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Review

An inventory of the human ABC proteins

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Abstract

Currently 30 human ABC proteins are represented by full sequences in various databases, and this paper provides a brief overview of these proteins. ABC proteins are composed of transmembrane domains (TMDs), and nucleotide binding domains (NBDs, or ATP-binding cassettes, ABSs). The arrangement of these domains, together with available membrane topology models of the family members, are presented. Based on their sequence similarity scores, the members of the human ABC protein family can be grouped into eight subfamilies. At present the MDR/TAP, the ALD, the MRP/CFTR, the ABC1, the White, the RNAseL inhibitor, the ANSA, and the GCN20 subfamilies are identified. Mutations of many human ABC proteins are known to be causative in inherited diseases, and a short description of the molecular pathology of these ABC gene-related genetic diseases is also provided.

Keywords: ABC subfamily; Membrane topology; Domain arrangement; ABC-related genetic disease

Contents

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1. Introduction

ABC (ATP binding cassette) proteins form one of the largest protein families and its members have been found in each kind of organism examined so far. The aim of this review is to provide an overview of the members of the ABC family in human. We present the basic genetic, structural, and functional information describing these human proteins. Since their mutations are causative in several genetic disorders, a brief summary of these phenotypes is also provided. This snapshot reflects the information available at the time of compilation of the manuscript (May, 1999), and most probably will be somewhat outdated already at the time of publication. Due to the progress of the Human Genome Project and to other mass sequencing efforts, almost half of the known human ABC proteins were discovered within the past two years. Partial ABC sequences (e.g. expressed sequence tags) can also be found in the corresponding databases, but in this review only those human ABC proteins are discussed for which the complete sequences are known. ABC proteins to which independent chapters are devoted in this Special Issue are discussed in less detail, and instead we refer to these relevant chapters.

ABC proteins are defined by the presence of the ABC unit, a 200–250 amino acid 'mini' protein, which harbors two short, conserved peptide motifs (Walker A and Walker B), both involved in ATP binding, and present in many other ATP utilizing proteins as well. A third conserved sequence, diagnostic to the ABC unit, is located between the Walker A and B sequences, and called 'ABC signature'. The PROSITE sequence-related database (http://www.expasy.ch/prosite/), which consists of biologically significant sites, patterns, and profiles that help to reliably identify which known protein family a new sequence belongs to, lists the following pattern for the ABC family: 'ABC transporters family signature': [LIVMFYC]-[SA]-[SAPGLVFYKQH]-G-[DENQMW]-[KRQASPCLIMFW]-[KRNQSTAVM]-[KRACLVM]-[LIVMFYPAN]-F{PHY}-[LIVMFW]-[SAGCLIVP]-{FYWHP}-{KRHP}-[LIVMFYWSTA]. In this description the standard IUPAC one-letter codes for the amino acids are used; ambiguities are indicated by listing the acceptable amino acids for a given position between square parentheses [ ]. Ambiguities are also indicated by listing the amino acids that are not accepted at a given position between a pair of curly brackets { }. Each amino acid element in the pattern is separated from its neighbor by a - sign.

Most ABC proteins are membrane transporters translocating various substrates to various compartments, which explains the wide spectrum of functions fulfilled by these proteins in different organisms. As membrane transporters, this class of molecules contains membrane-embedded, transmembrane domains (TMDs). These transmembrane domains are usually composed of six transmembrane (TM) helices. The minimal structural requirement for an active ABC transporter seems to be two TMD and two ABC units. These may be present within one polypeptide chain ('full transporters'), or within a membrane-bound multiprotein complex. In the group of active transporters, like the multidrug resistance proteins, the energy of ATP hydrolysis is utilized for transport by a mechanism which involves positive cooperativity between the two ABCs, and a tight molecular 'coupling' of the TMDs to the ABCs. These couplings ensure the transmission of the conformational changes caused by substrate binding and by the hydrolysis of ATP to active transport.

Although a large number of the known ABC proteins are active pumps (i.e. they can transport against

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The proteins are grouped by subfamilies. All common names of the ABC proteins are included. Phenotype refers to the abbreviation of the genetic disease in which mutations of the given ABC protein's gene is involved: Stargardt macular dystrophy (STGD1); fundus flavimaculatus (FFM); age-related macular degeneration (ARMD2); retinitis pigmentosa 19 (RP19); cone dystrophy (COD); cone-rod-retinal dystrophy (CRD); progressive familiar intrahepatic cholestasis type 2 and type 3 (PFIC2 and PFIC3); X-linked sideroblastic anemia and ataxia (XLSA/A); Dubin–Johnson syndrome (DJS); cystic fibrosis (CF); persistent hyperinsulinemic hypoglycemia of infancy (PHHI); adrenoleukodystrophy (ALD); cerebro-hepato-renal syndrome of Zellweger (ZWS2).

[a]For domain arrangement, see Fig. 2.

[b]OMIM number is the reference to the OMIM (Online Mendelien Inheritance in Man, http://www.ncbi.nlm.nih.gov/Omim/) entry to the gene (bold) or to the protein (plain).

Table 1
An inventory of human ABC proteins, May 1999

Name	Nomen-clature	Chromo-some	Protein (aa)	Domain arrangement[a]	Phenotype	OMIM number[b]
MDR/TAP subfamily						
Pgp1, MDR1	ABCB1	7q21	1280	(TMD-ABC)2		**171050**
TAP1	ABCB2	6p21.3	686	TMD-ABC		**170260**
TAP2	ABCB3	6p21.3	748	TMD-ABC		**170261**
Pgp3, MDR3	ABCB4	7q21	1279	(TMD-ABC)2	PFIC3	**171060**, 602347
ABC7	ABCB7	Xq13.1-13.3	752	TMD-ABC	XLSA/A	**300135**, 301310
M-ABC1	ABCB8	7q35-36	718	TMD-ABC		
BSEP, SPGP	ABCB11	2q24	1321	(TMD-ABC)2	PFIC2	**603201**, 601847
ALD subfamily						
ALD, ALDP	ABCD1	Xq28	745	TMD-ABC	ALD	300100
ALDL1, ALDR	ABCD2	12q11	740	TMD-ABC		**601081**
PXMP1, PXMP70	ABCD3	1p21-22	659	TMD-ABC	ZWS2	**170995**
PXMP1L, P70R	ABCD4	14q24.3	606	TMD-ABC		**603214**
MRP/CFTR subfamily						
MRP1	ABCC1	16p13.12-13	1531	TMD0(TMD-ABC)2		**158343**
MRP2, CMOAT	ABCC2	10q23-24	1545	TMD0(TMD-ABC)2	DJS	**601107**, 237500
MRP3, MOAT-D	ABCC3	17q21.3	1527	TMD0(TMD-ABC)2		
MRP4, MOAT-B	ABCC4	13q31-32	1325	(TMD-ABC)2		
MRP5, MOAT-C	ABCC5	3q27	1437	(TMD-ABC)2		
MRP6	ABCC6	16p13.1	1503	TMD0(TMD-ABC)2		
CFTR	ABCC7	7q31	1480	(TMD-ABC)2	CF	
SUR1	ABCC8	11p15.1	1581	TMD0(TMD-ABC)2	PHHI	**600509**, 601820
SUR2	ABCC9	12p12.1	1549	TMD0(TMD-ABC)2		**601439**
ABC1 subfamily						
ABC1	ABCA1	9q22-q31	2201	(TMD-ABC)2		**600046**
ABC3, ABC-C	ABCA3	16p13.3	1704	(TMD-ABC)2		**601615**
ABCR	ABCA4	1p22	2273	(TMD-ABC)2	STGD1/FFM, ARMD2, RP19, COD, CRD	**601691**, 248200, 153800, 601718
KIAA0822	ABCA7	17	1581	(TMD-ABC)2		
White subfamily						
ABC8 White	ABCG1	21q22.3	638	ABC-TMD		**603076**
MXR1, BRCP, ABCP	ABCG2	4q22	655	ABC-TMD		**603756**
OABP subfamily						
RNAseLI, OABP	ABCE1	4q31	599	(ABC)2		**601213**
ANSA subfamily						
ANSA1			332	ABC		
ANSA2			348	ABC		
GCN20 subfamily						
ABC50	ABCF1	6p21.33	807	(ABC)2		**603429**

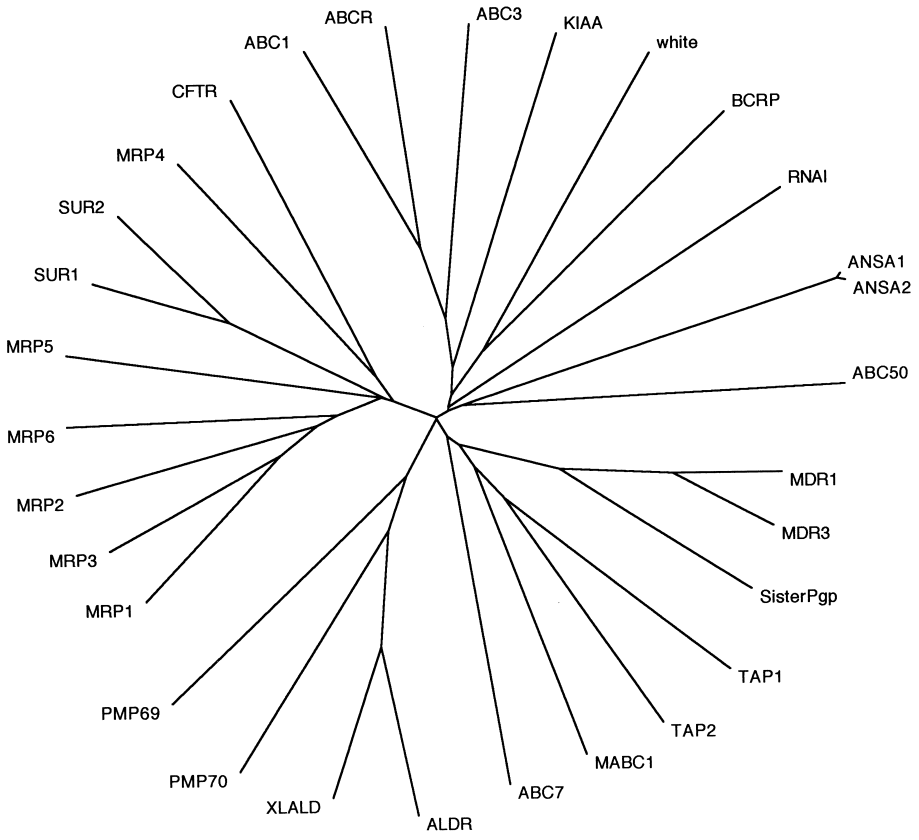


Fig. 1. The dendrogram of 30 human ABC proteins represented by complete sequences in the sequence databases. The multiple alignment of the sequences has been generated by the ClustalW program [137] at the WWW Service of the European Bioinformatics Institute (http://www2.ebi.ac.uk/clustalw). The 'full alignment' mode was used with Blosum matrix method, applying the following gap penalty values; gap open: 10, end gaps: 10, gap extension: 0.05, gap distance: 0.05.

the concentration gradient of the substrate), there are several examples deviating from this type of function. The human GCN20 homolog, ABC50, which is a dimeric ABC without TMDs, is most probably not a transporter at all; it has nuclear targeting signals and might be involved in aminoacyl-tRNA binding. The cystic fibrosis transmembrane conductance regulator, CFTR, is a chloride channel, and the sulphonylurea receptors, SUR1 and SUR2, are best described as intracellular ATP sensors regulating the permeability of potassium channels.

A highly informative website has been established at the University of Groningen by Micheal Muller's group (http://www.med.rug.nl/mdl/humanabc.htm) which is regularly updated, and at the time of preparation of this review lists 39 human ABC proteins. Twenty eight members of this list are represented by full sequences, the sequences of the remaining 11 proteins are partial. The HUGO, Human Gene Nomenclature Committee, would like to propose a new system of nomenclature for the ABC transporter genes. Detailed information on the nomenclature can be obtained electronically (http://www.gene.ucl.ac.uk/users/hester/abc.html). Throughout this review the most common names of the transporters are used, also mentioning the synonyms.

Table 1 lists the most important data and family relationships of the human ABC transporters covered in this review. This table is based on the list of these proteins at the University of Groningen website. We provide here the suggested names for each ABC transporter, the chromosomal localization of their genes, the number of amino acids in the gene product and the domain arrangements. Since mutations of many human ABC proteins are known to be causative in inherited diseases, we also list here the corresponding disease phenotypes. A large collection of medical, physiological and molecular genetic data

