The Human ATP-Binding Cassette (ABC) Transporter Superfamily

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Abstract

The ATP-binding cassette (ABC) transporter superfamily contains membrane proteins that translocate a wide variety of substrates across extra- and intracellular membranes, including metabolic products, lipids and sterols, and drugs. Overexpression of certain ABC transporters occurs in cancer cell lines and tumors that are multidrug resistant. Genetic variation in these genes is the cause or contributor to a wide variety of human disorders with Mendelian and complex inheritance including cystic fibrosis, neurological disease, retinal degeneration, cholesterol and bile transport defects, anemia, and drug response phenotypes. Conservation of the ATP-binding domains of these genes has allowed the identification of new members of the superfamily based on nucleotide and protein sequence homology. Phylogenetic analysis places the 48 known human ABC transporters into seven distinct subfamilies of proteins. For each gene, the precise map location on human chromosomes, expression data, and localization within the superfamily have been determined. These data allow predictions to be made as to potential function(s) or disease phenotype(s) associated with each protein. Comparison of the human ABC superfamily to that of other sequenced eukaryotes including *Drosophila* indicated that there is a rapid rate of birth and death of ABC genes and that most members carry out highly specific functions that are not conserved across distantly related phyla.

Introduction to ABC Protein and Gene Organization

The ATP-binding cassette (ABC) genes represent the largest family of transmembrane (TM) proteins. These proteins bind ATP and use the energy to drive the transport of various molecules across all cell membranes (1–3) (Figure 1). Proteins are classified as ABC transporters based on the sequence and organization of their ATP-binding domain(s), also known as nucleotide-binding folds (NBFs). The NBFs contain characteristic motifs (Walker A and B), separated by approximately 90–120 amino acids, found in all ATP-binding proteins (Figure 1). ABC genes also contain an additional element, the signature (C) motif, located just upstream of the Walker B site (4). The functional protein typically contains two NBFs and two TM domains (Figure 2). The TM domains contain 6–11 membrane-spanning α-helices and provide the specificity for the substrate. The

NBFs are located in the cytoplasm and transfer the energy to transport the substrate across the membrane. ABC pumps are mostly unidirectional. In bacteria, they are predominantly involved in the import of essential compounds that cannot be obtained by diffusion (sugars, vitamins, metal ions, etc.) into the cell. In eukaryotes, most ABC genes move compounds from the cytoplasm to the outside of the cell or into an intracellular compartment [endoplasmic reticulum (ER), mitochondria, peroxisome]. Most of the known functions of eukaryotic ABC transporters involve the shuttling of hydrophobic compounds either within the cell as part of a metabolic process or outside the cell for transport to other organs, or for secretion from the body.

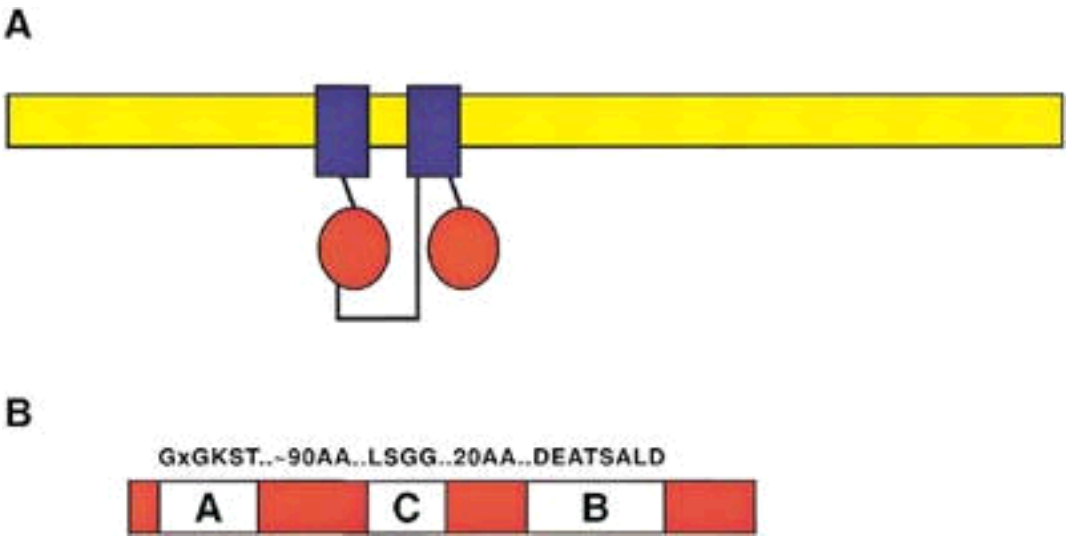

Figure 1: Diagram of a typical ABC transporter protein. A. A diagram of the structure of a representative ABC protein is shown with a lipid bilayer in *yellow*, the TM domains in *blue*, and the NBF in *red*. Although the most common arrangement is a full transporter with motifs arranged N-TM-NBF-TM-NBF-C, as shown, NBF-TM-NBF-TM, TM-NBF, and NBF-TM arrangements are also found. **B**. The NBF of an ABC gene contains the Walker A and B motifs found in all ATP-binding proteins. In addition, a signature or C motif is also present. Above the diagram are the most common amino acids found in these motifs; subfamilies often contain characteristic residues in these and other regions. From (5).

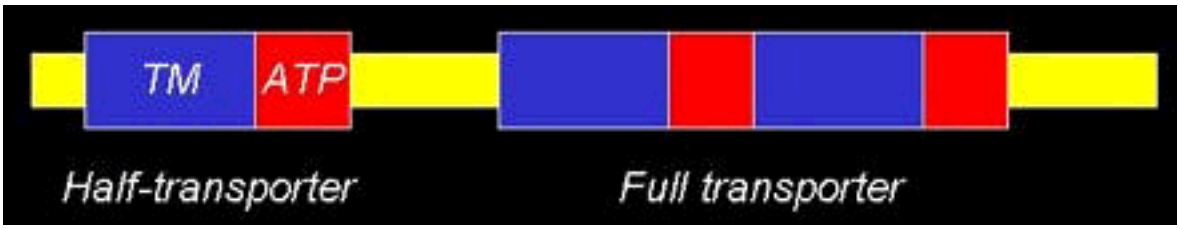

Figure 2: ABC gene structure. A diagram of an ABC half transporter and a full transporter. The half transporter can form homo- or heterodimers, whereas the entire full transporter is found in one transcript.

The eukaryotic ABC genes are organized either as full transporters containing two TMs and two NBFs, or as half transporters (4) (Figure 2). The latter must form either homodimers or heterodimers to form a functional transporter. ABC genes are widely dispersed in eukaryotic genomes and are highly conserved between species, indicating that most of these genes have existed since the beginning of eukaryotic evolution. The genes can be divided into subfamilies

based on similarity in gene structure (half *versus* full transporters), order of the domains, and on sequence homology in the NBF and TM domains. There are seven mammalian ABC gene subfamilies, five of which are found in the *Saccharomyces cerevisiae* genome (5).

A list of Web resources on ABC genes and products can be found in Box 1.

A more detailed account of each of the human ABC genes is given below. For each gene, a concise description is given on the known function and disease involvement, and links to other databases, such as UniGene, OMIM, and GenBank, are given where appropriate. This is a comprehensive treatment: even genes that are very poorly characterized are included. For genes such as *CFTR* and *ABCB1/PGP/MDR* that have been studied extensively, a brief review is given with links to other resources and review articles. Suggested corrections and additions are welcome for future updates of these pages and should be sent to the author (dean@ncifcrf.gov).

Nomenclature

All human and mouse ABC genes have standard nomenclature, developed by the Human Genome Organization (HUGO) at a meeting of ABC gene researchers. Details of the nomenclature scheme can be found at: http://www.gene.ucl.ac.uk/nomenclature/genefamily/abc.html [http://www.gene.ucl.ac.uk/nomenclature/genefamily/abc.html].

Researchers working on *ABCC7/CFTR*, *ABCB2/TAP1*, and *ABCB3/TAP2* have petitioned to keep their original gene designations. Official gene symbols are used in this monograph, but all known synonyms are also included to allow researchers to refer to the literature.

Overview of Human ABC Gene Subfamilies

A list of all known human ABC genes is displayed in Table 1. This list includes an analysis of the released genome sequences (6, 7). An analysis of the genome sequence indicates the presence of at least 19 pseudogenes (Dean, unpublished). There remain several sequences in the genome with homology to ABC genes that lie in incompletely sequenced regions and may represent additional pseudogenes or functional loci.

Table 1. List of human ABC genes, chromosomal location, and function.

Symbol	Alias	Location	Function
ABCA1	ABC1	9q31.1	Cholesterol efflux onto HDL
ABCA2	ABC2	9q34.3	Drug resistance
ABCA3	ABC3, ABCC	16p13.3	Surfactant secretion?
ABCA4	ABCR	1p21.3	*N*-Retinylidiene-PE efflux
ABCA5		17q24.3	
ABCA6		17q24.3	
ABCA7		19p13.3	
ABCA8		17q24.3	
ABCA9		17q24.3	
ABCA10		17q24.3	
ABCA12		2q34	
ABCA13		7p12.3	

Symbol	Alias	Location	Function
ABCB1	PGY1, MDR	7q21.12	Multidrug resistance
ABCB2	TAP1	6p21.3	Peptide transport
ABCB3	TAP2	6p21.3	Peptide transport
ABCB4	PGY3	7q21.12	PC transport
ABCB5		7p21.1	
ABCB6	MTABC3	2q35	Iron transport
ABCB7	ABC7	Xq21-q22	Fe/S cluster transport
ABCB8	MABC1	7q36.1	
ABCB9		12q24.31	
ABCB10	MTABC2	1q42.13	
ABCB11	SPGP	2q24.3	Bile salt transport
ABCC1	MRP1	16p13.12	Drug resistance
ABCC2	MRP2	10q24.2	Organic anion efflux
ABCC3	MRP3	17q21.33	Drug resistance
ABCC4	MRP4	13q32.1	Nucleoside transport
ABCC5	MRP5	3q27.1	Nucleoside transport
ABCC6	MRP6	16p13.12	
CFTR	ABCC7	7q31.31	Chloride ion channel
ABCC8	SUR	11p15.1	Sulfonylurea receptor
ABCC9	SUR2	12p12.1	K(ATP) channel regulation
ABCC10	MRP7	6p21.1	
ABCC11		16q12.1	
ABCC12		16q12.1	
ABCD1	ALD	Xq28	VLCFA transport regulation
ABCD2	ALDL1, ALDR	12q11	
ABCD3	PXMP1,PMP70	1p22.1	
ABCD4	PMP69, P70R	14q24.3	
ABCE1	OABP, RNS4I	4q31.31	Oligoadenylate binding protein
ABCF1	ABC50	6p21.1	
ABCF2		7q36.1	
ABCF3		3q27.1	
ABCG1	ABC8, White	21q22.3	Cholesterol transport?
ABCG2	ABCP, MXR, BCRP	4q22	Toxin efflux, drug resistance
ABCG4	White2	11q23	
ABCG5	White3	2p21	Sterol transport
ABCG8		2p21	Sterol transport

By aligning the amino acid sequences of the NBF domains and performing phylogenetic analysis with a number of methods, the existing eukaryotic genes can be grouped into seven major subfamilies. A few genes do not fit into these subfamilies, and several of the subfamilies can be further divided into subgroups.

