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REVIEW

MBOAT7 in liver and extrahepatic diseases

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Abstract

MBOAT7 is a protein anchored to endomembranes by several transmembrane domains. It has a catalytic dyad involved in remodelling of phosphatidylinositol with polyunsaturated fatty acids. Genetic variants in the *MBOAT7* gene have been associated with the entire spectrum of non-alcoholic fatty liver (NAFLD), recently redefined as metabolic dysfunction-associated fatty liver disease (MAFLD) and, lately, steatotic liver disease (SLD), and to an increasing number of extrahepatic conditions. In this review, we will (a) elucidate the molecular mechanisms by which *MBOAT7* loss-of-function predisposes to MAFLD and neurodevelopmental disorders and (b) discuss the growing number of genetic studies linking *MBOAT7* to hepatic and extrahepatic diseases. MBOAT7 complete loss of function causes severe changes in brain development resulting in several neurological manifestations. Lower MBOAT7 hepatic expression at both the mRNA and protein levels, due to missense nucleotide polymorphisms (SNPs) in the locus containing the *MBOAT7* gene, affects specifically metabolic and viral diseases in the liver from simple steatosis to hepatocellular carcinoma, and potentially COVID-19 disease. This body of evidence shows that phosphatidylinositol remodelling is a key factor for human health.

KEYWORDS
arachidonic acid, Land's cycle, LPIAT1, LPIAT11, MAFLD, SLD

1 | INTRODUCTION

The human Membrane Bound O-Acyltransferase Domain Containing 7 (MBOAT7), also known as lysophosphatidylinositol acyltransferase 1 (LPLAT1, or LPIAT11),[1] belongs to the MBOAT family composed of enzymes involved in lipid metabolism, namely acyl-CoA cholesterol acyltransferases 1 (ACAT1), ACAT2 and diacylglycerol O-acyltransferase (DGAT1), as well as the glycosylphosphatidylinositol anchor-remodelling enzyme (Gup1p)[2–6] (Figure 1A). MBOAT7 is highly conserved within species (Figure 1B,C) and takes part to the

Abbreviations: AA, arachidonic acid; ACAT1, acyl-CoA cholesterol acyltransferases 1; ACAT2, acyl-CoA cholesterol acyltransferases 2; ACC, acetyl CoA carboxylase; ALD, alcohol-related liver disease; ALT, alanine aminotransferases; AMI, myocardial infarction; ASO, second-generation antisense oligonucleotides; AST, aspartate aminotransferase; AT, adipose tissue; CAD, coronary artery disease; ccRCC, clear cell renal cell carcinoma; CDS, cytidine diphosphate diacylglycerol synthase; CKD, chronic kidney disease; COX, cyclooxygenases; CVD, cardiovascular disease; DAA, direct-acting antivirals; DAGs, diglycerides; DGAT1, diacylglycerol O-acyltransferase; EPA, eicosapentaenoic acid; ER, endoplasmic reticulum; FA, fatty acid; FAS, fatty acid synthase; FATP-1, fatty acid transport protein 1; Gup1p, glycosylphosphatidylinositol anchor-remodelling enzyme; GWAS, genome-wide association study; HCC, hepatocellular carcinoma; HFD, high-fat diet; ID, intellectual disability; LDs, lipid droplets; LOX, lipoxygenases; LPI, lysophosphatidylinositol; LPIAT1, lysophosphatidylinositol acyltransferase 1; MAFLD, metabolic-associated fatty liver disease; MAMs, mitochondria-associated membranes; MBOAT7, membrane bound O-acyltransferase domain containing 7; MUFA, monounsaturated fatty acid; NAFLD, non-alcoholic fatty liver; NASH, non-alcoholic steatohepatitis; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PI, phosphatidylinositol; PtdIns, phosphoinositides; PUFA, polyunsaturated fatty acid; SNP, single-nucleotide polymorphism; SREBP-1c, sterol regulatory element-binding protein 1; T2D, type 2 diabetes mellitus; TAGs, triglycerides; TLRs, Toll-like receptor (TLRs); TMC4, transmembrane channel like 4; WES, whole exome sequencing.

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phospholipid acyl-chain remodelling by introducing arachidonic acid into phosphatidylinositol (PI).[7] *MBOAT7* has been identified as an important genetic determinant of several human disorders, including cognitive development and metabolic dysfunction-associated fatty liver disease (MAFLD).

In this review, we will (a) elucidate the molecular mechanisms by which *MBOAT7* loss-of-function predisposes to MAFLD, recently renamed as steatotic liver disease (SLD), neurodevelopmental disorders and other pathological conditions, and (b) discuss the growing number of genetic studies linking *MBOAT7* to hepatic and extrahepatic diseases.

Key points

1. MBOAT7 contributes to the acyl-chain remodelling of phospholipids via the Land's cycle.
2. MBOAT7 catalyses the esterification of free arachidonoyl-CoA to lysophosphatidylinositol, releasing newly remodelled phosphatidylinositol with a higher degree of desaturation, thus affecting membrane fluidity and the availability of arachidonic acid, a known substrate for the synthesis of inflammatory lipid mediators.
3. The *MBOAT7 rs641738 C>T* genetic variant is a strong susceptibility risk factor for chronic liver disease.
4. *MBOAT7* gene has been identified as a key determinant of brain development and neurological disorders.
5. MBOAT7 gene and protein expression have been recently associated with extrahepatic dysfunctions.

2 | MBOAT7 STRUCTURE AND FUNCTION

The *MBOAT7* gene maps to human chromosome band 19q13.42 and consists of 8 exons encoding for a 472 amino acids-long protein highly expressed in liver, heart, testis and adipose tissue. MBOAT7 is anchored to endomembranes, namely the endoplasmic reticulum (ER), lipid droplets (LDs) and mitochondria-associated membranes (MAMs), by 11 transmembrane domains[8–10] (Figure 2). MBOAT7 has a catalytic dyad composed of the asparagine in position 321 and the histidine in position 356[9] (Figure 2).

