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In silico characterization of the INO80 subfamily of SWI2/SNF2 chromatin remodeling proteins

Rachit Bakshi,[a] Tulika Prakash,[b] Debasis Dash,[b] and Vani Brahmachari[a,*]

[a] *Dr. B.R. Ambedkar Centre for Biomedical Research, University of Delhi, Delhi 110007, India*
[b] *Institute of Genomics and Integrative Biology (CSIR), Mall Road, University of Delhi, Delhi 110007, India*

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Abstract

Proteins belonging to SNF2 family of DNA dependent ATPases are important members of the chromatin remodeling complexes that are implicated in epigenetic control of gene expression. The yeast Ino80, the catalytic ATPase subunit of the INO80 complex, is the most recently described member of the SNF2 family. Outside the conserved ATPase domain, it has very little similarity with other well-characterized SNF2 proteins hence it is believed to represent a new subfamily. We have identified new members of this subfamily in different organisms and have detected characteristic features of this subfamily. Using various data mining tools we have identified a new, previously undetected domain in all members of this subfamily. This domain designated DBINO is characteristic of the INO80 subfamily and is predicted to have DNA-binding function. The presence of this domain in all the INO80 subfamily proteins from different organisms suggests its conserved function in evolution.

Keywords: Chromatin remodeling; DNA dependent ATPase; SNF2 domain; INO80

Activation of transcription in eukaryotes requires a complex array of protein–protein and protein–DNA interactions. Several complexes of proteins are involved in the remodeling of chromatin. The most widely characterized chromatin-modifying complexes studied can be classified into two major groups based on their mode of action, (i) ATP-dependent complexes and (ii) histone acetyltransferase (HAT) and histone deacetylase (HDAC) complexes [1–4]. Assembly and the corresponding disassembly of the ATP-dependent multiprotein complexes are known to be essential for the DNA dependent processes of transcription, recombination, and repair [5]. An essential component of several such multiprotein complexes is a single protein subunit that is a member of the conserved SNF2 family of proteins [6]. The SNF2 proteins are the catalytic ATPase subunit of the multiprotein chromatin-remodeling complexes [7]. Members of the SNF2 family of proteins have been identified in organisms ranging from *Escherichia coli* to *Homo sapiens*. More than hundred SNF2 proteins are already known, some well characterized others computationally predicted, but all of them containing the conserved SNF2 domain. The SNF2 domain is defined by the existence of seven motifs (I, Ia, and II–VI) with sequence similarity to those motifs found in DNA and RNA helicases. Motifs I, Ia, and II make up the nucleotide binding site and are characterized by phosphate binding loop, often referred to as the Walker A and B boxes [8]. The properties of motif III are still unknown. Motifs IV, V, and VI are involved in DNA and ATP binding, their exact role being unknown [9].

SNF2-like family members can be further subdivided into several subfamilies according to the presence of protein motifs outside of the ATPase domain and the architecture of the ATPase region [6]. Some of the well-characterized subfamilies include the SNF2 subfamily (Snf2, Sth1, hBRM, and BRG1), ISWI subfamily (ISWI1, ISWI2, SNF2l, and SNF2h), CHD1 subfamily (CHD1, Mi-2α/CHD3, and Mi2β/CHD4), and the RAD54 subfamily (Rad54, ATRX, and ARIP4) [10]. The members of SNF2 subfamily contain a

* Corresponding author. Fax: +91-11-27666248.
E-mail address: v_brahmachari@hotmail.com (V. Brahmachari).

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bromodomain that interacts with acetylated peptides [11] in addition to the conserved SNF2 domain. The ISWI and the CHD1 subfamilies are characterized by the presence of SANT and the chromodomain, respectively [12,13]. The SANT domain interacts both with DNA and proteins and the chromodomain mediates specific interaction with proteins. The functions of gene products like snf2, MOT1, Brahma, BRG1, and hBRM include their role in transcription, RAD5, RAD16, RAD54, rad8, and ERCC6 in DNA repair or recombination, lodestar in chromosome segregation, and STH in cell cycle progression [14]. The INO80 complex in yeast is the most recently described chromatin remodeling complex comprising of twelve subunits [15]. The INO80 complex remodels chromatin, facilitates transcription in vitro, and displays 3′–5′ DNA helicase activity and in yeast it is known to be associated with chromosomes of dividing cells. The Ino80 gene from yeast forms a distinct subfamily which has not yet been well characterized. Here, we identify new members of the INO80 subfamily, which comprises of genes from yeast to humans with distinct sequence features. We have also identified a new, previously undetected domain in all members of the INO80 subfamily, which we predict would have DNA-binding functions.