ABCA (ABC1)

The human ABCA subfamily comprises 12 full transporters (Table 1) that are further divided into two subgroups based on phylogenetic analysis and intron structure (8, 9). The first group includes seven genes dispersed on six different chromosomes (*ABCA1*, *ABCA2*, *ABCA3*, *ABCA4*, *ABCA7*, *ABCA12*, *ABCA13*), whereas the second group contains five genes (*ABCA5*, *ABCA6*, *ABCA8*, *ABCA9*, *ABCA10*) arranged in a cluster on chromosome 17q24. The ABCA subfamily contains some of the largest ABC genes, several of which are over 2,100 amino acids long. Two

members of this subfamily, the ABCA1 and ABCA4 (ABCR) proteins, have been studied extensively. The ABCA1 protein is involved in disorders of cholesterol transport and HDL biosynthesis (see below). The ABCA4 protein transports vitamin A derivatives in the outer segments of rod photoreceptor cells and therefore performs a crucial step in the vision cycle.

The ABCA genes are not present in yeast; however, evolutionary studies of ABCA genes indicate that they arose as half transporters that subsequently duplicated, and that certain sets of ABCA genes were lost in different eukaryotic lineages (10).

ABCB (MDR/TAP)

The ABCB subfamily is unique in mammals in that it contains both full transporters and half transporters. Four full transporters and seven half transporters have currently been described as members of this subfamily. *ABCB1* (*MDR/PGY1*) is the first human ABC transporter cloned and characterized through its ability to confer a MDR phenotype to cancer cells. The physiological functional sites of ABCB1 include the blood-brain barrier and the liver. The ABCB4 and ABCB11 proteins are both located in the liver and are involved in the secretion of bile acids. The *ABCB2* and *ABCB3* (TAP) genes are half transporters that form a heterodimer to transport peptides into the ER that are presented as antigens by the class I HLA molecules. The closest homolog of the TAPs, the ABCB9 half transporter, has been localized to lysosomes. The remaining four half transporters, ABCB6, ABCB7, ABCB8, and ABCB10, localize to the mitochondria, where they function in iron metabolism and transport of Fe/S protein precursors.

ABCC (CFTR/MRP)

The ABCC subfamily contains 12 full transporters with a diverse functional spectrum that includes ion transport, cell-surface receptor, and toxin secretion activities. The CFTR protein is a chloride ion channel that plays a role in all exocrine secretions; mutations in CFTR cause cystic fibrosis (11). ABCC8 and ABCC9 proteins bind sulfonylurea and regulate potassium channels involved in modulating insulin secretion. The rest of the subfamily is composed of nine MRP-related genes. Of these, ABCC1, ABCC2, and ABCC3 transport drug conjugates to glutathionine and other organic anions. The ABCC4, ABCC5, ABCC11, and ABCC12 proteins are smaller than the other MRP1-like gene products and lack an N-terminal domain (12) that is not essential for transport function (13). The ABCC4 and ABCC5 proteins confer resistance to nucleosides including PMEA and purine analogs. The human genome contains a seemingly intact ABCC gene on chromosome 21 (*ABCCxP1*) that contains a frameshift in one exon and is therefore a pseudogene. The same frameshift mutation is present in the gorilla and chimpanzee homologs, but the gene appears to be functional and expressed in monkeys (Annilo et al., in preparation).

ABCD (ALD)

The ABCD subfamily contains four genes in the human genome and two each in the *Drosophila melanogaster* and yeast genomes. The yeast PXA1 and PXA2 products dimerize to form a functional transporter involved in very long chain fatty acid oxidation in the peroxisome (14). All of the genes encode half transporters that are located in the peroxisome, where they function as homo- and/or heterodimers in the regulation of very long chain fatty acid transport.

ABCE (OABP) and ABCF (GCN20)

The ABCE and ABCF subfamilies contain gene products that have ATP-binding domains that are clearly derived from ABC transporters but they have no TM domain and are not known to be involved in any membrane transport functions. The ABCE subfamily is solely composed of the oligo-adenylate-binding protein, a molecule that recognizes oligo-adenylate and is produced in response to infection by certain viruses. This gene is found in multicellular eukaryotes but not in yeast, suggesting that it is part of innate immunity. Each ABCF gene contains a pair of NBFs. The best-characterized member, the *S. cerevisiae GCN20* gene product, mediates the activation of the eIF-2α kinase (15), and a human homolog, ABCF1, is associated with the ribosome and appears to play a similar role (16).

ABCG (White)

The human ABCG subfamily is composed of six “reverse” half transporters that have an NBF at the N terminus and a TM domain at the C terminus. The most intensively studied ABCG gene is the *white* locus of *Drosophila*. The white protein, along with brown and scarlet, transports precursors of eye pigments (guanine and tryptophan) in the eye cells of the fly (17). The mammalian ABCG1 protein is involved in cholesterol transport regulation (18). Other ABCG genes include *ABCG2*, a drug-resistance gene; *ABCG5* and *ABCG8*, coding for transporters of sterols in the intestine and liver; *ABCG3*, to date exclusively found in rodents; and the *ABCG4* gene that is expressed predominantly in the liver. The functions of the last two genes are unknown.

ABC Genes and Human Genetic Disease

Many ABC genes were originally discovered during the positional cloning of human genetic disease genes. To date, 14 ABC genes have been linked to disorders displaying Mendelian inheritance (19) (Table 2). As expected from the diverse functional roles of ABC genes, the genetic deficiencies that they cause also vary widely. Because ABC genes typically encode structural proteins, all of the disorders are recessive or X-linked recessive and are attributable to a severe reduction or lack of function of the protein. However, heterozygous variants in ABC gene mutations are being implicated in the susceptibility to specific complex disorders.

Table 2. Diseases and phenotypes caused by ABC genes.

Gene	Mendelian disorder	Complex disease	OMIM
ABCA1	Tangier disease, FHDLD[a]		600046
ABCA4	Stargardt/FFM, RP, CRD, CD	AMD	248200
ABCB1	Ivermectin susceptibility	Digoxin uptake	171050
ABCB2	Immune deficiency		170260
ABCB3	Immune deficiency		170261
ABCB4	PFIC3	ICP	171060
ABCB7	XLSA/A		300135
ABCB11	PFIC2		603201
ABCC2	Dubin-Johnson Syndrome		601107
ABCC6	Pseudoxanthoma elasticum		603234
ABCC7	Cystic Fibrosis, CBAVD	Pancreatitis, bronchiectasis	602421
ABCC8	FPHHI		600509
ABCD1	ALD		300100
ABCG5	Sitosterolemia		605459
ABCG8	Sitosterolemia		605460

[a] FHDLD, familial hypoapoproteinemia; FFM, fundus flavimaculatis; RP, retinitis pigmentosum 19; CRD, cone-rod dystrophy; AMD, age-related macular degeneration; PFIC, progressive familial intrahepatic cholestasis; ICP, intrahepatic cholestasis of pregnancy; XLSA/A, X-linked sideroblastosis and anemia; CBAVD, congential bilateral absence of the vas deferens; FPHHI, Familial persistent hyperinsulinemic hypoglycemia of infancy; ALD, adrenoleukodystrophy.

Few ABC gene mutations are lethal. Untreated cystic fibrosis (*ABCC7*/*CFTR*) is typically lethal in the first decade, and adrenoleukodystrophy (*ABCD1*/*ALD*) can also be fatal in the first 10 years of life. The only mutations described in *ABCB7* are missense alleles, and the yeast homolog is essential to mitochondria, suggesting that this gene is essential. The only developmental defect ascribed to an ABC gene is the congenital absence of the vas deferens that occurs in both cystic fibrosis patients and patients with less severe alleles that present male sterility as their only phenotype. Thus, most ABC genes do not play an essential role in development.

Mouse Knockouts

Most of the human genes have a clear mouse ortholog; however, there are several exceptions (Table 3). Several ABC genes have been disrupted in the mouse (Table 3). These include some of the genes mutated in human diseases, as well as several of the known drug transporters. The *Abca1* and *Cftr* –/– mice show compromised viability; however, the remaining knockouts are viable and fertile, and many show either no phenotype or a phenotype only under stressed conditions.

Table 3. ABC genes: human and mouse orthologs.

Human gene	Mouse gene	Location[a]	Knockout	Reference
ABCA1	Abca1	4, 23.1 cM	Y[b]	Orso 2000; McNeish 2000
ABCA2	Abca2	2, 12.6	N	
ABCA3	Abca3	Unknown	N	
ABCA4	Abca4	3, 61.8	Y	Weng 1999
ABCA5	Abca5	Unknown	N	
ABCA6	Abca6	Unknown	N	
ABCA7	Abca7	10, 44	N	
ABCA8	Abca8a	Unknown	N	
	Abca8b	11, 69	N	
ABCA9	Abca9	Unknown	N	
ABCA10				
ABCA12	Abca12	1C1		
ABCA13	Abca13	11A1		
ABCB1	Abcb1a	5, 1	Y[c]	Schinkel 1994
	Abcb1b	5, 1	Y	Schinkel 1997
ABCB2	Abcb2 (Tap1)	17	Y	Van Kaer 1992
ABCB3	Abcb3 (Tap2)	17	N	
ABCB4	Abcb4	5, 1	Y	Smit 1993
ABCB5	Abcb5	12, 60		Dean, *et al.*, unpublished
ABCB6	Abcb6	1, C3	N	
ABCB7	Abcb7	X, 39	N	
ABCB8	Abcb8	Unknown	N	
ABCB9	Abcb9	5, F	N	
ABCB10	Abcb10	8, 67	N	
ABCB11	Abcb11	2, 39	N	
ABCC1	Abcc1	16	Y	Lorico 1997; Wijnholds 1997
ABCC2	Abcc2	19	Y[d]	Paulusma 1996
ABCC3	Abcc3	Unknown	N	
ABCC4	Abcc4	13, E4		Dean, *et al.*, unpublished
ABCC5	Abcc5	16, 14	N	
ABCC6	Abcc6	7, B3	N	
ABCC7	Abcc7 (Cftr)	6, 3.1	Y	Dorin 1992; Snouwaert 1992; van Doorninck 1995
ABCC8	Abcc8	7, 41	N	
ABCC9	Abcc9	6, 70	N	
ABCC10	Abcc10	Unknown	N	
ABCC11	Abcc11	8, 44-45		
ABCC12				
ABCD1	Abcd1	X, 29.5	Y	Forss-Petter 1997
ABCD2	Abcd2	15, E-F	N	
ABCD3	Abcd3	3, 56.6	N	
ABCD4	Abcd4	12, 39	N	
ABCE1	Abce1	8, 36	N	
ABCF1	Abcf1	17, 20.5	N	
ABCF2	Abcf2	13, 40	N	
ABCF3	Abcf3	16, 22	N	
ABCG1	Abcg1	17, A2-B	N	
ABCG2	Abcg2	6, 28.5	Y	Sorrentino and Schinkel, unpublished
	Abcg3	5, 59	N	
ABCG4	Abcg4	9, syntenic	N	
ABCG5	Abcg5	17, syntenic	N	
ABCG8	Abcg8	17, syntenic	N	

Human gene	Mouse gene	Location[a]	Knockout	Reference

[a] The chromosome location of the gene in the mouse is given along with either the distance from the centromere in centimorgans or the cytogenetic location.

[b] The WHAM chicken (a model of Tangier disease) (46) is suspected of being mutant in Abca1.

[c] Abcb1 mutant dogs have been described (84).

[d] Abcc2 mutant rats have been described (132).

Multidrug Resistance and Cancer Therapy

Cells exposed to toxic compounds can develop resistance by a number of mechanisms including decreased uptake, increased detoxification, alteration of target proteins, or increased excretion. Several of these pathways can lead to multidrug resistance (MDR) in which the cell is resistant to several drugs in addition to the initial compound. This is a particular limitation to cancer chemotherapy, and the MDR cell often displays other properties, such as genome instability and loss of checkpoint control, that complicate further therapy. ABC genes play an important role in MDR, and at least six genes are associated with drug transport.

