

The Genetics of Alzheimer Disease

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Family history is the second strongest risk factor for Alzheimer disease (AD) following advanced age. Twin and family studies indicate that genetic factors are estimated to play a role in at least 80% of AD cases. The inheritance of AD exhibits a dichotomous pattern. On one hand, rare mutations in *APP*, *PSEN1*, and *PSEN2* virtually guarantee early-onset (<60 years) familial AD, which represents ~5% of AD. On the other hand, common gene polymorphisms, such as the $\epsilon 4$ and $\epsilon 2$ variants of the *APOE* gene, can influence susceptibility for ~50% of the common late-onset AD. These four genes account for 30%–50% of the inheritability of AD. Genome-wide association studies have recently led to the identification of 11 additional AD candidate genes. This paper reviews the past, present, and future attempts to elucidate the complex and heterogeneous genetic underpinnings of AD.

GENETICS OF EARLY-ONSET FAMILIAL ALZHEIMER DISEASE

Following advanced age, family history is the second greatest risk factor for Alzheimer disease (AD). AD is considered to be a genetically dichotomous disease presenting in two forms: early-onset familial cases usually characterized by Mendelian inheritance (EO-FAD), and late-onset (≥ 60 years), with no consistent mode of transmission (LOAD; Bertram and Tanzi 2005; Tanzi and Bertram 2005). Familial clustering of AD cases is more obvious for the early-onset form that strikes under the age of 60 years. However, it is estimated that up to 80% of AD involves the inheritance of genetic factors, based on twin and family studies (Gatz et al. 2006). So-called “sporadic” AD is

strongly influenced by genetic variants combined with life exposure factors. EO-FAD is most often caused by rare, fully penetrant mutations in three different genes.

In 1987, we as well as others isolated the amyloid β (A β) protein precursor (*APP*; Goldgaber et al. 1987; Kang et al. 1987; Tanzi et al. 1987a, 1988) and mapped it to chromosome 21. The cloning of *APP* was carried out based on the hypothesis that it would be an AD gene. Glenner and Wong (1984) first put forward the prediction that the gene responsible for the production β -amyloid, which makes up senile plaques and cerebral blood vessel deposits of amyloid, would be on chromosome 21 and carry mutations causing AD. In that same seminal study, they were able to analyze cerebral β -amyloid deposits to derive the partial

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amino acid sequence of the amyloid β protein ($A\beta$). Glenner also proposed that AD is a cerebral amyloidosis, in which cerebral β -amyloid drives all subsequent pathology (see Fig. 1). This central thesis was later reinterpreted and reported as the “amyloid cascade hypothesis” of AD (Hardy and Higgins 1992; Hardy and Selkoe 2002; Tanzi and Bertram 2005).

In the same issue of *Science* reporting the isolation of APP (Goldgaber et al. 1987; Tanzi et al. 1987a), we simultaneously reported genetic linkage of EO-FAD to genetic markers on chromosome 21 in the vicinity of APP (St George-Hyslop et al. 1987). Interestingly, we would later show that the four large EO-FAD families used in that study were not genetically linked to APP (Tanzi et al. 1987b); they were ultimately demonstrated to carry *PSEN1* mutations (Sherrington et al. 1995). The concurrent genetic linkage of these four EO-FAD families to both *PSEN1* and markers on the proximal portion of chromosome 21 remains to be resolved.

These studies prompted other groups, including that of John Hardy, to test and confirm the genetic linkage of other independent EO-FAD families to our markers on chromosome 21. In 1991, the first EO-FAD mutation was found in APP by resequencing these independent EO-FAD families that were tightly linked to chromosome 21 (Goate et al. 1991). However, prior to the Goate et al. (1991) paper, Frangione and colleagues had already reported the first pathogenic mutation in APP (Levy et al. 1990). Their sequencing of exons 16 and 17 of APP, encoding the $A\beta$ portion, uncovered a pathogenic mutation in APP responsible for Dutch hereditary cerebral hemorrhage with amyloidosis. Goate et al. (1991), then resequenced the same two APP exons to reveal the first EO-FAD mutation (London mutation; V717I) in APP.

