REPORT

Mutations in *MBOAT7*, Encoding Lysophosphatidylinositol Acyltransferase I, Lead to Intellectual Disability Accompanied by Epilepsy and Autistic Features

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The risk of epilepsy among individuals with intellectual disability (ID) is approximately ten times that of the general population. From a cohort of >5,000 families affected by neurodevelopmental disorders, we identified six consanguineous families harboring homozygous inactivating variants in *MBOAT7*, encoding lysophosphatidylinositol acyltransferase (LPIAT1). Subjects presented with ID frequently accompanied by epilepsy and autistic features. LPIAT1 is a membrane-bound phospholipid-remodeling enzyme that transfers arachidonic acid (AA) to lysophosphatidylinositol to produce AA-containing phosphatidylinositol. This study suggests a role for AA-containing phosphatidylinositols in the development of ID accompanied by epilepsy and autistic features.

Intellectual disability (ID) is a common neurodevelopmental disorder affecting 1 in 100 children.[1,2] The more severe forms of ID or those with additional signs or symptoms are less common and have a prevalence of roughly 1 in 200.[3,4] Diagnosis of ID is based on the impairment of general mental abilities and activities of daily living.[2] In early childhood, the diagnosis of ID is based on global developmental delays affecting speech, motor, and cognitive function in combination with an IQ below 70.[2] It has previously been reported that rare de novo or recessive mutations play a major role in severe ID.[5,6] Interestingly, more complex forms of inheritance are thought to be involved in milder cases.[2,7,8] Although ID has a strong genetic influence, the involvement of non-genetic factors, such as infections, perinatal asphyxia, or environmental exposures, might play a role in the development of other forms.[9] To date, over 1,100 genes have been either confirmed or suggested in ID etiology, yet half of ID cases still remain undiagnosed.[4,10–12]

Many individuals with ID also present with other neurological conditions, such as epilepsy[13] and autism spectrum disorder (ASD),[14] which also have a strong genetic influence. The prevalence of epilepsy is ten times higher in individuals with ID than in the general population.[13] As in ID, de novo, recessive, and dominant variants in ASD can contribute to risk; however, a genetic diagnosis can be determined only in a relatively small portion of individuals.[15] ASD is characterized by repetitive behavior and varying degrees of impairment of social interaction and communication skills.[16] Many ASD-affected individuals show evidence of heritability.[17] Genetic evidence suggests the involvement of 200–1,000 genes, including both autosomal-recessive (AR) and de novo variants, in ASD susceptibility.[18–20]

In an effort to expand our understanding of the genetic composition of neurodevelopmental disorders with AR inheritance, several centers in the US, Canada, and Germany, in cooperation with colleagues from Egypt, Pakistan, and Jordan, joined efforts to examine and recruit a large number of consanguineous families with affected children. Analyses were performed in accordance with the ethical standards of institutional review boards, and informed consent was obtained for each individual participating in this study. Exome sequencing of our database consisting of >5,000 families with neurodevelopmental disease identified three families affected by biallelic, possibly pathogenic variants in membrane-bound O-acyltransferase family member 7 (*MBOAT7* [MIM: 606048]). These three families presented with overlapping clinical signs, including ID frequently acting with epilepsy (7/8 subjects) and autistic features (7/8 subjects). On the basis of exome findings, three additional families were identified from parallel international sequencing efforts through the sharing of gene names among collaborators.

