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EMERGENCE OF THE ABC TRANSPORTER ANTIBIOTIC RESISTANT GENE IN PATHOGENIC FUNGI USING IN SILICO ANALYSIS

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ABSTRACT

Adenosine triphosphate binding cassette proteins (ATP-ABC) transporters belong to a broad superfamily of proteins in all living organisms that have essential physiological functions. They are necessary for transporting a wide range of substrates across lipid membranes. ABC transport proteins share two conserved domain architectures: the multiple transmembrane helices (TMD) nucleotide binding protein domain (NBD). Fungi have evolved active transport pathways through endogenous and exogenous toxicants. Drug efflux from ABC transporters lowers the concentration of intracellular drugs, in many pathogens and cancer cells; therefore, efflux is subjected to extensive studies in pathogens. ABC transporter gene of *aspergillus* versicolor as reference and evaluated metadata of ABC transporter gene in comparison from dermatophyte and non-dermatophyte fungi using fungi DB and NCBI databases. ABC transporters gene was studied using gene homology via phylogenetic analysis. Study evaluated ABC transporters sub families, number of transcripts, exon, intron numbers sizes and position using gene sequence analysis by NCBI. The evolutionary history of ABC gene analyzed by using 12 proteins of both dermatophytes. Study also explored the single nucleotide polymorphism (SNPs) homology in dermatophytes using the NCBI SNP tool. ABC protein examined five sub-families which include ABC-B, ABC-C, ABC-D, ABC-F. Phylogenetic studies on ABC transporter genes showed its emergence in three major groups of dermatophytes and non- dermatophyte. Exon number of ABC transporter gene varies from 2 to 18 and one transcript number in dermatophytes and non-dermatophytes. The evolutionary history of ABC-B was analyzed by using 12 proteins of both dermatophytes and non-dermatophytes. ABC genes in dermatophytes were found in five subfamilies ABC-B, ABC-C, ABC-D, ABC-F and ABC-G. However, ABC transporter gene family survey suggested that ABC- C family is a highly emerged sub family in dermatophytes and non-dermatophytes. Study revealed that ABC protein has been found in five sub-families of ABC transporter gene in dermatophytes. It has one transcript number in dermatophytes and non-dermatophytes. Whereas, the exon numbers are varied from 2 to 18. Moreover, ABC transporter gene phylogenetic family survey suggested that ABC- C family is highly emerged in both fungal types.

1. INTRODUCTION

Dermatophytes are keratinophilic fungi invade keratinized tissue of human and other animals (skin, hair and nails) to create an infection. Fungal infections of the skin and nails are prevalent and currently affecting over 20-25% of the world's human and animal population (Vishnu et al., 2015: Gnat et al., 2019: Chang et al., 2017). There are three genera of dermatophytes known as *Microsporum*, *Trichophyton*, and *Epidermophyto* (Cafarchia et al., 2017).

Fungal pathogens have been adapted in antifungal targeted metabolic pathways and surpass the drug effectivity (White et al., 2008). Drug targeted metabolic pathway mainly target the fungal cell membrane proteins, which facilitate cellular permeability, such as the ABC transport protein. ABC proteins among the major protein families and individuals from this family are found in all living beings from microorganisms to human (Davies et al., 2000). In prokaryotes, these transporters serve both influx and efflux proteins bringing nutrients to the cells and remove toxins and drugs from the cells respectively. ABC transporters are expressed in eukaryotes as efflux

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transporter proteins that protect the cell against toxins (Higgins et al., 2001: El-Awady et al., 2017). ABC transporters are majorly in humans. However, their existence in dermatophytes is less studied. Drug efflux from ABC transporters lowers the concentration of intracellular drugs, causing chemotherapy failure (Deeley et al., 2006). Similarly, in ABC transport resistant mutant antifungal drug failure is common. A conventional standard ABC transport protein consisted of two NBDs and two TMDs arranged in forward (TMD-NBD) 2 or in reverse (NBD-TMD) 2 pattern. In addition, they are also comprised of half-sized transporters as well as with other modifications (Hollenstein et al., 2007). According to the ABC transporter gene domain architecture of NCBI databases. ABC transporters are divided into seven sub-families (A to G) (Perlin et al., 2014).

