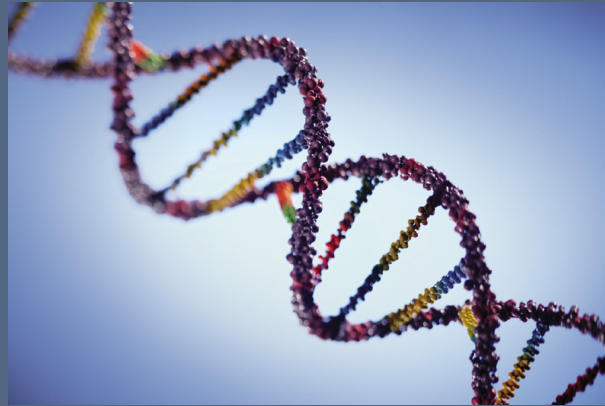




Centre for Molecular Medicine
and Therapeutics



The wiki-based Transcription Factor Encyclopedia and a model for robust community participation



Wyeth W. Wasserman

30 November 2010

<http://www.cisreg.ca/tfe>

Transcription Factors 101

- **Diverse set of proteins sharing common functional role in the regulation and production of RNA transcripts**
- **Present in all species**
- **For the purpose of today's talk, TF will refer to the subset of the proteins that bind to DNA in a sequence-specific manner**

Transcription Factors 102

- **Act cooperatively with other TFs to confer specific patterns of gene activity in response to developmental, physiological and environmental conditions**
- **Much of their function is defined by protein-protein interactions**
- **Understanding TFs is key to understanding developmental and tissue differentiation**

Resources for the Study of TFs



PAZAR
A PUBLIC DATABASE OF TRANSCRIPTION FACTOR AND REGULATORY SEQUENCE ANNOTATION

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Welcome to PAZAR!

PAZAR is your one stop shopping experience for transcription factors and regulatory sequence annotations. It is a software framework for the construction and maintenance of regulatory sequence data annotations; a framework which allows multiple boutique databases to function independently within a larger system (or information mail). Our goal is to be the public repository for regulatory data. [View our publications](#)
[View our first information webinar held on Nov 24th 2009](#)

Public projects	TFs	Genes	Seqs	Profiles
ABS ABS: a database of Annotated regulatory Binding Sites from orthologous promoters E.	152	205	611	+
AREs The ARE project contains twenty active antioxidant responsive elements (AREs) that	1	20	20	+
HNF1 TFBS Compilation of binding sites for the HNF1 transcription factor complex composed	1	55	80	+
WHEA The WHEA project houses data from the Stadel lab at UC Riverside	1	79	107	+
JASPAR CORE The JASPAR CORE database contains a curated, non-redundant set of 123	96	0	3,502	138
Kellis predictions Set of predicted motifs remapped from Vile et al., 2005. This set was	0	12,441	142,069	+
Trans set Set of liver-specific regulatory regions and transcription factor binding sites curated	0	14	62	+
TRANSFAC Transcription factor binding site annotations of the Mouse ENTPD1 gene	45	7	70	-



TFCT



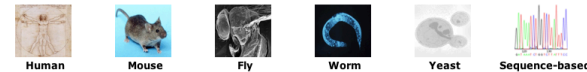
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Welcome to oPOSSUM

oPOSSUM is a web-based system for the detection of over-represented conserved transcription factor binding sites and binding site combinations in sets of genes or sequences.

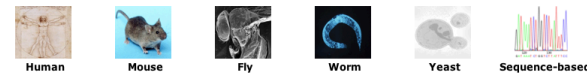
Single Site Analysis (SSA)

Detect over-represented conserved transcription factor binding sites in a set of genes or sequences.



Anchored Combination Site Analysis (aCSA)

Detect over-represented combinations of conserved transcription factor binding sites in a set of genes or sequences.



TFBS Cluster-based Analysis (TCA)

Detect over-represented clusters of conserved transcription factor binding sites in a set of sequences.



Wiki-in-the-classroom

Secreted frizzled-related protein 1

From Wikipedia, the free encyclopedia
(Redirected from [SFRP1](#))



This article is an **orphan**, as few or no other articles link to it. Please [introduce links](#) to this page from [related articles](#); suggestions may be available. (February 2009)

Secreted frizzled-related protein 1 also known as **SFRP1** is a [protein](#) which in humans is encoded by the *SFRP1* [gene](#).^[1]

[edit](#)

tumor tissue compared with normal and the expression of SFRP1 is lost in patient tumor samples. The role for the Wnt/ β -catenin signaling in cancer has been well defined: β -catenin drives transcription of genes that contribute to the tumor phenotype by regulating processes, such as proliferation, survival and invasion.^[8]

Gumz et al. showed that SFRP1 expression in UMRC3 cells (clear cell renal cell carcinoma cell line) resulted in a growth-inhibited phenotype. SFRP1 expression not only reduced the expression of Wnt target genes, but also markedly inhibited tumor cell growth in culture, soft agar and xenografts in athymic nude mice. Growth in culture and anchorage-independent growth were inhibited in SFRP1-expressing UMRC3 cells. The growth-inhibitory effects of SFRP1 were due primarily to decreased cell proliferation rather than an increase in apoptosis.^[8] This was consistent with the effect of SFRP1 on cellular proliferation as seen in prostate cancer, where retroviral-mediated expression of SFRP1 resulted in inhibited cellular proliferation but had no effect on apoptosis.^[10] Also, restoration of SFRP1 expression attenuated the malignant phenotype of cRCC; moreover, other studies showed reexpression of SFRP1 resulted in decreased colony formation in colon and lung cancer models.^{[11][12]}

Wnt-dependent signaling

[\[edit\]](#)

The [Wnt signaling pathways](#) are initiated by the binding of the Wnt ligand to the Fz receptor. There are three different molecular pathways downstream of the Wnt/Fz interaction. The majority of research has focused on the Wnt/ β -catenin pathway (also known as the "canonical" Wnt pathway), which manages cell fate determination by regulating gene expression. The Wnt/ Ca^{2+} and Wnt/polarity pathways are known as the "non-canonical pathways". The decision of which pathway is activated most likely depends on which Wnt ligand and Fz receptor are present, as well as the cellular context. Nineteen Wnt ligands and ten different members of the Fz seven-transmembrane receptor family have been described in the human genome. As a result, a large variety of responses could be initiated from the Wnt/Fz interactions.^[13]

The Wnt/ β -catenin pathway starts with the binding of Wnt to a receptor complex encompassing a Fz receptor and LRP co-receptor. After Wnt binds, an intracellular protein named [Dishevelled](#) (Dvl) is activated via phosphorylation. β -catenin degradation complexes in the cytoplasm are composed of adenomatous polyposis coli (APC), glycogen synthase kinase 3 β (GSK3 β) and Axin. APC promotes the degradation of β -catenin by increasing the affinity of the degradation complex to β -catenin. Axin is a scaffolding protein which holds the degradation complex together. The activated Dvl associates with Axin and prevents GSK3 β and casein kinase 1 α (CK1 α) from phosphorylating critical substrates, such as β -catenin. Phosphorylation of β -catenin marks the protein for ubiquitylation and rapid degradation by proteasomes. Thus, the binding of Wnt to the receptor results in a non-phosphorylated form of β -catenin which localizes to the nucleus and, after displacing the Groucho corepressor protein, forms a complex with Tcf/Lef transcription factors and co-activators (such as CREB binding protein) and induces the expression of downstream target genes.^[13]

