

Review



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# Sequence analysis and structure prediction of ABHD16A and the roles of the ABHD family members in human disease

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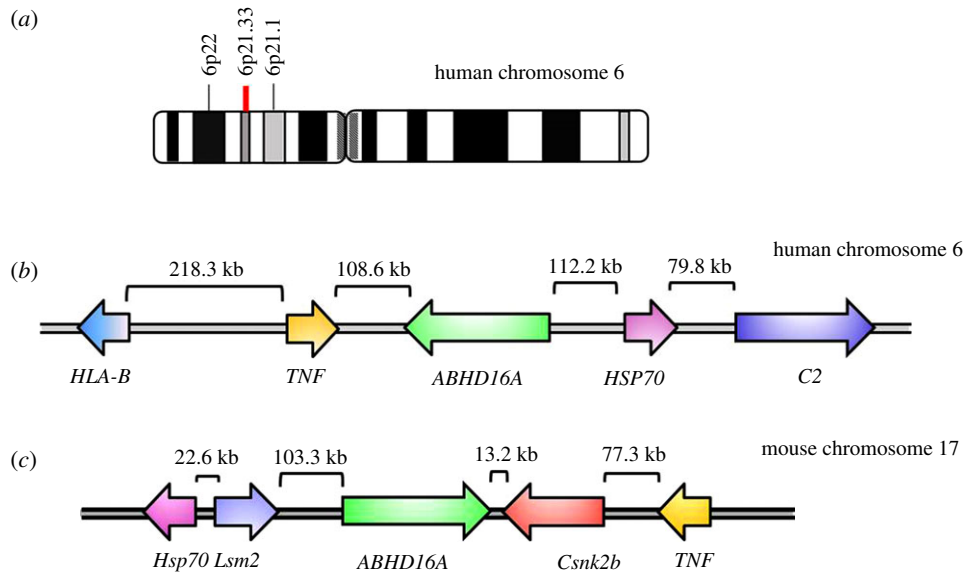
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Abhydrolase domain containing 16A (ABHD16A) is a member of the  $\alpha/\beta$  hydrolase domain-containing (ABHD) protein family and is expressed in a variety of animal cells. Studies have shown that ABHD16A has acylglycerol lipase and phosphatidylserine lipase activities. Its gene location in the main histocompatibility complex (MHC) III gene cluster suggests that this protein may participate in the immunomodulation of the body. The results of studies investigating nearly 20 species of ABHDs reveal that the ABHD proteins are key factors in metabolic regulation and disease occurrence and development. In this paper, we summarize the related progress regarding the function of ABHD16A and other ABHD proteins. A prediction of the active sites and structural domains of ABHD16A and an analysis of the amino acid sites are included. Moreover, we analysed the amino acid sequences of the ABHD16A molecules in different species and provide an overview of the related functions and diseases associated with these proteins. The functions and diseases related to ABHD are systematically summarized and highlighted. Future research directions for studies investigating the functions and mechanisms of these proteins are also suggested. Further studies investigating the function of ABHD proteins may further confirm their positions as important determinants of lipid metabolism and related diseases.

## 1. Introduction

Human adhydrolase domain containing 16A (ABHD16A) is a 63 kDa protein containing 558 amino acid residues that is expressed in cells in multiple species. ABHD16A is a serine metabolism enzyme that typically contains an  $\alpha/\beta$  hydrolase domain. Recently, studies have shown that ABHD16A is associated with neurodegenerative disease [1], immunoregulation [2], Kawasaki disease and coronary artery aneurysm [3]. Human ABHD16A is also known as human leucocyte antigen B (HLA-B) associated transcript 5 (BAT5). Because of its conserved features, ABHD was first identified in 1992 [4] and considered among the most diverse and widespread protein families, including esterases, proteases, lipases, peroxidases, epoxide hydrolases and dehalogenases [5]. Mammalian ABHDs, which are hydrolases, participate in lipid metabolism, intracellular signalling transduction and metabolic disorders [6]. Particularly within the prior 2–3 years, several groups have reported that ABHD2 [7], ABHD6 [8], ABHD12 [9], ABHD16 [2] and ABHD17 [10] could function in inflammation regulation and cancer pathogenesis. Although functional studies investigating the ABHDs are limited and the field is in its infancy, the growing awareness of the biological significance of the ABHDs has stimulated research



**Figure 1.** Position of the ABHD16A gene. Chromosome position of the human ABHD16A gene (a). ABHD16A is conserved in humans (b) and mice (c), and, together with other immunity-related genes, forms a gene cluster in the MHC III region. The coloured arrows indicate different genes and their transcriptional directions. The base pair numbers shown on the horizontal line indicate the distance between the genes.

in this field. Here, we discuss the current research state of ABHD16A, including its gene location and related functions. We also analysed the amino acid sequences and constructed a phylogeny tree of ABHD16A. The functions of other ABHD proteins are systematically summarized and discussed. Significant insights and future developments are also proposed.

