

# JASPAR 2018: update of the open-access database of transcription factor binding profiles and its web framework

Aziz Khan<sup>1,†</sup>, Oriol Fornes<sup>2,†</sup>, Arnaud Stigliani<sup>3,†</sup>, Marius Gheorghe<sup>1</sup>, Jaime A. Castro-Mondragon<sup>1</sup>, Robin van der Lee<sup>2</sup>, Adrien Bessy<sup>3</sup>, Jeanne Chèneby<sup>4,5</sup>, Shubhada R. Kulkarni<sup>6,7,8</sup>, Ge Tan<sup>9,10</sup>, Damir Baranasic<sup>9,10</sup>, David J. Arenillas<sup>2</sup>, Albin Sandelin<sup>11,\*</sup>, Klaas Vandepoele<sup>6,7,8</sup>, Boris Lenhard<sup>9,10,12,\*</sup>, Benoît Ballester<sup>4,5</sup>, Wyeth W. Wasserman<sup>2,\*</sup>, François Parcy<sup>3</sup> and Anthony Mathelier<sup>1,13,\*</sup>

<sup>1</sup>Centre for Molecular Medicine Norway (NCMM), Nordic EMBL Partnership, University of Oslo, 0318 Oslo, Norway, <sup>2</sup>Centre for Molecular Medicine and Therapeutics, Department of Medical Genetics, BC Children's Hospital Research Institute, University of British Columbia, 950 28th Ave W, Vancouver, BC V5Z 4H4, Canada, <sup>3</sup>University of Grenoble Alpes, CNRS, CEA, INRA, BIG-LPCV, 38000 Grenoble, France, <sup>4</sup>INSERM, UMR1090 TAGC, Marseille, F-13288, France, <sup>5</sup>Aix-Marseille Université, UMR1090 TAGC, Marseille, F-13288, France, <sup>6</sup>Ghent University, Department of Plant Biotechnology and Bioinformatics, Technologiepark 927, 9052 Ghent, Belgium, <sup>7</sup>VIB Center for Plant Systems Biology, Technologiepark 927, 9052 Ghent, Belgium, <sup>8</sup>Bioinformatics Institute Ghent, Ghent University, Technologiepark 927, 9052 Ghent, Belgium, <sup>9</sup>Institute of Clinical Sciences, Faculty of Medicine, Imperial College London, London W12 0NN, UK, <sup>10</sup>Computational Regulatory Genomics, MRC London Institute of Medical Sciences, London W12 0NN, UK, <sup>11</sup>The Bioinformatics Centre, Department of Biology and Biotech Research & Innovation Centre, University of Copenhagen, DK2200 Copenhagen N, Denmark, <sup>12</sup>Sars International Centre for Marine Molecular Biology, University of Bergen, N-5008 Bergen, Norway and <sup>13</sup>Department of Cancer Genetics, Institute for Cancer Research, Oslo University Hospital Radiumhospitalet, 0310 Oslo, Norway

Received September 25, 2017; Revised October 17, 2017; Editorial Decision October 18, 2017; Accepted October 27, 2017

## ABSTRACT

JASPAR (<http://jaspar.genereg.net>) is an open-access database of curated, non-redundant transcription factor (TF)-binding profiles stored as position frequency matrices (PFMs) and TF flexible models (TFFMs) for TFs across multiple species in six taxonomic groups. In the 2018 release of JASPAR, the CORE collection has been expanded with 322 new PFMs (60 for vertebrates and 262 for plants) and 33 PFMs were updated (24 for vertebrates, 8 for plants and 1 for insects). These new profiles represent a 30% expansion compared to the 2016 release. In addition, we have introduced 316 TFFMs (95 for vertebrates, 218 for plants and 3 for insects). This release incorporates clusters of similar PFMs in each taxon and each TF class per taxon. The JASPAR 2018 CORE vertebrate collection of PFMs was used to predict

TF-binding sites in the human genome. The predictions are made available to the scientific community through a UCSC Genome Browser track data hub. Finally, this update comes with a new web framework with an interactive and responsive user-interface, along with new features. All the underlying data can be retrieved programmatically using a RESTful API and through the JASPAR 2018 R/Bioconductor package.