β -catenin is actively stabilized in over 50% of breast cancers and its nuclear localization correlates with poor patient prognosis. Several target genes of the Wnt signaling pathway, such as cyclin D1, are activated in a significant proportion of breast tumours.^[2] It has been shown that SFRP1 transcription can be driven by β -catenin in normal intestinal epithelial cells. Neoplastic epithelial cells were treated with lithium chloride, which inhibits GSK3 β and thus stabilizes β -catenin. Lithium chloride is widely used to mimic Wnt signaling. Rather than suppressing SFRP1



transcription factor
encyclopedia

TFe

Goal: create an online encyclopedic collection of reviews about well-studied TFs, combining a mixture of **expert-curated** and automatic content.

The screenshot displays the Transcription Factor Encyclopedia (TFe) website interface. On the left is a sidebar with a search bar, a 'Sign in or sign up' button, and a 'Pages' menu containing links to About, Articles, Browse, Classification, Search, Authors, Feedback, Citation, and API. The main content area features the title 'NR2E1' with a small orange icon, followed by the description 'nuclear receptor subfamily 2, group E, member 1' and the authors 'By Charles N. de Leeuw and Elizabeth M. Simpson'. To the right of the title is a 3D ribbon diagram of the protein structure. Further right, a 'Classification' section lists the hierarchy: *Homo sapiens* » Zinc-coordinating Group » Hormone-nuclear Receptor Family » Subfamily 2 (HNF4, RXR, TR2/4, DHR78, TLL, COUP-TF and EAR2, NR2A2/3, and 19 individual genes). Below this, 'Related TF(s)' lists 'Nr2e1' and 'Nr2e1', 'Homologs' states '(none defined here)', 'Links' provides 'ENSG00000112333' (Ensembl), '7101' (Entrez Gene), and 'Homologene' '603849' (OMIM), and 'Synonyms' lists 'XTLL, TLX, TLL'. A progress bar indicates 'The article completion score for this TF is 78%' with a 'Refresh score' button and links to 'Download scoring guide' and 'see what's missing'. Below the progress bar is a tabbed interface with 'Summary' selected, and other tabs for Structure, TFBS, Targets, Protein, Interactions, Genetics, Expression, Ontologies, and Papers. At the bottom of the summary tab are links to 'Download article (PDF)', 'Download data (Excel)', and 'View recent activity', along with 'view content' and 'comments' links. The 'Overview' section contains two paragraphs: 'NR2E1 is a highly conserved^[1] human orphan nuclear receptor, consisting of a DNA-binding domain, hinge region, and ligand-binding domain. It is classified as an orphan as no ligand has yet been identified.' and 'NR2E1 is important for brain development and its function has been shown to be conserved in *Drosophila*^[2], Zebrafish^[3], and mouse^[4]. The mouse phenotype has been studied extensively and has proposed roles for NR2E1 in brain development, neural stem cells, and mental illness (see mouse Nr2e1 entry).'

<http://www.cisreg.ca/tfe>

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NR2E1

nuclear receptor subfamily 2, group E, member 1

By Charles N. de Leeuw and Elizabeth M. Simpson

Classification

Homo sapiens » Zinc-coordinating Group » Hormone-nuclear Receptor Family » Subfamily 2 (HNF4, RXR, TR2/4, DHR78, TLL, COUP-TF and EAR2, NR2A2/3, and 19 individual genes)

Related TF(s)

Nr2e1 Nr2e1

Homologs

(none defined here)

Links

ENSG00000112333 (Ensembl) 7101 (Entrez Gene)

Homologene 603849 (OMIM)

Synonyms

XTLL, TLX, TLL

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Summary

Structure TFBS Targets Protein Interactions Genetics Expression Ontologies Papers

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Overview

NR2E1 is a highly conserved^[1] human orphan nuclear receptor, consisting of a DNA-binding domain, hinge region, and ligand-binding domain. It is classified as an orphan as no ligand has yet been identified.

NR2E1 is important for brain development and its function has been shown to be conserved in *Drosophila*^[2], Zebrafish^[3], and mouse^[4]. The mouse phenotype has been studied extensively and has proposed roles for NR2E1 in brain development, neural stem cells, and mental illness (see [mouse Nr2e1](#) entry).

In humans, many different disorders including schizophrenia, socio- and psychopathy, and microcephaly have been investigated as having a potential underlying defect in *NR2E1*^{[5][6]}. Recently, a study has found a genetic association between a single nucleotide polymorphism in human *NR2E1* and Bipolar Disorder Type I^[7]. Some studies have also indicated a role of NR2E1 in brain tumour formation, such as glioblastomas^[8]^{[9][10][11]}. The closest homolog to NR2E1 is NR2E3 which has been demonstrated to cause Enhanced S-Cone Syndrome and implicated in some Retinitis Pigmentosa^{[12][13]}.

Molecularly, NR2E1 is described in the literature as mainly functioning by conferring strong repression upon target genes, including those expressed during differentiation of neural stem cells and regulators of cell cycle progression^{[14][15]}. New targets have also been revealed recently upon which NR2E1 activates expression^{[16][17][18]}.

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8

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Figures

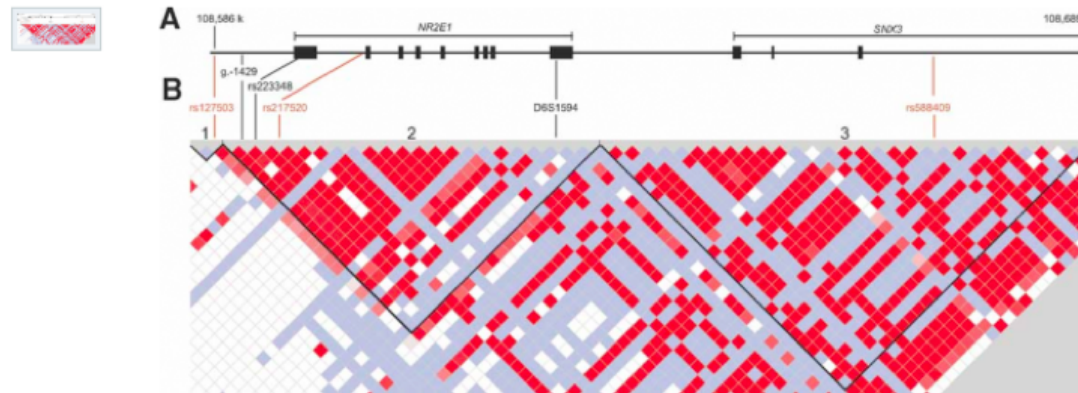



FIGURE 1 Linkage disequilibrium map with six markers chosen for association analysis in bipolar disorder and schizophrenia

Genomic structure of *NR2E1* and location of six markers selected for association analyses in bipolar disorder and schizophrenia.

