Alzheimer's Disease and Related Dementias

Genetic Pathway Reference

9 functional categories • ~95 SNPs catalogued across four dementias

Educational reference document | No personal genotype data

1. Purpose and Scope

This document is a standalone educational reference describing the biology of Alzheimer's disease and related dementias (vascular dementia, dementia with Lewy bodies, and frontotemporal dementia), the genes that govern each node of these pathways, the well-studied common and rare variants in those genes, the cofactors and biological inputs each pathway depends on, and the supplement and lifestyle targets that map to each pathway. It is intended for use by clinicians, researchers, or interested non-specialists who want a compact pathway primer that can later be paired with personal genotype results.

All variant interpretations are based on published GWAS literature, peer-reviewed mechanistic studies, and curated variant databases (OMIM, ClinVar, Alzforum). The document contains no personal genotype data, no medication or supplement regimens, and no individualized clinical recommendations. Most common variants catalogued here confer small individual effects (per-allele odds ratios 1.05–1.25); clinical significance arises from cumulative patterns and gene–environment interactions. A small number of variants — notably APOE rs429358 (ε4), TREM2 R47H (rs75932628), GBA pathogenic variants, NOTCH3 cysteine-altering missense variants, MAPT/GRN/C9orf72 monogenic variants, and SORL1 truncating variants — have substantially larger and clinically actionable effect sizes.

Heritability framework. Late-onset Alzheimer's disease has a heritability estimated at approximately 60–80% (Gatz et al., Arch Gen Psychiatry 2006), with APOE alone explaining roughly 25% of population risk, the 75 non-APOE common-variant loci identified by the Bellenguez et al. 2022 meta-analysis (Nat Genet 54:412–436) explaining roughly an additional 10–15%, and rare variants in SORL1, TREM2, ABCA7, ATP8B4, and ABCA1 contributing further. Lewy body dementia has heritability around 36% with the dominant signals at GBA, APOE, SNCA, BIN1, and TMEM175. Frontotemporal dementia has roughly 30% familial recurrence with three monogenic causes (MAPT, GRN, C9orf72) accounting for the majority of familial cases. Vascular dementia common-variant GWAS is sparse; the field is dominated by monogenic small-vessel disease genes (NOTCH3, HTRA1, COL4A1/2).

2. Pathway Biology

2.1 What dementia is, mechanistically

Dementia is the clinical syndrome of progressive cognitive decline severe enough to interfere with daily life. The biology underneath the syndrome is, in most cases, a proteinopathy: misfolded proteins accumulate in specific brain regions, the cells in those regions die, and the cognitive functions those regions supported are lost. The four dementia syndromes addressed in this document differ by which protein misfolds and where it strikes first. Alzheimer's disease is defined by extracellular β-amyloid (Aβ) plaques and intracellular hyperphosphorylated tau tangles, beginning in the entorhinal cortex and spreading through the medial temporal lobe and association cortices (Braak & Braak, Acta Neuropathol 1991). Dementia with Lewy bodies is

defined by intraneuronal α-synuclein aggregates (Lewy bodies and Lewy neurites) starting in brainstem and limbic structures. Frontotemporal dementia is a heterogeneous group defined either by tau aggregates or by TDP-43 (or rarely FUS) aggregates affecting the frontal and anterior temporal lobes. Vascular dementia is the only one of the four without a defining proteinopathy: it is caused by the cumulative effect of small-vessel and large-vessel ischemic injury on cognitive networks.

The genetic architecture follows the biology. AD genes cluster around Aβ generation, Aβ clearance, microglial response to Aβ, and brain lipid handling. DLB shares the AD lipid axis but adds α-synuclein and lysosomal genes. FTD genes cluster around tau biology, autophagy, and RNA metabolism. Vascular dementia genes cluster around vascular wall integrity and have substantial overlap with the cardiovascular and endothelial genetics covered in companion reports.

2.2 The amyloid cascade — the central Alzheimer's hypothesis

The canonical mechanistic model of AD (Hardy & Selkoe, Science 2002, refined extensively but not overturned) is the amyloid cascade. Amyloid precursor protein (APP) is a transmembrane protein cleaved by either α-secretase (ADAM10) in a non-amyloidogenic pathway or sequentially by β-secretase (BACE1) and γ-secretase (the PSEN1/PSEN2-containing complex) to release Aβ peptides into the extracellular space. The two main Aβ species are Aβ40 and Aβ42; the latter is more aggregation-prone, and the Aβ42:Aβ40 ratio is the central upstream variable. Aβ42 oligomerizes, then forms fibrils, then deposits as plaques. Plaques alone are not directly neurotoxic; soluble oligomers and the downstream tau pathology they trigger appear to drive synapse loss and neuron death. Tau is normally a microtubule-stabilizing protein in axons; in AD it becomes hyperphosphorylated, releases from microtubules, mislocalizes to dendrites, and aggregates into paired helical filaments — the neurofibrillary tangle.

The clinical proof of the amyloid cascade is the autosomal-dominant early-onset AD pedigrees: pathogenic variants in APP (the substrate), PSEN1, and PSEN2 (components of γ-secretase) all increase Aβ42 production and all cause near-fully-penetrant AD with onset typically in the 40s–50s. The recently approved anti-amyloid antibodies lecanemab (Van Dyck et al., NEJM 2023, CLARITY-AD) and donanemab (Sims et al., JAMA 2023, TRAILBLAZER-ALZ 2) provide further clinical confirmation by showing that removing plaques modestly slows clinical decline.

2.3 Aβ clearance — the second arm of the cascade

Aβ levels at any moment reflect the balance between production and clearance. Two main clearance pathways operate. The first is endo-lysosomal sorting and degradation by neurons themselves: APP-derived peptides are trafficked through the endosomal system, where SORL1 (encoding the SORLA receptor) is the central sorting molecule that diverts APP away from amyloidogenic cleavage and toward the recycling pathway. Truncating variants in SORL1 essentially eliminate this protective sort and substantially increase AD risk (Holstege et al., Eur J Hum Genet 2017). Other endo-lysosomal genes — BIN1, PICALM, CD2AP, RIN3, INPP5D, EPHA1 — modulate the same machinery and emerged from GWAS as AD risk loci.

