

Short Communication

A revised nomenclature for the human and rodent α -tubulin gene family

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Abstract

An essential component of microtubules, α -tubulin is also a multigene family in many species. An orthology-based nomenclature for this gene family has previously been difficult to assign due to incomplete genome builds and the high degree of sequence similarity between members of this family. Using the current genome builds, sequence analysis of human, mouse, and rat α -tubulin genes has enabled an updated nomenclature to be generated. This revised nomenclature provides a unified language for the discussion of these genes in mammalian species; it has been approved by the gene nomenclature committees of the three species and is supported by researchers in the field.

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α - and β -tubulin form heterodimers that are the basic building blocks for microtubule assembly throughout the eukaryotic superkingdom, and α -tubulin mutations have recently been associated with lissencephaly and impaired neuronal migration [1]. In contrast, while γ -tubulin is required for nucleation of the microtubule assembly, the roles of the remaining tubulin families remain less well characterized [2,3].

There are multiple copies of the α -tubulin genes in the human and rodent genomes. There is also a degree of tissue

specificity in the expression of some of the α -tubulins, with several mouse and human α -tubulins described as testis specific [4] or restricted to cells of a neurological origin [5]. However, mammalian nomenclature committees aim to avoid tissue-specific gene names, as these can be misleading in cases in which further studies show a more general expression pattern than originally thought.

The goal of the HUGO Gene Nomenclature Committee (HGNC) is to assign a unique and meaningful name to every human gene. The HGNC works in close collaboration with the Mouse Genomic Nomenclature Committee (MGNC) and the Rat Genome Nomenclature Committee (RGNC) to assign

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parallel gene nomenclature to human and rodent orthologs [6]. However, this was not accomplished with the previously assigned α -tubulin nomenclature (Table 1). This was partly due to the naming of α -tubulin genes by independent groups working on different species, which resulted in orthologous genes having different nomenclatures. Another reason for this discrepancy is inherent to the tubulins; there is a high level of similarity between members of this gene family. For example, several human α -tubulin proteins are greater than 99% identical, while at the nucleotide level all members of the human α -tubulin family are greater than 72% identical to one another. This high identity and gaps in previous genome builds made assigning orthology difficult.

Using whole genome analysis to identify known and predicted members of the α -tubulin gene family, we have been able to make orthology and subgroup assertions for the α -tubulin gene family. Subgroup assertions are based on phylogenetic analyses, with orthology determined using a combination of phylogenetic analyses, sequence comparison, and analysis of syntenic regions. Following the HGNC, MGNC, and RGNC nomenclature guidelines [6], we provide a new nomenclature system for the human, mouse, and rat α -tubulin gene family (Table 1). Gene nomenclature implying orthology is assigned only where the orthology is clear.

Results and discussion

From the phylogenetic analysis using the protein-coding nucleotide sequences of the α -tubulin genes it is clear that there are four α -tubulin subgroups ([7], Fig. 1A). Phylogenetic analysis using the amino acid sequence of these proteins suggests an orthology, within subgroups 1 and 2, across the human, mouse, and rat genomes (Fig. 1B). In the nucleotide-based analysis human TUBA4B falls within group 2, whereas the amino acid-based analysis positions TUBA4B outside the outgroup chosen for the phylogenetic analysis (see discussion of group 2).

Genome sequencing projects have identified α -tubulin related genes, *TUBAL3/Tubal3*. When included in phylogenetic analysis of the α -tubulin gene family these genes are positioned beyond the outgroup, *Caenorhabditis elegans* α -2 tubulin, used to root the tree (data not shown).