A: Schematic of *NR2E1* and closest neighboring gene *SNX3*.

B: Linkage disequilibrium (LD) map generated from the HAPMap data CEU population set. LD blocks (1, 2, and 3) were generated using the "Solid spine of LD" method. Markers that are tag SNPs are indicated in red. (Kumar *et al.* 2008)

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Links

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[Dr. Elizabeth M. Simpson \(new window\)](#) [†]Research on NR2E1 at the Centre for Molecular Medicine and Therapeutics, University of British Columbia

[Nuclear Receptor Signaling Atlas \(new window\)](#) [†]Home page

(a)

SOX9 

SRY (sex determining region Y)-box 9

By Ralf Kist

Classification **Homo sapiens** • Other Alpha-Helix Group • High Mobility Group (Box) Family


Related TF(s) • Sox9

Homologs (3) • Sox9

Links [ENSC00000125398*](#) (Ensembl) [6662*](#) (Entrez Gene) [Homologene*](#) [608160*](#), [114290*](#) (iOMIM)

Synonyms [SRA1](#), [CMPD1](#), [CMD1](#)

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(f) NR2E1 

nuclear receptor subfamily 2, group C, member 1

By Ralf Kist

Classification **Homo sapiens** • Nuclear Receptor subfamily 2, group C, member 1


Related TF(s) • NR2E1

Homologs (3) • NR2E1

Links [ENSC00000125398*](#) (Ensembl) [6662*](#) (Entrez Gene) [Homologene*](#) [608160*](#), [114290*](#) (iOMIM)

Synonyms [SRA1](#), [CMPD1](#), [CMD1](#)

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(g) EPAS1 

endothelial PAS domain protein 1

By Ralf Kist

Classification **Homo sapiens** • Endothelial PAS domain protein 1

Related TF(s) • EPAS1

Homologs (3) • EPAS1

Links [ENSC00000125398*](#) (Ensembl) [6662*](#) (Entrez Gene) [Homologene*](#) [608160*](#), [114290*](#) (iOMIM)

Synonyms [SRA1](#), [CMPD1](#), [CMD1](#)

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(b) NR2E1 

nuclear receptor subfamily 2, group C, member 1

By Ralf Kist

Classification **Homo sapiens** • Nuclear Receptor subfamily 2, group C, member 1

Related TF(s) • NR2E1

Homologs (3) • NR2E1

Links [ENSC00000125398*](#) (Ensembl) [6662*](#) (Entrez Gene) [Homologene*](#) [608160*](#), [114290*](#) (iOMIM)

Synonyms [SRA1](#), [CMPD1](#), [CMD1](#)

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(h) EPAS1 

endothelial PAS domain protein 1

By Ralf Kist

Classification **Homo sapiens** • Endothelial PAS domain protein 1


Related TF(s) • EPAS1

Homologs (3) • EPAS1

Links [ENSC00000125398*](#) (Ensembl) [6662*](#) (Entrez Gene) [Homologene*](#) [608160*](#), [114290*](#) (iOMIM)

Synonyms [SRA1](#), [CMPD1](#), [CMD1](#)

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(c) NR2E1 

nuclear receptor subfamily 2, group C, member 1

By Ralf Kist

Classification **Homo sapiens** • Nuclear Receptor subfamily 2, group C, member 1


Related TF(s) • NR2E1

Homologs (3) • NR2E1

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(i) EPAS1 

endothelial PAS domain protein 1

By Ralf Kist

Classification **Homo sapiens** • Endothelial PAS domain protein 1


Related TF(s) • EPAS1

Homologs (3) • EPAS1

Links [ENSC00000125398*](#) (Ensembl) [6662*](#) (Entrez Gene) [Homologene*](#) [608160*](#), [114290*](#) (iOMIM)

Synonyms [SRA1](#), [CMPD1](#), [CMD1](#)

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(d) NR2E1 

nuclear receptor subfamily 2, group C, member 1

By Ralf Kist

Classification **Homo sapiens** • Nuclear Receptor subfamily 2, group C, member 1


Related TF(s) • NR2E1

Homologs (3) • NR2E1

Links [ENSC00000125398*](#) (Ensembl) [6662*](#) (Entrez Gene) [Homologene*](#) [608160*](#), [114290*](#) (iOMIM)

Synonyms [SRA1](#), [CMPD1](#), [CMD1](#)

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(j) LMX1A 

limb motor 1, alpha

By Ralf Kist

Classification **Homo sapiens** • Limb motor 1, alpha


Related TF(s) • LMX1A

Homologs (3) • LMX1A

Links [ENSC00000125398*](#) (Ensembl) [6662*](#) (Entrez Gene) [Homologene*](#) [608160*](#), [114290*](#) (iOMIM)

Synonyms [SRA1](#), [CMPD1](#), [CMD1](#)

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(e) Nr2e1 

nuclear receptor subfamily 2, group C, member 1

By Ralf Kist

Classification **Homo sapiens** • Nuclear Receptor subfamily 2, group C, member 1


Related TF(s) • Nr2e1

Homologs (3) • Nr2e1

Links [ENSC00000125398*](#) (Ensembl) [6662*](#) (Entrez Gene) [Homologene*](#) [608160*](#), [114290*](#) (iOMIM)

Synonyms [SRA1](#), [CMPD1](#), [CMD1](#)

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(k) NFIA 

nuclear factor 1, A

By Ralf Kist

Classification **Homo sapiens** • Nuclear factor 1, A

Related TF(s) • NFIA

Homologs (3) • NFIA

Links [ENSC00000125398*](#) (Ensembl) [6662*](#) (Entrez Gene) [Homologene*](#) [608160*](#), [114290*](#) (iOMIM)

Synonyms [SRA1](#), [CMPD1](#), [CMD1](#)

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NR2E1

nuclear receptor subfamily 2,
group E, member 1

By [Charles N. de Leeuw](#) and [Elizabeth M. Simpson](#) (email authors)

Classification *Homo sapiens* » Zinc-coordinating Group » Hormone-nuclear Receptor Family » Subfamily 2 (HNF4, RXR, TR2/4, DHR78, TLL, COUP-TF and EAR2, NR2A2/3, and 19 individual genes)

Related TF(s) [Nr2e1](#) [Nr2e1](#)

Homologs [\(none defined here\)](#)

Links [ENSG00000112333](#) (Ensembl) [7101](#) (Entrez Gene)
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Synonyms XTLL, TLX, TLL

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NR2E1 is a highly conserved([pmid:12079282](#)) human orphan nuclear receptor, consisting of a DNA-binding domain, hinge region, and ligand-binding domain. It is classified as an orphan as no ligand has yet been identified.