The second clearance arm is microglial phagocytosis. Microglia, the resident innate immune cells of the brain, recognize Aβ — particularly Aβ complexed with apolipoproteins (APOE, CLU) and lipids — through receptors including TREM2, CD33/SIGLEC3, complement receptor 1 (CR1), and the MS4A cluster. They engulf and degrade plaques. The discovery in 2013 (Jonsson et al., Guerreiro et al., NEJM) that the rare TREM2 R47H missense variant confers an AD odds ratio of approximately 2.9 — comparable to one APOE ε4 allele — established

microglial dysfunction as a major causal contributor to AD, not merely a downstream consequence. The Bellenguez et al. 2022 Nature Genetics meta-analysis confirmed that pathway enrichment among 75 AD risk loci is dominated by amyloid/tau and microglial signatures.

2.4 APOE — the keystone of common-variant AD risk

APOE encodes apolipoprotein E, the principal lipid carrier of the central nervous system. Three common protein isoforms — ε2, ε3, ε4 — are determined by two non-synonymous SNPs in exon 4: rs429358 (Cys112Arg) and rs7412 (Arg158Cys). The ε4 isoform binds Aβ in a way that promotes oligomerization and impairs microglial clearance, while ε2 has the opposite effect. The result is an enormous range of population-level risk: a single ε4 allele approximately triples lifetime AD risk; two ε4 alleles raise it roughly 10–15-fold and shift the typical age of onset earlier by 5–10 years; one ε2 allele approximately halves risk and pushes onset later. APOE ε4 also amplifies risk for cerebral amyloid angiopathy, dementia with Lewy bodies, and post-stroke cognitive impairment, making it a cross-disease modifier rather than an AD-specific allele.

Beyond AD, APOE ε4 is an established risk factor for DLB (Bras et al., Hum Mol Genet 2014; Rongve et al., Sci Rep 2019), and APOE ε4 promotes both amyloid and α-synuclein pathology, which is why mixed AD–DLB pathology is so common at autopsy. APOE has very modest effect on FTD risk — a useful negative finding when interpreting APOE in someone with frontotemporal symptoms.

2.5 Microglia and the innate immune axis

The 2009–2013 wave of AD GWAS (Lambert, Harold, Hollingworth, Naj) and the rare-variant findings at TREM2 reframed AD as a disease in which the microglial response to Aβ is at least as important as Aβ itself. Microglia exist on a spectrum: a homeostatic surveillance state in the healthy brain, a 'disease-associated microglia' (DAM) state thought to be initially protective and Aβ-clearing, and a chronic pro-inflammatory state that drives synaptic pruning and neuron death. The transition between these states is regulated by TREM2/TYROBP signaling, by SPI1/PU.1 transcriptional control, by MS4A surface receptors (which set soluble TREM2 levels — Deming et al., Sci Transl Med 2019), and by CD33 (which inhibits microglial phagocytosis when engaged). Genetic variants that bias microglia toward the inflammatory or anti-phagocytic state (TREM2 R47H, ABI3 S209F, CD33 risk allele, PLCG2 LoF) increase AD risk, and variants that bias toward DAM/phagocytic states (PLCG2 P522R gain-of-function, MS4A protective alleles, CD33 protective haplotype) decrease it. Mendelian randomization for AD has not been definitive but the broad consensus is that microglial dysregulation is a causal contributor, not just a marker.

2.6 Tau, MAPT haplotypes, and the tauopathy spectrum

Tau is the second of the two AD aggregating proteins and the primary aggregating protein of progressive supranuclear palsy, corticobasal degeneration, Pick's disease, and a subset of frontotemporal dementias (FTD-tau). The MAPT gene exists in two extended haplotypes, H1 and H2, defined by an inversion polymorphism on chromosome 17q21. The H1 haplotype is the risk haplotype for PSP, CBD, and several FTD-tau presentations; the H2 haplotype is protective. Within H1, sub-haplotype H1c amplifies the risk further (Pittman et al., J Med Genet 2005; Höglinger et al., Nat Genet 2011 PSP GWAS). Rare missense and splice-site variants in MAPT (e.g., P301L, R406W, the IVS10+16 splice variant c.1920+16C>T) cause autosomal-dominant FTD-tau with high penetrance and onset typically in the 40s–60s.

In AD, the MAPT effect is much smaller but real: the BIN1 GWAS signal is now thought to act through tau pathology rather than directly through Aβ (Chapuis et al., Mol Psychiatry 2013). GSK3B is the main tau kinase and a candidate but not strongly replicated common-variant signal.

2.7 α-synuclein, lysosomes, and the Lewy body axis

Dementia with Lewy bodies is genetically a hybrid of Parkinson's disease and Alzheimer's disease. The largest LBD GWAS to date (Chia et al., Nat Genet 2021; whole-genome sequencing of 2,981 cases and 4,931 controls) identified five genome-wide significant loci: APOE, GBA, SNCA, BIN1, and TMEM175. APOE and BIN1 are AD loci; GBA, SNCA, and TMEM175 are PD loci. The molecular through-line is α-synuclein: SNCA is the gene that encodes it, GBA encodes the lysosomal enzyme glucocerebrosidase that degrades it, and TMEM175 is a lysosomal potassium channel that sets lysosomal pH and therefore degradative capacity. GBA variants cause AD-like cognitive trajectory in PD patients (Brockmann et al., Mov Disord 2011) and increase DLB risk roughly five-fold for the severe alleles (Nalls et al., JAMA Neurol 2013).

A recent 2025 LBD GWAS meta-analysis (Molecular Psychiatry) confirmed APOE, GBA, BIN1, and SNCA-AS1 and added SYT16 as a novel locus.

2.8 Frontotemporal dementia — three monogenic causes dominate

FTD is roughly 30% familial. Three genes — MAPT, GRN, and C9orf72 — together explain the majority of familial cases. MAPT pathogenic variants cause autosomal-dominant FTD-tau, typically with disinhibited behavioral variant or progressive supranuclear palsy syndrome, with mean onset in the 50s and high penetrance. GRN haploinsufficiency (caused by frameshift, nonsense, splice-site, or large deletion variants) reduces circulating progranulin to roughly half of normal and produces TDP-43 pathology, with age-dependent penetrance and a mean onset around 60. C9orf72 carries a hexanucleotide GGGGCC repeat in intron 1 that is normally fewer than 30 copies but in pathogenic cases expands to hundreds or thousands; the expansion produces both RNA foci sequestering RNA-binding proteins and dipeptide repeat proteins (DPRs) generated by repeat-associated non-ATG (RAN) translation. C9orf72 expansions are the single most common monogenic cause of FTD and ALS in European populations and frequently produce a mixed FTD–ALS phenotype.