Three ABC genes appear to account for nearly all of the MDR tumor cells in both human and rodent cells. These are *ABCB1/PGP/MDR1*, *ABCC1/MRP1*, and *ABCG2/MXR/BCRP* (Table 4). No other genes have been found overexpressed in cells that display resistance to a wide variety of drugs and in cells from mice with disrupted *Abcb1a*, *Abcb1b*, and *Abcc1* genes; the *Abcg2* gene was overexpressed in all MDR cell lines derived from a variety of selections (20).

Table 4. ABC transporters involved in drug resistance.

Gene	Substrates	Inhibitors
ABCB1	Colchicine, doxorubicin, VP16,[a] Adriamycin, vinblastine, digoxin, saquinivir, paclitaxel	Verapamil, PSC833, GG918, V-104, Pluronic L61
ABCC1	Doxorubicin, daunorubicin, vincristine, VP16, colchicines, VP16, rhodamine	Cyclosporin A, V-104
ABCC2	Vinblastine, sulfinpyrazone	
ABCC3	Methotrexate, VP16	
ABCC4	Nucleoside monophosphates	
ABCC5	Nucleoside monophosphates	
ABCG2	Mitoxantrone, topotecan, doxorubicin, daunorubicin, CPT-11, rhodamine	Fumitremorgin C, GF120918

[a] VP16, etoposide.

Inhibitors of the major ABC genes contributing to MDR have been developed, and extensive experimentation and clinical research have been performed to attempt to block the development of drug resistance during chemotherapy (Table 4). The latest experiments with high-affinity and high-specificity ABCB1 inhibitors show that the gene is expressed in many primary tumors in human patients and that its activity can be blocked with doses of inhibitor that do not have

adverse side effects or disrupt the pharmacology of the drug regimen (21). Thus, the development of highly specific inhibitors to the other major drug transporters could lead to the development of much more effective chemotherapy protocols.

Another limitation of chemotherapy is the narrow difference in sensitivity of the tumor cells to drugs and sensitivity of the patient's normal stem cells. ABC genes have also been used as tools to deliver drug transporters to early stem cells and to protect them from chemotherapeutic drugs. This strategy would allow high doses of drug to be given for longer periods of time.

Phylogenetic Analysis of Human ABC Genes

The identification of the complete set of human ABC genes allows a comprehensive phylogenetic analysis of the superfamily. Alignment of the NBFs from each gene and a neighbor-joining tree resulting from this analysis is displayed (Figure 3). The subclassification of ABC transporters is in excellent agreement with the phylogenetic trees obtained. In particular, all major ABC transporter families are represented in the human tree by stable clusters with high statistical significance.

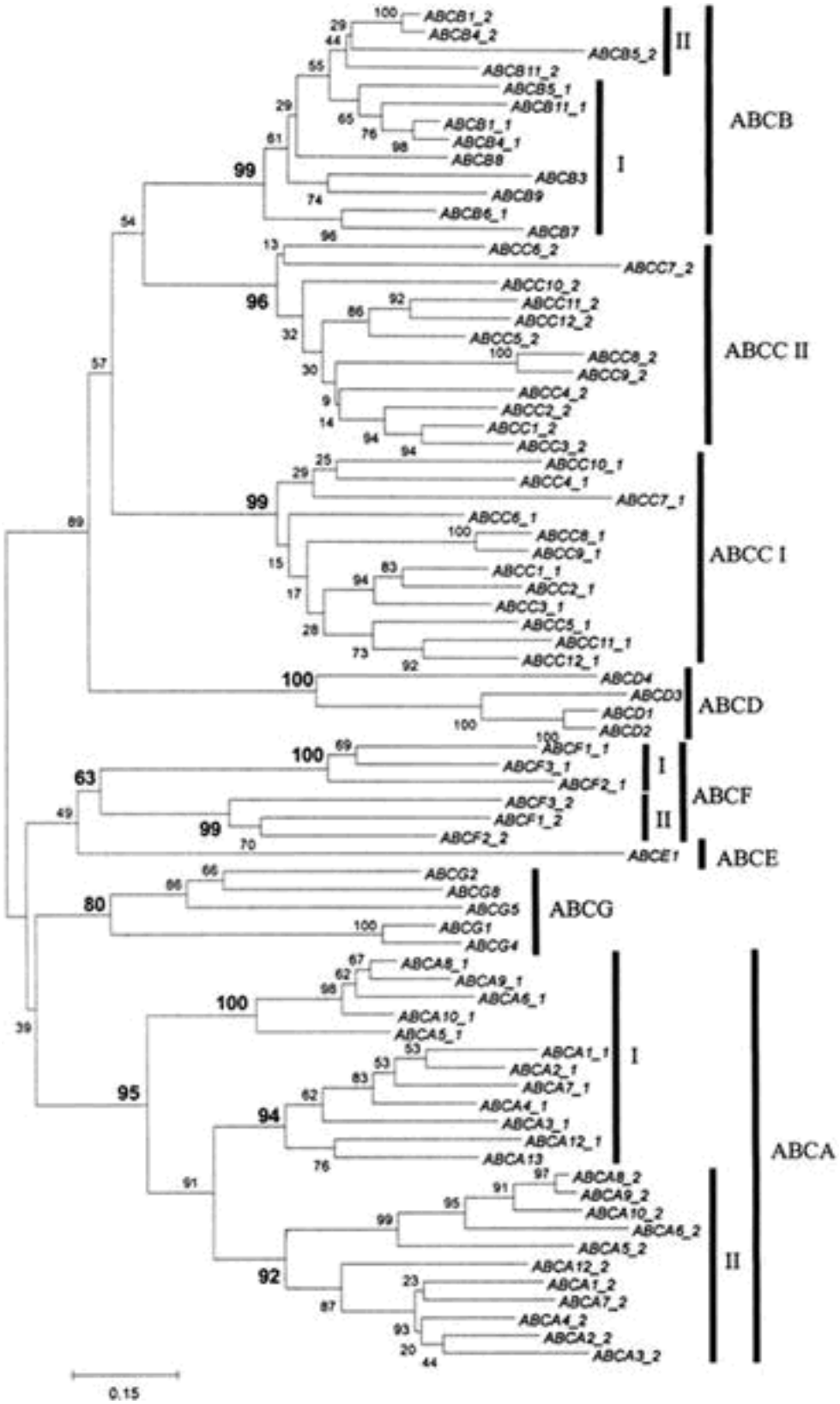

Figure 3: Phylogenetic tree of the human ABC genes. ATP-binding domain proteins were identified using the model ABC_tran of the Pfam database (250). The HMMSEARCH program from the HMMER package (251) and a set of custom-made service scripts were used to extract ATP-binding domains from all protein sequences of interest. Note that some proteins analyzed contain two ATP-binding

domains (*I* and *II*), whereas others contained only one ATP-binding domain. Alignments were generated with the hidden Markov model-based HMMALIGN program (252) using the ABC_tran model. The resulting multiple alignment was analyzed with NJBOOT (N. Takezaki, personal communication), implementing the neighbor-joining tree-making algorithm (253); the number at the branch of the nodes represents the value from 100 replications. The distance measure between sequences used for tree-making was the Poisson correction for multiple hits (254). To verify the position of the previously unknown subgroup of *Drosophila* genes (*CG6162*, *CG9990*, and *CG11147*), the genes were aligned with a representative of each of the human subfamilies. Because some of the human proteins had two ATP-binding domains, the set contained three *Drosophila* and 12 human sequences. The JTT model (255), as defined in the MOLPHY package with the "star decomposition" option, was used. The tentative best tree (the total number of possible trees for 15 sequences is too large for exhaustive search through all of these trees) was then used for local maximum likelihood search through the surrounding tree topologies. From (5).

This analysis provides compelling evidence for frequent domain duplication of ATP-binding domains in ABC transporters. Virtually invariably, both ATP-binding domains within a gene are more closely related to each other than to ATP-binding domains from ABC transporter genes of other subfamilies. This could represent a concerted evolution of domains within the same gene, but this seems unlikely because the two domains within each gene are substantially diverged. Therefore, it appears that duplication of ATP-binding domains within major ABC families was a result of several independent duplication events rather than a single ancestral duplication.

Mouse ABC Genes

Analysis of the Celera assembly of the mouse genome was used to identify homologs of the human ABC genes. With only a few exceptions, there is concordance between the two mammalian species (Table 3). The exceptions are a duplicated copy of the *ABCB1*/*PGP*/*MDR* gene (*Mdr1b*), an ABCG family gene related to *ABCG2* that is present in the mouse and not in the human (*Abcg3*) (22), loss of *Abcc11* (Dean, unpublished), duplication of the *ABCA8* gene in the mouse (*Abca8a*), and a loss in the mouse of *ABCA10* (Annilo et al., submitted). In addition, mice have a cluster of three ABCA family genes that is not characterized in the human genome (Chen, Annilo, Shulenin, and Dean, unpublished). This region of the human genome is incompletely characterized and does not currently contain any described functional loci. Therefore, mice have 52 ABC genes and most of the human genes have a single homolog in the mouse genome, indicating that the functions of the mouse genes should be highly similar to human genes.

Drosophila ABC Genes

The organization and annotation of the Drosophila ABC genes have been determined from the Celera (23) and Flybase (5) databases. Initial subfamily classifications were assigned based on homology and BLAST scores, and the location of each gene is shown (Table 5). In total, there are 56 genes with at least one representative of each of the known mammalian subfamilies (Table 6). The subfamily groupings were confirmed by phylogenetic analyses. A representative tree is shown in Figure 4. As expected, genes from the same subfamily cluster together and confirm the initial assignments made by inspection.

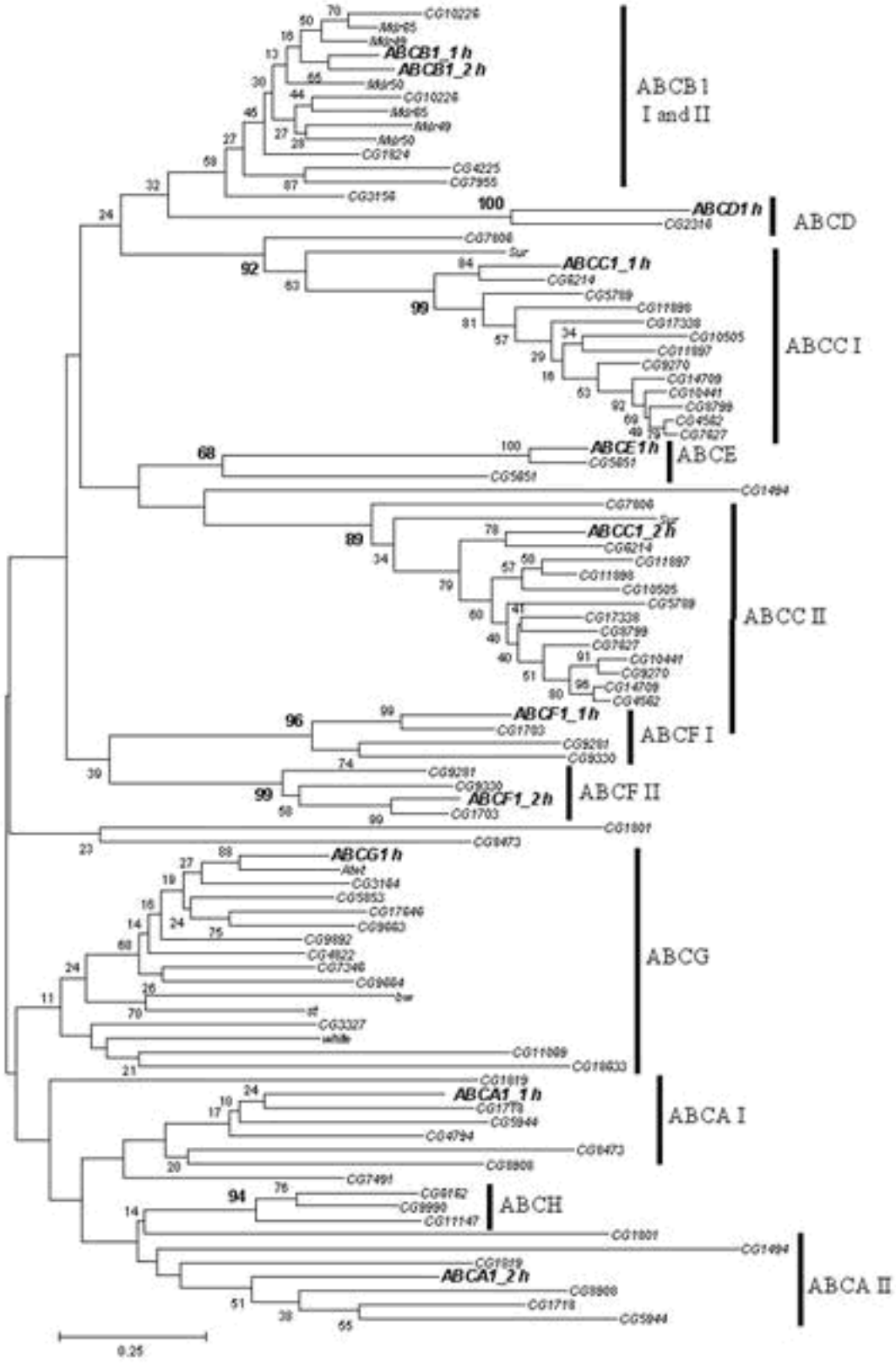

Figure 4: Phylogenetic tree of the human and *Drosophila* G subfamily ABC genes. An alignment of the G family genes from *Drosophila* and human genomes were aligned. Analysis was performed as described for Figure 3 (Annilo and Dean, unpublished).