By 1992, it was clear that mutations in APP accounted for only a tiny proportion of EO-FAD. In fact, none of the 50 EO-FAD families that we resequenced in our laboratory between

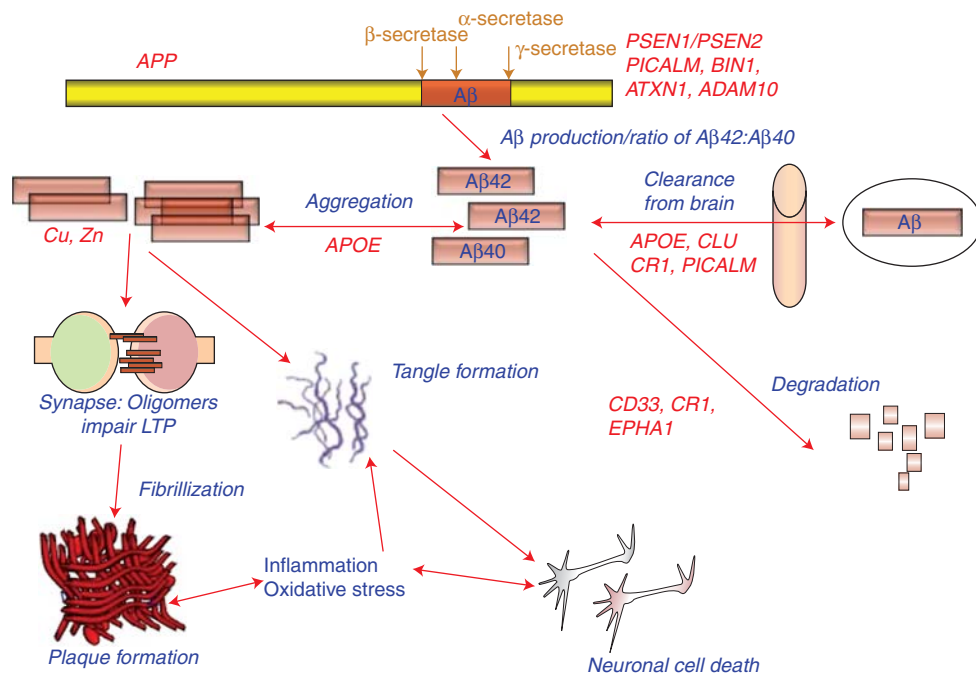


Figure 1. Potential roles of select Alzheimer disease (AD) genes in $A\beta$ -related pathogenesis of AD. (Modified from Bertram and Tanzi 2008; reprinted with permission from the author.)



1987 and 1988 revealed *APP* mutations. In 1995, several EO-FAD mutations were found in presenilin 1 (*PSEN1*; Sherrington et al. 1995) on chromosome 14. This was reported in a study led by Peter St. George-Hyslop and a large host of collaborators, including our laboratory. Shortly thereafter, we first reported a homolog of *PSEN1* called presenilin (*PSEN2*; Levy-Lahad et al. 1995) on chromosome 1 and showed that it harbors the N141I mutation in Volga-German EO-FAD families. This was confirmed by Rogaev et al. (1995) shortly afterward.

To date, 24 mutations (plus duplications) have been reported for *APP*, 185 for *PSEN1*, and 13 for *PSEN2* (Table 1; Alzheimer Disease and Frontotemporal Dementia Mutation Database; <http://www.molgen.ua.ac.be/ADMutations>). All but one of these mutations (*PSEN2*-N141I) is inherited with EO-FAD in a fully penetrant, autosomal-dominant manner. Another mutation in *APP* is transmitted in a recessive manner.