Common-variant GWAS for FTD has identified relatively few loci. TMEM106B is a strong modifier of GRN-related FTD: the protective haplotype dramatically reduces penetrance in GRN carriers (van der Zee et al., Brain 2011). The same TMEM106B variants are now established modifiers of LATE neuropathological change (limbic-predominant age-related TDP-43 encephalopathy) — a TDP-43 proteinopathy that mimics AD clinically and frequently coexists with it (Nelson et al., Brain 2019).

2.9 Cerebrovascular contribution and small-vessel disease

Vascular dementia and AD are no longer cleanly separable. Most clinically-diagnosed late-onset AD has co-existing cerebrovascular pathology, and APOE ε4 increases risk for both amyloid pathology and cerebral amyloid angiopathy. Cerebral small-vessel disease (cSVD) — manifesting as white matter hyperintensities, lacunes, microbleeds, and enlarged perivascular spaces — is the substrate of vascular cognitive impairment and an independent contributor to mixed dementia. Four monogenic cSVD genes account for the vast majority of familial cases: NOTCH3 (CADASIL — cerebral autosomal-dominant arteriopathy with subcortical infarcts and

leukoencephalopathy), HTRA1 (CARASIL when biallelic, autosomal-dominant cSVD when monoallelic), COL4A1, and COL4A2 (Joutel et al., Lancet 1996; Hara et al., NEJM 2009; Verdura et al., Brain 2015). Recent population sequencing has shown that variants identical to those that cause monogenic cSVD are present at unexpectedly high frequency in unselected populations (Rutten et al., Stroke 2020; Mancuso et al., Lancet Neurol 2020), suggesting that some sporadic small-vessel disease may have a single-gene cause.

Common-variant GWAS for vascular dementia per se is small, but stroke and white-matter hyperintensity GWAS have identified several relevant loci, and the Mendelian randomization signal from MTHFR C677T to small-artery-occlusion stroke is supported (Casas et al., Lancet 2005). Hyperhomocysteinemia is an independent risk factor for both stroke and dementia, providing a direct mechanistic bridge to the homocysteine-regulation pathway.

2.10 Synaptic and neuronal modifiers

A heterogeneous set of additional genes modulate neuronal resilience: KLOTHO (KL), where heterozygous carriage of the KL-VS variant is associated with better cognition in older adults and reduced AD risk (Dubal et al., Cell Rep 2014; Belloy et al., Neuron 2020); CALHM1, a calcium homeostasis modulator with mixed evidence; PLD3, a lysosomal phospholipase D; and ATP8B4, a phospholipid flippase whose rare damaging variants were identified by Holstege et al. (Nat Genet 2022) as conferring AD risk.

Mitochondrial function, oxidative stress, and the NRF2-ARE antioxidant program are all relevant to neurodegeneration but are catalogued in the companion Inflammation/Immune and Glycation reports rather than duplicated here.

3. Functional Categories

The pathway can be organized into nine functional categories, each corresponding to a distinct biochemical job. The categories below are used as the organizing scaffold for the SNP catalog in Section 4.

#	Category	Function	Key genes
1	APOE & lipid metabolism (keystone)	Brain lipid transport; modulate Aβ aggregation and microglial phagocytosis	APOE, APOC1, TOMM40, CLU, ABCA7, ABCA1, SORT1
2	Amyloid precursor processing	APP cleavage and Aβ generation; Aβ degradation	APP, PSEN1, PSEN2, BACE1, ADAM10, IDE, MME
3	Endosomal-lysosomal sorting & autophagy	Sort APP away from amyloidogenic cleavage; recycle membrane proteins	SORL1, BIN1, PICALM, CD2AP, RIN3, INPP5D, EPHA1
4	Microglia & innate immunity	Recognize and phagocytose Aβ; modulate neuroinflammation	TREM2, TYROBP, CD33, MS4A4A, MS4A6A, PLCG2, ABI3, SPI1, CR1, HLA-DRB1
5	Tau and microtubule biology	Tau aggregation, tauopathy, MAPT haplotype effects	MAPT (H1/H2), GSK3B
6	α-Synuclein / lysosomal (DLB axis)	α-synuclein production and aggregation; lysosomal clearance	SNCA, SNCA-AS1, GBA, TMEM175, SCARB2, LRRK2

#	Category	Function	Key genes
7	Frontotemporal dementia core	Progranulin, hexanucleotide expansion, FTD modifiers	GRN, C9orf72, MAPT, TMEM106B, CHMP2B, TBK1
8	Cerebrovascular integrity	Small-vessel wall, basement membrane, NO/endothelium	NOTCH3, HTRA1, COL4A1, COL4A2, MTHFR (cross-pathway)
9	Synaptic & neuronal modifiers	Neuronal resilience, Ca^{2+} homeostasis, lysosomal phospholipid handling	KL (KLOTHO), CALHM1, PLD3, ATP8B4, ZCWPW1

4. SNP Catalog by Functional Category

Each table below lists well-studied common and rare variants in the genes for that category, along with the variant name, the functional consequence, and the cofactor or biological dependency the gene's product requires. Effect sizes and GWAS p-values are noted where well-established. The most important single reference is the Bellenguez et al. 2022 GWAS meta-analysis (Nat Genet 54:412–436, 111,326 cases / 677,663 controls), which identified 75 genome-wide significant AD risk loci and which is referenced throughout this section as 'Bellenguez 2022'. The complementary Wightman et al. 2021 meta-analysis (Nat Genet 53:1276–1282) added independent confirmation.

4.1 APOE & lipid metabolism (keystone)

Gene	rsID	Variant / common name	Functional consequence	Cofactor / dependency
APOE	rs429358	C→T defines ε4 (Cys112Arg)	Reduced lipid-binding stability; promotes Aβ aggregation; impairs TREM2 ligand function. Single largest common-variant effect in AD genetics. Population OR ≈ 3 per ε4 allele, ≈ 12–15 for ε4/ε4 (Farrer et al., JAMA 1997 meta-analysis; Reiman et al., Nat Commun 2020).	Lipid handling; statin pharmacogenomics modifier
APOE	rs7412	C→T defines ε2 (Arg158Cys)	Reduced LDL receptor binding; binds Aβ in a configuration that slows aggregation. ε2 is protective for AD (β = –0.59, P = 1×10^{-9} in pooled analysis) but raises risk for type III hyperlipoproteinemia in homozygotes.	Lipid handling
APOC1	rs11568822	HpaI insertion (H1/H2) / promoter	Modulates APOC1 expression; effects on AD partly mediated through linkage with APOE ε4. Independent residual signal contested.	Lipoprotein metabolism
TOMM40	rs2075650	Intronic	Tags APOE ε4 in many genotyping	Mitochondrial