NR2E1 is important for brain development and its function has been shown to be conserved in '[Drosophila](#)'([pmid:2364433](#)), [Zebrafish](#)([pmid:17127102](#)), and mouse([pmid:11997145](#)). The mouse phenotype

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In humans, many different disorders including schizophrenia, socio- and psychopathy, and microcephaly have been investigated as having a potential underlying defect in '*NR2E1*'(pmid:17054721)(pmid:17655765). Recently, a study has found a genetic association between a single nucleotide polymorphism in human '*NR2E1*' and Bipolar Disorder Type I(pmid:18205168). Some studies have also indicated a role of NR2E1 in brain tumour formation, such as glioblastomas(pmid:18772396)(pmid:17135416)(pmid:16530701)(pmid:20360385). The closest homolog to NR2E1 is NR2E3 which has been demonstrated to cause Enhanced S-Cone Syndrome and implicated in some Retinitis Pigmentosa(pmid:10655056)(pmid:17564971).

Molecularly, NR2E1 is described in the literature as mainly functioning

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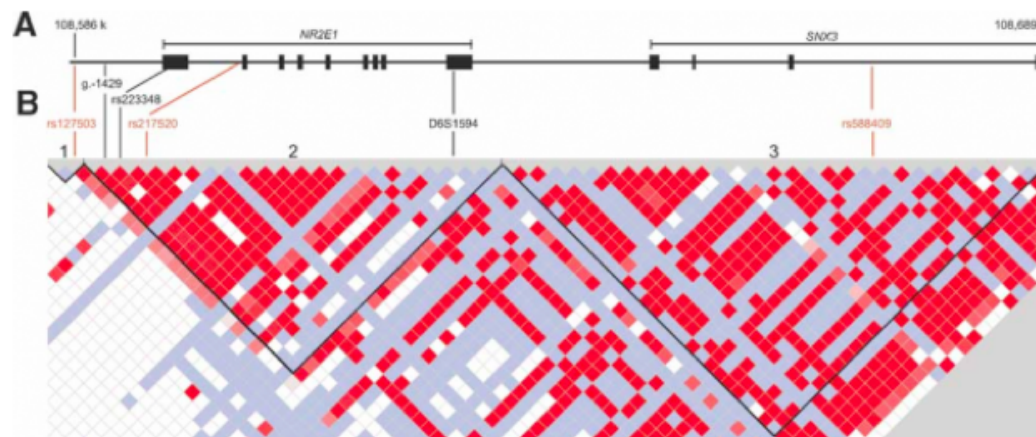


FIGURE 1 Linkage disequilibrium map with six markers chosen for association analysis in bipolar disorder and schizophrenia

Genomic structure of *NR2E1* and location of six markers selected for association analyses in bipolar disorder and schizophrenia.

A: Schematic of *NR2E1* and closest neighboring gene *SNX3*.

B: Linkage disequilibrium (LD) map generated from the HAPMap data CEU population set. LD blocks (1, 2, and 3) were generated using the "Solid spine of LD" method. Markers that are tag SNPs are indicated in red. (Kumar *et al.* 2008)



This figure is from a publication by the authors of this article. Please [click here](#) to view the publication's entry in Pubmed (PMID 18205168).

modify annotation

modify image

delete figure



Links

Authoring Interface - 4

Links

Links for this section

Links for other sections

[Dr. Elizabeth M. Simpson \(new window\)](#) [■] Research on NR2E1 at the Centre for Molecular Medicine and Therapeutics, University of British Columbia [\(delete\)](#)

[Nuclear Receptor Signaling Atlas \(new window\)](#) [■] Home page [\(delete\)](#)

Add an external link

Title

URL

Add

Description

TFBS Data Submission

Submit binding sites

 [About this section](#)

Mandatory fields

Your name	Dimas Yusuf
Email	dyusuf@cmmmt.ubc.ca
Re-enter email	dyusuf@cmmmt.ubc.ca
TF or TF complex Example: "NFE2L2" or "NFE2L2-MAFK"	Foxa2
Gene IDs of TF or TF complex Example: "ENSG00000116044" or "4780, 7975"	ENSRNOG00000013133
Sequences Please separate your sequences with line breaks	

Data within TFe

Summary

Forkhead box M1 superfamily which the cell cycle ^{[2][3][4]} angiogenesis ^[9], m exons of which tw

Overview

Text provided by the author with citations, ideally 500 words

[WEB](#) [PDF](#) [XLS](#) [API](#)

Structure

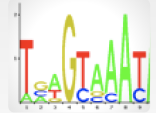
HNF4α contains tl (LBD). The DBD co comprised of 12 a was found in the l essential fatty aci

Overview

Text provided by the author with citations, ideally 200 words

[WEB](#) [PDF](#) [XLS](#) [API](#)

TFBS



TFBS logos

Tile of mini logos of TFBS models, available in TFe

[WEB](#) [PDF](#) [XLS](#) [API](#)

Targets

Murine knock out transcription facto the hematopoietic is not appropriate mediated by bindi

Overview

Text provided by the author with citations, ideally 200 words

[WEB](#) [PDF](#) [XLS](#) [API](#)

Protein

There are at least because attempts confirmed functio commonly overex the gene coding r

Isoforms

Text provided by the author with citations, ideally 200 words

[WEB](#) [PDF](#) [XLS](#) [API](#)

Interactions

The HMG domain believed that thes binding to DNA. N specific activation subunits of the m

Overview

Text provided by the author with citations, ideally 200 words

[WEB](#) [PDF](#) [XLS](#) [API](#)

Genetics

ATF2 is situated o associated with tu variants were gen instance inhibiting oncogenes or turn

Overview

Text provided by the author with citations, ideally 250 words

[WEB](#) [PDF](#) [XLS](#) [API](#)

Expression

During the earlies derived transcripti mammalian embry restricted to the d development. It is

Overview

Text provided by the author with citations, ideally 200 words

[WEB](#) [PDF](#) [XLS](#) [API](#)

Ontologies

molecular_functio binding (GO:00 nucleic aci DNA bi

Gene Ontology

Associated GO terms from Entrez Gene and Gene Ontology in tree and table view

tree view

[WEB](#) [PDF](#) [XLS](#) [API](#)

table view

[WEB](#) [PDF](#) [XLS](#) [API](#)

Papers

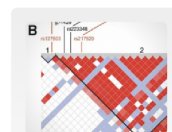
●● (2004) Nixon J lymphocyte subp View abstract and

[review article](#) ●

Papers

A list of relevant papers provided by the author

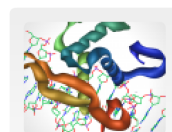
[WEB](#) [PDF](#) [XLS](#) [API](#)



Figures

Diagrams provided by the author with caption text and citations

[WEB](#) [PDF](#) [XLS](#) [API](#)