## INTRODUCTION

Transcription factors (TFs) are sequence-specific DNA-binding proteins involved in the transcriptional regulation of gene expression (1). TFs bind to DNA through their DNA-binding domain(s) (DBDs), which are used for TF classification (2). DNA regions at which TFs bind are defined as TF-binding sites (TFBSs) and can be identified

\*To whom correspondence should be addressed. Tel: +47 228 40 561; Email: anthony.mathelier@ncmm.uio.no  
Correspondence may also be addressed to Albin Sandelin. Tel: +45 2245 6668; Fax: +45 3532 2128; Email: albin@binf.ku.dk  
Correspondence may also be addressed to Boris Lenhard. Tel: +44 20 8383 8353; Email: b.lenhard@imperial.ac.uk  
Correspondence may also be addressed to Wyeth W. Wasserman. Tel: +1 604 875 3812; Fax: +1 604 875 3840; Email: wyeth@cmmmt.ubc.ca  
†These authors contributed equally to the paper as first authors.

**Table 1.** Overview of the growth of the number of PFMs in the JASPAR 2018 CORE collection compared to the JASPAR 2016 CORE collection

Taxonomic group	Non-redundant PFMs in JASPAR 2016	New non-redundant PFMs in JASPAR 2018	Updated PFMs in JASPAR 2018	Total PFMs (non-redundant) in JASPAR 2018	Total PFMs (all versions) in JASPAR 2018
Vertebrates	519	60	24	579	719
Plants	227	262	8	489	501
Insects	133	0	1	133	140
Nematodes	26	0	0	26	26
Fungi	176	0	0	176	177
Urochordata	1	0	0	1	1
<b>Total</b>	<b>1082</b>	<b>322</b>	<b>33</b>	<b>1404</b>	<b>1564</b>

*in vivo* by methods such as chromatin immunoprecipitation (ChIP) or *in vitro* by methods based on binding of large pools of DNA fragments (e.g. Systematic evolution of ligands by exponential enrichment (SELEX) or protein-binding microarrays (PBM)) (reviewed in (3)). Analysis of TFBSs for a given TF provides models for its specific DNA-binding preferences, which in turn can be used to predict TFBSs in DNA sequences (4). This is important as experiments can only identify TFBSs that are bound in the cell and state analyzed.

The computational representation of TF binding preferences has evolved over the years, from simple consensus sequences to position frequency matrices (PFMs). A PFM summarizes experimentally determined DNA sequences bound by an individual TF by counting the number of occurrences of each nucleotide at each position within aligned TFBSs. Such matrices can be converted into position weight matrices (PWMs), also known as position-specific scoring matrices, which are probabilistic models that can be used to predict TFBSs in DNA sequences (reviewed in (5)).

PFMs/PWMs have been the standard models for describing binding preferences of TFs for many years. The JASPAR database is among the most popular and longest maintained databases for PFMs and a standard resource in the field. In particular, the JASPAR CORE collection of the database, which is the most used, stores non-redundant TF binding profiles, providing a single representative DNA binding model per TF decided by expert curators. Exceptionally, multiple TF-binding profiles are associated to a TF when it is known to interact with DNA with multiple distinct sequence preferences, due to differential splicing for example (6,7). JASPAR was created and persists under three guiding principles: (i) unrestricted open-access; (ii) manual curation and non-redundancy of profiles; and (iii) ease-of-use. The 2016 release of the JASPAR CORE collection stored 1082 non-redundant and manually curated TF-binding profiles as PFMs for TFs from six different taxonomic groups (vertebrates, plants, insects, nematodes, fungi and urochordata) (8).

An intrinsic limitation to PFMs/PWMs is that they ignore inter-nucleotide dependencies within TFBSs (9–13). TF–DNA interaction data derived from next-generation sequencing assays has improved the computational modeling of TF binding (14–19). For example, the TF flexible models (TFFMs) (14), based on first-order hidden Markov models, capture dinucleotide dependencies within TFBSs and were introduced in the 2016 release of the JASPAR database.

In this report, we describe the seventh release of JASPAR (8,20–24), which comes with a major expansion and update of the CORE collection of TF-binding profiles as PFMs and TFFMs. These models have been manually assessed by expert curators who reconciled recent high-throughput data with available literature and linked the models to the classification of their TF DBDs from TFClass (2). The CORE collection expansion is supported by a range of new functionalities and resources, including PFM clustering, genome-wide UCSC tracks of predicted TFBSs and fully redesigned user and programming interfaces.

