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Human ATP Binding Cassette (ABC) Transporters: A Phylogenetic Investigation

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Abstract: ***Till date the largest known family of transporters is ABC transporter superfamily. The genes that encode ABC genes are widely dispersed in genome and show a high degree of amino acid sequence identity among eukaryotes. Phylogenetic analysis has allowed the gene superfamily divided into seven subfamilies containing 49 members of proteins in human. Despite the immense amount of biochemical studies, and recent advances in the visualization of ABC transporters, answers to critical questions about their translocation mechanisms have remained elusive. Hence, genomic identification of these transporters will allow choosing correct molecule based on their genomic heterogeneity and mode of behavior in human. The full amino acid sequences of all known seven subfamilies of human ABC transporter proteins were retrieved from NCBI website. Phylogenetic analysis was performed using "Phylogeny.fr". The topologies of the full (ABCB1) and half ABC (ABCG2) transporters were identified using TOPCONS consensus prediction. Secondary structures of full (ABCB1) and half (ABCG2) ABC transporters were also predicted by Protter. Our analysis showed that ABC proteins are a highly dynamic group that has undergone a significant diversification after the divergence of human species. High gene loss events were observed during the process of gene duplication and this resulted in a great variety of different subfamily of ABC proteins in human. A remarkable variation was observed in the members of the full-length transporters as compared to half-size transporters. The present study can be used for classifying human transporters from other individuals and for a further in-depth characterization of members of these highly important groups.***

Keywords: Human ABC transporters, phylogenetic analysis, secondary structure prediction, topology modeling, full and half-size ABC transporters

1. Introduction

In large human genome (3150Mb), 1022 transporters have been identified till date in which 0.32 transporters are found at per Mb genome. As compared to other transporters 36.1% ABC transporters have been documented throughout the human genome (Table 1). The transport of specific molecules across the cell membrane is an important function of all cellular living organisms. This function requires a large number of specific transporters. Till date the largest known family of such transporters is ABC transporter superfamily. The ABC proteins bind with ATP and utilize the energy to drive the necessary substrates across the plasma membrane as well as intracellular membranes of endoplasmic reticulum, mitochondria and peroxisome (Theodoulou et al. 2006). ABC transporters are organized as either full transporters containing two transmembrane or two nucleotide binding motif or as half transporters containing one of each domain (Vishwakarma et al. 2014). The genes that encode ABC genes are widely dispersed in genome and show a high degree of amino acid sequence identity among eukaryotes. Phylogenetic analysis has allowed the gene superfamily divided into seven subfamilies containing 49 members of proteins in human (Dean et al., 2001 & 2005). Most of these transporter proteins are involved in translocation of a variety of molecules including amino acids, sugars, metal ions and a variety of metabolites and hydrophobic compounds across extra and intra cellular membrane.

To date, there are 49 members of ABC transporters have been identified in human each has their own phylogenetic association in genome distribution (Dassa et al. 2001). The studies published related to human ABC transporters are very less and does not give very clear information for their involvement in different functions and genome wide variability in different subfamilies. Considerable efforts have been directed to understand the detailed mechanism of ABC transporters in bacteria and yeast (Kovalchuk et al. 2010; Gottesman et al. 2002). Despite the immense amount of biochemical studies, and recent advances in the visualization of ABC transporters, answers to critical questions about their translocation mechanisms have remained elusive. A better understanding of ABC transporters is required a combination of structural, biophysical, biochemical and physiological studies.

Table 1: Distribution of transporter proteins in human genome

Genome size (Mb) 3150	
Total transporters 1022	
No of transporters per Mb genome 0.32	
TRANSPORTER TYPE TOTAL PROTEINS (PERCENT)	
ATP-Dependent 139 (13.6%)	
Number Percent	
ABC Family 53	53
ArsAB Family 1	1
F-ATPase Family 2	2
IISP Family 15	15
MPT Family 23	23
P-ATPase Family 45	45

Our previous studies have revealed that ABC transporters are highly diversified molecules in their structure and function (Vishwakarma et al. 2014). Each transporter has different level of expression in different tissues. Hence, genomic identification of these transporters will allow choosing correct molecule based on their genomic heterogeneity and mode of behavior in human. Therefore, we focused on phylogenetic analysis of complete amino acid sequence of each subfamily of human ABC transporters separately and full-length and half-size transporters. We compared the membrane topology of full length and half-size human ABC transporters by predicting protein secondary structures and consensus prediction using TOPCONS.

