Blood-Brain Barrier and Brain Microvasculature

Genetic Pathway Reference — Addendum

Companion to: Dementia, Glycation, Endothelial Health, Homocysteine reports

Educational reference document | No personal genotype data

1. Purpose and Scope

This addendum characterizes the blood-brain barrier (BBB) genes that are relevant to late-life cognitive function but are not already covered in the main pathway-reference documents. It is explicitly an addendum — short, narrowly scoped, and cross-linked — rather than a standalone report. The biology of cerebrovascular small-vessel disease, complement and microglial Aβ clearance, brain lipid handling via APOE, NO/BH4 endothelial signaling, glucose transport across the BBB, advanced glycation end products and their receptor (RAGE), and homocysteine-mediated endothelial toxicity are all already documented in the Dementia, Endothelial Health, Glycation, and Homocysteine references and are NOT repeated here. The scope of this document is limited to four genuinely new genes that govern BBB transporter function and pericyte biology: MFSD2A, ABCB1 / MDR1 (P-glycoprotein), LRP1, and PDGFRB / PDGFB.

Effect sizes for common variants in BBB-transporter genes are generally smaller and less reproducibly replicated than the microglial and lipid-handling common variants catalogued in the main Dementia reference. The largest effect of BBB biology on late-life cognition operates through the APOE-ε4-specific pericyte cyclophilin-A / MMP-9 pathway documented by Montagne et al. (Nature 2020); that mechanism is not engaged in APOE ε3/ε3 carriers. Most of the value of this addendum is therefore biological documentation and lookup-completeness rather than novel risk identification.

2. The BBB as a Multi-Cell Functional Unit

The blood-brain barrier is not a single barrier. It is a neurovascular unit comprising brain capillary endothelial cells joined by tight junctions, surrounded by pericytes embedded in a shared basement membrane, surrounded in turn by astrocyte endfeet. Each cell layer fails in a genetically distinct way, and the disease-relevant phenotypes differ accordingly.

The endothelial layer performs four jobs simultaneously. First, a physical barrier function via tight-junction proteins (claudin-5, occludin, ZO-1) that restrict paracellular diffusion. Second, selective influx of essential nutrients via specific transporters: SLC2A1 (GLUT1) for glucose, the LAT family for amino acids, and MFSD2A for docosahexaenoic acid (DHA). Third, active efflux of xenobiotics and metabolic waste back to the systemic circulation, principally via ABC-family transporters with ABCB1 (P-glycoprotein) the dominant member. Fourth, bidirectional transcytosis of larger molecules, in which Aβ is the central species of interest: LRP1 is the abluminal receptor that effluxes Aβ from brain interstitial fluid, RAGE / AGER is the luminal receptor that imports Aβ from blood, and PICALM mediates the endothelial endocytic vesicle dynamics that connect them.

Pericytes wrap the capillaries at irregular intervals (greater coverage in higher-order brain regions, particularly hippocampus and prefrontal cortex). They communicate with endothelial cells via the PDGF-BB → PDGFRβ paracrine axis: endothelial cells secrete PDGF-BB, pericytes express PDGFRβ, and continuous receptor signaling keeps pericytes attached, keeps

endothelium quiescent, and keeps the basement membrane intact. Pericyte loss is one of the earliest detectable BBB changes in normal aging and in cognitive decline (Montagne et al., Neuron 2015; Nation et al., Nat Med 2019). The biomarker readout is rising soluble PDGFRβ in CSF, reflecting pericyte injury and shedding.

Astrocyte endfeet contribute the third layer of the unit, providing aquaporin-4 mediated water and solute regulation and orchestrating glymphatic-system clearance of brain interstitial fluid during sleep (Iliff et al., Sci Transl Med 2012; Xie et al., Science 2013). The astrocyte-endfeet axis is not a major common-variant genetic story for late-life cognitive decline and is not characterized here.