Phylogenetic analysis of the amino acid sequences suggests an orthology for each member of the group 1 α -tubulins across human, mouse, and rat (Fig. 1B). This orthology is confirmed by the conserved syntenic arrangement of the three human, mouse, and rat group 1 α -tubulin genes. In all three species these genes are in the same arrangement, human 12q13.12 cent (*TUBA1B*, *TUBA1A*, *TUBA1C*) tel, mouse 15F1 cent (*Tubal1b*, *Tubal1a*, *Tubal1c*) tel, and rat 7q36 cent (*Tuba1b*, *Tuba1a*, *Tuba1c*) tel, and in each species each cluster of group 1 genes is flanked by *LMBR1L/Lmbr1l* and *PRPH/Prph*. Reciprocal BLAT analysis of intergenic sequences between flanking genes and α -tubulin genes confirms that no inversions are present in this region.

A comparison of the transcript structure of each gene, when viewed in Ensembl GeneView, identifies that the four exon

Table 1
Orthology assertion and new gene nomenclature for the α -tubulin gene family

New α -tubulin gene nomenclature		Additional information about human, mouse, and rat α -tubulin genes										
Group	Human symbol	Rodent symbol	Gene name	Human			Mouse			Rat		
				Previous symbol	Location	Accession ID (DNA)	Previous symbol	Location	Accession ID (DNA)	Previous symbol	Location	Accession ID (DNA)
Group 1	<i>TUBA1A</i>	<i>Tubal1a</i>	Tubulin, α 1A	<i>B-ALPHA-1^a</i>	12q13.12	NM_006009	<i>Tuba1</i>	15 F1	NM_011653	<i>Tuba1</i>	7q36	NM_022298
	<i>TUBA1B</i>	<i>Tubal1b</i>	Tubulin, α 1B	<i>K-ALPHA-1^a</i>	12q13.12	NM_006082	<i>Tuba2</i>	15 F1	NM_011654	<i>LOC500929^a</i>	7q36	XM_001059275
	<i>TUBA1C</i>	<i>Tubal1c</i>	Tubulin, α 1C	<i>TUBA6</i>	12q13.12	NM_032704	<i>Tuba6</i>	15 F1	NM_009448	<i>Tuba6</i>	7q36	NM_001011995
Group 2	<i>TUBA4A</i>	<i>Tuba4a</i>	Tubulin, α 4A	<i>TUBA1</i>	2q35	NM_006000	<i>Tuba4</i>	1 C3	NM_009447	<i>Tuba4</i>	9q33	NM_001007004
	<i>TUBA4B</i>	–	Tubulin, α 4B	<i>TUBA4</i>	2q35	AK024002	–	–	–	–	–	–
Group 3	–	<i>Tuba3a</i>	pseudogene	–	–	–	<i>Tuba3</i>	6 F3	NM_009446	<i>LOC500319^a</i>	4q42	NM_001040008
	–	<i>Tuba3b</i>	Tubulin, α 3A	–	–	–	<i>Tuba7</i>	6 G3	NM_009449	<i>LOC500363^a</i>	4q44	NM_001024336
	<i>TUBA3C</i>	–	Tubulin, α 3B	<i>TUBA2</i>	13q12.11	NM_006001	–	–	–	–	–	–
Group 4	<i>TUBA3D</i>	–	Tubulin, α 3C	<i>H2-ALPHA^a</i>	2q21.1	NM_080386	–	–	–	–	–	–
	<i>TUBA3E</i>	–	Tubulin, α 3D	<i>LOC112714^a</i>	2q21.1	NM_207312	–	–	–	–	–	–
	<i>TUBA8</i>	<i>Tuba8</i>	Tubulin, α 3E	<i>TUBA8</i>	22q11.1	NM_018943	<i>Tuba8</i>	6 F1	NM_017379	<i>LOC500377^a</i>	4	NM_001024339
	<i>TUBAL3</i>	<i>Tubal3</i>	Tubulin, α 8	<i>TUBAL3</i>	10p15.1	NM_024803	<i>Tubal3</i>	13 A1	NM_001033879	<i>Tubal3</i>	17q12.3	XM_001068605
	–	–	Tubulin, α -like 3	–	–	–	–	–	–	–	–	–

^a Not a previously approved gene symbol, symbol used is a published alias or the temporary gene symbol from the Entrez Gene database.

transcripts of human *TUBA1C*, mouse *Tuba1c*, and rat *Tuba1c* are distinct from the exon structures of the other six genes in this group. The first exon of the *TUBA1C/Tuba1c* genes contains only untranslated region (UTR) sequences, whereas the first exon in the six other genes also includes protein coding sequence. This further suggests that human *TUBA1C*, mouse *Tuba1c*, and rat *Tuba1c* are orthologous.