MBOAT7 has been described as a lysophosphatidylinositol (LPI) acyltransferase that exerts its enzymatic activity as part of a more orchestrated remodelling pathway known as the Lands' cycle.[11] The Lands' cycle is the acyl-chain remodelling of phospholipids through two enzymatic reactions: the deacylation of unsaturated phospholipids from the *sn-2* position of phospholipids, catalysed by phospholipases, and the esterification of fatty acids (FAs) to lysophospholipids, catalysed by acyl-transferases, to release newly remodelled phospholipids[12,13] (Figure 3A). The synthesis and enzymatic activity of these enzymes modify the availability of acyl-CoA and lysophospholipids, thus affecting the fluidity, asymmetry and lipid composition of cellular membranes.[6]

Specifically, *MBOAT7* incorporates free polyunsaturated FAs (PUFAs) to LPI and other lysophospholipids[14–16] (Figure 3B,C). Phosphatidylinositol (PI) is one of the main glycerophospholipids in the eukaryotic cells contributing to about 2%–10% of the total phospholipid pool.[15] Once synthesized in the ER by the activity of cytidine diphosphate diacylglycerol synthase (CDS) and PI synthases,[17] PIs are usually enriched in saturated or monounsaturated FAs (MUFAs) as acyl chains. PIs are then modified via the Land's cycle during which PUFAs are esterified in the *sn-2* position, thus increasing the degree of unsaturation of phospholipids and regulating the availability of free PUFAs, such as arachidonic acid (AA). Indeed, *MBOAT7* showed a remarkable specificity for arachidonoyl-CoA, contributing to the intricate arachidonate recycling into lysophospholipids. Free cellular AA levels are under tight regulation of lipoxygenases (LOX) and cyclooxygenases (COX) that metabolize AA into its pro- and anti-inflammatory metabolites (Figure 3B,C). These molecules, such as prostanoids and eicosanoids, play a crucial role in the inflammatory response and cell signalling,[18] are typically higher in NASH patients,[19] and seem to be important for tumour growth by promoting cancer cell proliferation, migration, and apoptosis.[20]

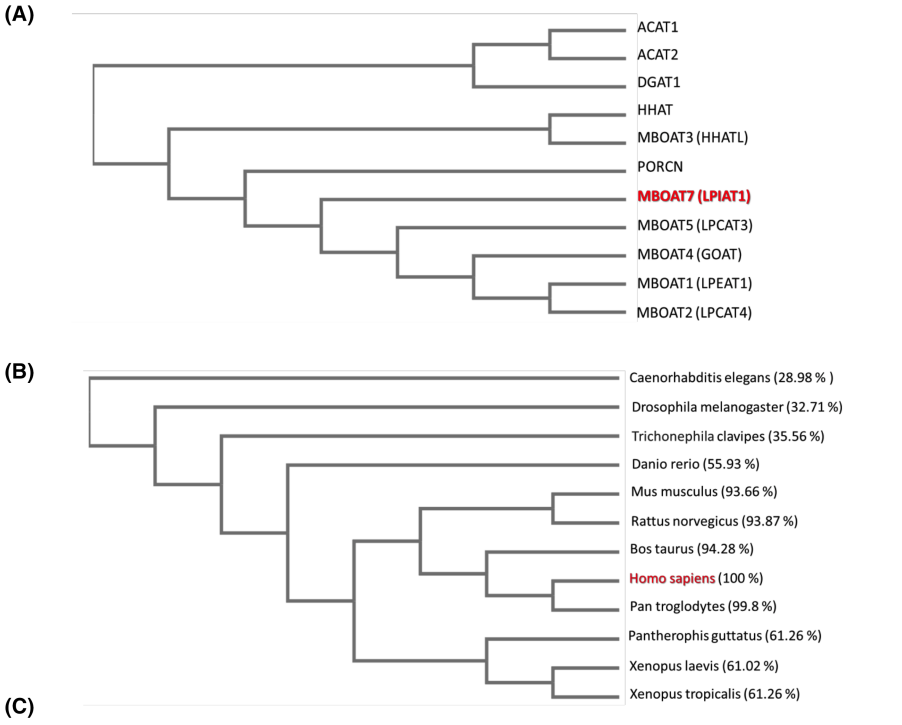
3 | REDUCED MBOAT7 EXPRESSION AND ENZYMATIC ACTIVITY AFFECT LIPID METABOLISM AND PREDISPOSE TO STEATOTIC LIVER DISEASE

The first evidence regarding MBOAT7 enzymatic activity was provided by Lee et al. in 2008.[21] By employing an RNA

FIGURE 1 Homology amongst MBOATs family members and amongst MBOAT7 proteins in different species. (A) Guide Tree of human MBOATs family. (B) Guide Tree of MBOAT7 in different species. The % shows the identity percentage of the protein sequences of the various species respect to Homo sapiens (100%). The guide tree was drawn by using ClustalW (www.ebi.ac.uk/clustalw). (C) Multiple Sequence Alignment of MBOAT7 in different species. * Conserved sequence (identical); : Conservative mutation; . Semi-conservative mutation; – Gap. The accession numbers for all the MBOAT proteins are as follows: ACAT1, Sterol O-acyltransferase 1 (NP_003092.4); ACAT2, Sterol O-acyltransferase 2 (NP_003569.1); DGAT1, Diacylglycerol O-acyltransferase 1 (NP_036211.2); PORCN, Porcupine (NP_073736.2); HHAT, hedgehog acyltransferase (NP_001116306.1); HHATL, MBOAT3 (NP_065758.3); GOAT, Ghrelin O-acyltransferase, MBOAT4 (NP_001094386.1); LPEAT1, MBOAT1 (NP_001073949.1); LPCAT3, MBOAT5 (NP_005759.4); LPCAT4, MBOAT2 (NP_620154.2); LPIAT1, MBOAT7, (NP_077274.3). The accession number for MBOAT7 in the different species are as follow: Caenorhabditis elegans (NP_509760.2); Drosophila melanogaster (NP_609029.1); Trichonephila clavipes (PRD24445.1); Danio rerio (NP_956831.1); Mus musculus (NP_084210.2); Rattus norvegicus (NP_001128450.1); Homo sapiens (NP_077274.3); Bos taurus (NP_001068620.1); Pantherophis guttatus (XP_034275367.1); Xenopus laevis (NP_001088606.1); Xenopus tropicalis (XP_012822891.2).

interference-based genetic screening using *Caenorhabditis elegans*, they identified a gene encoding an acyltransferase, namely mboa-7, that selectively incorporated free PUFAs, such as AA and eicosapentaenoic acid (EPA), into LPI, releasing newly-remodelled PI.[21] In the same year, Gijón et al. showed that Mboat7, the mammalian ortholog of mboa-7, catalyses the esterification of arachidonyl-CoA into LPI in neutrophils.[5] To prove the involvement of MBOAT7 in PI metabolism, several studies showed that *Mboat7* knockout mice have lower levels of hepatic and cerebral phosphoinositides (PtdIns), mostly AA-PI (38:4), while all the other lipid species were unchanged.[14,17]

In addition, the specific knockdown of *Mboat7* in the liver and adipose tissue (AT) in high-fat diet (HFD)-fed mice by using