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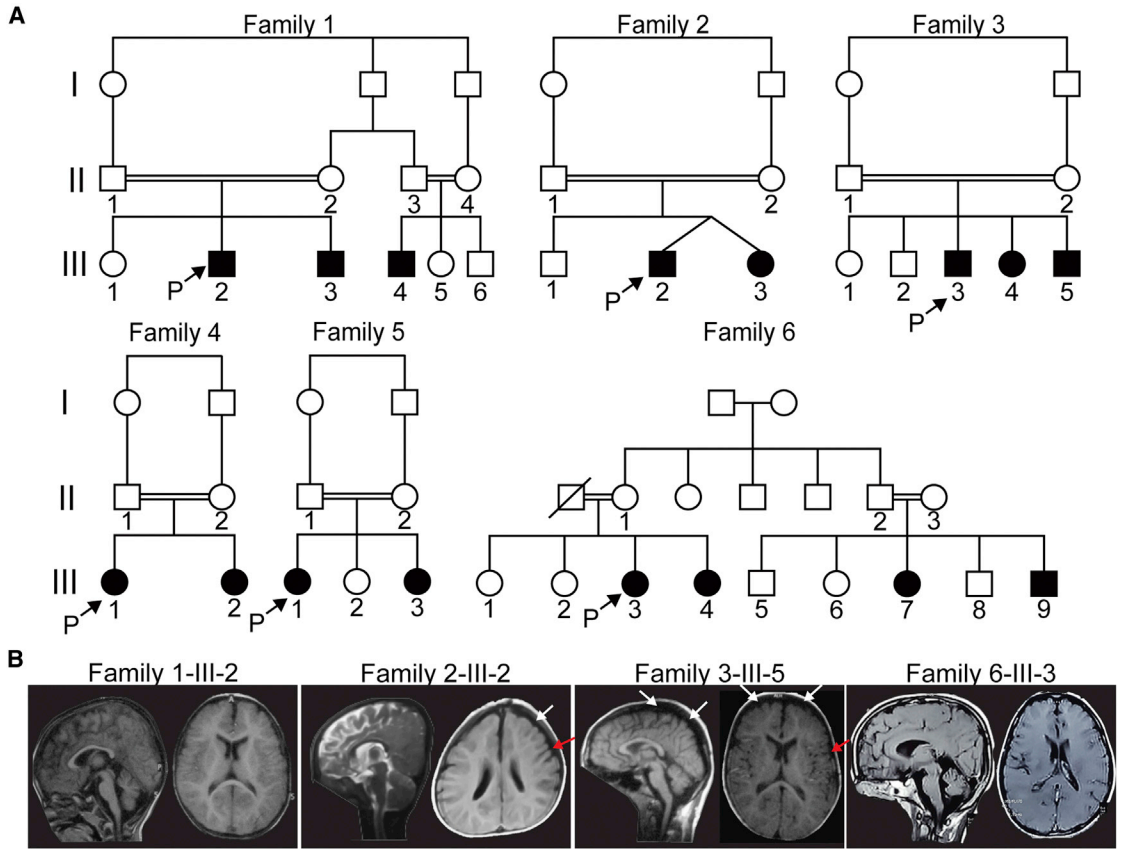

Figure 1. Consanguineous Families with Variants in *MBOAT7*, Encoding LPIAT1
(A) Pedigrees of families 1 to 6 show consanguineous marriages (double bars) with a total of 16 affected children. Probands are indicated with "P."
(B) Brain MRI for one affected individual from each of families 1–3 and 6. White arrows show cortical atrophy, and red arrows show possible polymicrogyria.

All 16 subjects were born to consanguineous parents (Figure 1A, Table S1, and Supplemental Note). The emerging clinical picture is one of moderate to severe ID given that the majority of subjects are not able to build sentences (14/16) and are non-verbal with delayed motor milestones (9/16). A few of the children (3/16) have never achieved the ability to walk, and the remaining 13 started to walk between the ages of 2 and 7 years. In 6/16 individuals, these clinical signs co-occur with infant-onset epilepsy (mostly focal and multifocal) that has been responsive to antiepileptic drugs. A further two individuals have seizures that began at 1.5 and 2.5 years, whereas another two have febrile seizures. Neurological examination showed that all children have truncal hypotonia and appendicular hypertonia. All subjects have a below-average head size, which is −2 to −3 SDs below the mean in 3/16 affected children, suggesting that microcephaly is not a consistent feature of *MBOAT7* variants. ASD was documented in only 7/16 children according to the Childhood Autism Rating Scale, and a further three showed clinical autistic features. Brain imaging was within normal limits, except in two subjects, in whom cortical atrophy was present (Figure 1B). There was some evidence of mild polymicrogyria.