Structures

Prediction of DBD structure as an image and downloadable PDB file

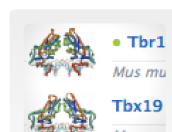
[WEB](#) [PDF](#) [XLS](#) [API](#)

image

[WEB](#) [PDF](#) [XLS](#) [API](#)

PDB file

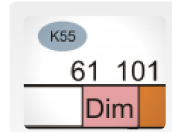
[WEB](#) [PDF](#) [XLS](#) [API](#)



Family

Tile of other TFs that belong to the same family based on DNA binding domain characteristics

[WEB](#) [PDF](#) [XLS](#) [API](#)



Figures

Diagrams provided by the author with caption text and citations

[WEB](#) [PDF](#) [XLS](#) [API](#)

PLZF contains 9 ca transcriptional repr in most cases bin The predicted bin interactions with f

Overview

Text provided by the author with citations, ideally 150 words

[WEB](#) [PDF](#) [XLS](#) [API](#)

Sequence
GTTCCCGGCCCTCTT
ACCTGCCCTCCCT

Binding site profiles

The logos, position frequency matrix (PFM), and sequence table of TFBS models

logos

[WEB](#) [PDF](#) [XLS](#) [API](#)

PFM

[WEB](#) [PDF](#) [XLS](#) [API](#)

sequence table

[WEB](#) [PDF](#) [XLS](#) [API](#)

ATOH1TM (human)
E2F1TM (human)
FGFBP1TM (human)

Targets (author curated)

Genomic targets provided by the author

[WEB](#) [PDF](#) [XLS](#) [API](#)

ESR1TM (human) p
G6pcTM (mouse) p
ID1TM (human) paz

Targets (automatic)

Genomic targets provided by PAZAR

[WEB](#) [PDF](#) [XLS](#) [API](#)

Apart from ligand PPARy1 on Ser82 by reducing its ab residue by Cdk9, the receptor^{[2][3]} I

Covalent modifications

Text provided by the author with citations, ideally 200 words

[WEB](#) [PDF](#) [XLS](#) [API](#)

1 EstradiolTM CID 5757
2 TretinoinTM CID 444795

Ligands

Interacting ligands (i.e. messengers) from the author

[WEB](#) [PDF](#) [XLS](#) [API](#)

Interactor
BCL6TM (human)
CEBPATM (human)

Interactions (author curated)

Protein interactors provided by the author

[WEB](#) [PDF](#) [XLS](#) [API](#)

CREB1TM (TF)
HNF1ATM (TF)

Interactions (automatic)

Protein interactors provided by BioGRID with additional author annotation

[WEB](#) [PDF](#) [XLS](#) [API](#)

FOXO1_HUMAN TF0000881TM
FOXO3_HUMAN TF0000812TM
Transcriptional

Anoxia 2.8 x 10⁻⁰¹ M
Signs and Sympt
Neoplasms by Sit
10⁻⁰¹ Carcinoma

MeSH cloud (disease)

TF-to-disease links based on NCBI data, from MeSHOP

[WEB](#) [PDF](#) [XLS](#) [API](#)

absent spleen (MP increased lympho abnormal spleen increased splenoc abnormal sensory MGI mammalian phenotype terms

Associated mouse phenotype terms from MGI

Associated mouse phenotype terms from MGI

[WEB](#) [PDF](#) [XLS](#) [API](#)

33. PB-BDCA4+
34. PB-CD14+
35. PB-CD56+
36. PB-CD4+ T

Expression (GNF)

Microarray data from the GNF Expression Atlas 2, as provided by the UCSC Genome Browser

[WEB](#) [PDF](#) [XLS](#) [API](#)

Mouse Brain Exp
Retinoic acid re

Expression (ABA)

A link to the mouse brain expression data from Allen Brain Atlas

[WEB](#) [PDF](#) [XLS](#) [API](#)

Other information

Mus musculus » Zin nuclear Receptor Fa TR2/4, DHR78, TLL, and 19 individual g

• HNF4A

Classification

TF classification information (group.

ENSMUSG00000017 Gene) Homologene Tcf4, Tcf14, Nr2a1,

External links

Links to external resources such as

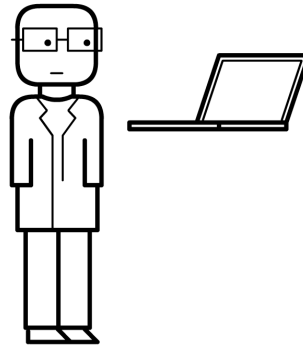
Johns Hopkins I
s. (2) Departme
Centre for Mole
s at the Child ar
f British Columbi

Authorship

Authors' names, contact information.

URL-based Data Extraction

- 1 Bioinformatician writes a small "script" program to automatically retrieve the desired information from the TFe Web API



Get all **TFe TFIDs**
For each **TFe TFID**,
Get the TFID's **symbol**
If symbol equals "ATF3",
Get **MeSH disease term**