2. Methods

The full amino acid sequences of all known seven subfamilies of human ABC transporter proteins were retrieved from National Centre of Biotechnology Information (NCBI) website. ABCISSE database site was used for getting information about sequence, structure and evolution of human ABC transporters (ABCISSE database). PROSITE was used understanding the site and patterns of transporter proteins (Bairoch, 1992). Phylogenetic analysis was performed using 'One click mode' with the online available tool "Phylogeny.fr" described elsewhere (Dereeper et al. 2008; Dereeper et al., 2010). It runs and connects various bioinformatics programs to reconstruct a robust phylogenetic tree from a set of sequences. The Phylogenetic tree was constructed using neighbor-joining, minimum evolution and maximum parsimony algorithms and bootstrapping with 500 replicates. First, ABC transporters of each family were separated into subfamilies by their comparison. Afterwards, full length and half-size transporters were analyzed separately. G Block program was used to eliminate poorly aligned positions and divergent regions. Further the topologies of the full (ABCB1) and half ABC (ABCG2) transporters were identified using TOPCONS consensus prediction. Secondary structures of full (ABCB1) and half (ABCG2) ABC transporters were also predicted by Protter online web tool.

3. Results and Discussion

Total known 49 human ABC transporters identified till date were used in our analysis. All the ABC transporters were grouped as per their seven designated subfamilies A to G. So within the defined orders of each subfamily, complete amino acid sequences of ABC transporters were aligned and subjected to phylogenetic analysis. Alignment results within the same group of transporters showed the same degree of conservation. The use of the members of all known ABC transporters subfamilies allowed us to unequivocally identify all known proteins. Considering all these in account, we concluded that our searches resulted in the identification of a complete set of each subfamily proteins from the whole human genome. However, all these transporters do not express in a single type of tissue in human body and vary as per their location. In our previous study we have demonstrated that out of total 49 ABC transporters only 15 are expressed in human brain. This data resulted in high degree of genetic similarity and their significance in various regulatory mechanisms. The HUGO-approved scheme was used to classify the identified ABC transporters and members of each subfamily were grouped accordingly.

3.1 Subfamily A

ABC-A subfamily previously have been reported in a variety of organisms genome such as protists, yeasts, plants and animals. Whereas these are very much diversified in these organisms, so we were interested to look for the similarity in their structure and evolutionary pattern. After analyzing whole protein sequence, we found that all the 12 proteins of this family were full length ABC transporters (Fig. 1).

Our analysis revealed an uneven distribution of ABC-A proteins for human indicating multiple loss events during evolution. All the ABC-A proteins were found distributed in three major evolutionary groups, i. e. Group I (ABCA12, ABCA2, ABCA7, ABCA4, ABCA1 and ANCA13), Group II (ABCA10, ANCA9, ABCA8, ABCA6 and ABCA5), and Group III (ABCA3). It represents high degree of variability among ABC-A subfamily where Group III protein ABCA3 was found outgroup with high degree of genetic change of 0.9 nucleotide substitution per site that is the number of changes or 'substitutions' divided by the length of the sequence (although they may be given as 90% change, i.e., the number of changes per 100 nucleotide sites). This shows that the Group I and Group II members of ABC-A subfamily are more closely related and genetically more similar during evolution as compared to Group III or ABCA3.

Clade transporters ABCA1 and ABCA4 seems very similar in their genome, hence it will be interesting to investigate in detail whether the function of these two transporters are same or different as compared to each other and also with other members of the subfamily.

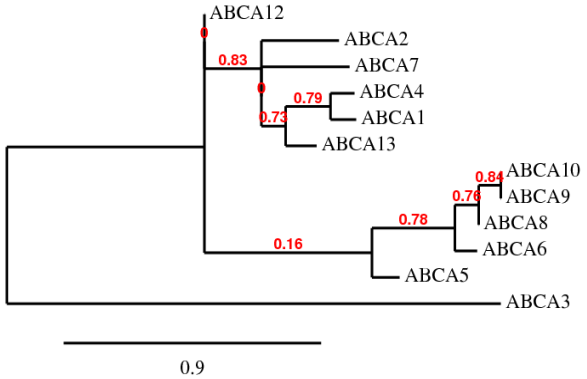

Figure 1: Phylogenetic tree of human ABC-A transporter proteins. Full length amino acid sequences for each member of ABC-A subfamily were aligned, and were used for the construction of phylogenetic tree using the neighbor-joining method. Numbers next to the branch indicates the relative supports from 500 replicates.