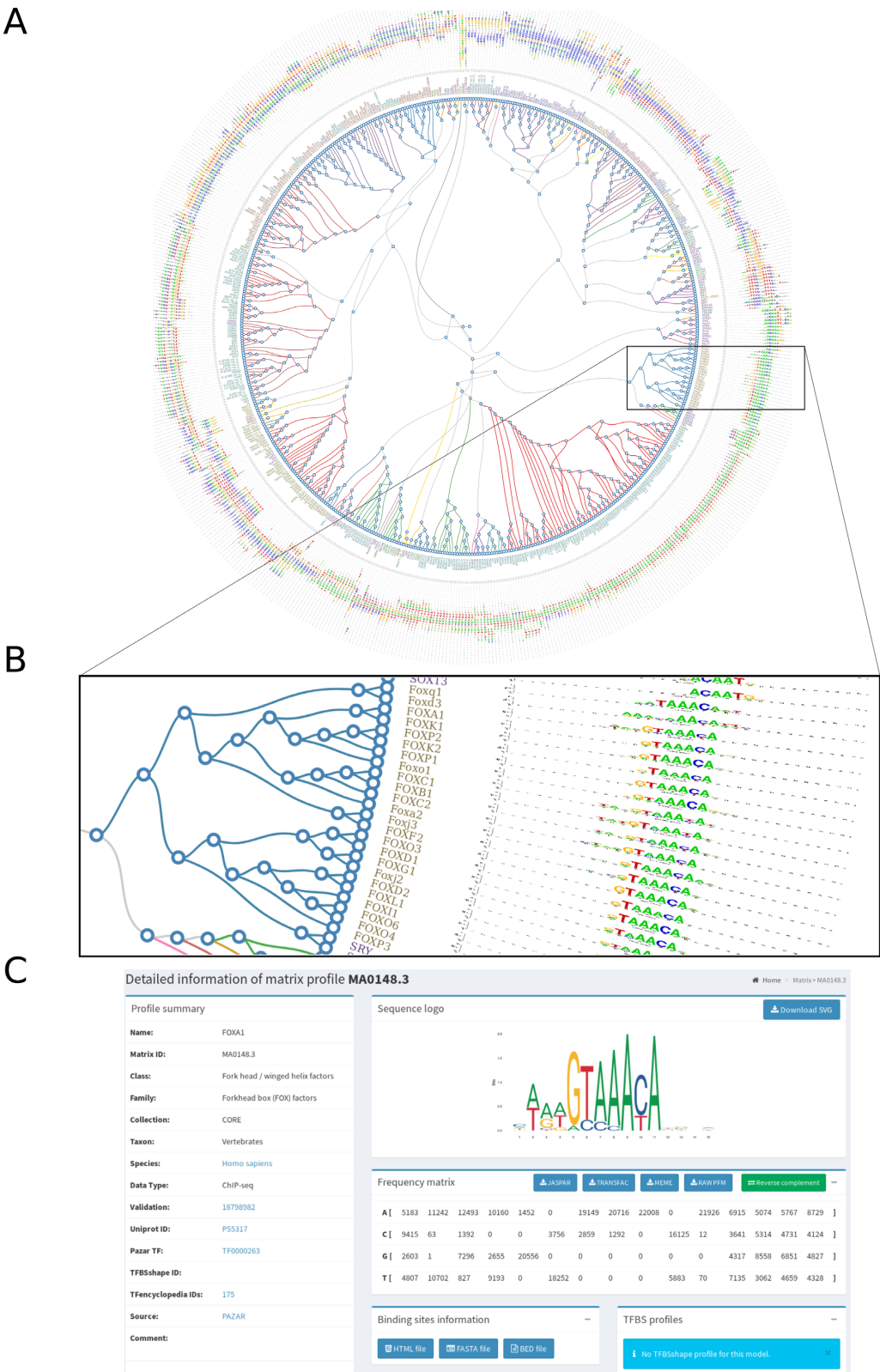
## EXPANSION AND UPDATE OF THE JASPAR CORE COLLECTION

In this 2018 release of the JASPAR database, we added 355 new PFMs for TFs from plants (270), vertebrates (84) and insects (1) to the JASPAR CORE collection (Table 1). Specifically, we added 322 PFMs (262 for plants, a 118% increase and 60 for vertebrates, an 11% increase) for TF monomers and dimers that were not previously present in JASPAR and updated 33 (8 in plants, 3% of JASPAR 2016, 24 in vertebrates, 5% of JASPAR 2016 and 1 in insects). The PFMs were manually curated using independent external literature supporting the candidate TF-binding preferences, as previously described in (23). The curated PFMs were derived from ChIP-seq (from ReMap (25) and (26–30)), DAP-seq (31), SMiLE-seq (32), PBM (33) and HT-SELEX (34) experiments. The JASPAR CORE collection now includes 1404 non-redundant PFMs (579 for vertebrates, 489 for plants, 176 for fungi, 133 for insects, 26 for nematodes and 1 for urochordata) (Table 1).

