The Human ATP-Binding Cassette (ABC) Transporter Superfamily

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Abstract

The ATP-binding cassette (ABC) transporter superfamily comprises membrane proteins that efflux various substrates across extra- and intra-cellular membranes. Mutations in ABC genes cause 21 human disorders or phenotypes with Mendelian inheritance, including cystic fibrosis, adrenoleukodystrophy, retinal degeneration, cholesterol, and bile transport defects. Common polymorphisms and rare variants in ABC genes are associated with several complex phenotypes such as gout, gallstones, and cholesterol levels. Overexpression or amplification of specific drug efflux genes contributes to chemotherapy multidrug resistance. Conservation of the ATP-binding domains of ABC transporters defines the superfamily members, and phylogenetic analysis groups the 48 human ABC transporters into seven distinct subfamilies. While the conservation of ABC genes across most vertebrate species is high, there is also considerable gene duplication, deletion, and evolutionary diversification.

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Key words: ATP-binding cassette transporter, human disease, evolution, lipid transport

This paper reviews the current knowledge on all human ABC genes in inherited disease and drug resistance. In addition, we review functional data in the mouse and other model organisms, genome-wide association loci in and near the human ABC genes, somatic mutations, and copy number alterations in cancer. The spectrum of rare variation in the gene family indicates that specific transporters are highly conserved and subject to purifying selection.

Introduction

ABC transporters are intricate molecular systems that characterize the vectorial transport of various substrates across biological membranes. They are present in all extant species ranging from prokaryotes to humans (Childs & Ling, 1994; Jones & George, 2004) and comprise the largest family of transmembrane proteins. These transmembrane proteins bind ATP and utilize the energy to drive the active transport of diverse molecules across all cell membranes against the concentration gradient (Dean & Annilo, 2005; Higgins, 1992; KM Moitra, 2012). Characterization of this important class of transporters, which contain one of the largest and ancient protein subfamilies that transport a myriad of substrates from sugars, amino acids, proteins to metal ions, will yield invaluable insights into the molecular basis and physiology of human diseases (Higgins, 1992).

Organization of ABC Genes and Proteins

The classification of proteins as ABC transporters is based on the sequence and organization of ATP-binding domain(s), also known as nucleotide-binding domains (NBDs) or nucleotide-binding folds. Characteristic motifs, the Walker A motif and Walker B motif separated by 90–120 amino acids, are found in the nucleotide-binding fold of all ATP-binding proteins. In addition, the ABC genes contain an additional distinctive component referred to as the signature motif or the C-loop situated upstream of the Walker B site (Hyde et al., 1990).

The typical ABC protein contains two NBDs and two transmembrane domains (TMDs). The TM domains generally have 6-12 membrane-spanning alpha-helices, which determine substrate specificity. The eukaryotic ABC genes can be structured as full transporters containing two TMs and two NBDs, or as half transporters (Hyde et al., 1990). Half transporters need to form either homodimers or heterodimers to create a functional transporter. Specific mutations in ABC genes can contribute to several human genetic disorders, including cystic fibrosis, neurological disease, cholesterol/bile transport defects, retinal degeneration, anemia, and differential drug response (Dean, Hamon, & Chimini, 2001).

In bacteria, ABC transporters tend to be unidirectional. Most of them are importers, which import essential molecules involved in bacterial metabolism such as vitamins, metal ions, and sugars. However, several MDR-like transporters (primarily involved in drug resistance) and other ABC ATPases involved in cellular processes like DNA repair or other regulatory functions have also been identified (Lubelski, Konings, & Driessen, 2007). Eukaryotic ABC transporters are mainly engaged in 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 secretion from the body.

ABC genes exhibit evolutionary conservation from bacteria to humans, and multiple gene duplication and deletion events in the ABC genes point to the fact that gene evolution is still ongoing. ABC genes are dispersed widely in eukaryotic genomes. In humans, the ABC transporter superfamily contains 48 genes, divided into seven subfamilies ranging from A to G based on similarity in gene structure, order of the domains, and sequence homology in the NBD and TM domains (Dean, Rzhetsky, & Allikmets, 2001). To date, mutations in 21 of the 48 human ABC genes cause a Mendelian disease or an inherited phenotype (**Table 1**)

Human ABC Gene Subfamilies and Disease Associations: An Overview

ABCA (ABC1)

The human ABCA subfamily contains 12 full transporters. These transporters separate into two subgroups

based primarily on phylogenetic analysis and intron structure (Arnould et al., 2001). The first group of transporters contains seven genes distributed among six chromosomes (ABCA1, ABCA2, ABCA3, ABCA4, ABCA7, ABCA12, and ABCA13), whereas the second group comprises five genes (ABCA5, ABCA6, ABCA8, ABCA9, and ABCA10) on chromosome 17q24.3 (Broccardo et al., 2001). Several ABCA sub-family genes are associated with human disease. The ABCA1 protein is definitively involved in disorders of cholesterol transport and HDL biosynthesis. Tangier Disease (TD), a rare genetic disorder of lipoprotein metabolism, is caused by mutations in the ABCA1 gene (Remaley et al., 1999; Rust et al., 1999). This disease presents with deficient levels of HDL cholesterol and apoprotein A-I causing a myriad of symptoms, including orange-yellow tonsils, anemia, thrombocytopenia, peripheral neuropathy, hepatosplenomegaly, lymphadenopathy, and corneal opacity. Tangier Disease can also be associated with an increased risk of coronary artery disease (Maranghi et al., 2019). The ABCA4 protein performs critical steps in the visual cycle by transporting vitamin A derivatives in the outer segments of rod photoreceptor cells. Pathogenic variants in *ABCA4* cause Stargardt disease (STGD1), which is a common early-onset maculopathy.

ABCB (TAP) The half transporters in this subfamily include *ABCB2* (*TAP1*) and *ABCB3* (*TAP2*) that need to form a

ABCC (CFTR/MRP)

Twelve full transporters make up the ABCC subfamily, and they have divergent functional roles that include ion transport, cell-surface receptor, and toxin secretion activities. These transporters are responsible for human diseases, including cystic fibrosis (ABCC7) and pseudoxanthoma elasticum (ABCC6). The cystic fibrosis transmembrane receptor (CFTR/ABCC7) protein functions as a chloride channel that plays a role in exocrine secretion. Different genetic mutations in the CFTR gene cause cystic fibrosis (Quinton, 1999; Rommens et al., 1989). Cystic fibrosis is an (autosomal recessive) disease that may affect the lungs and the digestive system. Mutations in the cystic fibrosis (CF) gene (ABCC7) result in the production of a thick, sticky mucous that can clog up the lungs and sometimes lead to life-threatening infections. In addition, CF can result in obstruction of the pancreas that has the effect of preventing certain enzymes from breaking down and absorbing food into the body (http://www.cff.org). The CF protein has a regulatory domain, otherwise called the R domain, located between NBD1 and TMD2 and contains several potential sites for phosphorylation by cAMP-dependent PKA or PKC. Kinase-mediated phosphorylation of the cytoplasmic R domain is required to transmit the signal from the NBDs to the channel gate. Hence this domain is essential for the functioning of the transporter.