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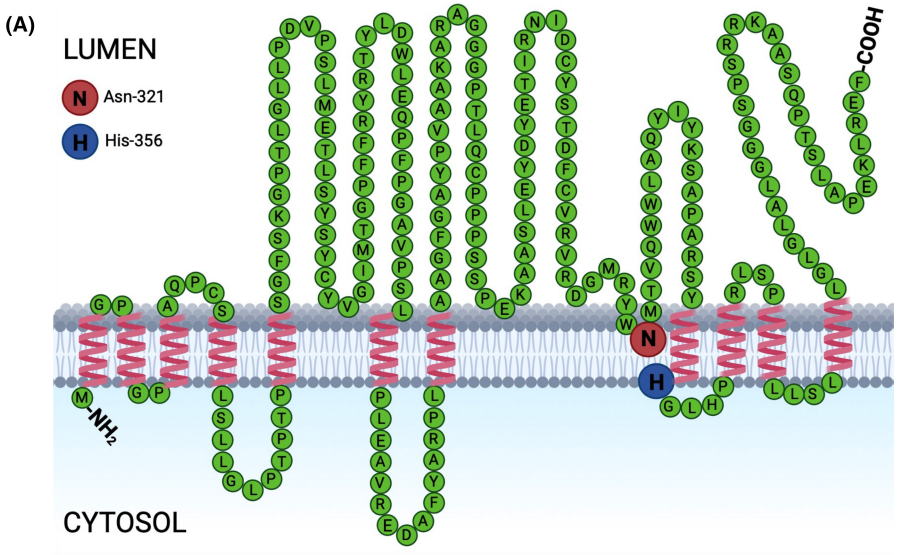

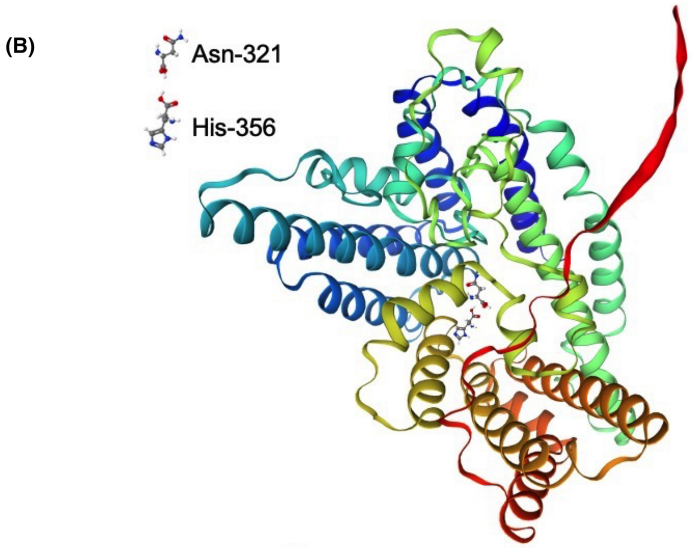

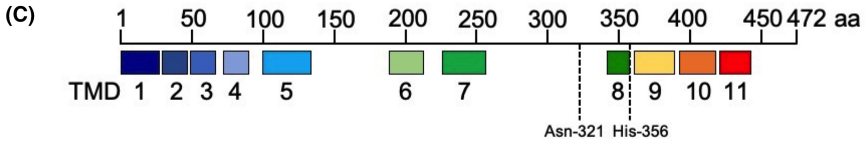

FIGURE 2 Illustration of 2D and 3D structure of MBOAT7 transmembrane domains and catalytic dyad. (A) MBOAT7 is a multispanning membrane protein. Transmembrane domains (TMDs) are shown as pink alpha-helixes. The asparagine in position 321 (Asn-321) and the Histidine in position 356 (His-356) composing the catalytic dyad of the protein are shown as a red or a blue dot, respectively. (B) 3D protein structure model of human MBOAT7 generated by using the SWISS-MODEL Repository database. The localization of the Asn-321 and His-356 is shown in the model. (C) MBOAT7 is a 472 amino acids-long protein consisting of 11 TMDs. TMDs along the protein structure are shown as coloured rectangles.

second-generation antisense oligonucleotides (ASOs) resulted in alterations in LPI and PI composition in the liver and AT, thus inducing a local imbalance of inflammatory lipid mediators.[22] In particular, the *Mboat7* loss led to a strong reduction of hepatic and serum 38:3 and 38:4-PI levels, while the levels of more saturated PI increased and the other major phospholipids were unaltered in the liver.[22] Importantly, the reduction of PI species due to hepatic *Mboat7* depletion caused the accumulation of LPI, a proinflammatory molecule involved in macrophage and endothelial cell activation.[23–25] Indeed, LPI induces de novo lipogenesis and inhibits β-oxidation in hepatocytes while promoting the activation of hepatic stellate cells through its receptor G protein-coupled receptors 55 (GPR55).[26,27] GPR55 silencing ameliorates the LPI-induced effects, thus suggesting an important contribution of GPR55 in mediating the progression of SLD. Moreover, circulating LPI and hepatic GPR55 levels were higher in patients with SLD compared with individuals without obesity and MAFLD.[26] The ability of LPI to induce hepatic inflammation in the absence of *Mboat7* has been demonstrated by Helsley et al. by injecting endogenous LPI intraperitoneally in mice, causing the overexpression of proinflammatory genes in *Mboat7* knockout mice, but not in those wild type.[22]

Moreover, by using human purified MBOAT7 protein, Caddeo et al. showed that human MBOAT7 preferentially transferred PUFAs, such as AA and EPA, to LPI, while displaying a weak enzymatic activity in transferring saturated and unsaturated FAs, regardless of the lipid substrate.[28] Missense mutations in the amino

