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FEBS J. Author manuscript; available in PMC 2014 September 12.

Published in final edited form as:
FEBS J. 2011 October ; 278(19): 3579–3595. doi:10.1111/j.1742-4658.2011.08281.x.

Mechanisms for ATP-dependent chromatin remodelling: The means to the end

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Summary

Chromatin remodelling is the ATP-dependent change in nucleosome organisation driven by Snf2 family ATPases. The biochemistry of this process depends on the behaviours of ATP dependent motor proteins and their dynamic nucleosome substrates, which brings significant technical and conceptual challenges. Steady progress has been made in characterizing the polypeptides that these enzymes are comprised of. Divergence in the sequences of different subfamilies of Snf2 related proteins suggests that the motors are adapted for different functions. Recently structural insights have suggested that the Snf2 ATPase acts as a context-sensitive DNA translocase. This may have arisen as a means to enable efficient access to DNA in the high density of the eukaryotic nucleus. How the enzymes engage nucleosomes and how the network of non-covalent interactions within the nucleosome respond to the force applied remains unclear, and it remains prudent to recognise the potential for both DNA distortions and dynamics within the underlying histone octamer structure.

Introduction

Chromatin remodelling is the directed alteration of genome packaging in the eukaryotic cell nucleus. The term is usually used to describe ATP-dependent changes in nucleosome organisation driven by Snf2 family ATPases, although it predates the discovery of those factors and is sometimes also applied to changes such as large scale nuclear reconfiguration or non-ATP driven nucleosome rearrangements.

The chromatin remodelling activity of Snf2 family ATPases was uncovered independently in *Saccharomyces cerevisiae* screens for factors contributing to expression of the *HO* nuclease required for mating type switching [1, 2], and sucrose fermentation by invertase encoded at *SUC2* [3]. Both the switching and sucrose non-fermenting (SWI and SNF) screens revealed the involvement of a gene at locus YOR290C encoding a large ATPase, since named *SNF2* [4]. Suppressors of *snf2* mutants in turn revealed SWI/SNF independent Sin^- mutants including point mutants of histone genes and other chromatin components [5-7]. Together with the observed changes to chromatin structure in *snf2* mutants at target

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loci [8], this suggested Snf2p affected chromatin structure [9]. The hypothesis was confirmed by mutagenesis *in vivo* and *in vitro* observation of the activity of complexes containing Snf2 family ATPases. Biochemical purifications and bioinformatic sequence comparisons have since revealed that Snf2 family members are ubiquitous and numerous across eukaryotes [10].

Although early identifications concentrated on Snf2 family members as general transcription factors, the *SNF2* locus had previously been identified as contributing to protection against DNA damage [11]. Subsequent investigations have shown that Snf2 family ATPases are involved in a wide variety of genomic processes including transcription, replication, repair and recombination. This suggests that ATP-dependent chromatin remodelling is a fundamental functional requirement in the nucleosome-packaged genomes of eukaryotes. However, the occurrence of Snf2 family ATPases in bacteria and archaea illustrates that the DNA-dependent ATP-driven translocase activity of the Snf2 family does not necessarily act on nucleosomes alone.

Biochemistry of chromatin remodelling

The biochemistry of ATP-dependent remodelling has been an active area of investigation for almost two decades. The challenges for this field arise because the enzymatic activities are provided by large protein complexes whose function often appears redundant and whose members are ubiquitous, and because the chromatin substrate is dynamic and its properties are incompletely understood. Although much of the published work has focused on the mechanism of remodelling on nucleosomes, several genetic screens have implicated Snf2 family members in a diverse range of functions.

Composition and structures of remodelling complexes

All recognised ATP-dependent chromatin remodelling complexes contain a large core polypeptide which includes a region of homology to the helicase-related Snf2 family ATPase (Fig. 1A). Having such a central molecular motor provides scope for a large number of potential mechanisms to drive the remodelling process. Therefore, a clear understanding of the composition and structure of remodelling complexes is crucial for constraining the many possible mechanistic models that can be imagined for remodelling.

The direct purification of remodelling complexes is technically challenging because many are large multi-protein associations comprising many small subunits (Table 1). A further complication is that some core Snf2 family polypeptides such as *S. cerevisiae* Sth1 and Isw1 participate in multiple variant complexes differing by only one or a few subunits [12, 13].

Characterising purified complexes is also challenging because of the difficulty of creating specific *in vitro* activity assays using typical methods such as changes restriction enzyme or nuclease accessibility, or in native gel mobility, which have low resolution and lack standardised kinetic parameters. Lack of clarity about the relevant biological function of complexes means defining an appropriate substrate can be confusing, and assembling substrates with specific histone post-translational modifications or defined nucleosomal arrays is technically difficult. In fact, most detailed *in vitro* assays are performed on

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nucleosomes comprising the “601” DNA sequence artificially selected for unusual stability [14] and core histones with sequence from the frog *Xenopus laevis* that lack any post-translational modifications because they are prepared in *Escherichia coli* [15].

Low resolution EM structural envelopes have been determined for the large RSC [16-19], PBAF [20] and Swi/Snf [21] remodelling complexes. These all reveal a large bowl-like shape with a central depression of appropriate size to hold a nucleosome [22]. Evidence for density consistent with the nucleosome is seen in the RSC structure [19]. A dimeric complex of Iswi subfamily member ACF on a nucleosome has also been observed [23].

Sequence classification of the Snf2 family ATPases

Due to the large number of genetic or functional investigations and the difficulty of biochemically characterising them, the core Snf2 family polypeptide is typically used as an identifier for chromatin remodeller complexes. Their sequences carry a characteristic conserved Snf2 family ATPase region, which can be located anywhere within the polypeptide (Fig. 1A). Consistent with this, exchange of the Snf2 family ATPase region has been shown to carry with it the properties of the remodelling complex [24].

An early analysis of the Snf2 family ATPase region based on only 30 sequences proposed 8 distinct subfamilies (Fig. 2A) [25]. A subsequent comprehensive classification was carried out using over 1300 family members that became available through the extraordinary recent progress in genome sequencing [26]. This confirmed the principles identified by Eisen *et al* [25], and revealed an expanded phylogeny of 23 subfamilies with the same effective topology as the original study (Fig. 2B). The equivalence based on this helicase region and the origins of nomenclature for the 17 proteins identified in *S. cerevisiae* and the 32 in the human genomes is shown in table 2. The subfamilies fall into 5 groupings, two of which contain the subfamilies most related to the archetypal *S. cerevisiae* Snf2p. These two ‘Snf2-like’ and ‘Swr1-like’ groupings were based on some 400 sequences and encompass 7 and 4 subfamilies respectively.