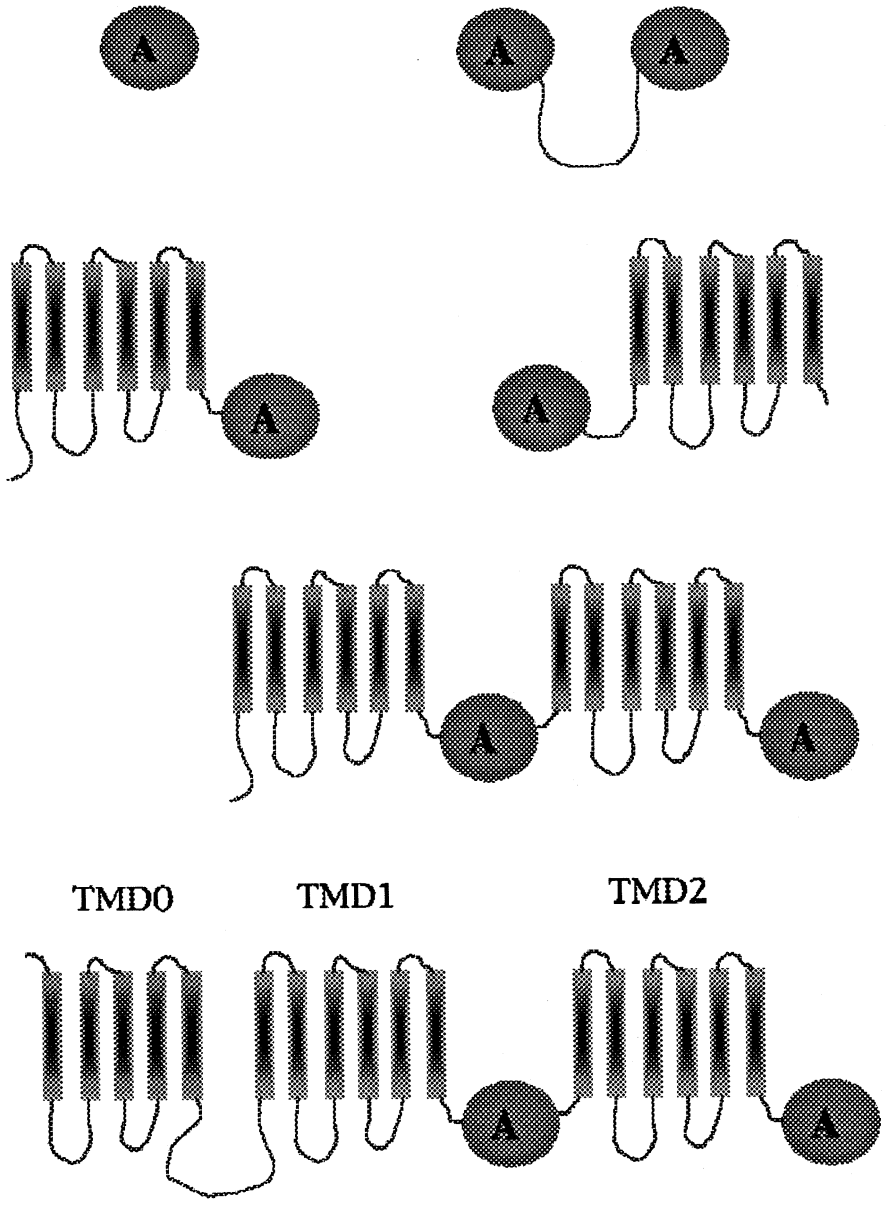
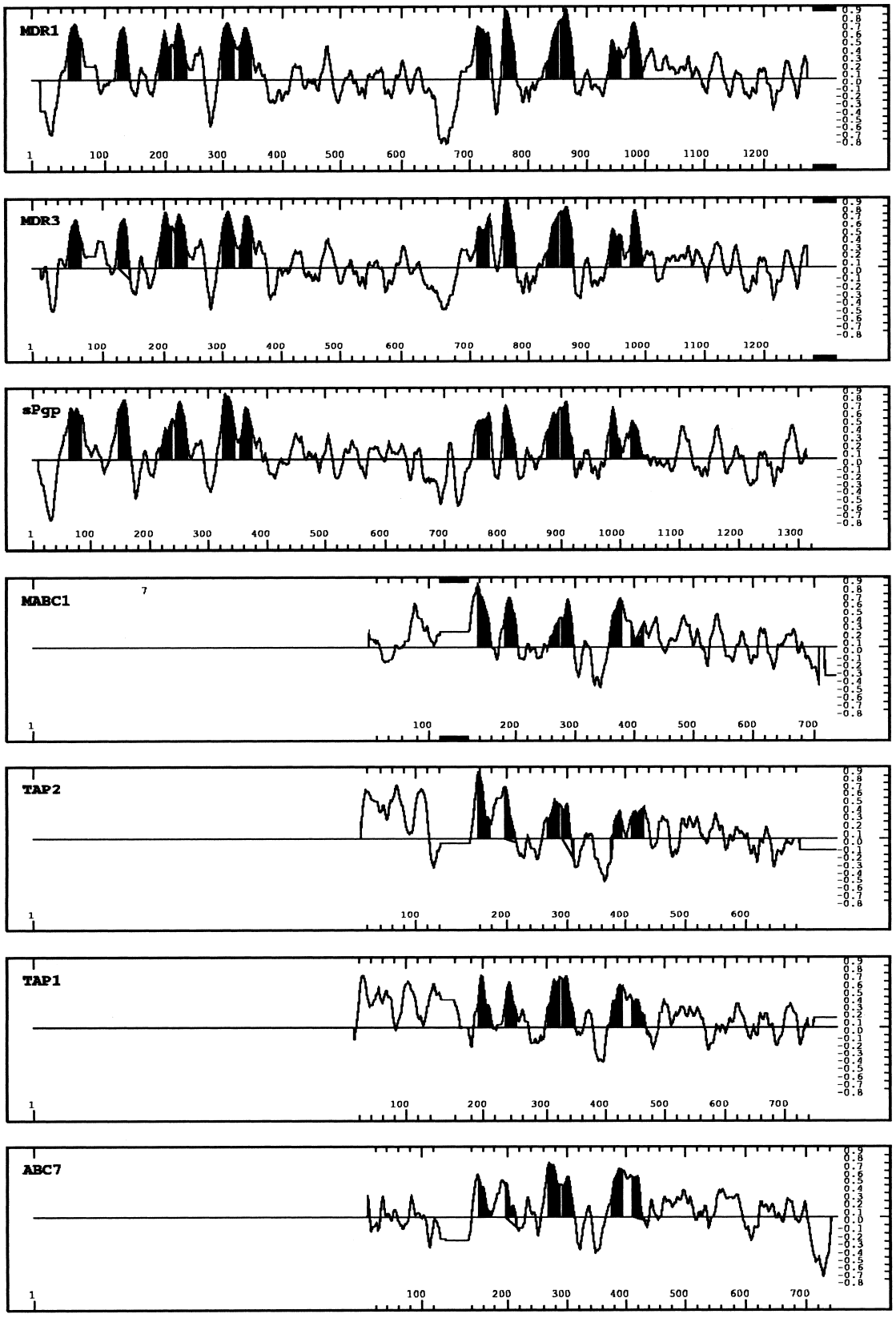


Fig. 2. Domain arrangement prototypes of human ABC proteins. Shaded circle with an A represents the ABC domain, vertical slabs represent transmembrane helices within the transmembrane domains (TMD). The following configurations are listed: 'ABC', ABC-ABC′, TMD-ABC, ABC-TMD, (TMD-ABC)2 and TMD0(TMD-ABC)2. The upper surface of the transmembrane domains represents extracellular orientation or facing the lumen of a cellular compartment (endoplasmic reticulum, peroxisome or mitochondrium), while the lower surface represents intracellular (cytosolic) localization.

is available electronically (OMIM, Online Mendelien Inheritance in Man, http://www.ncbi.nlm.nih.gov/Omim). References to the corresponding OMIM entries are also given in Table 1.

Analysis of the human ABC protein sequences revealed distinct subfamilies. The dendrogram of 30 human ABC proteins represented by complete sequences in the database is shown in Fig. 1. The separation of four larger subfamilies – MRP/CFTR (nine members), MDR/TAP (seven members), ALD (four members) and ABC1 (four members) – and four smaller groups – White (two members), ANSA


MDR1
MDR3
sPgp
MABC1
TAP2
TAP1
ABC7

(two members), and two 'single member' subgroups, GCN20 (i.e. ABC50) and RNAI – is obvious on the dendrogram.

Various arrangements of the TMD and ABC domains can be observed among the human ABC proteins (Fig. 2). The class of (TMD-ABC)2 represents full-size transporters, and can be found in the MDR/TAP, MRP/CFTR and ABC1 subfamilies. A third transmembrane domain, TMD0, composed of five TM helices, is attached to the N-terminus of several members of the MRP/CFTR family. This is designated as TMD0(TMD-ABC)2 arrangement. A more detailed analysis of this topology subgroup is given in the description of MRP/CFTR family in this Special Issue by several reviews. Two variations of 'half transporters' are represented among the human ABC proteins: TMD-ABCs are in the MDR/TAP subfamily, and four of such half transporters form the ALD subfamily of peroxisomal transporters. Two ABC/TMDs are found in the White subfamily. As a general rule, full transporters are mostly located in the plasma membrane of the host cell, while half transporters – in homo- or heterodimeric form – are targeted to the membranes of subcellular organelles, like the endoplasmic reticulum, peroxisome or mitochondria. One representative of the ABC-ABC arrangement belongs to the GNC20 subfamily and another protein, with the same arrangement, is identified as an RNAse L inhibitor. Two members of the single ABC type (ANSA subfamily) are also present in the human genome.

When the ABC protein classifications, based on linear amino acid sequences (Fig. 1), or considering domain arrangements (Fig. 2) are compared, the two schemes are not fully overlapping. This and other observations suggest a complex evolutionary scenario of the family, which is not the topic of the present review. Still, throughout this chapter we emphasize the membrane topology and domain arrangements, as these may provide important clues to the structure and function relationship.

A complete inventory of the yeast ABC proteins was published earlier [1], and an inventory is also provided in this Special Issue. These serve as useful templates for classification of human ABC proteins. Each kind of domain arrangement can be find among the yeast ABC proteins, although the TMD0(TMD-ABC)2 assembly, which is also represented by a few yeast ABCs, is not distinguished from the (TMD-ABC)2 configuration in the yeast inventory [1]. No human counterpart of the (ABC-TMD)2 arrangement in yeast has been identified so far. In the following sections we provide a description for each human ABC protein group.

2. Human ABC proteins

2.1. The MDR/TAP subfamily

Members of this subfamily are full transporters, like MDR1, MDR3 and SisterPgp, or half transporters, like TAP and TAP2, or the two mitochondrial transporters, M-ABC1 and ABC7. The membrane topology of MDR1 has been elucidated by epitope insertion experiments [2,3], fully supporting the original topology model of six TM helices in both TMDs of the protein [4]. In the representation presented in Fig. 3, the amino acid sequences of the MDR/TAP family members were aligned and the hydrophobicity plots of the aligned protein sequences were generated. The peptide segments of MDR1 spanning the membrane bilayer are shaded in the plot of this protein. The corresponding segments, as dictated by the multiple alignment, are also shaded in the other family members. As seen in this figure, the hydrophobicity plots of the family members are similar, suggesting similar membrane topologies. Still, additional possible membrane-spanning sequences in the half transporters are indicated by these plots.

2.1.1. MDR1/Pgp1

The multidrug transporter/P-glycoprotein (MDR1 or Pgp1) was the first human ABC protein cloned [4],

←

Fig. 3. Hydrophobicity plots of the aligned protein sequences of the members of the MDR/TAP subfamily. Peptide segments of MDR1 spanning the membrane bilayer, determined experimentally [2,3] are shaded in the plot of MDR1. The corresponding segments dictated by the multiple alignment are also shaded in the other family members' plots. Hydrophobicity plots were generated as described [66]. Proteins from the top are: MDR1, MDR3, SisterPgp, M-ABC1, Tap2, Tap1 and ABC7.

and it is still one of the most intensively studied proteins of the family. This special attention was attracted by the fact that multidrug resistance of cancer cells was found to be caused by this protein. MDR1 is localized in the plasma membrane, on the apical (or luminal) surface of polarized epithelial cells. These include the brush border membrane of intestinal cells, the biliary canalicular membrane of hepatocytes, and the luminal membrane in proximal tubules of kidney [5,6]. MDR1 is also present at the pharmacological barriers of the body, e.g. at the blood-brain barrier [7] and at the choroid plexus [8].

The MDR1 transporter can extrude a wide range of structurally unrelated hydrophobic toxic compounds from the cell. On the basis of its localization and its ability of vectorial transport of a range of toxic molecules, it is suggestive that the physiological function of MDR1 is the protection of the cells and organism against toxic compounds [9,10]. This physiological function of MDR1 was studied by a knockout mouse model, by disrupting one or both of the mdr1 genes in mice [9,10]. MDR1 knockout mice are viable and fertile, with no obvious physiological abnormality. However, the mice lacking both MDR1-like transporters were found to be hypersensitive to xenobiotic compounds. Detailed reviews of the MDR1/Pgp structure and function are provided by several papers in this Special Issue, and thus we refer to these communications for further detail.

2.1.2. sPgp/BSEP and MDR3

Two members of this family, 'the sister of P-glycoprotein', sPgp or 'bile salt export pump' (BSEP) and MDR3 are both involved in different types of progressive familiar intrahepatic cholestasis, PFIC2 and PFIC3, respectively. Both MDR3 and sPgp are full transporters with close sequence relationship to MDR1, with 75% and 50% identical amino acids, respectively.

sPgp was first described as a partial cDNA of a putative porcine canalicular ABC transporter of unknown function [11] and then the rat sPgp was cloned by a PCR-based approach using Walker A- and Walker B-specific degenerated oligonucleotides [12]. It was demonstrated that sPgp functions as an ATP-dependent bile salt transporter. This protein is expressed exclusively in the canalicular microvilli of the liver. These data strongly support that sPgp is the canalicular bile salt export pump of the liver [12].

The human ortholog of sPgp was identified by a positional candidate cloning strategy, as the disease gene of PFIC2, and termed bile salt export pump, BSEP [13]. Chromosomal region 2q24 was identified earlier as the locus of PFIC2 [14], characterized by persistent neonatal cholestasis with features of amorphous or finely filamentous bile, neonatal non-specific giant cell hepatitis and later biliary cirrhosis. Mutations of human sPgp/BSEP are causative in PFIC2 [13]; ten different mutations were discovered and all are predicted to be functionally significant.

MDR3 is a phospholipid (phosphatidyl choline) translocator [6], with a highly specific expression pattern in the canalicular membrane of the liver [15]. A knockout mice model was developed to elucidate the physiological function of the transporter, showing that the (−/−) mice did not secrete phospholipids into the bile and developed severe liver disease with symptoms similar to PFIC3 [16]. PFIC3 is caused by the reduction of biliary phospholipid secretion, with normal bile salt concentration. This form is accompanied with recurrent pruritus or jaundice in the first month of life, and then progresses to biliary cirrhosis. Liver histology shows portal inflammation and ductular proliferation in an early stage. The gene of PFIC3 was mapped to chromosomal region 7q21.3.

Defect of MDR3 expression in PFIC3 liver was first discovered by Northern blot analysis of mRNA, obtained from the liver tissue of a PFIC3 patient [17]. Liver sections of two PFIC3 patients were also studied after liver transplantation by immunohistochemistry, using an MDR3-specific polyclonal antibody [18]. No MDR3 staining was observed, indicating the complete loss of the protein from the canalicular membrane. Sequence analysis of the hMDR3 transcript in the liver identified a 7 bp deletion at one of the patients, and a non-sense mutation at a second patient. Analysis of genomic DNA was performed to clarify the pattern of inheritance: the parents of both patients were found to be heterozygous for the corresponding mutations [18].

Coexistence of PFIC3 and intrahepatic cholestasis of pregnancy associated with an MDR3 gene defect in a large family, was described recently [19]. A 1 bp deletion, 1712delT, in codon 571 of the MDR3 gene has been identified with a frameshift, and introduc-

tion of a stop codon downstream. The mutation resulted in an inactive truncated protein. Within this family, six women had at least one typical episode of intrahepatic cholestasis of pregnancy, resulting in the death of fetus in three cases. Cholestasis disappeared spontaneously and progressively after delivery. In the four women available for study, DNA showed heterozygosity for the 1 bp deletion [19]. All the data presented above clearly indicate that MDR3 is the disease gene of PFIC3.