Materials and methods

A search for Snf2 like genes, using hINO80 (GenBank Accession No. AB033085) as the query sequence, was made in the non-redundant database using BLASTp [16]. All significant hits with E value ranging between 5e − 36 and 4e − 04 were selected. These sequences were downloaded from NCBI (www.ncbi.nlm.nih.gov). The alignment of protein sequences was obtained using CLUSTALW [17] (www.ebi.ac.uk). The PSI-BLAST searches were made with an inclusion cut-off of 0.005 using the conserved 126 amino acid sequence at the N-terminal end of the protein. This conserved sequence is present approximately 100 amino acid upstream of SNF2 helicase domain. The secondary structure of this sequence was predicted using three web-based softwares namely NNPREDICT [18], SOPMA [19], and JPRED [20] and a consensus was drawn. The α-helical regions that were predicted by all the three softwares were utilized for hydropathy analysis using the HELICAL WHEEL module of Wisconsin GCG package [21]. In order to evaluate the evolutionary relationship among the proteins of the INO80 subfamily, we performed a phylogenetic analysis based on their SNF2 ATPase domain sequences. The neighbor joining tree of the above-mentioned sequences was generated using the alignment obtained using CLUSTALW. The phylogenetic tree was viewed using Tree View [22].

Results and discussion

The Ino80 gene (Accession No. YGL150C) was initially identified in a genetic screen for mutants affecting inositol biosynthesis [23]. The conserved ATPase domain is the only recognizable domain present in the protein comprising of 1440 amino acids. The protein is a part of a multiprotein complex INO80.com, involved in chromatin remodeling. Null mutants show hypersensitivity to alkylating agents and ultraviolet as well as ionizing radiations, in addition to defects in transcription. The *Drosophila* homolog CG3602 (Accession No. AY069786) is an uncharacterized protein of 1500 amino acid showing high similarity with yeast Ino80.

In an attempt to identify novel SNF2 proteins in the human genome, we computationally searched for SNF2 like genes in different organisms and identified an uncharacterized protein mapping on the chromosome 15 (q14) in the human genome (GenBank Accession No. AB033085). This putative SNF2 ATPase was initially identified as a homolog of yeast INO80 [15] and designated as hIN080. We have extensively analyzed hINO80 gene in silico. The human hINO80 gene comprises of 36 exons, which span a chromosomal region of 135 Kb at 15q14. At the protein level hINO80 has all the seven conserved motifs of the SNF2 helicase domain.

We searched for sequence similarity of hINO80 with unclassified SNF2 like proteins in various organisms apart from the Ino80 known in *Saccharomyces cerevisiae* We identified proteins from eukaryotes starting from *Schizosaccharomyces pombe*, *Neurospora crassa*, *Encephalitozoon cuniculi* to insects like *Drosophila melanogaster* and *Anopheles gambiae*, mammals like, *Rattus norvegicus*, *Mus musculus*, *H. sapiens*, and plant like *Arabidopsis thaliana* with significant similarity to human hINO80 at the peptide level. The genes identified, along with their accession numbers and position of the SNF2 domain within the protein sequence, are shown in Table 1. These proteins have high degree of similarity between them, but not with any known SNF2 proteins belonging to other subfamilies. A given subfamily is characterized not only by the similarity in the SNF2 helicase domain, but also by the similarity outside the helicase domain [6]. Therefore to further classify the hINO80 and all other similar proteins identified in different species, we examined them for similarity outside the helicase domain and found a significant similarity within this group in regions outside the SNF2 domain, but not with any member of the other known SNF2 subfamilies, thus segregating into a distinct SNF2 subfamily. The pairwise amino acid similarities were higher than 50% between the proteins of INO80 subfamily, a threshold conventionally used to classify a group of genes as a gene family. The regions of similarity are described below. The specialized domains present in the SWI2/SNF2 and other subfamilies like SANT domain and bromodomain are not present in this subfamily (Fig. 1).