## 2. Gene location of ABHD16A

Human ABHD16A is located on chromosome 6p21.33. This gene has 21 exons and four different transcripts, two of which encode proteins (NM\_001177515.1 and NM\_021160.2), while the other two transcripts encode long non-coding RNAs (NR\_033488.1 and NR\_033489.1). The *Abhd16a* and *bat2-bat5* genes are closely associated with tumour necrosis factor (TNF) and the complement gene cluster C2 genes (figure 1*a,b*), and are located within the human major histocompatibility complex class III (MHC III) region [11–13]. Homoplastically, the mouse ABHD16A gene is located between TNF and Heat shock protein 70 (HSP70) near the Ck2b protein kinase gene (figure 1*c*) in the cluster of MHC III [13–15]. Owing to the position characteristics of the ABHD16A gene described above, the BAT1–BAT5 proteins have been predicted to be associated with some aspects of immunity.

## 3. Protein structure of ABHD16A

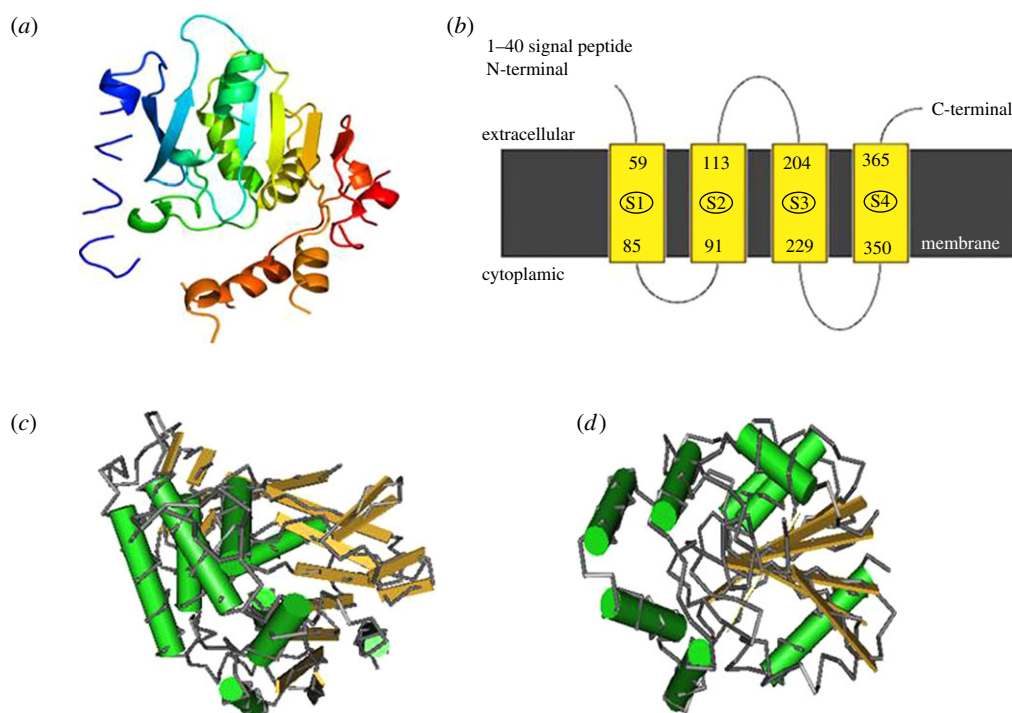
We submitted the amino acid sequence of human ABHD16A to the Phyre2 portal to predict its three-dimensional protein structure (figure 2*a*) and transmembrane region (figure 2*b*). The results revealed four transmembrane regions: residues 59–85, 91–113, 204–229 and 350–365. The sequence alignment against the BLAST and Conserved Domains Database of NCBI revealed that ABHD16A has three conserved domains similar to Abhydrolase 1 (figure 2*c*), BioH (figure 2*d*) and PldB (Phospholipase D-orthologue B). The Abhydrolase 1 domain comprises amino acid residues 280 to 408. Many hydrolytic enzymes possess this catalytic

domain. These enzymes conservatively preserve the catalytic residues, but not the binding sites, from their common ancestor [4]. BioH was identified as a biotin synthesis enzyme and was predicted to contribute to fatty acid synthesis because of its carboxylesterase activity in substrates with short acyl chains [16,17]. The BioH domain of ABHD16A is located in amino acids 276–428, but its precise function must be further investigated in greater detail. The PldB domain has a 3D structure similar to that of Abhydrolase 1, is located within amino acid residues 302–398 and exhibits lysophospholipase activity [18–20].

The predicted protein structure of ABHD16A is similar to that of other ABHDs. Approximately 23 different ABHD proteins belonging to the  $\alpha/\beta$ -hydrolase-fold superfamily have been reported thus far. A typical  $\alpha/\beta$ -hydrolase fold has 8  $\beta$ -strands and 6  $\alpha$ -helices [6]. The hydrolytic enzyme active centre is formed by histidine residues and surrounded by helices and loops linking the  $\beta$ -strands. In most cases, Ser and occasionally Cys or Asp lie in a compact loop. In addition, a highly conserved histidine residue is present in a variable loop behind  $\beta$ 8 [6].

