Insight into the genetic etiology of Alzheimer’s disease: A comprehensive review of the role of rare variants

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Abstract
Early-onset Alzheimer’s disease (EOAD) is generally known as a dominant disease due to highly penetrant pathogenic mutations in the amyloid precursor protein, presenilin 1 and 2. However, they explain only a fraction of EOAD patients (5% to 10%). Furthermore, only 10% to 15% of EOAD families present with clear autosomal dominant inheritance. Studies showed that only 35% to 60% of EOAD patients have at least one affected first-degree relative. Parent–offspring concordance in EOAD was estimated to be <10%, indicating that full penetrant dominant alleles are not the sole players in EOAD. We aim to summarize current knowledge of rare variants underlying familial and seemingly sporadic Alzheimer’s disease (AD) patients. Genetic findings indicate that in addition to the amyloid beta pathway, other pathways are of importance in AD pathophysiology. We discuss the difficulties in interpreting the influence of rare variants on disease onset and we underline the value of carefully selected ethnicity-matched cohorts in AD genetic research.

KEYWORDS
Alzheimer’s disease, biological pathways of disease, familial AD, genetic etiology, rare variants, sporadic AD

1 | INTRODUCTION

Alzheimer’s disease (AD; Online Mendelian Inheritance in Man [OMIM]#104300) is a complex, progressive, and irreversible neurodegenerative brain disease (NBD) representing the most common dementia subtype affecting more than 50 million people worldwide.1 AD is characterized by an insidious onset, progressive loss of memory and additional cognitive functions such as word finding, spatial cognition, and problem solving.2 While the clinical symptoms of AD display a substantial overlap between multiple other NBDs, neuropathological examination upon brain autopsy can confirm a definite diagnosis of AD.3,4 Neuropathological hallmarks of AD are extracellular depositions of amyloid beta (Aβ) peptides and intracellular neurofibrillary tangles of hyperphosphorylated tau protein, accompanied by gliosis and loss of neurons and synapses.5

Aging is the most prominent biological risk factor for developing AD at late age with up to 90% of AD patients diagnosed above 65 years (late-onset Alzheimer’s disease [LOAD]). LOAD is a complex and heterogeneous disorder with a genetic etiology of up to 82%.5 Approxi mately 10% of AD patients are diagnosed before the age of 65 years (early-onset Alzheimer’s disease [EOAD]) and present with a genetic etiology of up to 100%.5,6 EOAD and LOAD patients are clinically and pathologically similar and both occur in familial and sporadic patients. Approximately 35% to 60% of the EOAD patients have first-degree relatives with dementia, including 10% to 15% autosomal dominant families with three generation or more.7,8 These multi-generational EOAD patients...
families were essential for the identification of pathogenic mutations in three causal AD genes: amyloid precursor protein (APP) and presenilin 1 and 2 (PSEN1 and PSEN2), which are key players in the Aβ pathway (Table 1, Figure 1). The ε4 allele of the apolipoprotein E (APOE) gene was identified as a major genetic risk factor for LOAD, increasing risk 3 times in heterozygous and 15 times in homozygous carriers. In EOAD patients, risk is increased in homozygous ε4 carriers and in heterozygous ε4 carriers with a positive family history (Box 1).5,9}

The identification of Aβ plaques in autopsy brains of AD patients and the identification of pathogenic mutations in the three AD genes, which are key in the creation of the Aβ plaques, were at the basis of the Aβ hypothesis.10 The Aβ hypothesis dominated AD-related research for more than 25 years by stating that the accumulation of extracellular Aβ plaques in the brain was the central cause of AD pathology, though this was not accepted universally.10 The hypothesis states that Aβ plaques ultimately trigger a cascade of disease-causing events including inflammation, formation of tau tangles, and synaptic dysfunction.10 The observation of Aβ plaques in the brain of cognitively normal elderly and the absence in some AD patients created a lot of controversy.11,12 Suspected non-Aβ AD patients, describing AD patients lacking detectable Aβ in cerebrospinal fluid biomarker profiles or brain positron emission tomography imaging provided evidence for the existence of an AD pathology unrelated to the Aβ cascade.11 Aβ plaque burden in AD brains with Aβ pathology showed only a weak correlation with disease severity and high-profile clinical trials targeting Aβ failed to deliver functional treatment.13–16 Moreover, only 5% to 10% of the EOAD patients can be explained by the pathogenic mutations in the three familial AD genes, suggesting that potential non-Aβ pathways might also be involved in onset of AD.3 Concordance studies between parent–offspring and between siblings resulted in 5% to 10% parent–offspring concordance and 21.6% concordance among siblings.5 If AD is caused solely by full penetrant autosomal dominant alleles, concordance between parent–offspring would be estimated ≥50%.5 These observations indicate that other genes, pathways, and inheritance patterns are involved in the etiology of AD. Here, we summarized the current knowledge of rare variants (minor allele frequency [MAF] < 1%) underlying familial and (seemingly) sporadic AD patients and focus on genes including rare AD associated variants (Figure 2). We hereby highlight the contribution of additional molecular pathways to early disease etiology (Figure 1) and underline the relevance of carefully selected ethnicity-matched cohorts in AD genetic research.

