# Unified nomenclature for the winged helix/forkhead transcription factors

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The winged helix/forkhead class of transcription factors is characterized by a 100-amino-acid, monomeric DNAbinding domain. The structure of the DNA-binding domain of one of the class members, hepatocyte nuclear factor 3  $\gamma$  (HNF3 $\gamma$ ), in a complex with a DNA target has been solved (Clark et al. 1993). The DNA-binding domain folds into a variant of the helix-turn-helix motif and is made up of three  $\alpha$  helices and two characteristic large loops, or "wings." Therefore, the DNA-binding motif has been named the winged helix DNA-binding domain.

Over the past 9 years since the identification of the first member of this class, the Drosophila melanogaster gene Fork head, >100 members of this gene family have been identified (for review, see Kaufmann and Knöchel 1996) in species ranging from yeast to human. The rapid accumulation of sequences by many different laboratories has led to the use of multiple names and classification systems, making it very difficult to follow the literature and to name newly characterized winged helix/ forkhead transcription factors. This problem was recognized and discussed at the first International Meeting on Forkhead/Winged Helix Proteins, held in La Jolla, California, in November 1998. At that time a proposal was developed to standardize the nomenclature for these proteins. Fox (Forkhead box) was adopted as the unified symbol for all chordate winged helix/forkhead transcription factors. A winged helix/forkhead nomenclature committee was elected to implement this proposal, in consultation with the community at large. This final proposal has been endorsed by >20 scientists<sup>1</sup> as well as the Human and Mouse Gene Nomenclature Committees.

#### The Fox subclasses

All Fox proteins contain the characteristic 100-aminoacid winged helix domain, that defines this class of tran-

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which encode, for instance, transactivation or trans-repression domains, are highly divergent. We have utilized phylogenetic analysis to delineate 15 subclasses for all known chordate Fox proteins. The analysis included chordate sequences obtained from GenBank and sequences submitted directly to the nomenclature committee. The Fox domains of the proteins were aligned using Clustal W (Thompson et al. 1994), and a neighborjoining tree was generated using PAUP\* 4.0 (Swofford 1999); (Fig. 1). This phylogenetic tree will be updated regularly as new sequences are discovered and may be downloaded from http://www.biology.pomona.edu/fox. html. A complete phylogenetic analysis of all known forkhead proteins will be published elsewhere (D. Martínez and J.E. Signorovitch, pers. comm.).

scription factors. Other portions of the Fox proteins,

#### Numbering

Fox proteins were assigned to individual subclasses based on the phylogenetic analysis described above. Subclasses were designated by a letter, and within each subclass proteins were given an Arabic numeral. Therefore, the actual name of any Fox protein is "Fox, subclass N, member X", or for example, Foxd3. Abbreviations for the chordate Fox proteins will contain all uppercase letters for human (e.g., FOXD3); only the first letter capitalized for mouse (e.g., Foxd3); and the first and subclass letters capitalized for all other chordates (e.g., FoxD3). Current assignments for the chordate Fox proteins are listed in Table 1, together with previously used names. Whenever possible we have assigned the same name to ortholog proteins from different species. In a few cases where the phylogenetic affinities were not well resolved by the tree in Figure 1 (e.g., Foxd1 and Foxd2), a within-class phylo-

<sup>&</sup>lt;sup>4</sup>Fox Nomenclature Committee.

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<sup>&</sup>lt;sup>1</sup>The following scientists have endorsed the use of this nomenclature system: Frederic G. Barr, William Biggs, Peter Carlsson, James E. Darnell, Sven Enerbäck, Peter Gruss, Brigid Hogan, Andrew D. Hollenbach, Robert Hromas, Tsutomu Kume, Trish Labosky, Eseng Lai, Suzanne C. Li, Naoyuki Miura, Sally A. Moody, Sharon Plon, Hiroshi Sasaki, Günther Schütz, Mathias Treier, Malcolm Whitman, Jeffrey Whitsett, Stella Zannini, and Ken Zaret.

Fox nomenclature system



**Figure 1.** (*Continued on p. 144*) Neighbor-joining phylogeny of chordate Fox proteins based on the amino acid sequence of the Fox domain. The distance measure used was mean character difference. The tree was rooted using *Homo* QRF1 (AF086040) as the outgroup. The numbers in the interior branches are bootstrap percentages. For each protein we indicate the organism (genus), the name, the accession number, and the proposed Fox name.