More recently, an alternative classification has been adopted grouping remodelling complexes into a four nominal but separate families, typically SWI/SNF, ISWI, CHD and INO80 (Fig. 2C) [10, 27]. This classification based on empirical assignments of the ATPase and flanking regions is a simplification, obscuring diversity within the CHD grouping and making it is difficult to categorise enzymes such as Alc1 [28], Lsh [29] and ATRX [30] which are likely to have chromatin related functions. It also ignores relationships with the broader range of Snf2-related ATPases. Flanking domains are presently poorly categorised and standard domain finding tools leave large areas unassigned in many sequences, making this a difficult basis for classification.

The availability of a large number of sequences enables the explicit definition of the Snf2 family by multiple alignment. Early studies had identified the ATPase was a member of helicase-like superfamily 2 (SF2) through the presence of seven helicase motifs (Fig. 1B) [31], and this formed the basis for biochemical investigations demonstrating the underlying DNA translocase activity [32]. The Snf2 family ATPases are distinguished from other SF2 members by an extended span of sequence between the two RecA domains [33]. Together

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with historical quirks in seed alignments, this has led to the Snf2 ATPase being recognised by common motif-finding algorithms as bipartite “Snf2_N” and “HelicaseC” regions. Some Snf2 family members such as those in the Swr1-like grouping (Fig. 2B) contain very large sequence regions at a specific major insertion site that generate an expansion of such scale that it confound simple alignment algorithms [26] and they have been termed ‘split ATPases’ [34].

Sequence-structure relationships in Snf2 family ATPase region

The characteristic sequence features within Snf2 ATPases (Fig. 1B) can be interpreted through the Zebrafish Rad54 structure which remains the most relevant atomic resolution model of the Snf2 family (table 3) [35]. At its core the structure is composed of the same pair of RecA domain lobes as all helicase superfamily members (Fig. 3A). The extended span of sequence between the RecA domains contributes to two alpha helical ‘protrusions’ from the spherical RecA domains. The sequence of these protrusions is not itself conserved, but amino acid residues around their bases which stabilise or ‘glue’ the protrusions to the RecA domains comprise conserved boxes H, C, J and K (Fig. 1B). Box B within the flexible ‘linker’ passing across the groove between the RecA domains contains a pair of absolutely conserved arginine residues which are essential for function [36]. The major insertion region which accommodates such variation in length is situated behind the second RecA domain, but would be adjacent to DNA towards the back of the ATPase (Fig. 3). An additional region of alpha helical structure containing conserved boxes extends from the C-terminus of the second RecA domain, forming a ‘brace’ that stretches towards the modelled DNA and includes highly conserved charged residues in boxes M and N (Fig. 3).

A structure of a Snf2 family ATPase enzyme SSO1653 from the archaeal *Sulfolobus sulfotaricus* has determined in complex with double-stranded DNA (table 3) [37]. The first RecA lobe appears to be engaged in a relevant position based on other helicase complex structures, although the second RecA lobe is probably in an non-functional orientation [38]. Using the DNA and first SSO1653 RecA lobe enables the Rad54 structure to be oriented so that DNA can be modeled on it, and confirms that Snf2 family enzymes are likely to function by the same enzymatic mechanism as other SF2 helicase-like DNA translocases (Fig. 3B).

Snf2 family proteins as allosterically regulated ATPases

Surprisingly, modeling the DNA-bound structure did not reveal an obvious mechanistic role for the characteristic protrusions, brace or linker region of the Snf2 family. Clues are provided by the recent structural investigation of the *S. cerevisiae* Chd1 protein which can remodel nucleosomes without additional subunits (Fig. 4A) [39]. Although the Chd1 diffraction was at sub-atomic resolution, the Rad54 coordinates could be used to model the high resolution orientation. This and parallel biochemical experiments show that the chromo domains flanking the ATPase region contact the protrusions and are likely to block activity by occluding DNA from its binding site on the ATPase (Figs. 4A, 4B). This is consistent with earlier observations showing genetic linkages between adjacent domains and protrusion residues in Sth1 [40]. Hauk *et al* propose that this represents ‘modular allostery’ [41] whereby DNA binding and ATPase activity is inhibited by structurally independent domains

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encoded either in sequences flanking the Snf2 ATPase or in independent subunits of the chromatin remodeling complex. The domains act as a switch or 'gate' for translocase activity.

Since all Snf2 family polypeptides contain at least one domain-size region adjacent to the ATPase [26], this suggests a fundamental property of the Snf2 family could be as DNA-dependent ATPases whose activity can be modulated by adjacent inhibitory 'gate' domains (Figs. 4C, 4D). The highly conserved alpha helical organisation but not sequences of protrusions observed in the sequence analysis [26] could provide distinctive surfaces for interactions with the inhibitory domains to set up the gating.

The high local 'concentration' of an adjacent inhibitory domain from the same polypeptide or complex means only weak interfaces are required to stabilise inhibitory binding of the gate domain to the ATPase. This allows dynamic switching of the gate across a low energy barrier when an alternative interaction for the inhibitory domain is brought into proximity (Fig. 4C). Such a switch in gating could be driven by a higher affinity epitope for the inhibitory gate domain such as methylated histones for the Chromo domain in Chd1, or the ARID domain of BAF250 for the HSA domain in Snf2 [42]. Alternatively, the switch could occur when a feature brought into proximity competes with the inhibitory binding of the gate domain and displaces it (Fig. 4D), as preferred by Hauk *et al* to explain their biochemical observations for *S. cerevisiae* Chd1 [39].

Snf2 family as context-sensitive DNA-dependent ATPases

Tight regulation of DNA-dependent ATPases makes intuitive sense in biochemical terms. The expansion in genome size during the early evolution of eukaryotes required chromatin organisation to package DNA at high density into a membrane-enclosed nucleus [43]. Adaptation of existing archael histones as nucleosomes [44] for this task would in turn require a remodelling machinery which could be provided in part by the Snf2 family of ATP-driven, DNA-stimulated DNA translocases that also existed in archaea and bacteria [25, 26]. Their distinctive modular allosteric regulation would reduce wasteful turnover of ATP in the high concentration of DNA substrate by providing a context-dependent switch via the inhibitory gate domain [39]. Subsequent specialisation in this context-dependence would explain the diversity of Snf2 family members in eukaryotes that targets chromatin remodelling for highly specific functions.