All but a handful of the more than 200 EO-FAD mutations in *APP*, *PSEN1* and *PSEN2* lead to a common molecular phenotype: an increase in the ratio of $A\beta_{42}:A\beta_{40}$ (Scheuner et al. 1996; Tanzi and Bertram 2005). One mutation (Swedish) in *APP* increases all species of $A\beta$ and several others, resulting in amino acid substitution within the $A\beta$ domain and leading to increased aggregation of $A\beta$. However, most EO-FAD mutations increase the ratio of $A\beta_{42}:A\beta_{40}$ (Table 2). The relative increase in $A\beta_{42}$ promotes the aggregation of the peptide into oligomers and ultimately amyloid fibrils (Jarrett et al. 1993).

Three years after their discovery in 1995, the presenilins were shown to be necessary for the generation of $A\beta$ from *APP* (De Strooper et al.

1998). One year later, Wolfe et al. (1999) showed that the presenilins act as aspartyl proteases that carry out γ -secretase cleavage of *APP* to produce $A\beta$. γ -Secretase can generate a variety of $A\beta$ species ranging in size from 37 to 46 amino acids. Whether EO-FAD mutations appear in *APP* near the γ -secretase cleavage site or in the presenilins, the vast majority of them serve to increase the ratio of $A\beta_{42}:A\beta_{40}$. γ -Secretase modulators are aimed at reversing this ratio and represent very promising compounds for treating and preventing AD based on what has been garnered from studies addressing the molecular mechanism of EOFAD mutations (Table 1) in *APP*, *PSEN1* and *PSEN2* (Kounnas et al. 2010).

ADDITIONAL EO-FAD CANDIDATE GENES

Beyond *APP*, *PSEN1*, and *PSEN2* attempts to identify additional EO-FAD genes have led to potentially pathogenic mutations in three other genes. A missense mutation (R406W) in the tau gene (*MAPT*) on chromosome 17q was reported to be tightly linked to AD in a Belgian family (Rademakers et al. 2003; Ostojic et al. 2004). However, before, this mutation can be validated to cause AD, autopsy confirmation will be necessary to rule out a diagnosis of frontotemporal lobe dementia (FTDP-17). EO-FAD in a family from the Netherlands was also linked to chromosome 7q36 (Rademakers et al. 2005) near the PAX transcription activation domain interacting protein gene (*PAXIP1*). Finally, the gene for *PEN2* on chromosome 19, encoding the γ -secretase component, pen-2, was reported to harbor a missense mutation, D90N, in an AD family (Frigerio et al. 2005). To date, no functional consequences have been demonstrated for this mutation. Clearly, all three

Table 1. Early-onset familial Alzheimer disease genes and their pathogenic effects

Gene	Protein	Chromosome	Mutations	Molecular phenotype
<i>APP</i>	Amyloid β (A4) protein precursor	21q21	24 (duplication)	Increased $A\beta_{42}/A\beta_{40}$ ratio Increased $A\beta$ production Increased $A\beta$ aggregation
<i>PSEN1</i>	Presenilin 1	14q24	185	Increased $A\beta_{42}/A\beta_{40}$ ratio
<i>PSEN2</i>	Presenilin 2	1q31	14	Increased $A\beta_{42}/A\beta_{40}$ ratio

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Table 2. Results of select genome-wide association studies of late-onset Alzheimer disease

Genome-wide association studies	Study design	Population	Major genes identified
Reiman et al. 2007	Case-control	US	<i>APOE, GAB2</i>
Bertram 2008	Family-based	US	<i>APOE, ATXN1, CD33, GWA_14q31</i>
Lambert et al. 2009	Case-control	US, Europe	<i>APOE, CLU, CR1</i>
Harold et al. 2009	Case-control	US, Europe	<i>APOE, CLU, PICALM</i>
Seshadri et al. 2010	Case-control	US, Europe	<i>APOE, BIN1</i>
Naj et al. 2011	Case-control	US, Europe	<i>MS4A6A/MS4A4E, EPHA1, CD33, CD2AP</i>
Hollingworth et al. 2011	Case-control	US, Europe	<i>ABCA7, MS4A6A/MS4A4E, EPHA1, CD33, CD2AP</i>

of these additional EO-FAD candidate genes will require further confirmation.

