

Review

# ABC transporters: human disease and pharmacotherapeutic potential

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**Adenosine triphosphate (ATP)-binding cassette (ABC) transporters are a 48-member superfamily of membrane proteins that actively transport a variety of biological substrates across lipid membranes. Their functional diversity defines an expansive involvement in myriad aspects of human biology. At least 21 ABC transporters underlie rare monogenic disorders, with even more implicated in the predisposition to and symptomology of common and complex diseases. Such broad (patho)physiological relevance places this class of proteins at the intersection of disease causation and therapeutic potential, underlining them as promising targets for drug discovery, as exemplified by the transformative CFTR (ABCC7) modulator therapies for cystic fibrosis. This review will explore the growing relevance of ABC transporters to human disease and their potential as small-molecule drug targets.**

## ABC transporters: biological relevance

Adenosine triphosphate (ATP)-binding cassette (ABC) transporters are a large, phylogenetically conserved gene family (n=48) with broad physiological and pathological relevance [1,2]. In humans, they are expressed throughout the body and transport a diverse range of substrates across lipid membranes, including ions, lipids [2,3]. As such, ABC transporters are critical to a number of biological functions, including bile secretion, [4,5]  $\beta$ -oxidation, [6] and reverse cholesterol transport (RCT) [5]. Highlighting their importance, mutations in ABC transporter genes can cause or contribute to an array of diseases involving many different tissues. To date, 21 ABC transporters have been associated with monogenic disorders [2] with large genomic datasets and mechanistic studies identifying additional associations with more common and **complex disease** states (see [Glossary](#)), including Alzheimer's disease (AD) and coronary artery disease (CAD) [4]. At present, the cystic fibrosis transmembrane conductance regulator (CFTR [ABCC7]) is the only ABC transporter targeted by an approved drug, which is for the treatment of cystic fibrosis (CF) [2,3]. These CFTR-targeted pharmacological compounds can directly address the underlying genetic CFTR defects driving CF and re-establish chloride transport to dramatically improve pulmonary function [1]. Deepening understanding of the molecular mechanisms of action of these transformative therapies has illuminated the broader potential of this protein class as pharmacotherapeutic targets. Notably, recently published studies have demonstrated the ability of CFTR modulators, in addition to other pharmacological agents, to rescue and/or enhance the expression and function of other ABC transporters [1,7]. Thus, a growing awareness of ABC transporter pathophysiological salience, together with the ability of small-molecule compounds to modulate transporter function, has opened the door for the development of potential new first-in-class drugs that engage biologically rationalized ABC transporters for the treatment of human disease. Here we provide an updated summary of the ABC transporter literature as it pertains to their relevance to human disease and potential as pharmacotherapeutic targets. Furthermore, based on emerging understanding of ABC transporter structure and chemistry, we highlight the value of a class-based approach to drug discovery that leverages

## Highlights

ABC transporters are a 48-member superfamily of membrane proteins that move substrates across lipid membranes and have broad biological relevance based on tissue distribution and substrate specificity.

21 ABC transporters are known etiological drivers of rare monogenic disorders, most of which lack disease-modifying therapies; they are also genetically or mechanistically associated with susceptibility to more common and complex diseases.

CFTR (ABCC7) 2mutation causes cystic fibrosis, which is effectively treated with small molecule positive functional modulators that rescue CFTR dysfunction, offering proof of principle for the druggability of ABC transporters for the treatment of other diseases.

The relevance of ABC transporters to human disease and their amenability to drug discovery and development highlights their potential for the development of first-in-class therapeutics.

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understanding across all ABC transporters to drive the identification and optimization of novel drug-like molecules (Figure 1, Key figure).

### ABC transporter structure and function

ABC transporters are transmembrane, ATP-binding proteins that use the energy released during ATP hydrolysis to move substrates from one side of a lipid membrane to the other [2,4]. Overall, human ABC transporters are localized to the plasma membrane and export substrates from the cytoplasm; however, a subset of transporters are localized to specialized substructures, including peroxisomes, lysosomes, photoreceptor disc membranes, and mitochondria (see Table S1 in the supplemental information online) [3,8,9]. Generally, each ABC transporter protein is encoded by a single gene and has 2 nonidentical transmembrane (TM) and 2 nucleotide-binding (NB) domains [4]. These are called full transporters [3]. Other ABC transporters, called half transporters, are encoded by genes containing only one TM-NB unit and so must homo- or hetero-dimerize with another half transporter to form a functional protein [1,3,4,10]. TM domains (TMDs), which contain 6 TM  $\alpha$ -helices, are typically the site of substrate binding [1,3,4] and vary considerably in sequence to define substrate specificity [3,4]. By contrast, the structure and sequence of the NB domains (NBDs), which bind and hydrolyze ATP, is highly conserved [1,3,4,10]. ATP hydrolysis induces a conformational change in NBDs, which is transmitted to the TMDs to induce substrate transport (Box 1) [3,4,11].

ABC transporters are grouped into 7 families, ABCA through ABCG, based on sequence and structural homology [3,4]. Critically, many ABC transporter structures have been resolved to atomic resolution, significantly advancing a mechanistic understanding of this protein class and increasing their tractability for drug development (Table S1). Overall, the structural and functional biology of ABC transporters is well established and comprehensively reviewed [3,8,9,12–18]. This article will address on the roles of ABC transporters in human disease—largely focusing on ABC transporters with data supporting the potential for pharmacological correction—and how knowledge of underlying disease mechanisms can be harnessed for the development of transformative therapeutics that directly address ABC transporter dysfunction.

### ABC transporter mutations as drivers of monogenic disease

To date, 21 ABC transporters have been identified as etiological drivers of rare **monogenic disease** (i.e., with a Mendelian inheritance pattern) (Table 1). In such instances, rare mutations that grossly impact protein function give rise to disease states linked to the underlying gene's expression, localization, function, and/or substrate specificity (Table S1) [4,19]. While severe mutations that lead to complete loss of protein function (e.g., nonsense, frameshift, and structural mutations) are more recognizable as causes of disease, missense mutations, which account for many pathogenic mutations, can vary in mechanism and functional impact. Investigating and understanding pathogenic missense mutations is required to clarify their salience to disease presentation. As such, a deep understanding of the mutational landscape of a disease is critical for enabling the development of targeted precision therapies. However, based on a handful of characterized disorders, including CF, progressive familial intrahepatic cholestasis 2 (PFIC2), and Stargardt disease (STGD), there is a mechanistic commonality to pathogenic ABC transporter missense mutations, principally their impact on protein folding, leading to endoplasmic reticulum (ER) degradation (i.e., trafficking defects), or protein function, which leads to decreased substrate transport (i.e., transport defects). Small-molecule compounds have been identified that can rescue either reduced expression (through protein stabilization) or diminished function (through transport potentiation). This underscores the importance of a deep understanding of the molecular genetics of ABC transporter monogenic disease, both in terms of enabling diagnosis and ensuring the development of the most mechanistically relevant compounds.

### Glossary

**Complex disease:** a human disorder not exclusively defined by a single gene and for which many known or unknown genetic and environmental factors define susceptibility, onset, and severity

**Corrector:** a positive functional modulator that stabilizes ABC transporter protein folding in the ER to increase functional protein expression of trafficking mutants or wild-type protein

**Monogenic disease:** a human disorder, normally rare, in which mutations in a single gene are both necessary and sufficient for disease manifestation

**Positive functional modulator:** a small-molecule compound that enhances the function of an ABC transporter through any one of a number of mechanisms

**Potentiator:** a positive functional modulator that augments the function of a mutant or wild-type ABC transporter to increase substrate transport