Gene	rsID	Variant / common name	Functional consequence	Cofactor / dependency
			panels. Independent association with age-of-onset variability proposed (Roses et al., Pharmacogenomics J 2010) but not consistently replicated.	protein import
CLU (clusterin / APOJ)	rs11136000	Intronic	Major secondary lipid chaperone; complement regulator; protective C→T allele identified in Lambert et al. 2009 Nat Genet GWAS. Per-allele OR ≈ 0.86 for protective T (Lambert 2013 IGAP meta-analysis).	Lipid handling, complement
CLU	rs9331896	Intronic	Secondary fine-mapped CLU signal at the locus.	
ABCA7	rs3764650	Intronic	Cholesterol efflux to apoE; phagocytic role in microglia. Common variant OR ≈ 1.23 (Hollingworth 2011 Nat Genet).	Cholesterol, ATP
ABCA7	rs4147929	Intronic	Independently fine-mapped ABCA7 signal in Bellenguez 2022; primary signal in some cohorts.	
ABCA7	rare PTV burden	Frameshift, nonsense, splice	Truncating variants confer AD OR ~2–4 (Cuyvers et al., Lancet Neurol 2015; Holstege 2022 Nat Genet); enriched in early-onset cases.	
ABCA1	rs2230806	R219K (missense)	HDL cholesterol efflux; rare damaging variants associated with AD risk in Holstege 2022 Nat Genet exome-burden analysis.	Cholesterol, ATP
SORT1	rs141749679	Loss-of-function	LDL receptor regulator; primarily a CAD/LDL locus, modest AD signal.	

Cofactor / supplement note: Brain lipid handling is partly modifiable. DHA (omega-3) supports neuronal membrane composition; APOE ε4 carriers have been shown to have impaired brain DHA delivery (Yassine et al., JAMA Neurol 2017) and may benefit from higher DHA intake. Phosphatidylserine and phosphatidylcholine support neuronal membranes. Olive-derived oleocanthal has been reported to enhance Aβ clearance in vitro (Abuznait et al., ACS Chem Neurosci 2013) but human evidence is preliminary.

4.2 Amyloid precursor processing

Gene	rsID / region	Variant / common name	Functional consequence	Cofactor / dependency
APP	rs63750847	A673T (Icelandic protective)	Reduces β-secretase cleavage of APP by ~40%; reduces lifetime AD	—

Gene	rsID / region	Variant / common name	Functional consequence	Cofactor / dependency
			risk and age-related cognitive decline in carriers. Rare (MAF ~0.5% in Iceland, much lower elsewhere) but landmark protective allele (Jonsson et al., Nature 2012).	
APP	AD-causing region (exons 16–17)	KM670/671NL (Swedish), V717I (London), V717F (Indiana), E693G (Arctic), and >50 others	Increase Aβ42 generation or alter Aβ42/Aβ40 ratio; cause autosomal-dominant early-onset AD with near-complete penetrance.	—
PSEN1	Exons 4–11	>300 pathogenic missense variants	Alter γ-secretase substrate selectivity, raising Aβ42:Aβ40 ratio. The most common monogenic cause of early-onset AD; typical onset 30s–50s with high penetrance.	—
PSEN2	Exons 4–12	~50 pathogenic missense variants	Same mechanism as PSEN1, lower penetrance, broader age-of-onset distribution.	—
ADAM10	rs653765	Promoter	α-secretase, the non-amyloidogenic APP-cleaving enzyme. Rare missense variants Q170H and R181G (Suh et al., Neuron 2013) reduce activity and increase Aβ; common variant signal modest.	Zinc
BACE1	rs638405	Intronic	β-secretase activity; common-variant signal modest and inconsistent. BACE1 inhibitors as therapeutics have largely failed clinically.	—
MME (NEP / neprilysin)	rs3736187	Intronic	Aβ-degrading metalloendopeptidase; mixed common-variant signal.	Zinc
IDE	rs1887922, rs2149632	Intronic	Insulin-degrading enzyme; degrades both insulin and Aβ. Mixed common-variant evidence; biological plausibility links it to the metabolic-AD intersection.	Zinc

Note on the autosomal-dominant trio (APP, PSEN1, PSEN2): pathogenic variants are private or family-specific and typically not on common genotyping arrays. They can be found by 60× WGS but require careful variant-by-variant annotation against ClinVar and the Alzheimer Disease & Frontotemporal Dementia Mutation Database. Population prior probability is very low (<1% of all AD) absent a strong family history of early-onset AD.

4.3 Endosomal-lysosomal sorting & autophagy

Gene	rsID	Variant / common name	Functional consequence	Cofactor / dependency
SORL1	rs11218343	Intronic (common GWAS tag)	Common variant: protective T allele OR ≈ 0.78 for late-onset AD (Bellenguez 2022). The SORLA receptor sorts APP into the recycling endosome away from the amyloidogenic γ-secretase pathway.	—
SORL1	rare PTV (truncating) variants	Frameshift, nonsense, splice	Loss of SORLA function; raises AD risk approximately 12-fold for the rarest, most damaging variants (Holstege et al., Eur J Hum Genet 2017). Now considered the fourth causal AD gene after APP/PSEN1/PSEN2.	—
SORL1	rare missense (CADD>30, MAF<10^{-5})	Various	Most missense variants of unknown significance; the most strongly damaging variants by CADD score are enriched in AD cases. Variant-by-variant interpretation required.	—
BIN1	rs6733839	Intergenic, near BIN1	Regulates BIN1 isoform expression; modulates tau pathology (Chapuis et al., Mol Psychiatry 2013). T allele is risk; OR ≈ 1.20 (Lambert IGAP 2013).	—
BIN1	rs744373	Intergenic	Second tag SNP at the BIN1 locus, in LD with rs6733839; G allele is risk.	
PICALM	rs3851179	Intergenic	Clathrin-mediated endocytosis; modulates Aβ trafficking and APP internalization. Protective A allele OR ≈ 0.87 (Harold 2009 Nat Genet).	—
PICALM	rs10792832	Intronic	Secondary signal in LD with rs3851179.	
CD2AP	rs9296559 / rs9349407	Intergenic	Endocytic adaptor; expressed in microglia and endothelial cells; relevant to blood-brain barrier integrity. Risk per allele OR ≈ 1.10–1.15 (Hollingworth 2011).	—
RIN3	rs10498633	Intronic	Rab5 GEF; early endosome biology. Both common and rare-variant burdens highlighted in Bellenguez 2022.	—