The study has focused on the ABC transport proteins metadata analysis in major groups of dermatophytes using an ABC transport reference gene from non-dermatophyte *trichophyton versicolor* a non- dermatophyte.

2. MATERIALS AND METHODS

The study has been conducted to find out the potential drug-resistant ABC transporter gene and subfamily homology using the NCBI database.

Protein sequences

Protein sequences of ABC transporter gene from ten species of Aspergillus including *Aspergillus versicolor* (CBS 583.65), *Aspergillus mulundensis*, *Aspergillus sydowii* (CBS 593.65), *Aspergillus saccharolyticus* (JOP 1030-1), *Aspergillus nidulans* (FGSC A4), *Aspergillus steynii* (IBT 23096), *Aspergillus fischeri* (NRRL 181), *Aspergillus kawachii* (IFO 4308), *Aspergillus campestris* (IFO 4308) and *Aspergillus niger* (CBS 513.88) and eight species of dermatophytes including *Trichophyton mentagrophytes*, *Trichophyton interdigitale*, *Trichophyton benhamiae* (CBS 112371), *Trichophyton soudanense* (CBS 452.61), *Trichophyton violaceum*, *Trichophyton rubrum*, *Microsporum cannis*(CBS 113480) and *Nannizzia gypsea* (CBS 118893) were used and their sequences were downloaded from NCBI (https://www.ncbi.nlm.nih.gov) and fungidb.org.

Bioinformatics analysis of ABC transporter genes

ABC gene database for exon number, transcript number and amino acid length was predicted by using Fungidb (https://fungidb.org). NCBI Conserved Domain Database allowed us to identify ABC transporter related gene amino acid sequences at E-value=0. *Aspergillus versicolor* ABC protein was used as queries for the searches of Aspergillus and dermatophytes. The open reading frame (ORFs) were predicted by using the ORF finder (https://www.ncbi.nlm.nih.gov/orffinder). To detect the paralogs and orthologs of the ABC transporter gene, a protein NCBI blast was performed (blastp).

Phylogenetic analysis of ABC transporter gene

Alignment of all homolog sequences of ATP proteins was performed by using Clustal W (Larkin et al., 2007). Evolutionary analysis was performed using MEGA6 for 3 subfamilies ABC-B, C and G. Phylogenetic tree was prepared by using neighbour-joining methods (Tamura et al., 2013).

3. RESULTS AND DISCUSSION

Identification of Putative ABC transporter proteins

Protein sequences of the ABC transporter gene of *Aspergillus* were used as a query from non- dermatophytes and dermatophyte group. The amino acid length varies from 1232 to 1865aa. ABC-B family species have different exon number 7 to 14. Whereas, number of the transcript was one in all species as table 1. ABC-C subfamily species have 2 to 15 exon number. ABC gene in *Aspergillus versicolor* belong to ABC-D subfamily have 6 exon numbers, ABC-F family have 7 exon numbers. ABC-G sub-family species contain different exon number 6 to 11 as table no.1. Open reading frame ORFs encoding putative ABC proteins were varied in different species as shown in table 1. Whereas in the dermatophytes there are only three subfamilies (ABC-C, ABC-D and ABC-G) of ABC transporters existed. The amino acid length was varied from1266 to1851amino acid. The exon numbers were 18 in the ABC-B family. ABC-C have 2 to 4 exon number and ABC-G have 9 exon numbers. The open reading frame (ORF) was varied in three groups. Whereas, ABC- subfamilies have only one transcript as mentioned in table 2.

ABC transporter characterization

ABC transporter gene study was based on sequence data with E-value = 0 and highest query cover >95% to reduce false results. The classification was based on a conserved domain database. However, in dermatophyte fungi, it was found in five sub-families as shown in table 3, table 4 and figure 1.

ABC transporter gene Sub-Family Characteristics

ABC-B

The study evaluated, ABC-B transporter in dermatophytes with a maximum of 9 to 15 copies of complete genes. The evolutionary history of ABC-B was analyzed by using 12 proteins of both dermatophytes and non-dermatophytes as shown in figure 2.