We continued with the incorporation of TFFM models, initiated in JASPAR 2016. In this release of JASPAR, we introduced 316 new TFFMs for vertebrates (95), plants (218) and *Drosophila* (3), which represents a 243% increase in the number of non-redundant TFFMs stored in the JASPAR CORE collection.

## HIERARCHICAL CLUSTERING OF TF-BINDING PROFILES

While the non-redundancy of binding profiles is one of the guiding principles of JASPAR, TFs with similar DBDs often have similar binding preferences (35,36). To facilitate the exploration of similar profiles in the JASPAR CORE collection, we performed hierarchical clustering of PFMs using the RSAT matrix-clustering tool (37). Specifically, the tool was applied to PFMs in each taxon independently as



**Figure 1.** JASPAR PFM clustering. (A) Radial tree representing the clusterization of the JASPAR CORE vertebrate PFMs. (B) Zoom in view of the radial tree where the predicted clusters are highlighted at the branches and the TF classes are indicated with different colors at the leaves. (C) Clicking on a leaf in the radial tree will open a link to the corresponding motif description page on the JASPAR website (the MA0148.3 profile associated to FOXA1 is provided here as an example).



**Figure 2.** Overview of the JASPAR 2018 new web interface with interactive searching activity. (A) A quick and detailed search feature on the homepage. (B) A responsive table lists the searched profile(s), which can be further selected and added to the cart listed on the right panel for users to perform their own analyses. (C) A detailed page for the GATA3 matrix profile, which is divided into sub-panels including the profile summary, sequence logo, PFM, TF-binding information, external links, version information, ChIP-seq centrality, TFFM and other details. (D) The PFM for the GATA3 profile (MA0037.2) is downloaded in MEME format using the RESTful API.

well as in each TF class per taxon. The clustering results are provided as radial trees (Figure 1), which can further be explored through dedicated web pages (<http://jaspar.genereg.net/matrix-clusters>).

## JASPAR UCSC TRACKS FOR GENOME-WIDE ANALYSES OF TFBSs

A typical application of JASPAR TF-binding profiles in gene regulation studies is the identification of TFBSs in DNA sequences for further analyses. Although, we recognize that genome-wide PWM-based predictions contain a high number false positives, we believe that they are a powerful resource for the research community in the context

of a variety of genomic information, including transcription start site activity, DNA accessibility, histone marks, evolutionary conservation or *in vivo* TF binding (38–46). To facilitate such integrative analyses, we have performed TFBS predictions on the human genome using the JASPAR CORE vertebrate PFMs (see Supplementary Data for details on the computation). The predicted TFBSs are publicly available through a UCSC Genome Browser data hub (47) containing tracks for the human genome assemblies hg19 and hg38 (<http://jaspar.genereg.net/genome-tracks/>).



## A NEW, POWERFUL AND USER-FRIENDLY WEB INTERFACE

### A new web interface

The JASPAR 2018 release comes with a completely redesigned web interface that meets modern web standards. This interactive web framework is implemented using Django, a model-view-controller based web-framework for Python. We used MySQL as a backend database to store profile metadata and Bootstrap as a frontend template engine. We have greatly improved the visibility and usability of existing functionality, created easier navigation with semantic URLs, and enhanced browsing and searching. On the homepage, we provide a dynamic tour of JASPAR 2018, walking users through the main features of the new website. A video of the tour is available at <http://jaspar.genereg.net/tour>. The database can be browsed for individual collections by using the navigation links on the left sidebar. Moreover, it can be searched for each of the six different taxonomic groups included in the JASPAR CORE collection using the tabs available on the homepage (Figure 2). TF-binding profiles can be further filtered through the case insensitive search option available on the homepage. In addition, through the 'Advanced Options', the search criteria can be further restricted (Figure 2A). Search results are presented in a responsive and paginated table along with sequence logos of the PFMs, which can be selected for download or to perform a variety of analyses available on the right panel (Figure 2B). All information in the tables can be downloaded as comma-separated value files. Profile IDs and sequence logos can be clicked to view the detailed profile pages (Figure 2C). PFMs can be downloaded in several formats including JASPAR, TRANSFAC and MEME (Figure 2D). Furthermore, we have incorporated new features to the web interface, such as 'Add to Cart', where users can add TF profiles of interest for download or further analyses (Figure 2B). Finally, we have introduced semantic URLs to facilitate external linking to the detailed pages of individual profiles (e.g. <http://jaspar.genereg.net/matrix/MA0059.1/>). We have implemented a URL redirection mechanism to correctly direct the links pointing to previous JASPAR URL patterns from external resources.