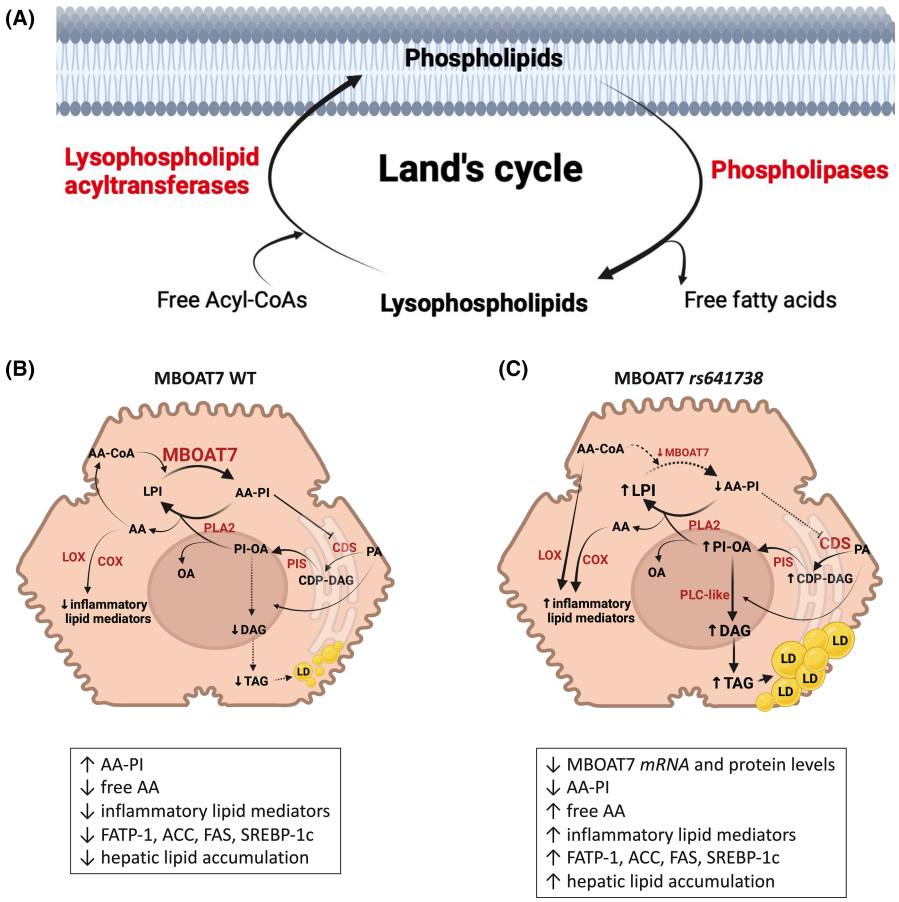

FIGURE 3 MBOAT7 remodelling of intracellular phosphatidylinositol and its consequences. Phospholipids are enzymatically modified by the activity of phospholipases and acyltransferases. (A) Phospholipid acyl-chain remodelling in the Land's cycle; (B) MBOAT7 incorporates free polyunsaturated fatty acids (PUFAs), such as arachidonic acid (AA), into lysophospholipids, to release newly remodelled phospholipids with a higher degree of unsaturation. (C) The MBOAT7 rs641738 variant is associated with reduced MBOAT7 mRNA and protein levels that induce an accumulation of intracellular free AA used as a substrate for the synthesis of inflammatory lipid mediators, such as prostaglandins and leukotrienes. Moreover, a weaker MBOAT7 enzymatic activity leads to a higher PI availability that can be used to synthesize DAGs by a PLC-like protein. DAGs are the main precursor of TAGs mainly stored in lipid droplets (LDs). AA, arachidonic acid; ACC, acetyl-CoA carboxylase; AA-CoA, arachidonoyl-CoA; AA-PI, arachidonic acid-containing phosphatidylinositol; CDP-DAG, cytidine diphosphate diacylglycerol; CDS, cytidine diphosphate diacylglycerol synthase; COX, cyclo-oxygenase; DAG, diacylglycerol; FAS, fatty acid synthase; FATP-1, Fatty acid transport protein 1; LD, lipid droplets; LOX, Lipoxygenase; LPI, lysophosphatidylinositol 1; MBOAT7, Membrane Bound O-acyltransferase domain-containing 7; OA, oleic acid; PA, palmitic acid; PI-OA, oleic acid-containing phosphatidylinositol; PIS, PI synthase; PLA2, phospholipase A2; PLC, phospholipase C; SREBP-1c, sterol regulatory element-binding protein-1c; TAG, triacylglycerol; WT, wild-type.

acid residues composing the catalytic dyad resulted in a loss of the O-acyltransferase activity of MBOAT7 in vitro.[28] Interestingly, the MBOAT7 enzymatic activity is inhibited by thimerosal, an organomercury compound used as antiseptic and antifungal agent, by ATR-101, a selective inhibitor of ACAT1, and by Sevenin-1 and Sevenin-2.[5,8]

In 2021, Thangapandi et al. showed that disturbance of the PI acyl chain remodelling pathway driven by hepatocyte-specific deletion of *Mboat7* (*Mboat7*$^{\Delta hep}$) in mice is sufficient to elicit hepatic steatosis without any significant changes in liver weight or inflammatory cell populations under a balanced basal diet. Moreover, total PI levels were reduced in *Mboat7*$^{\Delta hep}$ livers, and in particular, PI38:4, PI36:4 and PI38:5 were strongly downregulated as compared to *Mboat7*^{WT} livers, whereas all other PI species were increased or unaltered in *Mboat7*$^{\Delta hep}$ livers as compared to *Mboat7*^{WT} hepatic tissue.[29] Furthermore, *Mboat7*$^{\Delta hep}$ mice developed bridging fibrosis upon high-fat, methionine-low, choline-deficient diet due to the overexpression of extracellular matrix and tissue remodelling genes.[29] All these studies provided evidence that *Mboat7* deficiency drives hepatic steatosis and the progression to a more severe liver disease, regardless of dietary composition.

To understand the reduction in hepatic AA-PI content and the accelerated triglycerides (TAGs) synthesis, in the same year Tanaka et al. described a non-canonical pathway through which *MBOAT7* downregulation leads to fatty liver disease. They showed that hepatocyte-specific *Mboat7* depletion in vitro resulted in hepatic fat accumulation via TAG synthesis upregulation, without affecting either TAG degradation or secretion. Moreover, *MBOAT7* knock out promotes a spontaneous increase in hepatic collagen

deposition and triglyceride content fuelled by an accelerated PI turnover in both in vivo and in vitro models. The consequential reduced AA-PI content upregulates the activity of CDS causing an excess of saturated PI that can be used as a substrate by a phospholipase C-like protein for the synthesis of inositol monophosphate and diglycerides (DAGs), the main precursors of TAGs[30] (Figure 3B). To prove the causal involvement of MBOAT7 on lipid metabolism, Meroni et al. induced acute down-regulation of *Mboat7* in mice that displayed heightened hepatic TAG content and alteration of the lipid species, consistent with a defective MBOAT7 enzymatic activity.[31] In addition, MBOAT7 deletion in hepatocytes led to reduced concentration of LPI and AA containing-PI, that further confirmed the crucial role of MBOAT7 in the arachidonate recycling and caused the overexpression of the FA transporter Fatp-1, thus facilitating intracellular fat accumulation.[31]

Mboat7 liver-specific knock out in mice fed a Chow diet with a fasting-refeeding regime led to a strong upregulation of de novo lipogenesis due to the overexpression of Fatty acid synthase (FAS), Acetyl CoA carboxylase (ACC) and Sterol regulatory element-binding protein 1 (SREBP-1c), the most important membrane-bound transcription factor for the activation of genes involved in the FA biosynthesis.[32] The importance of the MBOAT7-SREBP-1c axis was confirmed by the hepatocyte-specific depletion of MBOAT7 and SREBP cleavage-activating protein (Scap) that mediated the activation of SREBP-1c and, consequently, the regulation of fatty acid metabolism.[32]

These studies showed that MBOAT7 depletion in the liver causes hepatic steatosis by at least two mechanisms.