Table 5. Drosophila ABC genes.

Gene	Alias	Protein Acc.[a]	DNA Acc.	Size[b]	Family	Location (Chr. Nuc.[c])	Cyto. Loc.[d]	Mutants
CG3156		AAF45509	AE003417	609	B	X 252038-254671	1B4	
CG2759	w	AAF45826	AE003425	696	G	X 2545753-2539884	3B4	
CG1703		AAF48069	AE003486	901	E	X 11393813-11396731	10C10	
CG1824		AAF48177	AE003489	761	B	X 12363742-12360802	11B16	
CG9281		AAF48493	AE003500	611	E	X 15454374-15450765	13E14	
CG8473		AAF48511	AE003500	2556	A	X 15513659-15523896	13E18-F1	
CG12703		AE003513	AE003513	618	D	X 19494615-19497465	18F1-F2	bth
CG1819		AAF50847	AE003569	1500	A	X 20757531-20763638	19F1	fir, ms, mit(1)20
CG1718		AAF50837	AE003568	1713	A	X 20909795-20902146	19F2	
CG1801		AAF50836	AE003568	1511	A	X 20924492-20917580	19F2	
CG1494		AAF50838	AE003568	1197	A	X 20896205-20901578	19F2	
CG3164		AAF51548	AE003590	620	G	2L 123902-117541	21B	
CG4822		AAF51551	AE003590	643	G	2L 112000-116000	21B	
CG17646		AAF51341	AE003585	627	G	2L 1720498-1727693	22B3	
CG9892		AAF51223	AE003582	615	G	2L 2649300-2658596	23A6	
CG9664		AAF51131	AE003580	609	G	2L 3211844-3209624	23E4-23E5	
CG9663		AAF51130	AE003580	812	G	2L 3214000-3220000	23E4-23E5	
CG3327		AAF51122	AE003580	729	G	2L 3257267-325948	23F	
CG2969	Atet	AAF51027	AE003576	832	G	2L 4251813-4262480	24F8	
CG11147		AAF52284	AE003611	705	H	2L 5656028-5653232	26A1	
CG7806		AAF52639	AE003620	1487	C	2L 8212839-8218079	29A3-A4	
CG7627		AAF52648	AE003620	1327	C	2L 8262316-8256791	29B1	
CG5853		AAF52835	AE003626	689	G	2L 9854119-9847658	30E1-30E3	
CG5772	Sur	AAF52866	AE003627	2250	C	2L 10105357-10089272	31A2	
CG6214		AAF53223	AE003637	1896	C	2L 12619174-12641593	33F2	
CG7491		AAF53328	AE003641	324	A	2L 13675599-13676775	34D1	
CG17338		AAF53736	AE003661	1275	B	2L 18829742-18834099	37B9	pre, MR

Gene	Alias	Protein Acc.[a]	DNA Acc.	Size[b]	Family	Location (Chr. Nuc.[c])	Cyto. Loc.[d]	Mutants
CG10441		AAF53737	AE003661	1307	B	2L 18835157-18839979	37B9	
CG9270		AAF53950	AE003668	1014	C	2L 20741821-20738317	39A2	
CG8799		AAF58947	AE003833	1344	C	2R 4426560-4431236	45D1	
CG3879	Mdr49	AAF58437	AE003820	1279	B	2R 7940090-7934079	49E1	
CG8523	Mdr50	AAF58271	AE003815	1313	B	2R 9235904-9241222	50F1	
CG8908		AAF57490	AE003792	1382	A	2R 15203694-15208725	56F11	
CG10505		AAF46706	AE003453	1283	C	2R 16226805-16222698	57D2	
CG17632	bw	AAF47020	AE003461	755	G	2R 18476505-18465883	59E3	
CG7955		AAF47526	AE003472	606	B	3L1597621-1602155	62B1	
CG10226		AAF50670	AE003563	1320	B	3L 6180561-6175400	65A14	
Mdr65		AAF50669	AE003563	1302	B	3L 6186691-6181468	65A14	
CG5651		AAF50342	AE003553	611	E	3L 8895129-8892720	66E3-E4	
CG7346		AAF50035	AE003544	597	G	3L 11555624-11559309	68C10-C11	vin, cln, rose
CG4314	st	AAF49455	AE003527	666	G	3L 16398050-16400715	73A3	
CG5944		AAF49305	AE003522	1463	A	3L 17695681-17689489	74E3-E4	
CG6052		AAF49312	AE003523	1660	A	3L 17627439-17622025	74E3-E4	
CG9330		AAF49142	AE003516	708	E	3L 1971540-1947231	76B6	
CG14709		AAF54656	AE003692	1307	C	3R 7362645-7369141	86F1	
CG4225		AAF55241	AE003710	866	B	3R 11615803-11612420	89A11-A12	
CG4562		AAF55707	AE003728	1348	C	3R 15626899-15619809	92B9	
CG4794		AAF55726	AE003728	711	A	3R 15725586-15728807	92C1	
CG5789		AAF56312	AE003748	1239	C	3R 29281221-20277309	96A7	fs, l, aor,
CG18633		AAF56360	AE003749	702	G	3R 29625526-29622829	96B5	mar, mfs
CG11069		AAF56361	AE003749	602	G	3R 20635134-20637920	96B6	
CG6162		AAF56584	AE003756	535	H	3R 22087630-22088417	97B1	ird15, smi97B, Spn-D
CG9990		AAF56807	AE003766	808	H	3R 24409613-24429503	98F1	spg, lethal
CG11898		AAF56870	AE003768	1302	C	3R 24887241-24892598	99A	

Gene	Alias	Protein Acc.[a]	DNA Acc.	Size[b]	Family	Location (Chr. Nuc.[c])	Cyto. Loc.[d]	Mutants
CG11897		AAF56869	AE003768	1346	C	3R 24881629-24885998	99A	
CG2316		AAF59367	AE003844	730	D	4 154260-145146	101F	Scn, 5 lethals

[a] Acc., Accession number.
[b] Number of amino acids.
[c] Chr. Nuc., chromosome nucleosides.
[d] Cyto. Loc., cytoplasm location.

As in the human and yeast genomes, the *Drosophila* ABC genes are largely dispersed in the genome. There are four clusters of two genes and one cluster of four genes (Figure 5). One of these clusters (on chromosome 2L, band 37B9) is composed of an ABCB and an ABCC gene, indicating that this is a chance grouping of genes. The remaining clusters are composed of genes from the same subfamily and are arranged in a head-to-tail fashion, consistent with gene duplication. Because the clusters are themselves dispersed and involve different subfamilies, they presumably represent independent gene duplication events.

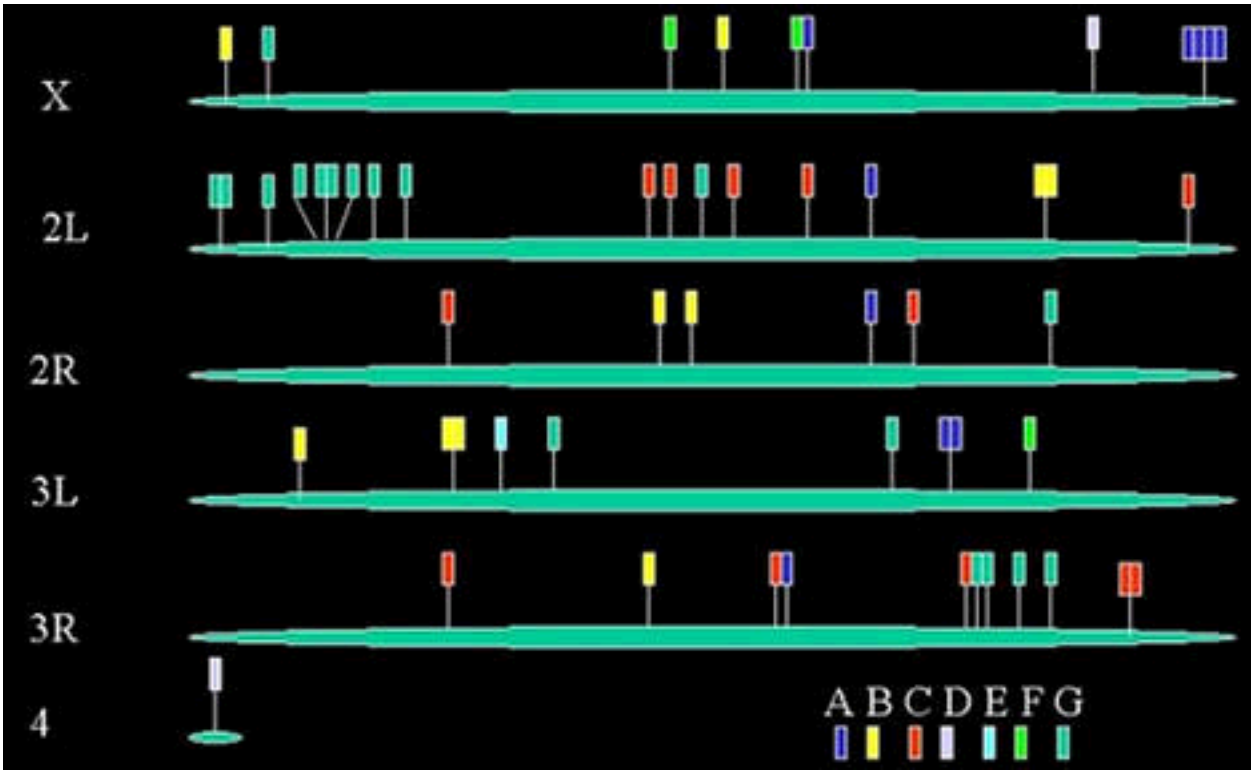

Figure 5: Map of the *Drosophila* ABC genes. A diagram of each *Drosophila* chromosome is shown with the location and gene subfamily designation of each gene.