Pseudoxanthoma elasticum (PXE) is an autosomal recessive Mendelian disease that affects multiple body systems caused by mutations in ABCC6 (Bergen et al., 2000). Its main characteristic feature is the mineralization of the soft connective tissue that primarily affects the skin, eyes, and arterial blood vessels. PXE has high phenotypic variability, likely modulated by variants in several modifier genes (K. Moitra et al., 2017). The ABCC8 and ABCC9 proteins bind sulfonylurea and can regulate potassium channels involved in modulating insulin secretion. The additional nine MRP-related genes in this superfamily have diverse functions. ABCC1, ABCC2, and ABCC3 transport drugs conjugated to glutathione and other organic anions. The N-terminal domain (TMD0) is absent in ABCC4, ABCC5, ABCC11, and ABCC12, so these proteins are smaller than the other MRP1-like gene products (Bakos et al., 2000). The remaining ABCC subfamily proteins, ABCC4 and ABCC5, confer resistance to nucleosides, including 9-(2-phosphonylmethoxyethyl) adenine (PMEA) and purine analogs. A recent study found an MRP4 variant (rs3751333) significantly associated with hepatitis B viral DNA level suppression in a cohort of chronic hepatitis B patients treated with entecavir. This result suggests that Han Chinese patients with the rs3751333 GG genotype may respond better to entecavir treatment (Yuan et al., 2016). ABCC4 inhibition, when coupled with phosphodiesterase inhibition in human platelets, convincingly impaired the process of platelet aggregation. The clinical implications of this finding shed light on a crucial relationship between ABCC4 transporter function and phosphodiesterases. The data suggests that the cAMP-directed activity of antithrombotic agents can reduce the occurrence of blood clots (Cheepala et al., 2015).

ABCD

The ABCD subfamily comprises four human genes, and ABCD1, ABCD2, ABCD3 encode proteins located in the peroxisome. The ABCD proteins are all half-transporters and, consequently, function as homo- or heterodimers, and two of these (ABCD1, ABCD2) take part in the regulation of very-long-chain fatty acid transport (Dean, 2002).

The mammalian peroxisomal ABC transporters are the adrenoleukodystrophy protein (ALDP/ABCD1), ALDP-related protein (ALDRP/ABCD2), and a 70-kDa peroxisomal membrane protein (PMP70/ABCD3). X-linked adrenoleukodystrophy (X-ALD) is associated with variants in *ABCD1 (Mosser et al., 1993)* . X-ALD is characterized by the accumulation of very long-chain fatty acids in the peroxisome that is an outcome of impaired beta-oxidation. Patients with X-ALD display progressive demyelination of the neurons in the central nervous system, testicular malfunction, and adrenal insufficiency (Smith et al., 1999). ABCD2 may be involved in the metabolic transport of VLCFA's (Morita & Imanaka, 2012). The function of ABCD3 consists of the transportation of branched-chain acyl-CoA into peroxisomes. ABCD4 resides in the mitochondria and the lysosomes. In the lysosomes, ABCD4 is involved in the transport of vitamin B12 from lysosomes into the cytosol. Mutations in *ABCD4* cause an inborn error of vitamin B12 metabolism, resulting in the lysosomes failing to release cobalamin resulting in symptoms mimicking cobalamin deficiency (Kawaguchi & Morita, 2016).

ABCE (OABP) and ABCF (GCN20)

The ABCE and ABCF subfamilies consist of gene products with no TM domain and are not involved in membrane transport functions. They have only ATP-binding domains and no TM domain. The ABCE subfamily has a single member – the oligo-adenylate-binding protein (OABP). This molecule recognizes oligo-adenylate and is produced in response to infection by certain viruses. For example, it interacts with HIV-1 proteins Vif and Gag and the HIV-2 protein GAG. (Dooher & Lingappa, 2004; Zimmerman et al., 2002).

In the ABCF gene family, each gene contains a pair of NBDs. The best-characterized member is the *S. cerevisiae GCN20* gene product that mediates the activation of the eIF-2a kinase (Marton, Vazquez de Aldana, Qiu, Chakraburtty, & Hinnebusch, 1997). The human homolog is named ABCF1 and is associated with the ribosome. It appears to have a similar functional role (Tyzack, Wang, Belsham, & Proud, 2000). ABCF1 was also identified as a new retinal pigment epithelium (RPE) phagocytotic ligand by functional screening assays, where it extrinsically promoted phagocytosis of shed photoreceptor cells by the RPE. This function is essential in the visual cycle because RPE cells are specialized phagocytes that maintain retinal homeostasis and prevent retinal degeneration (Guo et al., 2015). Additional roles of ABCF1 include regulating innate immune response and its role as a risk gene for autoimmune pancreatitis and arthritis. *Abcf1* expression also plays a role in the development of mouse embryos, and its expression in adult animals correlates with actively proliferating and differentiating cell types (Wilcox et al., 2017).

ABCG

The ABCG subfamily consists of six reverse-configured half transporters with a unique structural organization. The NBD is situated at the N-terminal half of the transporter, followed by the TMD. The*white* locus of *Drosophila* is one of the most extensively studied ABC proteins. The white protein (with brown and scarlet) transports precursors of eye pigments (guanine and tryptophan) in the eye cells of the fly (H. Chen et al., 1996). In addition, it can potentially transport biogenic amines, 5-hydroxytryptamine (5-HT), and dopamine that are essential in Drosophila for olfactory learning and memory *(Myers, 2017)* .

The ABCG1 protein in mammals is involved in cholesterol transport regulation (Klucken et al., 2000), and the gene is on chromosome 21q22.3 in humans. ABCG1 is a significant player in cholesterol efflux from macrophages to extracellular lipid acceptors that include high-density lipoprotein (HDL) and phosphatidylcholine (PC) vesicles (Wang, Lan, Chen, Matsuura, & Tall, 2004). In addition, ABCG1 may have a role in T-cell proliferation and provide a protective role for apoptosis in macrophages (Bensinger et al., 2008;

Wojcik, Skaflen, Srinivasan, & Hedrick, 2008).