The group 1 α -tubulin genes in human, mouse, and rat have been assigned the prefix *TUBA1/Tuba1*, with the suffix A/a, B/b, or C/c used to indicate orthology (Table 1).

The orthology of the mouse and rat group 2 α -tubulins is implied from the phylogenetic analysis of the nucleotide sequences (Fig. 1A). There is one group 2 gene in mouse and rat (*Tuba4a*), whereas in human there are two group 2 genes (*TUBA4A* and *TUBA4B*), clustered on 2q35. Further support for the grouping of rodent *Tuba4a* with human *TUBA4A* and *TUBA4B* comes from the syntenic arrangement of the rodent *Tuba4a* genes and the human *TUBA4A* and *TUBA4B* genes. In both Ensembl and the NCBI Map Viewer, human 2q35 is syntenic with mouse 1C3 and rat 9q33, and in all three genomes the group 2 α -tubulin genes are flanked by *STK16/Stk16* and *PTPRN/Ptprn* (data not shown).

In contrast to the nucleotide sequence analysis, phylogenetic analysis using the TUBA protein sequences suggests that *TUBA4B* is not a group 2 α -tubulin, as it is positioned beyond the outgroup (Fig. 1B). The human *TUBA4A* protein is 448 amino acids in length, whereas the human *TUBA4B* protein is only 241 amino acids. Aligning the nucleotide and predicted protein sequences reveals a frameshift at nucleotide position 790 of *TUBA4B* compared to *TUBA4A*; this is due to deletion of a C in the *TUBA4B* sequence. This C residue is also deleted in genomic DNA (which is covered by two independent clones) and is therefore unlikely to be a cDNA sequencing error, although this can be proven only experimentally. Compared to the other α -tubulins, the predicted *TUBA4B* protein is shorter, with a truncated C-terminal domain. Furthermore, the alignment of the *TUBA4A* cDNA to the *TUBA4B* genomic sequence provides evidence that another tubulin-related exon containing multiple frameshifts and stop codons is present in this region and is not transcribed. The approved designation, *TUBA4B*, tubulin, α 4B pseudogene, reflects these findings (Table 1).

