LIBYAN JOURNAL OF MEDICAL SCIENCES AND TECHNOLOGIES (LJMST)
Volume 1, Issue 1 | April - June 2026 | www.ijamred.com
Peer-Reviewed Open Access Journal
ID: ljmst.v1i1.005

Genetic Architecture of Alzheimer's Disease: From Monogenic Determinants to Polygenic Risk

Dr. Omar Agren[1], Prof. Abeer H. Amer[2]
[1,2] Faculty of Biomedical Science, Libyan International University, Benghazi, Libya

Abstract

Alzheimer's disease (AD) represents a paradigmatic example of a complex disorder in which rare monogenic determinants coexist with a broad polygenic susceptibility background. Although highly penetrant mutations in APP, PSEN1, and PSEN2 cause early-onset Alzheimer's disease, the vast majority of cases arise from the cumulative effect of common genetic variants modulated by aging and environmental factors. This mini-review synthesizes evidence from family studies, genome-wide association studies, and next-generation sequencing to delineate the evolving genetic architecture of AD. Particular emphasis is placed on convergent biological pathways, including amyloid processing, lipid metabolism, innate immunity, and endolysosomal trafficking. Finally, unresolved heritability gaps and emerging multi-omics strategies are discussed in the context of risk stratification and precision medicine.

Keywords: *Alzheimer's disease; genetic architecture; monogenic EOAD; polygenic risk score; GWAS; APO*

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the leading cause of dementia worldwide. Twin and family studies consistently estimate the heritability of AD to be between 60% and 80%, underscoring a substantial genetic contribution to disease risk. Despite this high heritability, AD does not conform to a single genetic model. Instead, it spans a continuum from rare autosomal dominant forms with near-complete penetrance to common late-onset disease driven by the additive effects of numerous low-impact variants. [1–4] This conceptual shift from a monogenic to a polygenic framework has profoundly influenced our understanding of AD pathogenesis. While early discoveries established amyloid dysregulation as a central pathogenic event, more recent studies highlight the importance of immune response, lipid homeostasis, and intracellular trafficking pathways. Understanding how these genetic components interact is essential for interpreting disease mechanisms and for developing predictive and therapeutic strategies.This review explores the basic science of the host-pathogen interface in TB. By mapping the molecular pathways of cellular evasion, metabolic adaptation, and granuloma dynamics, we provide a structured overview of Mtb pathogenesis and highlight how these pathways inform the next generation of host-directed therapies.

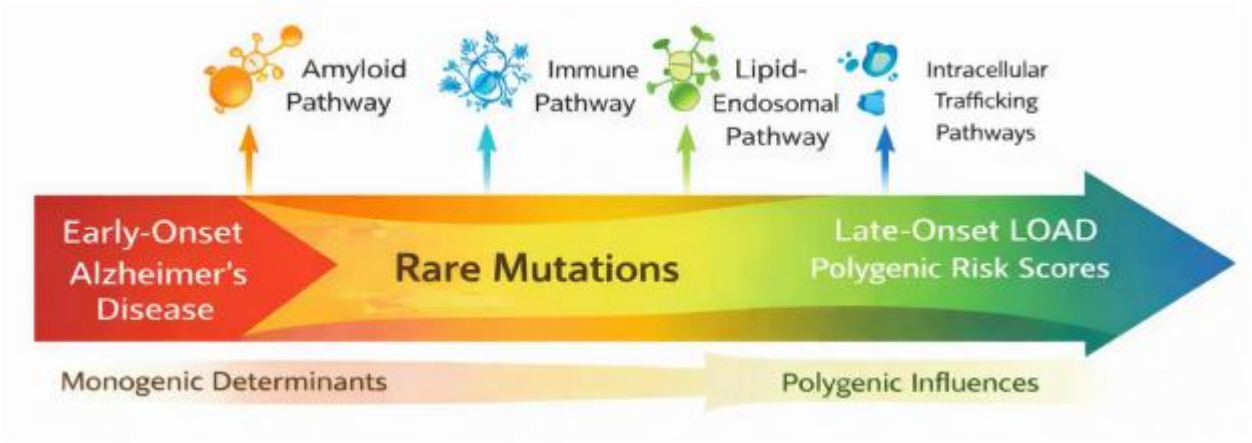

Figure 1. Genetic continuum of Alzheimer's disease.

Schematic illustration showing the spectrum from monogenic early-onset Alzheimer's disease to polygenic late-onset disease driven by cumulative genetic risk. The figure highlights convergent biological pathways including amyloid processing, lipid metabolism, immune response, and endolysosomal trafficking.

.