Other notable ABCG genes are *ABCG2* , which serves as a drug-resistance gene, and *ABCG5* and *ABCG8* , which encode sterols transporters in the intestine and liver. The excretion of sterols in the liver and intestines is facilitated by the ABCG5/ABCG8 heterodimer (G5G8). Specific mutations in G5G8 cause sitosterolemia, a genetic disease characterized by the accumulation of plant sterols and cholesterol, leading to premature atherosclerosis (Lee et al., 2016). A genome-wide association study (GWAS) revealed that a single nucleotide polymorphism, p.D19His in ABCG8, is a susceptibility factor for human gallstone disease (Buch et al., 2007). *Abcg3* is only found in rodents and has an unknown function. The last member of this family, ABCG4, is expressed in the brain, spinal cord, heart, and thymus in humans and the retina. ABCG4 facilitates the efflux of cellular cholesterol to high-density lipoproteins (Wang et al., 2004). Thus, the dual processes of 'gene birth' and 'gene death' are involved in the evolution of ABCG genes. By studying the evolution of these transporters in other vertebrate species, we can facilitate developing animal models for functional and clinical studies (K. Moitra, Silverton, Limpert, Im, & Dean, 2011).

Materials and Methods

Vertebrate ABC genes

Each human or other vertebrate ABC gene was queried in the ENSEMBL data base (ensemble.org). Full-length, partial, and apparently missing genes were recorded for 62 vertebrate ABC genes across 64 vertebrate species (12 primates, five rodents, 21 other mammals, three marsupials, five birds, 13 fish, two reptiles, and one amphibian). Details are in**Supplemental Table** 1.

Functional data for mouse and other organisms

The phenotype of mouse ABC gene alleles was queried in the Mouse Genome Informatics data base (http://www.informatics.jax.org). The gene symbol, phenotype and reference were recorded.

Human genome-wide association loci and rare germline and somatic variation

Genome-wide associations in or near Human ABC genes were queried in the GWAS Catalog (https://www.ebi.ac.uk/gwas). The gene, phenotype, associated SNP, P value, allele frequency and reference were recorded.

Rare human variants were obtained from the gnomAD database (https://gnomad.broadinstitute.org/). The gene, number of synonymous, non-synonymous, loss-of-function variants were recorded and adjusted for the length of the gene in amino acids.

Variation observed in tumor samples was obtained from the COSMIC database (https://cancer.sanger.ac.uk/cosmic). The number of synonymous, non-synonymous, loss-of-function variants were recorded as well as the tissue type that is most frequently mutated.

Results and Discussion

Conservation and gene birth and death across vertebrate species

To comprehensively understand the gene birth and death events for the ABC transporter superfamily invertebrates, we interrogated 62 vertebrate ABC genes across 64 vertebrate species (12 primates, five rodents, 21 other mammals, three marsupials, five birds, 13 fish, two reptiles, and one amphibian). Each gene was examined in the gene tree of the human or representative species in the ENSEMBL database. We noted the appearance of a full-length or partial gene as well as potential missing or duplicated genes. We compared these species against species with formal analyses of the ABC superfamily (human, mouse, zebrafish, and lamprey) (Dean, Rzhetsky, et al., 2001). There are high coverage genomes for 13 species that are likely to provide an accurate gene count (human, chimp, macaque, mouse, rat, dog, opossum, chicken, Xenopus, zebrafish, and fugu). This result provides at least one index species for most of the major orders of primates, rodents, carnivores, marsupials, birds, amphibians, and fish. However, as many of the remaining species have

low-coverage draft genome assemblies, many missing genes are not likely to be gene loss events (Milinkovitch, Helaers, Depiereux, Tzika, & Gabaldon, 2010).

The number of ABC genes in primates is very stable. The *ABCA10*gene is missing from the orangutan, gibbon, and marmoset genomes;*ABCA10* is part of a cluster of five *ABCA5* -related genes that are duplicated head-to-tail on human chromosome 17. The gene loss event converting *ABCC13* into a pseudogene (Annilo & Dean, 2004) appears to be confined to the great apes, as *ABCC13* is intact in all other primates. The bushbaby (*Otolemur garnettii*) genome seems to have an additional *TAP2* /*ABCB3* gene. The predicted amino acid sequences show that the two bushbaby *TAP2* genes are in the same sequence contig. Their amino acid sequences have diverged, consistent with gene duplication. TAP1 and TAP2 play essential roles in antigen presentation, and duplication of *TAP2* also occurs in many fish genomes. This result is of potential interest for the study of the evolution of immunogenetics of primates. In total, all primates contain between 48 and 50 ABC genes.

Rodents have many gene gain and loss events affecting the A, B, and G subfamilies. The *ABCA5* -like cluster contains from three to five genes, and a cluster of *Abca14* , *Abca15* , *Abca16* , and*Abca17* genes (Ban, Sasaki, Sakai, Ueda, & Inagaki, 2005; Z. Q. Chen, Annilo, Shulenin, & Dean, 2004) is present only in the mouse, rat, and squirrel genomes, not in the guinea pig or kangaroo rat. The well-described duplication of the *Abcb1* gene in the mouse and rat genomes is also found in the guinea pig but not in other rodents. The loss of the *ABCC11* gene from the mouse genome extends to all rodents, but *ABCC11* is present in the Lagomorphs (rabbit, pika), indicating that this gene loss is specific to rodents. *Abcg3* is a gene first discovered in the mouse genome closely related to*ABCG2,* a well-described efflux transporter (Mickley et al., 2001). *Abcg3* is only found in rodents, but the rat genome is predicted to have two *Abcg3* genes, and the hamster 4-6 copies.

Further examination of additional rodent genomes shows an *Abcg3*gene present in the prairie vole and up to four copies in the deer mouse genome. The function of Abcg3 is unknown but proposed to be an efflux pump due to its close sequence homology with ABCG2. However, it is exclusively expressed in the spleen and thymus in the mouse, suggesting it has a role in the immune response (Mickley et al., 2001). In addition, the presence of multiple *Abcg3* gene birth events in the rodent lineage suggests that it has an unknown vital function.

There are no other apparent ABC gene death or birth events within other mammalian genomes, and for those mammals with complete genome assemblies, there are 44-54 ABC genes annotated. However, it is difficult to accurately determine the gene counts in the ABCA5 and ABCA14 gene clusters. These clusters contain from 3 to 5 genes in most mammals and pseudogene fragments (Annilo, Chen, Shulenin, & Dean, 2003). Examination of the assemblies in these regions in species with apparently missing genes shows gaps in the assembly. More complete genomes, including long-range sequencing or assembly methods, are needed to resolve these areas. However, we did not search for species for new ABC genes, and there may be yet undiscovered gene birth events.