### RESTful API

In previous releases, the underlying data could be retrieved as flat files or by using programming language-specific modules. Associated with this release, we introduced a RESTful API to access the JASPAR database programmatically (see <https://www.biorxiv.org/content/early/2017/07/06/160184> for details). The RESTful API enables programmatic access to JASPAR by most programming languages and returns data in seven widely used formats: JSON, JSONP, JASPAR, MEME, PFM, TRANSFAC and YAML. Further, it provides a browsable interface and access to the JASPAR motif inference tool for bioinformatics tool developers. The RESTful API is implemented in Python using the Django REST Framework and is freely accessible at <http://jaspar.genereg.net/api/>. The source code for the website and RESTful API are freely available at <https://bitbucket.org/CBGR/jaspar> under GPL v3 license.

## CONCLUSION AND PERSPECTIVES

In this seventh release of the JASPAR database, we continue our commitment to provide the research community with high-quality, non-redundant TF-binding profiles for TFs in six taxa. As in previous releases, we have greatly expanded the number of available profiles in the database, both for PFMs and TFFMs. We also greatly improved user experience through a new easy-to-use website and a RESTful API that grants universal programmatic access to the database. Moreover, for the PFMs in the JASPAR CORE collection, we provide a hierarchical clustering and genome-wide TFBS predictions for the hg19 and hg38 human genome assemblies as UCSC tracks.

During the curation process, hundreds of PFMs were discarded because our curators failed to find any support from existing literature. As new experiments and data become available, binding preferences for these TFs will be considered for JASPAR incorporation. For instance, we re-examined data from (34) to incorporate seven previously excluded PFMs into JASPAR 2018. In the future, we would like to engage the scientific community in the curation process to increase our capacity to introduce new TF-binding profiles in JASPAR. We plan to dedicate a specific section of the website to hosting the profiles that were not introduced into JASPAR, to encourage researchers to perform experiments and/or point us to literature that our curators missed in order to support these profiles. We believe that the engagement of the scientific community to support JASPAR will further improve our capacity to expand the collection of high quality TF-binding profiles.

## SUPPLEMENTARY DATA

Supplementary Data are available at NAR Online.

## ACKNOWLEDGEMENTS

We thank the scientific community for performing experimental assays of TF–DNA interactions and for publicly releasing the data. We thank Georgios Magklaras and his team for IT support. We thank José Manuel Franco for sharing the plant PBM data, Jens De Ceuleire for help with plant ChIP-seq data processing and José Luis Villanueva-Cañas for sharing the *Drosophila* TFFMs prior to publication. We thank Rachelle Farkas for proofreading the manuscript.

## FUNDING

Norwegian Research Council, Helse Sør-Øst, and University of Oslo through the Centre for Molecular Medicine Norway (NCMM) (to A.M., M.G., A.K.); Genome Canada and Canadian Institutes of Health Research (On-Target Grants) [2550NT and BOP-149430 to W.W.W., O.F., R.v.d.L., D.J.A.]; Natural Sciences and Engineering Research Council of Canada (Discovery Grant) [RGPIN-2017-06824 to W.W.W.]; Weston Brain Institute [20R74681 to O.F.]; Agence Nationale de la Recherche [ANR-10-LABX-49-01 to F.P., A.S.]; IDEX graduate school (to A.S.); CNRS (to A.B., F.P.); Research Foundation–Flanders Grant [G001015N to S.R.K.]; French Ministry

of Higher Education and Research (MESR) PhD Fellowship (to J.A.C.-M.); Lundbeck Foundation (to A.S.); Independent Research Fund Denmark (to A.S.); Innovation Fund Denmark (to A.S.); Elixir Denmark (to A.S.); Wellcome Trust [106954 to G.T., D.B., B.L.]; Biotechnology and Biological Sciences Research Council [BB/N023358/1 to G.T., D.B., B.L.]; Medical Research Council UK [MC\_UP\_1102/1 to G.T., D.B., B.L.]. The open access publication charge for this paper has been waived by Oxford University Press - *NAR* Editorial Board members are entitled to one free paper per year in recognition of their work on behalf of the journal.