- 2 The program is set to run on its own

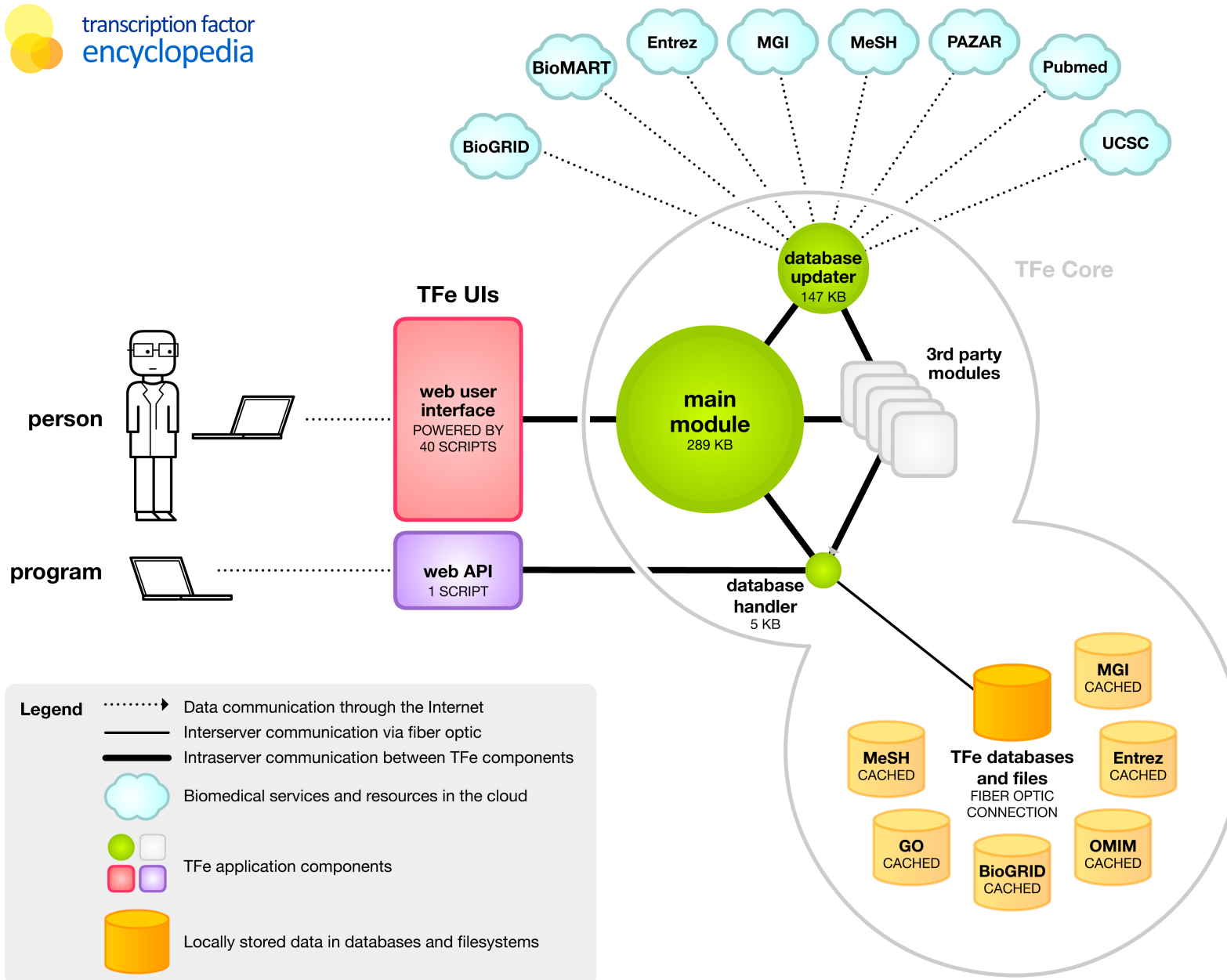


Get all **TFe TFIDs**
<http://www.cisreg.ca/cgi-bin/tfe/api.pl?code=all-tfids>

118
119
120
...

Web API

System Map



Author Recruitment

- **Stage 1 (alpha)**
 - Friends
 - Friends of Friends
 - ~10
- **Stage 2 (beta)**
 - PubMed mining to identify experts (> 10 published articles about a TF) with email solicitation
 - ~100

TFe Authors



+1 Australia

~15% of contacted experts agreed to participate

~60% of participants completed an entry

Author Motivation

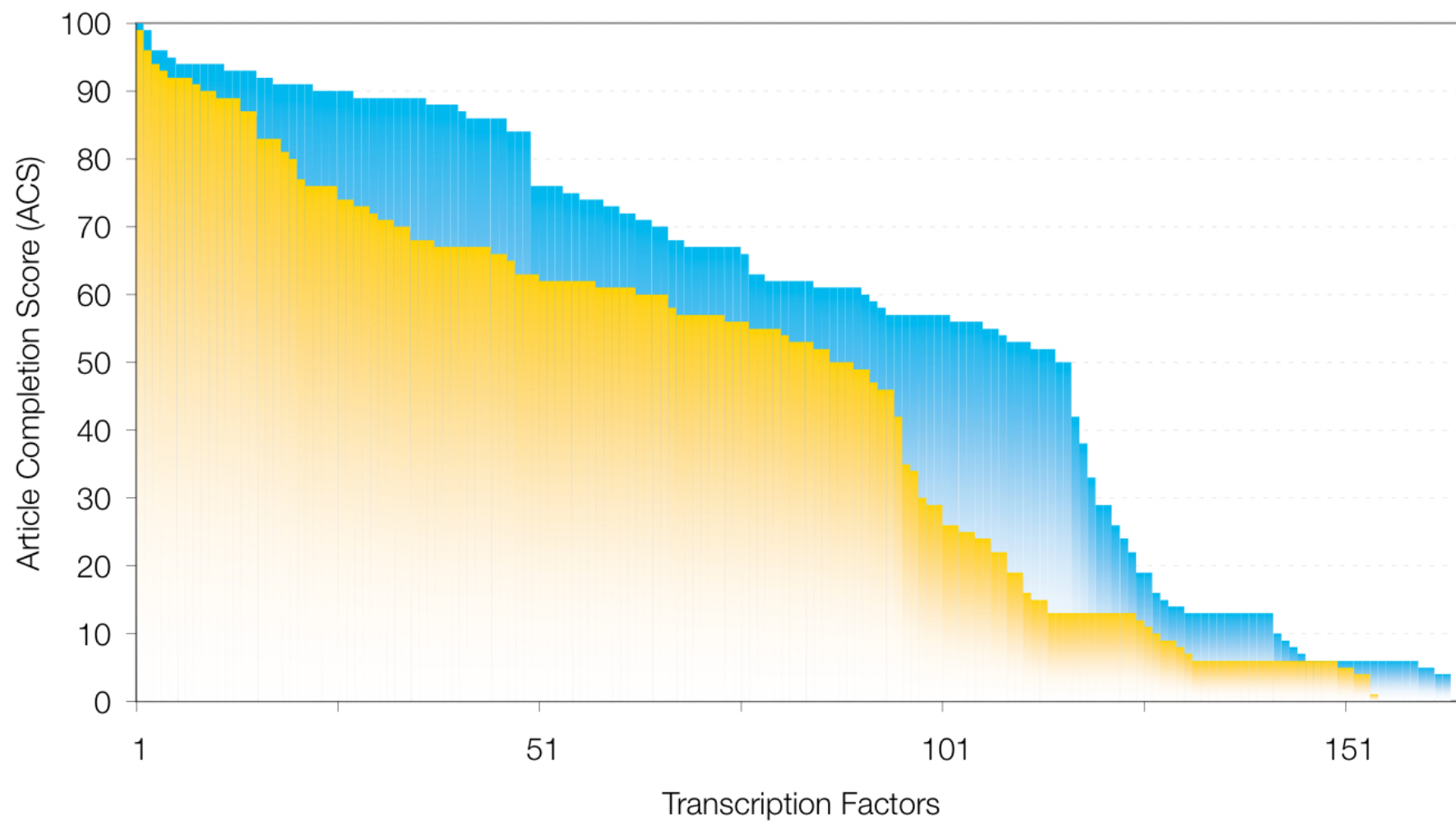
- **Sponsoring Journal**
 - Scientists more willing to commit time and effort to projects that give authorships
- **Progress Scores**
 - Many people are competitive and like to see their work achieve the best possible grade
- **Peer Review**
 - Respect of peers and fixing weaknesses