There has been no previous formal analysis of the ABC gene family for birds, amphibians, or marsupials. The opossum is the index marsupial species with a 7.3x genome coverage and contains 37 predicted full-length and ten partial ABC genes for 47 genes. The opossum appears to be missing *ABCA15* , *16* and *17* , *ABCB5* and*ABCB13* . These same genes were absent from the genomes of other marsupials, the Tasmanian devil, and the wallaby. The frog,*Xenopus tropicalis* , is an amphibian index species with 37 full and four partially predicted genes. There are two predicted*Xenopus ABCB5* genes on separate contigs. An alignment of these sequences shows considerable diversity in well-aligned regions, suggesting that this is an actual duplication. The anole lizard is the one reptile species with a high-density genome assembly (Alfoldi et al., 2011). There are 38 complete and four partial gene annotations for 42 ABC transporters. The lizard and other reptile genomes (snake, turtles, tortoises, tegu lizard, and tuatara) duplicate the *ABCG2* gene.

The chicken is the index bird species and has multiple apparent ABC gene loss events, with the genome lacking *ABCB12* and *ABCB13* ,*ABCD1* , and *ABCF1* . As *ABCD1* and *ABCF1* are very conserved

genes, this is unexpected. *ABCD1* and *ABCD2*are closely related, and a single *ABCD1/2* gene is found in invertebrates. However, fish have both *ABCD1* and *ABCD2*orthologs, suggesting that birds lost the *ABCD1* gene. In the human genome, the *ABCD1* gene is on the X chromosome, and mutations in *ABCD1* are responsible for the severe, often lethal, X-linked recessive disease, adrenoleukodystrophy. ABCD1 is expressed in the peroxisome and adrenoleukodystrophy is a demyelinating disorder, but the functional effect of ABCD1 defects in the disease is not clear.

There have been detailed analyses published of the ABC gene superfamily in zebrafish, carp, catfish, and lamprey (S. Liu, Li, & Liu, 2013; X. Liu et al., 2016; Ren et al., 2015). These studies all document multiple gene birth events in fish, such as duplications of *ABCA1* ,*ABCA4* , *ABCB3* , *ABCB6* , *ABCB11* , *ABCC5* ,*ABCC6* , *ABCG2* , and *ABCG4* . Only the *ABCC6*genes have been studied in detail, with the *Abcc6a* gene shown to be essential and *Abcc6b* expressed in the developing kidney (Li et al., 2010). As fish underwent a whole-genome duplication, the number of genes that have been retained and now carry out new functions is complex. Some duplications are confined to specific species, such as a duplicated *ABCF2* in zebrafish, catfish, and a few other species (S. Liu et al., 2013). Many other examples of lineage-specific duplications and losses in specific fish lineages have been described, and it will require highly accurate genome assemblies to understand the complexity (X. Liu et al., 2016). For example, there are four*ABCG2* -related genes in the zebrafish, and other fish species have complex combinations of these genes, including additional duplications. As a representative of a more primitive fish species, the lamprey has few of the gene duplications seen in jawed fish and has only 34 predicted ABC genes.

In conclusion, the availability of many vertebrate genome assemblies allows a more detailed analysis of the evolution of ABC transporters. There have been dynamic changes in the gene number in each of the seven common subfamilies, with the most dramatic changes in the A, B, and G subfamilies. Because ABC proteins can carry out a wide variety of transport functions, it is likely that individual lineages of species, and even specific animals, would develop specific transporters for highly specialized functions, probably due to environmental pressure. It is also apparent within the phylogenetic trees of individual genes that considerable diversification has taken place. As even a single amino acid change can alter the substrate specificity of an ABC transporter, the true diversity of substrates is enormous. One of the most diversified sets of genes is the multi-specific transporters ABCB1/PGP and ABCG2. This finding is consistent with an essential role for these pumps in xenobiotic elimination and maintenance of tissue barriers in the brain, intestine, and placenta. *ABCB1* has independently duplicated in several species such as certain rodents, the cow, and fish. Even more dramatic are the duplications of *ABCG2* that have taken place in fish species. As fish live in highly diverse aquatic environments, they are exposed internally and externally to an aqueous environment. Therefore, it is not surprising that they need to excrete many environmental toxins and protect internal organs from xenobiotics. For some gene clusters, particularly the *ABCA5* and *ABCA14*clusters, these genes are challenging to assemble, as the genes are large and closely related. Therefore, the complete annotation will require complete draft genome assemblies.

One of the most intriguing ABC gene subfamilies is the ABCH family. Initially identified in *Drosophila* and *Dictyostelium* , ABCH genes are half transporters, with an N-terminal NBD, the same structure as the ABCG genes. Invertebrates, the ABCH genes are only found in fish. There is a single ABCH1 in most fish species and the coelacanth, but the gene is missing from lamprey and other fish species (Jeong et al., 2015). A function in lipid transport has been described for an ABCH gene (LmABCH-9C) in the locust, *Locusta migratoria* (Yu et al., 2017). Still, to date, there is no functional information on this gene group in vertebrates.

Functional data in the mouse and other model organisms

As nearly all human ABC genes have a one-to-one ortholog in the mouse genome, murine knockouts and other modified alleles represent an excellent source of functional information in animal models for ABC gene diseases. Mutant alleles have been generated for all murine ABC genes allowing for phenotypic screens. Specific phenotypes are reported for 46 of the 53 murine ABC genes (**Table 2**). The reported phenotypes for mouse ABC genes are highly diverse. They include abnormal lipid, cholesterol, and glucose levels,

development of specific organ systems such as the eye, adrenal gland, lung, liver, thyroid, male reproductive tract, heart, spleen, thymus, arteries, lymphocytes, and brain. In mice, disruption (homozygous knockout) of the *Abca3* , *Abcb7* ,*Abcb10* , *Abce1* , and *Abcf1* genes results in embryonic lethality, and *Cftr* /*Abcc7* , *Abcc9* , and the*trac* allele in *Abcg5* are associated with premature lethality (Chase et al., 2010).

Many mouse ABC gene alleles recapitulate features of human Mendelian disorders or known human ABC gene function. *ABCA1* mutations in humans cause Tangier disease characterized by the defective formation of HDL particles, and *Abca1* $^{-/-}$ mice also have HDL deficiency. ABCA3 transports lipids into the lung's lamellar bodies, and mutations cause severe neonatal lung surfactant deficiency;*Abca3* $^{-/-}$ mice have abnormal lung development and morphology. ABCA4 flips retinoid-lipid complexes in photoreceptor disks (Molday, Zhong, & Quazi, 2009). *ABCA4* mutations cause Stargardt disease and related maculopathies, characterized by excessive lipofuscin (A2E) accumulation (Allikmets et al., 1997).*Abca4* $^{-/-}$ mice also accumulate lipofuscin/A2E, have abnormal dark adaptation, and thinning of the outer nuclear layer (Mata et al., 2001). *ABCA12* is expressed in the lamellar granules of the skin, and mutations cause two forms of recessive congenital ichthyosis (Kelsell et al., 2005; Lefevre et al., 2003).*Abca12* $^{-/-}$ mice also have abnormal scaly skin. Interestingly, *Abca12* $^{-/-}$ mice also have lung surfactant deficiency, lamellar body abnormalities, and alveolar collapse, demonstrating an essential function in lipid transport in the mouse lung.