**Conflict of interest statement.** None declared.

## REFERENCES

- Vaquerizas, J.M., Kummerfeld, S.K., Teichmann, S.A. and Luscombe, N.M. (2009) A census of human transcription factors: function, expression and evolution. *Nat. Rev. Genet.*, **10**, 252–263.
- Wingender, E., Schoeps, T., Haubrock, M. and Dönitz, J. (2015) TFCClass: a classification of human transcription factors and their rodent orthologs. *Nucleic Acids Res.*, **43**, D97–D102.
- Xie, Z., Hu, S., Qian, J., Blackshaw, S. and Zhu, H. (2011) Systematic characterization of protein-DNA interactions. *Cell. Mol. Life Sci.*, **68**, 1657–1668.
- Wasserman, W.W. and Sandelin, A. (2004) Applied bioinformatics for the identification of regulatory elements. *Nat. Rev. Genet.*, **5**, 276–287.
- Stormo, G.D. (2013) Modeling the specificity of protein-DNA interactions. *Quant. Biol.*, **1**, 115–130.
- Stormo, G.D. (2015) DNA motif databases and their uses. *Curr. Protoc. Bioinformatics*, **51**, 1–6.
- Badis, G., Berger, M.F., Philippakis, A.A., Talukder, S., Gehrke, A.R., Jaeger, S.A., Chan, E.T., Metzler, G., Vedenko, A., Chen, X. *et al.* (2009) Diversity and complexity in DNA recognition by transcription factors. *Science*, **324**, 1720–1723.
- Mathelier, A., Arenillas, D.J., Chen, C.-Y., Denay, G., Lee, J., Shi, W., Shyr, C., Tan, G., Worsley-Hunt, R. *et al.* (2016) JASPAR 2016: a major expansion and update of the open-access database of transcription factor binding profiles. *Nucleic Acids Res.*, **44**, D110–D115.
- Man, T.K. and Stormo, G.D. (2001) Non-independence of Mnt repressor-operator interaction determined by a new quantitative multiple fluorescence relative affinity (QuMFRA) assay. *Nucleic Acids Res.*, **29**, 2471–2478.
- Bulyk, M.L., Johnson, P.L.F. and Church, G.M. (2002) Nucleotides of transcription factor binding sites exert interdependent effects on the binding affinities of transcription factors. *Nucleic Acids Res.*, **30**, 1255–1261.
- Zhou, Q. and Liu, J.S. (2004) Modeling within-motif dependence for transcription factor binding site predictions. *Bioinformatics*, **20**, 909–916.
- Tomovic, A. and Oakeley, E.J. (2007) Position dependencies in transcription factor binding sites. *Bioinformatics*, **23**, 933–941.
- Chin, F. and Leung, H.C.M. (2008) DNA motif representation with nucleotide dependency. *IEEE/ACM Trans. Comput. Biol. Bioinform.*, **5**, 110–119.
- Mathelier, A. and Wasserman, W.W. (2013) The next generation of transcription factor binding site prediction. *PLoS Comput. Biol.*, **9**, e1003214.
- Zellers, R.G., Drewell, R.A. and Dresch, J.M. (2015) MARZ: an algorithm to combinatorially analyze gapped n-mer models of transcription factor binding. *BMC Bioinformatics*, **16**, 1–14.
- Eggeling, R., Roos, T., Myllymäki, P. and Grosse, I. (2015) Inferring intra-motif dependencies of DNA binding sites from ChIP-seq data. *BMC Bioinformatics*, **16**, 1–15.
- Siebert, M. and Söding, J. (2016) Bayesian Markov models consistently outperform PWMs at predicting motifs in nucleotide sequences. *Nucleic Acids Res.*, **44**, 6055–6069.
- Mathelier, A., Xin, B., Chiu, T.-P., Yang, L., Rohs, R. and Wasserman, W.W. (2016) DNA shape features improve transcription factor binding site predictions in vivo. *Cell Syst.*, **3**, 278–286.
- Omid, S., Zavolan, M., Pachkov, M., Breda, J., Berger, S. and van Nimwegen, E. (2017) Automated incorporation of pairwise dependency in transcription factor binding site prediction using dinucleotide weight tensors. *PLoS Comput. Biol.*, **13**, e1005176.
- Sandelin, A., Alkema, W., Engström, P., Wasserman, W.W. and Lenhard, B. (2004) JASPAR: an open-access database for eukaryotic transcription factor binding profiles. *Nucleic Acids Res.*, **32**, D91–D94.