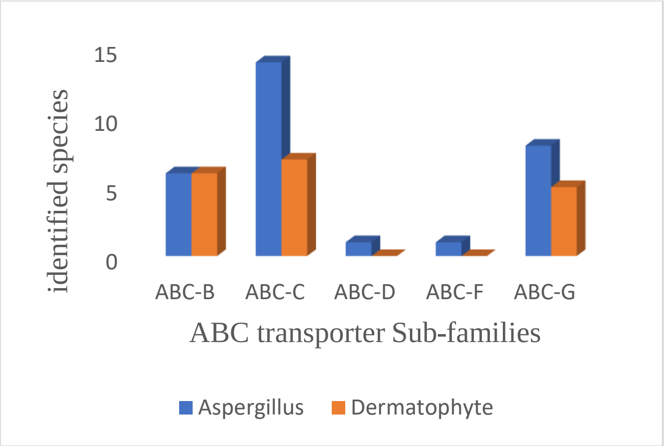

Figure 1. The graph shows the percentage of identified dermatophytes and non-dermatophytes (Y-axis) among sub-families of ABC (B, C, D, F and G) (X-axis).

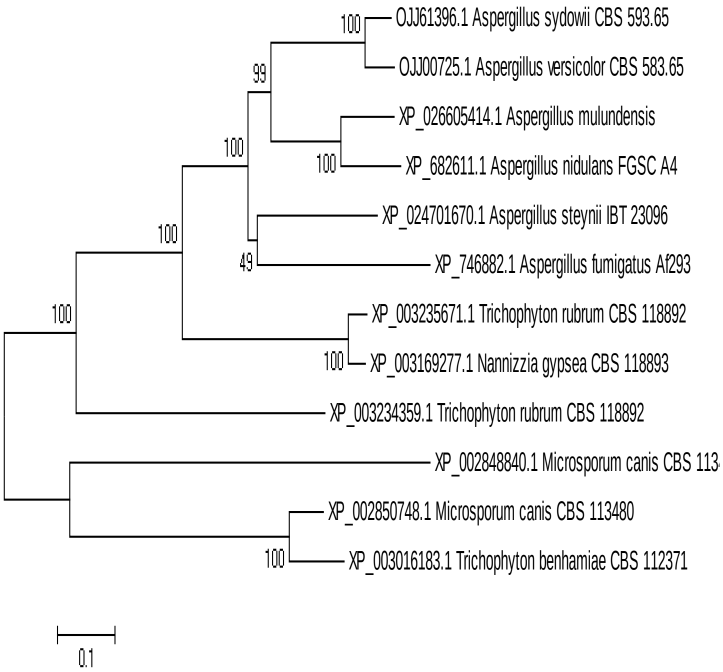

Figure 2. The tree indicates the phylogenetic relationship of the ABC-B subfamily in dermatophytes and non-dermatophyte species.

ABC-C

Multidrug resistance-associated proteins (MRP) are referred to as ABC-C transporters. ABC-C was found to be the largest subfamily which is divided into seven groups (C1–C7). The phylogenetic tree was constructed with 20 proteins in both dermatophytes and non-dermatophytes as shown in figure 3. ABC-C was the most prevalent subfamily of ABC transporters (Table 3 and Table 4).

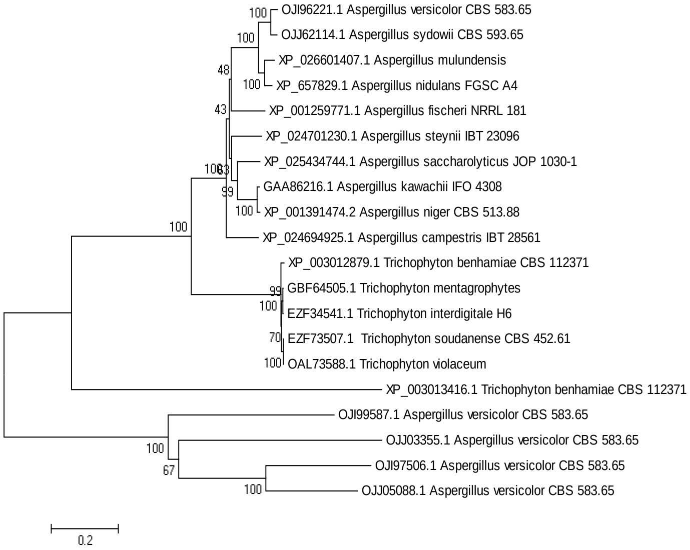

Figure 3. The phylogenetic relationship of ABC-C subfamily in dermatophytes and non-dermatophyte.