ABCB1 encodes P-glycoprotein, an efflux transporter found overexpressed in many chemotherapy multidrug-resistant tumor cell lines and plays a vital role in eliminating xenobiotics.*ABCB1* $^{-/-}$ collie dogs have sensitivity to ivermectin toxicity (Mealey, Bentjen, Gay, & Cantor, 2001), and*Abcb1a* /*Abcb1b* $^{-/-}$ mice have an abnormal distribution of compounds in the brain (Mason, Pariante, & Thomas, 2008). The TAP1 and TAP2 proteins (ABCB2 and ABCB3) together form a transporter for peptides subsequently loaded onto class I HLA molecules, and mutations in either gene cause immunodeficiency in humans, abnormal T cell levels, and antigen presentation in the mouse (de la Salle et al., 1994; Van Kaer, Ashton-Rickardt, Ploegh, & Tonegawa, 1992). ABCB4 transports phospholipids in bile and protein defects lead to recessive intrahepatic cholestasis in both humans and mice.*Abcb4* $^{-/-}$ mice also have extensive bone developmental abnormalities (Dixon et al., 2000; Hochrath et al., 2013).

ABCC2 transports organic anions, including bile salts, and recessive mutations cause Dubin-Johnson syndrome, a hereditary hyperbilirubinemia (Wada et al., 1998). A rat model, the TR rat, and*Abcc2* $^{-/-}$ mice have abnormal liver weight and physiology, bile secretion, and composition (Vlaming et al., 2006).*ABCC6* mutations cause pseudoxanthoma elasticum, a calcification disorder, and ABCC6 facilitates the release of nucleoside triphosphates, the source of pyrophosphate, and inhibitor of calcification (Bergen et al., 2000; Jansen et al., 2013; Le Saux et al., 2000; K. Moitra et al., 2017). Mouse *Abcc6* $^{-/-}$ mice have abnormal skin calcification and morphology (Gorgels et al., 2005). CFTR/ABCC7 encodes a chloride ion channel that plays a crucial role in exocrine secretion in the lung, intestine, pancreas, vas deferens, and skin, and recessive mutations cause cystic fibrosis (Anguiano et al., 1992; Quinton, 1999). Multiple *Cftr* mutations on different mouse backgrounds recapitulate nearly all the features of the human disease (O'Neal et al., 1993; Zeiher et al., 1995). ABCC8 and ABCC9 encode the sulfonylurea receptors SUR and SUR2, and mutations in ABCC8 (Chutkow et al., 2001) in humans cause non-insulin-dependent diabetes (Thomas et al., 1995). Knockouts of either *Abcc8* or *Abcc9* cause hypoglycemia and insulin abnormalities, and *Abcc9* $^{-/-}$ mice also die prematurely (Chutkow et al., 2001; Seghers, Nakazaki, DeMayo, Aguilar-Bryan, & Bryan, 2000).

ABCD1 mutations in humans cause the X-linked adrenoleukodystrophy; *Abcd1* $^{-/-}$ mice display abnormal myelination, brain cell morphology, astrocytosis, axon degeneration, and impaired coordination. Interestingly,*Abcd2* $^{-/-}$ mice manifest neuronal and axon degeneration, ataxia, hyperactivity, tremors, abnormal microglial cell morphology, posture, and coordination, suggesting that this protein also functions in the brain (Ferrer et al., 2005). A family with a bile acid synthesis defect and peroxisomal abnormalities displayed mutations in ABCD3(?). In addition, *Abcd3* $^{-/-}$ mice display increased liver size, abnormal peroxisomes, and a deficit in mature C24 bile acids (Ferdinandusse et al., 2015). ABCG2 is a uric acid transporter, and common variants in the *ABCG2* gene are associated with gout, a disorder of blood uric acid levels (Dehghan et al., 2008).*Abcg2* $^{-/-}$ mice display sensitivity to phytotoxins and increased blood and urine uric acid (Ichida

et al., 2012; Jonker et al., 2002). The *ABCG5* and *ABCG8* genes encode half-transporters that function as a heterodimer and transport phytosterols. Mutations in these genes cause recessive sitosterolemia in humans and abnormal blood lipid and cholesterol levels in the mouse (Chase et al., 2010; Klett et al., 2004).

Many mouse ABC gene mutations are associated with phenotypes likely to be caused by a defect in cellular transport or provide clues to human gene function. For example, the human *ABCA2* gene is highly expressed in the brain and closely related to the known lipid transporters ABCA1, ABCA3, and ABCA4. Disruption of the mouse*Abca2* gene leads to multiple behavioral and neurological phenotypes and decreased body weight (Sakai et al., 2007). ABCA7 is also a lipid transporter, and mouse *Abca7* disruption mice exhibit reduced HDL cholesterol, adipose tissue, and kidney size (Kim et al., 2005). There is an *ABCA5* -related gene cluster in all mammals, but the function of these genes is unknown.*Abca5* $^{-/-}$ mice display abnormal liver morphology and physiology and develop an adult lethal dilated cardiomyopathy-like heart phenotype. The protein locates primarily in the lysosomes (Kubo et al., 2005). *Abca6* knockout mice display decreased circulating serum albumin, decreased total protein, and increased hematocrit.*Abca8b* $^{-/-}$ mice show diminished cholesterol, HDL cholesterol, LDL cholesterol, and triglyceride levels, and humans with*ABCA8* mutations and low HDL cholesterol have been described (Trigueros-Motos et al., 2017). Expression of the *Abca9* gene is principally in the brain (Piehler, Kaminski, Wenzel, Langmann, & Schmitz, 2002).

The human *ABCG1* and *ABCG4* genes are evolutionarily related to each other and the sterol transporters ABCG5 and ABCG8, but their function in humans is unknown. The mouse *Abcg1* knockout results in the accumulation of neutral lipids and phospholipids in hepatocytes and macrophages and plays a role in loading cholesterol onto HDL particles (Kennedy et al., 2005). Loss of *Abcg1* can affect the immune function of macrophages (Wojcik et al., 2008). *ABCG4* is highly expressed in the brain, and the *Abcg4* $^{-/-}$mouse has abnormal sterol efflux in the brain (Annilo et al., 2001; Wang et al., 2008).