## 4. Conservation analysis of the amino acid sequence of ABHD16A

ABHD16A is a highly conserved protein in mammals that is expressed in cells in different tissues [19]. Using molecular evolutionary genetics analysis (MEGA) software, we analysed the amino acid sequences of ABHD16A in 13 mammalian species (table 1). The results revealed 412 conserved sites, 146 variable sites, 58 parsimony-informative sites and 88 singleton sites. Both the maximum-likelihood phylogenetic analysis and sequence comparison showed that the ABHD16A protein sequences could be divided into three categories (figure 3*a*). The significant differences in the length of the ABHD16A polypeptide chain imply that variable splicing occurs during the post-transcriptional processing of ABHD16A mRNA. For example, human isoforms a and b of ABHD16A have 558 and 525 aa, respectively; Sikkim mice isoforms a and b have



**Figure 2.** Structural prediction of the human ABHD16A protein. (a) Three-dimensional patterns predicted by Phyre2. (b) Transmembrane region predicted by Phyre2. (c) Abhydrolase onefold prediction by the Conserved Domains Database of NCBI. (d) BioH domain predicted by the Conserved Domains Database of NCBI.

**Table 1.** References of ABHD16A in 13 mammalian species.

species	GenBank GI no.
<i>Homo sapiens</i>	NP_066983.1(isoform a), NP_001170986.1(isoform b)
<i>Mus musculus</i>	NP_848707.1
<i>Rattus norvegicus</i>	NP_997696.1
<i>Pan troglodytes</i>	NP_001267411.1
<i>Bos taurus</i>	NP_001069073.1
<i>Microcebus murinus</i>	XP_012596454.1(isoform X1), XP_012596455.1(isoform X2), XP_012596456.1(isoform X3), XP_012596457.1(isoform X4)
<i>Mus pahari</i>	XP_021073260.1(isoform X1), XP_021073262.1(isoform X2)
<i>Castor canadensis</i>	XP_020032186.1(isoform X1), XP_020032188.1(isoform X2), XP_020032189.1(isoform X3)
<i>Papio anubis</i>	XP_003897405.1(isoform X1), XP_009203089.1(isoform X2), XP_021792374.1(isoform X3)
<i>Sus scrofa</i>	NP_001182255.1
<i>Aotus nancymae</i>	XP_012292099.1(isoform X1), XP_012292100.1(isoform X2)
<i>Macaca fascicularis</i>	NP_001271025.1
<i>Pongo abelii</i>	NP_001126487.1