It is interesting to note that in spite of the high level of sequence identity between MDR1 and MDR3, the latter one is not implied in multidrug resistance.

2.1.3. TAP1 and TAP2

The major histocompatibility complex (MHC) encodes the class I and class II families of glycoproteins that present peptides for immunorecognition by cytotoxic and helper T lymphocytes, respectively. Class II molecules associate mainly with peptides derived from endocytosed extracellular proteins, whereas class I molecules bind peptides generated by degradation of proteins intracellularly. TAP1 and TAP2 are half ABC transporters (TM-ABC arrangement), residents of the endoplasmic reticulum membrane. By forming a heterodimer, TAP1/TAP2 actively transports the peptides degraded by the peptidase complex from the cytosol into the ER lumen, where the peptides associate with class I molecules [20,21]. The TAP1 and TAP2 genes are located in the MHC class II region in chromosomal region 6p21.3 [22–26].

In mutant cell lines not expressing these transporters, most β2-microglobulin (β2M)-class I heavy chain complexes do not acquire peptides. Such empty complexes are unstable at physiological temperature and are inefficiently transported through the Golgi compartment. Relatively few peptide-free class I molecules reach the cell surface, where they can be stabilized by exogenous class I-specific peptides [27–29]. In a family from Morocco two of five children were homozygous for a mutation in the TAP2 gene, the expression of class I HLA proteins on the cell surface was deficient, and the cytotoxicity of natural killer cells was affected [30]. Human solid tumors and cell lines were studied for the genetic abnormalities of TAP1 transporter [31]. In a small cell lung cancer cell line a heterozygous mutation (R659Q) close to the Walker B motif has been found which resulted in the complete loss of peptide binding and antigen presentation. Interestingly, in the cell line only the mutant, R659Q allele was transcribed to RNA [31].

A detailed review of the TAP proteins is provided in this Special Issue.

2.1.4. M-ABC1 and ABC7

These two human ABC transporter proteins are localized to the mitochondrial membrane. Both proteins are 'half transporters' with a TMD-ABC arrangement.

M-ABC1 was cloned after a systematic search for ABC-like ESTs with the ABC signature motif of human MDR1 and the full-length cDNA was obtained from a lymphoblastic leukemia cDNA library [32]. The protein consists of 718 amino acids and the gene was mapped to chromosome 7q35-36. No disease genes have been mapped to this region. The M-ABC mRNA is widely expressed in human tissues. Immunostaining revealed a colocalization of M-ABC1 protein with the mitochondria, and it was shown that the N-terminal region of the protein contains the mitochondrial targeting signal. A segment extending form residue 1 to 55 was fused to a green fluorescent protein; cells transfected with this fusion cDNA construct displayed fluorescence almost exclusively at the mitochondria.

In order to identify the physiological role of M-ABC1 in the mitochondrial membrane, a double mutation was introduced into the Walker A motif (G495A, K496R). The mutant protein was transiently expressed in COS-7 cells with the expectation that the non-functional protein will show dominant negative phenotype by forming inactive hetero- or homodimers. Interestingly, the mutant protein was unstable and degraded rapidly [32].

ABC7 is the other member of the mitochondrial ABC transporter subfamily, which was also identified first as EST [33,34] then the full cDNA was cloned independently by several laboratories [35–37]. ABC7 is a 752 amino acid protein and shares 43% identical residues with the yeast ATM1, which has mitochondrial localization. Northern blot analysis detected an approximately 3 kb ABC7 transcript in human heart, skeletal muscle, pancreas, lung, liver, placenta, and several cell lines, but not in brain [34]. To investigate the subcellular targeting of hABC7, a fusion protein,

harboring the N-terminal 135 amino acids of the protein and the mouse dihydrofolate reductase, was synthesized and incubated with isolated yeast mitochondria. The fusion protein became processed to a shorter form, probably by the mitochondrial processing peptidase during incubation with mitochondria, and imported into the organelle [36]. ABC7 was found in mitochondria isolated from human liver as a 68 kDa protein, further supporting that it is localized in this organelle after processing [36]. It is noticeable that ABC7 was found to be highly expressed in tissues (heart, skeletal muscle, pancreas, lung, liver and placenta, see above) which are rich in mitochondria.

In elegant experiments it was demonstrated that the human ABC7 can functionally complement the deletion of yeast ATM1, thus compensating the growth defect of the mutant yeast strain, Δatm1 [36,37]. Expressing hABC7 in yeast strain, Δatm1 restored the level of cytochromes and other, heme-containing proteins. Mitochondria of the hABC7/Δatm1 yeast did not contain high level of iron, a phenotypical characteristic of the mutant Δatm1 yeast strain [36]. On the basis of these results it can be concluded that hABC7 is the functional ortholog of yeast ATM1, and both ABC transporters probably contribute in transporting the same substrate across the mitochondrial inner membrane where they function as exporters. The nature of this substrate needs to be identified, but it seems likely that these transporters play a crucial role in iron homeostasis of the cell.

The human ABC7 gene has been mapped to chromosome Xq13.1-q13.3 [34]. This chromosomal region has been implicated in X-linked sideroblastic anemia and ataxia (XLSA/A) [38]. XLSA/A is a recessive disorder characterized by an infantile to early childhood onset of non-progressive cerebellar ataxia, and mild anemia with hypochromia and microcytosis. Its main feature is that iron cannot be built into the heme so it forms deposits in the mitochondria of the erythroblasts. This can be detected with Prussian blue staining as ring sideroblasts.

Mutational analysis of the ABC7 gene has been performed in an XLSA/A family and a mutation of I400M was discovered, which segregates within the family [37]. It was not detected in the 600 control chromosomes. The functional consequences of the potential XLSA/A mutation were studied in yeast: the corresponding residue of the ATM1 protein was replaced with methionine (V365M). Wild-type and V365M ATM1 was expressed in yeast strain Δatm1. A pronounced difference in growth rate was observed in the presence of 10 μM $FeCl_3$: cells expressing the mutant form of the transporter had a growth defect [37]. This difference was maintained only under stringent conditions (i.e. at low iron concentration), which may mean that the mutation is accompanied with only partial loss of activity of ABC7. This suggestion is in harmony with the clinical picture of these patients who have only mild anemia [37].

All known half ABC transporters function as dimers; whether the two mitochondrial human ABC transporters, M-ABC1 and ABC7 form a heterodimer with each other, remains to be determined. The fact that ABC7 is involved in XLSA/A while the chromosomal region of M-ABC1 was not implicated in the disease apparently contradicts such a possibility. But ABC-M is localized to an autosome, to chromosome 7, and mutations in both alleles of M-ABC1 would be needed to cause a recessive hereditary disease like XLSA/A. On the other hand, a hemizygote (single) mutation of the ABC7 gene on chromosome X of a male will be causative in XLSA/A. This means that in case of a ABC7/M-ABC1 dimer with functional mutations of the ABC7 protein would lead to the disease phenotype much more frequently then those in M-ABC1.

2.2. The ALD subfamily

Four half transporters with TMD-ABC arrangement, ALDP, PMP70, ALDPR and PMP69, are members of this family; they are localized to the peroxisomal membrane and their mutant forms are involved in different peroxisomal disorders.

2.2.1. ALDP

Adrenoleukodystrophy (ALD) is a severe X-linked neurodegenerative disorder affecting about 1/20 000 males; it is the most frequent peroxisomal disorder. The disease is characterized by the accumulation of unbranched saturated fatty acids with a chain length of 24 to 30 carbons, particularly hexacosanoate (C26), in the cholesterol esters of brain white matter,

in the adrenal cortex and in certain sphingolipids of brain, and also, to a lesser extent, in other places like fibroblasts and red cell membranes. This alteration might interfere with myelin formation in the central nervous system and steroidogenesis in the adrenal. Subsequent studies showed that ALD is characterized by an impairment of degradation of very long chain fatty acids (VLCFAs) in the peroxisomes. Peroxisomes of ALD patients lack the ability to activate VLCFAs to their CoA esthers before entering the β-oxidation pathway. This activation step is carried out by very long chain fatty acid-CoA synthase (VLCFA-CoA). Affected males have diminished activity of this enzyme and this defect in their β-oxidation results in the accumulation of VLCFA cholesterol esthers. The biogenesis of the peroxisomes is not impaired.

The gene that encodes the primary biochemical defect in ALD maps to Xq28 [39]. and encodes a 745 amino acid protein, ALDP, a half ABC transporter [40]. It is a peroxisomal membrane protein orientated toward the cytosol [41]. It has been proposed that it plays a role in the import or anchoring of the peroxisomal enzyme VLCFA-CoA synthase, whose activity is defective [42] in ALD. The 75 kDa ALDP detected by monoclonal antibodies was absent in several ALD patients [41].

Less than 10% of the ALD patients have detectable deletions in the ALD gene [40] and about 50% of the mutations are missense mutations [42]. The majority of the mutations appear to be unique to each of the kindreds. A dinucleotide (AG) deletion at position 1801–1802 in exon 5 has been observed in seven different studies and in a total of 14 different kindreds. This is the most frequent mutation in ALD gene and it seems to represent a mutation hotspot [42]. A segment of the ALD gene harboring exons 7 to 10 has been duplicated and inserted into specific locations near the pericentromeric regions of chromosomes 2, 10, 16 and 22 [43]. Sequence analysis revealed 92–96% identity indicating a recent event of insertion into chromosome 2 some 5–10 million years ago followed by a rapid distribution of the duplication cassette [43].

2.2.2. PMP70

The cerebro-hepato-renal syndrome of Zellweger is a fatal inherited inborn error, caused by deficient import of peroxisomal matrix proteins. During fetal development of Zellweger patients the lack of assembly of functional peroxisomes is the physiological background of the multi-organ defect. Mutations of PMP70 were found in a subset of Zellweger patients [44]; an exon-intron splice junction mutation and a missense mutation (G17D) have been described.

2.2.3. PMP69 and ALDRP

As both ALDP and PMP70 are half ABC transporters, they may form homodimers or heterodimers with each other, or with other homologous proteins. It has been proposed that PMP69 [45] or ALDRP [46], two recently identified ALD-like genes, might be such partners. PMP69 and ALDRP may act as modifier proteins in determining the phenotypic variations observed in ALD. Alternatively, as potential heterodimer partners of PMP70, they might play a role in peroxisome biogenesis.

2.3. The MRP/CFTR subfamily

The MRP-CFTR subfamily is currently the largest in the human ABC family, consisting of nine members.

2.3.1. MRP1

The discovery of the human multidrug resistance associated protein (hMRP1), conferring a multidrug resistant phenotype to tumor cells was a landmark in our understanding of the molecular basis of multidrug resistance [47]. It subsequently became clear that the majority of non-P-glycoprotein mediated multidrug resistance is due to the overexpression of hMRP1. The clinical importance and the functional characteristics of this transporter are the subjects of several reviews in the present Special Issue.

According to our current understanding, hMRP1 probably transports both hydrophobic anticancer agents and anionic (e.g. glutathione) drug conjugates [48–51]. Its physiological functioning may provide a wide range of cellular xenobiotic resistance and MRP1 plays a key function in mediating the LTC-dependent inflammatory response [8,52,53]. In polarized epithelial cells MRP1 is routed to the basolateral membrane [138].

When hMRP was cloned and sequenced, analysis of its primary amino acid sequence revealed that this

protein is more closely related to the cystic fibrosis transmembrane conductance regulator (CFTR) than to MDR1. According to the original sequence analysis, MRP was predicted to contain eight+four transmembrane helices, each set of helices followed by an ABC unit [47] i.e. the canonical (TMD-ABC)2 domain arrangement was proposed. For members of the subfamily identified in the following years, e.g. SUR1 and SUR2 [54,55], cMOAT [56,57], the (TMD-ABC)2 arrangement was generally accepted, with predicting various numbers of membrane-spanning helices in each TMD.

Since numerous experimental data strongly argued against the first membrane topology model of hMRP1 [58,59], new models were elaborated to accommodate these data and to find the correct topology of the MRP-related proteins. The revised membrane topology models for hMRP1 have been independently forwarded by two research groups [58,60]. Bakos et al. [58] compared the amino acid sequence of hMRP1 with two members of the ABC protein family: the yeast cadmium resistance protein, YCF1 [61], which seemed to be one of the closest relatives of hMRP1; and the human CFTR, which belongs to this ABC subfamily, and whose membrane topology has been established experimentally [62]. They found that when the CFTR and MRP sequences were aligned, the hydrophobicity analysis of the aligned sequences yielded a close matching of the transmembrane segments, thus suggesting a six+six transmembrane helix topology for hMRP1 as well. However, hMRP1 contained an additional N-terminal segment of about 230 amino acids which had no counterpart in CFTR (or e.g. in MDRs), but closely resembled the N-terminal region of YCF1. On the basis of these hydropathy profiles and limited proteolysis experiments, the highly hydrophobic N-terminal segment of MRP1 was suggested to be membrane embedded with five transmembrane helices.

In parallel studies, with the cloning of the murine MRP [60] the hydropathy plots of several ABC transporters (mouse and human MRPs, Pgp, YCF1 and rat SUR) were aligned in order to analyze the organization of potential membrane-embedded domains. It was noticed that hMRP contains an N-terminal domain with no counterpart in Pgp, but closely related to that in mouse MRP, YCF1 and SUR1. Subsequent investigations of the membrane topology of hMRP1 by epitope insertion [63,64] and by mutation of glycosylation sites [65] fully supported the revised topology model.