Whole-exome sequencing identified a total of five distinct variants in *MBOAT7* (GenBank: NM_024298.3) from six families (Table S2). All variants were prioritized by allele frequency, conservation, blocks of homozygosity, and predicted effect on protein function. All variants were confirmed by Sanger sequencing and segregated with the disease as predicted for a fully penetrant recessive trait within all six families. Family 1, from Egypt, carries a homozygous frameshift deletion (c.126_145del [p.Leu43Hisfs*69]) in exon 3. Families 2 and 3, from Pakistan, harbor an in-frame deletion in exon 6 (c.758_778del [p.Gln253_Ala259del]). Using actual and inferred sequence data, we estimated the coalescence time of the shared founder mutation for families 2 and 3 to be 9.185 generations (SD ± 4.45 generations), or ~230 years with a generation time of 25 years. Sequencing data from family 4, from Jordan, revealed a homozygous deletion (c.423delG [p.Leu142Cysfs*8]) in exon 5. Family 5, from Iraq, carries a biallelic substitution (c.854+1G>C [p.?]) occurring at the canonical splice donor of exon 6. Family 6, from Pakistan, carries a 7 bp frameshift deletion (c.820_826del [p.Gly274Profs*47]) in exon 6. These variants were not found in dbSNP, the Greater Middle East (GME) Variome, the Exome Aggregation Consortium

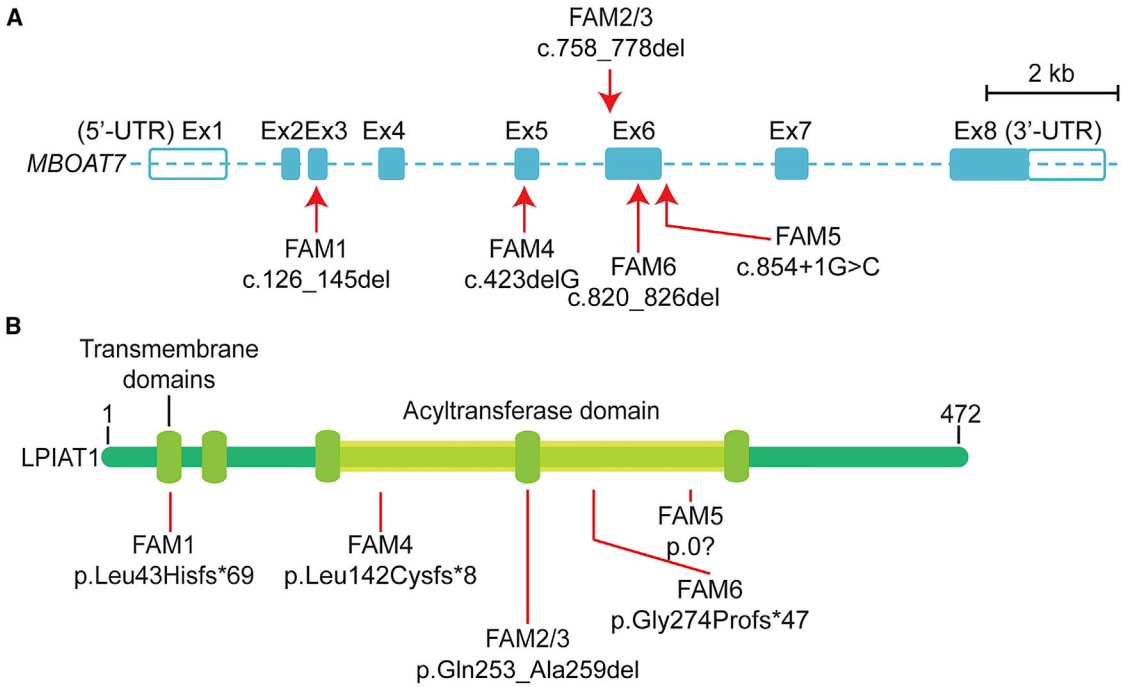

Figure 2. Location of Variants and Domains in *MBOAT7*, Encoding LPIAT1
(A) Genetic structure of *MBOAT7*. Mutations are indicated by red arrows (exons and numbers as in GenBank: NM_024298.3). In-solution exome capture was performed with the SureSelect Human All Exome 50 Mb Kit (Agilent Technologies) with 125 bp paired-end read sequences generated on a HiSeq2000 or HiSeq2500 (Illumina). Scale bar represents 2 kb.
(B) Structure of LPIAT1, which harbors five transmembrane domains and one catalytic acyltransferase domain. Variants are indicated with red lines. Amino acid numbers are provided above.

(ExAC) Browser, or 1000 Genomes and were also not present in our in-house whole-exome database (>5,000 subjects with neurodevelopmental conditions). The ExAC Browser includes over 8,000 South Asian control individuals, almost all Pakistani, from the Pakistan Risk of Myocardial Infarction study. Thus, these disease-related alleles are very rare even in ethnically similar control individuals.