The need to remodel the chromatin substrate for genomic access provides a large number of possible roles for Snf2 family proteins and is understandably the focus of most functional investigations. However, there are a number of other potential uses for DNA translocases regulated by context in the eukaryotic nucleus. Examples include the Rad54 subfamily role in establishment and progress of homologous recombination repair [45], the Mot1 subfamily role in TBP cycling at promoters [46], and the ERCC6 subfamily roles in RNA polymerase passage through DNA lesions [47]. Interestingly, Mot1 and ERCC6 subfamily members are the most similar to non-eukaryotic Snf2 family proteins (Fig. 2B) [26].

The biological function of *S. sulfotaricus* SSO1653 is unknown and the type strain has an inactivating transposon inserted in this gene. More distantly related bacterial RapA proteins

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are found at the edge of the Snf2 family and their *E. coli* archetype has been shown to have a role in RNA polymerase recycling at promoters [48]. The structure of RapA has been solved (table 3) [49] and its core retains a Snf2 family-like organisation with a protrusion and brace on RecA lobe 2, although the protrusion on lobe 1 is less similar to other structures (Fig. 5). The RapA structure contains additional domains that could act as allosteric gates (Fig. 5C), and biochemical observations are consistent with gating [50]. The yet more distant archael *Pyrococcus furiosus* Hef protein related to Mph1 in *S. cerevisiae* and human FANCM is a true DNA helicase and also has a protrusion and potential brace on RecA lobe 2 [51] (see supplementary data in [26]). Two distantly related non-Snf2 family helicases, archaeal *Archaeoglobus fulgidis* XPB and *Drosophila melanogaster* Vasa, mainly retain similarity to helicase motifs in the core RecA domains of the Snf2 family and lack any additional motifs in common with the Snf2 family (table 3).

Abundance and localisation of chromatin remodelling complexes

In addition to their diversity, remodelling complexes are surprisingly highly abundant nuclear components (table 1). In fact, the ATPase subunit of Swi/Snf is by far the least abundant of the recognised nucleosome-active remodelling complexes in *S. cerevisiae* and its less extensive roles may have facilitated its historical identification. The combined abundance of the Snf2 subfamily members Sth1 and Snf2 equates to approximately 1 enzyme for every 34 nucleosomes, or less than one per gene, and may correlate with an occasional requirement for these enzymes to undertake specific activities such as nucleosome ejection. The chromatin organizing enzymes Isw1, Isw2 and Chd1 are considerably more abundant at 1 enzyme for every 16 nucleosomes, perhaps reflecting a more general role for these enzymes in nucleosome spacing by sliding. The Fun30, Ino80 and Swr1 enzymes likely to have functions relating to histone exchange have overall abundance sufficient to equate to one for every 5 nucleosomes. The reason for requiring an average of more than one histone exchanger per gene is not yet apparent. It may be that in addition to performing functions relating to the directed incorporation of histone variants, some of these enzymes could have a destabilizing effect on chromatin by removing histone dimers, for example during the transit of polymerases.

Accessory subunits in multi-protein complexes and flanking domains in the Snf2 family ATPase polypeptide frequently encode subunits known to interact with chromatin, often with specificity for post-translational modifications or histone variants. This has led to the suggestion that a basic property of chromatin remodellers is that they recognise covalent histone modifications [10]. As discussed above, one function for histone recognition interactions may be to provide an allosteric regulatory mechanism to activate the remodeller in presence of its substrate [39]. A second function may be the need for the remodelling complex to maintain affinity with the nucleosome substrate.

However, the most widely recognised function for chromatin recognition domains in remodellers is to target remodelling complexes to sites of action. In this respect a potential problem is the fact that most histone binding domains have only modest affinity for epitopes. This would be anticipated to result in significant non-specific interactions with chromatin not bearing the appropriate modification. However, the localization of histone

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modification is often diffuse rather than punctuate meaning that the local concentration of epitopes in specific regions of the nucleus may be sufficient to generate a localised enrichment in enzyme (see accompanying review by Erdel and Rippe [52]). As some remodelling enzymes contain epitopes that are capable of recognising similar modifications [53], and many modifications share similar distributions [54], there is the potential for multiplicity and redundancy of remodelling complexes associated with large scale processes [52] such as the repair of DNA double strand breaks [55], in establishing higher order chromatin structures [56], or in transcription [57].

Translocation by Snf2 family ATPase acting on nucleosomes

Significance of the remodelling mechanism

The pathway of chromatin remodelling has great functional significance because of its implications for the exposure of DNA sequences, the organisation of the genome, and the exchange of histone proteins. Firstly, chromatin packaging generally obscures DNA so local recruitment of remodellers is required to facilitate access for genome-active processes. Secondly, genome-wide localisation shows that nucleosomes are very uniformly spaced despite the diversity of underlying DNA sequences. Deletion analysis in *S. cerevisiae* reveals that the spacing activity is contributed redundantly by Isw1, Isw2 and Chd1 [58], but can be locally manipulated by the effect of specialised sequences on remodelling [59]. Similar observations have been made in *Schizosaccharomyces pombe* for the role of related Mit1 family member [60]. Thirdly, remodelling has the potential to destabilise histone-DNA contacts that provide the link between histone post-translational modifications and bound DNA sequences [56]. The remodelling mechanism must be structurally conservative to avoid erasing such epigenetic information.

Chromatin remodelling as a nucleosome response

The molecular mechanism of remodelling has been the subject of hypothesis for many years, possibly because the mechanical parallels are intuitively accessible and because biochemical details of remodelling enzymes and chromatin substrates have been limiting.

Nucleosomes are the repeating molecular subunit of chromatin and therefore likely to be the direct substrate for chromatin remodelling. A number of different outcomes have been proposed as an end result of remodelling on nucleosomes [10], principally the repositioning of the histone octamer relative to DNA (sliding), replacement of part or all of the octamer (exchange) or removal of all or part of the histone octamer (ejection). It is also formally possible that the canonical nucleosome structure could be reconfigured to a stable alternative (switching), but this remains somewhat controversial [61-63].

Fundamentally ATP-dependent chromatin remodelling is an enzymatic process with the remodeller accelerating the rate of change between a substrate and product state. In contrast to textbook enzymology where individual covalent bonds are manipulated at localised sites, chromatin remodelling involves non-covalent process on a 200 kDa substrate. This can lead to confusions of scale because the end product of remodelling such as a slid nucleosome may be the result of a large number of stepwise turnovers of the ATPase enzyme itself. A destabilised nucleosome is not the ‘transition state’ of an individual enzyme cycle, it is the

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consequence of multiple enzyme cycle products building up on the nucleosome. This link between ATPase cycles of the remodelling enzyme and nucleosome outcomes is usually what is implied by “mechanism of remodelling”. It depends on how the ATPase cycle products are applied to the nucleosome, and the response of the nucleosome.