ABC-D

ABC-D subfamily proteins are related to peroxisomes and are involved in the transport of fatty acids. ABC-D sub-family was found to be the smallest in this study, with only one protein detected in *Aspergillus versicolor.*

ABC-F

ABC-F is another sub-family of ABC transporter. Its representatives are involved in regulating various translation processes. ABC-F sub-family was found to be the smallest in this study, with only one protein detected in *Aspergillus versicolor*.

ABC-G

ABC-G subfamily is limited to eukaryotes. They are called PDR transporters and are active in pleiotropic drug resistance (PDR). ABC-G subfamily was found to be less abundant in dermatophytes ranging from 2 to 4 copies of genes. The study identified only 13 representatives of this family from *aspergillus* and dermatophytes as shown in figure 4.

Single nucleotide polymorphism

Single nucleotide polymorphism (SNP) has been identified in ABC-G family homologs in human. SNP causes chemotherapy failure in humans. Polymorphism found in both coding and non-coding region. Nucleotide substitution varied in different exon numbers. Similarly, in *trichophyton rubrum* ABC transporter mutant found single nucleotide substitution at position 238 which replace

Guanine →Adenine with Valine to Methionine amino acid as mentioned in table 5.

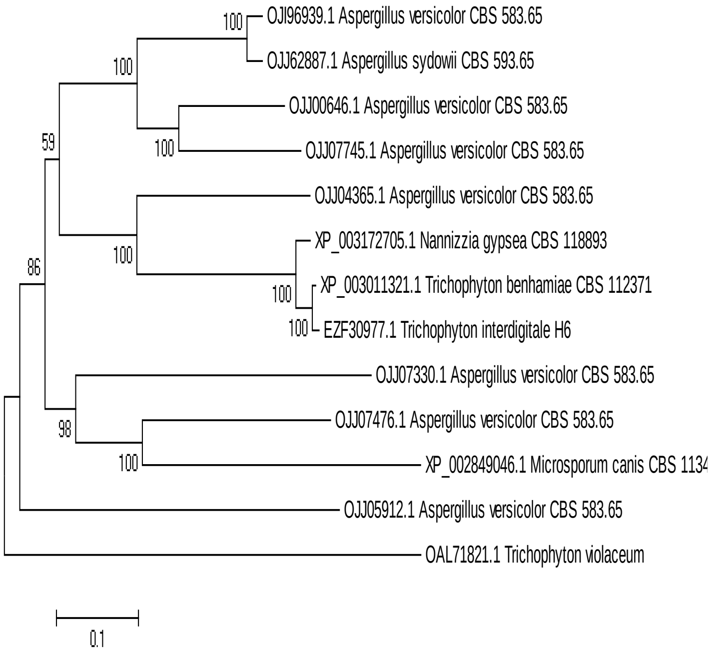

Figure 4. The tree indicates the phylogenetic relationship of the ABC-G subfamily in Dermatophytes and non-dermatophyte

ABC-G family with coding and non-coding single nucleotide polymorphism by nucleotide substitution. Classification of ABC transporter has been based on a Conserved domain database. According to Human Genome Organization (HUGO). The mammalian ABC superfamily has been divided into seven subfamilies (ABCA to ABCG) (Gadzalski et al., 2016). The bioinformatics survey of the ABC transporter gene in dermatophytes found five sub-families (ABC-B to ABC-G). ABC-B belong to multidrug resistance protein, ABC-C belongs to multidrug resistance-associated protein, ABC-D belongs to Peroxisomal Fatty Acyl CoA Transporter family protein, ABC-F belongs to ATPase components of ABC transporters protein and ABC-G family belong to Pleiotropic Drug Resistance family protein that is a well-known drug-resistant gene in yeast. ABC-C was found to be the most abundant subfamily of ABC transporter in dermatophytes. The study showed similarity with previous study (Paumi et al., 2009).