4 | MBOAT7 GENETIC VARIATION AND CHRONIC LIVER DISEASE IN HUMANS

4.1 | Fatty liver disease

Non-alcoholic fatty liver disease (NAFLD), or more recently redefined metabolic-associated fatty liver disease (MAFLD) or steatotic liver disease (SLD), has become the most common cause of liver disease in Western countries. It encompasses a spectrum of conditions ranging from simple steatosis (non-alcoholic fatty liver or NAFL), non-alcoholic steatohepatitis (NASH), NASH-related cirrhosis and hepatocellular carcinoma (HCC).[33] The risk of developing MAFLD is determined by the combination of epigenetic risk factors, such as obesity, metabolic syndrome, poor physical activity, viral infections, diabetes, and genetic risk factors.[34] Due to the strong interaction between these risk factors, it is of pivotal importance to consider the individual susceptibility to MAFLD. In the last decades, some of the most robust and reproducible association between genetic polymorphisms and the evolution of liver disease, such as common variants in *PNPLA3*, *TM6SF2*, *GCKR*, *HSD17B13*, *PSD3*, *APOE* and *GPAM* genes, have been identified by Genome-Wide Association Study (GWAS) technology.[35–40]

As a matter of interest, the *rs641738 C>T* single-nucleotide polymorphism mapped five hundred base pairs downstream of the 3′-UTR of the *MBOAT7* gene and in the exon 1 of the *Transmembrane Channel Like 4* (*TMC4*) gene was identified by GWAS. The T allele has an allelic frequency of 0.37 in the global population, but it is highly variable. Indeed, the allele frequency of the minor allele in 1000 Genomes project ranges from 0.32 in African to 0.44 in European and 0.22 in Asian ancestry. Despite the amino acid substitution (p.Gly17Glu) causing a missense change in *TMC4*, the effect of the variant is mediated by mRNA levels changes in *MBOAT7*. Indeed, genetic deletions of the *Tmc4* gene did not lead to hepatic steatosis in mice, while Mboat7 depletion led to hepatic fat retention.[22] The *rs641738 minor allele C>T* gene variant results in a reduction in the *MBOAT7* gene expression and protein synthesis levels favouring the accumulation of free AA, a known driver of hepatic inflammation as precursor of proinflammatory and anti-inflammatory lipid mediators such as prostaglandins, thromboxanes, and leukotrienes.[10,41,42] Recently, hepatic MBOAT7 overexpression by adeno-associated virus infection in mice fed either choline-deficient high-fat diet or Gubra Amylin NASH diet fails to improve NASH histology even if liver weight, hepatic TAG content, circulating alanine aminotransferases (ALT) and aspartate aminotransferase (AST) levels were significantly improved.[43]

Interestingly, Longo et al. showed that the co-presence of the most common genetic variants associated with NAFLD progression, such as *PNPLA3 148M*, *MBOAT7 rs641738* and *TM6SF2 E167K*, acts in an additive fashion attributing an increased risk of steatosis, cirrhosis severity and HCC development per each additional risk allele carried, by altering lipid droplets accumulation, mitochondrial morphology and metabolic reprogramming toward HCC in vitro.[44] This is consistent with a genetic risk score composed of these variants in humans that predicts the occurrence of severe liver disease and cancer.[45,46]

Moreover, the hepatic fat accumulation, and in particular the qualitative alterations in the fatty acid composition of liver fat, seems to play a critical role in liver disease progression.[34]

These data strengthen the hypothesis that phospholipid remodelling through MBOAT7 activity is involved in the pathogenesis of alcohol-related cirrhosis, as well as it predisposes to the genesis and development of the entire spectrum of liver damage related to MAFLD, including higher degree of steatosis, more severe necroinflammation and more advanced fibrosis stage in European individuals regardless obesity.[10]

In the same year, Krawczyk et al. confirmed the association between the *MBOAT7 rs641738* C>T variant and a more severe fibrosis stage, increased circulating TAGs, cholesterol, low-density lipoprotein and glucose levels, but they did not find any link with a more advanced steatosis stage in a smaller European cohort.[47,48]

In addition, the association between the *MBOAT7 rs641738* variant and chronic liver disease has been recently reported in other ethnicities. Raja et al. showed how the *MBOAT7 rs641738* risk allele is enriched in Pakistani individuals with chronic liver disease.[49] The *rs641738 T* allele emerged as a strong genetic contributor for the presence and severity of NAFLD in a Caucasian[50] and in a Chinese population[51] in which *MBOAT7 rs641738* was

associated with the occurrence and progression of MAFLD, while the same association was not significant in African American and Hispanic populations.[52] Since they detected reduced concentrations of AA-PI and higher concentrations of PI containing saturated or monounsaturated PI, these mechanisms are related to important changes in the PI remodelling. The association between the *MBOAT7 rs641738* variant and the increased risk of MAFLD is thus driven by changes in the hepatic PI acyl-chain remodelling in which MBOAT7 is involved via the Lands' cycle. A reduction in the hepatic PUFA-containing PI levels, such AA-PI/total PI and EPA-PI/total PI ratios in plasma and liver in patients carrying the *rs641738 C>T*, was associated with the number of T variant alleles, while all the other lipid classes remained unchanged when compared to homozygotes for the wild type allele.[10,53]

A profound remodelling of PI species was observed by Thangapandi et al. in *rs641738 TT* carriers by performing lipidomic analysis on human liver biopsies. *TT* group showed reduced levels of 40:4-PI, 36:4-PI, 38:4-PI and 20:4-LPI species, while 18:0-LPI levels were increased as compared with the *CC* group.[54]

Moreover, other groups did not find any association between the *rs641738* variant and the susceptibility or histological severity markers of NAFLD in different cohorts.[52,55–57] In a recent study conducted on a Swedish NAFLD cohort composed of 592 subjects, no association with any polymorphisms of *MBOAT7* and the presence of NASH, increased risk of development of severe long-term liver-related events, or increased mortality rate was found.[58]

To date, the *MBOAT7 rs641738 C>T* variant is one of the most replicated susceptibility genetic risk factors for the progression of alcohol-related cirrhosis in alcohol abusers.[42] Despite this, no significant association was found between the *MBOAT7 rs626283* or *rs641738* genetic variants and alcohol-related liver disease (ALD) in a Chinese Han population.[59] Moreover, the *rs641738* polymorphism was not linked to a higher risk of developing severe alcoholic hepatitis amongst heavy drinkers, probably due to the relatively small size of the cohort composed of 211 American patients.[60]

Altogether, the role of the *MBOAT7 rs641738 C>T* variant in predisposing to ALD and NAFLD remains controversial and yet to be validated in ethnicity-specific populations[61] to consider *MBOAT7* as a potential pharmaceutical target for the treatment of this condition.

4.2 | *MBOAT7 rs641738 C>T* variant effect interacts with BMI

The *rs641738 C>T* genotype was associated with the presence of histological fibrosis in NAFLD Caucasian patients with BMI ≤35 who underwent percutaneous or surgical liver biopsy. In patients with a BMI >35, the *rs641738C>T* genotype was no longer significantly associated with hepatic fibrosis. In severely obese individuals who underwent percutaneous liver biopsy performed during bariatric surgery and had no history or at-risk alcohol intake or other liver diseases, hepatic *MBOAT7* mRNA decreased from normal liver to steatohepatitis, independently of diabetes, inflammation and *MBOAT7* genotype.[31] In addition, the histological liver damage and the prevalence of significant fibrosis increased with the number of *MBOAT7 rs641738 C>T* variant allele in patients who underwent bariatric surgery.[53] These data suggest an interaction between the MBOAT7 variant and BMI where the effect of the variant increases with the increase in adiposity.