- Vlieghe, D., Sandelin, A., De Bleser, P.J., Vleminckx, K., Wasserman, W.W., van Roy, F. and Lenhard, B. (2006) A new generation of JASPAR, the open-access repository for transcription factor binding site profiles. *Nucleic Acids Res.*, **34**, D95–D97.
- Bryne, J.C., Valen, E., Tang, M.-H.E., Marstrand, T., Winther, O., da Piedade, I., Krogh, A., Lenhard, B. and Sandelin, A. (2008) JASPAR, the open access database of transcription factor-binding profiles: new content and tools in the 2008 update. *Nucleic Acids Res.*, **36**, D102–D106.
- Portales-Casamar, E., Thongjuea, S., Kwon, A.T., Arenillas, D., Zhao, X., Valen, E., Yusuf, D., Lenhard, B., Wasserman, W.W. and Sandelin, A. (2010) JASPAR 2010: the greatly expanded open-access database of transcription factor binding profiles. *Nucleic Acids Res.*, **38**, D105–D1010.
- Mathelier, A., Zhao, X., Zhang, A.W., Parcy, F., Worsley-Hunt, R., Arenillas, D.J., Buchman, S., Chen, C.-Y., Chou, A., Ienasescu, H. *et al.* (2014) JASPAR 2014: an extensively expanded and updated open-access database of transcription factor binding profiles. *Nucleic Acids Res.*, **42**, D142–D1427.
- Chèneby, J., Gheorghe, M., Artufel, M., Mathelier, A. and Ballester, B. (2017) ReMap 2018: An updated atlas of regulatory regions from an integrative analysis of DNA-binding ChIP-seq experiments. *Nucleic Acids Res.*, doi:10.1093/nar/gkx1092.
- Eveland, A.L., Goldshmidt, A., Pautler, M., Morohashi, K., Liseron-Monfils, C., Lewis, M.W., Kumari, S., Hiraga, S., Yang, F., Unger-Wallace, E. *et al.* (2014) Regulatory modules controlling maize inflorescence architecture. *Genome Res.*, **24**, 431–443.
- Verkest, A., Abeel, T., Heyndrickx, K.S., Van Leene, J., Lanz, C., Van De Slijke, E., De Winne, N., Eeckhout, D., Persiau, G., Van Breusegem, F. *et al.* (2014) A generic tool for transcription factor target gene discovery in Arabidopsis cell suspension cultures based on tandem chromatin affinity purification. *Plant Physiol.*, **164**, 1122–1133.
- Li, C., Qiao, Z., Qi, W., Wang, Q., Yuan, Y., Yang, X., Tang, Y., Mei, B., Lv, Y., Zhao, H. *et al.* (2015) Genome-wide characterization of cis-acting DNA targets reveals the transcriptional regulatory framework of opaque2 in maize. *Plant Cell*, **27**, 532–545.
- Cui, X., Lu, F., Qiu, Q., Zhou, B., Gu, L., Zhang, S., Kang, Y., Cui, X., Ma, X., Yao, Q. *et al.* (2016) REF6 recognizes a specific DNA sequence to demethylate H3K27me3 and regulate organ boundary formation in Arabidopsis. *Nat. Genet.*, **48**, 694–699.
- Birkenbihl, R.P., Kracher, B. and Somssich, I.E. (2017) Induced genome-wide binding of three Arabidopsis WRKY transcription factors during early MAMP-triggered immunity. *Plant Cell*, **29**, 20–38.
- O'Malley, R.C., Huang, S.-S.C., Song, L., Lewsey, M.G., Bartlett, A., Nery, J.R., Galli, M., Gallavotti, A. and Ecker, J.R. (2016) Cistrome and epicistrome features shape the regulatory DNA landscape. *Cell*, **165**, 1280–1292.
- Isakova, A., Groux, R., Imbeault, M., Rainer, P., Alpern, D., Dainese, R., Ambrosini, G., Trono, D., Bucher, P. and Deplancke, B. (2017) SMILE-seq identifies binding motifs of single and dimeric transcription factors. *Nat. Methods*, **14**, 316–322.
- Franco-Zorrilla, J.M., López-Vidriero, I., Carrasco, J.L., Godoy, M., Vera, P. and Solano, R. (2014) DNA-binding specificities of plant transcription factors and their potential to define target genes. *Proc. Natl. Acad. Sci. U.S.A.*, **111**, 2367–2372.
- Jolma, A., Yan, J., Whittington, T., Toivonen, J., Nitta, K.R., Rastas, P., Morgunova, E., Enge, M., Taipale, M., Wei, G. *et al.* (2013) DNA-binding specificities of human transcription factors. *Cell*, **152**, 327–339.
- Weirauch, M.T., Yang, A., Albu, M., Cote, A., Montenegro-Montero, A., Drewe, P., Najafabadi, H.S., Lambert, S.A., Mann, I., Cook, K. *et al.* (2014) Determination and inference of eukaryotic transcription factor sequence specificity. *Cell*, **158**, 1431–1443.