GENETICS OF LATE-ONSET AD: *APOE*

Late-onset Alzheimer is the most common form of the disease and is defined by onset age >65 years. Whereas EO-FAD is characterized by classic Mendelian inheritance usually in an autosomal-dominant manner, for LOAD, we observe a genetically complex pattern of inheritance in which genetic risk factors work together with environmental factors and life exposure events to determine lifetime risk for AD. Consequently, it is much more difficult to reliably identify novel LOAD loci, especially because efforts at replication are often plagued by a mixture of replications and refutations.

Thus far, the only gene variant considered to be an *established* LOAD risk factor is the $\epsilon 4$ allele of the apolipoprotein E gene (*APOE*; Strittmatter et al. 1993) on chromosome 19q13. The road to the identification of *APOE* as an AD gene began with genetic linkage of LOAD to chromosome 19 in the vicinity of *APOE* followed by the finding that apoE binds $A\beta$ in cerebrospinal fluid leading. Thus, *APOE* represented a viable AD candidate gene based on both functional data and genomic position. The three major alleles of *APOE* correspond to combinations of amino acids at residues 112 and 158 ($\epsilon 2$: Cys₁₁₂/Cys₁₅₈; $\epsilon 3$: Cys₁₁₂/Arg₁₅₈; $\epsilon 4$: Arg₁₁₂/Arg₁₅₈). The $\epsilon 4$ -allele of *APOE* increases AD risk by approximately fourfold when inherited in one copy and by greater than 10-fold for two doses of the allele. In contrast, the $\epsilon 2$ allele

of *APOE* exerts “protective” effects (Corder et al. 1994).

Whereas the EO-FAD mutations are sufficient, but not necessary, to cause AD, the *APOE* $\epsilon 4$ allele is neither necessary nor sufficient to cause AD. Instead, it operates as a genetic risk factor for AD that decreases the age of onset in a dose-dependent manner. Functionally, *APOE* normally plays a role in lipid metabolism and transport. However, in AD, it is believed to play a role in the clearance of $A\beta$ from brain.

Roses et al. (2010) has proposed that other genes in the genomic neighborhood of *APOE* may actually confer risk for AD, for example, a polymorphic poly-T variant in the *TOMM40* gene encoding the translocase of outer mitochondrial membrane 40 homolog. This gene is in complete linkage disequilibrium with *APOE* as it maps only ~2000 base pairs away. “Long” poly-T repeats have been reported to be associated with earlier onset regardless of *APOE* genotype. Whereas it is theoretically possible that both *APOE* and *TOMM40* contribute to AD risk and just happen to reside next to each other in the genome, “Occam’s razor” and simple reason would dictate that only one of these genes is responsible for AD risk in this region of chromosome 19. Because functional studies have shown that *APOE* genotype influences cerebral $A\beta$ clearance, *APOE* would appear to be the more likely candidate versus *TOMM40*.

It should also be noted that several other genes in linkage disequilibrium with *APOE*, in addition to *TOMM40*, also exhibit significant

association with AD including *BCAM*, *PVRL2*, and *APOC1*. However, in our own family-based association studies of AD, the strength of association of *APOE* with AD is 15 orders of magnitude higher than that observed for any of these other genes in this region, including *TOMM40* (unpublished data). This adds further support to the notion that *APOE* is the sole AD genetic risk factor in this region of linkage disequilibrium on chromosome 19.

GENETICS OF LATE-ONSET AD: ALZGENE

Since the original report of *APOE* as a genetic risk factor for LOAD, hundreds of genes have been tested for association with AD and reported in the literature. With the rapidly growing number of AD genetic studies published every month, it has become increasingly difficult to follow and interpret the published data. To address this problem, Lars Bertram, colleagues, and I started the online database, AlzGene.org, which provides a routinely updated online database and meta-analyses for the growing list of AD candidate genes (“AlzGene”; URL: www.alzgene.org; Bertram 2007; Bertram and Tanzi 2008).