2 | FAMILIAL AD

Linkage studies in multi-generational autosomal dominant EOAD families were crucial for the identification of three causal AD genes, APP on chromosome 21q, PSEN1 on 14q, and PSEN2 on 1q.4,17 and including full penetrant pathogenic mutations. Concordance studies between parent–offspring and between siblings, however, showed that AD is not solely the cause of full penetrant dominant alleles. In addition to the three known causal AD genes, other well-replicated genes, including rare heterozygous variants with reduced penetrance, are present in familial AD.

RESEARCH IN CONTEXT

1. Systematic review: PubMed search, meeting abstracts, and presentations were used to collect information concerning the role of rare variants in Alzheimer's disease (AD) genetics.

2. Interpretation of results: We provide a comprehensive review on the current knowledge of rare variants underlying familial and seemingly sporadic AD.

3. Future directions: The basis of the current knowledge of AD derived from genetic studies on large early-onset AD pedigrees in the early 1990s. Here, we underline the value of carefully selected ethnicity-matched cohorts in AD genetic research to understand the biology and to identify therapeutic targets in the search for medical treatment.

2.1 | Highly penetrant pathogenic mutations in APP, PSEN1, and PSEN2

Pathogenic missense mutations and whole gene duplications have been identified in APP (https://www.alzforum.org/mutations). Interestingly, most of the pathogenic missense mutations affect APP processing and are located near the β- or γ-secretase cleavage sites or in the Aβ sequence of the APP protein (amino acids 670 to 724).18 Pathogenic missense mutations appear to result in overproduction of either total Aβ or a shift in the Aβ1-40/Aβ1-42 ratio toward the more toxic Aβ1-42 peptide.19 APP duplications of variable size have been reported in AD families and underline the importance of APP gene dosage.2,19 Pathogenic mutations in APP account for <1% of EOAD patients.20 Besides pathogenic mutations, an Icelandic protective missense variant p.A673T was also identified in APP. This variant was associated with reduced production of the amyloidogenic Aβ1-40 and Aβ1-42 peptides (<40%).21 Finally, rare single nucleotide variants (SNVs) in the APP promoter have been associated with increased LOAD susceptibility.22 PSEN1 and PSEN2 are both essential proteins of the catalytic core of the γ-secretase complex, which catalyzes the cleavage of membrane proteins including APP.20 Mutant γ-secretase increases Aβ1-42 levels, while decreasing Aβ1-40 levels, leading to an increased Aβ1-42/Aβ1-40 ratio.17 The majority of pathogenic PSEN mutations are missense mutations; however, pathogenic amino acid insertions and deletions have also been described (https://www.alzforum.org/mutations). Mutations in PSEN1 are the most common cause of familial EOAD and are characterized by the earliest onset ages (on average 8.4 and 14.2 years earlier compared to APP and PSEN2 mutations, respectively).23,18 PSEN1
| Gene     | Inheritance pattern | Study | Implicated pathways                                                                 |
|----------|---------------------|-------|-------------------------------------------------------------------------------------|
| APP      | Dominant            | Alzforum | Aβ pathway<sup>5</sup>                                                                |
|          | Recessive           |        | Immune system<sup>131</sup>                                                          |
|          | de novo/mosaicism   | 78, 79 | BBB integrity<sup>132</sup>                                                            |
|          |                     | 108    | Synaptic plasticity<sup>18, 133</sup>                                                |
|          |                     |        | Gene expression regulation<sup>134, 135</sup>                                         |
|          |                     |        | Axonal guidance and cytoskeleton function<sup>136</sup>                              |
|          |                     |        | Apoptosis, phagocytosis, and autophagy<sup>135, 138</sup>                            |
| PSEN1    | Dominant            | Alzforum | Aβ pathway<sup>5</sup>                                                                |
|          | Recessive           | 74–77  | Immune system<sup>139</sup>                                                          |
|          | de novo/mosaicism   | 105, 107 | BBB integrity<sup>132</sup>                                                            |
|          |                     |        | Synaptic plasticity<sup>140, 141</sup>                                               |
|          |                     |        | Axonal guidance and cytoskeleton function<sup>142</sup>                              |
|          |                     |        | Apoptosis, phagocytosis, and autophagy<sup>143–145</sup>                             |
| PSEN2    | Dominant            | Alzforum | Aβ pathway<sup>5</sup>                                                                |
|          | de novo/mosaicism<sup>a</sup> | 146    | Immune system<sup>139</sup>                                                          |
|          |                     |        | BBB integrity<sup>132</sup>                                                            |
|          |                     |        | Synaptic plasticity<sup>140</sup>                                                   |
|          |                     |        | Apoptosis, phagocytosis, and autophagy<sup>144, 145, 147, 148</sup>                  |
| SORL1    | Dominant            |        | Aβ pathway<sup>169</sup>                                                              |
|          | Recessive           |        | Lipid metabolism<sup>150</sup>                                                       |
|          | de novo/mosaicism<sup>c</sup> | 112    |                                                                                      |