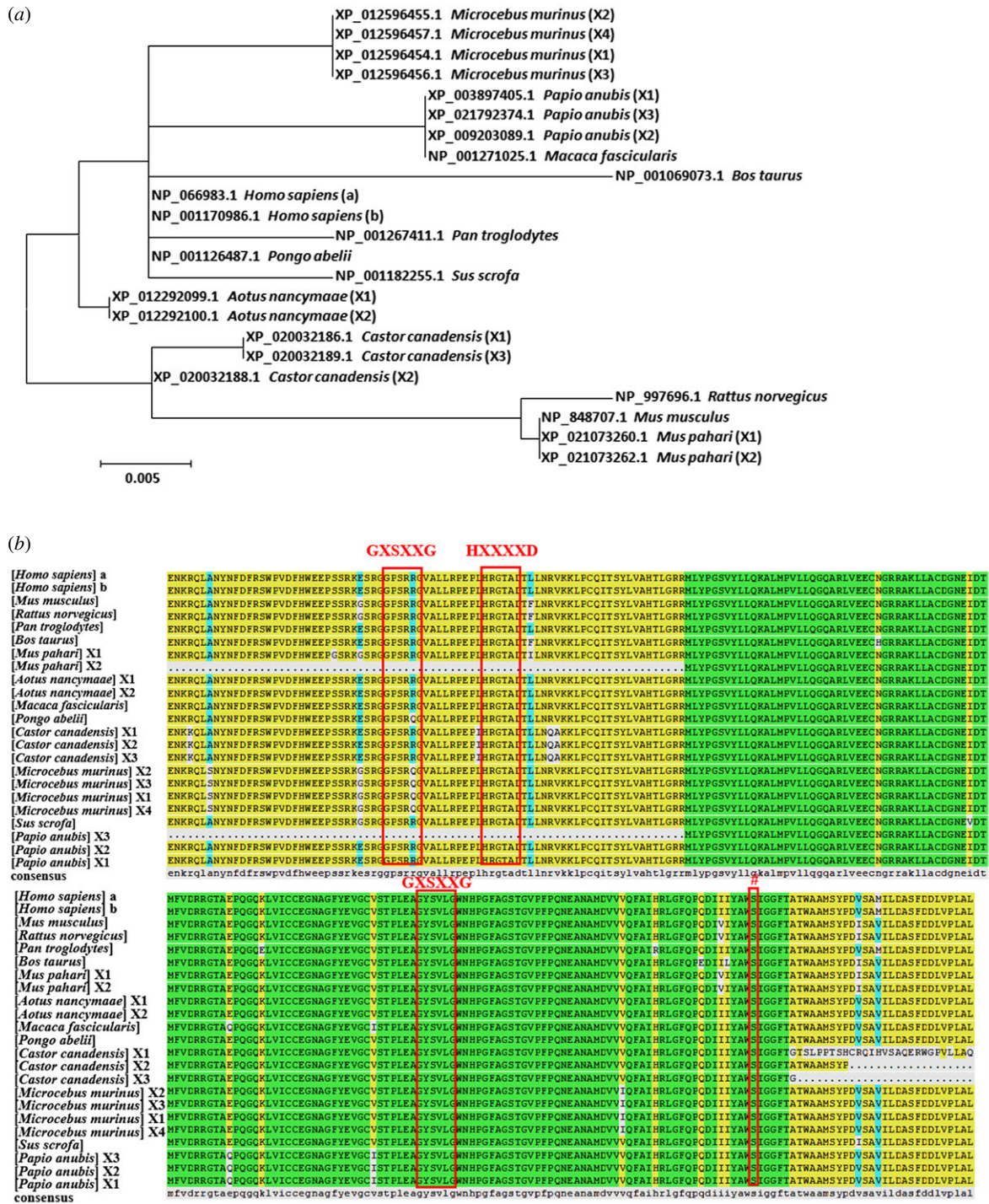
558 and 339 aa, respectively. However, the functional domains, including the alpha/beta hydrolytic enzyme domain, acyl-transferase motif HXXXXD (H, histidine; D, aspartic acid and X, any residues), lipase-like motifs GXSSXG (G, glycine; S, serine and X, any residues) and nucleophile centres (Ser, Cys or Asp), are highly conserved (figure 3b) [6]. The present analysis further confirmed the findings of previous reports [6,19] and that ABHD16A is genetically distant from the other members of the ABHD family [6].

## 5. Research progress related to ABHD16A

In 1989, Spies *et al.* [12] predicted that ABHD16 probably functioned in immune regulation processes because its gene location is similar to that of TNF and HSP70 in the MHC

III gene cluster [12,13]. However, during the following two decades, few gratifying results regarding ABHD16A were reported. Subsequently, Mathew's group reported that the expression of ABHD16A could influence the immunogenicity of bone marrow cells in recombinant B10.BR mice [21]. By analysing the polymorphisms and haplotypes of ABHD16A, Hsieh *et al.* [3] found several associations between ABHD16A and the genetic predisposition to coronary artery aneurysm and Kawasaki disease. However, during the following few years, the underlying mechanism was not further explored.

In 2014, Savinainen *et al.* pioneered a study investigating the enzymatic characteristics of human ABHD16A *in vitro* and revealed that it was a lipase with preference for medium-chain and long-chain fatty acids, especially



**Figure 3.** Conservation analysis of the amino acid sequence of ABHD16A. (a) Phylogenetic tree of the ABHD16A amino acid sequences from 13 mammalian species. Codes prefixed by X represent different variants. The phylogenetic tree was constructed using the neighbour-joining method by MEGA. (b) Multiple alignment of ABHD16A in 13 mammals using DNAMAN, and the different colours represent different homologies of amino acids. The amino acid residues in the red boxes indicate the predicted instructions of the lipase-like motif (GXSXXG), the conserved (HXXXX) motif and the active nucleophile centre (#, Ser, Cys or Asp), respectively.

long-chain unsaturated monoglycerides and 15-deoxy- $\Delta$ 12,14-prostaglandin J2–2-glycerol ester (15d-PGJ2-G) [19], and its esterase hydrolysis activity could effectively be inhibited by hormone-sensitive lipase inhibitors. Another important breakthrough was achieved by Kamat *et al.* [2] who showed that the interplay between ABHD16A and ABHD12 dynamically regulates immunomodulatory lysophosphatidylserines (lyso-PSs) and consequently affects the release of lipopolysaccharide-induced proinflammatory cytokines from macrophages. A previous study showed that homozygous mutations of ABHD12 could cause autosomal recessive neurodegenerative disease characterized by

polyneuropathy, hearing loss, ataxia, retinitis pigmentosa and cataract (PHARC) [22–24]. ABHD12 deficiency aggravated neuroinflammation and was closely associated with cerebellar atrophy and peripheral neuroinflammatory disease in cell models, murine PHARC and zebrafish [9,24]. ABHD16A has a higher specific activity with PS than with hydrolysing lysophospholipids, other diacylated phospholipids and neutral lipids [2]. Several selective inhibitors of ABHD16A have been identified through comparative activity-based protein profiling analyses [2,19]. In addition, a more recent study showed that ABHD16A is an immune-balancing regulator that catalyses the hydrolysis of prostaglandin-glycerol

(PG-G) in neutrophils [1]. In *Sus scrofa*, a correlation was observed between single nucleotide polymorphisms (SNPs) of the ABHD16A gene and back fat thickness, implying that ABHD16A performs a function in the metabolism of adipose tissue [25].

