

CORRESPONDENCE

Unified nomenclature for the winged helix/forkhead transcription factors

Klaus H. Kaestner,^{1,4,5} Walter Knöchel,^{2,4} and Daniel E. Martínez^{3,4,5}

¹Department of Genetics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104 USA;

²Abteilung Biochemie, Universität Ulm, D-89081 Ulm, Germany; ³Department of Biology, Pomona College, Claremont, California 91711 USA

The winged helix/forkhead class of transcription factors is characterized by a 100-amino-acid, monomeric DNA-binding domain. The structure of the DNA-binding domain of one of the class members, hepatocyte nuclear factor 3 γ (HNF3 γ), 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 α 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 scientists¹ as well as the Human and Mouse Gene Nomenclature Committees.

The Fox subclasses

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

scription factors. Other portions of the Fox proteins, 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 neighbor-joining 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.).

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-

⁴Fox Nomenclature Committee.

⁵Corresponding authors.

E-MAIL kaestner@mail.med.upenn.edu; FAX (215) 573-5892.

E-MAIL dmartinez@pomona.edu; FAX (909) 621-8878.

¹The 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 Zanini, and Ken Zaret.

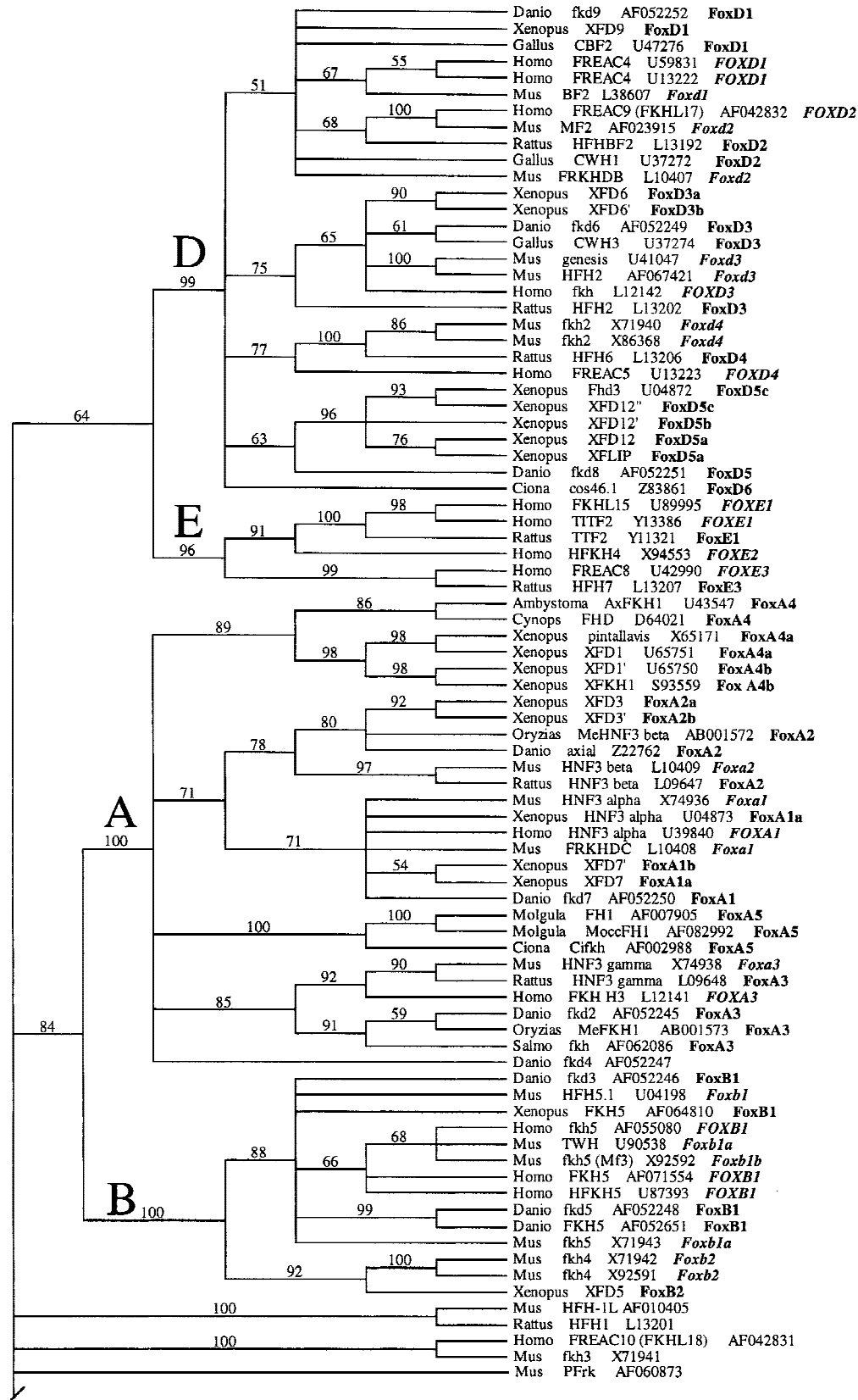
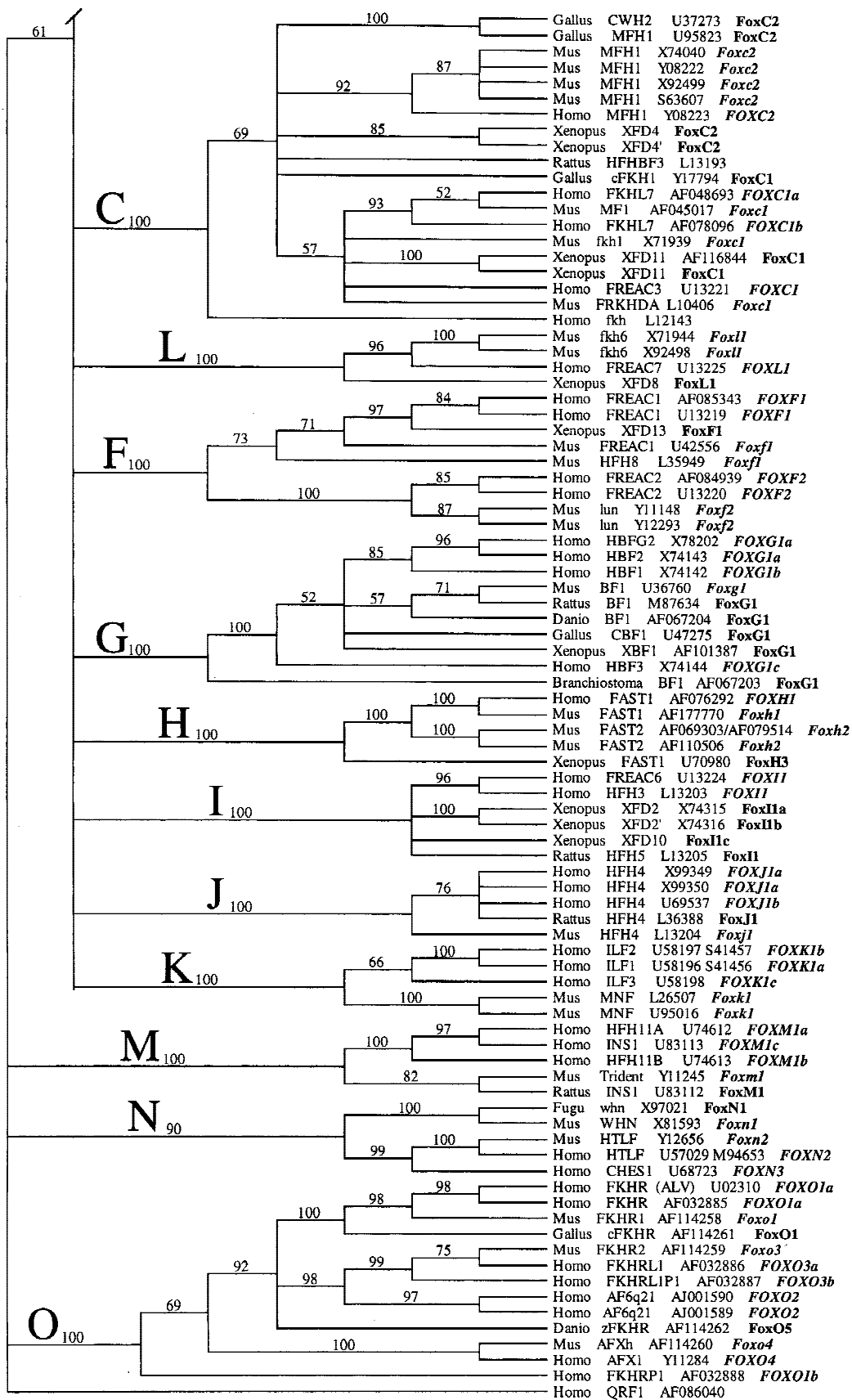