Remodelling complex structure and substrate binding

A crucial element in the mechanism of remodelling is the dynamic potential of the multiple of weak interactions within the nucleosome structure itself, and how the chromatin remodeller directs these along a specific pathway. Compositional and structural information gathered for chromatin remodellers (tables 1, 3) suggests two general classes by which remodelling enzymes might engage with the nucleosome substrate.

Firstly, a large remodelling machinery could envelop the entire nucleosome to control its dynamic properties (Fig. 6A). Since the nucleosome is a 200 kDa complex and volume scales with r^3 for a simple sphere, this implies that an enveloping structure twice the radius of a nucleosome will have approximately 8 times its mass. Many multi-protein remodelling complexes are in the range of 1-2 MDa and EM image reconstructions are consistent with the ability to surround substrate nucleosomes [19].

Secondly, a simplified remodelling machinery could cantilever across the nucleosome (Fig. 6B) as a minimal alternative to envelopment. The non-ATPase region of *D. melanogaster* ISWI describes a long cylinder-like structure of 100Å length and 20Å diameter composed of HAND, SANT and SLIDE domains [64] that would be of appropriate size for such a spanning capability, and its length is conserved across Iswi subfamily proteins [26]. Arrangements equivalent to a cantilever have been modelled [65].

One feature of both enveloping and cantilever complexes is that they achieve “template commitment” to allow multiple ATPase cycles while retaining interactions with transiently destabilised nucleosomes as effects are accumulated [66, 67]. A second feature of the stabilising interactions provided by the remodeller is that they will constrain the motions of the malleable nucleosome that could otherwise flex in different ways under an applied force. This feature may therefore be crucial to enabling the remodelling process to follow a specific mechanistic pathway.

Multiple remodellers or multiple nucleosomes

Although diagrams such as those in figures 6A and 6B show a single remodeller engaged with a single nucleosome, the dyad symmetry of the nucleosome implies chromatin remodellers should bind as dimers. Indeed there is evidence that the ATPase subunits of some enzymes are dimeric [68, 69], or bind to nucleosomes as dimers [23, 67]. Alternatively, it is possible that remodeller association creates asymmetry, for example by blocking binding of a second enzyme (Fig. 6C). Asymmetry is observed in some RSC structures [17].

It is also possible that one chromatin remodelling complex could work on a dinucleosome substrate. Nucleosomes are typically found in genomes at high densities meaning that following repositioning an encounter with a neighbour is a distinct possibility. It has been

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proposed that collisions between adjacent nucleosomes could act as a stage in the disassembly of nucleosomes [70-72]. Conversely, enzymes that act to space nucleosomes may stabilise chromatin. In this case, in order to prevent collisions a means of sensing the adjacent nucleosome is required. Possible binding arrangements could include cooperation between remodellers on adjacent nucleosomes, or binding of a single remodeller to span adjacent linkers. However, in the simplest case contacts with linker DNA adjacent to a nucleosome enzyme complex are important for full activity so when adjacent nucleosomes interfere with these linker DNA contacts, movement in the direction of the adjacent nucleosome would be reduced.

Mechanism of nucleosome dynamics

Snf2 translocation on nucleosomes

When a remodelling complex is bound to a nucleosomal substrate the core Snf2 ATPase motor provides a double-stranded DNA translocase which can move directionally on the DNA duplex (see accompanying review by Croquette *et al* [73]). Template commitment suggests that the complex also maintains contact with the histone components throughout the remodelling process. Termination will occur when the remodelling complex can no longer act on the nucleosome, for example because it has been disrupted or reached a position where necessary flanking DNA is not available due to proximity with another nucleosome or some other barrier.

The capability of the Snf2 translocase for processive and directional movement is demonstrated by single molecule observations showing rapid development of induced torsion, and biochemical experiments showing blockage by hairpins, or single stranded gaps [68, 74-77]. Other SF2 double-stranded DNA translocases are observed to have apparent ‘kinetic’ step sizes distinguished by rate-determining steps down to 3-4 bp, and distinct ‘mechanical’ step sizes of 3-11 bp per ATP hydrolysis cycle [78]. Some estimates of step sizes for Snf2 family proteins have been relatively large [76] but the advent of more sophisticated detection techniques has led to progressively smaller steps with pauses every few base pairs being detected [67]. Further studies will be required to determine whether movements of several bases can be broken down into single base steps and to establish whether this applies to all Snf2 related enzymes.

The step size is of great interest as it has the potential to influence the amount of rotation generated during the remodelling process. A series of recent observations support the association of the ATPase region with nucleosomal DNA at superhelical location 2 (SHL ±2). This includes evidence that DNA gaps appear to block the action of Snf2 and Iswi subfamily remodelers when introduced at this location [76, 77, 79] and directed crosslinking consistent with an interaction of the ATPase at SHL ±2 [65, 80]. This location coincides with an important structural feature within the nucleosome; the apparent high stability across the region between superhelical locations SHL −1.5 and SHL +1.5. Stability is reflected in the high uniformity and reduced dynamics of the region in crystal structures on multiple DNA sequences [81], increased number of histone-DNA contacts in the region [82], and histone SIN mutations reducing DNA contacts which also accelerate nucleosome sliding

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[83]. This has been taken to suggest that that Snf2 related enzymes target a region of the nucleosome that is rate limiting for dynamics.

It is possible that DNA sequences may affect the outcome of remodelling [84] either by affecting the opportunity for engagement by Snf2-related enzymes or the response of the nucleosome to forces applied by the remodeller.

A dynamic histone octamer?

Most commonly proposed mechanisms indirectly imply that DNA is being remodelled across a static histone octamer surface. However, recent interest in nucleosome dynamics has accumulated evidence that various parts of the histone octamer may readily flex and change their binding to DNA. For example, the most external turns of DNA are known to be readily released in the process of site exposure [85, 86], and H2A-H2B dimers can be displaced [87] such that they even become exchangeable at a significant rate during remodelling [88]. Tetramers of H3 and H4 have been observed to adopt conformations that differ from those observed within octamer and nucleosome structures [89-91]. It is possible that a concerted pathway occurs during remodelling involving rearrangements in the histone octamer that weaken histone-DNA contacts altering the energetics of DNA passage across its surface. The repertoire of mechanisms proposed for remodelling may be able to be expanded from the widely discussed twist defect and bulge diffusion models and variations on them (reviewed in [92] and accompanying review by Blossey and Schiessel [93]).