3.2 Subfamily B

This subfamily is most diversified group among all in their distribution and function. It contains both full and half-size transporters. These are involved in a variety of cellular mechanisms such as mitochondrial and pheromone export, antigen processing and most importantly in multidrug

resistance. P-gp (ABCB1) is the first and well known multidrug transporter involved in drug resistance in cancer cells (Gottesman et al., 2002). Both the full and half-size ABC-B transporters are abundantly distributed throughout the human genomes. However no outgroup transporters were found in phylogenetic tree. High diversity of 0.8 nucleotide substitution per site was observed among all groups of this family member (Fig. 2). The observed distribution also indicates that huge genetic changes occurred during evolution among all the members. Full size transporters (ABCB1, ABCB5, ABCB9, ABCB10 and ABCB11) of this subfamily resulted with large horizontal line showing larger diversity and genetic variation as compared to the half-size transporters (ABCB2, ABCB3, ABCB6, ABCB7 and ABCB8).

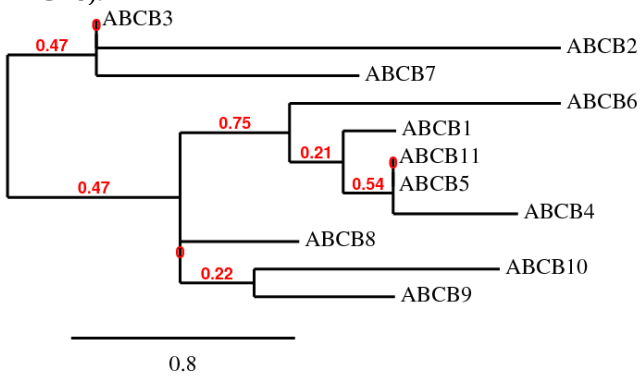

Figure 2: Phylogenetic tree of human ABC-B transporter proteins. Full length amino acid sequences for each member of ABC-B subfamily were used for the construction of phylogenetic tree

3.3 Subfamily C

All the members of this subfamily are full-size transporters in human and other eukaryotes. Some of the transporters of this subfamily are not primarily active transporters and functions as either ATP-gated chloride channels (ABCC7) or as potassium channel regulators (ABCC8 and ABCC9). Some of them are also involved in detoxification of toxic compounds. In our previous study we have identified two members of this subfamily (ABCC6 and ABCC8) are extensively found in human brain (Vishwakarma et al., 2014) and some of them are found in other tissues described elsewhere.

Phylogenetic analysis of human ABC-C subfamily transporters showed four clades having similar evolutionary pattern with common ancestry of the group and is distributed into three major groups (Group I: ABCC5 and Clade I: ABCC11 and ABCC12, GROUP II: Clade II: ABCC8 and ABCC9, ABCC2, ABCC3 and Clade III: ABCC1 and ACCC6, Group III: ABCC10 and Clade IV: ABCC7 and ABCC4). Transporters of the same clade represent less variability in their nucleotide sequences. When#compared to the other subfamilies ABC-C represented with less boot strap value (0.4) except ABC-F (0.3) and ABC-G (0.4) showing not much variation in their genetic constituent and of almost same fundamental structure and function in human tissue (Fig. 3).

However phylogenetic analysis also reveals that the transporters of ABC-C subfamily show high level of heterogeneity in their genome but less than ABC-B subfamily. Even the transporters of the same clade of ABC-C subfamily shows high variability in their boot strap value and line distribution except ABCC8 and ABCC9 to some extent.

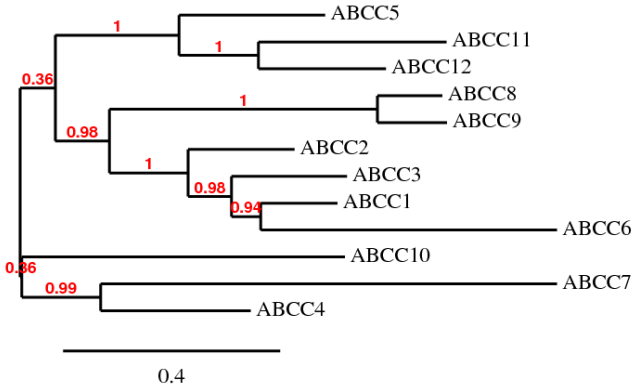

Figure 3: Phylogenetic tree construction of human ABC-C transporter proteins using full length amino acid sequences for each member of ABC-C subfamily