The amino acid length of ABC gene sequences of dermatophytes and non-dermatophytes was ranged from 744 to 1865. ABC-C subfamily was found in both dermatophytes and non- dermatophytes with 2 to15 exon number with increased potential of drug resistance as previously studied work (Paumi et al., 2009). Aspergillus versicolor species belong to ABC-D subfamily and ABC-F with 7 exon numbers, ABC-G sub-family species contain different exon number 2, 5, and 6. ABC-B family species also have different exon number 4-15 with one transcript and may be predicted as active drug-resistant target genes in other pathogenic fungi (Aller et al., 2009). Bioinformatics survey of ABC transporters revealed that the emergence of the ABC transporter gene in non-dermatophytes was most common than dermatophytes. ABC-B and ABC-C subfamily were common in dermatophytes but the ABC-G subfamily was most common in non-dermatophytes. The study showed similarity with the results of previous studies (Verrier et al., 2008: Kovalchuk et al., 2010: Lamping et al., 2010). The open reading frame (ORFs) is a continuous codon stretch with a start codon (AUG) and stop codon (UAA, UAG or UGA). ORFs coding putative proteins ABC were varied in both dermatophytes and non-dermatophytes as mentioned in a previous study (Haque et al., 2007: Sieber et al., 2018). ABC transporters gene family was also considered for the single nucleotide polymorphisms (SNPs) which are polymorphisms induced by point mutations, that give rise to various alleles at a given nucleotide location within a locus containing alternative bases. SNPs were found in both coding and non-coding regions.

However, ABC-G family is well reported with coding and non-coding single nucleotide polymorphism in human by nucleotide substitution in the coding region at 238 position Guanine → Adenine with Valine to Methionine amino acid replacement, at 625 position Cytosine → Adenine with Glutamine to Lysine amino acid replacement, at 1302 position Guanine →Adenine to Glutamate amino acid replacement, at 1629 position Adenine →Guanine with Leucine amino acid replacement. Similarly, in dermatophytes trichophyton rubrum found a single nucleotide at position 238 which changes Guanine →Adenine with amino acid change Valine to Methionine. Similarly, in candida albicans non-synonymous amino acid substitution was found in azole resistance in the ABC transporter gene (Honjo et al., 2002). Thus study has revealed new ABC transporter genes highly emerged in dermatophytes based on homology. They may potentially involve in drug resistance in human mycotic infections and as plant pathogens. The study has presented the possibilities of new homologs of pathogenic fungal ABC transporter family in drug resistance. To reduce their indulgence in eukaryotic drug resistance they should be studied on a molecular level for designing a more effective antifungal drug target.

4. CONCLUSION

ABC transporter gene was focused on the three fungal groups of dermatophytes *Trichophyton*, *Microsporum* and *Epidermophyton* and non-dermatophytes. The study revealed the occurrence of ABC transporter genes of five sub-families ABC-B, ABC-C, ABC-D, ABC-F and ABC-G. While ABC-B, ABC-C and ABC-G subfamily of ABC gene in dermatophytes. ABC-G family was found to be with single nucleotide polymorphism. It is suggested that ABC transporters homology has been found only in one transcript with various exons and multiple ORF open reading frame. However, Bioinformatics survey of ABC transporters revealed that the emergence of the ABC transporter gene in non-dermatophytes was most common than dermatophytes.

Significance Statement

This study has discovered the possible potential genes belong to the ATP family of membrane transporters that may involve in antifungal drug resistance. The information retrieved by this study can help the researchers to understand the bioinformatics of the understudied homologs of fungal drug transporters. Thus, these new insights will increase the more prospective aspects of antifungal drug designing.

5. ACKNOWLEDGEMENT

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6. CONFLICT OF INTEREST

All authors have declared that there is no conflict of interests regarding the publication of this article.

