated by REPA with at least 25 TFs. Many of the gene sets listed in Figure 3 are tightly regulated cellular processes. We examined the literature related to the regulation of the Reactome pathway and the KEGG pathway associated to the largest number of TFs.

The Reactome pathways metabolism of RNA and cell cycle mitotic were the Reactome pathways associated to the

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largest number of TFs. The Reactome pathway metabolism of RNA has been deleted from Reactome since version 50 (current version is 52); thus, we investigated the cell cycle mitotic pathway which contains 325 genes. Cell cycle regulation is critical for growth and development, and its misregulation plays an important role in diseases such as cancer. There is a large variety of cell cycle programs within a single species that corresponds to specific cell types, developmental stages or physiological conditions [24]. In the budding yeast, cell cycle is controlled by a large and complex interacting network of regulatory proteins, and the general organization of this control system is conserved across the Eukaryota [25]. REPA associated the following 41 TFs with the Reactome cell cycle mitotic pathway (literature supporting the involvement of these TFs during the cell cycle is referred to after the corresponding TF): AP2ALPHA [26], AP2GAMMA, ATF1 [27], BCLAF1, CBX3, CEBPB, CJUN, CREB1, E2F4, E2F6 [25], ELF1, ELK1 [28], ETS1 [29], FOXM1 [30], GABP [31], GR [20], [21], HEY1, INI1 [32], KAP1 [33], MAX [34], MTA3, MXI1 [35], MYBL2 [36], PAX5, PBX3, PML, POL2, POU2F2 [26], RUNX3, SIN3AK20, SMC3, SP1, STAT3, STAT5A, TAF1, TBLR1, TCF12, WHIP, YY1, ZNF143, and ZNF263. Thus, we found literature support for 14 (or 34%) of these TFs. The central components of the cell-cycle control system, cyclin-dependent protein kinases (CDKs), are missing from this list because they were missing from the linked-TFBD used as REPA's input.

The KEGG ribosome pathway consists of 135 genes including the ribosomal proteins and ribosomal RNAs. The mechanisms regulating ribosome biogenesis are only partially understood, and they are the focus of current research. Recently, ribosome biogenesis has been linked to various diseases and aging, and studies have revealed an elaborate control of ribosome biogenesis that requires coordinate regulation of all three RNA polymerases and that includes feedback and feed-forward loops [37], [38]. A large number of TFs have been implicated in ribosome biogenesis; for instance, roughly 80 factors have been associated in the maturation of the 60S subunit [38]. REPA predicted the following 38 TFs to be associated with the KEGG ribosome pathway (supporting literature is referred to after the corresponding TF): ATF1, ATF2, ATF3, BCL3, BCLAF1, CBX3, CEBPB, CJUN, CREB1 [39], ELF1 [40], ETS1, GABP [41], GR [42], HEY1, IRF3, MTA3, MYBL2, NFATC1, NFIC, NRSF, PML [43], POL2 [37], POU2F2, RFX5, RUNX3, SIN3AK20, SIX5, SP1 [41], SP4, STAT5A, TAF1 [44], TAF7, TBLR1, TCF12, WHIP, YY1 [41], ZNF143, and ZNF263. Thus, we found literature support for 9 (or 24%) of these TFs.

We found an intriguing gene set (i.e., systemic lupus erythematosus (SLE)) among the top 10 genes sets shown in Figure 3, and thus decided to look at the TFs inferred by REPA to be associated with this disease. SLE is an autoimmune disease with more than 40 genes and loci identified as associated with this disease. However, these genes and loci only account for 10 to 20% of disease heritability. This indicates that there are many factors still to be identified [45]. REPA inferred 37 TFs associated with the KEGG systemic lupus erythematosus pathway which consists of 138 genes. Out of those 37 TFs predicted to regulate genes in the SLE pathway, we found literature support for 13 (or 35%). The TFs associated by REPA with SLE are the following (supporting literature is referred to after the corresponding TF): ATF2, ATF3 [46], BCLAF1, CBX3, CEBPB, CEBPD, ETS1 [47], FOS [45], FOXM1, GR [48], HEY1, INI1, JUND [49], MBD4 [50], MTA3, MYBL2, NFATC1 [49], NFIC, P300 [51], PAX5 [52], PML, POL2, POU2F2, RUNX3 [53], RXRA, SIN3AK20, SP1 [54], SP4, STAT5A, TAF1, TAF7, TBP [55], TCF12, TCF3, TEAD4, YY1 [56], and ZBTB33.