The clinically relevant BBB-failure pattern in late-life cognitive decline, established by the Montagne / Nation series, is: pericyte injury → loss of endothelial PDGFRβ signaling → tight-junction dysfunction → leak of plasma proteins (fibrinogen, albumin) into the hippocampus and medial temporal lobe → cognitive impairment. Critically, this pathway has been shown to be APOE ε4-specific: BBB breakdown predicts cognitive decline in ε4 carriers but not in ε3/ε3 carriers (Montagne et al., Nature 2020). The implication for genetic risk stratification is that BBB-genetic findings carry the largest weight in ε4 carriers and are correspondingly less consequential in ε3/ε3 carriers.

3. Functional Categories

The BBB pathway is organized into four functional nodes for the purposes of this addendum. Genes characterized in detail here are listed in the third column; genes already covered in companion reports are noted in the fourth column with a cross-reference.

#	Node	Genes characterized here	Cross-reference (already covered)
1	Selective influx	MFSD2A (DHA)	SLC2A1 / GLUT1 — Glycation §2.1
2	Active efflux	ABCB1 / MDR1 (P-glycoprotein)	—
3	Aβ transcytosis	LRP1 (Aβ-efflux receptor)	AGER / RAGE — Glycation report; PICALM — Dementia §4.3
4	Pericyte–endothelial axis	PDGFRB, PDGFB	APOE ε4-driven pericyte cyclophilin-A / MMP-9 axis — Dementia §2.4 (NOT operative in ε3/ε3)

4. SNP Catalog by Functional Node

Each table below lists the well-studied common variants in the four BBB genes characterized in this addendum, with rsID, variant name, functional consequence, the cofactor or substrate the gene's product depends on, and an evidence-strength rating: ★★★ landmark / monogenic; ★★ robust common-variant replication; ★ single GWAS or candidate-gene study; ⚠ mixed or non-replicating evidence.

4.1 Node 1 — Selective influx: MFSD2A

MFSD2A is a sodium-dependent lysophosphatidylcholine-DHA symporter expressed exclusively in the endothelium of the blood-brain barrier. The transporter performs two coupled jobs: import of plasma LPC-DHA into brain, and suppression of non-selective vesicular transcytosis (Nguyen

et al., Nature 2014; Ben-Zvi et al., Nature 2014; Andreone et al., Neuron 2017). Biallelic loss-of-function causes severe microcephaly with hypomyelination and is incompatible with adult presentation absent severe developmental disease (Guemez-Gamboa et al., Nat Genet 2015; Alakbarzade et al., Nat Genet 2015). The clinically relevant question for adult BBB function is whether common variants modulate adult brain DHA delivery or BBB transcytosis quietness; the published evidence is limited and largely candidate-gene rather than genome-wide.

Gene	rsID	Variant	Functional consequence	Cofactor / dependency
MFSD2A	rs12083239	Intronic	Wu et al., 2022 (Lipids Health Dis) candidate-gene study in T2DM elderly: associated with serum total cholesterol and HDL-C in the T2DM subgroup. No direct CSF or brain DHA assay.	Na^+ gradient; plasma LPC-DHA
MFSD2A	rs4233508	Intronic	Wu 2022: T allele associated with lower HDL-C in T2DM subgroup. No direct BBB phenotype.	Na^+; LPC-DHA
MFSD2A	rs12072037	Intronic	Wu 2022: A allele associated with higher TG, lower HDL-C, lower LDL-C in T2DM subgroup. No direct BBB phenotype.	Na^+; LPC-DHA
MFSD2A	biallelic LoF (rare)	Various	Cause severe microcephaly with hypomyelination (Guemez-Gamboa 2015; Alakbarzade 2015). Not relevant for adult late-life cognition.	—

Evidence rating ★ for any individual common variant. The biology of MFSD2A as the BBB DHA gate is robust (★★★); the case that any individual common variant meaningfully modifies adult brain DHA delivery is weak. The most clinically actionable handle is at the cofactor level: ensuring adequate plasma LPC-DHA via dietary or supplemental DHA intake is the upstream lever, regardless of MFSD2A genotype.