TFe Article Scoring Procedure

Tab	Scoring element	Target	Maximum points	Weight
Summary	Overview text	500 words	10 points	8.333%
Summary	References in overview text	3 references	5 points	4.167%
Summary	Figures	1 figure	10 points	8.333%
Structure	Overview text	200 words	5 points	4.167%
TFBS	Overview text	150 words	5 points	4.167%
TFBS	Binding site profiles	1 binding site profile	10 points	8.333%
Targets	Overview text	200 words	5 points	4.167%
Targets	Targets	10 targets in total (both author and auto)	10 points	8.333%
Protein	Isoforms text	200 words	5 points	4.167%
Protein	Covalent modifications text	200 words	5 points	4.167%
Interactions	Overview text	200 words	5 points	4.167%
Interactions	Ligands	1 ligand	1 point	0.833%
Interactions	Interactions	10 interactors in total (both author and auto)	10 points	8.333%
Interactions	Interactions	All “nature of interaction” fields annotated	10 points	8.333%
Genetics	Overview text	250 words	5 points	4.167%
Expression	Overview text	200 words	5 points	4.167%
Papers	Papers	15 papers	10 points	8.333%
Papers	Papers	3 papers marked as “recommended”	3 points	2.500%
(all)	Links	1 link	1 point	0.833%
			120 points	100%

Progress of Transcription Factor Articles on TFe

Comparison between May 15th (yellow) and June 5th (blue), 2009



June 29th, 2010

<http://www.cisreg.ca/cgi-bin/tfe/articles.pl?tfid=444>

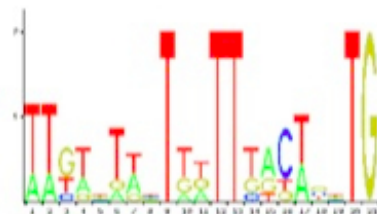
FOXO4

Homo sapiens forkhead box O4By Astrid Eijkelenboom¹ & Marrit Putker^{2*}

FOXO4 (also known as AFX) is a member of the Forkhead family of transcription factors¹ and forms a subclass with FOXO1 (FKHR), FOXO3A (FKHRL1) and FOXO6. The FOXO transcription factors are key players in regulation of cell-fate decisions (cell death, cell proliferation and cell metabolism, see FIGURE 1) and are considered to be tumor suppressors². In model organisms FOXO was shown to increase longevity³ and this function was shown to be dependent on FOXO's ability to induce oxidative stress inducing genes⁴. The FOXO subclass members 1, 3a and 4 are ubiquitously expressed, but their respective levels differ per cell type or organ⁵, whereas FOXO6 expression seems to be restricted to the brain. All FOXOs consist of a forkhead DNA binding domain, nuclear localization signal (NLS), nuclear export sequence (NES) and transactivation domain (TA). The DNA binding domain is highly conserved within the FOXO family and is shown to bind the core consensus DNA sequence 5' TTGTTTAC 3'⁵. Overlap in target genes is thus expected and has been shown. Indeed studies in FOXO1, FOXO3a and FOXO4 knockout mice show that FOXO tumor suppressive function is intact in mice lacking any combination of two, but not all three, FOXO genes⁶. Any functional specificity in function is likely to be obtained through posttranslational modifications and interaction with specific co-factors. The activity of FOXO family members FOXO1, FOXO3 and FOXO4 is regulated by cellular localization and several posttranslational modifications like phosphorylation, acetylation and ubiquitination (see FIGURE 2). Some of these modifications induce a change in subcellular localization of FOXO. For instance, FOXO activity is negatively regulated by PI3-K via PKB/Akt in response to insulin through phosphorylation, resulting in translocation of the transcription factors from nucleus to cytoplasm^{7,8,9,10}, whereas stress induced kinases like JNK positively regulate FOXO nuclear localization and transcriptional activity^{11,12,13} (see FIGURE 3 for a model of the regulation of FOXO transcriptional activity by posttranslational modifications). For more information and reviews, we would like to refer to an issue of *Oncogene Reviews*, completely dedicated to the FOXO family of forkhead transcription factors (volume 27, number 16 ? April 7, 2008).

Binding sites

Using in vitro experiments, the DBD of the FOXO proteins has been shown to bind the consensus sequence 5' TTGTTTAC 3'^{5,16}. Although overlap in target genes between the different members of the FOXO family has been shown, specificity in function is likely to be obtained through posttranslational modifications and interaction with specific co-factors. The TFBS below is based upon data obtained for FOXO4.

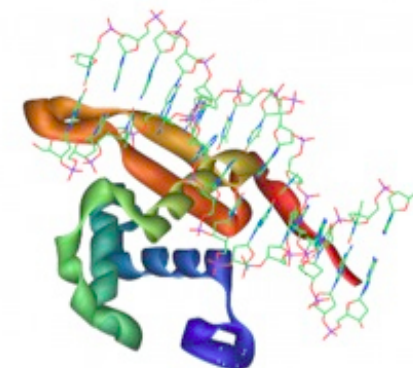


Binding profile from Pazar

Project name TFe
 TF name FOXO4_HUMAN
 TF species None
 Pazar ID TF0000771
 Ensembl ID ENST00000399704

This data is sourced from Pazar, a public database of transcription factor and regulatory sequence annotation. <http://www.pazar.info/>

PFM	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
A	2	2	0	2	2	1	3	2	0	1	2	0	0	0	4	0	3	1	2	0	0
C	0	0	1	0	1	0	0	2	0	0	0	0	0	1	0	5	0	2	1	0	0
G	0	0	4	1	2	1	1	1	0	2	2	0	0	2	2	1	0	3	2	0	7
T	5	5	2	4	2	5	3	2	7	4	3	7	7	4	1	1	4	1	2	7	0



Protein structure of FOXO4

FOXO proteins consist of four domains: a highly conserved DNA binding domain (DBD), a nuclear localization signal (NLS), a nuclear export sequence (NES) and a C-terminal transactivation domain. The structure of FOXO4 DBD with DNA has been resolved and shows high similarity with other forkhead DBDs¹⁴. We would like to refer to a recent review for more information on structural studies of forkhead transcription factors and the potential effects of posttranslational modifications on DNA binding¹⁵.

Classification

Group	Winged Helix-Turn-Helix
Family	Forkhead Domain Family
Subfamily	Not specified

Resources

Entrez Gene	4303
Ensembl	ENSG00000184481
Refseq	NP_005929, NP_001164402
Uniprot	P98177
OMIM	300033
Synonyms	MLLT7, AFX1, MGC120490, AFX

About

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Contact

Affiliation(s): (1) The Netherlands. (2) University Medical Centre Utrecht, Utrecht, Utrecht, The Netherlands. (*) Correspondence: Marrit Putker. Email: m.putker@umcutrecht.nl

Displaying the first 3 of 4 figures. [See more on site =](#)

