TFEA.ChIP: A tool kit for transcription factor binding site enrichment analysis capitalizing on ChIP-seq datasets

Laura Puente-Santamaria[1], Luis del Peso[1,2,3*]

1 Departamento de Bioquímica, Universidad Autónoma de Madrid (UAM) and Instituto de Investigaciones Biomédicas 'Alberto Sols' (CSIC-UAM), 28029 Madrid , Spain
2 IdiPaz, Instituto de Investigación Sanitaria del Hospital Universitario La Paz, 28029 Madrid, Spain.
3 CIBER de Enfermedades Respiratorias (CIBERES), Instituto de Salud Carlos III, 28029 Madrid, Spain.

* luis.peso@uam.es

Abstract

The identification of transcription factor (TF) responsible for the co-regulation of an specific set of genes is a common problem in transcriptomics. With the development of TFEA.ChIP we aim to provide a tool to estimate and visualize TF enrichment in a set of differentially expressed genes that takes into account the wide variation in TF's behavior across different cell types and stimuli. To that end, ChIP-Seq experiments from the ENCODE Consortium and GEO Datasets were gathered, and a database linking TFs with the genes they interact with in each ChIP-Seq experiment was generated. In its current state, TFEA.ChIP covers 333 different transcription factors in 1122 ChIP-Seq experiments, with over 150 cell types being represented.

Author summary

[I believe this is required for research articles, but not software papers.]

Introduction

In the most simple scenario, the comparison of the transcriptome of cells or organisms in two conditions leads to the identification of a set of differentially expressed (DE) genes, and the underlying assumption is that one or a few TFs regulate the expression of those genes. Traditionally, the identification of relevant TFs has relied on the use of position weight matrices (PWMs) to predict transcription factor binding sites (TFBSs) proximal to the DE genes [1]. The comparison of predicted TFBS in DE versus a set of control genes, reveals factors that are significantly enriched in the DE gene set. The prediction of TFBS using these approaches have been useful to narrow down potential binding sites, but can suffer from high rates of false positives. In addition, this approach is limited by design to sequence-specific transcription factors (TF) and thus unable to identify cofactors that bind indirectly to target genes. To overcome these limitations we developed the R package TFEA.ChIP, which exploits the vast amount of publicly available ChIP-Seq datasets to determine TFBS proximal to a given set of genes and computes enrichment analysis based on this experimentally-derived rich information. Specifically TFEA.ChIP, uses information derived from the hundreds of ChIP-Seq experiments from the ENCODE Consortium [2] expanded to include additional datasets contributed to GEO database [3] [4] by individual laboratories representing the binding sites of factors not assayed by ENCODE. The package includes a set of tools to customize the ChIP data, perform enrichment analysis and visualize the results. Herein we describe the main characteristics of the package and compare the results produced by TFEA.ChIP vs those generated by Oppossum, an state of the art TFBS identification software based on PWMs [5]. Our data indicate that the results of TFEA.ChIP and Opossum are coincident for those datasets where Oppossum identifies clear TFBS candidate(s). In addition, TFEA.ChIP identified enriched factors for some data sets where Opossum was unable to find a significant match.

Design and implementation

Database and algorithm

TFEA.ChIP package includes analysis and visualization tools intended for the identification of TFBS enriched in a set of DE genes. To this end the package uses experimental information derived from 1122 ChIP-seq datasets, generated by the ENCODE consortium and individual researchers, testing a total of 333 different human transcription factors in a variety of cell types and experimental conditions. Thus, this compiled database covers 20-24% of the 1,391 [6] to 1600 [7] transcription factors estimated to be encoded by the human genome and includes proteins from all the major classes of DNA binding domains (Fig 1).

The supplementary table S1 Table. contains the complete list of the datasets included in the package along with their GEO accession numbers. .Although the package is mainly focused towards analyzing expression data generated from human cells, TFEA.ChIP includes the option to use datasets coming from experiments in mice, translating mouse gene names to their equivalent ID on the human genome. For the analysis, either the actual set of DE genes or a list of genes sorted according to their expression in the conditions under study, must be provided as an input.

- Analysis of the association of TFBS and differential expression from 2x2 tables recording the presence of binding sites for a given TF in DE and control genes. The statistical significance of the association for each factor determined by a Fisher's exact test.
- GSEA analysis, based on the core function of the GSEA algorithm for R [8] [9], GSEA.EnrichmentScore.

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Results

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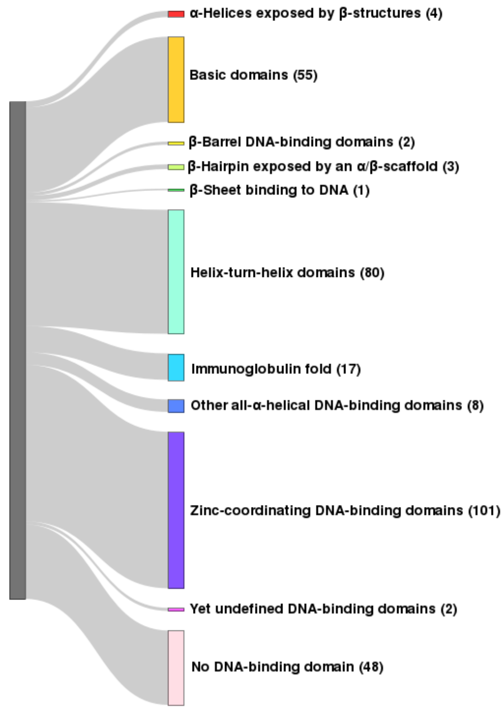

Fig 1. Structural diversity according to DNA-binding domains of the transcription factors included in the TFBS database. The 333 TFs included in TFEA.ChIP database were classified into families according to their DNA-binding domain composition. InterPro parent–child relationships between DNA-binding domains were used as the basis for TF family definition (Supplementary information S1 (PDF)). TFs with multiple DNA-binding domains were classified in each of their respective families. Families with less than five members were classified as 'other'.

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Discussion

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Conclusion

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Supporting information

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