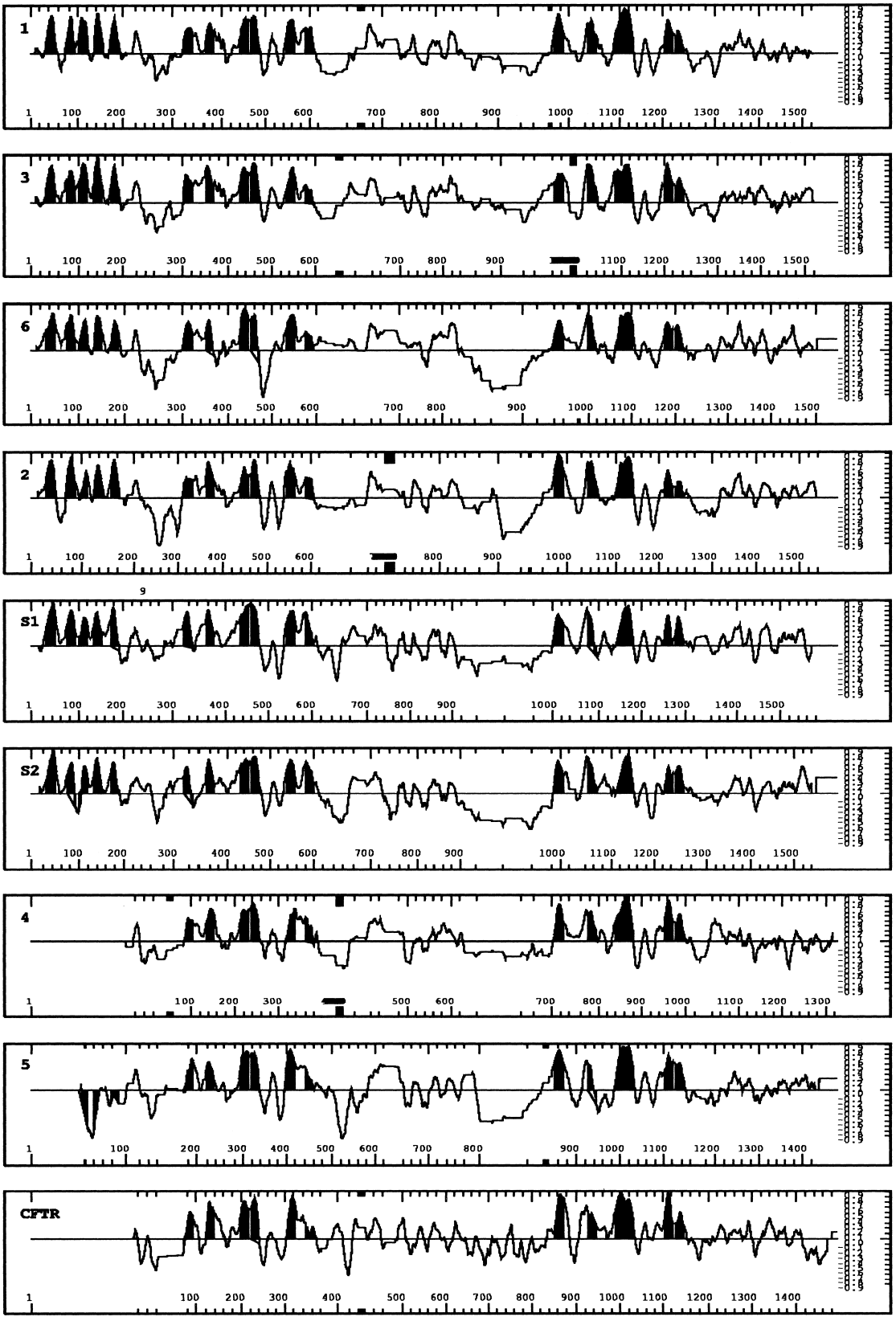
On the basis of amino acid sequence comparisons and alignments of hydrophobicity plots of all full-size ABC transporters present in the sequence database in 1997 it was concluded that common membrane topology with TMD0(TMD-ABC)2 domain arrangement distinguishes an MRP-like subfamily within the ABC kingdom [66].

Subsequently, new members of the MRP-CFTR subfamily have been discovered: MRP3/MOAT-D [67,68], MRP4/MOAT-B [69], MRP5/MOAT-C [68] and MRP6 [70].

In the study presented in Fig. 4, the amino acid sequences of the CFTR-MRP family members were aligned and the hydrophobicity plots of the aligned protein sequences were calculated. This comparison indicates that six proteins of the family (i.e. MRP1, MRP2, MRP3, MRP6, SUR1 and SUR2) form a subcluster within which each member possesses the N-terminal TMD0 domain first described for MRP1. Thus this group of MRP-like proteins are characterized by the TMD0(TMD-ABC)2 arrangement. The N-terminal TMD0 domain is absent from CFTR, MRP4 and MRP5. It is noticeable that the level of sequence identity is the lowest in the TMD0 domain within the TMD0(TMD-ABC)2 subcluster. However, the membrane topology, as indicated by the hydropathy plots, is most probably similar. Interestingly, recent studies of deletion mutants of MRP1, by the removal of the full TMD0 region, indicated that this region is neither required for the transport function of MRP1 nor for its proper routing to the lateral plasma membrane compartment [71].

→

Fig. 4. Hydrophobicity plots of the aligned protein sequences of the members of the MRP/CFTR family. Peptide segments of MRP1 spanning the membrane bilayer, determined experimentally [63–65] are shaded in the plot of MRP1. The corresponding segments dictated by the multiple alignment are also shaded in the other family members' plots. Hydrophobicity plots were generated as described [66]. Proteins from the top are: MRP1, MRP3, MRP6, MRP2, SUR1, SUR2, MRP4, MRP5 and CFTR.


1
3
6
2
S1
S2
4
5
CFTR

2.3.2. MRP2 (cMOAT)

Mutations of the canalicular multispecific organic anion transporter, MRP2 (cMOAT) are causative in the Dubin–Johnson syndrome (DJS). DJS is an inherited defect in the secretion of amphiphilic anionic conjugates from hepatocytes into the bile. The disorder is predominantly characterized by conjugated hyperbilirubinemia, deposition of melanin-like pigment in otherwise normal liver cells, in some cases hepatomegaly and abdominal pain, prolonged retention of sulfobromophthalein, and otherwise normal liver function. Detoxification of many endogenous and xenobiotic lipophilic compounds in the liver is accomplished by conjugation with glutathione, glucuronide, or sulfate moieties, resulting in negatively charged, amphiphilic compounds that are secreted into bile or urine. Hepatobiliary excretion of these conjugates is mediated by cMOAT, located exclusively in the canalicular membrane of the hepatocyte [57,72].

The identification of the transport-deficient mutant rat strain, TR(−), which shows chronic conjugated hyperbilirubinemia, as found in the human Dubin–Johnson syndrome, contributed to the functional characterization of cMOAT [57]. Consistent with findings of defects in the homologous cMOAT gene in rat models of hyperbilirubinemia [57,73] two deletions and a missense mutation were reported in the cMOAT gene in patients with DJS [74]. Still, several other members of the MRP family are present in the hepatocyte membrane, which may compensate for the canalicular defect and result in transport of conjugated compounds into the blood.

2.3.3. MRP3, MRP4, MRP5 and MRP6

The physiological function of MRP3, MRP4, MRP5 and MRP6 is not known. MRP3 (MOAT-D) is expressed in the liver, in the colon and in the kidney [68], and it is inducible by phenobarbital in HepG2 cells [67]. MRP4 (MOAT-B) is widely expressed, with a particularly high level in the prostate, but it is not found in the liver [69]. MRP5 (MOAT-C) is expressed at the highest level in skeletal muscle and at intermediate levels in kidney, testis, heart and brain. Interestingly, only a low abundance of the MRP5 transcript was detected in liver [68]. MRP6 is specifically expressed in liver and kidney, and it was suggested that MRP6 is not involved in conferring multidrug resistance to tumor cells [70].

When compiling the data for the MRP homolog proteins, it is important to note that two MRP-like sequences, which are due to interesting cloning artifacts, are still present in various databases.

The 'short type of multidrug resistance protein homologue' (SMRP) was cloned from a human lung cancer cell line [75] which encodes 946 amino acids. The predicted protein contains two ABC domains and only one transmembrane domain with six membrane-spanning helices (ABC-TMD-ABC). According to a homology search the deduced sequence is most closely related to the members of the MRP subfamily of the ABC transporters, but the protein is much shorter than the established members of this group (e.g. hMRP1: 1531 aa; cMOAT: 1545 aa). On the other hand, a conceptual translation of the published 5′ UTR sequence of SMRP cDNA revealed that it encodes a single open reading frame (ORF) of 189 amino acids with high sequence similarity to the corresponding regions of the MRP family members, and represents a segment covering four transmembrane helices of the 'missing transmembrane domain' of the hypothetical SMRP. On the basis of this observation it was suggested that SMRP represents the partial sequence of an MRP-like transporter [76]. As the full sequence of MRP5 became available [68], it is clear now that SMRP is a partial sequence of MRP5.

The 'anthracycline resistance protein' (ARA) was also reported as a novel MRP-like ABC protein which consists of only 453 amino acids and a domain arrangement of TMD-ABC. The overexpression of ARA has been first described in a drug selected leukemia cell line, in which the 'ARA gene' was amplified [77]. The ARA transcript has been shown to be co-expressed with MRP1 in a series of multidrug resistant leukemia cell sublines [78] and its predicted amino acid sequence was found to be closely related to the C-terminal portion of hMRP1. The hydrophobicity plot constructed for ARA and aligned with that of hMRP1 revealed that ARA contains a deletion in the transmembrane region. Thus the hypothetical ARA protein can not form the characteristic six transmembrane helix TMD of ABC proteins. A sequence alignment of the ARA cDNA revealed an unexpected composition of this transcript. The first

1–115 bp 5′ non-coding region is identical (100% similarity score) with the 5′ end of the MRP1 cDNA. The regions coding for the N-terminal eight amino acids of ARA and MRP1 (116–130 bp, ARA numbering) are also identical. The remaining sequences match completely with the eight 3′ exons of the MRP6 gene ([70], and Váradi, unpublished).

This composition clearly indicates that the ARA transcript is 'put together' from pieces of two neighboring homologous genes, MRP1 and MRP6. However, these two genes are situated in opposite reading directions on chromosome 16 (their 3′ ends are separated by 9 kb). It seems plausible to suppose that the ARA transcript resulted from an inverted and partially deleted chromosome, or amplified chromosomal fragment formed in a drug selected leukemia cell line. In the normal human genome there is no ARA gene, ARA is most probably a non-functional transcript of a largely rearranged tumor cell DNA.

2.3.4. SUR1 and SUR2

The sulfonylurea receptor, SUR1, is a representative of the TMD0(TMD-ABC)2 domain arrangement transporters within the MRP subfamily. Sulfonylureas promote insulin secretion, interact with the sulfonylurea receptor of pancreatic β cells and inhibit the conductance of ATP-dependent potassium channels [54]. Mutations of SUR1 has been found to cause a rare genetic disease, persistent hyperinsulinemic hypoglycemia of infancy (PHHI). PHHI is due to defective negative feedback regulation of insulin secretion by low glucose levels, resulting in excess insulin secretion and hypoglycemia. Most inherited cases follow an autosomal recessive pattern, and mutations of the SUR1 gene or the closely linked KIR6.2 gene have been found in several families. Both of these genes encode components of the potassium channels responsible for glucose-regulated insulin release [79–81].

The sulfonylurea receptor may sense changes in ATP and ADP concentration, affect K(ATP) channel activity, and thereby modulate insulin release [82]. Data in the literature indicate that both nucleotide binding fold regions of the sulfonylurea receptor are required for normal regulation of β cell ATP-dependent potassium channel activity and insulin secretion [83] (for details see the review in this Special Issue).

An isoform of SUR, designated as sulfonylurea receptor-2 (SUR2), was cloned [55] from a rat brain cDNA library. The 5300 bp cDNA sequence encodes a protein of 1545 amino acids that shares 68% identity with SUR1. Although the structural features of SUR1 and SUR2 are similar, the ATP sensitivity and pharmacological properties of the K(ATP) channel reconstituted from SUR2 are distinct from those obtained from the SUR1 [55].

2.3.5. CFTR

Cystic fibrosis (CF) is one of the most frequent inherited diseases with prevalence of 1 in 2500 births within the Caucasian populations. It is an autosomal recessive disorder affecting a variety of epithelial tissues. Manifestations relate not only to the disruption of exocrine function of the pancreas but also to intestinal glands (meconium ileus), biliary tree (biliary cirrhosis), bronchial glands (chronic bronchopulmonary infection with emphysema), and sweat glands (high sweat electrolyte). Infertility occurs in males and females. The CF gene has been cloned by positional cloning and the 'cystic fibrosis transmembrane conductance regulator' protein (CFTR) was identified [84]. CFTR forms a cAMP activated chloride channel and is characterized by a specific domain arrangement: TMD-ABC-R-TMD-ABC, in which R is a regulatory domain, the main target of phosphorylations regulating CFTR channel activity. Although the major mutation that results in a single amino acid deletion (ΔF508) accounts for 70% of the disease alleles, by now more than 800 disease-causing mutations are identified (http://www.genet.sickkids.on.ca/cftr/).

Many of these mutations can be divided into five general classes in terms of their demonstrated or presumed molecular consequences. These are no synthesis (e.g. G542X, 394delTT, 1717/G-A), a block in processing (e.g. ΔF508), a block in regulation (e.g. G551D), altered conductance (e.g. R117H) and reduced synthesis (e.g. A455E, 3849+10kb-T) of CFTR [85]. Existence of at least two genetic loci was demonstrated that could modify the severity of the disease [86].

An alternatively spliced form of CFTR mRNA has been identified in heart, which lacks a 30 amino acid segment of the first cytoplasmic loop [87,88]. Expression of this cDNA in Xenopus oocytes gave rise to robust cAMP-activated chloride currents [89].

Evaluation of human CFTR mRNA transcripts from epithelial and non-epithelial cells demonstrated a CFTR cDNA containing a 260 bp insertion between CFTR exons 23 and 24. This insertion introduces a premature stop codon that would result in a protein shortened by 61 amino acids at the carboxyl terminus [90]. Sequence analysis of intron 23 of the gene demonstrated that the 260 bp insertion (named exon 24a) is a part of intron 23. The exon 24a+ CFTR mRNA transcripts represented 3–16% of the total CFTR transcripts in epithelial and non-epithelial cells. These observations suggest an unexpected plasticity of the expression of the CFTR gene, where alternative splicing of precursor CFTR mRNA transcripts permits the use of an alternative exon, derived from a genomic segment previously believed to function as an intron [90].