Meta-analysis results on AlzGene reveal more than three dozen loci that show nominally significant association with risk for AD and 10 with nominal p -values $< 10^{-5}$. The 10 genes with the strongest signals for association with AD include *APOE* and nine others, all of which came from genome-wide association studies (GWASs). The GWAS hits are discussed in a separate section below.

Many genes with weak but significant meta-analysis signals have in common that they did not derive from GWASs. These include, for example, *SORL1* (sortilin-related receptor), which is a sorting receptor that regulates the intracellular trafficking of a variety of proteins, including APP (Andersen et al. 2005; Rogaeva et al. 2007). Another is *ACE* (angiotensin converting enzyme 1; Kehoe et al. 1999), a zinc metalloprotease involved in controlling blood pressure, which may increase the risk for AD. *ACE* is also able to degrade A β in vitro (Hu et al. 2001; Hemming et al. 2005). A third

example is *IL8* (interleukin 8), a cytokine mediating inflammatory responses (Mines et al. 2007). A final example is *LDLR* (low-density lipoprotein receptor), which serves as a receptor for APOE and removes low-density lipoproteins (LDL and VLDL) from circulation (Kim et al. 2009).

GENETICS OF LATE-ONSET AD: GENOME-WIDE ASSOCIATION STUDIES

Over the past several years, the most common strategy for finding novel AD gene candidates has been the genome-wide association study. In a GWAS, as many as one million genetic markers (single nucleotide polymorphisms, SNPs) are tested for genetic association with disease risk and/or phenotypic endophenotypes such as age-of-onset, biomarkers, imaging results, and neuropathological endpoints. More than a dozen GWASs have been reported for AD (reviewed in Bertram et al. 2009, 2010; Table 2). The first genome-wide significant finding was reported for *GAB2* (GRB2-associated binding protein 2) by (Reiman et al. 2007); however, it required post hoc stratification by *APOE* to reach significance. This association was followed up with a series of replications and refutations. *GAB2* has been proposed to influence tau phosphorylation (Reiman et al. 2007) and to modulate A β production by binding growth factor receptor-bound protein 2 (GRB2), which binds APP and the presenilins (Nizzari et al. 2007).

In 2008, we reported the first genes to directly exhibit genome-wide significant association with AD without the need for stratification on *APOE*. We employed a family-based GWAS approach (Bertram et al. 2008) and discovered three novel AD gene candidates including *ATXN1* (ataxin 1), *CD33* (siglec 3), and an uncharacterized locus on chromosome 14 (GWA_14q31.2). *ATXN1* can harbor an expanded polyglutamine repeat that causes spinocerebellar ataxia type 1. With regard to AD, we later showed that *ATXN1* affects A β levels by modulating β -secretase levels and cleavage of APP (Zhang et al. 2010). This finding was confirmed in vivo in *ATXN1* knockout

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mice, which also suffer cognitive impairment after 6 mo of age (unpublished data). *CD33* is a member of the family of sialic acid-binding, immunoglobulin-like lectins. These molecules promote cell-cell interactions that regulate the innate immune system (Crocker et al. 2007), including inflammation. Interestingly, the innate immune system has recently gained increased attention in AD, with our discovery that A β may act as an antimicrobial peptide in the brain's innate immune system (Soscia et al. 2010). *CD33* also resides in the top ten meta-analysis hits on AlzGene.org.

In 2009, two large case-control GWASs (Harold et al. 2009; Lambert et al. 2009) reported three novel AD genes: *CLU* (clusterin; apolipoprotein J), *CR1* (complement component (3b/4b) receptor 1), and *PICALM* (phosphatidylinositol binding clathrin assembly protein). These three loci have been widely replicated in independent follow-up studies and are listed in the top 10 of AlzGene.org meta-analysis hits. Like *APOE*, two of these genes (*CLU* on chromosome 8 and *CR1* on chromosome 1) map in previously implicated LOAD genetic linkage peaks (Butler et al. 2009). Despite the strong statistical support for these three candidates, the effects of these genes on risk for AD are exceedingly small with allelic odds ratios (ORs) of ~ 1.15 for all three genes, that is, increasing or decreasing risk by $\sim 1.15 \times$. In contrast, the OR for *APOE* $\epsilon 4$ is ~ 4 or 15 for one or two alleles, respectively.