2. Monogenic Determinants of Early-Onset Alzheimer's Disease

Early-onset Alzheimer's disease (EOAD), typically defined by symptom onset before 65 years of age, accounts for approximately 5% of all AD cases. Most familial EOAD cases are caused by pathogenic variants in APP, PSEN1, or PSEN2, which follow an autosomal dominant inheritance pattern with high penetrance. These discoveries provided the empirical foundation for the amyloid cascade hypothesis and demonstrated that altered processing of amyloid precursor protein is sufficient to trigger neurodegeneration. [3–7] Mutations in PSEN1 represent the most frequent cause of familial EOAD and are often associated with particularly early onset and aggressive clinical progression. In contrast, PSEN2 mutations are rarer and show more variable penetrance, sometimes resembling late-onset disease. Although APP mutations are uncommon, their identification was pivotal in establishing amyloid dysregulation as an initiating pathogenic event.

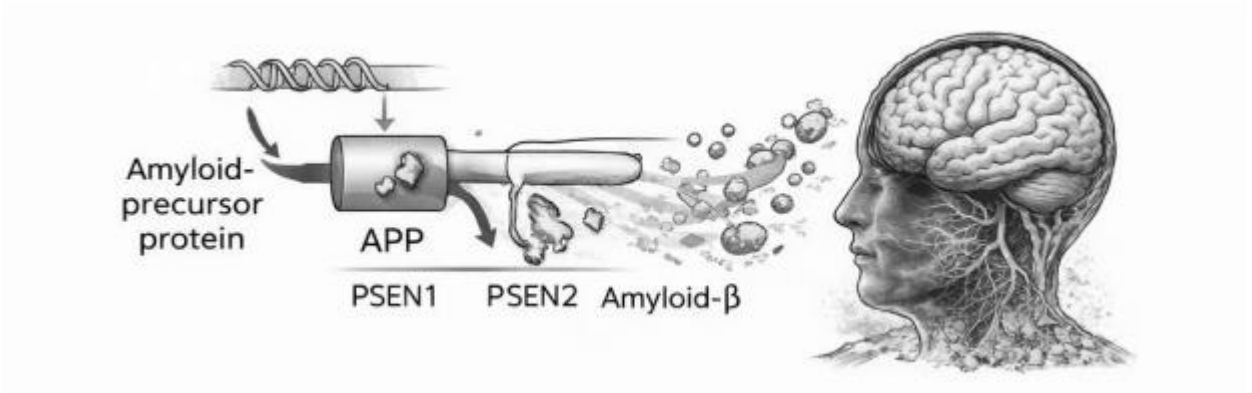

Figure 2. Schematic representation of the monogenic basis of early-onset Alzheimer's disease

Table 1. Monogenic Architecture of Early-Onset Alzheimer's Disease (EOAD)

Schematic representation of the monogenic basis of early-onset Alzheimer's disease, highlighting

Gene	Molecular Mechanism	Clinical Consequence
APP	Altered amyloid precursor protein cleavage	Early amyloid-β accumulation
PSEN1	Increased Aβ42/Aβ40 ratio due to γ-secretase dysfunction	Very early onset, aggressive neurodegeneration
PSEN2	Variable γ-secretase dysfunction	Later onset, incomplete penetrance

pathogenic mutations in APP, PSEN1, and PSEN2. These mutations disrupt amyloid precursor protein processing, leading to an increased amyloid-β burden and early, aggressive neurodegeneration. Adapted conceptually from genetic studies of EOAD [3–7**].**

3 . APOE as a Genetic Bridge Between Monogenic and Polygenic Risk

The apolipoprotein E (APOE) locus constitutes the strongest genetic risk factor for late-onset Alzheimer's disease. Unlike EOAD mutations, APOE alleles modulate susceptibility rather than determine disease inevitability. Carriers of the ε4 allele exhibit a dose-dependent increase in risk and earlier age at onset, whereas the ε2 allele confers partial protection [7–9]. Mechanistically, APOE influences multiple pathogenic processes beyond lipid transport, including amyloid clearance, tau pathology, neuroinflammation, and blood–brain barrier integrity. This multifunctional role positions APOE as a biological bridge linking deterministic monogenic drivers with the broader polygenic background characteristic of late-onset disease

Figure 3. Polygenic risk and biological pathway convergence in Alzheimer's disease.

Overview of key pathways implicated by genome-wide association studies, including microglial activation (TREM2, CD33), lipid metabolism (APOE, ABCA7), and intracellular trafficking (BIN1,

4 . Polygenic Architecture of Late-Onset Alzheimer's Disease

Genome-wide association studies have identified dozens of loci associated with late-onset AD, revealing a highly polygenic architecture. Most risk variants individually exert modest effects but converge on shared biological pathways, particularly those related to innate immunity, lipid metabolism, and endolysosomal trafficking [10–18].

Table 2. Core Biological Pathways Implicated in Alzheimer's Diseas

Biological Pathway	Representative Genes
Amyloid processing	APP, PSEN1, PSEN2, ADAM10
Lipid metabolism	APOE, ABCA7, CLU
Immune and microglial response	TREM2, CD33, CR1
Endolysosomal trafficking	BIN1, PICALM, SORL1

Polygenic risk scores (PRS) aggregate the effects of these variants into a quantitative measure of genetic susceptibility. Recent refinements incorporating functional annotation and multi-ancestry datasets have improved predictive performance, demonstrating that substantial genetic risk exists independently of APOE status. These findings support the use of PRS as a research tool for risk stratification and for enriching clinical trial populations.