Another alternative transcript, often present at high levels, results in the in-frame deletion of exon 9 [91]. Translation of this transcript would result in a CFTR protein missing the amino terminal portion of the first ABC. The protein produced by the CFTR Δ9 transcript is not properly processed and is not capable of generating Cl^- conductance in response to cAMP [91]. A unique feature of the acceptor splice site preceding this exon is a variable length polymorphism within the polypyrimidine tract, influencing the extent of exon 9 skipping in CFTR mRNA [91]. The 5-thymidine (5T) variant of the intron 8 polypyrimidine tract (IVS8-T tract) is the most frequent CFTR gene variant identified in men with congenital bilateral absence of vas deferens (CBAVD) [92]. These patients usually have none of the other clinical signs of classical cystic fibrosis. This alternative splicing variant gives rise to two transcripts, one normal with exon 9 intact and the other with in-frame deletion of exon 9. Correlation was found between the length of the IVS8-T tract and the level of alternatively spliced transcripts. Results from histological analysis also suggest an involvement of the alternative transcript in the spermatogenic status of patients, leading to a decreased number of mature sperm forms in the tubule [93]. A significantly higher level of transcripts lacking exon 9 was found in vas deferens than in nasal epithelia, regardless of the IVS8-T genotype [94]. These findings suggest that the splicing of CFTR precursor mRNA is less efficient in vasal epithelia, as compared to the respiratory epithelia. Thus, differential splicing efficiency between the various tissues which express CFTR provides one possible explanation for the reproductive tract abnormalities observed in infertile men with CFTR gene alterations but without other clinical manifestations of CF [95].

Searching for CFTR-related genes by hybridization screening of cDNA and genomic libraries led to the identification of several copies of CFTR exon 9 and its flanking introns [96]. These CFTR exon 9-related sequences were characterized and their chromosomal localization has been determined. At least 10 copies of this amplified CFTR exon 9 are present in the genome. It was revealed that these sequences are juxtapositioned with two segments of LINE1 (long interspersed nuclear elements) sequences. LINE1s are the most abundant retrotransposons in the human genome and LINE1 mediated transduction is a potential source of genome diversity [97]. It seems that these CFTR exon 9-related multicopy sequences were derived from a single retrotransposition event and subsequent DNA amplification. Sequence analyses of the 647 bp CFTR gene segments revealed identity of 92–96%. An estimation, based on the average mutation rate of the genome, suggests that the retrotransposition event might happen 7–10 million years ago [96].

2.4. The ABC1 family

Four members of this family, ABC1, ABCR, ABC3 and KIAA0822 are known today. They are full-size transporters, ABC1 and ABCR are the largest human ABC proteins with 2201 and 2273 amino acids, respectively; ABC3 consists of 1704, while KIAA0822 is composed of 1582 amino acids.

2.4.1. ABC1

The first member of the family, the mouse ABC1, was cloned by a PCR-based strategy [98] and the human ABC1 was identified by using sequence information of the mouse protein [99]. Both ABC1 and ABCR, which share 50% of identical amino acids, contain a large cytoplasmic domain of unknown origin and function. This region harbors a short hydrophobic segment, which is not long enough to expand the membrane twice, but may attach this region to the membrane on the cytoplasmic site or form a part

of the inner core of this globular domain. Interestingly, no counterpart of the ABC1 family is present in the yeast genome [1].

The mouse ABC1 is involved in the engulfment of apoptotic cells by macrophages [100]. The *Cenorhabditis elegans* structural homolog of ABC1, Ced-7, has similar function in this invertebrate, as Ced-7 loss of function phenotype results in impaired engulfment [101]. ABC1 was found to generate an electroneutral anion efflux when expressed in *Xenopus laevis* oocytes [102], and it was also shown to play a crucial role in macrophage interleukin-1β secretion [103]. The tissue-specific expression of human ABC1 has been determined: the highest expression levels were detected in placenta, liver, lung, adrenal glands and various fetal tissues. The high level of ABC1 mRNA and protein in fetal liver and placenta are in harmony with the role of the transporter in clearing the apoptotic cells by macrophages [99]. The expression of hABC1 in monocytes/macrophages is sterol dependent, it is inversely regulated by cholesterol import and export, which may suggest that ABC1 transports lipids in distinct cell membranes [99].

2.4.2. ABCR

ABCR is a retinal ABC transporter, which was discovered by positional candidate cloning and it was found to be mutated in the recessive Stargardt macular dystrophy (STGD) [104].

The gene encoding hABCR was mapped to a 2 cM interval at chromosome 1p21-p13, the interval previously shown by linkage analysis to harbor the STGD gene [105]. The first several hundred bases upstream of the transcription unit are relatively conserved between mouse and human and contain several predicted cis regulatory elements, including two Ret-4-like elements that reportedly confer photoreceptor-specific gene expression [106,107]. ABCR expression is found exclusively in the retinal rod photoreceptors and the protein is localized to the rim of the rod outer segment discs [108].

The physiological transport substrate of ABCR is currently unknown, but it is most probably a molecule or molecules playing important role in photoreceptor homeostasis. The bovine ABCR protein has been purified and reconstituted into liposomes and its ATPase activity was studied with the intention of identifying possible substrate(s) of the transporter [109]. Forty three different hydrophobic compounds, including MDR1 substrates, detergents and retinoids were tested for stimulation of the ABCR-ATPase activity. All-trans-retinal, 11-cys- and 13-cys-retinal showed stimulation with K_m values of 10–15 μM. These data suggest that retinoids are the natural substrates of ABCR [109].

Since the discovery of ABCR in 1997, it became one of the most studied genes involved in inherited eye diseases. Genetic eye diseases are the most common causes of blindness in the developed world and mutations of the retina-specific ABCR transporter is responsible for several inherited eye diseases. Mutations in the ABCR gene cause Stargardt disease (STGD), and fundus flavimaculatus (FFM) [110]. ABCR mutations in heterozygous form were also found in 16% of patients with age-related macular degeneration (AMD) [110] and were identified in recessive retinitis pigmentosa (RP19) [111], cone dystrophy (COD) and cone-rod dystrophy (CRD) [112]. Different combinations of ABCR mutations can give rise to different phenotypes, affecting predominantly the macula (STGD, COD, AMD) [113], the peripheral retina (RP), or both (CRD) [114].

An attractive model based on the genotype/phenotype relationship has been elaborated [114]. Retinitis pigmentosa 19, the most severe eye disease associated to ABCR mutations is caused by two severe mutations, e.g. frameshift due to a single base deletion (1847delA) and splice site mutations. CRD and STGD patients carry either two moderately severe mutations, or a severe mutation accompanied with a mild one on the other allele. Accordingly, no STGD patient has been diagnosed with two severe mutations so far. The risk of developing AMD (which is caused by heterozygous ABCR mutations) is related with the severity of the mutation, i.e. the penetrance of an AMD mutation depends on the remaining ABCR activity. The above model was supported recently by an extensive mutational study of 150 STGD families [117].

This development suggests that a gene causing a Mendelian disorder might also play a role in complex genetic diseases. That different ABCR mutations cause distinct chorioretinal diseases resembles the genotype vs. phenotype relationship observed in cystic fibrosis where the mutations of CFTR lead to phenotypes ranging from the absence of vas def-

erens in its mildest form, to severe pulmonary and pancreatic disease.

2.4.3. ABC3

ABC3 was cloned [118] and classified as a member of the ABC1 family. It was noticed that the *C. elegans* protein Ced-7 is homologous to human ABC3, not only to human ABC1 [119]. Ced-7 functions in the engulfment of cell corpses during programmed cell death, is broadly expressed during embryogenesis, and is localized to the plasma membrane. Mosaic analysis revealed that Ced-7 functions in both dying cells and engulfing cells during the engulfment process. It was proposed that Ced-7 functions to translocate molecules that mediate homotypic adhesion between the cell surfaces of the dying and engulfing cells [119]. These authors also suggested that ABC3 may be functionally similar and that the molecular mechanism underlying cell corpse engulfment during programmed cell death may be conserved from nematodes to mammals.

2.4.4. KIAA0822

The KIAA0822 transcript was identified during a mass sequencing project by determining the complete sequences of 100 new cDNA clones from human brain [120]. The gene of KIAA0822 was sequenced as part of sequencing chromosome 17, it is located on clone hRPK.235 I 10 (Accession number: AC005922), with currently unknown function.

2.5. The White subfamily

The subfamily is named after the White gene of *Drosophila melanogaster* and it is characterized by a unique ABC-TM domain arrangement. The Drosophila White gene is involved in the transport of eye pigment precursors and it has a historical interest: this was the first gene ever mapped [121].

In *Drosophila* the subfamily consists of the White (W), Scarlet (St), and Brown (Bw) proteins. These are parts of a membrane-spanning permease system, necessary for the transport of pigment precursors into pigment cells responsible for eye color. These half transporters dimerize to form an active transporter: White dimerizes with Brown for the transport of guanine and with Scarlet for the transport of tryptophan.

Two human ABC transporter genes, belonging to the White subfamily have been identified recently: the ABC8/hwhite mapped onto chromosome 21q22.3; the mitoxantrone resistance associated protein 1/breast cancer resistance protein/placenta-specific ABC protein mapped onto chromosome 4p22.

2.5.1. White/ABC8

The human white homolog/ABC8 was identified by two different approaches [122,123]. When creating the transcript map of human chromosome 21, Chen et al. [122] performed exon trapping to identify genes, and isolated two exons encoding protein sequences with homology to Drosophila White. They screened a retina library with one exon and isolated cDNAs corresponding to the entire coding region of the human white gene. The protein sequences of Drosophila White and the predicted 674 amino acid human protein share 33% identical amino acids. By sequencing additional cDNAs and by RT-PCR method, evidence of an alternative splicing has been found. A short exon, encoding 12 amino acids, corresponding to the region which serves as a linker between the ABC and the TMD unit, is spliced out in several cDNAs isolated from a human cDNA library [122].

Interestingly the mouse white gene transcript, which shares 97% identical amino acids with human white, lacks this 12 amino acid segment [123,124]. The 3′ UTR of the human white gene harbors a polymorphic site: the poly(T) region was found to be polymorphic in the population [122]. The Drosophila White gene also possesses a poly(T) segment at the 3′ UTR [125], which may suggest a possible functional role of this poly(T) sequence.

An alternative cloning strategy was also applied, which involved polymerase chain reaction using degenerated oligonucleotide primers, based on conserved sequence motifs within the White subfamily [123]. The human white transcript isolated by this strategy from a Jurkat T cell cDNA library predicts a protein of 638 amino acids. This sequence is shorter than that identified independently; the length difference is due to the difference in prediction of the position of the translation initiation codon at the 5′ end of the transcripts.

The human white protein most probably forms homodimer or heterodimer(s) with other half trans-

porter(s) to create active transporter(s). The physiological role of the human white gene is not known. In general, to predict possible function on the basis of cross-species sequence homology is very risky within the ABC protein family, as members of the same subfamily may transport different substrates in different species thus fulfilling different physiological roles. Nevertheless, hwhite can be considered as a positional candidate gene of several inherited diseases mapped to the chromosome 21q22.3 region. If the functional analogy holds, and human white plays a crucial role in tryptophan and guanine uptake, like Drosophila White, this transport system may determine some neurotransmitter metabolic pathways, as e.g. tryptophan is the major precursor of serotonin. On this line of reasoning it is noticeable that the chromosomal position of neurodegenerative disorders, like the autosomal recessive non-syndromic deafness, DFNB8, the manic-depressive psychosis MD1, and myoclonic epilepsy of Lafora, MELF, are in the region where human white is mapped.

2.5.2. BCRP/MXR1/ABCP

The second member of the White subfamily was discovered in different multidrug resistant cell lines by two independent studies. In a human breast cancer subline, MCF-7/AdrVp, that shows anthracycline resistance without the overexpression of MDR1 or MRP1, this protein was identified as the 'breast cancer resistance protein', BCRP [126]. In a human colon carcinoma line, S1-M1-80 with a similar phenotype, the gene product was cloned as the 'mitoxantrone resistance associated protein 1', MXR1 [127]. At the same time, a third approach, based on searching the EST sequence database for ABC gene products, led to the identification of the same transcript in placenta as the 'placenta-specific ABC gene, ABCP' [128]. The gene was mapped to chromosome 4q22 and encodes a protein of 655 amino acids which shares 31% identity with the Drosophila White and 30% identity with the human white/ABC8 protein.

It was demonstrated that a variety of drug-resistant human cancer cell lines, derived by selection with mitoxantrone, markedly overexpressed BCRP mRNA; these cell lines included sublines of human breast carcinoma (MCF-7), colon carcinoma (S1 and HT29), gastric carcinoma (EPG85-257), fibrosarcoma (EPF86-079), and myeloma (8226) origins. Analysis of genomic DNA from BCRP overexpressing MCF-7/MX cells demonstrated that the BCRP gene was amplified in these cells [129].

Several experimental data support that the protein is involved in multidrug resistance: upon transfection of the BCRP cDNA into drug-sensitive human breast cancer MCF-7 cells, the cloned transfected cells became resistant to mitoxantrone, daunorubicin and doxorubicin, displayed diminished intracellular accumulation of daunorubicin, and manifested an ATP-dependent increase in the efflux of rhodamine 123 [126]. The results of these experiments still can not answer the question whether this half transporter acts as a homo- or as a heterodimer. Furthermore, the eukaryotic ABC half transporters mostly reside in intracellular organelle membranes, like the endoplasmic reticulum (TAP1/TAP2) or the peroxisome (ALD transporter family). The cellular localization of the multidrug transporter, belonging to the White subfamily, remains to be determined. The multidrug transporters MDR1/Pgp1 and MRP1 are expressed at various tissue barriers; the high level of expression of the white-type multidrug transporter in placenta [128] may reflect a similar role of this transporter at the placental barrier.

2.6. The OABP (RNAse L inhibitor) subfamily

2.6.1. RNase L inhibitor

The 2-5A system is one of the major pathways induced by interferon; it is composed of three enzymatic activities, e.g. 2-5A synthetases, 2-5A phosphodiesterase, and RNase L. 2-5A synthetases belong to the family of four IFN-inducible enzymes which, upon activation by double-stranded RNA, convert ATP into the unusual series of oligomers known as 2-5As. The 2-5A-dependent endoribonuclease L, or RNase L, is the effector enzyme of this system. Its activation by subnanomolar levels of 2-5A leads to the inhibition of protein synthesis by cleavage of mRNAs. The cloning of a polypeptide inhibitor of the 2-5A pathway, RNase L inhibitor was described [130]. RNase L inhibitor is a regulatory protein whose co-expression inhibits the binding of 2-5A by the endogenous RNase L and, as a consequence, the 2-5A-dependent activation of RNase L is arrested [130]. Although it was not noticed in the original

paper, sequence comparisons revealed that RNase L inhibitor is an ABC protein of 599 amino acids, possessing two ABCs and no transmembrane domain(s), that is an ABC-ABC arrangement.