3.4 Literature-based evaluation of REPA's precision

Since REPA is the first approach to systematically inferred relationships between TFs and gene sets, there is no benchmark available to assess REPA's precision. Therefore, to gain intuition into the quality of REPA's predictions, we performed a literature analysis on 35 randomly selected predictions. The number of predictions we could examine was limited by available resources as literature curation is a time consuming effort. For this analysis, we focused on predictions associating KEGG pathways to TFs. To avoid over-weighting particular TFs, we only allowed two predictions per TF. Related literature was searched using PubMed, Disgenet [80], and ChEA [5]. Table 1 contains the list of predicted TF - gene set associations investigated. The number of genes in the gene sets examined varied from 57 to 327, and the percentage of genes in the gene set with a binding signal value varied from 18% to 94% (see third column of Table 1).

We classified evidence found in the literature into four categories: direct, binding, indirect and refuting. Direct evidence indicates that current literature directly links a TF with a given gene set; for example, the association of the TF YY1 with oxidative phosphorylation is supported by promoter analysis for a complex I gene (NDUFS8) [77]. Binding evidence indicates that targets of a TF identified by a published Chip-Seq or Chip-ChIP study are over-represented in a given gene set. This type of evidence was found using ChEA. In the case of binding evidence, current literature does not directly discuss the link of that TF with the given gene set. Indirect evidence indicates that current literature suggests the involvement of a TF in the regulation of a given gene set; for example, Taqi *et al.* [66] suggested that a single nucleotide polymorphism (SNP) in the promoter region of PDYN, which is associated with alcohol-dependence, may impact PDYN transcription in the human brain and that this SNP is located within a regulatory region that may be targeted by the TF JUND. Finally, refuting evidence indicates that current literature contains experimental data against the prediction; for example, REPA associated STAT5A with herpes simplex infection; however, current literature [76] shows that STAT1, but not STAT5A, binds to the herpes simplex virus latency-associated transcript promoter.

Out of the 35 predictions investigated, 15 (42.9%) were supported by direct evidence and 4 (11.4%) by binding evidence (see Table 1). These 19 (54.3%) associations supported by direct or binding evidence were correct or likely to be correct associations. Out of the 35 associations examined, 15 had indirect evidence or could neither be confirmed nor refuted by current literature. One (2.9%) of the 35 associations investigated was considered to be incorrect or likely to be incorrect based on current literature. These results suggest that REPA's precision lies above 54%. This level of

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TABLE 1
REPA's Predictions Evaluated based on the Literature. In the column type of evidence; B indicates binding, D direct, I indirect, NE "no evidence" and R refuting evidence.

TF	Gene Set (GS)	# of genes in GS with a binding signal value / # of genes in GS	Type of evidence	Ref.
ATF2	Ribosome	68/135	I	[57]
BCLAF1	Alcoholism	52/180	NE	
CEBPB	Spliceosome	69/131	B	[58]
CEBPB	Viral carcinogenesis	128/206	D	[59]
CJUN	FOXO signalling	36/133	D	[60]
CTCF	RAP1 signalling	107/213	NE	
E2F6	Pathways in cancer	145/327	D	[61]
ELF1	Huntington's disease	100/183	B	[62]
ELF1	Spliceosome	61/131	B	[62]
FOXM1	Alcoholism	49/180	NE	
GABP	Ribosome	64/135	D	[63]
GR	Acute myeloid leukemia	54/57	D	[64]
GR	Neurotrophin signalling	110/120	I	[65]
HEY1	RNA transport	75/164	NE	
JUND	Alcoholism	48/180	I	[66]
KAP1	miRNAs in cancer	69/296	D	[67]
MBD4	SLE	25/138	D	[50]
MTA3	Herpes simplex infection	106/188	NE	
MTA3	Ribosome biogenesis in eukaryotes	40/85	NE	
MYBL2	Alcoholism	52/180	NE	
NFATC1	SLE	45/138	D	[68]
NFIC	Viral carcinogenesis	107/206	I	[69]
PAX5	Epstein Barr virus infection	101/203	D	[70]
PML	HTLV I infection	129/263	D	[71]
POL2	Bacterial invasion of epithelial cells	65/76	D	[72]
POL2	Cytokine Cytokine receptor interaction	156/271	NE	
POU2F2	Transcriptional misregulation in cancer	47/179	NE	
RUNX3	Protein processing in endoplasmic reticulum	86/167	I	[73]
SP1	Alcoholism	63/180	D	[74]
SP1	Carbon metabolism	51/105	D	[75]
STAT5A	Herpes simplex infection	89/188	R	[76]
TAF1	Ribosome	65/135	D	[44]
YY1	Oxidative phosphorylation	61/133	D	[77]
YY1	Spliceosome	62/131	B	[78]
ZNF143	RNA Transport	70/164	I	[79]