The INO80 subfamily has certain features that make it characteristically distinct from those of other subfamilies. The SNF2 helicase domain in general comprises of a highly conserved stretch of 400 amino acids. The SNF2 helicase domain of the INO80 subfamily is

Table 1
Members of the *INO80* subfamily

S.No	Accession No	Gene name	Organism	Protein (aa)	SNF2 domain
1	YGL150C	Ino80	*S. cerevisae*	1489	709–1420
2	AY069786	CG3602	*D. melanogaster*	1638	538–1277
3	BAC98127	Mn1	*M. musculus*	1578	167–862
4	AB033085	hINO80	*H. sapiens*	1561	530–1240
5	XP_230473	RN1[a]	*R. norvegicus*	1514	512–1180
6	XM_313902.1	AG1[a]	*A. gambiae*	1207	398–1126
7	NP_594979	SP1[a,b]	*S. pombe*	1063	845–1063[b]
8	NP_191289.	AT1[a]	*A. thaliana*	1507	590–1330
9	CAD70746	NC1[a]	*N. crassa*	1955	1121–1773
10	NP_597114	EC1[a]	*E. cuniculi*	883	278–846

[a] These genes were identified from the whole or partial genome sequences available in the database, as uncharacterized gene sequences; accession numbers as given in the NCBI database are shown. We have given the gene names based on the analysis reported in this manuscript.
[b] The annotation of this sequence is incomplete.

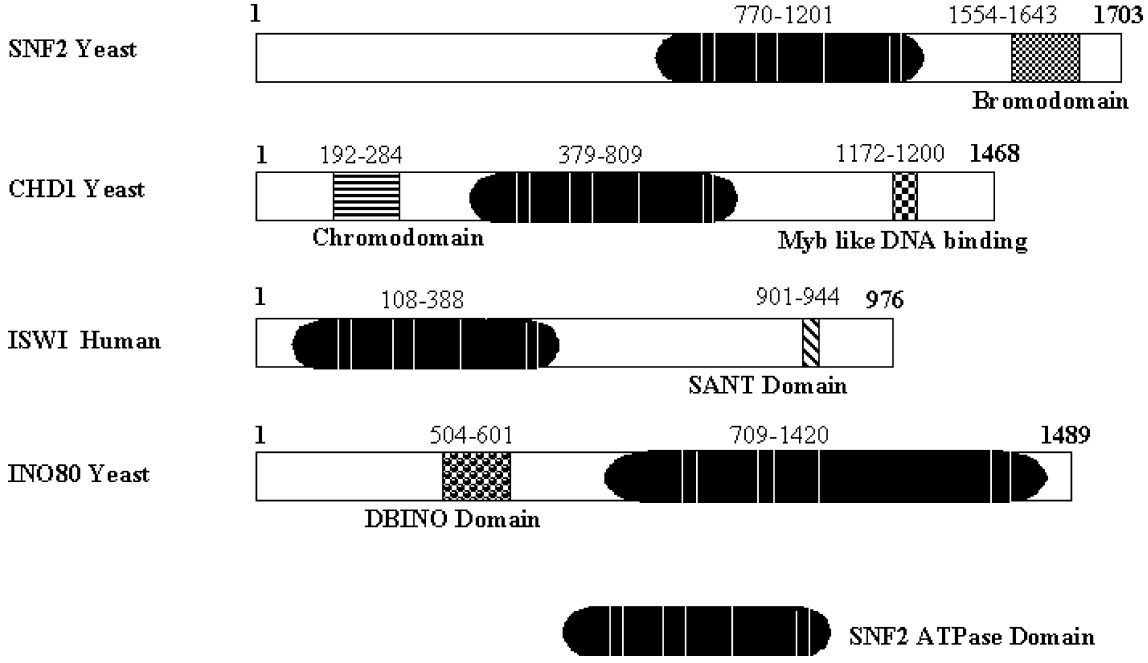

Fig. 1. Graphical representation of the members of SNF2 family. The enzymes in this family can be grouped into several subfamilies according to sequence features outside of their ATPase domains. The numbers indicate the amino acid positions on the respective protein. Vertical white lines indicate the seven motifs of SNF2 domain. The SNF2 domain of the INO80 is dispersed over 700 amino acids.