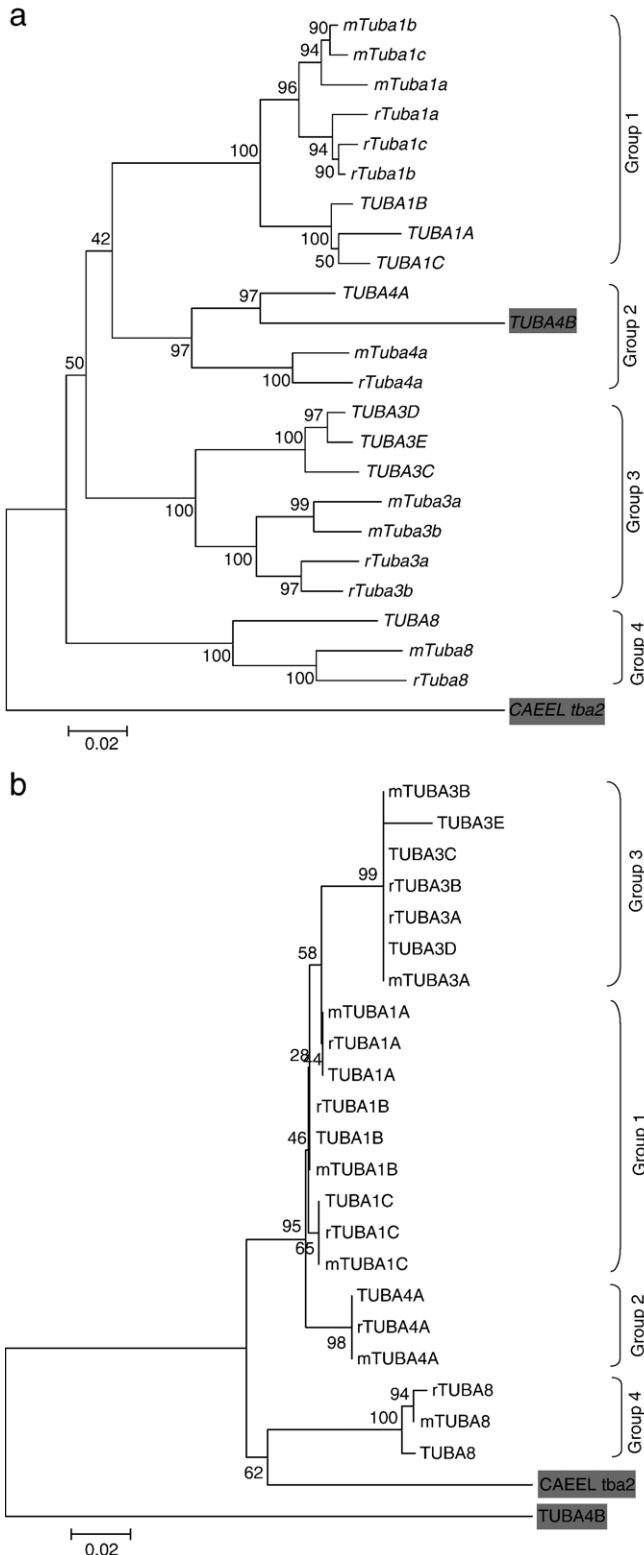


Fig. 1. (A) Phylogenetic analysis of human and rodent α -tubulin genes using the following MEGA 3.1 settings. (1) Include sites (a) gaps/missing data: complete deletion; (b) codon positions: 1st+2nd+3rd+noncoding. (2) Substitution model (a) model: Kimura 2-parameter; (b) substitutions to include: transitions+transversions; (c) rates among sites: uniform rates. Numbers on the branches refer to the bootstrap values expressed in percentage after 1000 replicates. Human (all capitals), mouse (m), and rat (r) DNA sequences listed in Table 1, rooted with *Caenorhabditis elegans* α -2 tubulin (*tba2*), D14965, are shown. The positions of *TUBA4B* and *C. elegans* α -2 tubulin are highlighted for clarity. (B) Phylogenetic analysis of human and rodent α -tubulin proteins using the following MEGA 3.1 settings. (1) Gaps/missing data: complete deletion. (2) Substitution model (a) model: Poisson correction; (b) substitutions to include: all; (c) rates among sites: uniform rates. Numbers on the branches refer to the bootstrap values expressed in percentage after 1000 replicates. Human sequences: *TUBA1A*, NP_006000; *TUBA1B*, NP_006073; *TUBA1C*, NP_116093; *TUBA3C*, NP_005992; *TUBA3D*, NP_525125; *TUBA3E*, NP_997195; *TUBA4A*, NP_005991; *TUBA4B*, BAB14767; *TUBA8*, NP_061816. Mouse sequences (m): *TUBA1A*, NP_035783; *TUBA1B*, NP_035784; *TUBA1C*, NP_033474; *TUBA3A*, NP_033472; *TUBA3B*, NP_033475; *TUBA4A*, NP_033473; *TUBA8*, NP_059075. Rat sequences (r): *TUBA1A*, NP_071634; *TUBA1B*, XP_001059275; *TUBA1C*, NP_001011995; *TUBA3A*, NP_001035097; *TUBA3B*, NP_001019507; *TUBA4A*, NP_001007005; *TUBA8*, NP_001019510. The tree is rooted with *C. elegans* α -2 tubulin (*TBA2*), BAA03610. The positions of *TUBA4B* and *C. elegans* α -2 tubulin are highlighted for clarity.