Conclusion

The biochemistry of chromatin remodelling remains a highly energetic and fruitful field. The complexity of understanding the behaviours of dynamic mechanical enzymes on dynamic mechanical substrates poses significant demands on biochemical techniques more suited to homogenous and stable molecules. Likewise, mechanistic thinking has been coloured by conceptual models of rigid bodies that hide details of local structure and malleability.

The growing sophistication of both experimental and conceptual analyses is therefore crucial to a full understanding. The biochemistry of the cell involves a number of fundamental processes for which one universal and highly conserved solution has evolved due to the complexity of factors involved. It appears that directed alteration of chromatin structure by Snf2 family enzymes is such a process. They provide the means to an end required as a consequence of high-density chromatin packaging in eukaryotes.

Acknowledgments

AF is supported by a Science Foundation Ireland and the Health Research Board of Ireland. TOH is supported by Wellcome Trust Senior Fellowship 064414.

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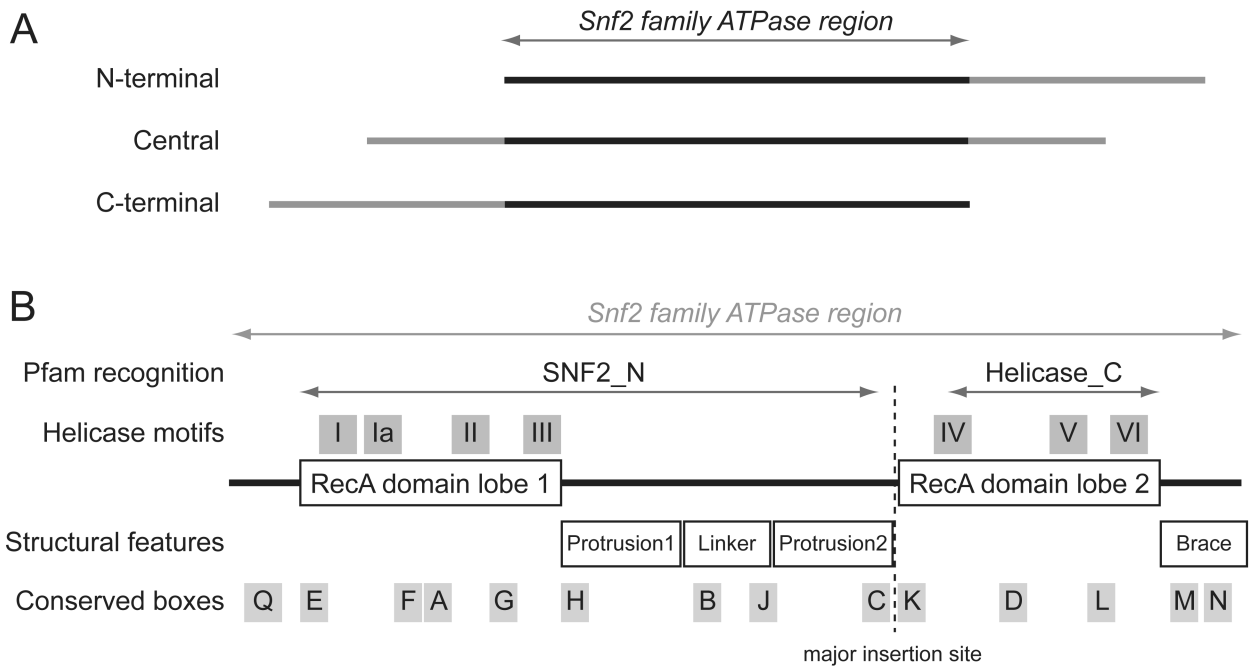

Fig 1.

Sequence and structural features of the Snf2 family ATPase region. (A) Snf2 ATPase region is embedded in full length polypeptide, and can be central, N-terminal or C-terminal. (B) Motifs, conserved boxes and structural elements within the Anf2 ATPase region as defined by Flaus *et al* [26] are shown relative to paired RecA domain lobes. Not to scale.

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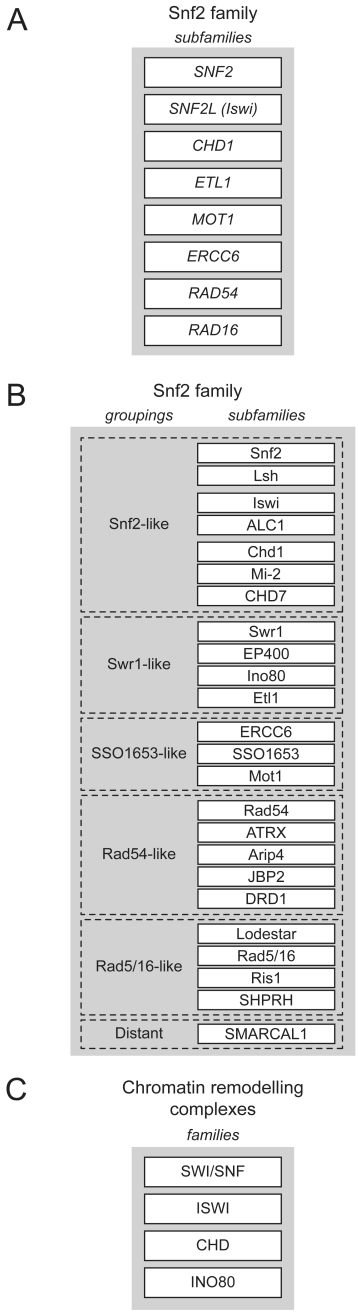

Fig 2.

Snf2 family classification schemes. (A) Original subfamilies defined by sequence comparison of Eisen *et al* using ATPase and flanking sequences [25]. (B) Schematic of subfamilies defined by expanded phylogenomic comparison of Flaus *et al* using Snf2 family ATPase region [26]. Subfamilies take name and nomenclature from first biochemically identified archetype. (C) Example of an empirical classification of chromatin remodelling enzymes into separate families [10].