dispersed within a region of 700 amino acids (Fig. 1). The spacing between motifs IV and V of the SNF2 domain is unusually large. The function of these approximately 300 additional amino acids is currently not known. Despite the spacing between the conserved motifs, the conservation of residues in the helicase domain is striking. The proteins of the INO80 subfamily contain all the characteristic seven motifs of the SNF2 helicase domain (Fig. 2). The ATPase domain of the yeast Snf2 protein, the founder member of the SNF2 family, is shown in Fig. 2 to highlight the differences with proteins of the INO80 subfamily. Within the motif 1 of the SNF2 domain the expected SNF2 pattern of GxGK[S/T]x (where x is any amino acid) is included. This subfamily exhibits certain unusual amino acid sequence within the nucleotide-binding site; the highly conserved DExH/D pattern in motif 2 is replaced by DEAQ motif (Fig. 2). Since DNA dependent ATPase activity is already demonstrated for INO80.com, it is apparent that the 4th position in DExH/D is perhaps not critical for the catalytic function. Although the significance of these substitutions is currently unknown, we postulate that they would influence the recognition of the target DNA sites by varying binding affinity and/or affinity to various other cofactors in the chromatin-remodeling complex.

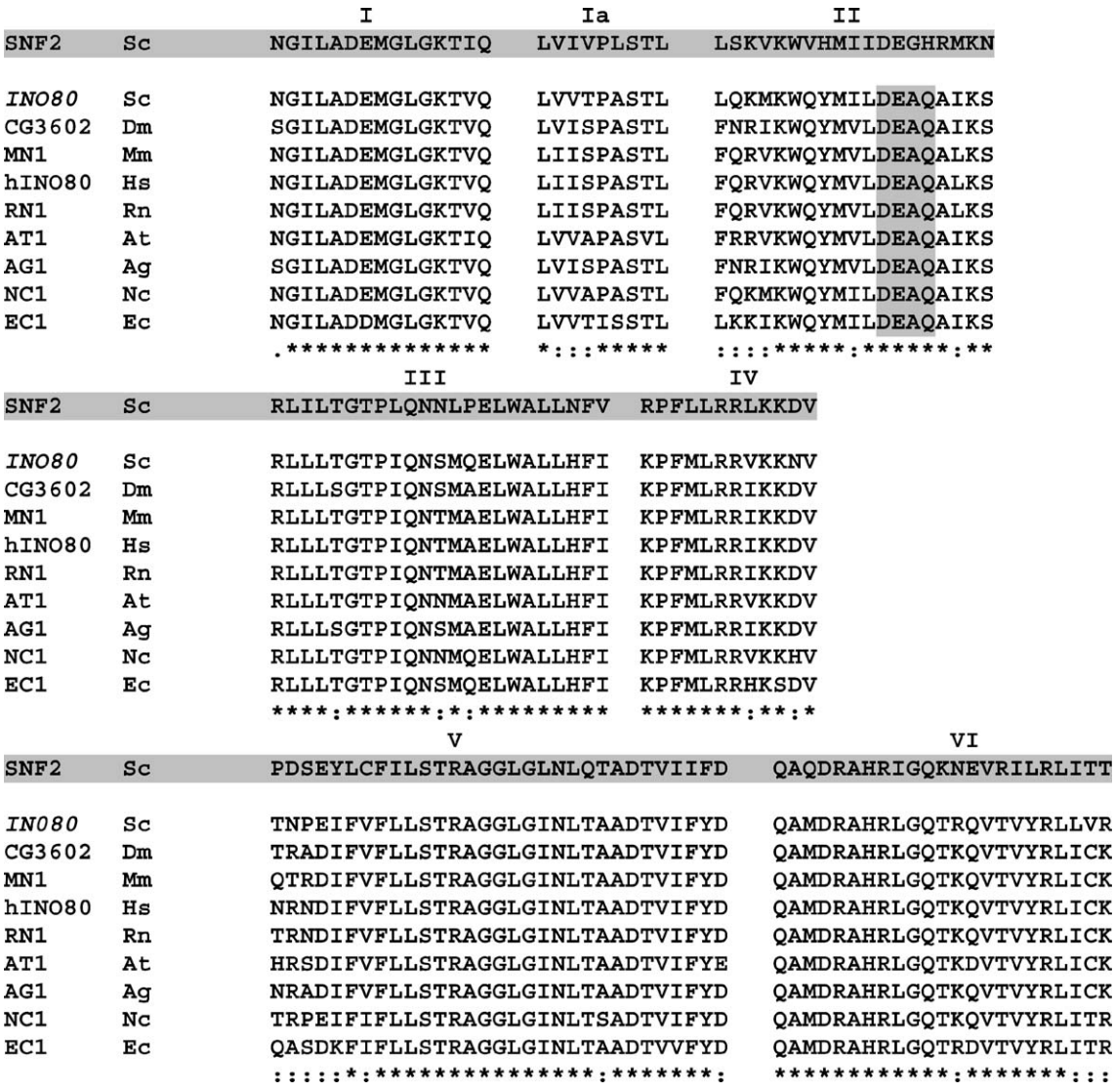

Fig. 2. Multiple sequence alignment of the proteins of the *INO80* subfamily. The alignment was derived by using CLUSTALW program (www.ebi.ac.uk using default parameters). The sequence stretches marked I–VI represent the seven highly conserved motifs of the SNF2 helicase domain. The shaded region depicts the unusual pattern that is distinct from the other known SNF2 proteins. The yeast SNF2, the founder member of the SNF2 family, is highlighted on the top. The species *abbreviations:* Rn, *R. norvegicus*; Mm, *M. musculus*; Hs, *Homo sapiens*; Dm, *D. melanogaster*; Ag, *A. gambiae*; Sp, *S. pombe*; Sc, *S. cerevisiae*; Nc, *N. crassa*; At, *A. thaliana*; and Ec, *Encephalitozoon cuniculi.*

Identification of DBINO domain

We analyzed amino acid sequences of proteins of INO80 subfamily by multiple alignments and detected a conserved sequence in all members of this family located near the N-terminus, upstream of the SNF2 helicase domain. This region is a 126 amino acid long peptide, which we designate DBINO. The selection of this stretch was based on the criterion of continuous longest conserved region in the alignment of the INO80 like proteins from different organisms (Fig. 3). In the alignment, the similarity score is found to decrease drastically beyond this region both on the N and C terminal ends of the protein. We failed to detect any known motif or domain within this sequence using databases like prosite, BLOCKS, and Pfam. Thus, in order to further characterize this domain we performed PSI BLAST searches using this sequence as a query. The PSI BLAST searches were done with an inclusion cut-off of 0.005. In the first iteration, 49 sequences were retrieved out of which 10 were above the cut-off value (*E* value range $6e-47$ to $3e-13$), all of them from SNF2 family, some of which are experimentally characterized and others computationally predicted. On further iteration as well as reverse PSI-BLAST with each member of the set as the query sequence, the same set of genes was retrieved. This implies that the point of convergence was obtained only after the first iteration of PSI BLAST. In all the proteins DBINO domain is present approximately 100 residues upstream of the SNF2 helicase domain. Fig. 3