3.4 Subfamily D

Human ABC-D subfamily contains a total of four half-size transporters that localize to the membrane of peroxisome. These transporters are involved in import of long-chain fatty acids. In plants both half and full size transporters are known of this subfamily whereas in human only half-size ABCD transporters are present representing more conserved feature and less nucleotide heterogeneity. Phylogenetic analysis separates human ABC-D transporters into two groups (Group I: ABCD4 and Group II: ABCD3, ABCD1 and ABCD2) containing one clade (ABCD1 and ABCD2) as their prototypic member. The boot strap value for all four members of ABC-D subfamily human ABC transporters was predicted as 0.4 nucleotide substitution per site showing less variability among other subfamily transporters (Fig. 4).

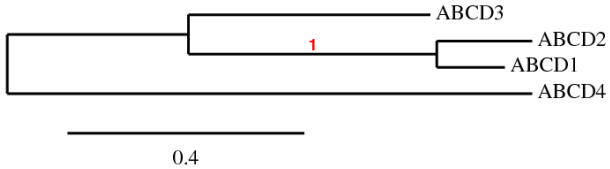

Figure 4: Phylogenetic tree construction of human ABC-D transporter proteins using full length amino acid sequences for each member of ABC-D subfamily

3.5 Subfamily E and F

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These are soluble proteins and lack transmembrane domains and contains only two nucleotide binding domains. Due to the lack of transmembrane domains these proteins does not transport. Most of the eukaryotic genomes analyzed so far contain a single member of ABC-E proteins however, plants contain two. The uniform distribution of ABC-E proteins among fungi and eukaryotes including human supports the notion that they are involved in a highly conserved activity

of the cell (Kovalchuk et al., 2010). However, many other types of transporters have been reported in other organisms with high nucleotide similarity.

The members of ABC-F subfamily are highly diversified in fungal and other organisms whereas human has only three members of this subfamily distributed into two groups having single clade (ABCF1 and ABCF2). They are not related with transport but are involved in different aspects of translational control, ribosome biogenesis and others. Clade members of the subfamily ABC-F showed 83% of similarity in their genome whereas ABCF3 was with high genome variation from clade members predicting the importance of their role in different cellular mechanisms and biological activities (Fig. 5).

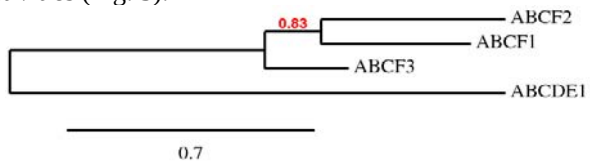


Figure 5: Phylogenetic tree construction of human ABCE and ABCF transporters using full length amino acid sequences

3.6 Subfamily G

The subfamily ABC-G has reverse topology as compared to other ABC transporter subfamilies i. e. nucleotide binding domain of these transporters precedes their transmembrane domain. Both full length and half-size transporters are known but human has only half transporters and also other animal's genome. Like subfamily ABC-B these transporters these are also known to be linked with pleiotropic drug resistance (PDR) phenomena. Many of the members of this subfamily are still unknown in many organisms whereas human possess only five members representing two groups with two clades (Group I: Clade I: ABCG1 and ABCG4 and Group II: Clade II: ABCG5 and ABCG8). Both the clades were found to have 93% sequence similarity after phylogenetic investigation. One of the important members of this subfamily ABCG2 was outgrouped from both the clades but physiologically is very important molecule showing high nucleotide variability as compared to the members of this subfamily (Fig. 6).

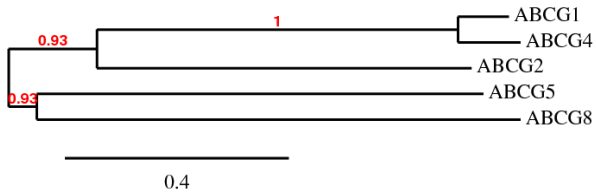


Figure 6: Phylogenetic tree construction of human ABC-G transporter proteins using full length amino acid sequences for each member of ABC-G subfamily

Taking ABCG2 into account with high variability and physiologically significant member of this subfamily further investigation of its protein secondary structures and interaction with biological molecules will provide significant advancements in understanding its more unknown biological phenomenon.