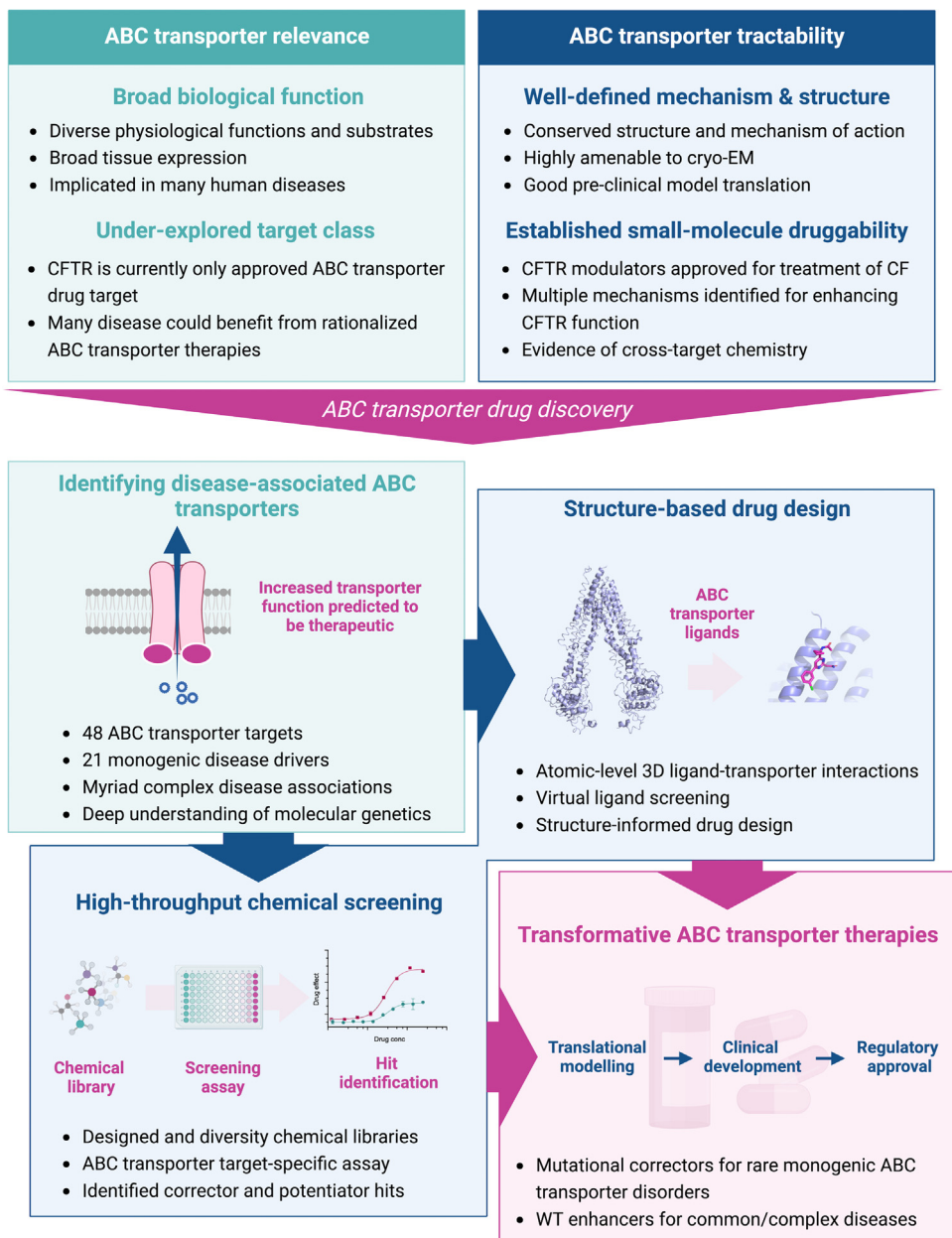
**Structure-based drug design:** a drug discovery approach that leverages atomic-resolution structures of drug targets to predict and inform the rational development of small-molecule therapies

**Trafficking mutation:** a genetic mutation (normally missense) that results in energetic instability during protein folding, leading to ER-associated degradation, preventing the protein from reaching its target membrane

**Transport mutation:** a genetic mutation (normally missense) in membrane transporters that results in impaired substrate movement across the membrane

**Key figure**

A drug discovery path towards transformative ABC transporter therapies



**Trends in Molecular Medicine**

(See figure legend at the bottom of the next page.)

**Box 1. ABC transporter functional mechanisms are not precisely known**

The exact mechanism by which ABC transporters move substrates across membranes is not yet fully understood, [3] but there are three models hypothesized [4]. Given their diversity, there may be no one unifying model for all transporters. However, greater insight into these mechanisms in specific ABC transporter-associated diseases will be invaluable in the discovery and development of therapeutic potentiator compounds.

**The alternating access model**

The TMD substrate-binding site faces either the cytoplasm or the extracellular space based on NBD ATP-binding status and therefore transporter conformation [4]

**The ATP switch model**

When facing the cytoplasm, the TMD binds the substrate with high affinity, but when the transporter changes conformation to face the extracellular space, the TMD binds the substrate with low affinity, facilitating its release extracellularly. Upon ATP hydrolysis, NBD conformational change translates to the TMDs returning to their cytoplasmic-facing orientation [3,4]

**The constant contact model**

One NBD in a transporter binds ATP with high affinity and the other with low affinity, alternating the high affinity domain with each reaction cycle. This would allow the NBDs to constantly be bound to either ATP or ADP during the reaction cycle [4,213]

**Monogenic liver disease****ABCB11, ABCB4, and Progressive Familial Intrahepatic Cholestasis**

Progressive familial intrahepatic cholestasis (PFIC) is a collection of 6 rare, autosomal recessive liver diseases, 2 of which—PFIC2 and PFIC3—are caused by mutations in ABC transporters (ABCB11 and ABCB4, respectively) [20,21]. *ABCB11* (also known as *BSEP*) and *ABCB4*, both expressed at the hepatocyte canalicular membrane, facilitate secretion of bile components into the biliary system [5,22–25]. *ABCB11* actively transports bile acids while *ABCB4* facilitates bile phosphatidylcholine content through its floppase activity [26].

Together with bilirubin and cholesterol, bile acids and phospholipids comprise bile, which is required for the digestion of fats and the absorption of dietary vitamins. Biallelic pathogenic mutations in *ABCB11* and *ABCB4* result in pediatric onset of hepatic bile acid accumulation, which leads to hepatotoxicity, resulting in fibrosis, cirrhosis, an increased risk of hepatocellular carcinoma, and ultimately, liver failure [1,5,20,24]. Malabsorption of fat and nutrients leads to poor growth and risk of failure to thrive [20]. Additionally, backflow of bile acids into the hepatic portal system leads to increased serum bile acid concentration and the manifestation of pruritus (severe skin itching) [27]. Ultimately, in PFIC2, the extent to which bile acids can be exported from hepatocytes defines the severity and onset of disease, such that more impactful mutations (e.g., nonsense and frameshift mutations) give rise to the most severe and earliest onset forms, while missense mutations, depending on their level of dysfunction, drive a varying degree of severity [28].

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**Figure 1.** ABC transporters have broad pathophysiological relevance and drug discovery tractability, identifying them as potential pharmacological entry points for the treatment of biologically rationalized monogenic and complex diseases. Drug discovery methods for the development of ABC transporter small molecules include the integrated use of 1) high-throughput screening of chemistry libraries against target specific assays to identify chemical hits that positively modulate target expression and/or function and, 2) structure-based drug design to inform the rationalized optimization or prediction of target active compounds facilitated by suitability of ABC transporters to cryo-EM structure determination. Together, these approaches may enable the development of transformative ABC transporter therapies that can correct underlying pathogenic mutations in monogenic disease or augment the function of wild-type ABC transporters within the context of other complex and common diseases. Image created with [BioRender.com](https://www.biorender.com). Abbreviations: ABC, ATP-binding cassette; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; cryo-EM, cryogenic electron microscopy; WT, wild-type.