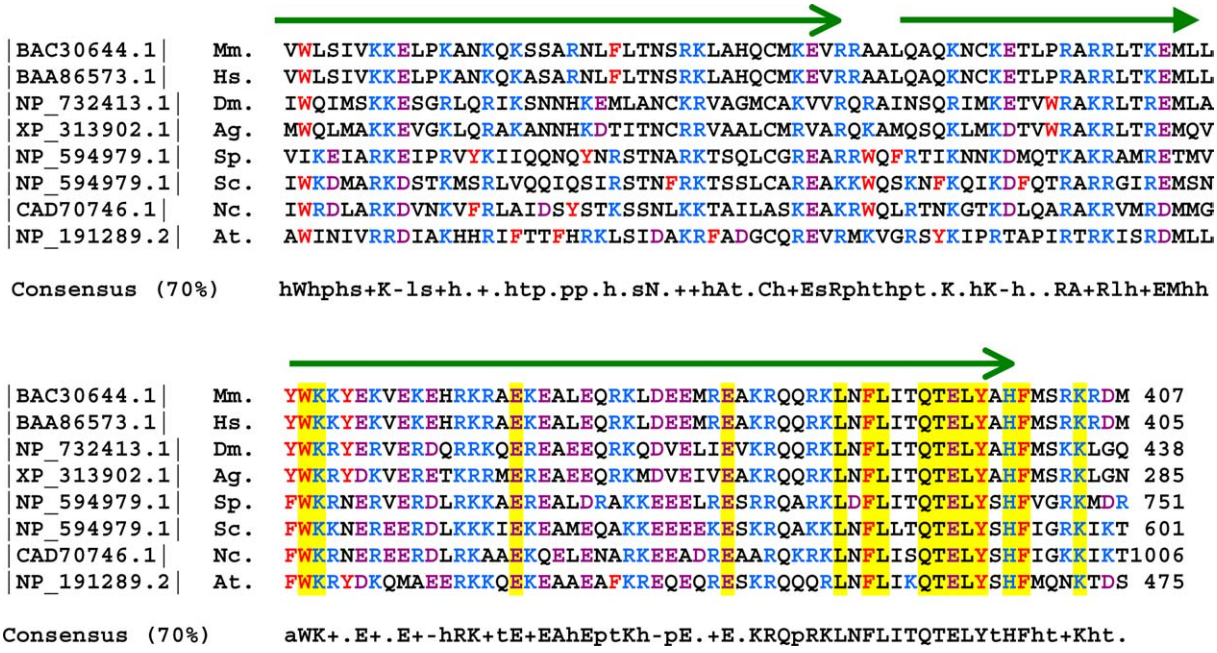

Fig. 3. Multiple sequence alignment of the DBINO domain. The alignment was constructed using PSI-BLAST searches. The sequences are denoted by accession numbers from GenBank database and abbreviated species name. The species *abbreviations:* Rn, *R. norvegicus*; Mm, *M. musculus*; Hs, *H. sapiens*; Dm, *D. melanogaster*; Ag, *A. gambiae*; Sp, *S. pombe*; Sc, *S. cerevisiae*; Nc, *N. crassa*; and At, *A. thaliana*. The positions of the last residue of the aligned region in the corresponding protein are indicated for each sequence. The positively charged residues (K, R, and H) are colored blue; the negatively charged residues (D, E) are colored purple, and the aromatic residues (F, Y, and W) are colored red. The highlighted regions show 100% homology, consensus (70%) is shown below the alignment, capital letters are specific amino acid residues, h, p denote hydrophobic (A, C, F, G, H, I, K, L, M, R, T, V, W, and Y) and polar (C, D, E, H, K, N, Q, R, S, and T) residues, respectively. The predicted α-helical regions are shown by an arrow over the aligned sequences. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this paper).

shows the multiple sequence alignment carried out using CLUSTALW.

A high degree of similarity among the protein sequences with conservation of similar amino acids at several relative positions can be seen in the alignment. The tryptophan (W) residue, having only one codon and known to be least mutable, is a rare residue in proteins, but is conserved in the DBINO domain at identical relative position in the INO80 subfamily. Such conserved tryptophan is also seen in eukaryotic homeodomain proteins, where it is essential for the stabilization of the 3D structure [24]. The most significant feature of DBINO domain is the occurrence of the positive amino acids arginine and lysine in tandem (RK/KR), in multiple positions, which are likely to bind DNA. Such motifs are also found in DNA binding proteins like chromosomal protein D1 and HMG-1, where it is thought to mediate protein interaction at A–T rich regions by contacts in the minor groove of DNA [25,26]. A similar motif is found in the C terminal end of the human homologs of yeast SNF2 (hBRM, BRG1) and within the DNA binding domain of the SNF2 gene family protein CHD1 [27,28].