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Table 1. ABC transporter gene subfamily (exon count, amino acid sequence length and number of transcripts) of non-dermatophytes

ABC- Sub-Families	Sr.no.	Species	Accession no.	Query cover	Exon no.	Amino acid length	Transcript no.	ORFs
ABC-B	1	*Aspergillus versicolor* CBS 583.65	OJJ00725.1	93%	11	1276	1	385
	2	*Aspergillus sydowii* CBS 593.65	OJJ61396.1	100%	10	1359	1	475
	3	*Aspergillus mulundensis*	XP_026605414.1	96%	8	1321	1	22
	4	*Aspergillus nidulans* FGSC A4	XP_682611.1	94%	14	1865	1	375
	5	*Aspergillus steynii* IBT 23096	XP_024701670.1	95%	7	1232	1	184
	6	*Aspergillus fumigatus* Af293	XP_746882.1	89%	10	1274	1	327
ABC-C	1	*Aspergillus versicolor* CBS 583.65	OJI96221.1	100%	2	1657	1	352
	2	*Aspergillus versicolor* CBS 583.65	OJI97506.1	100%	15	1508	1	414
	3	*Aspergillus versicolor* CBS 583.65	OJJ05088.1	96%	13	1459	1	117
	4	*Aspergillus versicolor*CBS583.65	OJJ03355.1	96%	6	1452	1	414
	5	*Aspergillus versicolor* CBS 583.65	OJI99587.1	96%	14	1475	1	385
	6	*Aspergillus sydowii* CBS 593.65	OJJ62114.1	100%	2	1657	1	294
	7	*Aspergillus mulundensis*	XP_026601407.1	99%	2	1660	1	260
	8	*Aspergillus saccharolyticus*	XP_025434744.1	99%	2	1664	1	415
	9	*Aspergillus nidulans* FGSC A4	XP_657829.1	99%	2	1667	1	354
	10	*Aspergillus steynii* IBT 23096	XP_024701230.1	99%	2	1666	1	27
	11	*Aspergillus fischeri* NRRL 181	XP_001259771.1	99%	2	1672	1	406
	12	*Aspergillus kawachii* IFO 4308	GAA86216.1	99%	2	1663	1	454
	13	*Aspergillus niger*CBS 513.88	XP_001391474.2	99%	2	1663	1	456
	14	Aspergillus campestris IBT 28561	XP_024694925.1	99%	2	1659	1	427
ABC-D	1	*Aspergillus versicolor* CBS 583.65	OJI96531.1	100%	6	1448	1	9
ABC-F	1	*Aspergillus versicolor* CBS 583.65	OJI97160.1	100%	7	744	1	195
ABC-G	1	*Aspergillus versicolor* CBS 583.65	OJI96939.1	100%	6	1508	1	117
	2	*Aspergillus versicolor* CBS 583.65	OJJ00646.1	99%	2	1498	1	385
	3	*Aspergillus versicolor* CBS 583.65	OJJ07745.1	99%	2	1492	1	404
	4	*Aspergillus versicolor* CBS 583.65	OJJ04365.1	96%	6	1494	1	436
	5	*Aspergillus versicolor* CBS 583.65	OJJ07476.1	94%	6	1502	1	393
	6	*Aspergillus versicolor* CBS 583.65	OJJ07330.1	96%	5	1470	1	393
	7	*Aspergillus versicolor* CBS 583.65	OJJ05912.1	95%	11	1457	1	332
	8	*Aspergillus sydowii* CBS 593.65	OJJ62887.1	100%	6	1507	1	294

Table 2. ABC transporter Gene exon count, amino acid sequence length and number of transcripts of dermatophytes.