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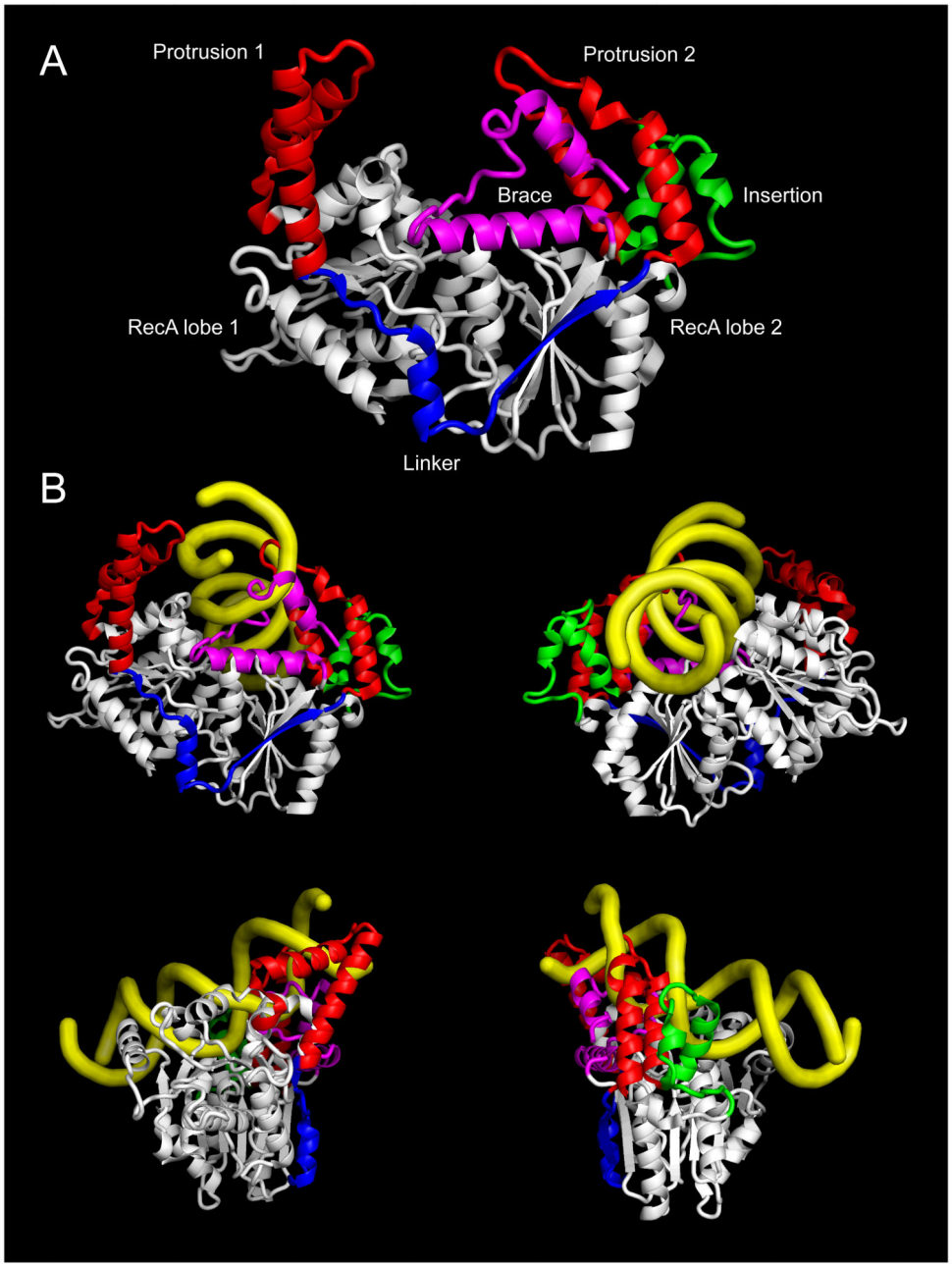

Fig 3.

Structural components of Zebrafish Rad54 Snf2 family ATPase region. (A) Snf2 ATPase region showing RecA domain lobes (white), protrusions (red), linker (blue), brace (magenta) and insertion (green). From PDB code 1Z3I. (B) Modelling of DNA path on Zebrafish Rad54 by alignment of RecA lobe 1 of *S. solfataricus* SSO1653 structure. Structure PDB codes 1Z3I and 1Z63 [35, 37].

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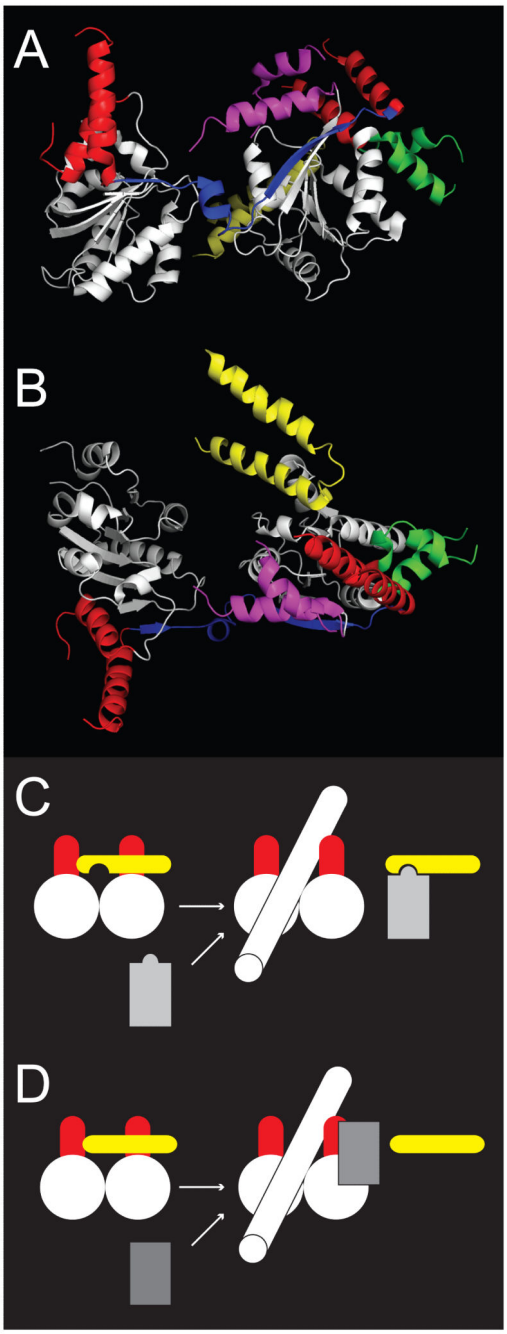

Fig 4.

Modular allostery by inhibitory gate domain to prevent DNA binding to Snf2 ATPase. (A) *S. cerevisiae* Chd1 ATPase region with equivalent orientation and colouring to Rad54 in fig 3A. Chromowedge domain (yellow) at rear. (B) View from A rotated 120° to illustrate Chromowedge domain association with protrusion 2 and RecA lobe 2. (C) Schematic of modulation by switching of ‘gate’ domain (yellow) on Snf2 ATPase through introduction of an alternative binding site (light grey). (D) Modulation by competition with ‘gate’ domain

(yellow) through introduction of a competitor for Snf2 ATPase binding (dark grey). Structure PDB code 3MWY [39].