The best-studied *Drosophila* ABC genes are the eye pigment precursor transporters white (*w*), scarlet (*st*), and brown (*bw*). These genes are part of the ABCG subfamily and have a unique NBF-TM organization. Surprisingly, there are 15 ABCG genes in the fly genome, making

this the most abundant ABC subfamily. This is in sharp contrast to the five or six known ABCG genes in the human and mouse genomes, respectively. The *Drosophila* ABCG genes are highly dispersed in the genome with only two pairs of linked genes. In addition, they are very divergent phylogenetically, suggesting that there were many independent and ancient gene duplication events. The *Atet* gene is the only *Drosophila* ABCG family gene that has a close ortholog in the human genome (*ABCG1* and *ABCG4*) (Figure 4).

Table 6. ABC gene subfamilies in characterized eukaryotes.

Subfamily	Yeast[a,b]	*Dictyostelium*[c]	*A. thaliana*[d]	*C. elegans*[d]	*Drosophila*[e]	Mouse[f]	Human[e]
A	0	12	12	7	10	15	12
B	4	9	27	23	10	12	11
C	6	14	16	8	12	11	12
D	2	3	2	5	2	4	4
E	1	1	3	1	1	1	1
F	5	4	5	3	3	3	3
G	10	21	39	11	15	6	5
H	0	0	0	0	3	0	0
Other	1	4	10	0	0	0	0
Total	**29**	**68**	**114**	**58**	**56**	**52**	**48**

[a] Decottignies and Goffeau (259).
[b] Michaelis et al. (260).
[c] Anjard et al. (10).
[d] Web address: http://www.pasteur.fr/recherche/unites/pmtg/abc/database.iphtml
[e] Dean et al. (5).
[f] Dean, unpublished.

Several *Drosophila* ABCB genes, *Mdr49*, *Mdr50*, and *Mdr65*, have also been well characterized. A fourth member of this group, *CG10226*, found clustered with *Mdr65*, was also identified (Table 5). These genes are closely related to the human and mouse P-glycoproteins (ABCB1 and ABCB4), and disruption of *Mdr49* results in sensitivity to colchicines (24).

Phenotypic mutants that are not assigned to genes and lie in the region of *Drosophila* ABC genes are shown (Table 5). The most promising connection is the identification of several eye phenotypes (*vin*, *rose*, *cln*) in the region of the *CG7346* gene. Because *CG7346* is part of the ABCG family and is therefore related to *w*, *st*, and *bw*, it is tempting to speculate that mutations in *CG7346* cause one or more of these phenotypes. Because ABC genes perform very diverse functions and are associated with varied phenotypes, it is hard to gather much additional insight from this analysis.

Three genes, *CG9990*, *CG6162*, and *CG11147*, were identified that do not fit into any of the known subfamilies and, in fact, are most closely related to ABC genes from bacteria. These genes are within large contigs and have introns and therefore do not represent contamination from bacterial sequences. This group forms a distinct cluster on the *Drosophila* tree. This new ABC transporter subfamily in *Drosophila* is significantly different from all known families of ABC transporters and might play an as-yet-unidentified functional role. These genes have been designated as subfamily H.

Because of the high rate of birth and death of ABC genes, very few *Drosophila* genes have a human ortholog. This indicates that the genes have evolved to carry out functions that are specialized to insects and mammals. This is borne out by the experimental data to date. For example, the insect and vertebrate eyes are convergent organs, and the eye pigment transporters in flies have no comparable functional homolog in vertebrates. Similarly, the vertebrate ABCA4 (photoreceptor-specific transporter), CFTR (chloride channel controlling exocrine secretion), and most other mammalian ABC genes have specialized functions that are not present in insects and nematodes. Therefore, the genetic and functional analysis of *Drosophila* genes is not likely to lead to the direct understanding of the function of the individual mammalian ABC genes.

ABCA Genes

ABCA1

The *ABCA1* gene was identified in the mouse and human genomes and mapped to human chromsome 9q31 and mouse chromosome 4, 23.1 cM (25). It was subsequently found that *ABCA1* is the causative gene in Tangier disease, a disorder of cholesterol transport between tissues and the liver, mediated by binding of the cholesterol onto high-density lipoprotein (HDL) particles (26–30). Patients with familial hypoalphalipoproteinemia have also been described that have mutations in the *ABCA1* gene, demonstrating that these disorders are allelic (31). Other patients with reduced levels of HDLs without the classical symptoms of Tangier disease have also been described with *ABCA1* mutations (32).

ABCA1 controls the extrusion of membrane phospholipid and cholesterol toward specific extracellular acceptors; however, the exact role of the protein in this process is not known. It has been proposed that ABCA1 carries out the flipping of membrane phospholipid, principally phosphatidylcholine, toward the lipid-poor, nascent apolipoprotein particle, which can now accept cholesterol (33). The ABCA1-dependent control on the lipid content of the membrane dramatically influences the plasticity and fluidity of the membrane itself and, as a result, affects the lateral mobility of membrane proteins and/or their association with membrane domains of special lipid composition. ABCA1 also plays a role in the engulfment of apoptotic bodies. Furthermore, the *ced-7* gene, which is a putative *ABCA1* ortholog in *Caenorhabditis elegans*, plays a role in phagocytosis by precluding the redistribution of phagocyte receptors around the apoptotic particle (34, 35).

The expression of *ABCA1* is induced by sterols (36) as well as nuclear hormone receptors, such as oxysterol receptors (LXRs) and the bile acid receptor (FXR), as heterodimers with retinoid X receptors (RXRs) (37). The promoter region contains multiple binding sites for transcription factors with roles in lipid metabolism (38–40).

Disruption of the mouse *Abca1* gene results in similarly low levels of HDLs and accumulation of cholesterol in tissues (41, 42). Analyses of *Abca1* –/– mice indicate that the transport of lipids from the Golgi to the plasma membrane is defective (41). However, these mice have normal secretion of cholesterol into bile, indicating that Abca1 does not play a role in this process (43). In

contrast, the constitutive overexpression of Abca1 results in a protection of animals against an atherosclerotic diet (44, 45). The Wisconsin hypoalpha mutant (WHAM) chicken has been characterized as a model for Tangier disease (46) and is suspected to be mutant in Abca1 (47).

Because of the important role of ABCA1 in cholesterol transport, several groups have examined the *ABCA1* gene for polymorphisms that might be associated with plasma lipid levels and cardiovascular disease. Common variation in noncoding regions of *ABCA1* may significantly alter the severity of atherosclerosis, without necessarily influencing plasma lipid levels (256)

The human ABCA1 protein has been expressed in Sf9 insect cells and was found to have Mg^{2+}-dependent ATP binding and low basal ATPase activity (257). The addition of lipid substrates did not modify the ATPase activity of ABCA1, and it was speculated that ABCA1 may be a regulatory protein or may require other protein partners for full activation.

ABCA2

The *ABCA2* gene maps to chromosome 9q34.3 and is most closely related to *ABCA1* (25, 48). *ABCA2* is highly expressed in the brain. Given the homology to *ABCA1* and its expression in the brain, it has been proposed that ABCA2 carries out similar cholesterol and phospholipid remodeling functions in neurons and glial cells.

An ovarian tumor cell line was characterized that contains an amplification of the *ABCA2* gene (49). These cells are resistant to estramustine and express high levels of *ABCA2* (49). Antisense treatment of these cells increases their sensitivity to the drug, supporting the idea that *ABCA2* can function as a drug efflux pump.

Characterization of the full-length *ABCA2* gene was performed, and antibodies to the protein demonstrate that it is localized to intracellular vesicles (258). Sterol-dependent regulation of the gene was observed, and the promoter contained several potential transcription factor-binding sites (50). The protein appears to be most highly expressed in oligodendrocytes in the brain (51).

ABCA3

The *ABCA3* gene maps to chromosome 16p13.3 and is expressed as a single 7.5-kb mRNA in the lung (52, 53). Recently, it was shown that a monoclonal antibody that detects a lamellar body-specific protein in alveolar type II is directed to ABCA3 (54, 55). The lamellar bodies of type II cells produce surfactants, lipid-rich secretions that are critical to the switch of the lung from an aqueous to an air environment at birth. Surfactants also play an important role in the homeostasis of the adult lung. Surfactants are also taken up by type II cells and recycled. These data suggest that ABCA3 is directly involved in transporting lipids within the cell and participating in the production of surfactants (56).

ABCA4

The *ABCA4* (ABCR) gene maps to chromosome 1p21.3 and is expressed exclusively in photoreceptors, where it believed to transport retinol (vitamin A)/phospholipid derivatives from the photoreceptor outer segment disks into the cytoplasm (52, 57, 58). These compounds are the likely substrates for ABCA4, because they stimulate the ATP hydrolysis activity of the purified protein

(59). Mice lacking *Abca4* show increased all-*trans*-retinaldehyde after light exposure, elevated phosphatidylethanolamine (PE) in outer segments, accumulation of the protonated Schiff base complex of all-*trans*-retinaldehyde and PE (*N*-retinylidene-PE), and striking deposition of a major lipofuscin fluorophore (A2-E) in retinal pigment epithelium (60). These data suggest that ABCR is an outwardly directed flippase for *N*-retinylidene-PE.

Mutations in the *ABCA4* gene have been associated with multiple eye disorders (61). A complete loss of ABCA4 function leads to retinitis pigmentosa, whereas patients with at least one missense allele have Startgardt disease (62–64). Startgardt disease is characterized by juvenile to early adult-onset macular dystrophy with loss of central vision (65) (OMIM:248200). Nearly all patients with recessive cone rod dystrophy also have mutations in *ABCA4* (64). Thus, three different recessive retinal degeneration syndromes are caused by ABCA4 mutations and are loosely correlated with the functional activity of the protein.

ABCA4 mutation carriers are also increased in frequency in age-related macular degeneration (AMD) patients (66). AMD patients display a variety of phenotypic features, including the loss of central vision, after 60 years of age. The causes of this complex trait are poorly understood, but a combination of genetic and environmental factors play a role. The abnormal accumulation of retinoids attributable to ABCA4 deficiency has been postulated to be one mechanism by which this process could be initiated. Defects in ABCA4 lead to an accumulation of retinal derivatives in the retinal pigment epithelium behind the retina. Consistent with this idea is the demonstration in *ABCA4* +/– mice of light-dependent accumulation of pigmented deposits in the retinal pigment epithelium, very reminiscent of AMD (67).

ABCA5

ABCA5 is one of five ABC genes in a cluster on chromosome 17q24.3 (9, 52). A similar cluster is found on mouse chromosome 11, although the mouse cluster lacks *ABCA10* and has a duplicated *ABCA8* homolog (68). This cluster of ABCA genes is evolutionarily distinct from that other ABCA genes, as evidenced from phylogenetic analysis as well as analysis of intron–exon boundaries. The chromosome 17 *ABCA* genes have 38 exons, whereas the other ABCA genes have 50–52 exons. Therefore, it appears that all of the genes on chromosome 17 arose from an ancestral ABCA gene. This cluster is not represented in plant, nematode, or insect genomes, and there is a single *ABCA5*-related gene in fish (Annilo et al, submitted). Thus *ABCA5* appears to be the ancestral gene for this cluster and seems to have arisen early in vertebrate evolution.

ABCA5 is expressed as a 6.5-kb mRNA with the highest levels in pancreas, muscle, and testes (9). Neither the substrate nor the function of this gene is known.

ABCA6

ABCA6 is another member of the chromosome 17 ABCA cluster (see *ABCA5*) and is also found in the mouse genome (9, 52, 68, 69). However, the human and mouse *ABCA6* genes display considerable differences, suggesting that there was a duplication of this gene and that mice and

humans retained different orthologs (Annilo et al., submitted). *ABCA6* is expressed as a 7.0-kb mRNA with the highest expression in the liver (9). Neither the substrate nor the function of this gene is known.