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Ciona intestinalis	ci cos46 1	Z83861	FoxD6	Homo sapiens	hs HBF2	X74143	FOXG1a	Mus musculus	mm Mf2	AF023915	Foxd2
Cynops pyrrhogaster	cp FHD	D64021	FoxA4	Homo sapiens	hs HBF3	X74144	FOXG1c	Mus musculus	mm MFH1	S63607	Foxc2
Danio rerio	dr axial	Z2762	FoxA2	Homo sapiens	hs HBFG2	X78202	FOXG1a	Mus musculus	mm MFH1	X92499	Foxc2
Danio rerio	dr 8F1	AF067204	FoxG1	Homo sapiens	hs HFH3	L13203	FOX11	Mus musculus	mm MFH1	X74040	Foxc2
Danio reno	dr 1Kd2 4+ 6-45	AF052245 AE062245	FOXA3	Homo sapiens	NG RFH4 he LICLA	V00340	FUXUIB EDV Ha	Mus musculus Mus musculus		1 26507	Foxer
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Danio rerio	dr fkd5	AF052248	FoxB1	Homo sapiens	hs HFH4 (DNA)	X99351	FOXJ1a	Mus musculus	mm PFrk	AF060873	
Danio rerio	dr fkd6	AF052249	FoxD3	Homo sapiens	hs HFH11A	U74612	FOXM1a	Mus musculus	mm Trident	Y11245	Foxm1
Danio renio	dr fkd7	AF052250	FoxA1	Homo sapiens	hs HFH11B	U74613	FOXM1b	Mus musculus	mm TWH	U90538	Foxb1a
Danio rerio	dr fkd8	AF052251	FoxD5	Homo sapiens	hs HFKH4	X94553	FOXE2	Mus musculus	mm WHN	X81593	Foxn1
Danio rerio	dr fkd9	AF052252	FoxD1	Homo sapiens	hs HFKH5	U87393	FOXB1	Molgula oculata	mo FH1	AF007905	FoxA5
Danio rerio	dr FKH5	AF052651	FoxB1	Homo sapiens	hs HNF3a	U39840	FOXA1	Molguia oculata	mo MoccFH1	AF082992	FoxA5
Danio rerio	dr zFKHR	AF114282	FoxO5	Homo sapiens	hs HTLF	U57029 M94653	FOXN2	Oryzias latipes	ol Mefkh1	AB001573	FoxA3
Fugu rubripes	fr whn	X97021	FoxN1	Homo sapiens	hs ILF1	U58196 S41456	FOXK1a	Oryzias latipes	ol MeHNF3ß	AB001572	FoxA2
Gallus gallus	gg CBF1	U47275	FoxG1	Homo sapiens	hs ILF2	U58197 S41457	FOXK1b	Rattus norvegicus	m BF1	M87634	FoxG1
Gallus gallus	gg CBF2	U47276	FoxD1	Homo sapiens	hs ILF3	U58198	FOXK1c	Rattus norvegicus	m fkh2 (DNA)	A4956527	
Gallus gallus	gg cFKH1	Y17794	FoxC1	Homo sapiens	hs INS1	U83113	FOXM1c	Rattus norvegicus	m FREACT (DNA)	AA817785	
Gallus gallus	gg cFKHR	AF114261	Fox01	Homo sepiens	hs MFH1	Y08223	FOXC2	Rattus norvegious	m FREAC1 (DNA)	AA819437	
Gallus gallus	99 CWH1	U37272	FoxD2	Homo sapiens	hs QRF1 (DNA)	AF086040	i	Rattus norvegicus	a HFH1	L13201	1
Gallus gallus	gg CWH2	U37273	FoxC2	Homo sapiens	hs TITF2	Y13386	FOXE1	Rattus norvegicus	m HFH2	L13202	FoxD3
Gallus gallus	gg CWH3	U37274	FoxD3	Mus musculus	mm AFXh	AF114260	Foxod	Rattus norvegicus	m HFH4	L36388	FoxJ
Gallus gallus	99 MFH1	U95823	FoxC2	Mus musculus	mm BF1 (Hmbr1)	U36/60	- xgi	Rattus norvegicus		L13205	
Homo sapiens	hs AF6q21	AJ001589	FOX02	Mus musculus	mm BF2	L38607	Foxd1	Rattus norvegicus		L13206	
Homo sapiens	hs AF6q21 (exon 1)	AJ001590	FOX02	Mus musculus	mm FAST1	AF17770	Foxh1	Rattus norvegicus	m HFH7	L13207	FoxEs
Homo sapiens	hs AFX1	Y11284	FOX04	Mus musculus	mm FAS12	AF069303	Foxh2	Kattus norvegicus	M HFHBF2	L13192	FoxD2
Homo sapiens	hs AFX1 (DNA exon 2)	Y11285	F0X04	Mus musculus	mm FASI2	AF0/9514	Foxh2	Kattus norvegicus	Ш НГНВГЗ .: 111700	L13193	:
Homo sapiens	hs AFX1 (partial)	U10072	FOX04	Mus musculus	ШП FASI2	AF110305	roxn2	Kattus norvegicus	m HNF36	100047	FOXAZ
Homo sapiens	he AFX1(DNA exon 3)	Y11286	FOX04	Mus musculus	rmm 11Kn 7	X/1939	Foxe1	Kanus norvegicus		100448	FOXA3
Homo sapiens	ns ALV (PAX3-FKHR)	002368	POX018	Mus musculus		X80308	Foxd4	Kattus norvegicus		U63112	FoxM1
Homo sapiens	hs ALV (PAX3-FKHK)	U02308	FUXU18	Mus musculus		X/194U X74044	POX04	Kanus norvegicus	m 1172	11321	LOXE1
Homo sapiens	hs CHES1	U68723	FOXN3	Mus musculus	mm fkh3	X71941	:	Salmo salar	ss tich	AF062086	FoxA3