4.2 Node 2 — Active efflux: ABCB1 / MDR1 (P-glycoprotein)

ABCB1 encodes P-glycoprotein, the ATP-dependent multi-substrate efflux pump on the luminal side of brain endothelial cells. P-gp ejects xenobiotics and metabolic substrates back to blood and contributes to Aβ efflux in series with LRP1. ABCB1 is the most-studied pharmacogenomic gene in BBB drug delivery: many statins (partial substrate), anti-epileptics, glucocorticoids, opioids, and many oncology drugs are P-gp substrates whose brain penetration is influenced by ABCB1 expression and activity.

Gene	rsID	Variant	Functional consequence	Cofactor / dependency
ABCB1	rs1128503	C1236T (synonymous)	Forms haplotype with rs2032582 and rs1045642. Independent functional effect modest. Verapamil-PET evidence (van Assema et al., J Cereb Blood Flow Metab 2012) suggests T-allele dose associated with reduced P-gp activity in AD patients but not healthy controls.	ATP
ABCB1	rs2032582	G2677T/A (Ala893Ser/Thr)	Triallelic. Non-synonymous (Ala→Ser or Ala→Thr). Functional effect on substrate	ATP

Gene	rsID	Variant	Functional consequence	Cofactor / dependency
			specificity proposed; evidence mixed. T-allele dose associated with reduced P-gp activity at the BBB in AD patients (van Assema 2012).	
ABCB1	rs1045642	C3435T (synonymous)	The most-studied ABCB1 SNP. C/C genotype associated with AD risk OR ~1.4 in the Cascorbi et al. 2014 candidate-gene study (J Alzheimers Dis), significant after multiple-testing correction. The C-allele correlates with higher P-gp expression in intestine but the SNP affects mRNA folding and tissue-specific protein conformation.	ATP

Evidence rating ★★ for rs1045642; ★ for the haplotype. The synonymous C3435T variant is one of the few well-replicated AD-modifier signals in BBB-transporter genetics, but effect sizes are modest and most of the evidence comes from candidate-gene work rather than genome-wide significance. Pharmacogenomic relevance for P-gp-substrate medications is independently established.

4.3 Node 3 — Aβ transcytosis: LRP1

LRP1 (low-density lipoprotein receptor-related protein 1) is the dominant abluminal-side receptor that retrieves Aβ from brain interstitial fluid and hands it to endothelial transcytosis machinery for delivery to blood (Storck et al., J Clin Invest 2016; Zhao et al., Nat Neurosci 2015). It pairs functionally with PICALM on the endothelial side and with ABCB1 on the luminal efflux side. LRP1 also has a separate intracellular role in APP processing and tau handling. The most-studied common variant is the silent rs1799986 in exon 3.

Gene	rsID	Variant	Functional consequence	Cofactor / dependency
LRP1	rs1799986	C766T (also called C667T; synonymous)	Bian et al., Sci Rep 2017 meta-analysis (26 studies, 6,455 cases / 6,304 controls): no significant AD association in Europeans (TT+CT vs CC OR 0.92, P=0.17). Significant T-allele protection in Asians (OR 0.79, P=0.028). Sehgal et al., Neuroimage Clin 2013 (n=72) reported amyloid-PET regional differences by genotype, but the sample is small.	—
LRP1	rs1140239	Intronic	Candidate-gene only; mixed signal.	—

Evidence rating ⚠ for AD risk in Europeans (null in the definitive meta-analysis); ★ in Asians (modest protection). Evidence rating ★★★ for the underlying biology of LRP1 as the BBB Aβ-efflux receptor (which is robust regardless of whether any individual common variant modifies it).

4.4 Node 4 — Pericyte-endothelial axis: PDGFRB / PDGFB

PDGFRβ (encoded by PDGFRB) is the receptor on pericytes for the ligand PDGF-BB (encoded by PDGFB) secreted by endothelial cells. Continuous receptor signaling keeps pericytes attached to capillaries; loss of signaling produces pericyte dropout, which is the earliest detectable BBB change in normal aging and in cognitive decline (Bell et al., Nature 2010; Sengillo et al., Brain Pathol 2013; Montagne et al., Neuron 2015; Nation et al., Nat Med 2019). The most clinically relevant biomarker is soluble PDGFRβ shed into CSF, which reflects pericyte injury and which predicts cognitive decline specifically in APOE ε4 carriers (Montagne et al., Nature 2020). Common variants in PDGFRB and PDGFB are not established as significant common-variant risk factors for late-life dementia and are catalogued here primarily for completeness.