Gene	rsID	Variant / common name	Functional consequence	Cofactor / dependency
INPP5D	rs35349669	Intronic	Microglial-expressed inositol phosphatase (SHIP1); converged signal in IGAP and Bellenguez. Modulates microglial phagocytosis.	—
EPHA1	rs11771145	Intergenic	Ephrin receptor; immune and endocytic functions. Protective A allele OR ≈ 0.90 (Naj 2011).	—
SORL1 (cross-link)	—	—	Note: SORL1 also implicated in DLB (Benussi et al., Int J Mol Sci 2021) and FTD — a candidate cross-disease endo-lysosomal node.	—

The endo-lysosomal cluster is one of the strongest pathway signals in AD genetics. Multiple independent loci converge on a single biological function: how APP is trafficked through the cell. This convergence is one of the principal arguments that the amyloid cascade is causal rather than incidental.

4.4 Microglia & innate immunity

Gene	rsID	Variant / common name	Functional consequence	Cofactor / dependency
TREM2	rs75932628	R47H (rare missense)	Reduces TREM2 binding to APOE/CLU/Aβ-lipid complexes; impairs microglial phagocytosis and the disease-associated microglia (DAM) state. Heterozygous OR ≈ 2.9 (Jonsson NEJM 2013); homozygous OR ≈ 97 under full genotype model (Sarica et al., NEJM 2024); diagnosis ~6 years earlier than APOE ε4 homozygotes.	—
TREM2	rs143332484	R62H (rare missense)	Less severe partial loss-of-function than R47H. OR ≈ 1.4 (Sims et al., Nat Genet 2017).	—
TREM2	rs2234253	T96K	Variable functional effect; secondary signal in some cohorts.	
TYROBP / DAP12	rare LoF burden	Various	TREM2 signaling partner; biallelic LoF causes Nasu–Hakola disease (early-onset dementia + bone cysts). Heterozygous LoF burden in AD shows OR ≈ 2.6 in Sarica 2024 NEJM.	—
CD33 / SIGLEC3	rs3865444	Promoter	Sialic-acid-binding inhibitory receptor; minor allele increases CD33 surface expression and	Sialic acid

Gene	rsID	Variant / common name	Functional consequence	Cofactor / dependency
			inhibits microglial Aβ uptake. Common-variant OR ≈ 1.10 (Naj 2011).	
MS4A6A	rs610932	Intergenic (MS4A locus)	Member of MS4A cluster regulating microglial activation and soluble TREM2 levels. Protective A allele.	—
MS4A4A	rs983392	Intergenic	Same MS4A cluster; modulates plasma soluble TREM2 (Deming et al., Sci Transl Med 2019). G allele protective.	—
PLCG2	rs72824905	P522R (rare protective)	Gain-of-function in microglial signaling; reduces AD risk OR ≈ 0.68 (Sims 2017 Nat Genet). Also protective for FTD and DLB.	—
ABI3	rs616338	S209F (rare)	Loss-of-function in microglial cytoskeletal regulator; OR ≈ 1.43 (Sims 2017).	—
SPI1 / PU.1	rs1057233	3'UTR	Master microglial transcription factor. Lower SPI1 expression delays AD onset (Huang et al., Nat Neurosci 2017).	—
HLA-DRB1 / DRB5	rs9271192	Intergenic	Antigen presentation; T-cell activation. Modest GWAS signal; HLA region calling from short-read WGS is unreliable.	—
CR1 (complement receptor 1)	rs6656401	Intronic	Complement-dependent Aβ clearance. Risk A allele OR ≈ 1.18 (Lambert 2009).	—
CR1	rs3818361	Intronic	Secondary fine-mapped CR1 signal.	
NLRP3	rs10754558	3'UTR (cross-pathway, see Inflammation/Immune report)	Inflammasome — drives chronic IL-1β release in AD brain (Heneka et al., Nature 2013).	—

The TREM2 and PLCG2 findings, in particular, anchor the microglial-causal interpretation of AD: the same gene with loss-of-function increases risk and with gain-of-function decreases risk, the cleanest possible Mendelian rebuttal to the 'inflammation is downstream' counter-argument.

4.5 Tau and microtubule biology

Gene	rsID	Variant / common name	Functional consequence	Cofactor / dependency
MAPT	rs8070723	H1/H2 haplotype-tagging SNP	Tags the chromosome 17q21 inversion. H1 is the risk haplotype for PSP (Höglinger 2011), CBD, and a subset of FTD-tau. Modest signal in AD (OR ≈ 1.05 for H1).	—
MAPT	rs1052553	A0/A1 (synonymous within H1)	Sub-haplotype marker; H1c (A1) amplifies PSP and FTD-tau risk further (Pittman 2005).	—
MAPT	Pathogenic missense / splice	P301L, R406W, V337M, IVS10+16 (c.1920+16C>T), N279K, and ~60 others	Cause autosomal-dominant FTD-tau or PSP-like syndromes. Penetrance high; mean onset 50s. Variant-by-variant annotation required.	—
GSK3B	rs334558	Promoter	Glycogen synthase kinase 3β — primary tau kinase. Common-variant signal modest.	—
BIN1 (cross-link)	—	—	BIN1 is also a tau pathology modifier (Chapuis 2013); see Section 4.3.	—

4.6 α-Synuclein / lysosomal (DLB axis)

Gene	rsID	Variant / common name	Functional consequence	Cofactor / dependency
SNCA	rs356181	3' of SNCA	α-synuclein expression; established DLB and PD risk locus (Chia et al., Nat Genet 2021; LBD GWAS 2025).	—
SNCA-AS1	rs7681440	Intergenic	Antisense regulator of SNCA; independent DLB signal.	—
GBA	rs76763715	N370S (Ashkenazi-enriched)	Mild-to-moderate loss of glucocerebrosidase activity. Heterozygous DLB OR ≈ 5–8; PD OR ≈ 4 (Sidransky et al., NEJM 2009).	—
GBA	rs421016	L444P	More severe loss of function; classic Gaucher-disease allele. DLB and PD risk allele.	—
GBA	rs2230288	E326K	Mild loss of function; small but real DLB and PD signal.	—
GBA	rs75548401	T369M	Mild loss of function; small PD/DLB	—