Figure 1. (Continued on p. 144) Neighbor-joining phylogeny of chordate Fox proteins based on the amino acid sequence of the Fox domain. The distance measure used was mean character difference. The tree was rooted using *Homo* QRF1 (AF086040) as the outgroup. The numbers in the interior branches are bootstrap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

Kaestner et al.



Kaestner et al.

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.

References

- Clark, K.L., E.D. Halay, E. Lai, and S.K. Burley. 1993. Co-crystal structure of the HNF-3/fork head DNA-recognition motif resembles histone H5. *Nature* **364**: 412–420.
- Kaufmann, E. and W. Knöchel. 1996. Five years on the wings of fork head. *Mech. Dev.* **57**: 3–20.
- Swofford, D.L. 1999. *PAUP*: Phylogenetic analysis using parsimony and other methods*. Sinauer, Sunderland, MA.
- Thompson, J.D., D.G. Higgins, and T.J. Gibson. 1994. CLUSTAL W: Improving the sensitivity of progressive multiple sequence alignment through sequence weighing, position specific gap penalties and weight matrix choice. *Nucleic Acid Res.* **22**: 4673–4680.



Unified nomenclature for the winged helix/forkhead transcription factors

Klaus H. Kaestner, Walter Knöchel and Daniel E. Martínez

Genes Dev. 2000, **14**:

Access the most recent version at doi:[10.1101/gad.14.2.142](https://doi.org/10.1101/gad.14.2.142)

License

Email Alerting Service

Receive free email alerts when new articles cite this article - sign up in the box at the top right corner of the article or [click here](#).