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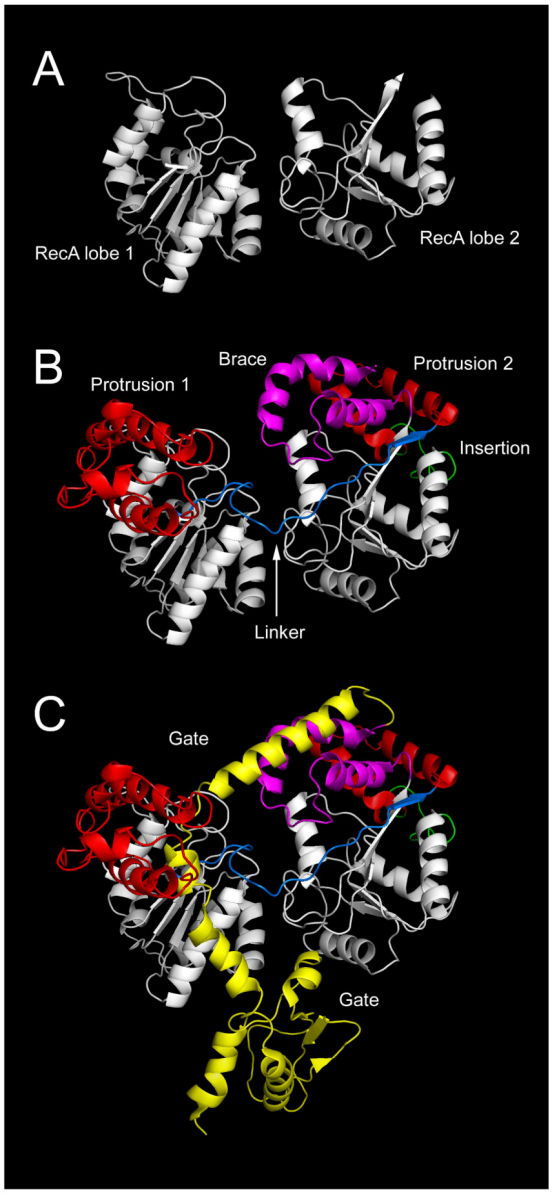

Fig 5.

Similarity of Rad54 and RapA structures. (A) Conserved RecA lobes in equivalent orientation to fig 3. (B) Characteristic Snf2 family structures including protrusions (red), linker (blue), insertion region (green) and brace (magenta). (C) Additional structure (yellow) potentially acting as modulatory gate in *E. coli* RapA. Structure PDB code 3DMQ [49].

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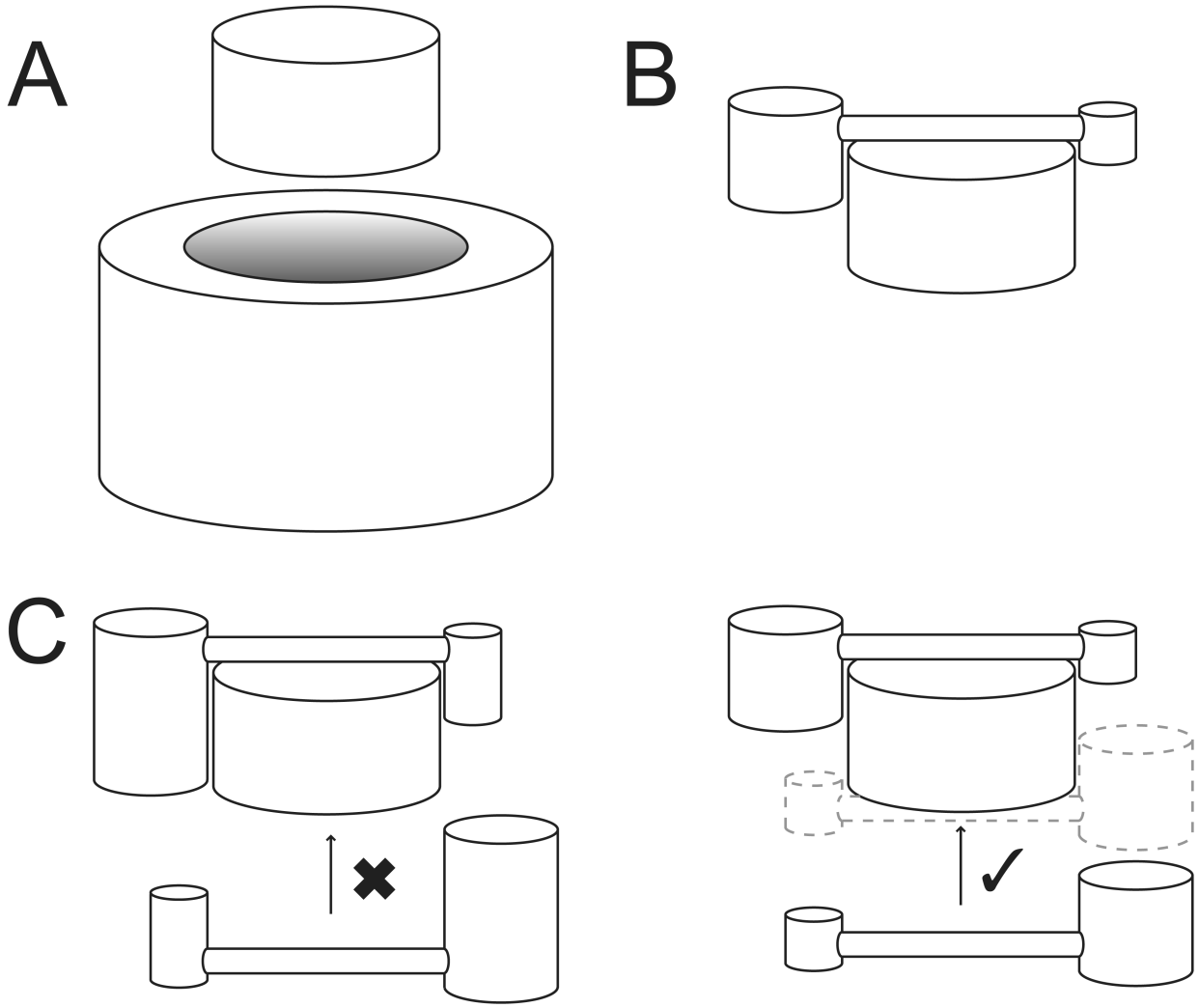

Fig 6.

Possible binding orientations for remodellers on nucleosomes. (A) Enveloping of nucleosome by remodeller. (B) Cantilevering of remodeller across nucleosome. (C) Examples of monomeric dimeric and dimeric remodeller binding to nucleosome by blocking (left) or enabling (right) of symmetric second site.