| ABCA7    | Dominant            |        | Aβ pathway<sup>151</sup>                                                              |
|          |                     | 41–46  | Immune system<sup>152</sup>                                                           |
|          |                     |        | Lipid metabolism<sup>153</sup>                                                       |
|          |                     |        | Apoptosis, phagocytosis, and autophagy<sup>154–156</sup>                             |
| TREM2    | Dominant            | 47–64  | Aβ pathway<sup>157</sup>                                                              |
|          |                     |        | Immune system<sup>157</sup>                                                           |
|          |                     |        | Lipid metabolism<sup>158</sup>                                                       |
|          |                     |        | Apoptosis, phagocytosis, and autophagy<sup>159</sup>                                 |
| BIN1     | Dominant            | 45, 65, 66 | Aβ pathway<sup>160</sup>                                                              |
|          |                     |        | Tau pathway<sup>161</sup>                                                             |
|          |                     |        | Synaptic plasticity<sup>162</sup>                                                    |
|          |                     |        | Apoptosis, phagocytosis, and autophagy<sup>163, 164</sup>                            |
| UNC5C    | Dominant            | 67–69  | Axonal guidance<sup>165</sup>                                                         |
|          |                     |        | Apoptosis, phagocytosis, and autophagy<sup>165</sup>                                 |
| AKAP9    | Dominant            | 67, 68 | Synaptic plasticity<sup>165</sup>                                                    |
| NOTCH3   | Dominant            | 70–73  | Aβ pathway<sup>166</sup>                                                              |
|          |                     |        | Gene expression regulation<sup>167</sup>                                             |
|          |                     |        | BBB integrity<sup>168</sup>                                                           |
|          |                     |        | Apoptosis, phagocytosis, and autophagy<sup>169, 170</sup>                            |
| 12S rRNA | Maternal            | 98–100 | Mitochondrial cascade hypothesis<sup>171</sup>                                       |
| CLU      | Dominant            | 101–103 | Aβ pathway<sup>172</sup>                                                              |
|          |                     |        | Immune system<sup>173</sup>                                                           |
|          |                     |        | Lipid metabolism<sup>174</sup>                                                        |
|          |                     |        | Apoptosis, phagocytosis, and autophagy<sup>145, 175</sup>                            |
| PLCG2    | Dominant            | 54, 56, 104 | Immune system<sup>56</sup>                                                            |
|          |                     |        | Apoptosis, phagocytosis, and autophagy<sup>176, 177</sup>                            |
| ABI3     | Dominant            | 54, 56, 104, 105 | Immune system<sup>56</sup>                                                            |

(Continues)
### Table 1 (Continued)

| Gene   | Inheritance pattern | Study   | Implicated pathways                                                                 |
|--------|---------------------|---------|-------------------------------------------------------------------------------------|
| APOE   | Modifier            | 114, 115| Aβ pathway<sup>178</sup>                                                             |
|        |                     |         | Immune system<sup>178</sup>                                                          |
|        |                     |         | Lipid metabolism<sup>178</sup>                                                       |
|        |                     |         | Synaptic plasticity<sup>178</sup>                                                    |
|        |                     |         | BBB integrity<sup>79</sup>                                                           |
|        |                     |         | Axonal guidance and cytoskeleton function<sup>180,181</sup>                          |
|        |                     |         | Tau pathway<sup>182</sup>                                                            |
|        |                     |         | Mitochondrial cascade hypothesis<sup>183</sup>                                        |
|        |                     |         | Apoptosis, phagocytosis, and autophagy<sup>184–186</sup>                             |

Note: Reported inheritance patterns and implicated pathways are mentioned alongside literature references. Abbreviations: Aβ, amyloid beta; Alzforum, Alzforum mutation database (https://www.alzforum.org/mutations); BBB, blood–brain barrier; MAF, minor allele frequency.

*Identified in a Braak II control subject in a single study.<sup>146</sup>
*Bi-allelic variants reported in SORL1 in a single study.<sup>80</sup>
*De novo variant (in brain) reported in SORL1 in one study, which could not be replicated by an independent study.<sup>112,187</sup>

### Figure 1

Schematic presentation of Alzheimer’s disease (AD) genes and implicated pathways. A. Pathways in which the AD genes are involved. B. Apolipoprotein E (APOE) is a major common AD susceptibility gene involved in nine different pathways and harbors one rare variant modifying onset age. C. Color-coded legend indicating the different genetic pathways associated with AD.