2.7. The ANSA subfamily

The multicomponent arsenite transporter system, encoded by the ars operon of *E. coli* contains two regulatory and three structural genes [131]. ArsA codes for an ABC-ABC dimeric ATPase, which associates with the product of the arsB gene, an inner membrane protein of 12 transmembrane helices. The complex of arsA and arsB transports arsenite and antimonite out of the bacteria. Homologs of arsA have been identified in many bacteria (e.g. upon whole genome sequencing), in yeast and in *C. elegans*; some of these proteins consist of two ABCs, while others are monomeric.

2.7.1. ANSAI and ANSAII

A human arsA homolog was cloned by a PCR strategy utilizing degenerated primers, corresponding to regions where arsA and the *C. elegans* homolog share identical amino acids [132]. The human homolog, hASNAI is a monomeric, single ABC ATPase of 332 amino acids. It shares 28% identical amino acids with both ABC units encoded by arsA, 46% with the yeast YDL100c homolog, and 54% with the *C. elegans* homolog; these two proteins are monomeric ABCs like hANSAI. Another human homolog, hANSAII, has been identified recently (AF-047469.1); the two human proteins, hANSAI and hANSAII, are 98% identical. The two human arsA homologs, hANSAI and hANSAII, are not listed in the 'human ATP binding cassette transporters' website (http://www.med.rug.nl/mdl/humanabc.htm). The chromosomal localizations of the genes of hANSAI and hANSAII are not known. They form a subfamily of single ABC domain proteins in the human ABC family.

One of the interesting features of *E. coli* arsA is that it has an allosteric activator site. Three cysteine residues, two situated at the N-terminal, one at the C-terminal ABC of *E. coli* ArsA, form a binding site, which effectively coordinates arsenite; saturation of this effector site facilitates the activity of arsA [133]. The two human arsA homologs do not possess Cys residues in the corresponding positions, indicating that this kind of allosteric effector site is not present. It is also noteworthy that the human arsA homologs (hASNAI and hASNAII) are more closely related to the arsenical pump-driving ATPases of two archaeas, *Methanobacterium thermoautotrophicum* [134] and *Methanococcus jannaschii* [135], with 36% identical amino acids in both cases, than to the *E. coli* arsA protein. The two archaea homologs are monomeric.

2.8. The GCN20 subfamily

2.8.1. ABC50

A search for new genes modulated by tumor necrosis factor-α (TNF-α) in the synoviocytes has been performed, utilizing a differential display PCR to produce cDNA fragments which correspond to TNF-α modulated genes. One of the identified transcripts encodes the ABC50 protein of 807 amino acids, a homolog of the yeast GCN20 [136]. This type of ABC proteins lacks transmembrane domains and consist of two ABC units, forming an ABC-ABC covalent dimer. The ABC50 sequence has many features which makes this protein unique within the human ABC kingdom: (i) it contains no transmembrane domain(s); (ii) it is much more hydrophilic than other members of the family, i.e. the ratio of charged residues in ABC50 is 36%, while it is between 18–27% for the other human ABC proteins. Considering these characteristics it can be concluded that ABC50 may not be a transporter. Three nuclear localization signals: KKKR at position 73, RRKK at position 82 and KRPK at position 564 can be identified in the sequence. Only one member of the subfamily is identified as of today in the human genome.

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References

[1] A. Decottignies, A. Goffeau, Complete inventory of the yeast ABC proteins, Nat. Genet. 15 (1997) 137–145.

[2] C. Kast, V. Canfield, R. Levenson, P. Gros, Membrane topology of P-glycoprotein as determined by epitope insertion, Biochemistry 34 (1995) 4402–4411.

[3] C. Kast, V. Canfield, R. Levenson, P. Gros, Transmembrane organization of mouse P-glycoprotein determined by epitope insertion and immunofluorescence, J. Biol. Chem. 271 (1996) 9240–9248.

[4] C.J. Chen, J.E. Chin, K. Ueda, D.P. Clark, I. Pastan, M.M. Gottesman, I.B. Roninson, Internal duplication and homology with bacterial transport proteins in the mdr1 (P-glycoprotein) gene from multidrug-resistant human cells, Cell 47 (1986) 381–389.

[5] F. Thiebaut, T. Tsuruo, H. Hamada, M.M. Gottesman, I. Pastan, M.C. Willingham, Cellular localization of the multidrug-resistance gene product P-glycoprotein, Proc. Natl. Acad. Sci. USA 84 (1987) 7735–7738.

[6] A. van Helvoort, A.J. Smith, H. Sprong, I. Fritzsche, A.H. Schinkel, P. Borst, G. van Meer, MDR1 P-glycoprotein is a lipid translocase of broad specificity, while MDR3 P-glycoprotein specifically translocates phosphatidylcholine, Cell 87 (1996) 507–517.

[7] C. Cordon-Cardo, J.P. O'Brien, D. Casals, L. Rittman-Grauer, J.L. Biedler, M.R. Melamed, J.R. Bertino, Multidrug-resistance gene (P-glycoprotein) is expressed by endothelial cells at blood-brain barrier sites, Proc. Natl. Acad. Sci. USA 86 (1989) 695–698.

[8] V.V. Rao, J.L. Dahlheimer, M.E. Bardgett, A.Z. Snyder, R.A. Finch, A.C. Sartorelli, D. Piwnica-Worms, Choroid plexus epithelial expression of MDR1 P glycoprotein and multidrug resistance-associated protein contribute to the blood-cerebrospinal-fluid drug-permeability barrier, Proc. Natl. Acad. Sci. USA 96 (1999) 3900–3905.

[9] A.H. Schinkel, J.J. Smit, O. van Tellingen, J.H. Beijnen, E. Wagenaar, L. van Deemter, C.A. Mol, M.A. van der Valk, E.C. Robanus-Maandag, H.P. te Riele et al., Disruption of the mouse mdr1a P-glycoprotein gene leads to a deficiency in the blood-brain barrier and to increased sensitivity to drugs, Cell 77 (1994) 491–502.

[10] A.H. Schinkel, U. Mayer, E. Wagenaar, C.A. Mol, L. van Deemter, J.J. Smit, M.A. van der Valk, A.C. Voordouw, H. Spits, O. van Tellingen, J.M. Zijlmans, W.E. Fibbe, P. Borst, Normal viability and altered pharmacokinetics in mice lacking mdr1-type (drug-transporting) P-glycoproteins, Proc. Natl. Acad. Sci. USA 94 (1997) 4028–4033.

[11] S. Childs, R.L. Yeh, E. Georges, V. Ling, Identification of a sister gene to P-glycoprotein, Cancer Res. 55 (1995) 2029–2034.

[12] T. Gerloff, B. Stieger, B. Hagenbuch, J. Madon, L. Landmann, J. Roth, A.F. Hofmann, P.J. Meier, The sister of P-glycoprotein represents the canalicular bile salt pump of mammalian liver, J. Biol. Chem. 273 (1998) 10046–10050.

[13] S.S. Strautnieks, L.N. Bull, A.S. Knisely, S.A. Kocoshis, N. Dahl, H. Arnell, E. Sokal, K. Dahan, S. Childs, V. Ling, M.S. Tanner, A.F. Kagalwalla, A. Nemeth, J. Pawlowska, A. Baker, G. Mieli-Vergani, N.B. Freimer, R.M. Gardiner, R.J. Thompson, A gene encoding a liver-specific ABC transporter is mutated in progressive familial intrahepatic cholestasis, Nat. Genet. 20 (1998) 233–238.

[14] S.S. Strautnieks, A.F. Kagalwalla, M.S. Tanner, A.S. Knisely, L. Bull, N. Freimer, S.A. Kocoshis, R.M. Gardiner, R.J. Thompson, Identification of a locus for progressive familial intrahepatic cholestasis PFIC2 on chromosome 2q24, Am. J. Hum. Genet. 61 (1997) 630–633.

[15] A.J. Smith, J.L. Timmermans-Hereijgers, B. Roelofsen, K.W. Wirtz, W.J. van Blitterswijk, J.J. Smit, A.H. Schinkel, P. Borst, The human MDR3 P-glycoprotein promotes translocation of phosphatidylcholine through the plasma membrane of fibroblasts from transgenic mice, FEBS Lett. 354 (1994) 263–266.

[16] J.J. Smit, A.H. Schinkel, R.P. Oude Elferink, A.K. Groen, E. Wagenaar, L. van Deemter, C.A. Mol, R. Ottenhoff, N.M. van der Lugt, M.A. van Roon et al., Homozygous disruption of the murine mdr2 P-glycoprotein gene leads to a complete absence of phospholipid from bile and to liver disease, Cell 75 (1993) 451–462.

[17] J.F. Deleuze, E. Jacquemin, C. Dubuisson, D. Cresteil, M. Dumont, S. Erlinger, O. Bernard, M. Hadchouel, Defect of multidrug-resistance 3 gene expression in a subtype of progressive familial intrahepatic cholestasis, Hepatology 23 (1996) 904–908.

[18] J.M. de Vree, E. Jacquemin, E. Sturm, D. Cresteil, P.J. Bosma, J. Aten, J.F. Deleuze, M. Desrochers, M. Burdelski, O. Bernard, R.P. Oude Elferink, M. Hadchouel, Mutations in the MDR3 gene cause progressive familial intrahepatic cholestasis, Proc. Natl. Acad. Sci. USA 95 (1998) 282–287.

[19] E. Jacquemin, D. Cresteil, S. Manouvrier, O. Boute, M. Hadchouel, Heterozygous non-sense mutation of the MDR3 gene in familial intrahepatic cholestasis of pregnancy, Lancet 353 (1999) 210–211.

[20] J.J. Neefjes, F. Momburg, G.J. Hammerling, Selective and ATP-dependent translocation of peptides by the MHC-encoded transporter, Science 261 (1993) 769–771.

[21] J.C. Shepherd, T.N. Schumacher, P.G. Ashton-Rickardt, S. Imaeda, H.L. Ploegh, C.A. Janeway Jr., S. Tonegawa, TAP1-dependent peptide translocation in vitro is ATP dependent and peptide selective, Cell 74 (1993) 577–584.

[22] S. Beck, A. Kelly, E. Radley, F. Khurshid, R.P. Alderton, J. Trowsdale, DNA sequence analysis of 66 kb of the human MHC class II region, J. Mol. Biol. 228 (1992) 433–441.

[23] S. Bahram, D. Arnold, M. Bresnahan, J.L. Strominger, T. Spies, Two putative subunits of a peptide pump encoded in the human major histocompatibility complex class II region, Proc. Natl. Acad. Sci. USA 88 (1991) 10094–10098.

[24] A. Kelly, S.H. Powis, L.A. Kerr, I. Mockridge, T. Elliott, J. Bastin, B. Uchanska-Ziegler, A. Ziegler, J. Trowsdale, A. Townsend, Assembly and function of the two ABC transporter proteins encoded in the human major histocompatibility complex, Nature 355 (1992) 641–644.

[25] J.J. Monaco, A molecular model of MHC class-I-restricted antigen processing, Immunol. Today 13 (1992) 173–179.
[26] S.H. Powis, I. Mockridge, A. Kelly, L.A. Kerr, R. Glynne, U. Gileadi, S. Beck, J. Trowsdale, Polymorphism in a second ABC transporter gene located within the class II region of the human major histocompatibility complex, Proc. Natl. Acad. Sci. USA 89 (1992) 1463–1467.
[27] A. Townsend, C. Ohlen, J. Bastin, H.G. Ljunggren, L. Foster, K. Karre, Association of class I major histocompatibility heavy and light chains induced by viral peptides, Nature 340 (1989) 443–448.
[28] H.G. Ljunggren, N.J. Stam, C. Ohlen, J.J. Neefjes, P. Hoglund, M.T. Heemels, J. Bastin, T.N. Schumacher, A. Townsend, K. Karre et al., Empty MHC class I molecules come out in the cold, Nature 346 (1990) 476–480.
[29] G.R. Otten, E. Bikoff, R.K. Ribaudo, S. Kozlowski, D.H. Margulies, R.N. Germain, Peptide and beta 2-microglobulin regulation of cell surface MHC class I conformation and expression, J. Immunol. 148 (1992) 3723–3732.
[30] H. de la Salle, D. Hanau, D. Fricker, A. Urlacher, A. Kelly, J. Salamero, S.H. Powis, L. Donato, H. Bausinger, M. Laforet et al., Homozygous human TAP peptide transporter mutation in HLA class I deficiency, Science 265 (1994) 237–241.
[31] H.L. Chen, D. Gabrilovich, R. Tampe, K.R. Girgis, S. Nadaf, D.P. Carbone, A functionally defective allele of TAP1 results in loss of MHV classI antigen presentation in human lung cancer, Nat. Genet. 13 (1996) 210–213.
[32] D.L. Hogue, L. Liu, V. Ling, Identification and characterization of a mammalian mitochondrial ATP-binding cassette membrane protein, J. Mol. Biol. 285 (1999) 379–389.
[33] R. Allikmets, B. Gerrard, A. Hutchinson, M. Dean, Characterization of the human ABC superfamily: isolation and mapping of 21 new genes using the expressed sequence tags database, Hum. Mol. Genet. 5 (1996) 1649–1655.
[34] S. Savary, R. Allikmets, F. Denizot, M.F. Luciani, M.G. Mattei, M. Dean, G. Chimini, Isolation and chromosomal mapping of a novel ATP-binding cassette transporter conserved in mouse and human, Genomics 41 (1997) 275–278.
[35] Y. Shimada, S. Okuno, A. Kawai, H. Shinomiya, A. Saito, M. Suzuki, Y. Omori, N. Nishino, N. Kanemoto, T. Fujiwara, M. Horie, E. Takahashi, Cloning and chromosomal mapping of a novel ABC transporter gene (hABC7), a candidate for X-linked sideroblastic anemia with spinocerebellar ataxia, J. Hum. Genet. 43 (1998) 115–122.
[36] P. Csere, R. Lill, G. Kispal, Identification of a human mitochondrial ABC transporter, the functional orthologue of yeast Atm1p, FEBS Lett. 441 (1998) 266–270.
[37] R. Allikmets, W.H. Raskind, A. Hutchinson, N.D. Schueck, M. Dean, D.M. Koeller, Mutation of a putative mitochondrial iron transporter gene (ABC7) in X-linked sideroblastic anemia and ataxia (XLSA/A), Hum. Mol. Genet. 8 (1999) 743–749.
[38] S. Koc, J.W. Harris, Sideroblastic anemias: variations on imprecision in diagnostic criteria, proposal for an extended classification of sideroblastic anemias, Am. J. Hematol. 57 (1998) 1–6.
[39] B.R. Migeon, T.R. Brown, J. Axelman, C.J. Migeon, Studies of the locus for androgen receptor: localization on the human X chromosome and evidence for homology with the Tfm locus in the mouse, Proc. Natl. Acad. Sci. USA 78 (1981) 6339–6343.
[40] J. Mosser, A.M. Douar, C.O. Sarde, P. Kioschis, R. Feil, H. Moser, A.M. Poustka, J.L. Mandel, P. Aubourg, Putative X-linked adrenoleukodystrophy gene shares unexpected homology with ABC transporters, Nature 361 (1993) 726–730.
[41] J. Mosser, Y. Lutz, M.E. Stoeckel, C.O. Sarde, C. Kretz, A.M. Douar, J. Lopez, P. Aubourg, J.L. Mandel, The gene responsible for adrenoleukodystrophy encodes a peroxisomal membrane protein, Hum. Mol. Genet. 3 (1994) 265–271.
[42] A. Dodd, S.A. Rowland, S.L. Hawkes, M.A. Kennedy, D.R. Love, Mutations in the adrenoleukodystrophy gene, Hum. Mutat. 9 (1997) 500–511.
[43] E.E. Eichler, M.L. Budarf, M. Rocchi, L.L. Deaven, N.A. Doggett, A. Baldini, D.L. Nelson, H.W. Mohrenweiser, Interchromosomal duplications of the adrenoleukodystrophy locus, Hum. Mol. Genet. 6 (1997) 991–1002.
[44] J. Gartner, H. Moser, D. Valle, Mutations in the 70K peroxisomal membrane protein gene in Zellweger syndrome, Nat. Genet. 1 (1992) 16–23.
[45] A. Holzinger, S. Kammerer, A.A. Roscher, Primary structure of human PMP69, a putative peroxisomal ABC-transporter, Biochem. Biophys. Res. Commun. 237 (1997) 152–157.
[46] G. Lombard-Platet, S. Savary, C.O. Sarde, J.L. Mandel, G. Chimini, A close relative of the adrenoleukodystrophy (ALD) gene codes for a peroxisomal protein with a specific expression pattern, Proc. Natl. Acad. Sci. USA 93 (1996) 1265–1269.
[47] S.P. Cole, G. Bhardwaj, J.H. Gerlach, J.E. Mackie, C.E. Grant, K.C. Almquist, A.J. Stewart, E.U. Kurz, A.M. Duncan, R.G. Deeley, Overexpression of a transporter gene in a multidrug-resistant human lung cancer cell line, Science 258 (1992) 1650–1654.
[48] G.J. Zaman, M.J. Flens, M.R. van Leusden, M. de Haas, H.S. Mulder, J. Lankelma, H.M. Pinedo, R.J. Scheper, F. Baas, H.J. Broxterman et al., The human multidrug resistance-associated protein MRP is a plasma membrane drug-efflux pump, Proc. Natl. Acad. Sci. USA 91 (1994) 8822–8826.
[49] G.J. Zaman, J. Lankelma, O. van Tellingen, J. Beijnen, H. Dekker, C. Paulusma, R.P. Oude Elferink, F. Baas, P. Borst, Role of glutathione in the export of compounds from cells by the multidrug-resistance-associated protein, Proc. Natl. Acad. Sci. USA 92 (1995) 7690–7694.
[50] G. Jedlitschky, I. Leier, U. Buchholz, M. Center, D. Keppler, ATP-dependent transport of glutathione S-conjugates by the multidrug resistance-associated protein, Cancer Res. 54 (1994) 4833–4836.
[51] Z. Hollo, L. Homolya, T. Hegedus, B. Sarkadi, Transport