MBOAT7 encodes lysophosphatidylinositol acyltransferase 1 (LPIAT1), which is a member of the MBOAT family of acyltransferases and originates from yeast Ale1p (Figure S1A).[21] The human MBOAT family has five members, each of which has a preference toward specific acyl donors and acceptors (Figure S1B).[21] LPIAT1 is the only family member that is known to primarily transfer arachidonic acid (AA) from arachidonoyl-CoA to lysophosphatidylinositol (Figure S1C),[22] suggesting an essential function. *MBOAT7* contains eight exons, resulting in four protein-coding transcripts, and three LPIAT1 isoforms. The five variants described in this study affect all protein-coding transcripts (Figure 2A), interfering with either transmembrane or catalytic domains of the protein (Figure 2B). Balanced translocation in *MBOAT1* in one subject has been linked to brachydactyly-syndactyly syndrome.[23] None of the other MBOAT genes have had genetic loss-of-function variants linked to human disease.

LPIAT1 contributes to the regulation of free AA in the cell through the remodeling of phospholipids.[24,25] Free cellular AA is under tight regulation, given that its pro-inflammatory metabolites could be harmful to cellular physiology.[26] Enzymes such as lipoxygenase (LOX) and cyclooxygenases (COX) metabolize AA into the pro-inflammatory eicosanoid lipids. The COX enzymes (1 and 2) are known targets of existing non-steroidal anti-inflammatory drugs, such as ibuprofen and aspirin.[27] There is compelling evidence linking pro-inflammatory processes to ASD, for instance, the activation of microglia and astrocytes and the overexpression of immune processes in the brains of individuals with ASD.[28–31]

A common variant in *TMC4* (rs641738), a gene adjacent to *MBOAT7*, is associated with a 20% increased risk of nonalcoholic fatty-liver disease in individuals of European descent. The variant is predicted to cause a substitution (p.Gly17Glu) early in TMC4.[32] Interestingly, this variant is just a few hundred base pairs downstream of the 3′ end of *MBOAT7*. Carriers of this allele who underwent liver biopsy were found to share reduced *MBOAT7* expression and altered phosphatidylinositol levels. None of our affected children or their parents showed evidence of clinically relevant liver disease, but no specific tests were performed. Despite a 49% carrier frequency for the minor allele in the GME Variome, none of our subjects are carriers. Therefore, the connection between this variant and the condition we describe remains uncertain.

In mice, *Mboat7* and its encoded protein, LPIAT1, are required for cortical lamination.[33] *Mboat7* knockout mice

are significantly smaller than their littermate controls and show reduced postnatal survival. In a recent study, histological analysis of embryonic day 18.5 *Mboat7*$^{-/-}$ brains showed a smaller cerebral cortex and hippocampus, abnormal cortical lamination, an increased number of apoptotic cells in the cortex, and dispersed MAP2^{+} subplate neurons.[33] The cerebral cortex showed evidence of gyral structures, whereas normally gyri are absent in the murine cortex, reminiscent of the polymicrogyria we observed in some subjects.

It is recognized that AA-containing phosphatidylinositol is a major lipid in the mammalian brain. It has been shown that *Mboat7* is required for cortical lamination is mice.[33] In this study, we have linked recessive mutations in *MBOAT7* with human neurodevelopmental disease, suggesting a critical role for AA-containing phosphatidylinositol in the developing human brain.

Supplemental Data

Supplemental Data include a Supplemental Note, one figure, and two tables and can be found with this article online at http://dx.doi.org/10.1016/j.ajhg.2016.07.019.

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Web Resources

1000 Genomes, http://www.1000genomes.org/
dbSNP, http://www.ncbi.nlm.nih.gov/SNP/
ExAC Browser, http://exac.broadinstitute.org/
GenBank, http://www.ncbi.nlm.nih.gov/genbank/
Genome Analysis Toolkit (GATK, version 2.2), http://www.broadinstitute.org/gatk/
Greater Middle Eastern (GME) Variome Project, http://igm.ucsd.edu/gme/
HGNC, http://www.genenames.org/
Mutalyzer, https://mutalyzer.nl/
NHLBI Exome Sequencing Project (ESP) Exome Variant Server, http://evs.gs.washington.edu/EVS/
OMIM, http://www.omim.org
PolyPhen-2, http://genetics.bwh.harvard.edu/pph2/
Primer3, http://biotools.umassmed.edu/bioapps/primer3
SeattleSeq (version 134), http://snp.gs.washington.edu/SeattleSeqAnnotation134/