ABCA7

ABCA7 maps to chromosome 19p13.3 and is highly expressed in spleen, thymus and lymphoid cells (70, 71). *ABCA7* is part of the *ABCA1*/ *ABCA2*/ *ABCA3*/ *ABCA4* subgroup of ABCA genes. *ABCA7* has 46 introns and the 3' end overlaps that of a minor histocompatabillity antigen, HA-1 (72). Intriguingly, the autoantigen SS-N, an epitope of Sjögren's syndrome, is encoded by a segment at the N terminus of the ABCA7 protein (73). Resequencing of the *ABCA7* gene in 48 Japanese identified 67 single nucleotide polymorphisms, 64 of which are newly described (74). Neither the substrate nor the function of this gene is known.

ABCA8

ABCA8 is another member of the chromosome 17 ABCA cluster (see *ABCA5*) and is also found in the mouse genome (9). However, the mouse genome contains two *ABCA8*-like genes that clearly arose by duplication (68) (Annilo et al., submitted). Intriguingly there are several regions of the *ABCA8* and *ABCA9* genes in the mouse and human genome that display evidence of gene conversion-like events. Resequencing of the *ABCA8* gene from 48 Japanese people identified 88 single nucleotide polymorphisms, 78 of which are newly described (74). *ABCA8* is expressed in ovary, testes, heart, and liver (Schriml and Dean, unpublished data). Neither the substrate nor the function of this gene is known.

ABCA9

ABCA9 is another member of the chromosome 17 ABCA cluster (see *ABCA5*) and is also found in the mouse genome (9, 75). *ABCA9* is expressed at the highest levels in the heart and brain and induced during monocyte differentiation into macrophages and suppressed by cholesterol import (9, 75) . Neither the substrate nor the function of this gene is known.

ABCA10

ABCA10 is a member of the chromosome 17 ABCA cluster (see *ABCA5*), but the gene is absent from the mouse genome (9) (Annilo et al., submitted). *ABCA10* is expressed in skeletal muscle and heart (9). Neither the substrate nor the function of this gene is known.

ABCA12

ABCA12 maps to chromosome 2q34 and is weakly expressed in the stomach (Arnould et al., in preparation). A nearly full-length sequence has also been deposited in the public databases (GenBank) by Bonner et al. The mouse gene is located on chromosome 1C3 (Dean, unpublished). Neither the substrate nor the function of this gene is known.

ABCA13

ABCA13 maps to chromosome 17p12.3 and is weakly expressed in the stomach (Annilo, in preparation). The mouse gene is located on chromosome 11A1 (Dean, unpublished). All ABCA genes are predicted to have a large extracellular loop between the first and second TM domains. However, ABCA13 contains a domain in this region that is over 3500 amino acids and is encoded by exons of 4.8 and 1.7 kb. These are among the largest exons described to date for any gene. This domain is conserved in the mouse, as are the large exons. The domain is hydrophilic and has no obvious homology to any other protein domains. The ABCA13 protein is predicted to be 5058 amino acids in length and is therefore the largest ABC protein described to date and among the largest mammalian proteins. The gene is very poorly expressed, and only 18 expressed sequence tags have been identified. Neither the substrate nor the function of this gene is known.

ABCB Genes

ABCB1

The *ABCB1* (*PGP/MDR1*) gene maps to chromosome 7q21.1 and is the best characterized ABC drug pump. Formerly known as *MDR1* or *PGY1*, *ABCB1* was the first human ABC transporter cloned and characterized through its ability to confer a multidrug resistance phenotype to cancer cells that had developed resistance to chemotherapy drugs (76–79). ABCB1 has been demonstrated to be a promiscuous transporter of hydrophobic substrates including drugs such as colchicine, etoposide (VP16), Adriamycin, and vinblastine as well as lipids, steroids, xenobiotics, and peptides (for reviews, see Refs. 21, 80). The gene is thought to play an important role in removing toxic metabolites from cells but is also expressed in cells at the blood–brain barrier and presumably plays a role in transporting compounds into the brain that cannot be delivered by diffusion. ABCB1 also affects the pharmacology of the drugs that are substrates, and a common polymorphism in the gene affects digoxin uptake (81).

The ABCB1 protein is expressed in many secretory cell types such as kidney, liver, intestine, and adrenal gland, where the normal function is thought to involve the excretion of toxic metabolites. Mice have two closely related homologs of *ABCB1* (*Abcb1a*, *Abcb1b*). Mice homozygous for a disrupted *Abcb1a* gene are phenotypically normal but are sensitive to certain neurotoxins such as ivermectin (82). Disruption of *Abcb1a* alone and together with *Abcb1b* was also accomplished (83). The double-knockout mice are viable and fertile and show similar sensitivity to ivermectin (83). These studies led to the characterization of an important role of ABCB1 in transport across the blood–brain barrier. Certain dogs of the collie breed are highly sensitive to ivermectin and have mutations in the *Mdr1* gene (84).

ABCB1 is also highly expressed in hematopoietic stem cells, where it may serve to protect these cells from toxins (83, 85). ABCB1 has been shown to play a role in the migration of dendritic cells (86).

ABCB2 / TAP1

The *TAP1* (*ABCB2*) and *TAP2* (*ABCB3*) genes are on chromosome 6p21.3 in the HLA gene complex. They are half transporters that form a heterodimer that serves to transport peptides into the ER, where they can be complexed with class I HLA molecules for presentation on the cell surface (87–89). TAP expression is required for the stable expression of class I proteins (90). *In vitro* systems have been used to define the substrate specificity of the transporter (91, 92). These studies have shown that the TAP complex preferentially transports 9–12 amino acid peptides (93) with a preference for Phe, Leu, Arg, and Tyr at the C terminus, similar to the specificity of the HLA class I proteins (93, 94). Tap1-deficient mice are deficient in antigen presentation and surface class I molecules and lack CD8+ cells (95).

Several DNA viruses such as herpes simplex virus express molecules that interfere with antigen expression by disrupting the function of the TAP complex (96–99). In addition, tumor cell lines have been described that are mutated and deficient in TAP activity (100). Patients with inherited immunodeficiency because of TAP1 mutations have been described (101).

ABCB3 / TAP2

The *TAP2* (*ABCB3*) gene maps to chromosome 6p21.3 and functions as a heterodimer with TAP1 (see TAP1). A family with recessive inheritance of class I HLA deficiency was described that has a nonsense mutation in the *TAP2* gene (102).

ABCB4

The *ABCB4* (*MDR3/PGY3*) gene maps to 7q21.1, adjacent to the *ABCB1* (*PGP/MDR1*) gene, and encodes a full transporter with high homology to *ABCB1*. These genes clearly arose by duplication, although the function of *ABCB4* is very different from *ABCB1*. *ABCB4* is principally expressed in the bile cannilicular membrane of the liver, but is also found in the heart, muscle and in B cells. Disruption of the gene in the mouse resulted in liver pathology because of a deficiency in fatty acid secretion in bile (103). *In vitro* experiments confirm that ABCB4 can transport phophatidylcholine from the inner to the outer leaflet of the membrane (104, 105). Mutations in this gene cause PFIC3 (106, 107) and are associated with intrahepatic cholestasis of pregnancy (108, 109).

ABCB5

The *ABCB5* gene maps to 7p21.1 and encodes a full transporter molecule (52) (Allikmets, unpublished). The gene is expressed as a 7.5-kb transcript in all cells and has no described function.

ABCB6

The *ABCB6* gene maps to chromosome 2q35, and the protein is localized to the mitochondria (52, 110). It is closely related to the ABCB7 protein: both are half transporters. The *ABCB6* gene, similar to *ABCB7,* can complement yeast cells that are defective in the *ATM1* gene, a mitochondrial ABC gene that is involved in the transport of a precursor of the Fe/S cluster from mitochondria to the cytosol (110).

ABCB7

The *ABCB7* gene maps to chromosome Xq21–q22, and the protein is localized to the mitochondria (52, 111). It is closely related to the *ABCB6* gene, both of which are half transporters. The human *ABCB7* gene can complement yeast cells that are defective in the *ATM1* gene, a mitochondrial ABC gene that is involved in the transport and/or maturation of a precursor of the Fe/S cluster from mitochondria to the cytosol (111, 112). The *ABCB7* gene is mutated in patients with X-linked sideroblastic anemia and ataxia (XLSA/A) (112, 113). XLSA/A is a recessive disorder characterized by infantile to early childhood onset of non-progressive cerebellar ataxia and mild anemia with hypochromia and microcytosis.

An I400M variant in *ABCB7* was identified in a predicted TM segment of the *ABCB7* gene in patients from an XLSA/A family. The mutation was shown to segregate with the disease in the family and was not detected in at least 600 chromosomes of general population controls. Introduction of the corresponding mutation into the *S. cerevisiae ATM1* gene resulted in a partial loss of function of the yeast Atm1 protein (112). A second family with an E433K mutation was also identified. The analogous E433K mutation in the yeast *ATM1* gene (D398K) also results in loss of function, as assessed by cytosolic Fe/S protein maturation (113).

ABCB8

The *ABCB8* (*M-ABC1*) gene maps to 7q36.1 and encodes a half transporter protein located in the mitochondria, although its function is unknown (52, 114).

ABCB9

The *ABCB9* gene maps to 12q24.31 and encodes a half transporter protein located in the lysosomes, the function of which is unknown (52, 115).

ABCB10

The *ABCB10* (*M-ABC2*) gene maps to 1q42.13 and encodes a half transporter protein located in the mitochondria, although its function is unknown (48, 116).

ABCB11

The *ABCB11* (*BSEP/SPGP*) gene maps to 2q24.3 and encodes a full transporter protein located principally, if not exclusively, in the liver (117, 118). The protein localizes to bile canalicular membrane of the liver and participates in the secretion of bile salts such as taurocholate (118). ABCB11 protein is localized to vesicles within liver cells lining the bile duct.

Mutations in *ABCB11* are found in patients with progressive familial intrahepatic cholestasis, type 2 (PFIC2) (119). Disruption of the murine *Abcb11* gene results in intrahepatic cholestasis. However, the phenotype is less severe and indicates that mice display compensatory changes (120). Analysis of the *ABCB11* promoter showed a farnesoid X receptor (FXR)-responsive element (FXRE) at position –180 (121). The FXR functions as a heterodimer with the retinoid X receptorα (RXRα) and can be activated by the bile salt chenodeoxycholic acid. Thus, similar to several ABC genes, *ABCB11* is regulated by its ligand.

ABCC Genes

ABCC1

The *ABCC1* (*MRP1*) gene maps to chromosome 16p13.1 and is expressed in tumor cells (122). *ABCC1* is adjacent to the *ABCC6* gene, and one of these genes undoubtedly arose by gene duplication. It encodes a full transporter that is the principal transporter of glutathione-linked compounds from cells. The *ABCC1* gene was identified in the small cell lung carcinoma cell line NCI-H69, a multidrug-resistant cell that does not overexpress *ABCB1* (123). The ABCC1 pump confers resistance to doxorubicin, daunorubicin, vincristine, colchicines, and several other compounds, very similar profile to that of ABCB1 (124). However, unlike ABCB1, ABCC1 transports drugs that are conjugated to glutathione by the glutathione reductase pathway (12, 122, 125–127).

Disruption of the *Abcc1* gene demonstrated that it is not essential for viability or fertility (128, 129). However, these mice do display an impaired inflammatory response and they are hypersensitive to the anticancer drug etoposide.

ABCC1 can transport leukotrienes such as leukotriene C_4 (LTC_4). LTC_4 is an important signaling molecule for the migration of dendritic cells. Migration of dendritic cells from the epidermis to lymphatic vessels is defective in *Abcc1* –/– mice, implicating a role for LTC_4 in the response of dendritic cells to chemokines (130). The ABCC1 protein is thought to play both a role in protecting cells from chemical toxicity and oxidative stress and to mediate inflammatory responses involving cysteinyl leukotrienes (122).