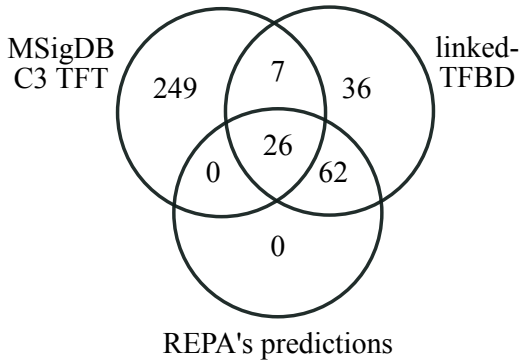

Fig. 4. Venn diagram indicating the number of TFs in common between MSigDB C3-TFT collection, ENCODE's TFBD and REPA's predictions.

precision is quite promising as several of REPA's predictions are expected to be novel and therefore lack literature support. Moreover, gene function predictions with similar precision levels have been successfully used in yeast [81] and mouse [82]. Based on this, we expect REPA's predictions to be an useful resource to guide further biological research.

3.5 Estimation of REPA's recall

Collection C3-TFT of the MSigDB consist of 615 gene sets formed by genes that share a DNA-binding motif defined in the TRANSFAC database [83]. Additionally, the TF known to bind the given motif is provided for 500 of these 615 gene sets. In total, 282 TFs are matched to a given DNA-binding motif in the C3-TFT collection. Out of these 282 TFs, 33 are also present in the linked-TFBD used as REPA's input, and REPA generated a prediction for 26 of them (see Figure 4). The 7 TFs for which REPA did not make a prediction had binding signal values for very few genes (four of them had binding signal values for less than 505 genes). To estimate REPA's recall, we counted the number of TFs associated by REPA with the corresponding C3-TFT gene set; for instance, since REPA associated SP1 to the V$SP1_01 gene set (which consists of genes whose promoter regions contain the motif GGGGCGGGGT which matches annotation for SP1) we counted SP1 as successfully retrieved by REPA. REPA associated 14 TFs to their corresponding C3-TFT gene set. Based on this, REPA's recall is around 53.8% (14/26).

3.6 Enhancing the interpretation of expression profiling studies

One of the goals of this work is to provide the research community with a resource to guide further biological research, and one logical application of REPA's predictions is to enhance the interpretation of expression profiling studies by suggesting putative regulators underlying the observed transcriptional responses. To illustrate this, we present two case studies where the results obtained from carrying out GSA on gene expression data are integrated with REPA's predictions. The purpose of these case studies is to demonstrate the utility of REPA's predictions and to evaluate the

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TABLE 2
Combining REPA's Predictions with Pathway Analysis on Gene Expression Data. Statistically differentially expressed gene sets (FDR-corrected pvalue < 0.0001) between histologically normal and ductal carcinoma in situ samples from patients with estrogen receptor positive sporadic breast cancer were identified by GAGE and their putative regulators were obtained from REPA's predictions. The character between brackets before the gene set names indicates the database providing the gene set: K indicates KEGG, H MSigDB hallmark gene sets and R Reactome.