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Table 1. Human ABC transporters are involved in a variety of monogenic diseases<sup>a</sup>

Transporter	Monogenic disorder	OMIM	Mode	System	Symptomology	Mechanism of disease	3D Protein structure	Evidence of pharmacological correction
<i>ABCA1</i>	Tangier disease	205400	AR	Liver	HDL deficiency, accelerated atherosclerosis, coronary artery stenosis, hepatosplenomegaly, tonsils with orange deposits, progressive peripheral neuropathy, distal muscle weakness	Reduced export of cholesterol and phospholipids to apolipoproteins, resulting in decreased HDL biogenesis	Cryo-EM	Yes
<i>ABCA2</i>	Intellectual developmental disorder with poor growth with or without seizures or ataxia	618808	AR	CNS	Global developmental delay, hypotonia, ataxia, seizures, dysmorphic features	Unknown	Predicted AlphaFold	N/A
<i>ABCA3</i>	Pulmonary surfactant metabolism dysfunction type 3	610921	AR	Lung	Respiratory distress, hypoxemia, pulmonary hypertension	Reduced export of surfactant components, leading to reduced surfactant production and pulmonary alveolar proteinosis	Cryo-EM	Yes
<i>ABCA4</i>	Stargardt disease	248200	AR	Retina	Decreased visual acuity and macular atrophy	Reduced NRPE export, leading to accumulation of toxic bisretinoids, RPE cell death, and photoreceptor death	Cryo-EM	Yes
<i>ABCA12</i>	Autosomal recessive congenital ichthyosis 4A	601277	AR	Skin	Abnormal skin scaling over the whole body	Reduced glucosylceramide export required for proper formation of intercellular lipid layer of the stratum corneum and secretion of kallikrein	Predicted AlphaFold	N/A
<i>ABCB2</i>	Bare lymphocyte syndrome type I	604571	AR	Immune	Recurrent pulmonary bacterial infections, chronic skin lesions, bronchiectasis, immunodeficiency	Loss of antigen transport from cytosol into ER to form peptide:MHC I	Cryo-EM	N/A
<i>ABCB3</i>	Bare lymphocyte syndrome, type I due to TAP2 deficiency	604571	AR	Immune	Recurrent pulmonary bacterial infections, chronic skin lesions, bronchiectasis, immunodeficiency	Loss of antigen transport from cytosol into ER to form peptide:MHC I	Cryo-EM	N/A
<i>ABCB4</i>	Progressive familial intrahepatic cholestasis 3	602347	AR	Liver	Jaundice, diarrhea, pruritis, hepatosplenomegaly, elevated serum liver enzymes and bile acids	Reduced export of hepatic phospholipids, leading to increased biliary free bile acids concentration, cholangitis, and cholestasis	Cryo-EM	Yes
<i>ABCB6</i>	Dyschromatosis universalis hereditaria 3	615402	AD	Skin	Hyperpigmented and hypopigmented macules of the skin	Decreased melanosome function	Cryo-EM	N/A
<i>ABCB7</i>	X-linked sideroblastic anemia with ataxia	301310	X-linked	Hemato-poietic	Hypochromic microcytic anemia with ring sideroblast, nonprogressive cerebellar ataxia	Decreased iron homeostasis and cytosolic iron-sulfur containing proteins due to lack of	Cryo-EM	N/A

Table 1. (continued)

Transporter	Monogenic disorder	OMIM	Mode	System	Symptomology	Mechanism of disease	3D Protein structure	Evidence of pharmacological correction
						iron-sulfur cluster export from mitochondria		
<i>ABCB11</i>	Progressive familial intrahepatic cholestasis 2	601847	AR	Liver	Jaundice, diarrhea, pruritis, hepatosplenomegaly, elevated serum liver enzymes and bile acids	Decreased hepatic bile efflux, leading to cholestasis	Cryo-EM	Yes
<i>ABCC2</i>	Dubin-Johnson syndrome	237500	AR	Liver	Jaundice, fatigue, dark urine, abdominal pain, hepatomegaly	Decreased export of bilirubin conjugates to bile ducts, leading to hepatic buildup	Predicted AlphaFold	N/A
<i>ABCC6</i>	Pseudoxanthoma elasticum	264800	AR	Skin, eye, vascular	Ivory colored papules, lesions of the posterior segment of the eye, peripheral and coronary arterial occlusive disease	Decreased export of ATP, resulting in reduced circulating PP <sub>i</sub> and an increase in ectopic calcification	X-ray diffraction (NDBs only)	Yes
<i>ABCC6</i>	Generalized atrial calcification of infancy type 2	614473	AR	Cardio-vascular	Early onset vaso-occlusion and cardiomyopathy	Severe calcification of arterial internal elastic lamina	X-ray diffraction (NDBs only)	Yes
<i>ABCC7</i>	Cystic fibrosis	219700	AR	Lung	Persistent coughing, frequent pulmonary infections, shortness of breath, exocrine pancreatic insufficiency, increased NaCl in sweat	Decreased chloride ion efflux, resulting in dehydrated mucus in the airways and blockage of pancreatic exocrine outflow	Cryo-EM	Yes
<i>ABCC8</i>	Familial hyperinsulinemic hypoglycemia	256450	AR	Pancreas	Hypoglycemia and hyperinsulinemia	Decreased ATP sensing resulting in inactivation of the K <sub>ATP</sub> channel, leading to constitutive insulin secretion	Cryo-EM	Yes
<i>ABCC9</i>	Intellectual disability myopathy syndrome	619719	AR	Cardiac, Skeletal, vasculature	Global developmental delay, hypotonia, muscle weakness and fatigue, brain white matter abnormalities	Loss of channel activity impacting cerebral vasculature, impairing blood flow to brain, and cardio-myocyte electrical activity	Predicted AlphaFold	N/A
<i>ABCD1</i>	X-linked adrenoleukodystrophy	300100	X-linked	CNS/PNS	ADHD, cognitive deficits, diminished visual acuity, motor incoordination, spastic paraplegia, adrenal insufficiency	Decreased peroxisomal import of cytoplasmic VLCFA, leading to cytotoxicity and inflammatory response	Cryo-EM	N/A
<i>ABCD3</i>	Congenital bile acid synthesis defect 5	616278	AR	Liver	Hepatosplenomegaly, cholestasis, fat-soluble vitamin malabsorption, jaundice, elevated liver enzymes	Decreased transfer of LCFA and bile acids from cytosol to peroxisome for $\beta$ -oxidation	Predicted AlphaFold	N/A
<i>ABCD4</i>	Methylmalonic aciduria and homocystinuria, cblJ type, inborn error of vitamin B12 metabolism	614857	AR	Metabolic	Failure to thrive, pale appearance, hypotonia, seizures	Decreased cobalamin transport from lysosome to cytosol	Cryo-EM	N/A

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Table 1. (continued)

Transporter	Monogenic disorder	OMIM	Mode	System	Symptomology	Mechanism of disease	3D Protein structure	Evidence of pharmacological correction
<i>ABCG5</i>	Sitosterolemia	618666	AR	Liver/GI	High cholesterol, premature CAD, accelerated atherosclerosis, tendon and tuberous xanthomas	Decreased sterol transport in liver and intestine	Cryo-EM	N/A
<i>ABCG8</i>	Sitosterolemia	210250	AR	Liver/GI	High cholesterol, premature coronary artery disease, accelerated atherosclerosis, tendon and tuberous xanthomas	Decreased sterol transport in liver and intestine	Cryo-EM	N/A

<sup>a</sup>Abbreviations: AD, autosomal dominant; ADHD, attention-deficit/hyperactivity disorder; AR, autosomal recessive; CAD, coronary artery disease; CNS, central nervous system; Cryo-EM, cryogenic electron microscopy; ER, endoplasmic reticulum; GI, gastrointestinal tract; HDL, high-density lipoprotein;  $K_{ATP}$ , ATP-sensitive potassium channel; LCFA, long-chain fatty acid; MHC I, major histocompatibility complex I; N/A, not available; NBD, nucleotide-binding domain; NRPE, N-retinylidene-phosphatidylethanolamine; PNS, peripheral nervous system; RPE, retinal pigment epithelium; VLCFA, very long-chain fatty acid.

In *ABCB4* deficiency, cholestasis is secondary to cholangiopathy in which the absence of neutralizing phospholipids promotes accumulation of toxic bile, leading to cholangiocyte damage. *ABCB4* genotypes drive a spectrum of disease phenotypes, with the most impactful *ABCB4* deficiency engendering earlier onset cholangiopathy and subsequent cholestasis (i.e., PFIC3), and milder genotypes predisposing to less severe and later-onset forms of cholestasis [29,30].