Several ABCB family half transporters proteins localize to the mitochondria, and their functions were elucidated from mouse models. In*Abcb6* $^{-/-}$ mice, the gene is expressed in the mitochondria and transport coproporphyrin III into the mitochondria (Ulrich et al., 2012). The ABCB8 protein localizes to the mitochondria, and *Abcb8* disruption leads to defects in mitochondrial iron export, cytosolic Fe/S protein levels, and cardiomyopathy (Ichikawa et al., 2012). In addition, disruption of Abcb10 leads to a lack of heme biosynthesis and erythropoiesis (Yamamoto et al., 2014).

In summary, for nearly all the human ABC genes causing Mendelian disorders, the mouse knockout strains recapitulate one or more phenotypes and serve as valuable models for further studies and development of therapeutics. In addition, the disruption of mouse ABC genes of unknown function has ascribed multiple cellular transport properties to several transporters, leading to extensive new knowledge on the full spectrum of ABC transporter efflux properties.

GWAS loci in or near ABC genes

Genome-wide association studies (GWAS) entail the genotyping of large numbers of single nucleotide polymorphisms (SNP) and individuals with (cases) and without (controls) for a specific genetic disease or phenotype. By applying conservative statistical correction and replication in additional datasets, many loci in the human genome are associated with a wide range of conditions. Most GWAS loci are in non-coding regions of the genome and often affect the expression of nearby genes (Visscher et al., 2017). To identify common variants in or near ABC genes that may provide insight into their function, we searched the GWAS catalog, as well as the publicly available data from the UK Biobank study (**Table 3**).

There are several GWAS loci associated with levels of known substrates of ABC transporter genes. The *ABCA1* gene is the cause of the recessive Tangier disease, a disorder of cholesterol transport to ApoA1 molecules. An SNP in an intron of *ABCA1* , rs1883025, is highly associated ($<10^{-50}$) in multiple studies with HDL and total cholesterol levels and to a lesser extent with triglyceride levels and metabolic syndrome (Spracklen et al., 2017; Willer et al., 2013). However, neither this SNP nor the closely linked rs2575876 are eQTLs for *ABCA1* , and both have low regulomeDB scores, so the specific mechanism of action of this locus is unclear. Several studies link the *ABCB4* gene (a bile acid transporter) to gallstone disease and gallbladder

cancer, as well as cholesterol levels (Ferkingstad et al., 2018; Mhatre et al., 2017). The lead SNP for the gallstone association of *ABCB4* , rs4148808, is in a large LD block in the gene's promoter, with multiple predicted protein binding sites. Several GWAS studies for gout and uric acid levels identified associations in the *ABCG2* gene in diverse populations (Dehghan et al., 2008; Woodward et al., 2009). The association peaks are inside the*ABCG2* gene and contain common functional missense and stop-codon variants (Q141K, Q126X) in the gene (Ichida, 2009; Matsuo et al., 2009; Woodward et al., 2009). The *ABCG5* and *ABCG8* genes are closely linked in a head-to-head arrangement. The rs6756629 SNP in an*ABCG8* intron is associated with cholesterol levels and gallstone disease. This SNP is in a block of polymorphisms that includes variants with high regulomeDB scores for adipose tissues.

Several additional GWAS loci near ABC genes involve plausible substrates. For example, the rs2062541 SNP in the *ABCC1* gene is associated with blood carnitine levels (Shin et al., 2014) and N-acetylcarnosine levels. Response to the irinotecan chemotherapy drug is associated with loci near *ABCC4* (Han et al., 2014). A locus in the *ABCA6* gene is associated with LDL cholesterol levels and a locus in *ABCA8* with HDL cholesterol (Surakka et al., 2015; Willer et al., 2013). Therefore, several phenotypes associated with variants in and near multiple ABC genes could be the basis for further functional follow-up studies.

The spectrum of rare variation in humans

Through interrogation of the gnomAD database (Karczewski, 2019) of publicly available exome and whole genome sequence, the number of synonymous (SYN), non-synonymous (NS), and loss-of-function (LOF) variants were tabulated (**Figure 1, Supplemental Table 2**). In addition, we determined the number of individuals homozygous for LOF variants and adjusted for gene size. The frequency of NS and LOF variants varies widely by gene. Therefore, this data can provide information on how essential a gene is by lower-than-expected levels of LOF mutations, rate of LOF variants per gene, and the ratio of NS/SYN variants. As expected, the essential, X-linked genes (*ABCD1* ,*ABCB7*) and the essential *ABCA3* and *ABCE1* genes all have no or a deficient level of LOF variants and a low to very low ratio of NS/SYN variants.

Interestingly the *ABCA2* , *ABCB1* , *ABCC5* , and*ABCG1* also have low levels of LOF variants, suggesting that they do not tolerate loss-of-function. Genes with a higher rate of NS and LOF variants include *ABCC7/CFTR* and *ABCG2* . Several groups have proposed a heterozygous advantage for LOF alleles of CFTR to account for the high frequency of cystic fibrosis mutations in multiple populations (Angelicheva et al., 1994; Bosch et al., 2017; Prince, 1998). Furthermore, the increased blood uric acid levels in *ABCG2* mutant carriers may also have a selective advantage against infectious diseases.

Analysis of specific predicted LOF mutations showed that all the cytoplasmic ABC genes (*ABCE1* , *ABCF1* , *ABCF2* , and*ABCF3*) have no reported homozygotes for LOF mutations, suggesting that they are essential. Similarly, almost all the half transporters (except for *ABCB6* and *ABCG2*) also have no homozygous LOF individuals (**Supplemental Table 2**). In contrast, nearly half (46%) of all ABC full-transporters have at least 1 LOF allele reported to be homozygous in at least one individual (**Figure 2**). Interestingly some predicted LOF variants are frequent, including in some specific populations. For example, several genes in the *ABCA5* gene cluster (*ABCA6* , *ABCA8* ,*ABCA10*) have common LOF alleles in Latin American and African populations. *ABCA7* , *ABCA13* , *ABCB5* , *ABCC11* , and *ABCC12* also have specific common predicted LOF variants. Some of the predicted LOF alleles are in splice sites, and it may be that they can produce a functional protein by alternative splicing.

Somatic mutations in cancer

Many ABC genes are efflux transporters involved in the resistance to multiple chemotherapy drugs. However, there are no ABC transporters amongst the 299 documented frequently mutated genes, or driver genes, in cancer (Bailey et al., 2018). Therefore, to determine the potential role of somatic mutations in ABC genes in cancer, we tabulated the number and class of modifications along with the rate of gene amplification, overexpression, or gene fusion (**Supplementary Table 3**).

Nearly all ABC genes have low levels of somatic mutations and no observed gene fusions. The most frequently

mutated ABC gene in cancer is*ABCA13* , but this is a large gene with low expression and late replication timing. However, neither *ABCA13* nor any other ABC gene passes the criteria for a significantly mutated gene in cancer. Common recurrent missense mutations are found in many oncogenes and are usually associated with a gain of function. There are a few common recurrent mutations such as p.R1476Q in *ABCA5* , p.S422F in*ABCC7/CFTR* , and p.S606P and p.G608D in *ABCD1* . The*ABCD1* mutations are found primarily in lung cancer and the conserved LSGG motif in the ATP-binding domain. This data suggests that ABCD1 may play a role in a subset of lung malignancies.