36. Sandelin, A. and Wasserman, W.W. (2004) Constrained binding site diversity within families of transcription factors enhances pattern discovery bioinformatics. *J. Mol. Biol.*, **338**, 207–215.
37. Castro-Mondragon, J.A., Jaeger, S., Thieffry, D., Thomas-Chollier, M. and van Helden, J. (2017) RSAT matrix-clustering: dynamic exploration and redundancy reduction of transcription factor binding motif collections. *Nucleic Acids Res.*, **45**, e119.
38. Kwon, A.T., Arenillas, D.J., Worsley Hunt, R. and Wasserman, W.W. (2012) oPOSSUM-3: advanced analysis of regulatory motif over-representation across genes or ChIP-Seq datasets. *G3*, **2**, 987–1002.
39. Mathelier, A., Lefebvre, C., Zhang, A.W., Arenillas, D.J., Ding, J., Wasserman, W.W. and Shah, S.P. (2015) Cis-regulatory somatic mutations and gene-expression alteration in B-cell lymphomas. *Genome Biol.*, **16**, 1–17.
40. Verfaillie, A., Imrichova, H., Janky, R. and Aerts, S. (2015) iRegulon and i-cistarget: reconstructing regulatory networks using motif and track enrichment. *Curr. Protoc. Bioinformatics*, **52**, 1–39.
41. Arenillas, D.J., Forrest, A.R.R., Kawaji, H., Lassmann, T. and FANTOM Consortium (2016) CAGED-oPOSSUM: motif enrichment analysis from CAGE-derived TSSs. *Bioinformatics*, **32**, 2858–2860.
42. Shi, W., Fornes, O., Mathelier, A. and Wasserman, W.W. (2016) Evaluating the impact of single nucleotide variants on transcription factor binding. *Nucleic Acids Res.*, **44**, 10106–10116.
43. Arner, E., Daub, C.O., Vitting-Seerup, K., Andersson, R., Lilje, B., Drablos, F., Lennartsson, A., Rönnerblad, M., Hrydziusko, O., Vitezic, M. *et al.* (2015) Transcribed enhancers lead waves of coordinated transcription in transitioning mammalian cells. *Science*, **347**, 1010–1014.
44. FANTOM Consortium and the RIKEN PMI and CLST (DGT), Forrest, A.R.R., Kawaji, H., Rehli, M., Baillie, J.K., de Hoon, M.J.L., Haberle, V., Lassmann, T., Kulakovskiy, I.V., Lizio, M. *et al.* (2014) A promoter-level mammalian expression atlas. *Nature*, **507**, 462–470.
45. Neph, S., Vierstra, J., Stergachis, A.B., Reynolds, A.P., Haugen, E., Vernot, B., Thurman, R.E., John, S., Sandstrom, R., Johnson, A.K. *et al.* (2012) An expansive human regulatory lexicon encoded in transcription factor footprints. *Nature*, **489**, 83–90.
46. Thurman, R.E., Rynes, E., Humbert, R., Vierstra, J., Maurano, M.T., Haugen, E., Sheffield, N.C., Stergachis, A.B., Wang, H., Vernot, B. *et al.* (2012) The accessible chromatin landscape of the human genome. *Nature*, **489**, 75–82.
47. Raney, B.J., Dreszer, T.R., Barber, G.P., Clawson, H., Fujita, P.A., Wang, T., Nguyen, N., Paten, B., Zweig, A.S., Karolchik, D. *et al.* (2014) Track data hubs enable visualization of user-defined genome-wide annotations on the UCSC Genome Browser. *Bioinformatics*, **30**, 1003–1005.