Mutations causing the most severe form of AD explain ≈6% of EOAD patients.<sup>5</sup> In comparison, PSEN2 mutations are rare, explaining <1% of EOAD patients, and may show incomplete penetrance.<sup>5</sup> Carriers present with higher onset ages; however, onset ages are highly variable even between members of the same family.<sup>24,25</sup>

#### 2.2 Familial AD genes including rare mutations with reduced penetrance

Common variants in the sortilin-related receptor 1 gene (SORL1) were associated with AD for the first time in 2007<sup>26</sup> and several later studies attempted to replicate these findings with mixed results (e.g., Bettens et al.<sup>27</sup> and Li et al.<sup>28</sup>) (Table 1). Ultimately, a meta-analysis of 30,393 individuals in 2011 confirmed the association of common SORL1 variants with AD risk.<sup>29</sup> In 2013, genome-wide association studies (GWAS) also pinpointed SORL1 as a risk gene for AD.<sup>30</sup> Since the association of common SORL1 variants with AD, rare variants in the gene have also received more attention. In 2012, whole-exome sequencing (WES) in 14 unrelated EOAD probands of families with suggestive autosomal dominant inheritance, identified 5/14 carriers of SORL1 protein truncating variants, suggesting an important role for rare SORL1 variants in familial EOAD.<sup>31</sup> Unfortunately, the lack of DNA of affected family members did not allow segregation analysis of the SORL1 variants in these particular families. Multiple additional studies have described the association of rare SORL1 variants with AD risk.<sup>32–34</sup> Recently, a meta-analysis of gene based burden association tests was performed, combining data of five studies.<sup>32,33,35–37</sup> Including 9204 cases and 9646 controls of European ancestry,<sup>38</sup> Results showed that estimated AD risk was maximal for premature stop codon (PTC) mutations, which...
variants co-segregated with disease. 

3 | FROM FAMILIAL TO SPORADIC AD

There are rare heterozygous variants described to be involved in the genetic etiology of AD. Independent studies replicated many of these associations but seem to explain more isolated patients rather than autosomal dominant families. Most of these genes linked to AD by means of multiple statistical association studies in unrelated case control cohorts and co-segregating with disease observed in one or two families. Additionally, an underlying recessive genetic aspect or maternal inheritance might in part explain seemingly sporadic AD patients.

3.1 | Dominant AD

In 2013, Guerreiro et al. identified significantly more heterozygous variants in exon two of the triggering receptor expressed on myeloid cells 2 (TREM2) gene in Caucasian AD patients (n = 1092) compared to Caucasian control individuals (n = 1107) (Table 1). In particular, the p.R47H rare variant showed the strongest association, which was confirmed by direct genotyping in an extended cohort of 1887 AD patients and 4061 control individuals (Caucasian) and meta-analysis of three independent GWAS. In the same year, the p.R47H association with AD was also reported in Icelandic, American, German, Dutch, and Norwegian study populations, and was later also confirmed by subsequent studies. In a large LOAD family (n = 21 affected individuals), p.R47H was found to co-segregate completely with disease. Other TREM2 rare variants that are significantly associated with AD were reported, for example, p.R62H, p.H157Y (initially associated with AD in Han Chinese, and further supported by additional meta-analyses, p.D87N, p.G1732A) and p.L211P (African-American populations). However, with the exception of p.R47H and p.R62H, the other associations need to be considered necessary nor sufficient to fully explain reduced penetrance of ABCA7 variants in general. Further research remains necessary to fully comprehend the impact of ABCA7 missense and PTC variants in AD pathology.

BOX 1: APOE

A genome-wide linkage study in familial LOAD patients and subsequent association studies identified APOE as the major susceptibility gene for AD. APOE has three common isoforms, APOE ε2, ε3, and ε4, which have a general frequency of 8.4%, 77.9%, and 13.7%, respectively (calculated in 5930 patients and 8607 controls). APOE ε3/ε3 is the most common APOE genotype and is neutral concerning AD risk. The APOE ε2 allele is considered to decrease AD risk and is associated with later AD onset ages. The APOE ε4 allele frequency is drastically increased in AD patients to almost 40%, pinpointing a risk increasing effect of this isoform which is associated with earlier disease onset ages. In comparison to mutations in APP, PSEN1, and PSEN2, the ε4 allele of APOE was neither considered necessary nor sufficient to cause the disease and was therefore categorized as a risk allele for AD. Yet, dependent lifetime risk for AD (assessed in 7351 patients and 10,132 control individuals from Caucasian ancestry) was consistent with semi-dominant inheritance of a moderately penetrant gene. AD risk at age 85 ranged from 5% in male APOE ε4/ε4 carriers to 60% in female APOE ε4/ε4 carriers. These results urge the consideration of APOE as a gene with semi-dominant inheritance rather than a risk gene in the genetics of AD.
indicated to cause a partial loss of TREM2 function.\textsuperscript{47,61} Of note, the association of p.R47H was mainly observed in Caucasian populations and TREM2 variants in general were not associated with AD in Iranian,\textsuperscript{62} Japanese,\textsuperscript{63} and Korean\textsuperscript{64} populations, hereby indicating that TREM2 influences are most likely population specific.