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Supplemental Data

Mutations in *MBOAT7*, Encoding Lysophosphatidylinositol Acyltransferase I, Lead to Intellectual Disability Accompanied by Epilepsy and Autistic Features

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Supplemental Note: Case Reports

Family 1 is from Egypt with 2 affected children (III-2, III-3), and a similarly affected cousin (III-4), all born to 1st degree cousin marriages. The older affected boy (III-2) was born via normal spontaneous vaginal delivery (NSVD) following an uneventful pregnancy with normal birth centiles. He was hypotonic as an infant and did not reach any milestones until 7 months when myoclonic and focal seizures with secondary generalization were observed. The subject was started on antiepileptic drug (AED), which after trial of multiple regimens has been successful to control the seizures at age 6, and has been seizure free for the last 2 years. He started to walk at 4.5 years of age, but still speak no meaningful words. At his last examination at 8 years of age, his head circumference (HC) was 52.5 cm (-1 SD), and also his height and weight were within normal limits. He seemed hyperactive, and had repetitive behaviors such as rocking and hand flapping. Physical examination was otherwise unremarkable. In addition, he presented autistic features, and Childhood Autism Rating Scale (CARS) showed a score of 28 (>30 implies evidence of ASD).[1] Brain magnetic resonance imaging (MRI) was within normal limits.

The younger affected boy (III-3) was born via NSVD at term with normal birth centiles. Seizures, of the same character as for his older brother, began at 6 months of age and he was seizure free at 5 years of age with AED. At his last examination at age 5, his head circumference was 51 cm (-1 SD), with the height and weight also being within normal limits. He had started to walk at age 4, but he lacked any speech and did not follow any commands. He also had autistic features similar to his brother, and did not have any sphincter control. His CARS score was 30, supporting a diagnosis of ASD.

The similarly affected cousin (III-4) was born following an unremarkable pregnancy with normal birth centiles. Myoclonic seizures started at the age of 3 months and were generalized at 7 months. The seizures were under control at 3 years of age by multiple antiepileptic drugs. At his last examination at age 3, his head circumference was 48 cm (-1 SD) with other measurements being also within normal limits. He was taking a few steps on his own and had no meaningful speech. There were no dysmorphisms or any systemic malformations. Like his cousins, he displayed hyperactivity and repetitive behaviors. His CARS score was also 30. Thus Family 1 shows full expressivity of ID and epilepsy with borderline ASD features.

Family 2 is Pakistani with affected dizygotic twins (III-2, III-3) born to a 1st degree consanguineous marriage. The older affected boy (III-2) was born at term with no complications and unknown birth centiles. Hypotonia was observed during infancy, and no gross motor milestones were reached until the age of 2 years when he started having generalized tonic clonic seizures. His head control was at 2.5 years of age, and he started sitting at 3.5 years of age. His seizures were controlled at age 4 by AED. At his last examination at age 4, he presented with microcephaly (head circumference was 46 cm (-3 SD)). He was not able to walk, and there was no meaningful speech. The tone and reflexes were increased in all four extremities with bilateral positive Babinski sign. The systemic examination was otherwise normal. He displayed minimal eye contact, and had stereotypical hand movements with no social smile, and no response to his name. His CARS score was 44. Brain MRI revealed cortical atrophy and possible polymicrogyria.

The affected girl (III-3) was born without complications following her twin brother with unknown birth centiles. Hypotonia was noted during infancy, and her

developmental milestones were severely delayed. She could hold her head at 2 years of age, and started sitting without support at 3 years. At her last physical examination at 4 years, her head circumference was noted to be 45 cm (-2 SD). She had no meaningful speech and could not walk. Hypertonia and brisk reflexes were present, without dysmorphisms or any other systemic malformations. She had similar autistic features to her brother, and her CARS score was 42. There was no history of seizures so far.