3.7 Structural annotation of full-length and half-size human ABC transporters based on phylogeny

All the members of subfamily A and C, and five of most diversified subfamily B were identified as full-size transporters. Although few transporters have been studied well in bacteria, yeast and other organism's genome, still there is need to investigate their functional annotation. Based on their structural organization ABC transporters have been classified into two groups: 1) Full-length transporters and 2) Half-size transporters. Each of them has been identified by different molecular signatures being the most important component in drug resistance, absorption and defense mechanisms.

Secondary structure prediction of full-size human ABC transporters has found to have mirror image halves which are separated by a linker catalytic region. Each halve has a six transmembrane scanning domains blocking them to the membrane (Fig. 7a). While compared to the full transporters, half-size ABC transporter proteins has only one halve. These transporters require their association with other half transporters in the membrane to form a pure complex. They do not contain any linker region (Fig. 7b).

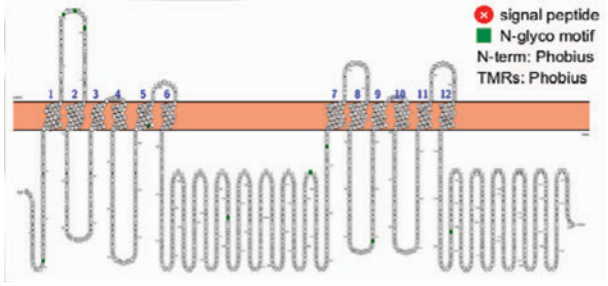


Figure 7[A]: Predicted secondary structure of full ABC transporter (ABCB1)

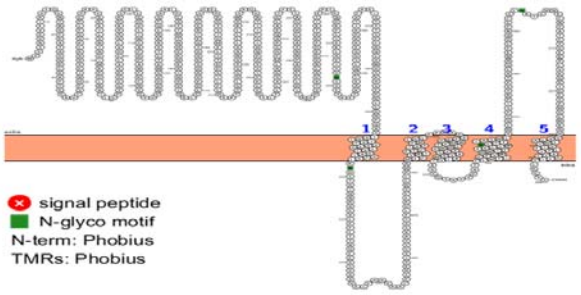


Figure 7[B]: Predicted secondary structure of half ABC transporter (ABCG2)

Because of the transmembrane domains, these transporters play very crucial role in the modulation of absorption and excretion of xenobiotics across the membrane barrier. Phylogenetic evaluation of full length human ABC trasnporters showed three groups with boot strap value of 0.8 showing high degree of variation and changes occurred during evolution of these molecules based on their functional location. They were found to be distributed into three groups when analyzed in Phylip phylogeny (Fig. 8a). Among all three groups of full transporters a total of 8 clades were found. Group I contained two clades (ABCB9 and ABCB10, ABCB1 and ABCB5), Group II had three clades (ABCC11 and ABCC12, ABCC1 and ABCC6, ABCC8 and ABCC9) and group III had three clades (ABCA4 and ABCA7,

ABCA2 and ABCA13, ABCA9 and ABCA9). Some of these transporters such as ABCA1, ABCA3 and ABCA5 looked somewhat out grouped representing high variability in their genome. Hence, investigation of these transporters in different cellular mechanisms would be of utmost important due to high degree of variability.

Likewise half-size ABC transporters were found to be grouped into three groups. Group I contained a single clade I (ABCD and ABCD2), group II had two clades (ABCB2 and ABCB3, ABCB6 and ABCB7) and group III had one clade (ABCG1 and ABCG4) representing much diversified members in their structure and function.

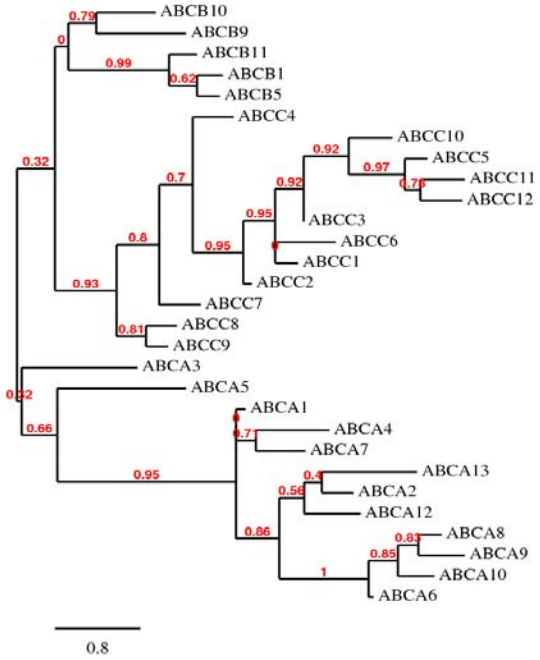


Figure 8[A]: Phylogeny of full-length human ABC transporters (Phylip view)