In the bridging integrator 1 gene (BIN1), the p.K358R rare variant was found to be significantly associated with LOAD in Caribbean Hispanics and segregated in 2/6 Caribbean Hispanic families in which the variant was identified (Table 1).\textsuperscript{45} Another BIN1 rare variant, p.P318L, was significantly associated with LOAD in Han Chinese study cohorts including 1133 LOAD patients and 1159 control individuals; however, it was not identified in the study of Vardarajan et al.\textsuperscript{66} Additionally, rare variants in BIN1 were associated with AD by an independent study.\textsuperscript{66}

Rare variants in the Unc-5 homolog C (UNC5C) and A kinase anchor protein 9 (AKAP9) genes were also associated with AD\textsuperscript{67,68} (Table 1). A rare UNC5C variant p.T835M, was found to segregate completely with disease in one LOAD family and was associated with disease in four large cohorts of LOAD patients (n = 8050) and control individuals (n = 98,194).\textsuperscript{67} The specific p.T835M variant was found to cause increased cell death among different cell types including neurons.\textsuperscript{67} Association of p.T835M with AD risk was not replicated in a study in Chinese AD patients (n = 360) and control individuals (n = 400); however, the investigated cohort might be too underpowered to identify significant association of ultra-rare variants.\textsuperscript{65} Of note, four novel variants were identified in exon 15 of UNC5C in the Chinese AD patient cohort.\textsuperscript{69}

Another study identified two rare AD associated AKAP9 variants (in tight linkage disequilibrium) in African-American study populations (Table 1).\textsuperscript{68} The study performed WES for seven African-American familial AD patients and 44 rare variants were selected, based on frequency, sequencing quality, and relationship to previously implicated AD genes, for further investigation in 422 cases and 396 control individuals.\textsuperscript{68} Two rare AKAP9 variants (rs149979685 and rs144662445) were associated with AD risk and this association was replicated in extended cohorts of 1037 cases and 1869 control individuals from African-American descent.\textsuperscript{68} Another AKAP9 rare variant, p.R434W, was found to segregate with LOAD in two large families.\textsuperscript{66}

Multiple studies also identified mutations in the notch receptor 3 (NOTCH3) gene in clinically diagnosed AD patients. To start, WES performed in a Turkish patient from a consanguineous AD family identified a rare heterozygous variant in NOTCH3, p.R1231C, as a potential culprit\textsuperscript{70} (Table 1). Segregation analysis of the identified NOTCH3 variant p.R1231C was performed in additional family members and was identified in one unaffected at-risk individual (younger than the reported age at onset in the family and therefore still uninformative).\textsuperscript{70} NOTCH3 resequencing in 95 EOAD patients and 95 control individuals did not identify additional rare NOTCH3 variants.\textsuperscript{70} Possible incomplete penetrance of the p.R1231C variant in the Turkish family and the complexity of the family (consanguineous) complicate interpretation of the pathogenic nature of this variant.\textsuperscript{70} Another study investigated the role of adult-onset leukodystrophy genes, including NOTCH3, in AD.\textsuperscript{71} Adult-onset leukodystrophies represent a spectrum of rare inherited progressive neurodegenerative disorders affecting the white matter of the central nervous system, which are often misdiagnosed with common sporadic dementing phenotypes.\textsuperscript{71} Genetic screening of NOTCH3 was performed in 332 Caucasian AD patients and 676 Caucasian elderly control individuals. Gene-based analysis was significant for NOTCH3 and this signal was driven by one common synonymous variant (p.P1521P) and three rare coding variants with large effect size (p.V1952M, p.V1183M, and p.H170R). Carrier frequency of the three rare coding variants was two to three times higher in LOAD patients compared to control individuals.\textsuperscript{71} Importantly, all three variants had previously been significantly associated with severity of white matter lesions in elderly with hypertension.\textsuperscript{72} The most recent study associating NOTCH3 rare variants with AD, applied a strategy focused on rare variants occurring only in cases to identify high penetrant rare variants, using data of the Alzheimer’s Disease Sequencing Project (ADSP; 5617 AD patients and 4594 controls individuals).\textsuperscript{73} Results identified one rare missense variant in NOTCH3 p.A284T that was present in 10 AD patients and absent from control individuals, and hereby provided the strongest link to date between NOTCH3 and AD.\textsuperscript{73}