Several interaction partners of ABHD16A, including IFITM1 (interferon-induced transmembrane proteins), hnRNP1 (heterogeneous nuclear ribonucleoprotein A1), RNF5 (RING zinc-finger domain protein), SPP (signal peptide peptidase), COX II (Mitochondrial cytochrome oxidase II), ATP5G3 (subunit of mitochondrial ATP synthase H<sup>+</sup> transporter) and NAD3 (Mitochondrial NADH dehydrogenase), were identified through a high-throughput yeast two-hybrid screening [26]. The functions of the interaction proteins above suggest that ABHD16A might play a role in multiple physiological processes. However, no further studies investigating the function or mechanism of these interactions have been reported. A microarray-based long non-coding RNA (lncRNA) expression profiling study showed that the lncRNA of ABHD16A could be a novel biomarker of coronary aneurysm [27]. In activated B cells, the reduced mRNA expression of ABHD16A by MiR-155 provided a clue regarding ABHD16A functions based on the important role played by mic-155 in various physiological and pathological processes [28]. Our latest studies showed that ABHD16A inhibited the application of Japanese encephalitis virus *in vitro* and was associated with the risk of inflammation-related liver disease (JX 2018 unpublished data).

## 6. Research progress related to the ABHD family members

Different members of the ABHD family are located on different chromosomes. These proteins have different numbers of exons and amino acid residues and show expression differences in different tissues. Although the functions of several members are unknown, studies have shown that these proteins play significant roles in glucose and lipid metabolism, immunoregulation and many human diseases (table 2).

### 6.1. Direct contribution to lipid metabolism

The biosynthesis and degradation of lipids are vital for organisms to sustain normal life activities, because lipids are important components of cellular structures, sources of energy, intracellular signalling molecules and are also involved in the acyl modification of proteins. The results showed that, in the ABHD protein family, ABHD2, ABHD3, ABHD4, ABHD5, ABHD6, ABHD12 and ABHD16 participated in the metabolism of glycerine esters or phospholipids. ABHD2 is a new triglyceride lipase with an ester hydrolysing capacity [34]. In addition, ABHD2 acted as a progesterone receptor associated with lipid hydrolase in the activation of sperm in the reproductive process [35]. ABHD3 selectively cleaved medium-chain phospholipids and oxidized short phospholipids [45]. In the mammalian nervous system, ABHD4 was a major regulator of *N*-acyl phospholipid metabolism, and had the capacity to hydrolyse *N*-arachidonoyl phosphatidylethanolamine nape, lyso-nape, *N*-acyl-phospholipid serine and other *N*-acyl phospholipids [47,48,102]. ABHD5 could promote the decomposition of

triglyceride due to its fatty triglyceride lipase activity [50,53,54]. ABHD6, which is a monoacylglycerol hydrolase, functions in balancing energy, regulating the function of brown adipose and modulating white adipose browning [72]. Both ABHD6 and ABHD12, which are 2-arachidonoylglycerol hydrolases, are involved in the endocannabinoid and eicosanoid signalling pathways in the brain [44]. A transcriptome analysis indicated that ABHD18A was probably related to the modulation of fatty acid composition in pig muscle [101].

### 6.2. An important role in liver diseases

The liver is the largest digestive gland and the centre of material and energy metabolism in the human body. As lipases, the ABHD proteins exert significant effects on hepatic glucose and lipid metabolism. The results of one study [59] showed that several members of the ABHD family were related to the occurrence and development of hepatopathy. Liver-specific ABHD5 knockout mice exhibit hepatomegaly and steatosis, and with increasing age the expression of inflammation factors and fibrosis factors at the mRNA level were significantly increased. These results suggest that the deletion of ABHD5 in the liver not only directly leads to liver steatosis but is also involved in steatohepatitis and fibrosis. The mice treated with the ABHD5 antisense oligonucleotide showed severe hepatic steatosis and increased hepatocellular diacylglycerol (DAG), which is a well-documented trigger of insulin resistance, but unexpectedly remained insulin-sensitive [61]. The molecular mechanism could be that a reduction in ABHD5 promotes the isolation of hepatocellular DAG in the lipid droplet/ER section and that the DAG redistribution from the plasma membrane precludes the PKC $\epsilon$  translocation to the plasma membrane, which leads to liver insulin resistance [61,63]. ABHD18 was identified as a risk factor for liver cirrhosis and HCC because of the genetic variations at loci involved in the immune response [100].