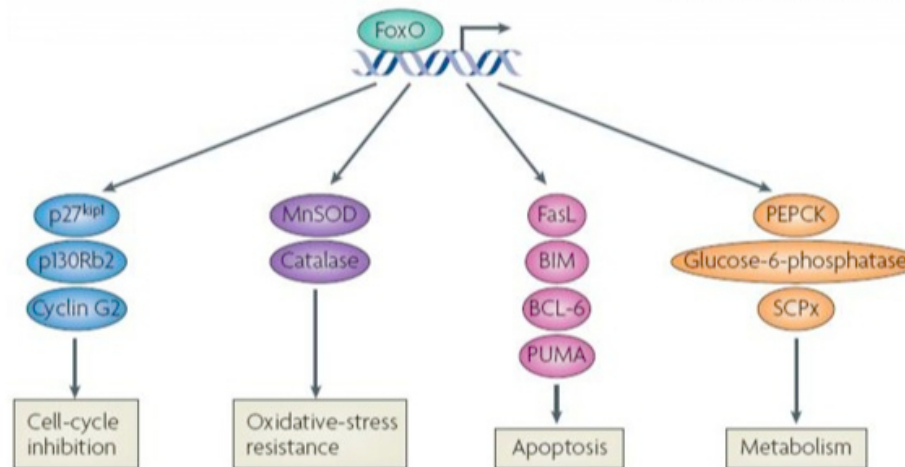


FIGURE 1 | Figure 1: Transcriptional outputs of FoxO activity. Increased class O forkhead box transcription factor (FoxO) activity participates in several cellular processes, most notably inhibition of the cell cycle, regulation of cell death, protection from cellular (oxidative) stress and regulation of cellular metabolism (gluconeogenesis and fatty-acid oxidation). FoxO-regulated genes that are linked to these processes are indicated. The outcome of FoxO function is likely to be determined in conjunction with other genetic determinants, for example, the function of the tumour-suppressor protein p53. MnSOD, manganese superoxide dismutase; PEPCK, phosphoenolpyruvate carboxykinase; SCPx, sterol carrier protein-x.

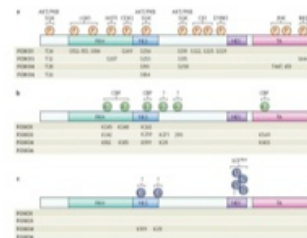


FIGURE 2 | Figure 2: Summary of post-translational modifications on the various FoxO isoforms. The class O forkhead box transcription factor (FoxO) isoforms contain a forkhead domain (FKH, the DNA-binding domain), a nuclear localization signal (NLS), a nuclear export sequence (NES) and a transactivation domain (TA). Modified residues are indicated and amino-acid numbers are given for the individual isoforms. Enzymes responsible for these modifications are indicated above the modification. However, when a residue is conserved but no positive evidence for the modification has been obtained in other isoforms, the residue is not specified for those isoforms.

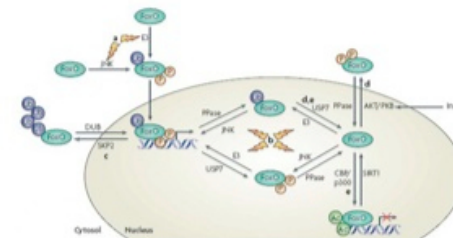


FIGURE 3 | Figure 3: An integrated model for FoxO activity control through stress-induced post-translational modifications. Following increased cellular oxidative stress (for example, by hydrogen peroxide treatment of cells) class O forkhead box transcription factors (FoxOs) translocate from the cytosol to the nucleus. This process correlates with c-Jun N-terminal kinase (JNK)-mediated phosphorylation (residues Thr447 and Thr451 in FOXO4) and monoubiquitination of FoxO. The cellular location at which these modifications occur is not known but two possibilities are indicated: in the cytosol (a) or in the nucleus (b). Monoubiquitination might occur in either location but the identity of the E3 ligase is unknown. (continued on site)

Isoforms

Two isoforms of FOXO4 (AFX) have been described in non-cancer cells: AFX7 (regular) and AFX7 (lacking aminoacid 58-112 and thus the first 16 aminoacids of the forkhead domain). The AFX7 splice variant shows a somewhat different transcriptional activity compared to the regular form of AFX. It is even proposed that the two isoforms antagonize each other^{20,21}. In cancer cells, three other isoforms of FOXO4 have been described. Two of them are produced by aberrant splicing: AFXtr1 and AFXtr2 are short N-terminal FOXO4 proteins of respectively 90 and 101 amino acids long. However, no protein expression could be detected of these splice variants. The third isoform identified is translated from a downstream start site and is thus a N-terminally deleted isoform: AFX7(198-505). This isoform of FOXO4 shows similar transcriptional activity as AFX7, not being able to induce apoptosis and interfering with AFX7 function when both overexpressed²¹.

Covalent modifications

FOXO transcription factors are regulated by several posttranslational modifications including phosphorylation, acetylation and ubiquitination. The precise mechanisms and the effects of these modifications are still not completely understood. Several modifications might interfere with DNA binding or affect binding with other proteins involved in the localization of the transcription factor. Upon insulin signaling, active PKB (AKT) phosphorylates FOXO4 on three sites: T28, S193 and S258⁸. Close relative of PKB SGK is able to phosphorylate FOXO on the same sites²². These phosphorylations lead to inhibition of FOXO4 activity due to reduced DNA binding and to binding to 14-3-3, leading to relocalization of FoxO4 to the cytoplasm^{23,24,25}. In the cytoplasm, FOXO4 can be polyubiquitinated by Skp2, leading to proteosomal degradation²⁶. Elevated cellular levels of ROS activate JNK, which in turn phosphorylates FOXO4 at at least two sites: T447, T451. Phosphorylation at these sites activates FOXO4 by inducing its nuclear localization¹¹. FOXO4 is monoubiquitinated at several sites by MDM2, leading to nuclear localization and thus induction of transcriptional activity²⁷. Deubiquitination occurs by DUB USP7/HAUSP²⁸. P300 and CBP (Creb binding protein) regulate FOXO4 activity by acetylating it on several sites. Deacetylation occurs by HDAC and Sirt1²⁹. (continued on site)

Other Features

- **Predicted Binding Domain Structures (Phil Bradley, FHCRC)**
- **MeSH Over-representation Profiles – Attribute Clouds (Warren Cheung)**
- **TF Binding Site Profiles (Elodie Portales-Casamar)**
- **Parent-Child Relationships (inherit ortholog content if no species-specific version)**

Sustainability

- **Unclear if it can be sustained – not proven**
- **Continuing journal sponsorships to motivate authors to update articles (or for new authors to take on abandoned articles)**
- **Focused TF Family-based papers (e.g. Nuclear Receptors)**

Lessons Learned

- **Motivation for authors – Sponsor Journals**
- **Simple interfaces with extremely short learning periods to keep authors' attention**
- **Dedicated manager to engage authors, suggest changes and resolve issues**
- **Focus allows the system to be tailored to the needs of the field**

Thanks!

THE LAB

- **Dimas Yusuf**
- Elodie Portales-Casamar
- Warren Cheung
- Stefanie Butland
- Magdalena Swanson

- Virginie Bernard
- Rebecca Hunt-Newbury
- Andrew Kwon
- Miroslav Hatas
- David Arenillas
- Jonathan Lim
- Dora Pak

- And many alumni

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- Frances Sladek (UC – Riverside)

- ~100 TFe Authors – The people most responsible for the success of the TFe

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- Genome Canada / Genome BC
- Canadian Institutes for Health Research
- Canada Foundation for Innovation