properties of the multidrug resistance-associated protein, FEBS Lett. 383 (1996) 99–104.
[52] J. Wijnholds, G.L. Scheffer, M. van der Valk, P. van der Valk, J.H. Beijnen, R.J. Scheper, P. Borst, Multidrug resistance protein 1 protects the oropharyngeal mucosal layer and the testicular tubules against drug-induced damage, J. Exp. Med. 188 (1998) 797–808.
[53] J. Wijnholds, R. Evers, M.R. van Leusden, C.A. Mol, G.J. Zaman, U. Mayer, J.H. Beijnen, M. van der Valk, P. Krimpenfort, P. Borst, Increased sensitivity to anticancer drugs and decreased inflammatory response in mice lacking the multidrug resistance-associated protein, Nat. Med. 3 (1997) 1275–1279.
[54] L. Aguilar-Bryan, C.G. Nichols, S.W. Wechsler, J.P. Clement, A.E. Boyd, G. Gonzalez, H. Herrera-Sosa, K. Nguy, J. Bryan, D.A. Nelson, Cloning of the beta cell high-affinity sulfonylurea receptor, Science 268 (1995) 423–426.
[55] N. Inagaki, T. Gonoi, J.P. Clement, N. Namba, J. Inazawa, G. Gonzalez, L. Aguilar-Bryan, S. Seino, J. Bryan, Reconstitution of IKATP: an inward rectifier subunit plus the sulfonylurea receptor, Science 270 (1995) 1166–1170.
[56] M. Buchler, J. Konig, M. Brom, J. Kartenbeck, H. Spring, T. Horie, D. Keppler, cDNA cloning of the hepatocyte canalicular isoform of the multidrug resistance protein, cMrp, reveals a novel conjugate export pump deficient in hyperbilirubinemic mutant rats, J. Biol. Chem. 271 (1996) 15091–15098.
[57] C.C. Paulusma, P.J. Bosma, G.J. Zaman, C.T. Bakker, M. Otter, G.L. Scheffer, R.J. Scheper, P. Borst, R.P. Oude Elferink, Congenital jaundice in rats with a mutation in a multidrug resistance-associated protein gene, Science 271 (1996) 1126–1128.
[58] E. Bakos, T. Hegedus, Z. Hollo, E. Welker, G.E. Tusnady, G.J. Zaman, M.J. Flens, A. Varadi, B. Sarkadi, Membrane topology and glycosylation of the human multidrug resistance- associated protein, J. Biol. Chem. 271 (1996) 12322–12326.
[59] M.J. Flens, M.A. Izquierdo, G.L. Scheffer, J.M. Fritz, C.J. Meijer, R.J. Scheper, G.J. Zaman, Immunochemical detection of the multidrug resistance-associated protein MRP in human multidrug-resistant tumor cells by monoclonal antibodies, Cancer Res. 54 (1994) 4557–4563.
[60] B.D. Stride, G. Valdimarsson, J.H. Gerlach, G.M. Wilson, S.P. Cole, R.G. Deeley, Structure and expression of the messenger RNA encoding the murine multidrug resistance protein, an ATP-binding cassette transporter, Mol. Pharmacol. 49 (1996) 962–971.
[61] M.S. Szczypka, J.A. Wemmie, W.S. Moye-Rowley, D.J. Thiele, A yeast metal resistance protein similar to human cystic fibrosis transmembrane conductance regulator (CFTR) and multidrug resistance-associated protein, J. Biol. Chem. 269 (1994) 22853–22857.
[62] X.B. Chang, Y.X. Hou, T.J. Jensen, J.R. Riordan, Mapping of cystic fibrosis transmembrane conductance regulator membrane topology by glycosylation site insertion, J. Biol. Chem. 269 (1994) 18572–18575.
[63] C. Kast, P. Gros, Topology mapping of the amino-terminal half of multidrug resistance-associated protein by epitopee insertion and immunofluorescence, J. Biol. Chem. 272 (1997) 26479–26487.
[64] C. Kast, P. Gros, Epitope insertion favors a six transmembrane domain model for the carboxy-terminal portion of the multidrug resistance-associated protein, Biochemistry 37 (1998) 2305–2313.
[65] D.R. Hipfner, K.C. Almquist, E.M. Leslie, J.H. Gerlach, C.E. Grant, R.G. Deeley, S.P. Cole, Membrane topology of the multidrug resistance protein (MRP), J. Biol. Chem. 272 (1997) 23623–23630.
[66] G.E. Tusnady, E. Bakos, A. Varadi, B. Sarkadi, Membrane topology distinguishes a subfamily of the ATP-binding cassette (ABC) transporters, FEBS Lett. 402 (1997) 1–3.
[67] Y. Kiuchi, H. Suzuki, T. Hirohashi, C.A. Tyson, Y. Sugiyama, cDNA cloning and inducible expression of human multidrug resistance associated protein 3 (MRP3), FEBS Lett. 433 (1998) 149–152.
[68] M.G. Belinsky, L.J. Bain, B.B. Balsara, J.R. Testa, G.D. Kruh, Characterization of MOAT-C and MOAT-D, new members of the MRP/cMOAT subfamily of transporter proteins, J. Natl. Cancer Inst. 90 (1998) 1735–1741.
[69] K. Lee, M.G. Belinsky, D.W. Bell, J.R. Testa, G.D. Kruh, Isolation of MOAT-B, a widely expressed multidrug resistance-associated protein/canalicular multispecific organic anion transporter-related transporter, Cancer Res. 58 (1998) 2741–2747.
[70] M. Kool, M. van der Linden, M. de Haas, F. Baas, P. Borst, Expression of human MRP6, a homologue of the multidrug resistance protein gene MRP1, in tissues and cancer cells, Cancer Res. 59 (1999) 175–182.
[71] E. Bakos, R. Evers, G. Szakacs, G.E. Tusnady, E. Welker, K. Szabo, M. de Haas, L. van Deemter, P. Borst, A. Varadi, B. Sarkadi, Functional multidrug resistance protein (MRP1) lacking the N-terminal transmembrane domain, J. Biol. Chem. 273 (1998) 32167–32175.
[72] R. Evers, M. Kool, L. van Deemter, H. Janssen, J. Calafat, L.C. Oomen, C.C. Paulusma, R.P. Oude Elferink, F. Baas, A.H. Schinkel, P. Borst, Drug export activity of the human canalicular multispecific organic anion transporter in polarized kidney MDCK cells expressing cMOAT (MRP2) cDNA, J. Clin. Invest. 101 (1998) 1310–1319.
[73] K. Ito, H. Suzuki, T. Hirohashi, K. Kume, T. Shimizu, Y. Sugiyama, Functional analysis of a canalicular multispecific organic anion transporter cloned from rat liver, J. Biol. Chem. 273 (1998) 1684–1688.
[74] M. Wada, S. Toh, K. Taniguchi, T. Nakamura, T. Uchiumi, K. Kohno, I. Yoshida, A. Kimura, S. Sakisaka, Y. Adachi, M. Kuwano, Mutations in the canalicular multispecific organic anion transporter (cMOAT) gene, a novel ABC transporter, in patients with hyperbilirubinemia II/Dubin-Johnson syndrome, Hum. Mol. Genet. 7 (1998) 203–207.
[75] T. Suzuki, K. Nishio, H. Sasaki, H. Kurokawa, F. Saito-Ohara, T. Ikeuchi, S. Tanabe, M. Terada, N. Saijo, cDNA cloning of a short type of multidrug resistance protein ho-

mologue, Biochem. Biophys. Res. Commun. 238 (1997) 790–794.
[76] G.E. Tusnady, A. Varadi, Short MRP may not be short, Biochem. Biophys. Res. Commun. 242 (1998) 465–466.
[77] T.J. Longhurst, G.M. O'Neill, R.M. Harvie, R.A. Davey, The anthracycline resistance-associated (ara) gene, a novel gene associated with multidrug resistance in a human leukemia cell line, Br. J. Cancer 74 (1996) 1331–1335.
[78] G.M. O'Neill, G.B. Peters, R.M. Harvie, H.B. MacKenzie, S. Henness, R.A. Davey, Amplification and expression of the ABC transporters ARA and MRP in a series of multidrug-resistant leukaemia cell sublines, Br. J. Cancer 77 (1998) 2076–2080.
[79] J.A. Fantes, K. Oghene, S. Boyle, S. Danes, J.M. Fletcher, E.A. Bruford, K. Williamson, A. Seawright, A. Schedl, I. Hanson et al., A high-resolution integrated physical, cytogenetic, and genetic map of human chromosome 11: distal p13 to proximal p15.1, Genomics 25 (1995) 447–461.
[80] B. Glaser, K.C. Chiu, R. Anker, A. Nestorowicz, H. Landau, H. Ben-Bassat, Z. Shlomai, N. Kaiser, P.S. Thornton, C.A. Stanley et al., Familial hyperinsulinism maps to chromosome 11p14-15.1, 30 cM centromeric to the insulin gene, Nat. Genet. 7 (1994) 185–188.
[81] P.M. Thomas, G.J. Cote, N. Wohllk, B. Haddad, P.M. Mathew, W. Rabl, L. Aguilar-Bryan, R.F. Gagel, J. Bryan, Mutations in the sulfonylurea receptor gene in familial persistent hyperinsulinemic hypoglycemia of infancy, Science 268 (1995) 426–429.
[82] J. Bryan, L. Aguilar-Bryan, The ABCs of ATP-sensitive potassium channels: more pieces of the puzzle, Curr. Opin. Cell. Biol. 9 (1997) 553–559.
[83] P.M. Thomas, N. Wohllk, E. Huang, U. Kuhnle, W. Rabl, R.F. Gagel, G.J. Cote, Inactivation of the first nucleotide-binding fold of the sulfonylurea receptor, and familial persistent hyperinsulinemic hypoglycemia of infancy, Am. J. Hum. Genet. 59 (1996) 510–518.
[84] J.M. Rommens, M.C. Iannuzzi, B. Kerem, M.L. Drumm, G. Melmer, M. Dean, R. Rozmahel, J.L. Cole, D. Kennedy, N. Hidaka et al., Identification of the cystic fibrosis gene: chromosome walking and jumping, Science 245 (1989) 1059–1065.
[85] J. Zielenski, L.C. Tsui, Cystic fibrosis: genotypic and phenotypic variations, Annu. Rev. Genet. 29 (1995) 777–807.
[86] J. Zielenski, M. Corey, R. Rozmahel, D. Markiewicz, I. Aznarez, T. Casals, S. Larriba, B. Mercier, G.R. Cutting, A. Krebsova, M. Macek Jr., E. Langfelder-Schwind, B.C. Marshall, J. DeCelie-Germana, M. Claustres, A. Palacio, J. Bal, A. Nowakowska, C. Ferec, X. Estivill, P. Durie, L.C. Tsui, Detection of a cystic fibrosis modifier locus for meconium ileus on human chromosome 19q13, Nat. Genet. 22 (1999) 128–129.
[87] P.C. Levesque, P.J. Hart, J.R. Hume, J.L. Kenyon, B. Horowitz, Expression of cystic fibrosis transmembrane regulator Cl-channels in heart, Circ. Res. 71 (1992) 1002–1007.
[88] B. Horowitz, S.S. Tsung, P. Hart, P.C. Levesque, J.R. Hume, Alternative splicing of CFTR Cl-channels in heart, Am. J. Physiol. 264 (1993) H2214–H2220.
[89] P. Hart, J.D. Warth, P.C. Levesque, M.L. Collier, Y. Geary, B. Horowitz, J.R. Hume, Cystic fibrosis gene encodes a cAMP-dependent chloride channel in heart, Proc. Natl. Acad. Sci. USA 93 (1996) 6343–6348.
[90] K. Yoshimura, C.S. Chu, R.G. Crystal, Alternative splicing of intron 23 of the human cystic fibrosis transmembrane conductance regulator gene resulting in a novel exon and transcript coding for a shortened intracytoplasmic C terminus, J. Biol. Chem. 268 (1993) 686–690.
[91] T.V. Strong, D.J. Wilkinson, M.K. Mansoura, D.C. Devor, K. Henze, Y. Yang, J.M. Wilson, J.A. Cohn, D.C. Dawson, R.A. Frizzell et al., Expression of an abundant alternatively spliced form of the cystic fibrosis transmembrane conductance regulator (CFTR) gene is not associated with a cAMP-activated chloride conductance, Hum. Mol. Genet. 2 (1993) 225–230.
[92] T. Dork, F. Mekus, K. Schmidt, J. Bosshammer, R. Fislage, T. Heuer, V. Dziadek, T. Neumann, N. Kalin, U. Wulbrand et al., Detection of more than 50 different CFTR mutations in a large group of German cystic fibrosis patients, Hum. Genet. 94 (1994) 533–542.
[93] S. Larriba, L. Bassas, J. Gimenez, M.D. Ramos, A. Segura, V. Nunes, X. Estivill, T. Casals, Testicular CFTR splice variants in patients with congenital absence of the vas deferens, Hum. Mol. Genet. 7 (1998) 1739–1743.
[94] H. Teng, M. Jorissen, H. Van Poppel, E. Legius, J.J. Cassiman, H. Cuppens, Increased proportion of exon 9 alternatively spliced CFTR transcripts in vas deferens compared with nasal epithelial cells, Hum. Mol. Genet. 6 (1997) 85–90.
[95] V. Mak, K.A. Jarvi, J. Zielenski, P. Durie, L.C. Tsui, Higher proportion of intact exon 9 CFTR mRNA in nasal epithelium compared with vas deferens, Hum. Mol. Genet. 6 (1997) 2099–2107.
[96] R. Rozmahel, H.H. Heng, A.M. Duncan, X.M. Shi, J.M. Rommens, L.C. Tsui, Amplification of CFTR exon 9 sequences to multiple locations in the human genome, Genomics 45 (1997) 554–561.
[97] J.V. Moran, R.J. DeBerardinis, H.H. Kazazian Jr., Exon shuffling by L1 retrotransposition, Science 283 (1999) 1530–1534.
[98] M.F. Luciani, F. Denizot, S. Savary, M.G. Mattei, G. Chimini, Cloning of two novel ABC transporters mapping on human chromosome 9, Genomics 21 (1994) 150–159.
[99] T. Langmann, J. Klucken, M. Reil, G. Liebisch, M.F. Luciani, G. Chimini, W.E. Kaminski, G. Schmitz, Molecular cloning of the human ATP-binding cassette transporter 1 (hABC1): evidence for sterol-dependent regulation in macrophages, Biochem. Biophys. Res. Commun. 257 (1999) 29–33.
[100] M.F. Luciani, G. Chimini, The ATP binding cassette transporter ABC1, is required for the engulfment of corpses generated by apoptotic cell death, EMBO J. 15 (1996) 226–235.