### 6.3. A regulator or marker of certain cancers

Many people worldwide suffer from various cancers, particularly metastatic cancer. Cancer cells have more active motility, stronger drug resistance and a greater tolerance to the host immune system. Cancer cells acquiring anoikis resistance survive after detaching from their primary origin and spreading throughout the body through the circulatory and lymphatic systems. A functional genomics study identified that ABHD2 was a regulator of anoikis resistance in ovarian cancer [7]. The results showed that the silencing of ABHD2 could cause OVCA420 cell apoptosis resistance, and the overexpression of ABHD2 could decrease cell resistance to apoptosis. In addition, the expression of ABHD2 is lower in clinical serous ovarian cancer specimens [7]. Studies have suggested that the expression inhibition of ABHD2 may promote a malignant phenotype and contribute to an adverse prognosis in patients with serous ovarian cancer. ABHD4 is a novel regulator of anoikis sensitivity because ABHD4 knockdown could inhibit anoikis in prostate cells and reduce anoikis sensitivity in nasopharyngeal and ovarian cancer cells, while the overexpression of ABHD4 increased anoikis sensitivity [49]. A deficiency of ABHD5 could promote a shift of metabolism to aerobic glycolysis and contribute to colorectal carcinoma development and progression [55].

**Table 2.** Mammalian ABHD superfamily members. The data regarding the number of exons were obtained from BioGPS, and the data regarding the relatively high expression in normal human tissues were primarily obtained from the BioGPS portal and the reported references.

protein name	molecular weight (kDa)	aliases	gene location in humans	number of exons	relatively high expression in normal human tissues (BioGPS)	related function or role in disease
ABHD1	45	LABH1	2p23.3	9	testis, sperm saphenous	related to oxidative stress in mouse and rat models [29–32]; expression downregulation is driven by hepatic steatosis and insulin resistance induced by Notch signalling [33]
ABHD2	48	HS1–2, LABH2, PHPS1–2	15q26.1	16	prostate, lung, NK cells, whole blood	a glyceridase and ester hydrolase cleaving 2AG and leading to sperm hyperactivation in a progesterone-dependent manner [34–36]; an androgen-regulated gene promoting prostate cancer growth and resistance to chemotherapy [37]; essential for the reproduction of HBV [38,39]; involved in calcium transfer from the endoplasmic reticulum to mitochondria [40] and chronic obstructive pulmonary disease (COPD) in a Chinese Han population [41]; associated with anoikis resistance in ovarian cancer [7] and possibly associated with tumorigenesis in hepatocytes, stomach cells and colon cells [42,43]
ABHD3	46	LABH3	18q11.2	12	colon, small intestine, whole blood	a brain serine hydrolase related to the activation of the endocannabinoid system [44]; a lipase playing the role of a physiological regulator in the metabolism of medium-chain phospholipids [45]; possibly influences innate immunity by transcription factor T-bet [46]
ABHD4	39	ABH4	14q11.2	8	adipocyte, testis	functions in <i>N</i> -Acyl ethanolamine synthesis as a (lyso) <i>N</i> -acyl phosphatidylethanolamine-selective lipase [47,48]; a novel regulator of anoikis resistance [49]

(Continued.)

**Table 2.** (Continued.)

protein name	molecular weight (kDa)	aliases	gene location in humans	number of exons	relatively high expression in normal human tissues (BioGPS)	related function or role in disease
ABHD5	39	CGI58; IECN2; NCIE2; CDS	3p21.33	8	adipose tissue, bone marrow	a critical acyltransferase with lysophosphatidylglycerol acyltransferase and adipose triglyceride lipase activities and is involved in metabolic disorders; as a lysophosphatidylglycerol acyltransferase, prompts autophagy and is associated with Chanarin-Dorfman syndrome by attenuating inflammatory responsiveness via the promotion of PPAR gamma signalling [50–52]; activates other adipose triglyceride lipases and stimulates triglyceride breakdown as an adipose triglyceride lipase [50,53,54]; a tumour suppressor in human colorectal carcinoma development and progression [55] and serves as a novel tumour marker in sebaceous carcinoma [56]; plays an important role in protecting against atherosclerosis development in macrophages in mice [57]; tissue-specific ABHD5 deficiency leads to lipid imbalance in the liver and plasma caused by the insufficient secretion of postprandial lipoprotein [58], and upregulates gene expression related to hepatic insulin resistance, neutral lipid storage disease, fibrosis, inflammation and hepatic steatosis [59–62]; downregulation of ABHD5 in the heart stimulates the development of diabetic cardiomyopathy by aggravating myocardial steatosis and oxidative stress [63]
ABHD6	38		3p14.3	10	small intestine, spleen, duodenum	as a monoacylglycerol hydrolase, involved in the activation of the endocannabinoid signalling system [44,64–67] and systemic lupus erythematosus [68]; negatively regulates AMPAR-mediated synaptic transmission in hippocampal neurons in HEK293 T cells [69,70]; acts as a critical regulator of metabolic syndrome [71] and energy balance, including the functional realization of brown adipose and the browning of white fat by promoting glucose-stimulated insulin secretion [72]; participates in the pathogenesis of obesity and fatty liver due to its degradation functions in late endosomal/lysosomal lipid Bis [64]; a new potential diagnostic marker or an alternative therapeutic target in Ewing family tumours [73]
ABHD7	42	EPHX4; EH4; EPHXRP	1p22.1	7	brain	a high-activity epoxide hydrolase for fatty acids [74]
ABHD8	47		19p13.11	5	brain	underlying breast and ovarian cancer risk [75]

(Continued.)