Family 3 is also of Pakistani origin with 3 affected children (III-3, III-4, III-5) born to a 1st degree consanguineous marriage. The oldest affected boy (III-3) was born via NSVD at term following an uneventful pregnancy. His birth centiles are unknown. His development as an infant and toddler was slow and he was able to sit independently at 18 months of age when myoclonic seizures started. Secondarily generalized seizures started around the same age and were under control at age 5 by AED. He has been seizure free for the last 7 years and is no longer taking AED. He was able to walk at age 3.5 years and had his first words at age 5. He could build two word sentences by age 7. At his last examination at age 12, his head circumference was 53 cm (-1.1 SD), with height and weight being also appropriate for his age. He was able to build simple sentences. He was following simple orders in an occasional manner, was hyperactive with repetitive behavior, and had fleeting eye contact. Sphincter control was present. The examination was otherwise unremarkable. His CARS score was 41. Brain imaging showed cortical atrophy and possible polymicrogyria.

The affected girl (III-4) was born at term with no complications. Her birth centiles were also unknown. She also had hypotonia as an infant and an onset of seizures at the age of 4 months. The focal seizures progressed to generalized tonic-clonic and were

under control at age 9 by AED. She has been seizure free for the last 2 years. She was able to sit independently at 1.5 years of age and was walking at 2 years of age. Her first words were at 4 years of age and she was talking in 2 word sentences by 5 years of age. Her head circumference was 51 cm (-2.5 SD) at age 12. No overt dysmorphisms were observed and systemic examination was normal. She had a CARS score of 42. Brain MRI was unremarkable.

The youngest affected (III-5) was delivered at term following an uneventful pregnancy. Myoclonic seizures started at 6 months with secondary generalization. He is now seizure free at 2 years of age with AED. He was able to sit independently at 1.5 years of age. At his last examination at the age of 2, he had a head circumference of 45 cm (-2.8 SD). He could stand on his own, but no independent walking was achieved yet. He could say 'mama' and 'papa'. Like his siblings, he demonstrated moderate-severe autistic features. His CARS score was recorded as 42.

Family 4 is a 1st degree consanguineous family from Jordan, with two affected girls (III-1 and III-2). The oldest affected sibling (III-1) was born via caesarian section with a birth weight of 3 kg due to pelvic presentation. Parents noticed developmental delay at 7 months of age. Developmental milestones including head control, sitting and walking were delayed with sitting at 3 and walking at 4 years of age after extensive physiotherapy. She also had myoclonic seizures at 7 months of age. Adaptation and muscular tonus were unremarkable. Seizures were controlled by AED, and she was taken off the medication at 2 years of age. Brain MRI at 6 years of age was unremarkable. Sexual maturation at the age of 13 was unremarkable. At last examination (age 14), she could say a few words, and her HC was normal with 53 cm (-1.2 SD).

The second affected individual in family 4 (III-2) was born via NVSD following an uneventful pregnancy. Her birth weight was 2.8 kg. Following an unremarkable neonatal phase, the family sought medical consultation due to delay in developmental milestones. At the age of 1.5 years, she could sit with support, she had increased deep tendon reflexes, and appendicular hypotonia. No seizures were reported. At last examination at age 9, she could walk and speak only a few words and HC 51.1 cm (-1.5 SD). Her receptive language was better than her expressive skills.

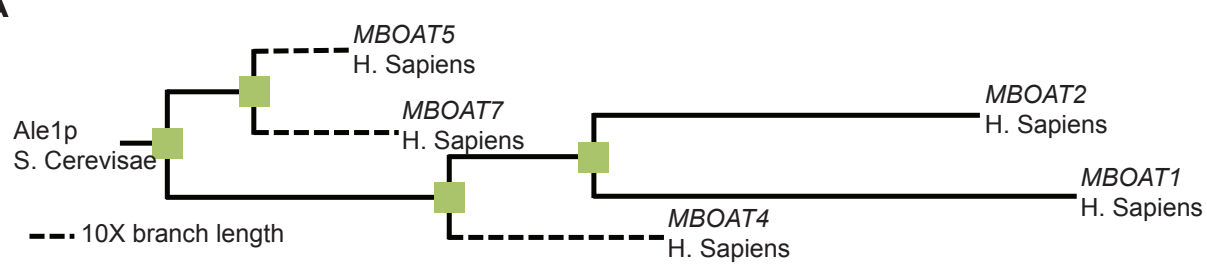
Family 5 is an Iraqi family with two affected sisters (III-1, III-3) born to a 1st degree consanguineous marriage. Both affected individuals were born at term with no complications. Their birth parameters were not available. Developmental delay, hypotonia with spasticity of the extremities in both sisters were observed at about 6 months of age. The younger sister (III-3) had one episode of febrile seizure around 2 years of age. Both could walk at about 2 years. At the last physical examination at age 11 years and 4 months, the older sister III-1 had a HC of 52 cm (-0.9 SD). Her developmental course showed ID without regression. She was able to walk with help. According to her parents she could speak 10 to 20 words. She was a friendly and hyperactive child with behavioral anomalies. The younger sister (III-3) was aged 7 years and 6 months at the last physical examination. She had a HC of 50.5 cm (-1.5 SD). She was able to walk unsteadily with help and showed muscular hypotonia. Like her older sister she spoke 10 to 20 words but mostly used signs and utterances to communicate, indicating delays in expressive skills. During examination she was conscious, hyperactive and showed behavioral problems like her sister. Both affected sisters shared only minor