Some of the out clade transporters like ABCG2, ABCG5 and ABCG8 may have significant role in many physiological processes in normal and diseased conditions. Hence, finding the role of these transporters will provide a better insight for understanding their role in early prognosis and the more accurate cause of the disease (Fig. 8b).

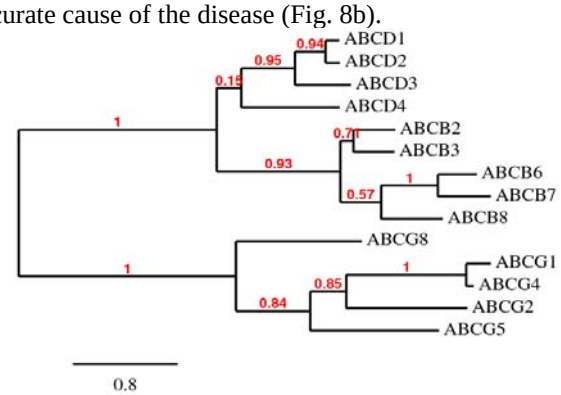


Figure 8[B]: Phylogeny of half-size human ABC transporters (Phylip view)

However, Phylip phylogeny gives much of the important clues for molecular evolution of both the full-length and half-size transporters, we were interested to know the effect of graphical changes in phylogeny. When we generated phylogeny of full-length and half-size transporters in radial layout, it provided more clear view for molecular distribution and showed only two groups for both types of transporters arranged in head to tail clusters (Fig. 9a). The first group (ABCA5, ABCA3, ABCC9, ABCC8, ABCC7, ABCC2, ABCC1, ABCC6, ABCC3, ABCC12, ABCC11, ABCC5, ABCC10, ABCC4, ABCB5, ABCB1, ABCB11, ABCB9, and ABCB10) includes 19 genes that map to 10 different chromosomes. The second group included less number (10) of transporters (ABCA1, ABCA4, ABCA7, ABCA13, ABCA2, ABCA12, ABCA8, ABCA9, ABCA6 and ABCA10) mapped on 6 different chromosomes. Few transporters of both these groups have been found to highly express in various tissues/organs but the function of many of them are not known. Hence, further functional investigation of these transporters would be of great insight for disease specifications.

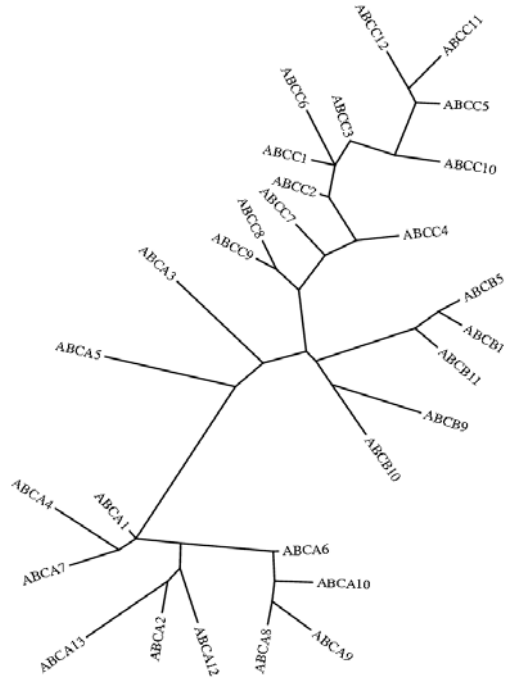


Figure 9[A]: Phylogeny of full-length human ABC transporters (Radial view)

Likewise comparison of half-size transporters Phylip phylogeny to its radial Phylogenetic analysis more apparent discrimination was observed in radial view (Fig. 9b). All the members of subfamily G were found at root of the phylogeny in one group distributed in 4 different chromosomes and another group was located at top of the tree and contained members of ABCB (ABCB2, ABCB3, ABCB6, ABCB7 and ABCB8) and ABCD (ABCD1, ABCD2, ABCD3 and ABCD4) distributed in 7 different chromosomes.