### 3.2 Recessive AD

An underlying recessive genetic aspect could in part explain sporadic AD patients. Important differences between sporadic AD patients and seemingly isolated patients with underlying recessive AD are observable in the recurrence risk in parent–offspring. A study by Wingo et al. investigated parent–offspring concordance and concordance among siblings in an attempt to identify the likely mechanism of inheritance in the majority of non-autosomal dominant EOAD cases.\textsuperscript{6}
A parent–offspring concordance of ≤10% and a concordance among siblings of 21.6% were estimated. These results indicate that autosomal recessive inheritance is the most likely mechanism of inheritance in these particular cases.7

Two known dominant causal alleles, p.E693Δ and p.A713T in APP, and one p.E280A in PSEN1, were identified in homozygous state in one Japanese,74 one Italian,75 and one Columbian76 AD family, respectively. In all three families, homozygous carriers, however, were not more severely affected with the disease. Another homozygous PSEN1 mutation p.A431E was observed in a 35-year-old male with early-onset dementia, presenting with a relatively aggressive phenotype.77 These observations demonstrated that homozygous variants in known AD genes are not lethal, as previously assumed.76 Another homozygous APP variant, p.A673V, was found to cause disease only in homozygous state, whereas heterozygous carriers were unaffected.78 The APP p.A673V was shown to have two pathogenic effects, shifting APP processing to the amyloidogenic pathway and increasing the aggregation property of the Aβ fibrils.78 The effect of interaction between wild-type and mutated alleles was investigated to unravel the seemingly protective effect of heterozygous p.A673V. Results showed that this interaction hinders amyloidogenesis and neurotoxicity, thereby protecting heterozygous carriers.78 Another mutation at the same APP position, p.A673T, was reported in a patient without clinical signs of dementia and no deposition of Aβ plaques in the brain.79 Yet, when the mutation was introduced in a synthetic Aβ peptide, the susceptibility to aggregate increased.78

Both observations underlie that benign heterozygous variants in known causal AD genes could harbor pathogenic effects in homozygous state.78 Finally, bi-allelic loss-of-function of SORL1 was described in one AD patient with maternal and paternal history of dementia in one study. The compound SORL1 variant carrier presented with an earlier onset age (55 years) than the parents, yet, the onset age is in the same range as other heterozygous SORL1 PTC variant carriers.80 Bi-allelic variants have also been described by single studies in two novel AD candidate genes: VWA2 and CTSP81,82 (see supporting information). Replication of these findings in larger cohorts is necessary to fully comprehend their contribution to the etiology of AD. Additionally, genome-wide linkage analysis performed in an extended recessive LOAD family identified a linked region on chromosome 8p22-p21.2.83 More than 50 genes are included in the linked region and therefore, further analysis of these genes is necessary (e.g., by means of whole-genome sequencing in the LOAD family).83

To identify additional novel loci harboring AD-associated recessive variants, several studies investigated extended runs of homozygosity (ROHs) in case–control cohorts of different ethnic backgrounds.84–89 One study performed ROH mapping in 837 LOAD and 550 controls from Northern European and Northern American ancestry and identified excess ROHs in cases versus controls, with the most significant LOAD associated ROH on chromosome 8p11.23.84 Another study in 1955 AD cases and 955 control individuals with British/Irish ancestry failed to replicate the chromosome 8 finding.86 The study did not identify an excess of ROHs in cases compared to controls and none of the ROHs showed significant association with AD.86 Explanations for the discrepancy in results can be found in the study of McQuillan et al., who showed that the genomic location where ROHs could occur can differ significantly between different Caucasian populations.86,88 Another study showed that the burden of ROHs was associated with AD, but the mean length of ROHs per person was significantly larger in AD patients compared to control individuals.85 Results suggest that recessive risk loci exist in the Caribbean Hispanic population.85 In addition, in African-American cohorts including 1917 AD patients and 3858 control individuals, significantly more ROHs > 1, >2, and >3 Mb in AD patients versus control individuals were observed.87 Smaller ROHs (>0.5 Mb) were also significantly associated with AD in this study population. In addition, in an isolated Arab community from Israel, specific AD-associated ROHs was observed.89 Overall, these results suggest that recessive AD risk loci are present in multiple ethnic subgroups; yet, replication studies are needed to prove their involvement in AD.