On the contrary, the *MBOAT7 rs626283* polymorphism was not associated with increased intrahepatic triglyceride content, liver stiffness and circulating ALT regardless of the BMI in a cohort composed of Asian lean adult subjects.[62]

4.3 | MBOAT7, glucose and lipoprotein metabolism

The *MBOAT7 rs641738* has been described as one of the main genetic determinants of hepatic fat accumulation and the full spectrum of liver damage related to NAFLD in a liver biopsy cohort but, despite being directionally concordant, the association of the *MBOAT7* variant with insulin resistance and a higher risk of type 2 diabetes mellitus (T2D) developing was not significant.[45]

On the contrary, Helsley et al. showed that *Mboat7* depletion by second-generation antisense oligonucleotides (ASOs) promoted hyperinsulinemia and insulin resistance by impairing insulin action in mice. Besides, hepatocyte- and adipocyte-specific *Mboat7* knockdown caused steatosis, early fibrosis, increased liver weight and circulating ALT and AST levels in HFD-fed mice.[63] They further showed that hepatic expression of MBOAT7 was reduced in obese humans and rodents regardless the presence of the *rs641738* variant, as Meroni et al. revealed that the *MBOAT7* gene expression levels decreased with the severity of hepatic injury in severely obese patients regardless the genetic background.[31] Moreover, *MBOAT7 mRNA* and protein levels were reduced in murine models of fatty liver, following a refeeding or by hyperinsulinemia induced by acute treatment with insulin, suggesting a new mechanism linking MBOAT7 enzymatic activity to SLD independently of the genetic background. Interestingly, Tanaka et al. observed that, despite the VLDL secretion rate between *Mboat7* wild-type and knockout mice was unchanged, *Mboat7* knockout mice showed 50% lower total plasma TAG and VLDL particles levels probably due to an accelerated VLDL-TAG catabolism mediated by lipoprotein lipases (LPL).[30]

Finally, and most importantly, a recent meta-analysis of studies including more than 1 million individuals elucidated the association between *MBOAT7 rs641738C>T* and MAFLD confirming that the *rs641738 C>T* variant is a risk factor for the development and severity of MAFLD in individuals of European descent.[64] In particular, *rs641738C>T* was positively associated with higher hepatic fat content, advanced fibrosis, diagnosis of more severe MAFLD, higher ALT and cholesterol levels, and lower serum TAG levels, whilst no consistent effect was found in adults of other ancestries or in children. Despite the large number of individuals analysed, no evidence of an effect of the *MBOAT7 rs641738C>T* variant on markers of insulin resistance and dyslipidemia was found.[64]

4.4 | MBOAT7 and viral diseases

MAFLD will become soon the main cause of hepatocellular carcinoma (HCC) in Western countries as hepatocellular fat accumulation has been described as a key feature of hepatic carcinogenesis progression; meanwhile, HCV- and HBV-related HCC are projected to decline.[65] On the one hand the *MBOAT7 rs641738 C>T* variant has been linked to a higher risk of HCC development in non-cirrhotic NAFLD patients, suggesting its use as a novel non-invasive biomarker for NAFLD-induced HCC progression in pre-cirrhotic NAFLD individuals.[66] Notably, Donati et al. found that the MBOAT7 *rs641738* variant in HCC patients without severe fibrosis was in high linkage with the *MBOAT7* 3′-UTR variant *rs8736 C>T* polymorphism. This new variant might influence MBOAT7 mRNA expression and, therefore, its hepatic protein expression, suggesting that the *rs641738 C>T* may not be the causal variant linking MBOAT7 to SLD.[66] On the other hand, several studies showed that neither heterozygous nor homozygous carriage of the *MBOAT7 rs641738* variant confer any increased risk of HCC development or HBV infection persistency or clearance.[67–69]

Recently, this variant has been also described as one of those risk factors that, by modulating liver fat and lipogenesis, are crucial for HCC development amongst cirrhotic C patients treated with direct-acting antivirals (DAA).[70] The progression of HCC after DAA is driven by severity of liver disease due to the carriage of genetic risk factors, including the *MBOAT7 rs641738 C > T* variant.

A recent study on a Thai cohort composed of HCC patients with different etiological backgrounds did not reveal any association between the *MBOAT7 rs641738* polymorphism and the development of HCC.[71] The same *MBOAT7 rs641738* variant did not have a statistically significant association with advanced liver stiffness[72,73] or hepatitis C virus-induced liver cirrhosis, probably due to the etiological heterogeneity of the liver cirrhosis cohort and to a small number of patients within the subgroup analysis.[68,74]

Interestingly, the *rs641738* variant has been associated with increased risk of liver inflammation and fibrosis progression in patients with chronic viral hepatitis B and C infections.[75,76] On the other hand, Dunn et al. showed that the *MBOAT7* genetic variant, associated with cirrhosis and fibrosis progression in HCV infection, was not inversely associated with clinical recovery and fibrosis regression after the resolution of the active disease in patients with decompensated HCV cirrhosis treated with an interferon-free DAA regimen.[77]

Finally, carriers of the *MBOAT7 rs641738 C>T* allele variant showed a more advanced steatohepatitis and liver fibrosis in a cohort composed of people living with HIV having elevated aminotransferases and NAFLD, suggesting the use of a routine genotyping for these people to identify their predisposition in developing NAFLD and, thus, to limit the progression of this condition.[78]

5 | MBOAT7 INVOLVEMENT IN EXTRAHEPATIC DISEASES

5.1 | MBOAT7 and neurodevelopmental disorders

PUFAs in membrane phospholipids play a major part in the regulation of the structure, dynamics, and permeability of cell membranes. AA (20:4, n-6), the predominant FA in the *sn-2* position of PI in mammals, is the most enriched *n-6* PUFA in the brain. Indeed, AA is involved in multiple aspects of neuronal development and function, including neurite outgrowth, signal transduction, membrane fluidity and cognitive function.[18] Homozygosity for severe loss of function genetic variants in *MBOAT7* results in human neurodevelopmental disorders and ID, suggesting a key role for AA containing-PI remodelling in the development of human brain.[79]

Mboat7-deficient mice (*Mboat7*$^{-/-}$) showed severe developmental brain defects, atrophy of the cerebral cortex and hippocampus, abnormal cortical lamination and a higher number of apoptotic cells in the cortex.[18]

LPIAT1-deficient mice (*Lpiat1*$^{-/-}$) displayed 43% less AA content in PI and PI phosphates in the brain than *Lpiat1*$^{+/+}$. The amount of 18:0/20:4-PI (38:4-PI) was significantly reduced in the *Lpiat1*$^{-/-}$ brain, while the acyl chain compositions of phosphatidylcholine (PC) and phosphatidylethanolamine (PE) were not significantly affected. PI content was slightly decreased in the *Lpiat1*$^{-/-}$ brain.