**Table 2.** (Continued.)

protein name	molecular weight (kDa)	aliases	gene location in humans	number of exons	relatively high expression in normal human tissues (BioGPS)	related function or role in disease
ABHD9	41	EPHX3; EHS	19p13.12	8	skin, oesophagus	a high-activity epoxide hydrolase for fatty acids [74]; the promoter hypermethylation of ABHD9 possibly leads to prostate cancer recurrence and serves as a marker for prostate cancer prognosis [76,77]
ABHD10	34		3q13.2	6	pineal, kidney, thyroid	affects the formation of immunotoxic metabolites, mycophenolic acid acyl-glucuronide [78,79]; acyl glucuronide and probenecid acyl glucuronide in human liver [80]
ABHD11	35	PP1226; WBSR21	7q11.23	7	colon, prostate	is associated with the development of distant metastases and serves as a novel biomarker of lung adenocarcinoma [81]
ABHD12	45	PHARC; ABHD12A; BEM46L2; C20orf22; dJ965G21.2	20p11.21	17	thyroid, brain	participates in the breakdown of 2-AG in the central nervous system and along with MAGL and ABHD6, controls 99% of 2-AG hydrolysis in the brain [65,82]; serves as a lysophospholipase and metabolizes lysophosphatidylserine, which participates in the endocannabinoid signalling pathway [9,18]; associated with PHARC [9,22,23,83,84]; a potential indicator of liver diseases in plasma [12]
ABHD12B	41	BEM46L3; C14orf29; c14_5314	14q22.1	15	skin	a gene potentially related to obesity [85], chronic periodontitis [86] and longitudinal changes in ventricle size [87]
ABHD13	39	BEM46L1; C13orf6; bA153I24.2	13q33.3	2	bone marrow, thyroid	very little known
ABHD14A	30	DORZ1	3p21.2	5	kidney, thyroid, adrenal	a candidate gene for autism spectrum disorder [88]; plays a potential role in cerebellar development through Zic1, which is a finger protein that controls vertebrate neural development [89]
ABHD14B	22	CIB; HEL-S-299	3p21.2	4	fat, kidney, liver	a potential structural distinctive cofactor with hydrolase activity for transcription initiation factor [90]; a marker of tumour progression in an unknown primary syndrome in neuroendocrine tumours [91]
ABHD15	52		17q11.2	2	fat	is involved in insulin signalling in adipocytes [92–94]; Plays an important role in the development of adipocytes and apoptosis [95]
ABHD16A	63	BAT5; NG26; PP199; D6S82E	6p21.33	21	testis, brain	refer to the fourth part of the text

(Continued.)



Table 2. (Continued.)

protein name	molecular weight (kDa)	aliases	gene location in humans	number of exons	relatively high expression in normal human tissues (BioGPS)	related function or role in disease
ABHD16B	53	C20orf135; dJ591C20.1	20q13.33	1	testis	the methylation of the abhd16b gene was related to COPD [96]
ABHD17A		C19orf27; FAM108A1	19p13.3	7	spleen, bone marrow	as a depalmitoylating enzyme, depalmitoylates Ras [97,98], PSD95 [10,98] and MAP6 [99]
ABHD17B		CGI-67; C9orf77; FAM108B1	9q21.13	8	brain	a depalmitoylating enzyme [10,97–99]
ABHD17C		FAM108C1	15q25.1	3	colon	a depalmitoylating enzyme [10,97–99]
ABHD18	46.9	C4orf29	4q28.2	18	ubiquitously expressed at low to moderate levels	very little is known about this protein; probably associated with human hepatocellular carcinoma (HCC) [100] and fatty acid composition in pig muscle [101]

Moreover, ABHD5 was identified as a novel reliable marker for distinguishing sebaceous carcinoma from non-sebaceous tumours [56]. Compared with the expression seen in normal tissues, the high expression of ABHD6 in the Ewing sarcoma family of tumours suggested that ABHD6 might be a potential diagnostic marker or drug target [73]. The results from an expression quantitative trait locus (eQTL) analysis showed that the expression of ABHD8 was higher in breast cancer and ovarian cancer than that in normal corresponding organs [75]. Using an activity-based biomarker discovery platform, Wiedl *et al.* identified that ABHD11 is a novel biomarker that, through its activities, could predict the presence of aggressive lung adenocarcinomas and the development of distant metastases [81]. By analysing SNPs and copy number variations in the peripheral blood, Clifford *et al.* [100] found that ABHD18 was an important factor in hepatocellular carcinoma in the Asian population.