PFIC is one of the top 5 reasons for liver transplant in children, [20] highlighting the need for improved treatment options. Current pre-transplant approaches include detoxification of bile through administration of ursodeoxycholic acid and reduction of bile acid reabsorption through surgical or pharmacological biliary diversion [20,24,31,32]. In surgical biliary diversion, the bile duct's connection to the intestine is moved from the ileum, which typically reabsorbs bile acids into circulation, to the large intestine; pharmacological biliary diversion uses ileal bile acid transporter inhibitors to prevent this reabsorption. However, the long-term efficacy and response rate to these therapies is limited and can be affected by patient genotype [31,32]. As such, a disease-modifying treatment directly addressing underlying *ABCB11* or *ABCB4* mutations could transform the care of PFIC2/3.

While not explicitly monogenic in nature, there is significant evidence of the involvement of ABC transporter genes, especially *ABCB4* and *ABCB11*, in cholestatic disease (Table 2). *ABCB4* mutations are associated with low-phospholipid-associated cholelithiasis, [33,34] while *ABCB11* mutations are linked to drug-induced liver injury, [35,36] biliary atresia, [37] primary intrahepatic stones, [33,34]. Finally, mutations in both *ABCB4* and *ABCB11* are linked to intrahepatic cholestasis of pregnancy [38,39].

Importantly, for the development of novel therapeutics to address these disorders, mutant *ABCB11* and *ABCB4* demonstrate the capacity for pharmacological correction. *In vitro*, US Food and Drug Administration (FDA)-approved *CFTR* mutation-correcting CF therapeutics have been shown to rescue the dysfunction of PFIC associated *ABCB11* and *ABCB4* mutations [41,43,44]. The pharmacological chaperone 4-phenylbutyrate (4-PBA; see later) has similarly demonstrated the capacity to correct protein folding and trafficking of these [44,45] and other ABC transporter targets. Moreover, a short-term 4-PBA treatment in a pediatric patient with PFIC2 decreased serum bile acid levels, attenuated pruritus, and increased canalicular BSEP expression [46]. Collectively, these data speak to the potential and promise of developing small-

Table 2. ABC transporters are associated with a variety of complex cardiometabolic, neurological, and liver diseases<sup>a</sup>

Disease	Transporter	Evidence	Refs
Cardiometabolic disease			
Atherosclerosis/ coronary artery disease	ABCA1	Strong GWAS association with <i>ABCA1</i> mutations. ABCA1 is involved in foam cell formation. Negative association between <i>ABCA1</i> expression and atherosclerosis pathogenesis in human cells and in many LoF models.	[119–121]
	ABCA5	<i>ABCA5</i> -deficient macrophages increase susceptibility to atherosclerosis on LDLR KO background. <i>ABCA5</i> -deficient cells had defective cholesterol efflux to HDL.	[122]
	ABCC6	<i>ABCC6</i> polymorphisms associated with risk of atherosclerosis or CAD—vascular calcification is a risk factor for CAD. <i>In vitro</i> Kos show decreased cholesterol efflux and decreased HDL. <i>In vivo</i> mouse Kos show increased HDL, but no increase in atherosclerotic plaques.	[123–125]
	ABCG1	<i>ABCG1</i> mutations associated with risk of CAD/atherosclerosis. Negative correlation between protein expression and atherosclerosis pathogenesis in human cells., Overexpression <i>in vivo</i> decreases atherosclerosis. Involved in foam cell formation.	[126–129]
	ABCG5/G8	Genetic associations between <i>ABCG5</i> and <i>ABCG8</i> polymorphisms and atherosclerosis or CAD risk. Hepatic overexpression <i>ABCG5/G8</i> in mice reduced atherogenic risk. Involved in the lipid-lowering effects of phytosterols.	[130–132]
Dyslipidemia	ABCA1	Genetic associations between <i>ABCA1</i> variants and altered blood lipid levels, specifically blood HDL. In animal cells, reducing ABCA1 expression decreases cholesterol efflux, and increased ABCA1 and ABCG1 expression elevates HDL efflux. In mice fed high-fat and high-cholesterol diets, upregulating <i>ABCA1</i> expression increased HDL levels, but this effect was eliminated following <i>ABCA1</i> KO.	[83,133]
	ABCA5	<i>ABCA5</i> -KO macrophages have decreased cholesterol efflux and, <i>in vivo</i> , can give rise to atherosclerosis. <i>ABCA1</i> -KO macrophages are associated with increased ABCA5 expression. In a hyperlipidemia mouse model, downregulating <i>ABCA1</i> was associated with increased ABCA5 expression.	[122,134]
	ABCA8	<i>ABCA8</i> mutations are associated with decreased HDL-C levels in humans and mice. <i>Abca8</i> overexpression in mice resulted in higher HDL levels.	[135]
	ABCC6	<i>ABCC6</i> variants are associated with increased plasma lipid and cholesterol levels. Macrophage-specific <i>ABCC6</i> KO in mice leads to reduced cholesterol efflux. Heterozygous <i>ABCC6</i> mutation carriers exhibit hypercholesterolemia.	[123,124,136]
	ABCG1	DNA methylation sites on <i>ABCG1</i> are associated with changes in lipid levels. Increased ABCG1 and ABCA1 expression correlates with high HDL-C in healthy individuals. Increased ABCA1 and ABCG1 levels <i>in vitro</i> leads to increased HDL efflux.	[137–139]
	ABCG5/G8	Genetic associations between <i>ABCG5</i> and <i>ABCG8</i> variants and altered blood lipid levels. <i>ABCG5/G8</i> overexpression in mice decreases dietary cholesterol uptake. In mice and humans, <i>ABCG5/G8</i> is involved in transintestinal cholesterol transport and potential increase of cholesterol excretion.	[133,140,141]
Type 2 diabetes	ABCA1	Genetic studies link T2D and <i>ABCA1</i> variants. <i>In vitro</i> , <i>ABCA1</i> LoF and GoF variants are associated with T2D outcomes. $\beta$ -cell-specific <i>ABCA1</i> KO resulted in $\beta$ -cell cholesterol accumulation and decreased glucose-dependent insulin secretion, while adipocyte-specific <i>ABCA1</i> KO in mice fed a high-fat diet resulted in elevated cholesterol storage in adipose, impaired glucose tolerance, and reduced peripheral insulin sensitivity.	[83,142,143]
	ABCA12	Beta-cell-specific <i>ACBA12</i> deletion in mice results in impaired glucose-stimulated insulin secretion in addition to other diabetes outcomes.	[144]
	ABCG1	<i>In vitro</i> , ABCG1 LoF is associated with T2D pathogenesis. T2D patients have decreased ABCG1 expression in macrophages. <i>In vivo</i> , ABCG1 LoF is associated with T2D outcomes.	[145–147]
	ABCG5/G8	<i>ABCG8</i> mutations are a risk factor for T2D in some populations. Decreased ABCG8 expression detected in intestine of T2D patients. In a model of nutritionally induced T2D, obese mice had decreased ABCG8 protein levels in the liver and intestine.	[148–150]
Neurological disease			
Alzheimer's disease	ABCA1	Strong genetic association between <i>ABCA1</i> and AD. LoF and expression evidence of ABCA1 correlate with A $\beta$ levels in human cells <i>in vitro</i> and multiple ABCA1 LoF animal models and one GoF animal model.	[82,85,91,96]
	ABCA2	Variant identified as risk factor for EOAD and sporadic AD. Increased expression <i>in vitro</i> increases A $\beta$ levels while KD decreases A $\beta$ levels. Regulates sphingosine levels, impacting APP transcription.	[12]
	ABCA5	<i>ABCA5</i> expression influences A $\beta$ deposition <i>in vitro</i> . <i>Ex vivo</i> evidence indicates increased expression of ABCA5 in the hippocampus of patients with AD.	[151]

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Table 2. (continued)