Table 3. Polygenic Architecture of Late-Onset Alzheimer's Disease (LOAD)

Feature	Description
Genetic Variants	Multiple common variants with small individual effect sizes
Risk Quantification	Polygenic Risk Scores (PRS)
Risk Modifiers	Age, vascular risk factors, lifestyle, environment
Outcome	Probabilistic disease susceptibility

5. Missing Heritability and Future Directions

Despite major advances, currently identified genetic variants explain only a portion of the estimated heritability of Alzheimer's disease. This so-called 'missing heritability' likely reflects contributions from rare variants, structural variation, gene–gene interactions, epigenetic mechanisms, and somatic mosaicism within the brain. [18–22] Future progress will depend on integrating genomic data with transcriptomic, proteomic, and metabolomic approaches, as well as expanding genetic studies to underrepresented populations. Such strategies are essential for translating genetic discoveries into precision prevention and personalized therapeutic interventions

6. Conclusion

The genetic architecture of Alzheimer's disease encompasses a continuum from rare monogenic determinants to complex polygenic risk. Although individual genetic triggers differ, they converge on a limited set of biological pathways that shape disease vulnerability and progression. A

comprehensive understanding of this architecture provides a foundation for earlier risk identification and the development of more targeted therapeutic strategies. [1,2,21–25]

References

[1]. Gatz M, Reynolds CA, Fratiglioni L, et al. Role of genes and environments for explaining Alzheimer disease. Arch Gen Psychiatry. 2006;63(2):168–174.

[2]. Scheltens P, De Strooper B, Kivipelto M, et al. Alzheimer's disease. Lancet. 2021;397(10284):1577–1590.

[3]. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science. 2002;297(5580):353–356.

[4]. Tanzi RE. The genetics of Alzheimer disease. Cold Spring Harb Perspect Med. 2012;2(10):a006296.

[5]. Lambert JC, Ibrahim-Verbaas CA, Harold D, et al. Meta-analysis of 74,046 individuals identifies susceptibility loci for Alzheimer's disease. Nat Genet. 2013;45(12):1452–1458.

[6]. Guerreiro R, Wojtas A, Bras J, et al. TREM2 variants in Alzheimer's disease. N Engl J Med. 2013;368(2):117–127.

[7]. Sims R, van der Lee SJ, Naj AC, et al. Rare coding variants implicate microglial immunity in Alzheimer's disease. Nat Genet. 2017;49(9):1373–1384.

[8]. Rogaeva E, Meng Y, Lee JH, et al. The neuronal sortilin-related receptor SORL1 is associated with Alzheimer disease. Nat Genet. 2007;39(2):168–177.

[9]. Small SA, Petsko GA. Endosomal recycling and Alzheimer's disease. Nat Rev Neurosci. 2020;21(8):429–440.

[10]. Andrews S, et al. Association between polygenic risk for Alzheimer's disease and brain structure across the lifespan. UK Biobank analysis. 2025.

[11]. Dumont J, et al. Polygenic score integrating neurodegenerative and vascular risk informs dementia risk stratification. Nat Commun. 2025.

[12]. Ertekin-Taner N. Genetic architecture of Alzheimer's disease: from monogenic to polygenic. Annu Rev Genomics Hum Genet. 2025.

[13]. Giri M, et al. Genes associated with Alzheimer's disease: an overview. Clin Interv Aging. 2016.

[14]. Harold D, et al. Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. Nat Genet. 2009.

[15]. Hollingworth P, et al. Common variants at ABCA7 and MS4A6A are associated with Alzheimer's disease. Nat Genet. 2011.

[16]. Holstege H, et al. Characterization of pathogenic rare variants in CLU and SORL1 in Alzheimer's disease. Nat Commun. 2017.

[17]. Jones L, et al. Genetic evidence implicating immune response and cholesterol metabolism in Alzheimer's disease. PLoS One. 2010.

[18]. Jonsson T, et al. Variant of TREM2 associated with the risk of Alzheimer's disease. N Engl J Med. 2013.

[19]. Kakkar A, et al. A comprehensive review of genetic risk factors for Alzheimer's disease development. Curr Gene Ther. 2025.

[20]. Lee S, et al. Polygenic risk score of Alzheimer's disease is associated with cognitive trajectories and cerebral organoid phenotypes. Alzheimers Dement. 2025.

[21]. Rogaeva E, et al. The SORL1 receptor and Alzheimer's disease. Nat Genet. 2007.

[22]. Scheltens P, et al. Alzheimer's disease. Lancet. 2016.

[23]. Stancheva I, et al. Polygenic hazard scores in preclinical Alzheimer's disease. 2025.

[24]. Steinberg S, et al. Loss-of-function variants in ABCA7 confer risk of Alzheimer's disease. Nat Genet. 2015.

[25]. Van Acker ZP, et al. Lipid metabolism in Alzheimer's disease: from genetics to therapy. J Lipid Res. 2024.