Although analysis of the α -tubulins shows group 3 as a distinct clade, phylogenetic analysis using untranslated 5' and 3' regions and syntenic region comparisons do not identify any rodent orthologs of the human group 3 α -tubulins. In contrast, the conserved synteny around the mouse and rat group 3 α -tubulin genes enables mouse–rat orthology predictions to be made. Mouse chromosome 6F3 cent (*Cd27*, *Tuba3a*, *Ltbr*) tel is syntenic with rat chromosome 4q42 cent (*Cd27*, *Tuba3a*, *Ltbr*) tel; similarly, mouse chromosome 6G3 cent (*Kras*, *Ifltd1*, *Tuba3b*, *Rassf8*) tel is syntenic with rat chromosome 4q44 cent (*Kras*, *Ifltd1*, *Tuba3b*, *Rassf8*) tel. The approved nomenclature for the rodent group 3 genes is based on this predicted orthology (Table 1).

The genes flanking both of the rodent group 3 genes do have well-established human syntenic orthologs on chromosome 12; however, there are no human α -tubulin-like sequences in 12p13 and 12p12, the regions syntenic to mouse 6F3 and 6G3. Mouse 6F3 has the genes cent (*Tapbpl*, *Cd27*, *Tuba3a*, *Ltbr*, *Scnn1a*) tel on a single genomic clone, AC140324. Human 12p13 has the genes cent (*TAPBPL*, *CD27*, *SRP14P1*, *RPL31P10*, *LTBR*, *SCNN1A*) tel also on a single genomic clone, AC005840. It appears to be unlikely that the lack of a mouse *Tuba3a* ortholog within the syntenic region of human chromosome 12 is due to a mistake in the genomic assembly. However, the human 12p12 genomic assembly covering *IFLTD1* and *RASSF8*, a region syntenic with the regions around the rodent *Tuba3b* gene (*Kras*, *Ifltd1*, *Tuba3b*, *Rassf8*), is based on several genomic clones, so an error here cannot be ruled out.

The genes flanking the human group 3 α -tubulin genes do have orthologs in rodents. However, no rodent α -tubulin genes have been identified near these genes. Human *TUBA3C* maps to 13q12.11 between the centromere and *TPTE2*, whereas mouse *Tpte2* is located on a nonsyntenic region on chromosome 5F (covered by several overlapping genomic clones). There are no other confirmed genes between *TUBA3C* and the centromere and *TUBA3C* is on a single genomic clone (AL139327). Although it is possible that the location of these clones may be updated or that other genes may be identified in later genome builds, at present it is not possible to assign a mouse ortholog for the human *TUBA3C* gene.

The two remaining human group 3 α -tubulin genes, *TUBA3D* and *TUBA3E*, are on chromosome 2q21.1. Some parts of human chromosome 2 are syntenic with mouse chromosome 6 (over 100 genes in the MGI Oxford grid); however, *TUBA3D* and *TUBA3E* are not in these syntenic regions. Genes on the telomeric side of human *TUBA3E*, cent (*CCDC115*, *IMP4*, *PTPN18*) tel, have murine orthologs on mouse chromosome 1B. However, in the current build there are no mouse α -tubulin genes within chromosome 1B. Genes on the centromeric side of human *TUBA3E*, cent (*SMPD4*, *FAM128B*) tel, are part of a segmental duplication spanning chromosome 2: 130595672–130715155. The duplication of this region is also on chromosome 2, spanning genomic coordinates chromosome 2 131907249–132025390, and it is within this region that *TUBA3D* is also located. Many of the genes within this duplicated region are present in a single copy in the mouse genome and the duplication has been found (or predicted) only in primates [8].