Differentially expressed gene sets	**REPA's predicted putative regulators**
(K) Protein processing in endoplasmic reticulum	ATF1, BCLAF1, BRCA1, CEBPB, CJUN, CREB1, E2F6, ELF1, ETS1, GR,HEY1, KAP1, MTA3, PAX5, PML, POL2, POU2F2, RUNX3, SIN3AK20, SMC3, SP1, STAT5A, TAF1, TCF12, YY1, ZNF143, ZNF263
(K) Lysosome	BHLHE40, CEBPB, CREB1, E2F6, ELF1, ETS1, GR, MTA3, PAX5, POL2, SIN3AK20, USF1, YY1
(K) Protein export	GR, POL2
(K) Phagosome	CBX3, CEBPB, CREB1, E2F6, GR, MTA3, PML, POL2, POU2F2, SIN3AK20, STAT5A, YY1
(K) Antigen processing and presentation	BCLAF1, CEBPB, GR, MTA3, NFATC1, PML, POL2, POU2F2, STAT5A, YY1
(K) Focal adhesion	CJUN, E2F6, GR, MTA3, PML, POL2, SIN3AK20, YY1
(R) Class I MHC mediated antigen processing presentation	AP2GAMMA, BAF155, BCLAF1, CBX3, CEBPB, CJUN,CREB1, E2F6, ELF1, ETS1, GABP, GR, HEY1, MTA3, PAX5, PML, POL2,POU2F2, RUNX3, SIN3AK20, SP1, STAT5A, TAF1, TCF12, YY1, ZNF143
(R) Cell cycle mitotic	AP2ALPHA, AP2GAMMA, ATF1, BCLAF1, CBX3, CEBPB, CJUN, CREB1, E2F4,E2F6, ELF1, ELK1,ETS1, FOXM1, GABP, GR, HEY1, INI1, KAP1, MAX, MTA3, MXI1,MYBL2, PAX5, PBX3, PML, POL2, POU2F2, RUNX3, SIN3AK20, SMC3, SP1, STAT3, STAT5A, TAF1, TBLR1, TCF12, WHIP, YY1, ZNF143, ZNF263
(R) Post translational protein modification	CEBPB, E2F6, ELF1, GR, HEY1, MTA3, PML, POL2, POU2F2, TAF1, YY1
(R) Membrane trafficking	CEBPB, CJUN, CREB1, ELF1, GABP, GR, PML, POL2, SIN3AK20, TAF1, YY1
(R) MHC class II antigen presentation	CREB1, ELF1, GR, POL2, SIN3AK20, YY1
(R) 3 UTR mediated translational regulation	ATF2, ATF3, BCL3, BCLAF1, CBX3, CEBPB, CJUN, CREB1, E2F6, ELF1, ETS1, GABP, GR, HEY1, MTA3, NFATC1, NRSF, PML, POL2, POU2F2, RFX5, SIN3AK20, SP1, SP4, STAT5A, TAF1, TAF7, TCF12, WHIP, YY1, ZNF143, ZNF263
(H) MTORC1 signalling	ATF1, BCLAF1, CBX3, CEBPB, CJUN, CREB1, E2F6, ELF1, GR, HEY1, KAP1, MTA3, MYBL2, PAX5, PML, POL2, POU2F2, RUNX3, SIN3AK20, SP1, SP4, STAT5A, TAF1, TCF12, YY1, ZNF143
(H) E2F targets	AP2ALPHA, AP2GAMMA, ATF1, BCL3, BCLAF1, CBX3, CEBPB, CJUN, CREB1, E2F4, E2F6, ELF1, ETS1, FOXM1, GR, HEY1, KAP1, MAX, MTA3, MYBL2, NFIC, PAX5, PML, POL2, POU2F2, RUNX3, SIN3AK20, SP1, SP4, STAT5A, TAF1, TAF7, TCF12, YY1, ZNF143, ZNF263
(H) Oxidative phosphorylation	AP2GAMMA, CBX3, CEBPB, CJUN, COREST, CREB1, E2F6, ELF1, ELK1, ETS1, GR, HEY1, KAP1, MTA3, PML, POL2, RUNX3, SIN3AK20, SMC3, SP1, STAT5A, TAF1, TBLR1, TCF12, YY1, ZNF143, ZNF263
(H) G2M checkpoint	AP2ALPHA, AP2GAMMA, ATF1, BCLAF1, CBX3, CEBPB, CJUN, CREB1, E2F4, E2F6, ELF1, ETS1, FOXM1, GABP, GR, HEY1, INI1, KAP1, MTA3, MYBL2, PAX5, PML, POL2, POU2F2, RUNX3, SIN3AK20, SP1, STAT5A, TAF1, TCF12, YY1, ZNF143, ZNF263
(H) MYC targets V1	AP2ALPHA, AP2GAMMA, ATF2, ATF3, BCL3, BCLAF1, CBX3, CEBPB, CJUN, COREST, CREB1, E2F6, ELF1, ETS1, FOXM1, GABP, GR, HEY1, KAP1, MAX, MBD4, MTA3, MYBL2, NFATC1, NFIC, NRSF, PAX5, PML, POL2, POU2F2, RUNX3, SIN3AK20, SMC3, SP1, SP4, STAT5A, TAF1, TAF7, TCF12, YY1, ZNF143, ZNF263
(H) Estrogen response late	CEBPB, E2F6, GR, POL2
(H) Glycolysis	ATF1, CEBPB, CREB1, E2F6, ELF1, GR, HEY1, MTA3, PML, POL2, SIN3AK20, SP1, TAF1, YY1
(H) Protein secretion	CREB1, ELF1, GABP, GR, POL2, SIN3AK20, TAF1, YY1
(H) Interferon gamma response	CEBPB, CJUN, E2F6, EBF, ELF1, GR, HEY1, IKZF1, MTA3, PAX5, PML, POL2, POU2F2, RUNX3, SMC3, STAT5A, YY1
(H) Unfolded protein response	ATF2, BCLAF1, CEBPB, CJUN, CREB1, E2F6, ELF1, GR, HEY1, MTA3, PML, POL2, POU2F2, SIN3AK20, SP1, STAT5A, TAF1, TCF12, YY1, ZNF143
(H) Apical junction	CBX3, CEBPB, E2F6, GR, MTA3, PAX5, PML, POL2, SP1, STAT5A, YY1
(H) Myogenesis	E2F6, GR, POL2
(H) Epithelial mesenchymal transition	E2F6, GR, POL2