unspecific dysmorphic features, the most obvious being dense eyebrows, hypertrichosis, wide palpebral fissures and dysmorphic ears.

Family 6 is a 2-branch consanguineous Pakistani family; two affected sisters were present in the first branch, and two similarly affected cousins (1 female and 1 male) were born to the second branch. All 4 subjects had ID. They started walking between ages 4 and 7. The oldest (III-3) spoke a few words, the other subjects did not exhibit any expressive language. Only III-3 had febrile seizures at age 1 which lasted a few days. None had any signs of autistic features during the examination. They were sociable and maintained eye contact. On observation their interaction with the examiner included greeting with a smile and waving hands. They engaged in play and communication with their family members. They could feed themselves and go to the restroom independently. Two individuals (III-3, III-7) became physically aggressive when frustrated. HC was between -1 and -2 SD at the latest examination. Brain imaging from the youngest affected (III-9) was within normal limits.

Figure S1

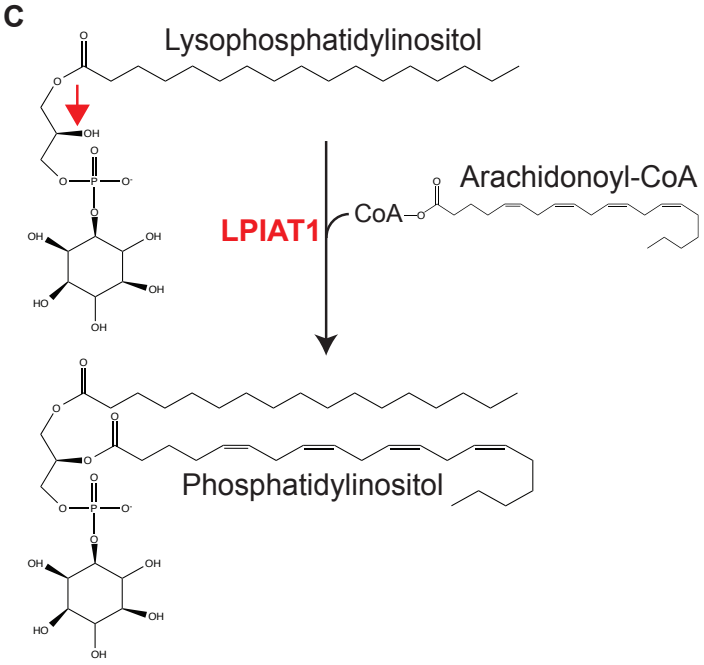
A



B

Gene	Acyl donor	Acyl acceptor
MBOAT1	Oleoyl-CoA	LysoPS
MBOAT2	Oleoyl-CoA	LysoPA, -PE
MBOAT4	Octanoic-, decanoic-, tetranoic acid	Grehlin
MBOAT5	Lineoyl-CoA, arachidonoyl-CoA	LysoPC, -PS
MBOAT7	Arachidonoyl-CoA	LysoPI

C



Supplemental figure.

Figure S1. The yeast *Ale1p* founded the 5 MBOAT paralogs in human. (A) Length of line corresponds to genetic change over time. Dashed line indicates 10X length. MBOAT1: NP_001073949. MBOAT4: NP_001094386. MBOAT7: NP_077274. HGNC provided symbols for MBOAT5: LPCAT3 (NP_005759), and MBOAT2: LPCAT4 (NP_705841). **(B)** Each of the MBOAT family members has a preference towards acyl donors and acyl acceptors. *MBOAT7*/LPIAT1 has a preference for arachidonoyl-CoA and lysophosphatidylinositol as acyl donor and acceptor, respectively. **(C)** *MBOAT7*/LPIAT1 facilitates the transfer of arachidonic acid from arachidonoyl-CoA to the sn2 position (red arrow) of lysophosphatidylinositol.