[101] R.E. Ellis, D.M. Jacobson, H.R. Horvitz, Genes required for the engulfment of cell corpses during programmed cell death in Caenorhabditis elegans, Genetics 129 (1991) 79–94.
[102] F. Becq, Y. Hamon, A. Bajetto, M. Gola, B. Verrier, G. Chimini, ABC1, an ATP binding cassette transporter required for phagocytosis of apoptotic cells, generates a regulated anion flux after expression in Xenopus laevis oocytes, J. Biol. Chem. 272 (1997) 2695–2699.
[103] Y. Hamon, M.F. Luciani, F. Becq, B. Verrier, A. Rubartelli, G. Chimini, Interleukin-1beta secretion is impaired by inhibitors of the Atp binding cassette transporter, ABC1, Blood 90 (1997) 2911–2915.
[104] R. Allikmets, N.F. Shroyer, N. Singh, J.M. Seddon, R.A. Lewis, P.S. Bernstein, A. Peiffer, N.A. Zabriskie, Y. Li, A. Hutchinson, M. Dean, J.R. Lupski, M. Leppert, Mutation of the Stargardt disease gene (ABCR) in age-related macular regeneration, Science 277 (1997) 1805–1807.
[105] J. Kaplan, S. Gerber, D. Larget-Piet, J.M. Rozet, H. Dollfus, J.L. Dufier, S. Odent, A. Postel-Vinay, N. Janin, M.L. Briard et al., A gene for Stargardt's disease (fundus flavimaculatus) maps to the short arm of chromosome 1, Nat. Genet. 5 (1993) 308–311.
[106] R. Allikmets, W.W. Wasserman, A. Hutchinson, P. Smallwood, J. Nathans, P.K. Rogan, T.D. Schneider, M. Dean, Organization of the ABCR gene: analysis of promoter and splice junction sequences, Gene 215 (1998) 111–122.
[107] S.M. Azarian, C.F. Megarity, J. Weng, D.H. Horvath, G.H. Travis, The human photoreceptor rim protein gene (ABCR): genomic structure and primer set information for mutation analysis, Hum. Genet. 102 (1998) 699–705.
[108] H. Sun, J. Nathans, Stargardt's ABCR is localized to the disc membrane of retinal rod outer segments, Nat. Genet. 17 (1997) 15–16.
[109] H. Sun, R.S. Molday, J. Nathans, Retinal stimulates ATP hydrolysis by purified and reconstituted ABCR, the photoreceptor-specific ATP-binding cassette transporter responsible for Stargardt disease, J. Biol. Chem. 274 (1999) 8269–8281.
[110] R. Allikmets, N. Singh, H. Sun, N.F. Shroyer, A. Hutchinson, A. Chidambaram, B. Gerrard, L. Baird, D. Stauffer, A. Peiffer, A. Rattner, P. Smallwood, Y. Li, K.L. Anderson, R.A. Lewis, J. Nathans, M. Leppert, M. Dean, J.R. Lupski, A photoreceptor cell-specific ATP-binding transporter gene (ABCR) is mutated in recessive Stargardt macular dystrophy, Nat. Genet. 15 (1997) 236–246.
[111] A. Martinez-Mir, E. Paloma, R. Allikmets, C. Ayuso, T. del Rio, M. Dean, L. Vilageliu, R. Gonzalez-Duarte, S. Balcells, Retinitis pigmentosa caused by a homozygous mutation in the Stargardt disease gene ABCR, Nat. Genet. 18 (1998) 11–12.
[112] F.P. Cremers, D.J. van de Pol, M. van Driel, A.I. den Hollander, F.J. van Haren, N.V. Knoers, N. Tijmes, A.A. Bergen, K. Rohrschneider, A. Blankenagel, A.J. Pinckers, A.F. Deutman, C.B. Hoyng, Autosomal recessive retinitis pigmentosa and cone-rod dystrophy caused by splice site mutations in the Stargardt's disease gene ABCR, Hum. Mol. Genet. 7 (1998) 355–362.
[113] K. Gregory-Evans, S.S. Bhattacharya, Genetic blindness: current concepts in the pathogenesis of human outer retinal dystrophies, Trends Genet. 14 (1998) 103–108.
[114] M.A. van Driel, A. Maugeri, B.J. Klevering, C.B. Hoyng, F.P. Cremers, ABCR unites what ophthalmologists divide(s), Ophthalmic Genet. 19 (1998) 117–122.
[117] R.A. Lewis, N.F. Shroyer, N. Singh, R. Allikmets, A. Hutchinson, Y. Li, J.R. Lupski, M. Leppert, M. Dean, Genotype/Phenotype analysis of a photoreceptor-specific ATP-binding cassette transporter gene, ABCR, in Stargardt disease, Am. J. Hum. Genet. 64 (1999) 422–434.
[118] N. Klugbauer, F. Hofmann, Primary structure of a novel ABC transporter with a chromosomal localization on the band encoding the multidrug resistance-associated protein, FEBS Lett. 391 (1996) 61–65.
[119] Y.C. Wu, H.R. Horvitz, The C. elegans cell corpse engulfment gene ced-7 encodes a protein similar to ABC transporters, Cell 93 (1998) 951–960.
[120] T. Nagase, K. Ishikawa, M. Suyama, R. Kikuno, M. Hirosawa, N. Miyajima, A. Tanaka, H. Kotani, N. Nomura, O. Ohara, Prediction of the coding sequences of unidentified human genes. XII. The complete sequences of 100 new cDNA clones from brain which code for large proteins in vitro, DNA Res. 5 (1998) 355–364.
[121] T.H. Morgan, Sex limited inheritance in Drosophila, Science 32 (1910) 120–122.
[122] H. Chen, C. Rossier, M.D. Lalioti, A. Lynn, A. Chakravarti, G. Perrin, S.E. Antonarakis, Cloning of the cDNA for a human homologue of the Drosophila white gene and mapping to chromosome 21q22.3, Am. J. Hum. Genet. 59 (1996) 66–75.
[123] J.M. Croop, G.E. Tiller, J.A. Fletcher, M.L. Lux, E. Raab, D. Goldenson, D. Son, S. Arciniegas, R.L. Wu, Isolation and characterization of a mammalian homolog of the Drosophila white gene, Gene 185 (1997) 77–85.
[124] S. Savary, F. Denizot, M. Luciani, M. Mattei, G. Chimini, Molecular cloning of a mammalian ABC transporter homologous to Drosophila white gene, Mamm. Genome 7 (1996) 673–676.
[125] K. O'Hare, C. Murphy, R. Levis, G.M. Rubin, DNA sequence of the white locus of Drosophila melanogaster, J. Mol. Biol. 180 (1984) 437–455.
[126] L.A. Doyle, W. Yang, L.V. Abruzzo, T. Krogmann, Y. Gao, A.K. Rishi, D.D. Ross, A multidrug resistance transporter from human MCF-7 breast cancer cells, Proc. Natl. Acad. Sci. USA 95 (1998) 15665–15670.
[127] K. Miyake, L. Mickley, T. Litman, Z. Zhan, R. Robey, B. Cristensen, M. Brangi, L. Greenberger, M. Dean, T. Fojo, S.E. Bates, Molecular cloning of cDNAs which are highly overexpressed in mitoxantrone-resistant cells: demonstration of homology to ABC transport genes, Cancer Res. 59 (1999) 8–13.
[128] R. Allikmets, L.M. Schriml, A. Hutchinson, V. Romano-Spica, M. Dean, A human placenta-specific ATP-binding

cassette gene (ABCP) on chromosome 4q22 that is involved in multidrug resistance, Cancer Res. 58 (1998) 5337–5339.
[129] D.D. Ross, W. Yang, L.V. Abruzzo, W.S. Dalton, E. Schneider, H. Lage, M. Dietel, L. Greenberger, S.P. Cole, L.A. Doyle, Atypical multidrug resistance: breast cancer resistance protein messenger RNA expression in mitoxantrone-selected cell lines, J. Natl. Cancer Inst. 91 (1999) 429–433.
[130] C. Bisbal, C. Martinand, M. Silhol, B. Lebleu, T. Salehzada, Cloning and characterization of a RNAse L inhibitor. A new component of the interferon-regulated 2-5A pathway, J. Biol. Chem. 270 (1995) 13308–13317.
[131] P. Kaur, B.P. Rosen, Plasmid-encoded resistance to arsenic and antimony, Plasmid 27 (1992) 29–40.
[132] B. Kurdi-Haidar, S. Aebi, D. Heath, R.E. Enns, P. Naredi, D.K. Hom, S.B. Howell, Isolation of the ATP-binding human homolog of the arsA component of the bacterial arsenite transporter, Genomics 36 (1996) 486–491.
[133] H. Bhattacharjee, B.P. Rosen, Spatial proximity of Cys113, Cys172, and Cys422 in the metalloactivation domain of the ArsA ATPase, J. Biol. Chem. 271 (1996) 24465–24470.
[134] D.R. Smith, L.A. Doucette-Stamm, C. Deloughery, H. Lee, J. Dubois, T. Aldredge, R. Bashirzadeh, D. Blakely, R. Cook, K. Gilbert, D. Harrison, L. Hoang, P. Keagle, W. Lumm, B. Pothier, D. Qiu, R. Spadafora, R. Vicaire, Y. Wang, J. Wierzbowski, R. Gibson, N. Jiwani, A. Caruso, D. Bush, J.N. Reeve et al., Complete genome sequence of Methanobacterium thermoautotrophicum, J. Bacteriol. 179 (1997) 7135–7155.
[135] C.J. Bult, O. White, G.J. Olsen, L. Zhou, R.D. Fleischmann, G.G. Sutton, J.A. Blake, L.M. FitzGerald, R.A. Clayton, J.D. Gocayne, A.R. Kerlavage, B.A. Dougherty, J.F. Tomb, M.D. Adams, C.I. Reich, R. Overbeek, E.F. Kirkness, K.G. Weinstock, J.M. Merrick, A. Glodek, J.L. Scott, N.S.M. Geoghagen, J.C. Venter, Complete genome sequence of the methanogenic archaeon, Methanococcus jannaschii, Science 273 (1996) 1058–1073.
[136] M. Richard, R. Drouin, A.D. Beaulieu, ABC50, a novel human ATP-binding cassette protein found in tumor necrosis factor-alpha-stimulated synoviocytes, Genomics 53 (1998) 137–145.
[137] J.D. Thompson, D.G. Higgins, T.J. Gibson, CLUSTAL W: improving the sensitivity of progressive multiple sequence alignment through sequence weighting, position-specific gap penalties and weight matrix choice, Nucleic Acids Res. 22 (1994) 4673–4680.
[138] R. Evers, G.J. Zaman, L. van Deemter, H. Jansen, J. Calafat, L.C. Oomen, R.P. Oude Elferink, P. Borst, A.H. Schinkel, Basolateral localization and export activity of the human multidrug resistance-associated protein in polarized pig kidney cells, J. Clin. Invest. 97 (1996) 1211–1218.