However, the phylogenetic relationship in human was identified well in molecular distribution evaluation of full as well as half-ABC transporters. After evaluation of this significant diversity in human we were interested to see their distribution among closely related model animals and plant.

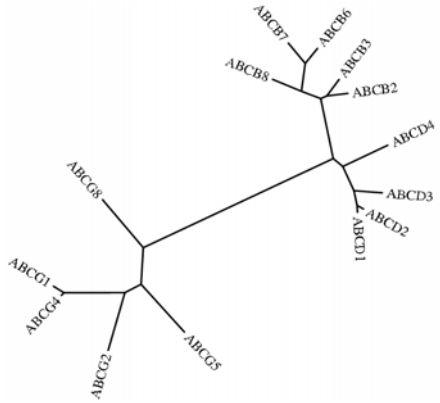


Figure 9[B]: Phylogeny of half-size human ABC transporters (Radial view)

This type of relationship revealed two groups of organisms in both full and half-size transporters. First group included animals and second group plant. This demonstrates that animal transporters are different from plant transporters and have much diversity among their genome. Further closer evaluation revealed that Macaca mulatta as most close during evolution, whereas Canis lupus familiaris, Felis catus and Bos taurus were somewhat closely associated with human transporter origin and Mus musculus and Rattus novegicus were different and far associated as compared to above once (Fig. 10a and Fig. 10b). It provides an important clue to really understand which model is better and closer to human studies for both full and half-size human ABC transporters.

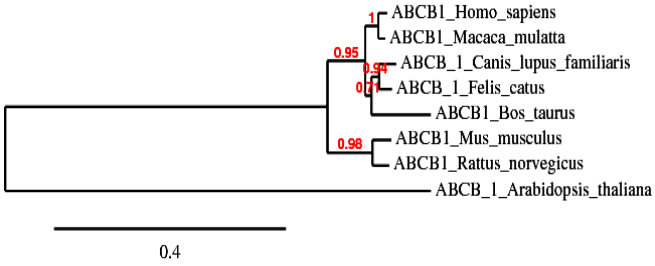


Figure 10[A]: Phylogenetic tree for full-size human ABC transporter (ABCB1) in different eukaryotic organisms and plant (Arabidopsis thaliana)

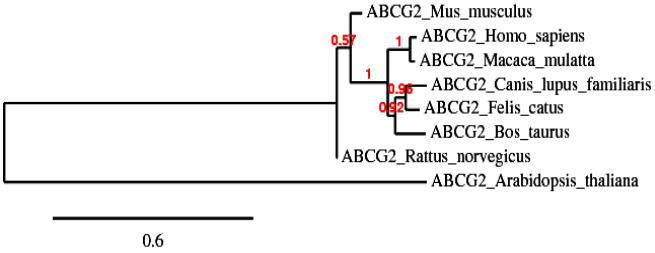


Figure 10[B]: Phylogenetic tree for half-size human ABC transporter (ABCG2) in different eukaryotic organisms and plant (Arabidopsis thaliana)

3.8 Topology modeling for full and half ABC transporters

After secondary structure prediction we analyzed the topology of full and half human ABC transporters using TOPCONS. Full transporters showed high number of transmembrane domains predicting their high level of transmembrane activities as compared to half transporters. High level of diversity was observed for full transporter in their ΔG values and predicted distances to the membrane center (Z=0) from first amino acid to the last (Fig. 11a). Topological evaluation of full transporters predicted that most of the protein sequences made transmembrane motifs inside the cellular membrane and only four motifs are extracellular. A total of six transmembrane helix (IN>OUT) and six (OUT>IN) were found. Whereas only three transmembrane helix (IN>OUT) and six (OUT>IN) were found in half-size transporters (Fig. 11b). The protein sequences ranging from one to 300 and 700 to 1000 amino acids contained transmembrane domains whereas only one constant region ranging from 400 to 700 amino acids were found to have transmembrane domains for half transporters.