No mouse α -tubulin genes are located near the orthologs of any of these flanking genes.

There are also differences in the tissue specificity of the human and mouse group 3 α -tubulin genes. From the mouse gene expression data at MGI [9] *Tuba3a* and *Tuba3b* appear to be germ cell specific, whereas, from the human gene expression data available at GeneCards [10], the three human *TUBA3* genes are more ubiquitously expressed. Consequently, it is not possible to suggest orthology between any of the human and mouse genes based on their tissue localization.

The approved nomenclature for the group 3 α -tubulin genes reflects these findings (Table 1). The two orthologous rodent genes have been approved as *Tuba3a* and *Tuba3b*, the three human genes as *TUBA3C*, *TUBA3D*, and *TUBA3E*.

As there is only one gene from each species in group 4, the orthology assertion is implicit from the initial phylogenetic analysis (Fig. 1A). The orthology of the group 4 genes is also agreed upon by all genome browsers, with the human and mouse genes in syntenic regions (data not shown). To avoid unnecessary confusion the current nomenclature of *TUBA8/Tuba8* has been maintained (Table 1).

Human *TUBAL3* (NM_024803), mouse *Tubal3* (NM_001033879), and rat *Tubal3* (XM_225547) were identified as genes with similarity to the α -tubulins at the nucleotide and amino acid level in a genomic survey for α -tubulin gene family members. When included in phylogenetic analysis these genes are positioned beyond the outgroup chosen to root the tree (data not shown). As these three genes map to syntenic regions across the human, mouse, and rat genomes they are predicted to be orthologous. The approved gene nomenclature for these genes, *TUBAL3/Tubal3*, tubulin, α -like 3, reflects this predicted orthology and the lack of any functional evidence that these genes are true members of the α -tubulin gene family (Table 1).

The nomenclature of the α -tubulins has previously been confusing, with many different gene symbols being used in publications and the same gene symbol being used for different genes across species. Using a range of bioinformatic tools, including phylogenetic analyses, synteny, and primary sequence analyses, we have generated an orthology-based nomenclature system for the human, mouse, and rat α -tubulin genes (Table 1). This nomenclature has been approved by the human and rodent nomenclature committees and made public via the HUGO Gene Nomenclature Committee database (<http://www.gene.ucl.ac.uk/nomenclature/>), the Mouse Genome Informatics database (<http://www.informatics.jax.org/>), and the Rat Genome Database (<http://rgd.mcw.edu/>).

Materials and methods

Curated human, mouse, and rat cDNA and protein RefSeqs (identified by NM_# and NP_#, respectively) or electronically generated RefSeqs (identified by XM_# and XP_#) were used where possible. Only the protein-coding portion of each cDNA was used, to prevent differences in length of the UTRs biasing the alignments. Phylogenetic and molecular evolutionary analyses were conducted using Molecular Evolutionary Genetics Analysis (MEGA) version 3.1 [11]. Nucleotide and protein sequences were aligned using the CLUSTALW algorithm and a neighbor-joining tree was generated using the *C. elegans* α -2 tubulin as an outgroup. One thousand bootstrap replicates were performed for each analysis.

Nucleotide and protein sequences were analyzed using the reciprocal Basic Local Alignment Search Tool [12]. Intergenic sequences were compared using BLAT from UCSC Genome Bioinformatics [13]. The NCBI Map Viewer [14], Ensembl [15], and UCSC [13] genome browsers were used to view syntenic regions for each of the proposed orthologous genes from the following genome builds: human builds 35 (May 2004) and 36 (March 2006), mouse builds 35 (August 2005) and 36 (February 2006), and rat build 3 (November 2004). The Mouse Genome Informatics Oxford grid and comparative maps were also used to identify syntenic regions [9]. The HGNC Comparison of Orthology Predictions search tool [16,17] was used to compare predicted human–mouse orthologous pairs from Ensembl [15], Homologene [14], Inparanoid [18], and PhIGS [19].

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