Disease	Transporter	Evidence	Refs
	ABCA7	Strong genetic association between <i>ABCA7</i> and AD. Suppression of endogenous <i>ABCA7</i> in several different <i>in vitro</i> human cell lines resulted in increased $\beta$ -secretase cleavage and elevated A $\beta$ levels. High <i>ABCA7</i> protein levels are associated with early- and late-onset AD in <i>ex vivo</i> human tissue as well as in multiple LoF animal models and one GoF animal model.	[82,115–117]
	ABCB1	Directly interacts with A $\beta$ to mediate efflux from CNS across BBB. Acts as gatekeeper for peripheral A $\beta$ entry into the CNS. LoF increases CNS levels, and pharmacological GoF increases cerebral clearance of A $\beta$ in a transgenic mouse model of AD.	[152]
	ABCC1	Increased <i>ABCC1</i> expression <i>in vitro</i> reduced extracellular A $\beta$ and the ratio of $\alpha$ - versus $\beta$ -secretase-mediated APP cleavage. <i>ABCC1</i> -deficient mice had increased A $\beta$ levels, and, in a mouse model of AD, activation of <i>ABCC1</i> reduced A $\beta$ load.	[153,154]
	ABCG1	Genetic association between <i>ABCG1</i> variants and AD risk. In a human cell line, <i>ABCG1</i> suppression led to increased A $\beta$ , whereas increased <i>ABCG1</i> reduced A $\beta$ levels. CNS A $\beta$ levels were elevated in <i>ABCG1</i> KO mice.	[155–157]
	ABCG2	<i>ABCG2</i> directly interacts with A $\beta$ . LoF increases cerebral A $\beta$ . Acts as gatekeeper for peripheral A $\beta$ entry into CNS: KO increased flow of A $\beta$ from lateral to basolateral side of BBB.	[152]
	ABCG4	Increased <i>ABCG4</i> expression found in human AD brain cells, which the literature suggests is compensatory. <i>ABCG4</i> is important in A $\beta$ export and memory in mouse models.	[157–159]
Parkinson's disease	ABCA5	Elevated <i>ABCA5</i> in human PD brains and in a human neuronal cell line. <i>ABCA5</i> KO mice develop a lysosomal disorder, which is a leading risk factor of PD, but do not develop significant brain abnormalities.	[160,161]
	ABCB2	<i>ABCB2</i> ( <i>TAP1</i> ) was elevated in both in an <i>in vitro</i> (mouse) PD model and <i>in vivo</i> (PD brain tissue, rat PD model); could act as a compensatory pathway of neuroinflammation. No causative LoF or GoF <i>in vivo</i> associations are known.	[162,163]
	ABCB3	<i>ABCB3</i> ( <i>TAP2</i> ) was elevated in an <i>in vivo</i> rat model of PD as a compensatory pathway of neuroinflammation. No causative LoF or GoF <i>in vivo</i> associations are known.	[163,164]
Multiple sclerosis	ABCA1	Evidence of <i>ABCA1</i> LoF was found in active lesions from MS donors. Differential <i>ABCA1</i> protein expression seen in multiple studies, with one study demonstrating a strong correlation between <i>ABCA1</i> expression levels and MS severity.	[165,166]
Huntington's disease	ABCB10	Evidence of LoF and GoF was found in a <i>Hdh</i> <sup>Q111</sup> mutant striatal mouse cell line. <i>ABCB10</i> is downregulated in a HD patient fibroblast cell line and in the R6/2 HD mouse model.	[167]
Frontotemporal dementia	ABCD1	Case studies link a single <i>ABCD1</i> mutation to FTD. <i>ABCD1</i> is upregulated in FTD brain tissue in response to excess VLCFAs, which build up in patients with FTD—because <i>ABCD1</i> typically is responsible for removing VLCFAs, upregulation of <i>ABCD1</i> is a compensation mechanism.	[168–170]
Hirschsprung disease	ABCD1	Two variants of <i>ABCD1</i> were found in HSCR patients. <i>ABCD1</i> KO in neuronal cells demonstrated impaired development of a neuronal-like phenotype, delayed network formation, higher apoptosis rates, and fewer proliferative cells, suggesting that <i>ABCD1</i> may contribute to disease risk based on the multifactorial origin of HSCR.	[171]
Neuropathic pain	ABCC8	<i>ABCC8</i> ( <i>SUR1</i> ) deletion prevents and ameliorates development of NP behaviors. However, some <i>in vivo</i> animal model studies suggest that reductions in <i>K<sub>ATP</sub></i> channel activity can worsen NP symptoms. One <i>in vitro</i> study showed that enhancing the function of the <i>K<sub>ATP</sub></i> channel could be a potential therapeutic for NP.	[172–174]
Chemotherapy-induced peripheral neuropathy	ABCA1	Microglia-specific <i>ABCA1/G1</i> KD induces pain in naïve mice and prevents AIBP from reversing CIPN allodynia; additionally, <i>ABCA1/G1</i> deficiency reprograms microglia to a CIPN-like phenotype.	[175]
Psychiatric disorders	ABCA13	Disease cohort and pedigree analyses indicate enrichment of rare coding and cytogenic <i>ABCA13</i> mutations in patients with schizophrenia, depression, and bipolar disorder. <i>ABCA13</i> -KO mice exhibit a decreased prepulse inhibition response, indicating changes to sensorimotor gating also observed in patients with psychiatric disorders, including schizophrenia and bipolar disorder.	[176,177]
Liver disease			
Nonalcoholic steatohepatitis	ABCB11	<i>ABCB11</i> ( <i>BSEP</i> ) expression was altered in liver biopsies from patients with NASH/NAFLD. <i>In vitro</i> data suggests improved disease outcomes associated with <i>ABCB11</i> upregulation. <i>BSEP</i> deletion aggravates NASH in mice, and overexpression is protective.	[178–181]
Cholestasis	ABCC4	<i>ABCC4</i> -KO mice have worsened disease outcomes in obstructive cholestasis. <i>ABCC4</i> expression in liver samples of patients with obstructive cholestasis was significantly increased when compared with control liver tissue samples.	[182–184]

Table 2. (continued)

Disease	Transporter	Evidence	Refs
	ABCC12	A homozygous truncating pathogenic variant of <i>ABCC12</i> and 5 additional rare variants were identified in a whole-exome and candidate gene sequencing study of children with cholestasis. Loss of <i>ABCC12</i> in zebrafish and mice resulted in cholangiocyte apoptosis.	[185]
	ABCG8	Multiple genetic associations between <i>ABCG8</i> variants and cholestasis. <i>Ex vivo</i> data demonstrate reduced <i>ABCG8</i> protein expression in human cholestatic livers. <i>ABCG8</i> -KO mice are more susceptible to bile acid-induced cholestasis than non-KO mice.	[186–188]
Intrahepatic cholestasis of pregnancy	ABCC2	Multiple genetic studies show <i>ABCC2</i> associations with ICP. <i>Ex vivo</i> human and <i>in vivo</i> mouse studies demonstrate both GoF and LoF models.	[189,190]
	ABCB11	Multiple genetic studies link <i>ABCB11</i> mutations with ICP.	[38,39]
	ABCB4	Multiple genetic studies link <i>ABCB4</i> mutations with ICP.	[39]
Low phospholipid-associated cholelithiasis	ABCB4	Multiple genetic studies link <i>ABCB4</i> mutations with LPAC.	[34]
Rheumatoid disease			
Gout	ABCG2	Both common and rare <i>ABCG2</i> variants cause gout.	[191,192]
Ophthalmological disease			
Age-related macular degeneration	ABCA1	Multiple genetic studies link mutations in <i>ABCA1</i> with AMD. Conditional KO mouse develops drusenoid-like deposits, photoreceptor dysfunction, and delayed dark adaptation.	[83]
Glaucoma	ABCA1	Several GWAS studies have identified <i>ABCA1</i> to be associated with POAG. <i>ABCA1</i> regulates Cav1/eNOS/NO signaling to influence ocular hypertension and annexin, which then modulate ocular inflammation.	[83]

<sup>a</sup>Abbreviations: AD, Alzheimer's disease; AIBP, apolipoprotein AI-binding protein; AMD, age-related macular degeneration; APP, amyloid precursor protein; BBB, blood-brain barrier; BSEP, bile salt export pump; CAD, coronary artery disease; Cav1, caveolin-1; CIPN, chemotherapy-induced peripheral neuropathy; CNS, central nervous system; eNOS, endothelial nitric oxide synthase; EOAD, early-onset Alzheimer's disease; FTD, frontotemporal dementia; GoF, gain of function; GWAS, genome-wide association study; HD, Huntington's disease; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; HSCR, Hirschsprung disease;  $K_{ATP}$ , ATP-sensitive potassium channel; KD, knockdown; KO, knockout; LAPC, low phospholipid-associated cholelithiasis; LDLR, low-density lipoprotein receptor; LoF, loss of function; LPAC, low phospholipid-associated cholelithiasis; MS, multiple sclerosis; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NO, nitric oxide; NP, neuropathic pain; PD, Parkinson's disease; POAG, primary open-angle glaucoma; T2D, type 2 diabetes; VLCFA, very long-chain fatty acid.

molecule ABCB11 and ABCB4 positive functional modulators for the treatment of PFIC2/3, and other associated diseases.