relevance of the associated TFs with the biological phenomena under study rather than to re-analyze the original gene expression data.

3.6.1 Case 1: Estrogen receptor positive sporadic breast cancer

We used gene expression data of patient-matched histologically normal (HN) and ductal carcinoma in situ (DCIS) sam-

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ples from 6 patients with estrogen receptor positive sporadic breast cancer [16]. In the original study, ORA was performed using DAVID [84]; while, we performed GSA using GAGE. As in the original study [16], focal adhesion was identified as one of the pathways differentially expressed between the HN and DCIS samples. Upon identification of the differentially expressed gene sets, we used REPA's predictions to list putative regulators of those differentially expressed gene sets (see Table 2). This list provides clues about likely regulatory mechanisms underlying the observed gene expression changes.

REPA's predictions associated 58 TFs with the gene sets identified as differentially expressed in the breast cancer expression profiling study. Out of these 58 TFs, 50 (or 86%) have previously been directly linked to breast cancer; namely, AP2ALPHA [85], AP2GAMMA [85], ATF1 [86], ATF2 [87], ATF3 [88], BAF155 [89], BCL3 [90], BCLAF1 [91], BHLHE40 [92], [93], BRCA1 [94], CBX3 [95], CEBPB [96], CJUN [97], COREST [98], CREB1 [99], E2F4 [100], E2F6 [61], EBF [101], ELF1 [102], ELK1 [103], ETS1 [104], FOXM1 [105], GABP [106], GR [107], HEY1 [108], IKZF1 [109], INI1 [110], KAP1 [111], MAX [112], MBD4 [113], MTA3 [114], MXI1 [115], MYBL2 [116], NFATC1 [117], NFIC [118], NRSF [119], PAX5 [120], PML [121], POL2 [122] RUNX3 [123], SMC3 [124], SP1 [125], SP4 [126], STAT3 [127], STAT5A [128], TAF1 [129], TBLR1 [130], TCF12 [131], USF1 [132], and YY1 [133], [134]. This result indicates that REPA's precision may be higher than the one suggested by our literature-based evaluation. Moreover, REPA's predictions suggested eight additional TFs that may play a role in breast cancer. These additional TFs are PBX3, POU2F2, RFX5, SIN3AK20, TAF7, WHIP, ZNF143, and ZNF263. Some of these eight additional TFs have already been implicated in other types of cancer.