Several homozygous null mutations have been identified in individuals with severe ID, epilepsy, and autistic phenotypes.[80–83] Johansen et al. originally described five distinct variants in coding regions of *MBOAT7* (c.126_145del [p.Leu43Hisfs * 69]; c.758_778del [p.Gln253_Ala259del]; c.423delG [p.Leu142Cysfs * 8]; c.820_826del [p.Gly274Profs * 47]; c.854+1G>C splicing site variant) from six consanguineous families harbouring homozygous inactivating variants in *MBOAT7*, all of which were predicted to affect protein expression and function.[79]

Through genome-wide genotyping and exome sequencing, five different homozygous mutations in the *MBOAT7* gene were identified in 12 patients from seven families all born to consanguineous parents: p.Arg87 *, p.Leu227ProfsX65, p.Gln376Lys, p.Trp426 * and chr19: 54.666.173–54.677.766/11594. Patients showed global developmental delay, particularly in language skills, ID, stereotyped behaviour, ataxic gait, early onset epilepsy with good response to medical treatment, cross-eyed seizures and similar facial features. Moreover, authors found by neuroimaging wavy appearance of disorganized cerebellar leaves, accompanied sometimes by cerebellar atrophy, prominent perivascular spaces, and T2 hyperintensity in both dentate and globus pallidus, sometimes accompanied by a relatively thin corpus callosum and a subtle brain stem atrophy. All this could provide complementary data to the presumed clinical diagnosis.[83] An Italian study reported the first known Italian patient affected by *MBOAT7*-related ID, whom is one of the oldest reported to date (22.5-year-old). She was born to consanguineous healthy parents, she is affected by neurodevelopmental disorder caused

by a novel unreported homozygous variant in the *MBOAT7* gene, an indel variant (c.1057_1058delGCinsCA) with a missense effect (p.Ala353His) on the protein. Other three missense mutations have been described in this gene, of which two in the same exon 8, leading to amino acid changes in position 357 and 376 of the protein.[84]

The *MBOAT7* c.757G>A, p.Glu253Lys variant was found in three patients born to consanguineous parents who shared clinical phenotype, ID, seizure and common brain MRI findings. The in silico molecular modelling of this human MBOAT7 variant predicted the molecular pathological mechanisms in patients with ID. The variant amino acid Lys253 is located on the funnel surface and it is expected to alter the surface charge distribution thus affecting function, structural flexibility and substrate specificity, resulting in MBOAT7 enzyme dysfunction.[85]

In addition, a homozygous in-frame deletion (c. 758_778del; p. Glu253_Ala259del) in *MBOAT7* was reported to be the genetic cause of severe ID in two consanguineous Pakistani families, indicating that it could be a regional prevalent founder mutation.[86] Moreover, 12 individuals from four consanguineous Pakistani families with a similar neurodevelopmental phenotype have now been reported as homozygous for the *MBOAT7* c.758_778del variant. The authors described two different homozygous variants in *MBOAT7* within three consanguineous Pakistani families; a 7 bp frameshift deletion (c.820_826del [p.Gly274Profs*47]) in exon 6 in a single family, an in-frame deletion (c.758_778del [p.Glu253_Ala259del]) in exon 6 from two unrelated families, and the same 21 base pair in-frame deletion (c.758_778del; p.Glu253_Ala259del) in two families, which co-segregated as appropriate for an autosomal recessive condition.[81]

Another study examined three consanguineous Pakistani families with features of autosomal recessive neurological disorders in order to identify a precise molecular diagnosis by using a combination of genome-wide single-nucleotide polymorphism (SNP) mapping and a whole exome sequencing (WES). This research added seven affected individuals from two Pakistani families to the literature, with a total of 43 individuals now described with biallelic pathogenic *MBOAT7* variants and similar overlapping phenotypes. To date, a total of 13 *MBOAT7* variants associated with autosomal recessive neurodevelopmental disorder have been described.[81]

In 2020, a group of researchers identified by WES two novel homozygous nonsense variants in *MBOAT7*, c.1062C>A; p.(Tyr354*) and c.1135del; p.(Leu379Trpfs*9), in three individuals from two different Iranian families whose parents were consanguineous for both families. Moreover, magnetic resonance analysis detected globus pallidus alterations in all three patients that could be used as a marker of *MBOAT7* deficiency in the analysis of patients with similar phenotypes. Interestingly, liver sonography showed no specific sign of fatty liver or other liver dysfunctions.[82]

Recently, it was described a further novel, homozygous, pathogenic variant in *MBOAT7* (p.R271Pfs*25), in two brothers with global developmental and speech delay accompanied by basal ganglia hyperintensities, born to healthy consanguineous parents with no family history of neurologic diseases.[87]

In a report, WES identified a homozygous, likely pathogenic variant in the *MBOAT7* gene (c.855-2A>G). Co-segregation analysis of the c.855-2A>G alteration revealed that the proband's asymptomatic parents were both carriers for the variant.[80]

Despite all these studies reporting the strong association between *MBOAT7* mono-allelic or bi-allelic loss of function mutations and autosomal recessive mental retardation, in most of them no evidences of liver disease or specific liver phenotype were reported. It is important to stress that most of the patients were in their early childhood and might manifest liver disease later in life, therefore further analyses are needed to link neurodevelopmental disorders caused by MBOAT7 deficiency to the progression of SLD.

In Figure 4 the *MBOAT7* genetic variants of clinical relevance.

5.2 | MBOAT7 and cardiovascular disease

In the last years, *MBOAT7* has been associated with the progression and severity of extrahepatic conditions. MAFLD was linked to

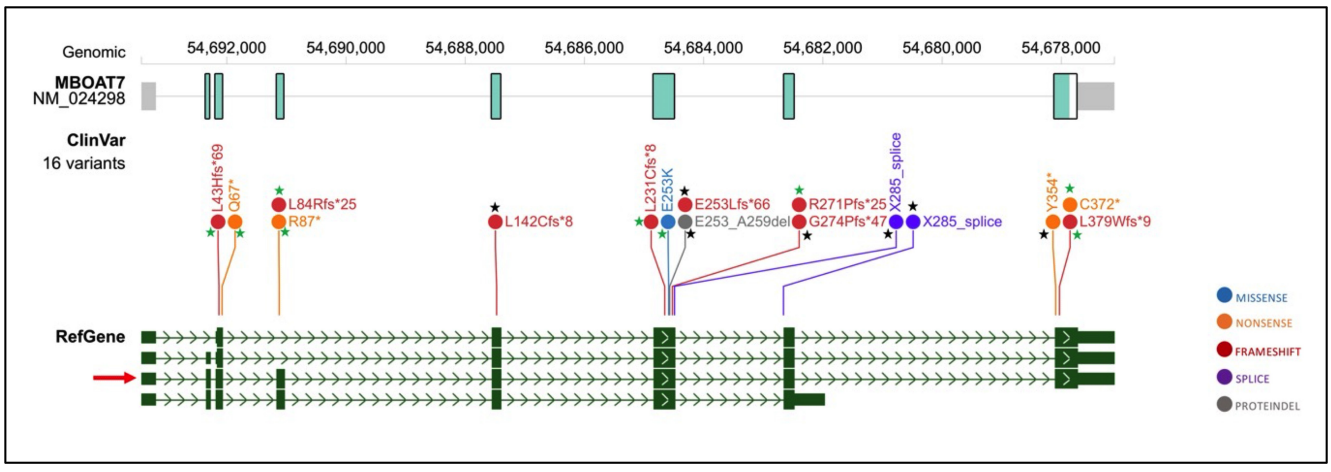

FIGURE 4 Location of reported MBOAT7 loss of function variants causing intellectual disability (ID) in homozygosity. ProteinPaint representation of pathogenic (black stars) or likely pathogenic (green stars) MBOAT7 variants reported in ClinVar database. The red arrow shows full-length transcript (eight exons). (ProteinPaint, https://pecan.stjude.org/proteinpaint/).