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Table 1

S. cerevisiae Snf2 family abundance and complex involvement.

Snf2 family member	Grouping	Molecules/cell	Nucleosome/remodeller	Complex	Subunits/complex	Refs
Snf2	Snf2-like	217	337	SWI/SNF	11	[21, 94, 95]
Sth1	Snf2-like	1990	37	RSC	15	[12, 96, 97]
Isw1	Snf2-like	1500	49	Isw1a/Isw1b	2/3	[13]
Isw2	Snf2-like	1520	48	Isw2	4	[80, 98]
Chd1	Snf2-like	1620	45	Chd1	1	[99, 100]
Irc5	Snf2-like	-	-	Lsh	?	
Swr1	Swr1-like	656	112	Swr1	~12	[101-104]
Fun30	Swr1-like	6800	11	Fun30	1	[69, 105]
Ino80	Swr1-like	6280	12	Ino80	~12	[106, 107]
Rad54	Rad54-like	-	-	Rad54	1-2	[108, 109]
Rdh54	Rad54-like	1270	58	Rdh54	?	[109-111]
Rad5	Rad5/16-like	1520	48	Rad5	3	[112, 113]
Rad16	Rad5/16-like	358	204	Rad16	2-3	[114, 115]
Irc20	Rad5/16-like	143	512	?	?	[116]
Ris1	Rad5/16-like	-	-	Ris1	?	[109, 117]
Rad26	Sso1653-like	-	-	Rad26	?	[118, 119]
Mot1	Sso1653-like	6260	12	Mot1	2	[120-122]

Subfamily groupings from [26]. Molecules per cell from [123]. Nucleosomes per remodeller based on 1 nucleosome per 165bp in 12Mbp genome. Complex subunits from indicated references. No data available for abundance of Irc5, Rad54, Rad26 or Ris1.

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Table 2

Nomenclature of Snf2 family members in *S. cerevisiae* and Human

Snf2 subfamily	Grouping	*S. cerevisiae* genes	*S. cerevisiae* nomenclature	Human genes	Human nomenclature
Snf2	Snf2-like	SNF2, STH1	Sucrose Non Fermenting, Snf Two Homolog	SMARCA4/BR G1, SMARCA2/hB RM	Brm-Related Gene, human BRahMa-like
Iswi	Snf2-like	ISW1, ISW2	Imitation SWitch	SMARCA1/SN F2L, SMARCA5/hS NF2H	SNF2-Like, human SNF2 Homologue
Lsh	Snf2-like	IRC5	Increased Recombination Centres	HELLS/SMAR CA6	HELicase, Lymphoid-Specific
ALC1	Snf2-like	-		ALC1	Amplified in Liver Cancer
Chd1	Snf2-like	Chd1	Chromo Domain containing	CHD1L	CHD1-Like
Mi-2	Snf2-like	-		CHD3, CHD4, CHD5	CHD1-like
CHD7	Snf2-like	-		CHD6, CHD7, CHD8, CHD9	Chd1-like
Swr1	Swr1-like	SWR1	?	SRCAP	Snf2-related CREBBP activator protein
EP400	Swr1-like	-		EP400	E1A binding protein p400
Ino80	Swr1-like	INO80	INOsitol biosynthesis	INO80	INO80 homolog
Etl1	Swr1-like	FUN30	Function UNknown	SMARCAD1	SMARCA containing DEAD/H box
Rad54	Rad54-like	RAD54	RADiation sensitive	RAD54L, RAD54B	RAD54-Like, RAD54 homologue B
ATRX	Rad54-like	-		ATRX	Alpha Thalassemia/mental Retardation syndrome X-linked
Arip4	Rad54-like	-		RAD54L2	RAD54-Like 2
Rad5/16	Rad5/16-like	Rad5, Rad16	RADiation sensitive	HLTF/SMARC A3	Helicase-Like Transcription Factor
Ris1	Rad5/16-like	ULS1	Ubiquitin Ligase for SUMO conjugates	-	
Lodestar	Rad5/16-like	-		TTF2	Transcription Termination Factor, RNA polymerase II
SHPRH	Rad5/16-like	IRC20	Increased Recombination Centres	SHPRH	SNF2 Histone linker PHD RING Helicase
Mot1	Sso1653-like	MOT1	Modifier Of Transcription	BTAF1	B-TFIID Transcription Associated Factor
ERCC6	Sso1653-like	RAD26	RADiation sensitive	ERCC6, ERCC6L, C9orf102	Excision Repair Cross-Complementing rodent repair deficiency, complementation group 6, chromosome 9 open reading frame 102
SMARCAL1	Smarcal1-like	-		SMARCAL1, ZRANB3	SMARCA Like, Zinc finger, RAN-Binding domain containing 3

Nomenclature of Snf2-related proteins using subfamily and grouping classifications from [26] based on alignments of the helicase-like region. Subfamilies are named from the first reported archetype in any organism. *S. cerevisiae* nomenclature is from Saccharomyces Genome Database and human nomenclature is from ENSEMBL using official Human Genome Naming Commission symbols. Some members are known by a SMARCA acronym standing for for “SWI/SNF-related, Matrix-associated, Actin-dependent Regulator Chromatin group A”. Where common alternatives are used alongside SMARCA nomenclature, the official HGNC name is shown first.

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Table 3

Structures related to Snf2 family ATPase region.

Protein	Organism	PDB	Resolution	Snf2 family homology	Identity/Similarity to Snf2p	Ref
Chd1	*S. cerevisiae* Budding yeast	3mwy	3.7Å	e^{-144}	45%/65%	[39]
Rad54	*D. rerio* Zebrafish	1z3i	3.0Å	e^{-128}	33%/54%	[35]
Sso1653	*S. sulfotaricus* Archaea	1z63	3.0Å	e^{-125}	26%/44%	[37]
RapA	*E. coli* Bacteria	3dmq	3.2Å	e^{-36}	27%/46%	[49]
Hef	*P. furiosus* Archaea	1wp9	2.9Å	e^{-16}	28%/49%	[51]
XPB	*A. fulgidus* Archaea	2fwr	2.6Å	e^{-16}	15%/34%	[124]
Vasa	*D. melanogaster* Fruit fly	2db3	2.2Å	e^{-13}	19%/38%	[125]

Helicase-like superfamily 2 (SF2) structures in Protein Data Bank (PDB) related to Snf2 family by homology of ATPase region. Similarity shown as expectation value for hmmsearch hit with Snf2 family model [26] to PDB database. Identity and similarity for global alignment to Snf2 residues 767-1222 using EMBOSS stretcher. PDB code is for most relevant structure where multiple related accessions deposited.