We investigated whether the 58 TFs associated with the differentially expressed genes were themselves differentially expressed. None of the TFs was deemed statistically differentially expressed using a FDR-corrected p-value of 0.01 as significance threshold. The TF with the lowest FDR-corrected p-value was BCL3 (FDR-corrected p-value of 0.07). Nevertheless, the 58 TFs were highly expressed in the samples having half of them an average expression measurement higher than the expression measurement of 66% of genes in the experiment.

3.6.2 Case 2: Infection of influenza A viruses

We used gene expression data of uninfected cells and cells infected with H1N1pdm isolates from a nonfatal case (A/KY/136/09) from a study profiling host transcriptional responses of well-differentiated, primary human bronchial epithelial cells during infection of influenza A viruses [17]. The data set contains 3 biological replicates for each group. In the original study, pathway analyses were performed using Ingenuity Pathway Analysis (IPA, Ingenuity Systems) software. As in the original study, we identified gene sets related to cytokine signalling, interferon signalling, apoptosis, complement system, and antigen presentation. In addition, we identified several influenza-related gene sets (see Table 3).

Upon identification of the differentially expressed gene sets, we used REPA's predictions to list putative regulators of those differentially expressed gene sets (see Table 3). REPA's predictions associated 58 TFs with the gene sets identified as differentially expressed in the influenza infection transcriptional profiling study. These 58 TFs are the following (supporting literature is referred to after the corresponding TF): AP2ALPHA, AP2GAMMA, ATF1, ATF2 [135], ATF3 [136], BAF155, BCL3, BCLAF1, BRCA1, CBX3, CEBPB [137], CEBPD, CJUN [138], COREST, CREB1 [139], E2F4 [137], E2F6 [137], EBF, ELF1, ELK1 [140], ETS1, FOXM1, GABP, GR [141], HEY1, IKZF1, INI1, JUND, KAP1, MAX, MBD4, MTA3, MYBL2, NFATC1 [142], NFIC, NRSF, P300, PAX5 [143], PML [144], POL2, POU2F2 [145], PU1, RFX5, RUNX3, SIN3AK20, SMC3, SP1 [146], SP4, STAT5A, TAF1, TAF7, TBLR1, TCF12, TCF3, USF2, YY1, ZNF143, and ZNF263. We found literature linking with influenza infection 14 (or 24%) of these TFs. Additionally, ATF3 and SP1 were found to be expressed in cells infected with pandemic influenza A virus (H1N1pdm) but not in cells infected with seasonal influenza virus [17].

We looked into whether the 58 associated TFs were statistically differentially expressed in the transcriptional profiling study. We deemed genes with a FDR-corrected p-value of less than 0.01 to be differentially expressed. At this threshold of significance, 29 (or 50%) of the 58 listed TFs were found to be differentially expressed between the H1N1pdm infected and uninfected cells. Eight (ATF3, BAF155, BRCA1, CEBPB, HEY1, PAX5, PML, and PU1) of these 29 differentially expressed TFs had an absolute log2 fold change of at least 1.

3.7 Limitations and future work

One of the challenges we faced while doing this project is the lack of TFBD for all human transcription factors. There are over 1,391 known sequence-specific DNA-binding human transcription factors [147]; however, in this project we have TFBD of only 131 transcription factors, roughly a tenth of the total number of human TFs. As more TFBD is generated, REPA's accuracy and coverage will increase. Similarly, we have used a fixed number of base pairs upstream of coding regions as promoter regions; however, promoter regions are in fact of variable length. Using experimentally determined promoter sequences or promoter sequences obtained by promoter prediction programs may improve REPA's predictions. Additionally, REPA currently considers proximal promoter sequences; however, long-range regulatory interactions play an important role in mammalian genomes [148]. As our knowledge of functional long-range regulatory interactions and of the location of distal regulatory regions increases, this knowledge could also be incorporated into REPA.