### *ABCC6 and Pseudoxanthoma Elasticum*

Pseudoxanthoma elasticum (PXE), caused by biallelic mutations in *ABCC6*, is a mineralization disorder affecting elastic fiber-rich tissues, including the retina, circulatory system, and skin [5,47,48]. There are approximately 150,000 cases of PXE worldwide, and symptoms include vision loss, atherosclerosis, and skin lesions [49].

*ABCC6* is primarily expressed in the liver and kidney, [5,50,51] and though it does not directly affect liver function, hepatic *ABCC6* is significant in releasing ATP from the hepatocyte basolateral membrane into the bloodstream [5,51,52] where it is converted by ectonucleotidases such as ENPP1 to adenosine monophosphate (AMP) and pyrophosphate (PP<sub>i</sub>). Normally, PP<sub>i</sub> prevents calcification, but in the absence of *ABCC6* function, circulating PP<sub>i</sub> is decreased, leading to ectopic mineralization of elastin fibers in the midlaminal layer of the dermis, in Bruch's membrane of the eye, and in mid-sized arteries [5,49,51–53]. Symptomologically, PXE presents with yellowish skin lesions, retinal neovascularization leading to central vision loss, and progressive claudication from arterial narrowing, which also increases risk of cardiovascular events [54].

Along with PXE, *ABCC6* mutations can lead to other types of arterial calcification, [5,47,55] which are associated with increased risk of cardiovascular disease. Most notably, generalized arterial calcification of infancy type 2 (GACI-2), a rare, severe, and early onset form of *ABCC6* deficiency,

leads to vaso-occlusion and cardiomyopathy in children [56]. There is no established genotype-phenotype correlation between *ABCC6* mutations, disease onset, and disease severity, suggesting the role for genetic modifiers [57]. Currently, PXE and GACI-2 are treated using the standard of care for individual symptom sets, such as for choroidal neovascularization, atherosclerosis, or skin lesions; no *ABCC6*-focused therapies exist [54]. However, pharmacotherapeutics that increase circulating  $PP_i$  concentrations (through inhibiting  $PP_i$  degradation or promoting synthesis) are currently under clinical investigation. Notably, and in line with observations of other ABC transporters, the butyrate analogue, 4-PBA, demonstrates the capacity to rescue PXE-associated *ABCC6* trafficking mutations. Specifically, 4-PBA-mediated restoration of *ABCC6* plasma membrane expression has been observed in mutant *ABCC6*-expressing cell lines, zebrafish models, and mouse models of PXE, [58–60] again highlighting a path towards novel PXE and GACI-2 therapies.

#### Monogenic retinal disease

##### *ABCA4 and Stargardt Disease*

Stargardt disease (STGD) describes several forms of juvenile macular degeneration due to mutations in *ABCA4* [4,61]. STGD is one of the more common causes of vision loss in young adults, with a prevalence of 1:8,000 to 1:10,000 [62]. Characteristic pathological features of STGD include macular atrophy with conserved peripapillary area around the optic nerve, and fundus flecks [61].

In a healthy retina, photoreceptor cell-localized *ABCA4* protein flips the retinoid *N*-retinylidene-phosphatidylethanolamine (NRPE) from the lumen-facing leaflet of the disc membrane to the cytoplasmic face, which is required for proper NRPE clearance [4]. Clearance of NRPE is vital to photoreceptor survival, as its breakdown products, including bisretinoid *N*-retinyl-*N*-retinylidene ethanolamine, are cytotoxic, leading to lipofuscin generation and retinal pigment epithelial cell degeneration following disc phagocytosis [4].

The molecular genetics of STGD have been extensively researched and reviewed [4]. *ABCA4* is one of the largest ABC transporter genes, comprised of 50 exons in which >1000 mutations have been identified, many of which can impact both protein expression and activity [4]. Of these, 60% are missense mutations [4]. More functionally deficient mutations generally give rise to earlier onset and more severe clinical presentations, [63] presumably due to the more rapid accumulation of NRPE. At present, treatment of STGD is limited to occupational therapy and visual aids. However, relying on previously identified pharmacological correctors used to modify CFTR in CF, could potentially improve STGD-associated mutations as lumacaftor successfully rescued plasma membrane expression of STGD-associated *ABCA4* trafficking mutations *in vitro* [64].

#### Monogenic nervous system disease

##### *ABCD1 and X-linked adrenoleukodystrophy*

X-linked adrenoleukodystrophy (X-ALD), driven by mutations in *ABCD1*, defines 3 clinical disease subtypes classified by age of onset and symptom severity, and in total affecting approximately 1:20,000 males [65]. The 2 most common types of X-ALD—childhood cerebral ALD (cALD) and adrenomyeloneuropathy (AMN)—account for ~40% and ~50% of X-ALD cases, respectively [6].

Fatal if untreated, [6,66] cALD is a rapidly progressing, central demyelinating, and inflammatory disease resulting in cognitive and sensory decline [6,66]. By contrast, AMN develops in early adulthood and involves slower but progressive peripheral and sometimes spinal demyelination, [6] leading to weakness, spasticity, and bowel and bladder dysfunction among other symptoms [6,66]. The remaining 10% of patients are characterized as having Addison's disease, a form of primary adrenal insufficiency that leads to corticosterone deficiency without neurodegeneration [67].

ABCD1 is a half-transporter expressed in many cell and tissue types throughout the body with the highest expression in fat, such as in the white matter of nervous system tissues [66]. ABCD1 is a peroxisomal transporter that traffics very-long-chain fatty acids (VLCFAs) from the cytosol into the peroxisome for degradation via beta-oxidation [2,3,68]. A lack of ABCD1 function, then, allows for the buildup of VLCFAs in plasma and tissues, which are hallmarks of X-ALD [2,6,65]. This leads to reactive oxygen species generation, apoptosis, and the progression of disease symptoms [3,66].

Despite the spectrum of disease severity, there is no established genotype-phenotype correlation that predicts disease progression, suggesting a strong role for as yet unidentified disease modifiers. Hematopoietic stem cell transplantation (HSCT) can be an effective, therapeutic approach to cALD, suggesting that neuroinflammation differentiates cALD from other forms of X-ALD [69]. Importantly, while HSCT is effective at treating the neuroinflammation associated with cALD, patients can still develop AMN symptoms later in life, highlighting the need for additional therapeutic options [70]. The specific cell types driving AMN and Addison's disease are not well established and, at present, there are no approved therapies for the treatment of AMN. However, pharmacological agents that augment ABCD2 expression, which is a peroxisomal VLCFA transporter, demonstrate preclinical efficacy in mouse models of X-ALD and are currently under clinical investigation [71]. Moreover, 4-PBA-induced ABCD2 expression and function in patient-derived cells and *ABCD1* KO mice, [72] opening the door to new pharmacotherapeutic strategies for treating X-ALD through directly augmented ABCD2 and/or rescued ABCD1 function.

### ABC transporters in multigenic disease

While mutations in ABC transporter genes exert significant effects in isolation, they also occur alongside other disease-causing mutations or disease processes. Loss of ABC transporter function, then, can be one of many simultaneous factors that contribute to disease pathogenesis as evidenced by the role of ABC transporters in multigenic/complex diseases. These associations span the spectrum of therapeutic areas and are too numerous for comprehensive discussion, but associations around neurodegeneration, cardiometabolic, and liver disease warrants mention (see Table 2).

#### ABCA1

*ABCA1* is expressed across many cell types, including endothelial cells and hepatocytes [5,73,74]. ABCA1 transports phospholipids and cholesterol, but importantly, also transports cholesterol from peripheral cells and onto lipid-poor apolipoprotein A1 [5,75–79]. Loss of ABCA1 function, then, leads to insufficient cholesterol excretion, as exemplified by its role in Tangier disease (Table 1). While Tangier disease is rare and generally well-managed, ABCA1's role in lipid homeostasis is of relevance to a number of other human disorders, including AD and cardiovascular disease (Table 2).