#### 6.4. A helper or restriction factor in virus infection

Using a human genome-wide bioarray, Ding *et al.* [38] found that ABHD2 could contribute to the proliferation of hepatitis B viruses (HBVs) by analysing the differential expression of HBV-expressing and control cells through a wholegenome expression profiling of hepatitis B. The antisense oligodeoxynucleotides targeting ABHD2 successfully blocked the replication and expression of HBV [38]. Vieyres *et al.* [103] demonstrated that ABHD5 was a new host factor contributing to virus morphogenesis in hepatitis C virus production and could trigger the mobilization and consumption of the luminal lipid droplet, which is important for the envelopment, maturation and budding of infectious virions. Our latest results show that ABHD16A inhibits the proliferation of Japanese encephalitis virus (JX 2018, unpublished data). The finding above suggested that the ABHD proteins might be potential targets in therapies for viral infectious diseases.

#### 6.5. A key gene in other diseases

ABHD2 was found to be a critical gene in chronic obstructive pulmonary disease (COPD) by evaluating the genetic variation in the ABHD2 gene among Han Chinese COPD patients and normal controls [41]. The analysis of the DNA methylation data of genes throughout the genome showed that COPD is associated with DNA methylation at the CpG sites of the ABHD16B gene [96]. A mutation of the ABHD5 gene could lead to a rare genetic disorder called Chanarin-Dorfman Syndrome because such patients accumulate excess triacylglycerol caused by a functional defect in ABHD5 in certain tissues and ichthyosis [52,53]. In addition, a reduction in the ABHD5 expression levels in the heart may aggravate myocardial steatosis, oxidative stress and diabetic cardiomyopathy [63]. ABHD6, which is an MAG hydrolase, stimulated insulin secretion induced by glucose in pancreatic beta cells, participated in the regulation of energy homeostasis via PPAR gamma and may represent a new drug target for obesity and type 2 diabetes [72]. Based on genome-wide association studies investigating chronic periodontitis, Rhodin *et al.* [86] found that ABHD12B was associated with chronic periodontitis and worthy of further investigation. ABHD14A was identified as a candidate gene for autism spectrum disorder in an analysis of homozygous haplotype mapping of SNPs [88].

## 7. Conclusion and perspectives

Here, we analysed the gene and protein structure, molecular evolution and existing or presumed functions of ABHD16A, and reviewed the functions of the other ABHD family members. Based on previous findings, we highlight the important roles played by the ABHDs during the occurrence and development of diseases related to lipid metabolism and inflammation.

Human ABHD16A might be a potential diagnostic marker of inflammatory-related diseases or play critical roles in the progress of such diseases. The high conservation of its amino acid sequences, lipase motifs and acyltransferase motifs indicates to a certain extent the necessity of this gene for specific cellular functions in mammalian species. ABHD16A not only participates in lipid metabolism but is also involved in the regulation of inflammation and immunity. Many studies have shown that other members of the ABHD protein family are associated with different diseases, such as cancer, lipid metabolism, liver disease and pulmonary disease. Studies investigating these proteins could not only enhance our understanding of the molecular mechanisms of related illnesses but also contribute to screening novel targets and new drugs. The regulation of virus infection suggested that ABHD could not be ignored as a potential marker or target, especially in an era of emerging and re-emerging viruses that unexpectedly appear.

Therefore, the following are potential future directions: (i) the identification or establishment of the inner link between the ABHD proteins and diseases; (ii) the identification of the enzymatic characteristics of ABHD proteins whose activity remains unknown; (iii) the exploration of the molecular mechanisms or pathways of disease-related ABHD proteins; (iv) the screening of proteins interacting with ABHD, especially in the field of intracellular transport and acylation modification (although ABHD16A and ABHD17

could be involved in the palmitoylation/depalmitoylation cycle, protein transport, organelle localization or special functions [10,104,105], their mechanism and targets must be further studied); and (v) the establishment of model cells or animals. The proper experimental model is crucial for studies investigating diseases. Some techniques (e.g. siRNA or CRISPR/CAS9) have been widely used in studies examining molecular mechanisms, especially of human diseases. Tissue-specific or conditional transgenic mice and gene knockout mice are needed if the offspring have a lower positive rate or the knockout leads to a failure in embryogenesis.

In conclusion, the human ABHD protein family has many members and performs a variety of biological functions. These proteins could play an important role in the regulation of lipid metabolism and signalling transduction pathways, and are possibly directly or indirectly correlated with several human diseases. Although interesting results have been obtained, the functions and molecular mechanisms remain unclear and should be explored in more detail in the future. For researchers, studies in this field could be promising, interesting and significant, especially for understanding several human diseases.

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