### 3.3 Maternal AD

Several studies reported a higher frequency of progressive dementia in mothers compared to fathers of AD patients,90–92 suggestive for maternal inheritance. Even after correcting for the longer life expectancy of women, higher mother–to-father ratios have been observed in affected parents of AD patients.91 Other studies, however, contradict these observations, with mothers of AD patients not often more affected compared to mothers of control individuals.93 However, additional evidence for the presence of maternal transmission was found through brain imaging studies showing that maternal AD history predisposes to: reduced brain glucose metabolism,94 increased atrophy in AD sensitive brain regions,95 and smaller baseline hippocampi.96 Additionally, having an AD-affected mother was associated with poorer cognitive performance in later life and earlier ages at onset in the offspring compared to having an affected father.97 The involvement of rare homoplasmic variants in mtDNA in AD has been suggested by several studies. Two rare variants in 12S rRNA (np 956-965 and 856 A>G) have been described in AD patient cohorts. The np 956-965 insertion (3-4-5 base pairs) was described in AD patients in three independent studies in European and Japanese cohorts and was absent from control individuals (Table 1).98–100 Also, the 856 A>G variant was observed in two independent studies in AD patients but not in control individuals.98,99 These studies suggest that variants in 12S rRNA might increase risk of developing AD.

### 4 SPORADIC AD

Particular genes are linked with AD through significant association in independent case control studies but never described as cosegregating in families. Hence, these genes seem to be predominantly involved in the genetic etiology of sporadic patients unless there are families segregating extremely rare variants and yet not observed. In this review article, we categorize these genes as non-familial AD genes.
Also, de novo mutations and genetic modifiers have been associated with sporadic AD and are described in this section.

### 4.1 Non-familial AD genes

Evidence was provided for a role of rare heterozygous variants in the clusterin (CLU) gene in AD. The CLU protein is a multifunctional protein showing striking similarities with the common risk gene APOE (Box 1), and CLU expression is increased in AD-related brain regions (e.g., hippocampus and entorhinal cortex). Unbiased resequencing of all CLU coding exons in AD patients and control individuals from Flanders-Belgium (n = 1930), identified 19 rare (MAF < 1%) to intermediate rare (MAF = 1% to 5%) non-synonymous missense variants and one in-frame 9 bp deletion p.T445-D447del, carried by three AD patients. Fourteen out of 19 missense variants were identified in 31 AD patients and eight variants were only in patients. Five variants, present only in controls, were identified in 21 control individuals, but all were labeled as benign by PolyPhen and SIFT prediction tools. These observations were replicated in French and Canadian replication cohorts (n = 2755) and a meta-analysis study including Portuguese, UK, and US Caucasian AD cohorts (n = 11,544).

In 2017, rare coding variants were identified in the Phospholipase C y2 (PLCG2) and B3-domain containing transcription factor ABI3 (ABI3) genes, showing genome-wide significant association with AD in Caucasian study populations. Results included one protective variant in PLCG2 (p.P522R) and one risk variant in ABI3 (p.S209F) (Table 1). These findings were replicated in 2742 Caucasian AD cases, 3351 Caucasian controls, 181 African-American AD cases, and 331 African-American controls, genotyped for both variants. Significant association of both the PLCG2 and ABI3 variants with AD was observed. The association of the p.P522R protective PLCG2 variant with AD was also replicated. The frequencies of PLCG2 p.P522R and ABI3 p.S209F were also investigated in an Argentinian population (419 AD cases and 486 controls). Both variants were observed in similar frequencies as reported by the International Genomics Alzheimer’s Project (IGAP) and both modulated susceptibility to AD in populations from Argentina.

### 4.2 De novo alleles

Somatic de novo variants are post-zygotic variants, which may lead to (somatic and germline) mosaicism, that is, cells with genetic differences in one organism. Pathogenic germline mosaic mutations have already been identified in the known AD genes. So far, 19 de novo PSEN1 mutations (absent from both parents, paternity assessed) with onset ages as early as 23 years old and two de novo APP duplications have been described. Beck et al. reported in 2004 the first confirmed evidence of both a somatic and germline mosaicism in a sporadic EOAD patient. To this date, this is the only proven pathogenic somatic brain mutation ever identified in an AD patient. Nevertheless, involvement of somatic brain variants in AD was further investigated. Several studies described an enrichment of APP recombination and mutation (structural variations as well as SNVs). However, the exact role of the observed APP recombinants will need further investigation. Based on the current studies, one can conclude that somatic brain variations are not a common cause of sporadic AD, especially not in APP, PSEN1, and PSEN2. Some factors might explain the absence of confirmation of the contribution of somatic variants. Neuropathological AD is characterized by loss of neurons and synapses, including neuronal DNA content. Somatic variants, potentially underlying AD etiology, could be lost in advanced stages of the disease. Also, neuronal DNA is collected post mortem, potentially causing fragmentation of the DNA and complicating somatic variant detection. Follow-up studies are needed to obtain evidence of the recurrence of somatic brain variants and providing a definite link to AD etiology.