Alzheimer's disease (AD), the most common form of dementia, is characterized by the formation of amyloid- $\beta$  (A $\beta$ ) plaques and neurofibrillary tangles, which interfere with normal cellular function, causing progressive neurodegeneration and cognitive decline [80]. A $\beta$  peptides, the major protein component of A $\beta$  plaques, are generated by  $\beta$ -secretase-mediated proteolysis of amyloid precursor protein (APP), which occurs in ordered microdomains of the plasma membrane called lipid rafts [81]. A number of ABC transporters have been associated with AD, most based on their transport of lipid species that indirectly influence A $\beta$  generation and clearance or their direct transport of A $\beta$  to facilitate clearance from the central nervous system (CNS) [12].

Multiple genome-wide association studies (GWAS) have identified *ABCA1* variants contributing to AD susceptibility [82]. ABCA1 promotes cholesterol efflux from numerous cell types, including neurons and glia [83]. Loss of ABCA1 function, then, leads to insufficient cholesterol excretion;

this association with disturbances in lipid homeostasis provides biological evidence for its involvement in AD (Table 2). Mechanistically, ABCA1 is involved in both A $\beta$  generation and clearance [83–85] through its cholesterol-mediated regulation of lipid raft formation and function [86,87]. Cellular and thus lipid raft cholesterol content is a critical determinant of A $\beta$  generation, [88] as APP is processed into A $\beta$  at lipid rafts; [88,89] a decrease in ABCA1-mediated cholesterol efflux from the cell, then, increases lipid raft cholesterol levels, driving pathogenic processing of APP to A $\beta$  [84,90]. This impact of ABCA1 on APP processing has been repeatedly observed in various mouse models of AD: *ABCA1*-knockout mice exhibit elevated A $\beta$  levels, increased plaque deposition, and finally, impaired learning and memory [85,91,92].

ABCA1 can also impact the clearance of A $\beta$  through lipidation and regulation of the abundance of apolipoprotein E (ApoE) [83,85]. Lipidated ApoE binds to and promotes the degradation and receptor-mediated export of A $\beta$  from the CNS, helping prevent plaque formation [93–95]. ABCA1-mediated loss of cholesterol efflux, leads to reduced levels of lipidated ApoE, thereby hindering A $\beta$  degradation and increasing amyloid plaque formation [82,83].

While loss of ABCA1 function may be pathogenic in AD, data on augmented ABCA1 function indicate that it may help reduce AD-related effects. *ABCA1* overexpression in a murine AD model decreased A $\beta$  levels, plaque load, and reactive microglia [96]. Additionally, ABCA1 agonism in a mouse expressing human ApoE4 enhanced cholesterol efflux, thereby decreasing A $\beta$ , increasing ApoE4 lipidation, and improving cognitive deficits [97]. Administration of the same peptide to non-human primates transiently increased ApoE plasma levels and A $\beta$ 42/40 ratio [98]. Together, these data indicate that targeted enhancement of ABCA1 function has therapeutic potential for AD.

Because *ABCA1* disturbance reduces effective cholesterol excretion and overall lipid homeostasis, it is biologically linked not only in AD, but also CAD (Table 2). Mutations in *ABCA1* are associated with susceptibility to both AD and CAD [82]. Pharmacologic therapies currently being investigated for ABCA1 dysfunction in AD are also gaining traction in the cardiometabolic state with promising preclinical evidence.

For example, CS-6523, a small-molecule ApoE mimetic, is an ABCA1 agonist, leading to enhanced lipid transport through ABCA1, which supports multiple anti-atherogenic pathways [99,100]. Preclinically, intravenous CS-6523 reduced cholesterol and high-density lipoprotein (HDL)-cholesterol levels while increasing HDL particle levels [98]. Additionally, CS-6523 promoted A $\beta$  clearance from the brain [98]. At the level of gene and protein expression, the small molecule E17241 upregulates *ABCA1* mRNA and protein expression via protein kinase C zeta (PKC $\zeta$ ), eliciting similar changes in lipid dynamics as CS-6523: increased ABCA1-mediated cholesterol efflux and reduced total cholesterol levels [101].

Additionally, liver X receptor (LXR) agonists, which promote expression of RCT genes, including *ABCA1*, have also shown therapeutic potential for the treatment of CAD (Table 2) [102]. Notably, a non-lipogenic LXR- $\beta$  small-molecule inducer of *ABCA1* expression effectively reduced weight and improved glucose homeostasis in mice fed a high-fat diet [103].

### ABCA7

Like *ABCA1*, GWAS have repeatedly identified *ABCA7* as a risk factor for AD [82]. *ABCA7* is the strongest genetic risk factor for AD in the African American population outside of ApoE, [104] and loss-of-function mutations are associated with an 80% increased risk in African American ancestry [105] and a 100% to 400% increased risk in populations with European ancestry [106,107]. *ABCA7* single-nucleotide polymorphisms are associated with brain amyloidosis, [108] changes

in gray matter density, [109] and Braak staging, a measure of neurofibrillary tangle development, which is associated with cognitive decline [110].

ABCA7 facilitates the efflux of phospholipids, and to a lesser extent cholesterol, from inside the cell [82]. Similar to ABCA1, changes in ABCA7 function impact membrane composition and apolipoprotein expression and lipidation levels, thereby altering A $\beta$  generation and clearance. ABCA7 additionally promotes microglial phagocytosis through an unknown mechanism, linking AD-related mutations to neuroinflammation [82]. Accordingly, loss of ABCA7 function increases pathological APP processing and decreases A $\beta$  transport across cells in an *in vitro* model of the blood-brain barrier [82,111]. Other studies have demonstrated a decrease in microglial phagocytosis of A $\beta$  and mislocalization of a receptor facilitating A $\beta$  clearance (LRP1) in the absence of ABCA7 [112,113]. Deletion of ABCA7 from multiple animal models of AD increased A $\beta$  levels and plaque formation and reduced spatial learning [114–117]. The role of ABCA7 on microglial activation and immune response [114] is less clear but increasing interest in A $\beta$ -independent mechanism of AD treatment make these worthy avenues to pursue, especially in light of the increased focus on triggering receptor expressed on myeloid cells 2 (TREM2) in both AD and other neurodegenerative disorders [118].

### Therapeutic potential of ABC transporter pharmacotherapies

ABC transporters have broad pathophysiological relevance to both rare monogenic and common human diseases [2,193]. As such, they represent a compelling opportunity for both drug and gene therapy discovery. Currently, there are four FDA-approved pharmacological therapies for the monogenic, *ABCC7*-associated CF—ivacaftor (KALYDECO®, Vertex Pharmaceuticals), lumacaftor/ivacaftor (ORKAMBI®, Vertex Pharmaceuticals), tezacaftor/ivacaftor (SYMDEKO®, Vertex Pharmaceuticals), and elexacaftor/tezacaftor/ivacaftor (TRIKAFTA®, Vertex Pharmaceuticals) [194]—and they provide robust proof of principle for the small-molecule druggability of ABC transporters. Most importantly, they offer valuable insight into early research strategies to identify and develop **positive functional modulators** of other ABC transporters.

As with other ABC transporter-related diseases, CF was previously only treated symptomatically, [195] but more sophisticated pharmacological compounds that directly address the underlying genetic *CFTR* defects are demonstrating excellent success in CF treatment [196]. The current stable of approved therapies all directly engage CFTR protein to reduce dysfunction and are most effective when used in combination. Indeed, while ivacaftor acts as a **potentiator** of CFTR chloride efflux, lumacaftor, tezacaftor, and elexacaftor serve as synergistic **correctors** of mutant CFTR protein trafficking. Thus, in combination, these compounds enable the pharmacological rescue of both trafficking and **transport mutations**. Importantly, these therapies work across multiple genotypes, [197] addressing approximately 90% of the CF population, [198] which highlights how small-molecule modulators can address multiple disease genotypes. The convergence of genetic testing and mutation characterization can help clarify how mutations in one target predict functional changes in others [40,82]. In many cases, such a strategy for understanding and targeting the molecular pathology at the heart of CF could be generalized to other ABC transporter-associated diseases (see [Clinician's Corner](#)). Additionally, gene, mRNA, and precision gene editing therapies to address rare genetic forms of ABC transporter disease are also currently under investigation, including in CF [199].