Several ABC genes have frequent copy number gains (>10%) in specific cancers. The amplifications include *ABCB10* in liver cancer, *ABCC4* in colon cancer, *ABCC9* in testicular cancer, and *ABCC5* and *ABCF3* in cervical cancer. The role of these events in these cancers is unknown, although *ABCF3* is overexpressed in cervical cancer (Choi et al., 2007). In addition, there is an elevated expression of many ABC genes >30% of specific tumors. For example, *ABCA7* and *ABCC8* expressed are high in 33% of adrenal tumors, *ABCC5* in 45% of esophageal cancers, and *ABCF3* in 45% of cervical cancers. Whether these over-expressed genes contribute to drug resistance or other phenotypes of these cancers remains undetermined.

Conclusions

Analysis of the presence or absence of a gene in the ABC transporter superfamily across vertebrates demonstrates a tremendous diversity in potential efflux functions. Nearly all the ABC genes have been disrupted in the mouse, and most display a phenotype, often including lipid and cholesterol transport, blood chemistry, developmental or neurological abnormalities, or lethality. Several polymorphisms in or near human ABC genes are genome-wide associated with either known important human traits or new phenotypes. For example, there is an association of polymorphisms in the *ABCA5* gene cluster with HDL- and LDL-cholesterol levels providing strong evidence that one or more genes in this locus are essential for cholesterol homeostasis. Somatic mutations in ABC transporters do not seem to be a significant mechanism of carcinogenesis; however, several genes are amplified or overexpressed in specific tumor types, suggesting future research areas. Finally, several ABC genes have deficient levels of loss-of-function mutation and are likely to be essential genes. In contrast, at least three genes (*CFTR* , *ABCG2* , and *ABCG8*) have an apparent excess of non-synonymous or loss-of-function mutations. Future genomic, genetic, and functional studies of these transporters across vertebrate species will likely yield important new insights into biology and disease.

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Table 1. ABC genes and Mendelian disease

Symbol	**Location**	**Mendelian disease**	**OMIM**
ABCA1	09q31.1	Tangier Disease	205400
		HDL deficiency, type 2	604091
ABCA2	09q34.3		
ABCA3	16p13.3	Neonatal respiratory failure	610921
ABCA4	01p21.3	Stargardt Disease	248200
		Cone-rod dystrophy 3	604116
		Retinitis pigmentosa 19	601718
ABCA5	17q24.3	Hypertrichosis	135400
ABCA6	17q24.3		
ABCA7	19p13.3		
ABCA8	17q24.3		
ABCA9	17q24.3		
ABCA10	17q24.3		
ABCA12	02q34	Ichthyosis, autosomal recessive	242500, 601277
ABCA13	07p12.3		
ABCB1	07q21.12		
ABCB2	06p21	Bare lymphocyte syndrome	604571
ABCB3	06p21	Bare lymphocyte syndrome	604571
ABCB4	07q21.12	Cholestasis, intrahepatic	171060, 171060
ABCB5	07p21.1		
ABCB6	02q35	Dyschromatosis universalis	605452
		Microphthalmia, isolated, with coloboma	614497
		Lan Blood group	605452
ABCB7	Xq21-22	Anemia, sideroblastic, with ataxia	301310
ABCB8	07q36.1		
ABCB9	12q24.31		
ABCB10	01q42.13		
ABCB11	02q24.3	Hepatic cholestasis	605479, 601847
ABCC1	16p13.12		
ABCC2	10q24.2	Dubin-Johnson syndrome	237500
ABCC3	17q21.33		
ABCC4	13q32.1		
ABCC5	03q27.1		
ABCC6	16p13.12	Pseudoxanthoma elasticum	264800
		Arterial calcification in infancy	614473
ABCC7	07q31.31	Cystic fibrosis	219700
		CBAVD	277180
ABCC8	11p15.1	Diabetes mellitus, permanent neonatal	606176, 610374
		Hyperinsulinemic hypoglycemia,	256450, 240800
ABCC9	12p12.1	Hypertrichotic osteochondrodysplasia	239850

Symbol	Location	Mendelian disease	OMIM
		Cardiomyopathy, dilated, 10	608569
ABCC10	06p21.1		
ABCC11	16q12.1	Earwax, (wet/dry), colostrum secretion, odor	117800
ABCC12	16q12.1		
ABCD1	Xq28	Adrenoleukodystrophy	300100
ABCD2	12q11		
ABCD3	01p22.1	Bile acid synthesis defect, congenital, 5	616278
ABCD4	14q24.3	Methylmalonic aciduria and homocystinuria, cblJ type	603214
ABCE1	04q31.31		
ABCF1	06p21.1		
ABCF2	07q36.1		
ABCF3	03q27.1		
ABCG1	21q22.3		
ABCG2	04q22	Junior blood group system, Gout	614490
ABCG4	11q23		
ABCG5	02p21	Sitosterolemia	210250
ABCG8	02p21	Sitosterolemia	210250

Table 2.

Symbol	Phenotype
Abca1	HDL deficiency, foam cell accumulation
	HDL cholesterol levels
Abca2	Multiple behavioral/neurological phenotypes
	Decreased body weight
Abca3	Abnormal lung development, morphology
Abca4	Abnormal dark adaptation, photoreceptor morphology and degeneration
	Vertebral fusion, respiratory quotient
Abca5	Abnormal liver morphology and physiology
	Tremors, cardiomyopathy, absent thyroid gland, decreased thyroid activity
Abca6	Decreased circulating serum albumin, decreased total protein and increased hematocrit
Abca7	Decreased HDL cholesterol, adipose tissue, kidney size
Abca8a	nd
Abca8b	Decreased cholesterol, HDL cholesterol, LDL cholesterol, and triglyceride levels
	Abnormal eye morphology
Abca9	Abnormal behavioral response to light
Abca12	Reddish, scaly, abnormal, tight skin
	Dehydration, no suckling reflex
	Surfactant deficiency, lamellar body, alveolar collapse
Abca13	Abnormal male genitalia morphology, decrease blood urea nitrogen level
Abca14	Decreased total body fat amount
Abca15	nd
Abca16	nd
Abca17	Decreased circulating potassium level
Abcb1a	Abnormal intestinal epithelium and ulcers, colitis
	Xenobiotic sensitity
	Hippocampal neuronal degeneration, tremors, catapsy