Gene	rsID	Variant / common name	Functional consequence	Cofactor / dependency
			signal.	
TMEM175	rs34311866	M393T	Lysosomal K^+ channel; gain-of-risk variant for PD and DLB. Confirmed in Chia 2021 LBD GWAS.	—
LRRK2	rs34637584	G2019S (rare)	PD-causing in autosomal-dominant pedigrees; modest DLB association. Founder allele in Ashkenazi and North African populations.	—
SCARB2	rs6812193	Intronic	Lysosomal trafficking partner of GBA. Modest PD/DLB signal.	—
BIN1 (cross-link)	—	—	BIN1 is also a DLB locus (Chia 2021); see Section 4.3.	—
APOE (cross-link)	—	—	APOE ε4 is a DLB risk allele (Bras et al., Hum Mol Genet 2014; Rongve 2019).	—

GBA variants are interesting clinically because the GBA-specific therapeutics in development (substrate reduction and chaperone therapies for PD) may eventually be relevant for DLB carriers. Routine ambroxol-based chaperone therapy remains investigational.

4.7 Frontotemporal dementia core

Gene	rsID / type	Variant / common name	Functional consequence	Cofactor / dependency
GRN (progranulin)	LoF variants	Frameshift, nonsense, splice, large deletions	Haploinsufficiency reduces circulating progranulin to ~50%. Causes autosomal-dominant FTD with TDP-43 pathology. Penetrance age-dependent (~90% by age 70). Plasma progranulin level is a reliable carrier biomarker (Ghidoni et al., Neurology 2008).	—
GRN	rs5848	3'UTR (miR-659 binding site)	T allele lowers progranulin levels by reducing miR-659-mediated repression efficiency. Modest sporadic FTD risk; modifier in AD (Hsiung et al., Brain 2011).	—
C9orf72	GGGGCC repeat in intron 1	Repeat expansion >30 (often >100s)	Most common monogenic cause of FTD–ALS in European populations. Produces both RNA foci sequestering RNA-binding proteins and dipeptide repeat proteins via repeat-associated non-ATG translation. Not	—

Gene	rsID / type	Variant / common name	Functional consequence	Cofactor / dependency
			detectable by standard short-read WGS — requires repeat-primed PCR or long-read sequencing.	
MAPT (FTD-tau)	—	P301L, IVS10+16, etc.	See Section 4.5; FTD-tau presentations are dominated by these variants.	—
TMEM106B	rs1990622	Intronic	T allele is FTD-TDP risk modifier; especially strong effect in GRN carriers (van der Zee et al., Brain 2011). Same haplotype is the major modifier of LATE neuropathological change (TDP-43 proteinopathy) in late life (Nelson et al., Brain 2019).	—
CHMP2B	Rare	Various splice / missense	Multivesicular body biogenesis (FTD-3, Danish family).	—
TBK1	Rare LoF	Various	Autophagy and innate immunity; FTD–ALS spectrum.	—
SQSTM1	Rare	Various	p62 / autophagy adaptor; FTD–ALS spectrum.	—
VCP	Rare	Various	Inclusion body myopathy + Paget disease + FTD (IBMPFD).	—

Critical short-read limitation: the C9orf72 GGGGCC hexanucleotide expansion cannot be reliably identified from standard 60× short-read WGS. A negative finding in the VCF does not exclude the expansion. If clinically suspected (FTD–ALS phenotype, family history of bvFTD or ALS), specific repeat-primed PCR or long-read sequencing is required.

4.8 Cerebrovascular integrity

Gene	rsID / region	Variant / common name	Functional consequence	Cofactor / dependency
NOTCH3	EGF repeats 1–6 (exons 2–11)	Cysteine-altering missense (R75P, R90C, R141C, R153C, R169C, R182C, etc.)	CADASIL — cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Aggregation of mutant NOTCH3 ECD around vascular smooth muscle cells; gain-of-function. Cumulative cysteine-altering variant frequency in unselected populations is approximately 1 in 300 (Rutten et al., Stroke 2020).	—
NOTCH3	Other regions / GOM-negative	Various	Atypical CADASIL or modest cSVD risk; ECG-negative cysteine-altering variants exist (Joutel et al.,	—

Gene	rsID / region	Variant / common name	Functional consequence	Cofactor / dependency
			Lancet 2001).	
HTRA1	Protease domain	Homozygous LoF (CARASIL)	Loss of HTRA1 serine protease activity; TGF-β pathway dysregulation; recessive form, severe early-onset cSVD with alopecia and spondylosis (Hara et al., NEJM 2009).	—
HTRA1	Heterozygous	Various missense	Autosomal-dominant cSVD with adult onset; haploinsufficiency mechanism. Verdura et al., Brain 2015.	—
COL4A1	Glycine substitutions in collagen domain	Missense at G-X-Y triplet glycines	Type IV collagen basement membrane disruption; small vessel stroke and intracerebral hemorrhage; can include retinal, renal, and porencephaly phenotypes (Plaisier et al., NEJM 2007).	—
COL4A2	Glycine substitutions	Missense at G-X-Y glycines	Same mechanism; less common than COL4A1.	—
MTHFR (cross-pathway)	rs1801133	C677T (Ala222Val)	Thermolabile enzyme; raises tHcy in low-folate states. Mendelian randomization signal for small-artery-occlusion stroke (Casas et al., Lancet 2005). See Homocysteine Regulation reference.	FAD (B2)
F5, F2 (cross-pathway)	rs6025, rs1799963	Factor V Leiden, Prothrombin G20210A	Thrombophilia; relevant to embolic dementia. See Endothelial Health reference.	—

Variant-level interpretation note: NOTCH3 cysteine-altering variants need to be inspected one-by-one against the curated CADASIL mutation database (LOVD), not relied upon from rsID-only queries. Standard SNP arrays generally do not interrogate the relevant positions, but 60× WGS can identify them — though clinical reporting of CADASIL variants typically proceeds through a dedicated NOTCH3 sequencing analysis.