*In vitro* data indicate that approved CFTR modulators can act through a conserved mechanism against other disease-associated ABC transporters, such as the successful preclinical use of ivacaftor in correcting disease-associated transporter dysfunction due to mutations in *ABCB4*, [200] *ABCB11*, [41] and *ABCA3* [42] as well as lumacaftor in rescuing STGD-associated mutations in *ABCA4* [64]. Beyond CFTR modulators and as discussed earlier, the most widely

examined ABC transporter pharmacological corrector is the pharmacological chaperone 4-PBA, which has consistently demonstrated an ability to rescue expression of folding and trafficking mutations in various ABC transporters, including *ABCA1*, [201] *ABCC6*, [1] *ABCB4*, [44] *ABCB11*, [45] and *ABCA4* [40]. These observations speak to the value of leveraging learnings from CFTR modulator biochemistry to address ABC transporters as a holistic class of targets. To this end, a deep understanding of the mechanisms of action of CFTR modulators and the techniques used to explore them will greatly advance research of ABC transporters overall.

One such technique, cryogenic electron microscopy (cryo-EM), has revolutionized the understanding of structurally challenging membrane proteins, such as ABC transporters (Table S1; reviewed in Hou et al, 2022 [202]), ion channels, and G-protein-coupled receptors. Over the last several years, cryo-EM has emerged as a foundational technique for **structure-based drug design** (Box 2), which enables the identification, design, and optimization of small-molecule compounds based on an understanding of the molecules' physical engagement with a biological target [203]. Building upon a foundation established through earlier homology modeling and ligand-directed drug design based on ABC transporter modulators, cryo-EM structures of membrane proteins are now providing key insights into modulator binding and pharmacological mechanisms of action for ABC transporters. Notably, newly identified structures illustrate how approved CF therapies bind CFTR and provide key insights into the mechanisms of small-molecule correction of protein trafficking and gating defects [204–206]. The potential to understand how bound drug molecules interact with target proteins and elicit pharmacological effects will prove to be a transformational tool in accelerating drug design efforts for other therapeutically important ABC transporters. Atomic-level insights of ligand-protein interactions at binding sites within a transporter can provide critical data into mechanism of action of a compound class, while computational leveraging of the observed topologies of binding “hotspots” from one transporter to another can provide the basis for understanding target druggability across the ABC transporter proteome using a platform approach [207]. Indeed, the computational modeling of CFTR modulators at other ABC transporters, [208] highlight the potential for structure-directed development of novel small-molecule therapeutics for the treatment of ABC transporter-associated disease. Furthermore, next-generation, predictive, artificial intelligence-driven structural 3D-homology modelling (i.e., AlphaFold [209]) fill a gap for understanding ABC transporters currently lacking experimentally determined structures.

While CFTR modulators and 4-PBA provide pharmacological proof of principle for the clinical rescue of pathogenic ABC transporter mutations associated with rare, monogenic disease, the well-established biology of these transporters highlights further opportunity to treat more common or complex diseases. For example, while *ABCB11* mutations can cause PFIC2, they are also linked to more transient forms of cholestasis, such as ICP and benign recurrent

### Clinician's Corner

ABC transporters both cause and contribute to human disease. Rare monogenic ABC transporter diseases are likely to be underdiagnosed and generally lack meaningful therapeutic options.

Diagnosis of patients with these disorders is a significant challenge and a subsequent barrier to both a biological understanding of disease (e.g., its mechanism and natural history) and the initiation and success of drug development.

In rare genetic disease, an understanding of the disease's genetic landscape and the functional impact of pathogenic mutations is imperative for both informing diagnosis and enabling precision drug development.

A concerted research effort that integrates real-world clinical data and experience with nonclinical, mechanistic research can significantly advance the understanding of these diseases, enabling both patient identification and drug discovery.

Cystic fibrosis serves as a model for how such a collaborative approach can empower drug discovery and the delivery of life-changing medications. The clinical success of CFTR-targeting drugs has opened a world of therapeutic possibilities for targeting other ABC transporters known to play an etiologic role in both rare and common diseases.

### Box 2. Structure-informed drug design facilitates small-molecule modulator development

- Structure-based drug design (SBDD) is a highly effective drug discovery strategy that incorporates high-resolution structural information of drug targets with computational modeling to design novel small molecules that bind and modulate target activity
- Iterative structural modeling of proteins, nucleic acids and large protein assemblies, and structures of multiple liganded complexes can be used to drive ligand design
- Ligand design is often conducted using algorithms for computational docking of known ligands to target active sites, as well as docking and scoring of large virtual compound libraries to a given structural model
- Protein structures have traditionally been determined via X-ray crystallography, and for smaller targets (<30 kDa), nuclear magnetic resonance (NMR)
- In recent years, transformative advances in technologies and data analysis have brought the use of cryo-electron microscopy (cryo-EM) to the forefront for solving structures of highly challenging targets such as membrane proteins and large molecular assemblies, including liganded complexes with active drug molecules

intrahepatic cholestasis. Though *ABCB11* mutations are neither necessary nor sufficient for these disorders, it is plausible that elevated wild-type *ABCB11* expression and function could hold therapeutic benefit for patients with or without *ABCB11* mutations [45] by increasing bile acid efflux for the treatment of these forms of cholestasis. Similarly, for ABC transporters without monogenic associations, both GWAS and mechanistic data can support their potential as pharmacological entry points into the modulation of disease-relevant biology. In this manner, *ABCA1* is a well-rationalized drug target for AD, [85,91,92] CAD, [210] and diabetes, [211] among others. Recent pharmacological data have demonstrated that gain of *ABCA1* function has potential for the treatment of both AD and type 2 diabetes [85,91,92,102,212]. A multitude of other transporters have similar connections to human pathology, warranting further research to uncover opportunities to leverage the ABC transporter class for drug development.

### Concluding remarks

From perspectives of both relevance and tractability, ABC transporters represent a compelling protein class for drug discovery. Biologically, their expansive involvement in human physiology is defined by their broad expression profile and diverse array of endogenous substrates. These myriad and complex roles have implicated many individual transporters in both the causation and/or susceptibility to disease. Pharmacologically, a growing body of literature highlights that small-molecule compounds can correct trafficking and transport deficits that arise from ABC transporter mutations, as exemplified by the success of FDA-approved CFTR positive functional modulators, and furthermore, may be effective in enhancing wild-type transporter expression and function. Moreover, the highly conserved structure and mechanism of both the folding and function of ABC transporters support pharmacological target hopping and will accelerate ABC transporter-related drug discovery. A future goal will be to reconcile the mechanisms of action for both current and new ABC transporter-directed modulators with target structure and disease-relevant molecular genetics. Such unified, class-based understanding will greatly enable rationalized, precision drug design for ABC transporter targets (see [Outstanding questions](#)). Thus, further research into the basic biology and disease relevance of ABC transporters, combined with a focused drug discovery approach to what is a relatively underexplored drug target class, could deliver first-in-class therapeutics to significantly transform the treatment of ABC transporter-associated disease.

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### Declaration of interests

None are declared.

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### Outstanding questions

What exact protein-folding and ER degradation pathways are involved in ABC transporter synthesis and trafficking, and how are these processes disrupted in ABC transporter-related disease?

What are the biophysical mechanisms driving substrate transport for disease-relevant ABC transporters, and how are they altered by ABC transporter mutation?

What are the molecular- and atomic-level mechanisms of action of the approved CFTR potentiator, corrector, and amplifier compounds?

How can lessons from other membrane protein classes, such as ion channels, solute carriers (SLCs), and G-protein-couple receptors (GPCRs), enable drug discovery?

What is the contribution of monogenic disease-causing ABC transporters to more common and complex disease states?

How do pathogenic missense mutations cause ABC transporter dysfunction, and is there a conserved cross-target mechanism for rationalized identification of novel therapeutics?

What are the genetic disease modifiers that influence the presentation of several ABC transporter-related diseases?



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