4 Conclusion

We developed REPA to apply gene set analysis (GSA) to genome-wide transcription factor binding data (TFBD). To the best of our knowledge, this is the first application of gene set analysis to TFBD. The results show that currently available TFBD for human allow to infer associations for 88 TFs and 8277 gene sets. We estimated REPA's precision based on a literature assessment and REPA's recall using

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TABLE 3
Combining REPA's Predictions with Pathway Analysis on Gene Expression Data. Statistically differentially expressed gene sets (FDR-corrected pvalue < 0.0001) between uninfected and influenza infected cells were identified by GAGE and their putative regulators were obtained from REPA's predictions. The character between brackets before the gene set names indicates the database providing the gene set: K indicates KEGG, H MSigDB hallmark gene sets and R Reactome.

Differentially expressed gene sets	**REPA's predicted putative regulators**
(K) Viral carcinogenesis	AP2ALPHA, AP2GAMMA, ATF2, BCL3, BCLAF1, CBX3, CEBPB, CJUN, CREB1, E2F6, ELF1, FOXM1, GR, HEY1, MTA3, NFATC1, NFIC, PAX5, PML, POL2, POU2F2, RUNX3, SIN3AK20, SP1, STAT5A, TAF1, TBLR1, TCF12, TCF3, YY1
(K) Influenza A	BCLAF1, CEBPB, CJUN, E2F6, ELF1, GR, MTA3, NFATC1, PML, POL2, POU2F2, PU1, STAT5A, YY1
(K) NF KAPPA B signalling pathway	BCLAF1, CEBPB, E2F6, GR, MTA3, PML, POL2, POU2F2, STAT5A, YY1
(K) Antigen processing and presentation	BCLAF1, CEBPB, GR, MTA3, NFATC1, PML, POL2, POU2F2, STAT5A, YY1
(K) Viral myocarditis	GR, MTA3, NFATC1, POL2
(K) Hepatitis B	BCLAF1, CEBPB, CJUN, E2F6, ELF1, GR, HEY1, MTA3, PML, POL2, POU2F2, RUNX3, SIN3AK20, STAT5A, TAF1, TCF12, YY1
(K) Natural killer cell mediated cytotoxicity	CEBPB, GR, MTA3, POL2, STAT5A, YY1
(K) Cytokine cytokine receptor interaction	CEBPB, E2F6, GR, POL2
(K) Transcriptional misregulation in cancer	CEBPB, E2F6, GR, MTA3, NFIC, PML, POL2, POU2F2, SP1, TAF1, TCF12, YY1
(K) TNF signalling pathway	BCLAF1, CEBPB, E2F6, ELF1, GR, MTA3, PAX5, PML, POL2, POU2F2, RUNX3, TCF12, YY1
(R) Cytokine signalling in immune system	BCLAF1, CBX3, CEBPB, CJUN, CREB1, E2F6, ELF1, GR, HEY1, MTA3, PAX5, PML, POL2, POU2F2, RUNX3, SIN3AK20, STAT5A, TAF1, YY1
(R) Innate immune system	AP2GAMMA, ATF1, CEBPB, CJUN, CREB1, E2F6, ELF1, ELK1, GR, HEY1, MTA3, PAX5, PML, POL2, RUNX3, SIN3AK20, SP1, STAT5A, TAF1, YY1, ZNF263
(R) Class I MHC mediated antigen processing presentation	AP2GAMMA, BAF155, BCLAF1, CBX3, CEBPB, CJUN, CREB1, E2F6, ELF1, ETS1, GABP, GR, HEY1, MTA3, PAX5, PML, POL2, POU2F2, RUNX3, SIN3AK20, SP1, STAT5A, TAF1, TCF12, YY1, ZNF143
(R) Influenza viral RNA transcription and replication	ATF2, BCL3, BCLAF1, CEBPB, CJUN, CREB1, ELF1, ETS1, GABP, GR, HEY1, MTA3, NFATC1, PML, POL2, POU2F2, RFX5, SIN3AK20, SP1, SP4, STAT5A, TAF1, TAF7, TCF12, USF2, YY1, ZNF263