Symbol	Phenotype
	Abnormal immunoglobulin and T cell levels
Abcb1b	Abnormal xenobiotic sensitivity
Tap1/Abcb2	Abnormal T cell levels, antigen presentation
Tap2/Abcb3	Abnormal T cell levels, antigen presentation
Abcb4	Abnormal bile secretion, bile salt level, gallstones
	Decreased bone mineral density and morphology, calcium level
	Liver cirrhosis,
Abcb5	Abnormal cornea and retina morphology
Abcb6	Abnormal erythropoiesis, mitochondrial physiology
Abcb7	Prenatal, postnatal lethality, hemorrhage, liver morphology
Abcb8	Abnormal heart morphology, weight, cardiac output, cardiomyopathy, heart iron levels
Abcb9	Small adrenal glands
Abcb10	Embryonic lethal, oxidative stress, abnormal mitochondrial physiology
Abcb11	Abnormal bile secretion, bile salt level, enlarged liver, cholestasis
Abcc1	Increased sensitivity to xenobiotics
	Decreased inflammatory response, mast cell physiology
Abcc2	Abnormal liver weight and physiology, bile secretion and composition
	Increased sensitivity to xenobiotics
Abcc3	Abnormal bile salt and bilirubin levels, bile salt homeostasis
	Abnormal xenobiotic pharmacology
Abcc4	Abnormal intestinal morphology, mucosa morphology and inflammation
	Small spleen, thymus cortex hypoplasia
	Abnormal blood-brain barrier function
Abcc5	Decreased circulating glucose level
	Decreased circulating eosinophils, leukocyte and lymphocytes
	Limb grasping
Abcc6	Calcified arteries and retina, calcified skin, decreased HDL levels
	Abnormal vibrissa follicle morphology
Cftr/Abcc7	Abnormal intestinal development, lacrimal gland atrophy, pancreatic atrophy,
	Postnatal lethality
	Impaired fertilization, azoospermia, decreased litter size and sexual maturation
Abcc8	Hypoglycemia, abnormal insulin secretion, circulating glucose
Abcc9	Premature death
	Hypoglycemia, increased insulin sensitivity
	Hypertension
Abcc10	Decreased and abnormal spleen, decreased leukocytes and bone marrow cells, and body weight
	Thymus cortex hypoplasia
Abcc12	nd
Abcd1	Abnormal myelination, brain cell morphology, astrocytosis, axon degeneration, impaired coordination
	Cataract
	Increased fatty acid, levels, lipid homeostasis
	Abnormal adrenal cortex morphology
Abcd2	Neuronal and axon degeneration, ataxia, hyperactivity, tremors, microglial cell morphology, posture, coordina
Abcd3	Enlarged liver, abnormal bile composition
Abcd4	Abnormal startle reflex, response to tactile stimulation, new environment
Abce1	Compete embryonic lethal
Abcf1	Embryonic lethality prior to jax.organogenesis
Abcf2	nd
Abcf3	nd
Abcg1	Abnormal blood cell levels, macrophage physiology, cytokine secretion

Symbol	Phenotype
	Hypoglycemia
	Hyperactivity, increased energy expenditure
Abcg2	Increased blood and urine uric acid,
	Abnormal mitochondria morphology and ox phos, porphyria
Abcg3	nd
Abcg4	Abnormal lipid level
Abcg5	Premature death at 4-6 months
	Abnormal lipid levels, bile secretion
	Male and female infertility
Abcg8	Decreased cholesterol levels, circulating triglyceride levels

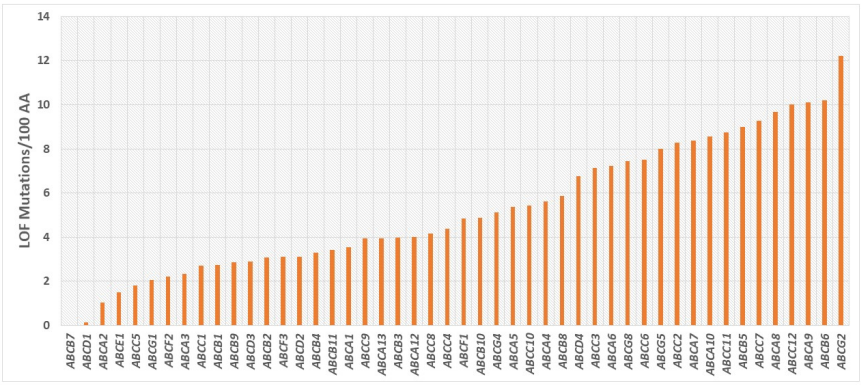
Available phenotype data from the Mouse Genome Informatics Database (MGI) http://www.informatics.jax.org is shown. nd-not determined.

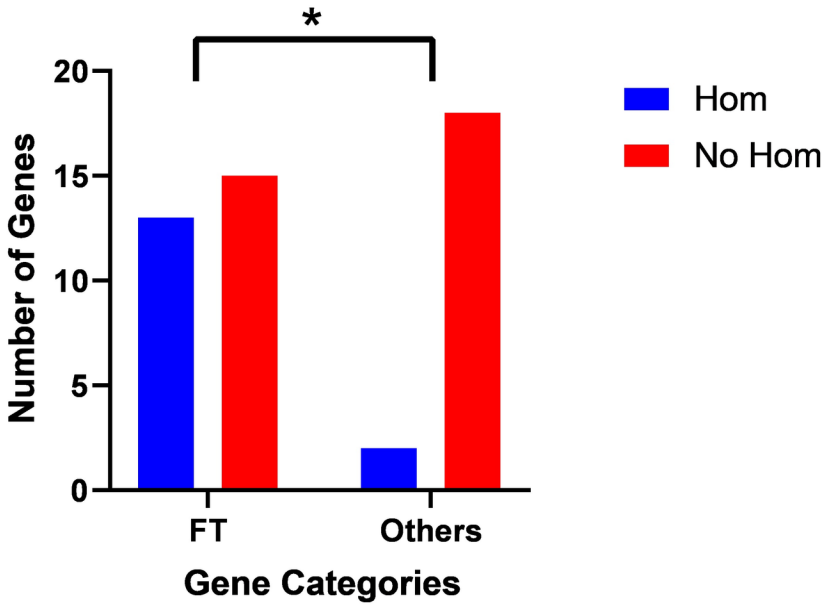
Figure Legends

Figure 1. Rate of loss-of-function mutations . The number of loss-of-function mutations in the gnomAD database of exome and whole-genome sequences is shown. The values are adjusted for gene size. The ABCB7 and ABCD1 genes are on the X-chromosome.

Figure 2. Genes with individuals homozygous for loss-of-function mutations. The number of full-transporters (FT) with at least one individual with loss-of-function mutations is shown to that of other genes (half-transporters and cytoplasmic). * P-value less than 0.05 (Actual P-value 0.012).

Figure 1.





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