an increased risk of developing fatal and non-fatal cardiovascular events. More severe forms of MAFLD are associated with an even greater risk of cardiovascular disease (CVD) events, the leading cause of mortality and morbidity worldwide, regardless the presence of other cardiovascular risk factors.[88] *MBOAT7* genetic variants were also associated with an increased risk of CVD and venous thromboembolism in a GWAS analyses of lipidomic profiles of more than two thousand individuals, followed by phenome-wide scans with 25 CVD-related phenotypes.[89] On the other hand, in other two studies the *MBOAT7 rs641738* variant showed a neutral effect on coronary artery disease (CAD) development, one of the main causes of death in patients with NAFLD.[90,91] Interestingly, *MBOAT7* mRNA levels were elevated in the leukocytes of patients with acute myocardial infarction (AMI), suggesting the use of the *MBOAT7* mRNA levels in the peripheral blood as a biomarker for AMI.[92]

5.3 | MBOAT7 in kidney function

MAFLD has been described as an independent risk factor for the development of chronic kidney disease (CKD) as these two conditions share a metabolic and proinflammatory pathogenesis and several risk factors, including the presence of the *MBOAT7 rs641738 C>T* variant. In particular, carriers of the *T* allele showed higher sensitivity C-reactive protein (hsCRP) levels, a reduced glomerular filtration rate and a more advanced CKD stage.[93] In 2020, Neumann et al. found that MBOAT7 expression increases with clear cell renal cell carcinoma (ccRCC) severity, a tumour strongly associated with obesity. In addition, MBOAT7 depletion in ccRCC cells reduces cell proliferation and migration in vitro, and tumour formation in an in vivo xenograft mice model.[94] Metastatic ccRCC is characterized by the accumulation of AA-PI lipids. Indeed, the expression of AA-PI synthesizing enzyme MBOAT7 was found increased in ccRCC tumours and the genetic deletion of *MBOAT7* in ccRCC cells resulted in reduced AA-PI levels and increased LPIs. The MBOAT7/AA-PI axis was identified as a key new lipid metabolic dependency in ccRCC as it plays a crucial role in regulating ccRCC migration and epithelial-to-mesenchymal transition (EMT). Therefore, selective MBOAT7 inhibitors may hold promise to blunt the progression of metastatic ccRCC.[94]

On the contrary, Baratta et al. suggested that the *MBOAT7 rs641738 C>T* variant does not have any impact on glomerular renal function, while metabolic risk factors, such as the presence of metabolic syndrome and arterial hypertension, have a stronger effect on the decline of kidney function.[95]

5.4 | MBOAT7 and adipose tissue

Recently, Massey et al. underlined the importance of MBOAT7 in adipose tissue in which MBOAT7 is the major source of AA-PI (38:4) and regulates the LPI/PI homeostasis. They showed that adipocyte-specific *Mboat7* knockout promotes diet-induced metabolic disturbances, such as hepatic fat accumulation, hyperinsulinemia and systemic insulin resistance in mice. Further studies are required to determine how adipocyte MBOAT7 activity and the LPI-MBOAT7-PI axis affects insulin secretion in pancreatic beta cells.[63]

5.5 | MBOAT7 in childhood

Although MAFLD is a chronic and progressive disease where end-stage manifestations, such as cirrhosis and HCC, are usually displayed in adults, there has been a striking increase in the prevalence of MAFLD in young children and adolescents.[96] Recently, an increasing number of evidences are proving that *MBOAT7* loss of function may also be linked to paediatric MAFLD progression.

Considering that obesity predisposes to MAFLD in childhood, MAFLD is becoming an issue in the young population due to the high prevalence of obese paediatric individuals, with a higher rate in males compared with females.[97] On the one hand, the *MBOAT7 rs641738 C>T* variant was not associated with NAFLD in overweight or obese NAFLD-affected children and adolescences, regardless the obesity status.[98,99] The link between the presence of this polymorphism and liver injury or higher levels of ALT was not found in a population of obese Taiwanese children, as well as in obese American children of Hispanic ethnicity.[61,100] On the other hand, the *rs626283* polymorphism in the *MBOAT7* locus has been associated with ALD and NAFLD in adults, and with insulin resistance driven by the presence of hepatic steatosis in Caucasian obese children,[101] while the *rs641738* polymorphism leads to higher ALT serum levels and to a more severe fibrosis stage in obese children and adolescents.[102,103]

Recently, *MBOAT7* has been suggested to be part of a combinatorial panel of biomarkers to assess the risk of MAFLD and its progression in paediatric patients.[99]

5.6 | MBOAT7 and COVID-19

Toll-like receptor (TLRs) signalling has been implicated in a wide range of human diseases.[104] A potential plausible link between fatty liver disease and COVID-19 severity may be mediated by the interaction of TLRs, MBOAT7 and *MBOAT7* genotype. This relationship is further supported by similarities in the range of pro-inflammatory cytokines, such as TNF-α, induced by MBOAT7 repression in patients with severe COVID-19, and in MAFLD.[105] MBOAT7 is a negative regulator of TLR signalling and its deficiency alters membrane phospholipid composition in macrophages as observed in individuals with COVID-19. These alterations are associated with a redistribution of AA toward pro-inflammatory eicosanoids, induction of endoplasmic reticulum stress, mitochondrial dysfunction, and remodelling of the accessible inflammatory-related chromatin landscape culminating in macrophage inflammatory responses to TLRs. Activation of *MBOAT7* reverses these effects.[106]

Recently, the presence of the *MBOAT7 rs641738 C>T* variant was linked to a more severe liver injury during hospitalization for

COVID-19. Carriers of the *MBOAT7 rs641738 C>T* variant displayed more severe liver injury characterized by increased ALP, GGT, ALT, and bilirubin and decreased albumin levels during hospitalization for COVID-19, as compared to wild type. Moreover, a higher percentage of patients carrying the recessive allele had a more severe respiratory disease.[107]

6 | CONCLUSION

In summary, MBOAT7 is an enzyme involved in remodelling of phosphatidylinositol with PUFAs. MBOAT7 complete loss of function leads to severe neurodevelopmental disorders resulting in several neurological manifestations, whilst lower hepatic MBOAT7 expression levels and weaker enzymatic activity have been linked to MAFLD and potentially COVID-19 disease. Further studies are necessary to understand whether carriers of *MBOAT7* pathogenic variants associated with liver diseases may be the cause of neurological dysfunctions, and whether the PI remodelling, a key factor for human health, would be the link between these conditions.

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The authors do not declare any conflict of interest.

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