Secondary structure of the domain was predicted using various softwares such as NNPREDICT, SOPMA, and JPRED and a consensus was drawn. The predicted α-helical segments are marked in Fig. 3. Hydropathy analysis of the α-helical segments identified the α helices as amphipathic wherein they expose hydrophilic side chains on one side of the helix and hydrophobic side chains on the opposite side (Fig. 4). A closer examination of the multiple sequence alignment reveals a 24 amino acid subset in the domain that has a higher identity than the neighboring amino acids among the members of this subfamily. This motif may be a part of the highly conserved core of the DBINO that is crucial for its function.

To further characterize the INO80 subfamily we generated phylogenetic trees of the proteins of the known SNF2 sub-families. These trees were generated by comparisons of the entire SNF2 helicase domain as well as the conserved motifs within the SNF2 domain. Molecular phylogenetic analysis segregates the INO80 proteins into a new single subfamily (Fig. 5). Here, we have taken representative members from all well-defined subfamilies of the SNF2 family. The Tree, which is generated for the entire ATPase domain clearly shows that the proteins of the *INO80* family are monophyletic. Earlier Linder et al. [29] have grouped Ino80 with EP400 and SRCAP based on a comparison between human SNF2-domain proteins. Similarly, Swr1, one of the SNF2 ATPases characterized recently, was suggested to

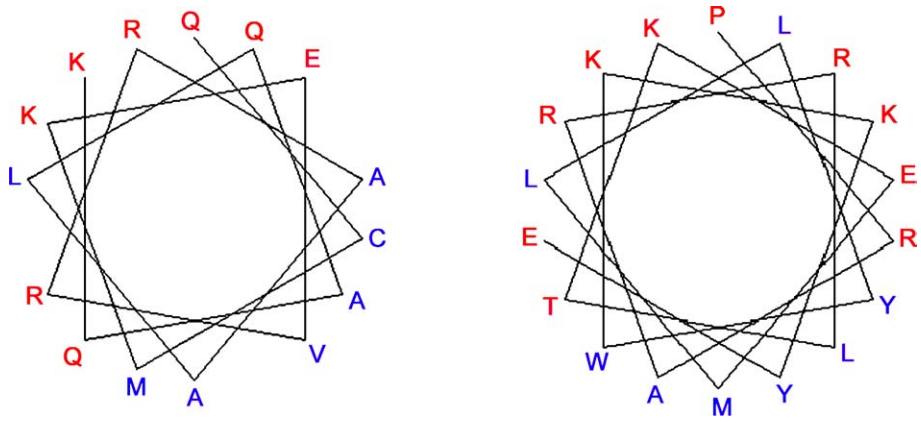

Fig. 4. The helical wheel representation of the predicted α helices. The hydrophobic residues (blue) and polar (red) are indicated. The amphipathic nature of the helices is evident. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this paper).