Gene	rsID	Variant	Functional consequence	Cofactor / dependency
PDGFRB	rs2229558	V249I (missense)	Reported in stroke-association candidate-gene studies; effect mixed and small.	ATP (kinase activity)
PDGFRB	rs246395	Intronic	Candidate-gene only.	—
PDGFRB	Pathogenic missense (rare)	Various	Cause idiopathic basal ganglia calcification (Nicolas et al., Neurology 2013; Keller et al., Nat Genet 2013); not common-variant relevant.	—
PDGFB	rs2285097	Intronic	Modest white-matter-hyperintensity associations.	—
PDGFB	Pathogenic LoF (rare)	Various	Cause idiopathic basal ganglia calcification (Keller 2013); not common-variant relevant.	—

Evidence rating ★ at best for any individual common variant. The biology of the pericyte-endothelial axis is robust; the common-variant signal for late-life cognition is modest to absent. The lookup is mostly a negative-finding documentation exercise.

5. Categories → Genes → Cofactors → Targets

Compact mapping of the four BBB nodes to the cofactors and biological inputs they depend on, and the dietary or supplement inputs that support those cofactors. Most BBB-transporter activity is not directly modifiable by supplementation; the actionable handles are at the substrate and systemic-level levers.

Node	Genes	Cofactors / inputs	Modifiable inputs
1. Selective influx (DHA)	MFSD2A	Plasma LPC-DHA; Na^+ gradient	Dietary DHA (oily fish, algal oil); LPC-DHA preferentially over triglyceride-DHA may be more bioavailable to the brain (Sugasini et al., Sci Rep 2017)
2. Active efflux	ABCB1 / P-gp	ATP	P-gp inducers (rifampin — not relevant here); avoidance of P-gp-inhibitor co-medications when brain penetration matters; pharmacogenomic awareness for substrate drugs
3. Aβ transcytosis	LRP1	Aβ–chaperone complex (apoE, α2-macroglobulin)	Indirect: anti-amyloid therapy (lecanemab, donanemab — not for primary prevention); LDL-lowering reduces vascular Aβ deposition and supports clearance; APOE ε3/ε3 background already favorable
4. Pericyte axis	PDGFRB, PDGFB	(Receptor signaling, no small-molecule cofactors)	Cardiovascular and metabolic risk-factor control (BP, glucose, lipids); pericyte preservation is essentially a vascular-aging lever

6. Cross-Reference Map

Where each BBB-relevant gene is characterized in the broader report suite. This addendum points to rather than duplicates these characterizations.

BBB function	Gene(s)	Where covered
Glucose import (GLUT1)	SLC2A1	Glycation Pathway Reference §2.1 — characterized as homozygous risk locus; mesangial GLUT1 plus brain endothelial GLUT1 both relevant
Selective influx of DHA	MFSD2A	This addendum, Node 1
Active efflux (xenobiotics, Aβ)	ABCB1 / P-gp	This addendum, Node 2
Aβ-efflux receptor at BBB	LRP1	This addendum, Node 3
Aβ-influx receptor at BBB (RAGE)	AGER	Glycation Pathway Reference — RAGE characterized in the AGE/RAGE axis; also one of the BBB Aβ-influx mechanisms (Deane et al., Nat Med 2003)
Endothelial Aβ transcytosis adapter	PICALM	Dementia Genetic Pathway Reference §4.3 — characterized as endo-lysosomal sorting gene; PICALM also operates at the brain endothelial cell to mediate Aβ transcytosis (Zhao et al., Nat Neurosci 2015)
Microglial-endothelial bridge	CD2AP	Dementia Genetic Pathway Reference §4.3 — endo-lysosomal/microglial; expressed in endothelial cells with