ABCC2

The *ABCC2* (*MRP2/cMOAT*) gene maps to chromosome 10q24 and is expressed in canalicular cells in the liver (52, 131). It functions as the major exporter of organic anions from the liver into the bile. The role of ABCC2 in organic ion transport was first elucidated by the discovery that this gene is mutated in the TR-rat, a rat strain that displays jaundice and a deficiency in organic ion

transport (132). Subsequently, it was found that the gene is also mutated in patients with Dubin–Johnson syndrome, a human disorder of organic ion transport (133, 134). ABCC2 overexpression can confer drug resistance to cells, but the physiological importance of this observation is not clear (12, 124, 135).

The localization of the ABCC2 protein on the membrane of the bile canaliculus is dependent of the expression of the radixin (*RDX*) product. *Rdx* –/– mice have increased bilirubin and develop liver injury, similar to Dubin–Johnson patients (136).

ABCC3

The *ABCC3* (*MRP3*) gene maps to 17q21.3 and is expressed primarily in the liver (52, 131). Similar to ABCC2, ABCC3 can confer the ability to efflux organic ions, and cells become resistant to certain cytotoxic compounds (137, 138).

ABCC4

The *ABCC4* (*MRP4*, *MOATB*) gene maps to 13q32 and is expressed at low levels in many cell types and tissues (52, 131, 139). Overexpression and amplification of the *ABCC4* gene is found in cell lines resistant to nucleoside analogues such as azidothymidine monophosphate (140). Transfection of *ABCC4* into cells confers resistance to these compounds (140). Thus, ABCC4 may be an important factor in the resistance to nucleoside analogues. Because these drugs are important antiviral and anticancer agents, this has importance in therapies for human immunodeficiency virus 1 infection and other disease.

ABCC5

The *ABCC5* (*MRP5/MOATC*) gene maps to 3q27 and is ubiquitously expressed in tissues and cells (52, 131, 141). It is closely related to the *ABCC4* gene and also confers resistance to nucleoside analogues (142).

ABCC6

The *ABCC6* (*MRP6*) gene maps to 16p13.1, adjacent to the *ABCC1* gene. The gene is principally expressed in the liver and kidney. *ABCC6* is mutated in pseudoxanthoma elasticum, a recessive genetic disorder characterized by calcification of the connective fibers of the skin, ocular bleeding, and cardiovascular disease (143–147). Several pseudogenes of *ABCC6* have been identified that also map to 16p (148, 149).

Expression of the human ABCC6 protein in Sf9 insect cells demonstrated that the protein is present in isolated membranes and can transport glutathione conjugates including LTC_4 (150). Organic anions inhibit transport, and the expression of three missense mutations found in PXE patients abolished transport activity. Expression and purification of the rat Abcc6 protein demonstrated Mg^{2+}-dependent trapping of 8-azido-ATP. However, stimulation of nucleotide binding could not be demonstrated by glutathione conjugates (151), and glutathione conjugate transport by the purified rat gene was not detected (152).

Analysis of the *ABCC6* gene for variants has identified a number of common polymorphisms including missense alleles (148). One of these variants, R1268Q, is associated with plasma triglyceride and HDL levels (148). The R1141X mutation is the most prevalent *ABCC6* mutation in PXE patients of European descent, and this variant has been found at levels approaching 1% in these populations. An association of this variant with premature atherosclerotic vascular disease has been reported (153).

ABCC7 / CFTR

The *CFTR* (*ABCC7*) gene maps to chromosome 7q31.2 and is a protein kinase A-dependent chloride channel expressed in exocrine tissues such as the sweat duct, pancreas, intestine, and kidney. The gene is mutated in the recessive genetic disease cystic fibrosis (154–156).

Cystic fibrosis (CF) is the most common fatal childhood disease in Caucasian populations and is characterized by defective exocrine activity of the lung, pancreas, sweat ducts, and intestine (11, 157). The disease is found at frequencies ranging from 1/900 to 1/2500. This corresponds to a carrier frequency of 1/15 to 1/25. The disease is much less common in African and Asian populations, where carrier frequencies of 1/100 to 1/200 have been estimated. In most populations, the disease frequency correlates with the frequency of the major allele of the *CFTR* gene, a deletion of 3 base pairs (ΔF508) (158). However, at least two other populations have high-frequency *CFTR* alleles. The W1282X allele is found on 51% of the alleles in the Ashkenazi Jewish population, and the 1677delTA allele has been found at a high frequency in Georgians and is also present at an elevated level in Turkish and Bulgarian populations. This has led several groups to hypothesize that these alleles arose through selection of an advantageous phenotype in the heterozygotes (159). It is through CFTR that some bacterial toxins, such as cholera toxin, and those from *Escherichia coli* cause increased fluid flow in the intestine and result in diarrhea. Therefore, several researchers have proposed that the CF mutations have been selected for in response to this disease(s). This hypothesis is supported by studies showing that: (*a*) CF homozygotes indeed fail to secrete chloride ions in response to a variety of stimulants; and (*b*) mice in heterozygous null animals showed reduced intestinal fluid secretion in response to cholera toxin (160). CFTR is also the receptor for *Salmonella typhi* toxin and has an implied functional role in the innate immunity to *Pseudomonas aeruginosa* (161).

Cftr –/– mice display many of the hallmarks of the human disease, including defects in the bowel and male reproductive tract (162, 163). A mouse model of the ΔF508 mutation has also bee generated (164).

Patients with two severe *CFTR* alleles such as ΔF508 typically display severe disease with inadequate secretion of pancreatic enzymes leading to nutritional deficiencies, bacterial infections of the lung, and obstruction of the vas deferens leading to male infertility (165, 166). Patients with at least one partially functional allele display enough residual pancreatic function to avoid the major nutritional and intestinal deficiencies (167), and subjects with very mild alleles display only congenital absence of the vas deferens with none of the other symptoms of CF (168, 169). Recently, heterozygotes of CF mutations have been found to have an increased frequency of pancreatitis (170) and bronchiectasis (171). Thus, there is a spectrum of severity in the pheno-

types caused by this gene that is inversely related with the level of CFTR activity. Clearly, other modifying genes and the environment also affect disease severity, particularly the pulmonary phenotypes.

Several research groups have approached gene therapy in the lung as a potential treatment for CF. This approach has proved extremely difficult and may require more detailed insight into the cell types that express *CFTR* in the lung (reviewed in Refs. 172, 173).

The identification of the *CFTR* gene led to expression of both the wild-type and mutant forms of the protein and to considerable insight into its function, regulation, and ability to regulate other ion channels (reviewed in Refs 174–176). Although a large number of CF mutations occur in the NBFs and function to inactivate the protein, a number of *CFTR* alleles also cause misprocessing of the protein (reviewed in Ref. 177). The CFTR protein is unusual amongst ABC genes in having a large, hydrophilic domain after the first NBF (154). This domain, the R domain, is phosphorylated by cAMP-dependent kinases and serves to regulate the activity of the channel (reviewed in Ref. 178).

ABCC8

The *ABCC8* (*SUR1*) gene maps to chromosome 11p15.1 and encodes a full transporter molecule. The gene is closely related to *ABCC9* (*SUR2*). The *ABCC8* gene codes for a high-affinity receptor for the drug sulfonylurea. Sulfonylureas are a class of drugs widely used to increase insulin secretion in patients with non-insulin-dependent diabetes. These drugs bind to the ABCC8 protein and inhibit an associated potassium channel K(ATP). Familial persistent hyperinsulinemic hypoglycemia of infancy is an autosomal recessive disorder in which subjects display unregulated insulin secretion. The disease was mapped to 11p15–p14 by linkage analysis, and mutations in the *ABCC8* gene are found in PHHI families (179). *Sur1* –/– mice also lack K(ATP) channels; however, they show normal glucose levels, suggesting that compensatory pathways are present in mice (180).

The *ABCC8* gene has also been implicated in insulin response in Mexican-American subjects (181) and in type II diabetes in French Canadians (182) but not in a Scandinavian cohort (183).

ABCC9

The *ABCC9* (*SUR2*) gene maps to 12p12.1 and is closely related to the *ABCC8* (*SUR1*) gene on chromosome 11. ABCC9 shows low-affinity binding to sulfonylurea and is the primary regulator of K(ATP) channels in muscle. *Sur2* –/– mice display enhanced insulin-stimulated glucose uptake in skeletal muscle (184).

ABCC10

The *ABCC10* gene (*MRP7*) maps to 6p21.1 and groups with the other *ABCC1*-related genes (*ABCC2*, *ABCC3*, *ABCC4*, *ABCC5*, *ABCC6*, *ABCC11*, and *ABCC12*) (52). However, the function of *ABCC10* is not known.

ABCC11

The *ABCC11* (*MRP8*) gene maps to 16q12.1 in a cluster with the *ABCC12* (*MRP9*) gene (185–187). A human T cell leukemia cell line that is resistant to nucleoside drugs overexpresses *ABCC11* (188). The mouse appears to have only a single gene in this cluster, indicating that the duplication occurred relatively recently (Dean, unpublished).

ABCC12

The *ABCC12* (*MRP9*) gene maps to 16q12.1 in a cluster with *ABCC11* (185, 187). The function and substrates of the gene are unknown.

ABCD Genes

ABCD1

The *ABCD1* (*ALD*) gene maps to Xq28 and expresses a peroxisomally located half transporter that is mutated in adrenoleukodystrophy (ALD). X-ALD is an X-linked recessive disorder characterized by neurodegenerative phenotypes with onset typically in late childhood (189). Adrenal deficiency commonly occurs, and the presentation of ALD is highly variable. Childhood ALD, adrenomyeloneuropathy, and adult onset forms are recognized, but there is no apparent correlation to *ABCD1* alleles (190). Female heterozygotes can display symptoms including spastic paraparesis and peripheral neuropathy (191).

More than 406 mutations have been documented in the *ABCD1* gene and a database of ALD mutations has been created (190) (http://www.x-ald.nl [http://www.x-ald.nl]). Although most mutations are point mutations, several large intragenic deletions have also been described (192). A contiguous gene syndrome, contiguous *ABCD1DXS1357E* deletion syndrome (CADDS), has been described that includes *ABCD1* and the adjacent *DXS1357E* gene. These patients present with symptoms at birth, as opposed to X-ALD, which present after 3 years of age (193).

ALD patients have an accumulation of unbranched saturated fatty acids, with a chain length of 24–30 carbons, in the cholesterol esters of the brain and in adrenal cortex. The ALD protein is located in the peroxisome, where it is believed to be involved in the transport of very long chain fatty acids (VLCFAs). A treatment consisting of erucic acid, a C22 monounsaturated fat, and oleic acid, a C18 monounsaturated fat (Lorenzo's oil), was developed that results in a normalization of the VLCFA levels in the blood of patients but does not appear to dramatically slow the progression of the disease (194). This is probably because the treatment fails to lower fatty acid levels in the brain (195). An *Abcd1 –/–* mouse has been generated, and the animals display accumulation of VLCFAs in kidney and brain; however, they do not show the severe neurological abnormalities of the childhood cerebral form of X-ALD (196, 197). The mice do show evidence of a late-onset neurological disorder characterized by slower nerve conduction and myelin and axonal anomalies detectable in the spinal cord and sciatic nerve (198).

ABCD1 is one of four related peroxisomal transporters that are found in the human genome, the others being ABCD2, ABCD3, and ABCD4. These genes are highly conserved in evolution, and a pair of homologous genes is present in the yeast genome, *PXA1* and *PXA2*. The *PXA2* gene has been demonstrated to transport long-chain fatty acids (199, 200). A defective *pxa1* gene in *Arabidopsis thaliana* results in defective import of fatty acids into the peroxisome (201).