ABC-Sub Families	**Sr.no**	**Species**	**Accession no.**	**Query cover**	**Exon no**	**Amino acid length**	**Transcript no.**	**ORFs**
ABC-B	1	*Trichophyton rubrum*CBS 118892	XP_003235671.1	98%	18	1298	1	403
	2	*Trichophyton rubrum* CBS 11892	XP_003234359.1	97%	9	1292	1	280
	3	*Trichophyton benhamiae* CBS 112371	XP_003016183.1	97%	4	1266	1	407
	1	*Microsporum canis* CBS 113480	XP_002848840.1	97%	3	1280	1	370
	2	*Microsporum canis* CBS 113480	XP_002850748.1	95%	4	1297	1	378
	3	*Nannizzia gypsea* CBS 118893	XP_003169277.1	97%	18	1302	1	392
ABC_C	1	*Trichophyton mentagrophyte*	GBF64505.1	99%	NA	1680	1	394
	2	*Trichophyton interdigitale* H6	EZF34541.1	99%	2	1680	1	264
	3	*Trichophyton benhamiae* CBS 112371	XP_003013416.1	84%	4	1687	1	426
	4	*Trichophyton benhamiae* CBS 112371	XP_003012879.1	99%	4	1851	1	363
	5	*Trichophyton interdigitale*	KAF3893579.1	99%	2	1680	1	420
	6	*Trichophyton soudanense* CBS 452.61	EZF73507.1	99%	NA	1679	1	395
	7	*Trichophyton violaceum*	OAL73588.1	99%	2	1679	1	4
ABC_G	1	*Trichophyton benhamiae* CBS 112371	XP_003011321.1	92%	6	1531	1	421
	2	*Trichophyton interdigitale* H6	EZF30977.1	95%	4	1502	1	103
	3	*Trichophyton violaceum*	OAL71821.1	96%	6	1558	1	409
	4	*Microsporum canis* CBS 113480	XP_002849046.1	95%	9	1506	1	370
	5	*Nannizzia gypsea* CBS 118893	XP_003172705.1	97%	4	1503	1	315

Table 3. Identified ABC transporters in Aspergillus (non-dermatophytes)

Conserved domain	**Sub-family**	***A. versicolor***	***A. sydowii***	***A. mulundensis***	***A. steynii***	***A. nidulans***	***A. fischeri***	***A. kawachii***	***A. campestris***	***A. fumigatus***
multidrug resistance protein (mdr)	ABC-B	1	1	1	1	1	0	0	0	1
multi drug resistance-associated protein (MRP)	ABC-C	5	1	1	1	1	1	1	1	0
Peroxysomal Fatty Acyl CoA Transporter (FAT) Family protein	ABC-D	1	0	0	0	0	0	0	0	0
ATPase components of ABC transporters with duplicated ATPase domains	ABC-F	1	0	0	0	0	0	0	0	0
Pleiotropic Drug Resistance (PDR) Family protein	ABC-G	7	1	0	0	0	0	0	0	0

Table 4. Summary of identified ABC transporters in dermatophytes

Conserved domain	**Sub-family**	***T. mentagrophyte***	***T. interdigitale H6***	***T. benhamiae CBS 112371***	***T. soudanense CBS 452.61***	***T. violaceum***	***T. rubrum***	***M. canis* CBS 113480**	***Nannizzia gypsea* CBS 118893**
multidrug resistance protein (mdr)	ABC-B	0	0	1	0	0	2	2	1
multi drug resistance-associated protein (MRP)	ABC-C	1	1	2	1	1	0	0	0
Peroxysomal Fatty Acyl CoA Transporter (FAT) Family protein	ABC-D	0	0	0	0	0	0	0	0
ATPase components of ABC transporters with duplicated ATPase domains	ABC-F	0	0	0	0	0	0	0	0
Pleiotropic Drug Resistance (PDR) Family protein	ABC-G	0	1	1	0	1	0	1	1

Table 5. SNP analysis in ABC-G family

S. No.	**Exon**	**Nucleotide**	**Wild-type allele**	**SNP**	**Amino acid**	**Specie**	**Reference**
1	1	91 175	C A	T G	Noncoding Noncoding	Human	Honjo et al., 2002
2	2	238	G	A	Val to Met	Human Trichophyton Rubrum	This study
3	5	625	C	A	Gln to Lys	Human	Honjo et al., 2002
4	9	1302	G	A	Glu to Glu	Human	Honjo et al., 2002
5	12	1629	A	G	Leu to Leu	Human	Honjo et al., 2002
6	16	2062 2597	G C	A A	Asp toAsn Noncoding	Human	Honjo et al., 2002