Homo sapiens	hs FAST1	AF076292	FOXH	Mus musculus	mm fich4	X71942	Foxb2	Xenopus laevis	xi FAST1	086020	FoxH3
Homo sapiens	hs fikh (DNA)	L12142	FOXD3	Mus musculus	mm tkh4	LECZEX	Poxb2	Xenopus leevis	XI FNG3	Z/8600	FoxU5c
Homo sapiens	hs fkh (DNA)	L12143		Mus musculus		X/1943	FoxD1a	Xenopus laevis	XI FKH5	AFU64810	FoxB1
Homo sapiens	hs FKH H3	L12141	FOXA3	Mus musculus	mm tkn5 (Mr3)	ZRGZRY	FoxD1D	Xenopus laevis		0048/3	FoxAla
Homo sapiens	hs tkh5	AFUSSOBU	FOXB1	Mus musculus	mm ikne	X/1944		Xenopus laevis	XI pintaliavis	1/160X	FoxA4a
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Homo seriens	hs FKHP (DNA)	1137335	FOXO1	Mire musculus	mm FRKHDC	110408	Foxet	Xennus laevis	xi XFD4	• *	Earch
Homo sapiens	hs FKHRL1	AF032886	FOX03a	Mus musculus	mm genesis	U41047	Foxd3	Xenopus laevis	XI XFD4'	*	FoxC2
Homo sapiens	hs FKHRL1P1 (DNA)	AF032887	FOX03b	Mus musculus	mm HFH1L	AF010405		Xenopus faevis	xI XFD5	*	FoxB2
Homo sapiens	hs FKHRP1 (DNA)	AF032888	FOX01b	Mus musculus	mm HFH2	AF067421	Foxd3	Xenopus laevis	xi XFD6	*	FoxD3a
Homo sapiens	hs FREAC1	U13219	FOXF1	Mus musculus	mm HFH4	L13204	Foxi1	Xenopus laevis	XI XFD6'	*	FoxD3b
Homo sapiens	hs FREAC1	AF085343	FOXF1	Mus musculus	mm HFH4 (DNA)	AF006200	Fox1	Xenopus laevis	XI XFD7	* :	FoxA1a
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Homo sapiens	hs FREAC2 (DNA expn1)	AF084938	FOXF?	Mus musculus	mm HNF3a (DNA)	X76684	Foxat	Xenopus laevis	XI XFD10	* *	Fortie
Homo saniens	hs FREAC3	U13221	FOXCI	Mus musculus	mm HNF3a (DNA)	X76685	Foxe1	Xenopus laevis	xI XFD11	AF116844	FoxCf
Homo sapiens	hs FREAC4	U13222	FOXD1	Mus musculus	mm HNF3a (DNA)	X76686	Foxa1	Xenopus laevis	XI XFD11	*	FoxCl
Homo sapiens	hs FREAC4	U59831	FOXD1	Mus musculus	mm HNF38	U04197	Foxa2	Xenopus laevis	xi XFD12	*	FoxD5a
Homo sapiens	hs FREAC4	U59832	FOXD1	Mus musculus	mm HNF3ß	L10409	Foxa2	Xenopus laevis	xI XFD12'	*	FoxD5b
Homo sapiens	hs FREAC5	U13223	FOXD4	Mus musculus	mm HNF38	X74937	Foxa2	Xenopus laevis	XI XFD12"	* :	FoxD5c
Homo saplens	NS FREACO	U13224 1112276	FUXIT	MUS MUSCUIUS Mire mirerultis	mm HTI F	X/4830 V17856	FOXEJ Forno	Xenopus laevis Yenoniis laevis	XI AFUIJ VI XFKH1	* 503559	FOXF I EnvAdh
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genetic analysis was performed using the full sequence of the proteins (data not shown). We have used lowercase letters to distinguish between virtually identical proteins (e.g., Foxa4a and Foxa4b), presumably derived from duplicated genes, a case commonly found in polyploid species like *Xenopus laevis*. Please note that the phylogenetic tree includes several proteins that have not received a Fox designation because as yet, their phylogenetic relationships remain unclear due to limited sequence information.

#### Naming new sequences

A new Fox protein is defined as a fully sequenced gene, cDNA, or protein that belongs to the Fox family of proteins based on sequence homology of its winged helix DNA-binding domain. We have established a Fox Nomenclature web site (http://www.biology.pomona.edu/ fox.html) that provides a form for submitting protein sequences to the Fox Nomenclature Committee. We encourage investigators who have discovered new Fox sequences to submit them to the committee for assignment of the proper Fox name. These sequences will be kept confidential until publication of the sequence by the investigators. We recommend that this new system of nomenclature be used in all future publications.

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