BBB function	Gene(s)	Where covered
		relevance to BBB integrity
Vessel wall structure (small-vessel)	NOTCH3, HTRA1, COL4A1, COL4A2	Dementia Genetic Pathway Reference §2.8 / §4.8 — cerebrovascular monogenic biology
Endothelial NO / BH4 production	NOS3, GCH1, SPR, XDH	Endothelial Health Pathway Reference — full characterization; the same NO/BH4 machinery operates at the BBB endothelium
Hcy-mediated endothelial toxicity	MTHFR (and downstream)	Homocysteine Regulation Pathway Reference; cross-link in Dementia §2.8
Pericyte-endothelial axis	PDGFRB, PDGFB	This addendum, Node 4
APOE ε4-driven pericyte CypA-MMP9 BBB breakdown	APOE	Dementia Genetic Pathway Reference §2.4 — mechanism described; ε4-specific (Montagne et al., Nature 2020)
Lipid handling at BBB	APOE, ABCA7, CLU, ABCA1	Dementia Genetic Pathway Reference §2.1

7. Bibliography

BBB biology and structure

- Iadecola C. The neurovascular unit coming of age: a journey through neurovascular coupling in health and disease. Neuron 2017;96:17–42.
- Zlokovic BV. The blood-brain barrier in health and chronic neurodegenerative disorders. Neuron 2008;57:178–201.
- Sweeney MD, Zhao Z, Montagne A, Nelson AR, Zlokovic BV. Blood-brain barrier: from physiology to disease and back. Physiol Rev 2019;99:21–78.

MFSD2A and brain DHA delivery

- Nguyen LN, Ma D, Shui G, et al. Mfsd2a is a transporter for the essential omega-3 fatty acid docosahexaenoic acid. Nature 2014;509:503–506.
- Ben-Zvi A, Lacoste B, Kur E, et al. Mfsd2a is critical for the formation and function of the blood-brain barrier. Nature 2014;509:507–511.
- Andreone BJ, Chow BW, Tata A, et al. Blood-brain barrier permeability is regulated by lipid transport-dependent suppression of caveolae-mediated transcytosis. Neuron 2017;94:581–594.e5.
- Guemez-Gamboa A, Nguyen LN, Yang H, et al. Inactivating mutations in MFSD2A, required for omega-3 fatty acid transport in brain, cause a lethal microcephaly syndrome. Nat Genet 2015;47:809–813.

- Alakbarzade V, Hameed A, Quek DQ, et al. A partially inactivating mutation in the sodium-dependent lysophosphatidylcholine transporter MFSD2A causes a non-lethal microcephaly syndrome. Nat Genet 2015;47:814–817.
- Quek DQ, Nguyen LN, Fan H, Silver DL. Structural insights into the transport mechanism of the human sodium-dependent lysophosphatidylcholine transporter MFSD2A. J Biol Chem 2016;291:9383–9394.
- Wu Y, Sun C, Xie L, et al. Association of CD36, SCARB1, and MFSD2A genetic polymorphism with serum lipid profile in aging population with type 2 diabetes mellitus. Lipids Health Dis 2022 (PMC9515475).
- Sugasini D, Thomas R, Yalagala PCR, et al. Dietary docosahexaenoic acid (DHA) as lysophosphatidylcholine, but not as free acid or triglyceride, increases retina DHA. Sci Rep 2017;7:11263.

ABCB1 / P-glycoprotein

- Cirrito JR, Deane R, Fagan AM, et al. P-glycoprotein deficiency at the blood-brain barrier increases amyloid-beta deposition in an Alzheimer disease mouse model. J Clin Invest 2005;115:3285–3290.
- Cascorbi I, Flüh C, Remmler C, et al. Association of ATP-binding cassette transporter variants with the risk of Alzheimer's disease. Pharmacogenomics 2013;14:485–494.
- van Assema DM, Lubberink M, Boellaard R, et al. Blood-brain barrier P-glycoprotein function in healthy subjects and Alzheimer's disease patients: effect of polymorphisms in the ABCB1 gene. EJNMMI Res 2012;2:57.
- Wang JS, DeVane CL, Gibson BB, et al. Population pharmacokinetic analysis of drug substrates of P-glycoprotein. Pharmacogenet Genomics 2013.
- Chen Q, Lin W, Yang J, et al. Prognostic value of two polymorphisms, rs1045642 and rs1128503, in ABCB1 following taxane-based chemotherapy: a meta-analysis. Asian Pac J Cancer Prev 2021;22:3–10.