### 5 Genetic Modifiers and Oligogenic Inheritance

Numerous novel alleles are associated with AD (Table 1). Yet, progress in understanding the effect of the genetic background on the penetrance and expressivity of causal and/or risk alleles is limited. This limited knowledge on the impact of modifiers and oligogenic interactions can be partially explained by the methodological difficulty of identifying interactions of multiple genes on similar phenotypes. Oligogenic interactions could shed light on the network and functioning of AD-associated genes; however, so far, no conclusive results have been obtained to conclude they are involved in AD etiology.

Identification of modifier genes can act as potential novel therapeutic targets, as they might influence the phenotype of certain pathogenic variants. APOE is probably the most common AD onset-age modifier (Box 1). In 2019, the first rare modifying AD variant in APOE was described in a woman from the largest autosomal dominant Columbian AD kindred, segregating the pathogenic PSEN1 e280A mutation. The mutation carriers are developing disease in their 40s, but this carrier showed the first signs at age 73. WES identified two copies of the rare APOEe3 p.R136S variant (Christchurch). The woman presented with an unusually high ApoE brain load and limited tau and other NBD measurements. Given its pronounced protective effect on disease onset, this variant could be of high value in development of novel therapeutic approaches.

### 6 Lessons Learned from Rare Variants in the Genetic Etiology of AD

In this review article, we focused on replicated rare variants and observed three main features in AD genetic research. First, there is a discrepancy in impact of the variants between ethnic groups. Examples include the TREM2 variants, with strong associations in,
for example, Caucasian, African American, and Han Chinese populations and not in, for example, Iranian, Japanese, and Korean populations, suggesting population-specific influences. Second, it is pivotal to evaluate pathogenicity of each of the variants independently in addition to gene-based statistical tests taking into account all observed rare variants in one gene. Evidence can be found in the same TREM2 example in which patient-specific variants were found to be enriched in exon 2. Also in APP, a pathogenic mutation hot spot was observed in exons 16 to 17. Third, the type of variation should also be taken into account. Good examples are SORL1 and ABCA7 in which PTC variants seem to be more penetrant compared to missense variants. Taken together, these observations underline that AD-associated genes harbor pathogenic variants with variable penetrance as well as benign or even protective variants that cannot be otherwise classified in the absence of functional testing (variants of uncertain significance [VUS]), and that this effect is population specific. The observation of these effects complicates the interpretation of statistical analyses, especially in larger cohorts including individuals of different ethnicities. VUS are in general difficult to interpret. Even the causal AD genes harbor substantial proportions of VUS (>200 known pathogenic variants and more than 90 VUS identified in APP, PSEN1, and PSEN2 [≥45%]), with unknown contribution to disease onset. Functional profiling of the identified VUS remains crucial to make a link to relevant disease processes. Carefully selected ethnicity-matched study cohorts with availability of patient-derived biomaterials are therefore of high value in AD genetic research, especially for ultra-rare and rare variants that cannot be replicated in large independent studies but might have a clear functional association with AD pathology.

Identification of underlying genetic mechanisms in AD patients is often challenging, especially in seemingly sporadic AD patients. The presence of (ultra-) rare mutations, de novo alleles, and mosaicisms often make it extra difficult to identify underlying inheritance. Yet, understanding this complexity of the genetic etiology of AD is of high importance, especially to estimate the recurrence risk in patient offspring.

The current knowledge of AD-associated rare variants provides insights into the pitfalls and difficulties of AD genetic research. In addition, it provides important insights into the molecular pathways that are involved in early disease etiology. As AD is characterized by highly heterogeneous pathological processes, it is not convenient to distinguish disease-causing pathways from downstream consequences. Genetic research provides evidence for the involvement of the immune system, lipid metabolism, and synaptic functioning in early AD etiology in addition to the Aβ pathway. Also, cytoskeleton function, axonal transport, regulation of gene expression, and post-translational modification of proteins were found to be implicated in the etiology of AD. Phagocytic, apoptotic, and autophagic processes have also been associated with AD pathology. Evidence was also provided for the early involvement of the alternatively proposed tau, dual Aβ-tau, mitochondrial cascade- and neurovascular (blood-brain barrier integrity) pathways (Table 1, Figure 1). Important is that the three AD genes also have biological functions unrelated to the Aβ pathway (Table 1). All these observations can help explain the high heterogeneous etiology of AD, in which apart from the Aβ pathway, other pathological pathways are involved in disease onset and progression and might deliver other potential therapeutic targets. Also, many other rare variants in different genes were associated with AD, which we did not discuss as they had little evidence due to limited number of studies (Table S1 in supporting information). Independent replication studies are essential to unravel the potential role of these rare variants and genes in the heterogeneous genetic etiology of AD.

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