4.9 Synaptic & neuronal modifiers

Gene	rsID	Variant / common name	Functional consequence	Cofactor / dependency
KL (KLOTHO)	rs9536314	F352V (KL-VS heterozygosity)	Heterozygous KL-VS associated with better cognition in older adults and reduced AD risk; the effect is heterozygote-specific (homozygotes do not benefit). Dubal et al., Cell Rep 2014; Belloy	—

Gene	rsID	Variant / common name	Functional consequence	Cofactor / dependency
			et al., Neuron 2020.	
KL	rs9527025	C1818G (linked to KL-VS)	Often inherited together with rs9536314 to define the VS haplotype.	—
CALHM1	rs2986017	P86L	Calcium homeostasis modulator; possibly associated with later-life AD risk in some cohorts. Mixed evidence.	Ca^{2+}
PLD3	rs145999145	V232M	Phospholipase D3; rare missense initially associated with AD (Cruchaga et al., Nature 2014); replication mixed.	—
ATP8B4	rare predicted-damaging variants	Various	Phospholipid flippase. Holstege 2022 Nat Genet identified rare-variant burden as significant AD risk factor.	—
ZCWPW1	rs1476679	Intronic	Zinc-finger gene; rare-variant burden highlighted in Holstege 2022 as candidate driver of GWAS locus.	Zinc
ACE	various missense	—	Holstege 2022 highlighted ACE as a potential rare-variant driver of an AD GWAS locus, separate from its established cardiovascular role.	—

5. Categories → Genes → Cofactors → Supplement Targets

The table below maps each functional category to the relevant biological inputs and the supplement / dietary / lifestyle targets that have at least preliminary evidence for the corresponding mechanism. This is a generic mapping; it is NOT a recommendation that any individual should supplement everything listed. Personalization depends on individual genotype, intake, lab values, and clinical context.

Category	Key genes	Cofactors / biological inputs	Supplement / dietary / lifestyle targets
1. APOE & lipid metabolism	APOE, CLU, ABCA7, ABCA1	Membrane lipid composition, cholesterol efflux capacity	DHA (omega-3), phosphatidylserine, phosphatidylcholine, citicoline, MUFA-rich diet (Mediterranean), oleocanthal-containing extra-virgin olive oil
2. Amyloid precursor processing	APP, PSEN1/2, BACE1, ADAM10, IDE	Zinc (ADAM10, IDE, MME); insulin	Zinc; glucose control; physical exercise

Category	Key genes	Cofactors / biological inputs	Supplement / dietary / lifestyle targets
		sensitivity (IDE)	(raises ADAM10 / α-secretase activity)
3. Endo-lysosomal sorting	SORL1, BIN1, PICALM, CD2AP, RIN3	Endosomal acidification; autophagic flux	Spermidine; trehalose (preclinical); time-restricted eating (autophagy activation); urolithin A (mitophagy)
4. Microglia & innate immunity	TREM2, CD33, MS4A, PLCG2, CR1	ω-3 PUFAs (resolution mediators); polyphenols (microglial polarization)	DHA + EPA; cocoa flavanols; curcumin; sulforaphane (NRF2 activation in microglia); minocycline (research only)
5. Tau and microtubule biology	MAPT, GSK3B, BIN1	Lithium (mood doses inhibit GSK3B); insulin signaling	Microdose lithium (preclinical and small RCTs in MCI); methylene blue (LMTM, mixed clinical results); not a settled supplement target
6. α-Synuclein / lysosomal	SNCA, GBA, TMEM175	Glucocerebroside substrate flux; lysosomal pH and Ca^{2+}	Ambroxol (chaperone, investigational); coffee (epidemiologic PD signal); not a settled supplement target
7. Frontotemporal dementia core	GRN, C9orf72, MAPT, TMEM106B	Progranulin levels; autophagy	No proven supplement intervention. Genetic counseling and surveillance for at-risk relatives
8. Cerebrovascular integrity	NOTCH3, HTRA1, COL4A1/2, MTHFR	BP control, glucose control, lipid control, homocysteine levels	Standard cardiovascular prevention: BP control, statins, antiplatelets where indicated, methyl-folate / methyl-B12 / TMG for hyperhomocysteinemia (see Homocysteine reference)
9. Synaptic & neuronal modifiers	KL, CALHM1, PLD3, ATP8B4	Ca^{2+} homeostasis; FGF23/Klotho axis	Magnesium L-threonate (brain-penetrant Mg, NMDA modulation); resistance exercise (Klotho expression);

Category	Key genes	Cofactors / biological inputs	Supplement / dietary / lifestyle targets
			citicoline
Cross-pathway: oxidative stress	(see Inflammation, Glycation, Endothelial reports)	Glutathione substrate, NRF2 activation	NAC / NACET; glycine; sulforaphane; ergothioneine; PQQ; ubiquinol
Cross-pathway: methylation	MTHFR, MTR, MTRR (see Homocysteine reference)	Methyl-folate, methyl-B12, B6 (P5P), riboflavin, betaine	5-MTHF, methylcobalamin, P5P, R5P, TMG (betaine) — same as homocysteine pathway

It is important to note that, with the exception of management of vascular risk factors, no supplement intervention has been shown in adequately powered randomized trials to prevent dementia. The strongest preventive evidence base is for blood-pressure control, physical activity, hearing-loss treatment, smoking avoidance, and diabetes management — the modifiable risk factors identified by the Lancet Commission on Dementia (Livingston et al., Lancet 2024). Supplements above are mechanistically aligned with specific genetic vulnerabilities but should be discussed with a treating physician in the individual's context.

6. Complete SNP Lookup Table

Quick reference for all SNPs catalogued in this document, sorted alphabetically by gene. Coordinates are GRCh38, assembled from dbSNP. The list includes principal common-variant tags and a small number of well-established rare/landmark variants (TREM2 R47H, APP A673T, GRN rs5848). Truly rare or family-private variants in APP/PSEN1/PSEN2/MAPT/GRN/NOTCH3/HTRA1/COL4A1/2 cannot be enumerated by rsID and require a gene-region scan (see Section 8 for the bcftools approach).