(R) Processing of capped intron containing pre mRNA	BCL3, BCLAF1, BRCA1, CBX3, CEBPB, CJUN, COREST, CREB1, E2F6, ELF1, ETS1, GABP, GR, HEY1, INI1, KAP1, MTA3, MYBL2, PAX5, PML, POL2, POU2F2, RUNX3, SIN3AK20, SP1, SP4, STAT5A, TAF1, TCF12, YY1, ZNF263
(R) Formation of tubulin folding intermediates by CCT TRIC	POL2
(R) Recruitment of mitotic centrosome proteins and complexes	CREB1, E2F6, ELF1, GR, MTA3, POL2, SIN3AK20, TAF1, YY1
(H) Interferon gamma response	CEBPB, CJUN, E2F6, EBF, ELF1, GR, HEY1, IKZF1, MTA3, PAX5, PML, POL2, POU2F2, RUNX3, SMC3, STAT5A, YY1
(H) TNFA signalling via NFKB	AP2GAMMA, ATF2, BAF155, BCL3, BCLAF1, CEBPB, CEBPD, CJUN, CREB1, E2F6, ELF1, GR, HEY1, JUND, MTA3, NFATC1, NFIC, P300, PAX5, PML, POL2, POU2F2, RUNX3, SIN3AK20, SP1, STAT5A, TAF1, TCF12, TCF3, YY1
(H) Inflammatory response	CEBPB, E2F6, GR, MTA3, POL2, POU2F2
(H) Complement	CEBPB, GR, HEY1, MTA3, PAX5, PML, POL2, POU2F2, RUNX3, YY1
(H) Apoptosis	CEBPB, E2F6, GR, MTA3, PML, POL2, POU2F2, SIN3AK20, TAF1, TCF12, YY1
(H) KRAS signalling up	E2F6, GR, MTA3, POL2, YY1
(H) Allograft rejection	ATF2, BCLAF1, CEBPB, CJUN, GR, MTA3, NFATC1, PML, POL2, POU2F2, RUNX3, STAT5A, TAF1, YY1
(H) MYC targets V1	AP2ALPHA, AP2GAMMA, ATF2, ATF3, BCL3, BCLAF1, CBX3, CEBPB, CJUN, COREST, CREB1, E2F6, ELF1, ETS1, FOXM1, GABP, GR, HEY1, KAP1, MAX, MBD4, MTA3, MYBL2, NFATC1, NFIC, NRSF, PAX5, PML, POL2, POU2F2, RUNX3, SIN3AK20, SMC3, SP1, SP4, STAT5A, TAF1, TAF7, TCF12, YY1, ZNF143, ZNF263
(H) E2F targets	AP2ALPHA, AP2GAMMA, ATF1, BCL3, BCLAF1, CBX3, CEBPB, CJUN, CREB1, E2F4, E2F6, ELF1, ETS1, FOXM1, GR, HEY1, KAP1, MAX, MTA3, MYBL2, NFIC, PAX5, PML, POL2, POU2F2, RUNX3, SIN3AK20, SP1, SP4, STAT5A, TAF1, TAF7, TCF12, YY1, ZNF143, ZNF263

gene sets consisting of genes sharing DNA-binding motifs. To demonstrate the utility of REPA we presented two case studies showing that by combining REPA's predictions with the results of GSA on expression data, it is possible to

enhance the interpretation of expression profiling studies by providing putative regulators underlying the observed transcriptional responses. Our results suggested that REPA's precision lies between 24% and 86%, and REPA's recall is around 54%. This level of precision is encouraging as some of REPA's predictions are expected to be novel. To facilitate the use of REPA's predicted regulatory associations, a web application to query, browse and download REPA's predictions is available at bengi.cs.mun.ca/repa. In this website, REPA's source code is also available.

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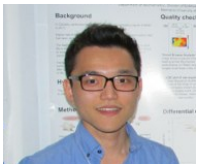

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