LRP1 and Aβ transcytosis

- Storck SE, Meister S, Nahrath J, et al. Endothelial LRP1 transports amyloid-β1-42 across the blood-brain barrier. J Clin Invest 2016;126:123–136.
- Zhao Z, Sagare AP, Ma Q, et al. Central role for PICALM in amyloid-β blood-brain barrier transcytosis and clearance. Nat Neurosci 2015;18:978–987.
- Bian L, Yang JD, Guo TW, et al. Association of LRP1 C766T polymorphism with Alzheimer's disease: a meta-analysis. Sci Rep 2017;7:8197.
- Sehgal N, Gupta A, Valli RK, et al. LRP-1 polymorphism is associated with global and regional amyloid load in Alzheimer's disease in humans in-vivo. Neuroimage Clin 2014;4:296–301.
- Kanekiyo T, Bu G. The low-density lipoprotein receptor-related protein 1 and amyloid-β clearance in Alzheimer's disease. Front Aging Neurosci 2014;6:93.
- Deane R, Du Yan S, Submamaryan RK, et al. RAGE mediates amyloid-beta peptide transport across the blood-brain barrier and accumulation in brain. Nat Med 2003;9:907–913.

PDGFRB / PDGFB and pericyte biology

- Bell RD, Winkler EA, Sagare AP, et al. Pericytes control key neurovascular functions and neuronal phenotype in the adult brain and during brain aging. Neuron 2010;68:409–427.
- Montagne A, Barnes SR, Sweeney MD, et al. Blood-brain barrier breakdown in the aging human hippocampus. Neuron 2015;85:296–302.
- Nation DA, Sweeney MD, Montagne A, et al. Blood-brain barrier breakdown is an early biomarker of human cognitive dysfunction. Nat Med 2019;25:270–276.
- Montagne A, Nation DA, Sagare AP, et al. APOE4 leads to blood-brain barrier dysfunction predicting cognitive decline. Nature 2020;581:71–76.
- Sengillo JD, Winkler EA, Walker CT, et al. Deficiency in mural vascular cells coincides with blood-brain barrier disruption in Alzheimer's disease. Brain Pathol 2013;23:303–310.
- Keller A, Westenberger A, Sobrido MJ, et al. Mutations in the gene encoding PDGF-B cause brain calcifications in humans and mice. Nat Genet 2013;45:1077–1082.
- Nicolas G, Pottier C, Maltête D, et al. Mutation of the PDGFRB gene as a cause of idiopathic basal ganglia calcification. Neurology 2013;80:181–187.

Glymphatic and sleep-related clearance (cross-link)

- Iliff JJ, Wang M, Liao Y, et al. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β. Sci Transl Med 2012;4:147ra111.
- Xie L, Kang H, Xu Q, et al. Sleep drives metabolite clearance from the adult brain. Science 2013;342:373–377.

8. Disclaimer

This document is an educational reference. It does not constitute medical advice and is not a substitute for individualized evaluation by a qualified healthcare provider. The biology of the blood-brain barrier in late-life cognition is well-established (★★★); the contribution of any individual common variant in the four genes characterized here is generally smaller and less reproducibly replicated than the microglial and lipid-handling variants catalogued in the main Dementia reference. The largest BBB-genetic effect known — the APOE ε4-specific pericyte cyclophilin-A / MMP-9 mechanism (Montagne 2020) — is not engaged in APOE ε3/ε3 carriers, and most BBB-genetic findings should be interpreted in the context of APOE genotype.

This addendum does not duplicate the biology of cerebrovascular monogenic disease (NOTCH3, HTRA1, COL4A1/2 — covered in the Dementia reference §2.8 / §4.8), endothelial NO / BH4 signaling (covered in the Endothelial Health reference), homocysteine-mediated endothelial toxicity (Homocysteine Regulation reference), advanced glycation end-products and RAGE (Glycation reference), or APOE-mediated brain lipid handling (Dementia reference §2.4). Cross-references in Section 6 indicate where each of those topics is characterized.