Gene	rsID / region	GRCh38 position	Category
ABCA1	rs2230806	9:104865808	APOE & lipid
ABCA7	rs3764650	19:1043104	APOE & lipid
ABCA7	rs4147929	19:1046520	APOE & lipid
ABI3	rs616338	17:49219935	Microglia
ADAM10	rs653765	15:58590060	APP processing
APOC1	rs11568822	19:44919589	APOE & lipid
APOE	rs429358	19:44908684	APOE keystone
APOE	rs7412	19:44908822	APOE keystone
APP	rs63750847	21:25891796	APP processing (A673T protective)
BACE1	rs638405	11:117291923	APP processing

Gene	rsID / region	GRCh38 position	Category
BIN1	rs6733839	2:127135234	Endo-lysosomal
BIN1	rs744373	2:127137039	Endo-lysosomal
CALHM1	rs2986017	10:103571534	Synaptic
CD2AP	rs9296559	6:47432637	Endo-lysosomal
CD2AP	rs9349407	6:47487762	Endo-lysosomal
CD33	rs3865444	19:51224706	Microglia
CLU	rs11136000	8:27607002	APOE & lipid
CLU	rs9331896	8:27608798	APOE & lipid
COL4A1	(glycine substitutions)	13:110148963 (gene region)	Cerebrovascular (CADASIL-like)
COL4A2	(glycine substitutions)	13:110307908 (gene region)	Cerebrovascular
CR1	rs6656401	1:207577223	Microglia / complement
CR1	rs3818361	1:207611623	Microglia / complement
EPHA1	rs11771145	7:143415088	Endo-lysosomal
F2	rs1799963	11:46761055	Cerebrovascular (cross-link)
F5	rs6025	1:169549811	Cerebrovascular (cross-link)
GBA	rs76763715	1:155235843	DLB / lysosomal (N370S)
GBA	rs421016	1:155235205	DLB / lysosomal (L444P)
GBA	rs2230288	1:155235698	DLB / lysosomal (E326K)
GBA	rs75548401	1:155236246	DLB / lysosomal (T369M)
GRN	rs5848	17:44345302	FTD
GSK3B	rs334558	3:119821482	Tau
HLA-DRB1	rs9271192	6:32591291	Microglia
HTRA1	(missense, region)	10:122461524 (gene region)	Cerebrovascular (CARASIL)
IDE	rs1887922	10:93737596	APP processing
IDE	rs2149632	10:93736880	APP processing
INPP5D	rs35349669	2:233117202	Microglia
KL (KLOTHO)	rs9536314	13:33054427	Synaptic (KL-VS F352V)
KL	rs9527025	13:33054508	Synaptic

Gene	rsID / region	GRCh38 position	Category
LRRK2	rs34637584	12:40340400	DLB / PD (G2019S)
MAPT	rs8070723	17:45942346	Tau (H1/H2)
MAPT	rs1052553	17:45996523	Tau (A0/A1, H1c)
MME	rs3736187	3:155090107	APP processing (neprilysin)
MS4A4A	rs983392	11:60254475	Microglia
MS4A6A	rs610932	11:60254475 (locus)	Microglia
MTHFR	rs1801133	1:11796321	Cerebrovascular (cross-link)
NOTCH3	(cysteine-altering region)	19:15159038 (gene region)	Cerebrovascular (CADASIL)
PICALM	rs3851179	11:86157598	Endo-lysosomal
PICALM	rs10792832	11:86157598	Endo-lysosomal
PLCG2	rs72824905	16:81942028	Microglia (P522R)
PLD3	rs145999145	19:40364085	Synaptic (V232M)
PSEN1	(pathogenic region)	14:73136417 (gene region)	APP processing (autosomal-dominant AD)
PSEN2	(pathogenic region)	1:226870568 (gene region)	APP processing (autosomal-dominant AD)
RIN3	rs10498633	14:92932828	Endo-lysosomal
SCARB2	rs6812193	4:76928420	DLB / lysosomal
SNCA	rs356181	4:89724099	DLB
SNCA-AS1	rs7681440	4:89821430	DLB
SORL1	rs11218343	11:121564878	Endo-lysosomal
SORT1	rs141749679	1:109292538	APOE & lipid
SPI1	rs1057233	11:47376409	Microglia
TBK1	(LoF burden region)	12:64452088 (gene region)	FTD
TMEM106B	rs1990622	7:12229967	FTD modifier / LATE
TMEM175	rs34311866	4:933331	DLB / lysosomal
TOMM40	rs2075650	19:44892362	APOE & lipid
TREM2	rs75932628	6:41161514	Microglia (R47H)
TREM2	rs143332484	6:41161470	Microglia (R62H)
TREM2	rs2234253	6:41162497	Microglia (T96K)

Gene	rsID / region	GRCh38 position	Category
TYROBP	(LoF burden region)	19:35903129 (gene region)	Microglia
ZCWPW1	rs1476679	7:100412710	Synaptic (cross-link)

Note on coordinates: GRCh38 positions above are best-effort references compiled from dbSNP. Verify against your VCF's contig naming convention ('chr1' vs '1') before running positional lookups. Some entries above are gene regions rather than single positions because the relevant variants are private or family-specific (APP, PSEN1, PSEN2, MAPT, GRN, NOTCH3, HTRA1, COL4A1/A2, TBK1, TYROBP); those genes require a region-based scan with variant-level annotation rather than rsID lookup.

7. Bibliography and Source Notes

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- ClinVar (NCBI) — pathogenicity classifications for individual variants.
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- OMIM — Mendelian phenotypes (Alzheimer #104300; FTD-tau #600274; FTD-GRN #607485; ALS-FTD-C9orf72 #105550; CADASIL #125310; CARASIL #600142; LBD #127750).
- gnomAD v4 — population allele frequencies and constraint metrics.

8. Disclaimer

This document is an educational reference. It does not constitute medical advice, does not establish a clinician–patient relationship, and is not a substitute for individualized evaluation by a qualified healthcare provider. Genetic variants are described at the level of common-population biology; clinical interpretation in any individual depends on the full genetic background, lab measurements, medical history, current medications, and other factors that this document does not address.

Each common variant catalogued here typically confers a small individual effect (per-allele odds ratios in the 1.05–1.25 range, with a small number of larger-effect exceptions noted in the text). Cumulative significance arises from patterns across multiple variants and from interaction with environmental factors (cardiovascular health, education, sleep, hearing loss treatment, social engagement, physical activity, diet).

It also bears explicit emphasis: dementia genetic risk is probabilistic, not deterministic. The Lancet Commission on Dementia 2024 estimates that approximately 45% of dementia cases

are attributable to 14 modifiable risk factors. Genetic predisposition does not commit any individual to a specific outcome, and known carriers of even high-risk genotypes (APOE ε4/ε4, TREM2 R47H heterozygotes) frequently live to advanced age without dementia. Conversely, absence of identified risk variants does not exclude future disease.

It should not be acted upon clinically without consultation with a treating physician, ideally in collaboration with a clinical geneticist or genetic counselor when high-impact variants (APOE ε4 homozygosity, TREM2 R47H, SORL1 truncating, NOTCH3 cysteine-altering, MAPT/GRN pathogenic, suspected C9orf72 expansion) are identified or suspected.