Supplemental tables.

Table S1. Clinical table.

Clinical presentation for affected subjects from families 1 to 6. HC: head circumference. AED: anti-epileptic drug. Consang: consanguinity. MRI: magnetic resonance image. CARS: child autism rating scale. PMG: polymicrogyria. DTR: deep tendon reflexes. GTC: generalized tonic-clonic.

Table S1

Family	Family 1			Family 2		Family 3			Family 4		Family 5		Family 6			
Subject	III-2	III-3	III-4	III-2	III-3	III-3	III-4	III-5	III-1	III-2	III-1	III-3	III-3	III-4	III-7	III-9
Gender	M	M	M	M	F	M	F	M	F	F	F	F	F	F	F	M
Origin	Egypt			Pakistan					Jordan		Iraq		Pakistan			
Consang.	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HC at birth (SD)	0	0	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Milestones																
Head Control	7 mos	8 mos	6 mos	2.5 yrs	2 yrs	8 mos	8 mos	1 yr	1 yr	1 yr	8 mos	9 mos	1 yr	1 yr	1 yr	1 yr
Unsupp. sitting	2 yrs	2.5 yrs	2 yrs	3.5 yrs	3 yrs	1.5 yrs	1.5 yrs	1.5 yrs	3 yrs	2 yrs	1 yr	1 yr	3 yrs	4 yrs	4 yrs	5 yrs
Unsupp. walking	4.5 yrs	4 yrs	3 yrs	-	-	3.5 yrs	2 yrs	-	4 yrs	3.5 yrs	2 yrs	2 yrs	4 yrs	6 yrs	5 yrs	7 yrs
Words	-	-	-	-	-	7 yrs	4 yrs	-	6 yrs	5 yrs	5 yrs	5 yrs	6 yrs	-	-	-
Two word sentence	-	-	-	-	-	7 yrs	5 yrs	-	-	-	-	-	-	-	-	-
Seizures																
Onset	7 mos	6 mos	7 mos	2.5 yrs	-	18 mos	4 mos	6 mos	7 mos	-	2 yrs	-	1 yr	-	-	-
Type	Myoclonic Focal		Myo-clonic	GTC	-	Myo-clonic	Focal	Myoclonic		-	Febrile (1 ep.)	-	Febrile (a few days)	-	-	-
Frequency	Under control by AED	Under control by AED	Under control by AED	Under control by AED	-	Under control by AED	Under control by AED	Under control by AED	Under control by AED	-	-	-	-	-	-	-
Autism																
CARS score	28	30	30	44	42	41	42	42	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Neurological																
HC at last exam (SD)	-1	-1	-1	-3	-2	-1.1	-2.5	-2.8	-1.2		-1.1	-0.9	-1.5	-1	-2	-2
Hypotonia (infancy)	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
Hypertonia	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Brain MR imaging	Normal	N/A	Norma l	PMG & cortical atrophy	N/A	PMG & cortical atrophy	Normal	N/A	N/A							Normal

Table S2. Detailed information for all mutations detected in affected individuals from families 1-6, including gene name, transcript number, genetic (gDNA) and complementary DNA (cDNA) position, and protein position.

Family	Gene	Transcript	gDNA pos.	cDNA pos.	Protein pos.
Family 1	*MBOAT7*	NM_024298.3	g.1583_1602del	c.126_145del	p.Leu43Hisfs*69
Family 2/3	*MBOAT7*	NM_024298.3	g.9148_9168del	c.758_778del	p.Gln253_Ala259del
Family 4	*MBOAT7*	NM_024298.3	g.6260delG	c.423delG	p.Leu142Cysfs*8
Family 5	*MBOAT7*	NM_024298.3	g.9245G>C	c.854+1G>C	p.0?
Family 6	*MBOAT7*	NM_024298.3	g.9210_9216del	c.820_826del	p.Gly274Profs*47

References:

1. Schopler, E., Reichler, R.J., and Renner, B.R. (2002). The childhood autism rating scale (CARS).(Western Psychological Services Los Angeles).