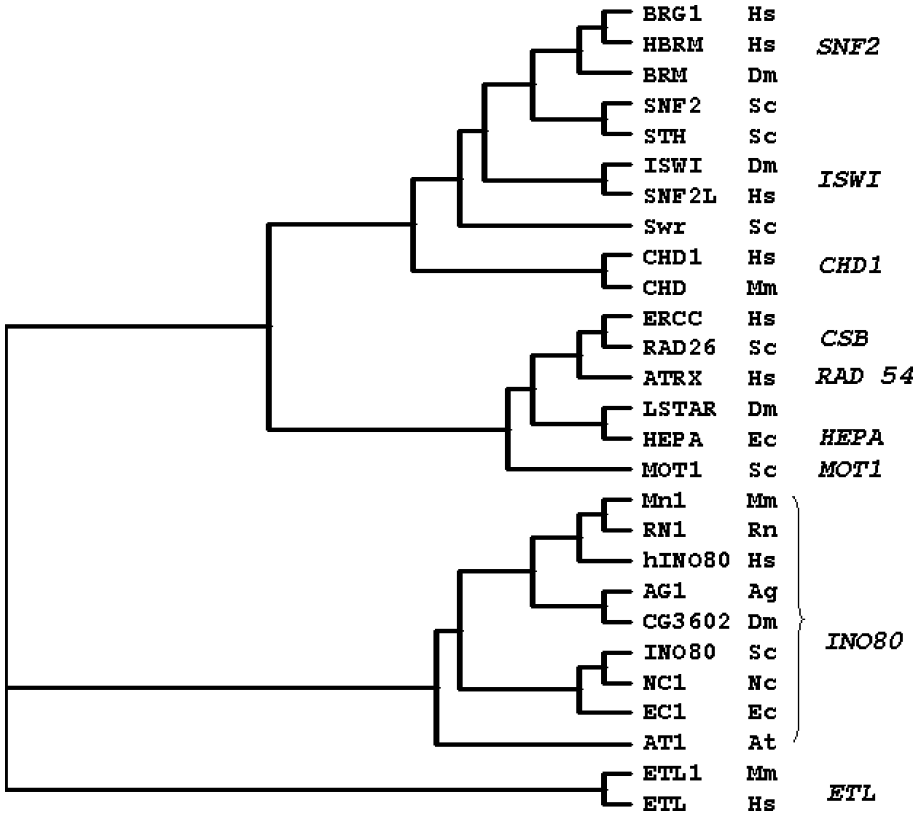

Fig. 5. Organization of the SNF2 family based on molecular phylogenetics. The tree is generated using the entire ATPase domain. The Ino80 like protein segregates into a new subfamily. The italicized font indicates the various subfamilies. Members of each subfamily are indicated in smaller font.

be similar to Ino80 based on the unusually large insertion between ATPase motifs IV and V and presence of 700 amino acids N terminal to the ATPase domain in both the proteins [30]. We find that there is no sequence conservation in the 700 amino acid stretch N terminal to the SNF2 ATPase domain between Ino80 and Swr1. Further, Swr1 does not have the DBINO domain and therefore it was not identified in the present analysis.

Putative DNA binding domains like the DBINO reported here may confer specificity on the SNF2 proteins in interactions, which target these proteins/complexes to particular structure or sequence of DNA. Recently Shen et al. [31] have reported a detailed study of the role of Actin-related proteins in INO80 complex. They demonstrated that deletion of about 326 amino acids from the N-terminal region of INO80 results in the loss of DNA

binding activity of this complex. It is interesting to note that the DBINO domain reported here maps within this region. Shen et al. [31] also show the loss of ATPase as well as DNA binding activity of INO80.com when there is deletion of ARP5 and ARP8 [31]. It may be speculated that the association of Arp may influence the conformation of INO80 protein, which in turn may have an effect both on ATPase and DNA binding activity. A preliminary result from cloned and expressed DBINO domain shows DNA binding activity (unpublished results).

Chromatin remodeling involves varied forms of protein–DNA interactions and the complexes exhibit functional differences. The SWI2/SNF2 subfamily with members like *Drosophila* brahma and the human BRM and BRG1 has an additional bromodomain in the C-terminal region and is generally involved in destabilizing DNA–histone interaction [32], while ISWI complexes possess nucleosome spacing and disruption activity [33]. The INO80 complex remodels chromatin, facilitates transcription in vitro, and displays 3′–5′ DNA helicase activity and in yeast it is known to be associated with chromosomes of dividing cells [15]. So far, other than SNF2 domain no other DNA binding domain is identified in INO80. In fact, DNA binding domain has not been identified in several SNF2 proteins. Since the putative DNA binding domain reported here is present in INO80, it is designated DBINO (DNA binding domain of INO80). The sequence conservation within, but not between, subfamilies is due to conservation of function within a subfamily. The functions of some of the uncharacterized proteins in the subfamily can be predicted by comparison with other members of the same subfamily. As *INO80* is a part of a chromatin-remodeling complex and is involved in transcription as well as DNA repair, similar functions for yet to be characterized members can be predicted. Recently, it has been reported that inositol polyphosphates can modulate the activities of several chromatin-remodeling complexes in vitro [34]. The understanding of involvement of INO80 and other multiprotein complexes in cell signaling pathways can lead to further insights into the complex mechanism of regulation of transcription in eukaryotes.

Acknowledgments

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