ABCD2

The *ABCD2* (*ALDR*) gene maps to chromosome 12q11 and encodes a 741-amino acid half transporter that is 66% identical at the amino acid level with ABCD2 (202, 203). The ABCD2 protein is expressed in peroxisomes and is particularly abundant in the brain and adrenal gland (202). The *ABCD1* and *ABCD2* genes share the same exon/intron structure, further evidence that they are closely related (204). Overexpression of the *ABCD2* gene in cells from X-ALD patients at least partially restores the impaired peroxisomal β-oxidation in fibroblasts (205). The *ABCD2* gene is induced by fibrates (cholesterol-lowering drugs) in a peroxisome proliferator-activated receptor (PPARα)-dependant fashion, providing a potential therapeutic strategy to treat X-ALD (206).

ABCD3

The *ABCD3* (*PMP70/PXMP1*) gene maps to chromosome 1p21–p22 and encodes a peroxisomal protein. Although mutations in *ABCD3* were found in two patients with Zellweger syndrome (207), further evidence does not support a role for *ABCD3* in this disorder (208).

ABCD4

The *ABCD4* (*PXMP1L/P70R/PMP69*) gene maps to chromosome 14q24.3 and encodes the fourth peroxisomal half transporter (52, 209, 210). ABCD4 shares 25–27% amino acid identity with the ABCD1, ABCD2, and ABCD3 proteins. The gene contains 19 exons and spans approximately 16 kb and encodes several differentially spliced mRNAs (211).

ABCE Genes

ABCE1

The *ABCE1* (*RNS4I*) gene maps to 4q31 (52, 212) and encodes a protein with two ATP-binding domains with high homology to other ABC genes but no TM domains. Along with the genes in the ABCF subfamily, ABCE genes are cytosolically expressed ABC genes that are not membrane transporters. However, they all clearly possess ABC-type NBFs and are therefore included in the gene superfamily (3, 5).

ABCE1 inhibits the RNaseL protein, a ribonuclease that is activated by interferons (213). The *ABCE1* gene is expressed as 2.4- and 3.8-kb mRNAs in all tissues (214). ABCE1 has been found recently to be essential for the assembly of immature human immunodeficiency virus capsids (215).

ABCF Genes

ABCF1

The *ABCF1* (*ABC50*) gene is localized to chromosome 6p21.33 inside the class I HLA complex and encodes a protein with two ATP-binding domains and no TM domains (52). The gene is activated by tumor necrosis factor-α stimulation of cells (216). The human genome contains three ABCF genes of unknown function. The yeast ABCF homologs include the *GCN20* gene, which codes for a protein required for the activation of a kinase that phosphorylates the translation initiation factor eIF2 (15). The ABCF1 protein associates with human ribosomes and copurifies with eIF2, suggesting that it performs an analogous function in human cells (16).

ABCF2

The *ABCF2* gene maps to chromosome 7q36 and encodes a protein of unknown function (52).

ABCF3

The *ABCF3* gene maps to chromosome 7q36 and encodes a protein of unknown function (52).

ABCG Genes

ABCG1

The *ABCG1* gene is located on chromsome 21q22.3 and encodes a half transporter (17, 217, 218). Similar to all ABCG family genes, the NBF is at the N terminus, and the TM domains are at the C terminus, the opposite orientation of all other eukaryotic ABC genes. The *ABCG1* gene is 31% identical to the *Drosophila white* gene, a transporter of eye pigment precursors. It is most closely related to the *ABCG4* gene, and these two genes are the only human ABCG genes that share a conserved intron location, indicating that they arose from a recent duplication (219).

The *ABCG1* gene is induced by cholesterol in monocyte-derived macrophages during cholesterol influx mediated by acetylated low-density lipoprotein (18). This suggests that, similar to *ABCG5* and *ABCG8*, *ABCG1* is involved in cholesterol efflux (33, 220). ABCG1 contains a TATA-less, GC-rich promoter that contains silencing elements that can mediate transcriptional repression (221). Multiple alternative transcripts affecting the N terminus of the protein have been identified, as has a second promoter region. Both promoters were found to be responsive to hydroxycholesterol and retinoic acid in macrophages.

The mouse *Abcg1* gene maps to chromosome 17A2-B and has 97% identity to the human locus (217, 218).

ABCG2

The *ABCG2* (*MXR/BCRP/ABCP*) gene maps to chromosome 4q22 and encodes a half transporter with a NBF–TM orientation (52, 222). Analysis of cell lines resistant to mitoxantrone that do not overexpress *ABCB1* or *ABCC1* led several laboratories to identify the *ABCG2* gene as a drug

transporter (222-224). *ABCG2* confers resistance to anthracycline anticancer drugs and is amplified or involved in chromosomal translocations in cell lines selected with topotecan, mitoxantrone, or doxorubicin treatment. It is suspected that *ABCG2* functions as a homodimer because transfection of the gene into cells confers resistance to chemotherapeutic drugs (225). Variations at residue 482 of ABCG2 are found in many resistant cell lines, and the alteration of the wild-type arginine at this position for either threonine or glycine imparts the ability to transport rhodamine and alters the substrate specificity (226).

ABCG2 can also transport several dyes, such as rhodamine and Hoechst 33462, and the gene is highly expressed in a subpopulation of hematopoetic stem cells (side population) that stain poorly for these dyes (227–229). However, the normal function of the gene in these cells is unknown. *ABCG2* is highly expressed in the trophoblast cells of the placenta (230). This suggests that the pump is responsible either for transporting compounds into the fetal blood supply or removing toxic metabolites (231). The gene is also expressed in the intestine, and inhibitors could be useful in making substrates orally available.

In mouse cells from animals deficient in the *Abcb1*, *Abcb1a*, and *Abcc1* genes, exposure to mitoxantrone, topotecan, or doxorubicin results in amplification of the *Abcg2* gene (20). This strongly suggests that *ABCG2* is one of three major transporter genes involved in drug resistance in mammalian cells. Inhibitors of ABC drug transporters represent a potential strategy for preventing the development of drug-resistant tumors (21). Effective inhibitors of ABCG2, such as fumitrimorgin C, a natural product from *Aspergillus,* and GF120918 have been described (223, 232–234).

ABCG3

The *Abcg3* (*Abcp2*) gene maps to chromosome 4 and is highly related to *ABCG2*. The gene is principally expressed in murine hematopoeitic cells and has no ortholog in the human genome, although other rodents appear to have a orthologous sequence (22). The gene has an unusual NBF domain that has alternative residues in several conserved positions, suggesting that it might either fail to bind or hydrolyze ATP (22).

ABCG4

The *ABCG4* gene maps to 11q23 and expresses a half transporter protein that is highly related to *ABCG1*. *ABCG4* has the same intron/exon structure as *ABCG1*, suggesting that they arose by a relatively recent gene duplication event (219). The gene is primarily expressed in the brain; however, there are several alternative transcripts that are specifically expressed in either hematopoetic cells and in the lung (219). Similar to *ABCG1*, *ABCG4* is also induced by oxysterols and retinoids (235). The murine *Abcg4* gene is 98% identical to the human gene and is highly expressed in the brain, spleen, eye, and bone marrow (236).

ABCG5

The *ABCG5* gene maps to chromosome 2p21 and is adjacent to and arranged head-to-head with the *ABCG8* gene (237–239) (Figure 6). Both of these genes are mutated in families with sitosterolemia, a disorder characterized by defective transport of plant and fish sterols and cholesterol (238–243). Most likely, the two half transporters form a functional heterodimer, and they appear to be regulated by the same promoter (244).

Patients mutated in either *ABCG5* or *ABCG8* have similarly elevated levels of sitosterol, suggesting that it is the heterodimer that is the principal transporter of sitosterol (245). However, Asian sitosterolemia patients have almost exclusive mutations in *ABCG5*, and Caucasian patients have mutations in *ABCG8* (245–247). This suggests that there are independent functions of the two genes, and that they may also form heterodimers to transport some of the wide variety of non-cholesterol sterols found in plants and shellfish.

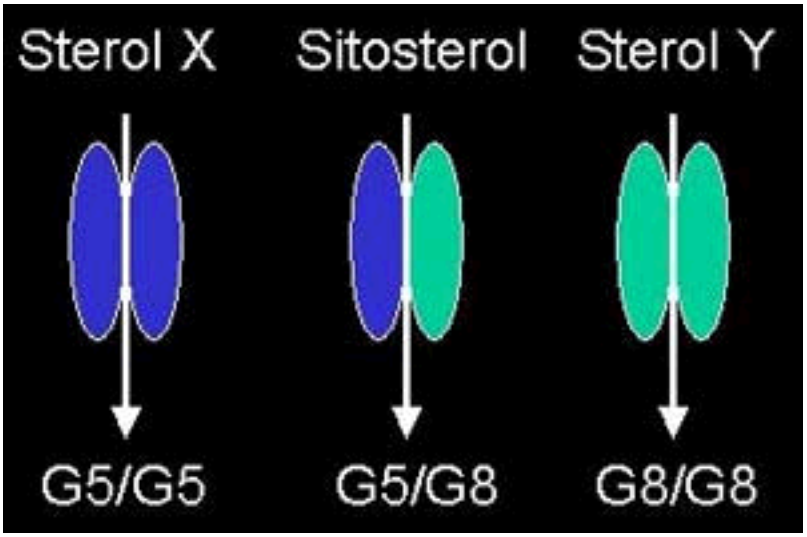

Figure 6: Model of ABCG5 and ABCG8 dimers. A diagram of the potential dimers that can be formed from the ABCG5 and ABCG8 half transporters. Although the heterodimer is speculated to be the major transporter of sitosterol, the homodimers are proposed to transport some of the other sterols encountered in the diet.

ABCG8

The *ABCG8* gene is adjacent to the *ABCG5* gene on chromosome 2p21, and the two genes are coordinately induced by cholesterol (238) (Figure 6). The levels of sterols in blood were demonstrated to be highly heritable, and at least two variants in *ABCG8* (D19H and T400K) were shown to be associated with lower concentrations of sterols in parents and their offspring (248). Several additional frequent missense variants in the *ABCG8* gene were also described (245, 249), suggesting that both *ABCG5* and *ABCG8* are functionally polymorphic, perhaps in response to selection based on dietary sterol exposure.

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Box 1: ABC transporter superfamily web resources.

Gene nomenclature.

http://www.gene.ucl.ac.uk/nomenclature/genefamily/abc.html [http://www.gene.ucl.ac.uk/nomenclature/genefamily/abc.html]

Phylogenetic analysis of ABC genes from all species.

http://www.pasteur.fr/recherche/unites/pmtg/abc/database.iphtml [http://www.pasteur.fr/recherche/unites/pmtg/abc/database.iphtml]

ABCdb ABC gene database.

http://ir2lcb.cnrs-mrs.fr/ABCdb/ [http://ir2lcb.cnrs-mrs.fr/ABCdb/]

Michael Muller's ABC transporter page.

http://nutrigene.4t.com/translink.htm [http://nutrigene.4t.com/translink.htm]

ABC database at Kyoto Encyclopedia of Genes and Genomes (KEGG).

http://www.genome.ad.jp/kegg/ortholog/tab02010.html [http://www.genome.ad.jp/kegg/ortholog/tab02010.html]

Human Gene Mutation Database. For mutations in many disease genes, including ABC genes, see:

http://archive.uwcm.ac.uk/uwcm/mg/hgmd0.html [http://archive.uwcm.ac.uk/uwcm/mg/hgmd0.html]

Cystic fibrosis mutation database.

http://www.genet.sickkids.on.ca/cftr/ [http://www.genet.sickkids.on.ca/cftr/]

X-ALD mutation database.

http://www.x-ald.nl [http://www.x-ald.nl]

Alliance for Cellular Signaling. For detailed information and functional data of all signaling genes, including ABC genes, see:

http://afcs.org/ [http://afcs.org/]