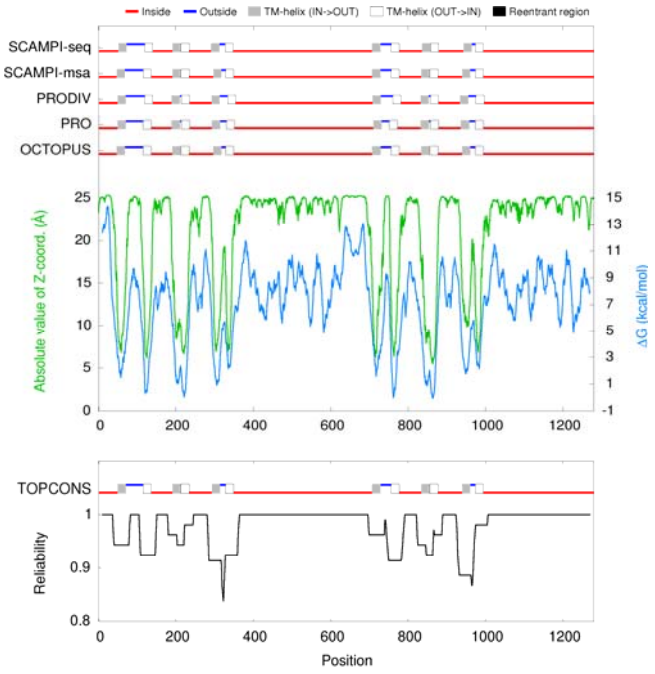
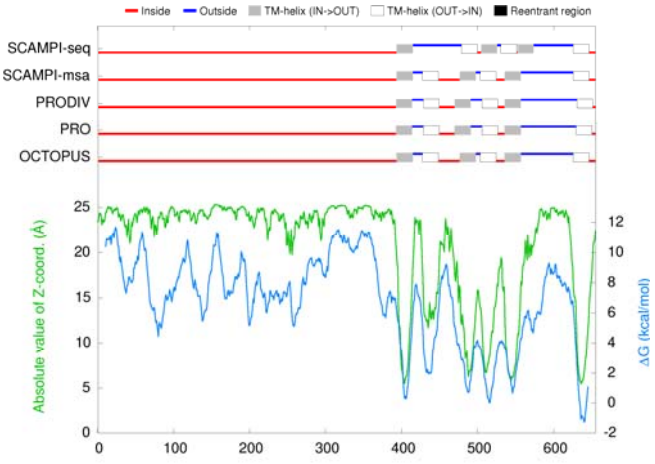


Figure 11[A]: Full-size human ABC transporter (ABCB1): predicted topologies, ΔG values and predicted distances to the membrane center (Z=0)



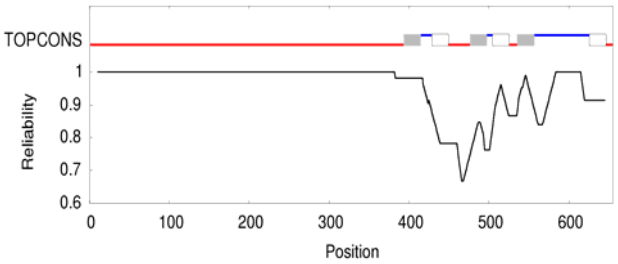


Figure 11[B]: Half-size human ABC transporter (ABCG2): predicted topologies, ΔG values and predicted distances to the membrane center (Z=0)

4 Conclusions

The large group of ABC transporter proteins are well studied in prokaryotes and yeasts but in human very few studies have been reported (Lubelski et al. 2007; Bouige et al. 2002; Iwaki et al. 2006; Schuller et al. 2003; Decottignies et al. 1997). Our analysis of human ABC transporter proteins provides an insight into the diversity of this group of proteins within the human lineage. This analysis has showed that ABC proteins are a highly dynamic group that has undergone a significant diversification after the divergence of human species. High gene loss events were observed during the process of gene duplication and this resulted in a great variety of different subfamily of ABC proteins in human. Among all seven subfamily two major categories were identified as full-size and half-size ABC transporters. A remarkable variation was observed in the members of the full-length transporters as compared to half-size transporters. Functionally relevant members of both these types of transporters (ABCB1 and ABCG2) in human analyzed for their secondary structure and topological evaluation predicted difference in their transmembrane domains and genomic variability. Most of the known human ABC transporters are not known well and need to analyze at functional level in different tissues in normal and diseased conditions. The present study has shown an intense path towards their phylogenetic relationship and genome variability. It provides many significant clues towards the selection of exact transmembrane molecules in various organs for drug targeting and early disease prognosis.

Although our study does not cover the whole ABC transporters found in various organisms, it provides an insight into their astonishing diversity. These results can be used for classifying human transporters from other individuals and for a further in-depth characterization of members of these highly important groups.

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