At the functional level, clusterin (*CLU*) has been reported to be involved in transport of A β from plasma to brain and A β fibrillization (DeMattos et al. 2004; Nuutinen et al. 2009). *PICALM* is involved in clathrin-mediated endocytosis (Tebar et al. 1999), which is necessary for APP to be processed by γ -secretase into A β (Koo and Squazzo 1994). *CR1* is the receptor for complement C3b, a key inflammatory molecule that is activated as part of the brain's innate immune system in AD (Khera et al. 2009), and may be able to protect against A β -induced neurotoxicity (Rogers et al. 2006).

In 2010, the results of another large case-control GWAS were reported, suggesting the

existence of additional AD genetic risk factors (Seshadri et al. 2010). Among them was the gene *BIN1* (bridging integrator 1), which had previously been reported to be associated with AD with subgenome-wide significance (Lambert et al. 2009). *BIN1* is also a top 10 meta-analysis hit on AlzGene and has a tiny effect on AD risk with an allelic OR of ~ 1.15 . *BIN1* (amphiphysin II) is highly expressed in the central nervous system and plays a role in receptor-mediated endocytosis (Pant et al. 2009), which could theoretically affect APP processing and A β production or A β clearance from brain.

In 2011, two more large case-control GWASs were reported, leading to four more Alzheimer gene candidates: *CD2AP*, *MS4A6A/MS4A4E*, *EPHA1*, and *ABCA7* (Hollingworth et al. 2011; Naj et al. 2011). These studies also identified an additional SNP in *CD33* that influenced risk for AD. Whereas we had previously reported a *CD33* SNP that increased risk for AD with genome-wide significant association (Bertram et al. 2008) using family-based GWASs, these two case-control GWASs reported an SNP roughly 1400 base pairs away that conferred protection against AD. Collectively, our 2008 study along with this 2011 study shows that *CD33* is now the only gene besides *APOE* that exhibits genome-wide significance for association with AD in both case-control and family-based GWASs. Additionally, both genes harbor SNPs that can confer either risk or protection for AD.

When one considers the three EO-FAD genes (*APP*, *PSEN1*, and *PSEN2*), the LOAD gene (*APOE*), and the 11 genes (*CD33*, *GWA_14q31.2*, *ATXN1*, *CLU*, *PICALM*, *CR1*, *BIN1*, *ABCA7*, *MS4A6E/MS4A4E*, *CD2AP*, and *EPHA1*) exhibiting genome-wide significance for association with LOAD, we now have 15 established AD genes (Table 2). However, we only know the pathogenic gene variants/mutations for the original four. With regard to function, roles for these genes in AD pathogenesis can be divided into three basic categories: production, degradation, and clearance of A β , lipid metabolism, innate immunity, and cellular signaling (Table 3 and Fig. 1).

Table 3. Predicted pathogenic mechanisms of late-onset Alzheimer disease genes from GWASs

Gene	Protein	Location	Risk change (%)	Proposed molecular phenotype
<i>APOE</i>	Apolipoprotein E	19q13	~400%–1500%	Clearance of A β ; lipid metabolism
<i>CD33</i>	CD33 (Siglec 3)	19q13.3	~10%	Innate immunity; degradation of A β
<i>CLU</i>	Clusterin	8p21.1	~10%	Clearance of A β ; innate immunity
<i>CR1</i>	Complement component (3b/4b) receptor 1	1q32	~15%	Clearance of A β ; innate immunity
<i>PICALM</i>	Phosphatidylinositol binding clathrin assembly molecule	11q14	~15%	Production and clearance of A β ; cellular signaling
<i>BIN1</i>	Bridging integrator 1	2q14	~15%	Production and clearance of A β ; cellular signaling
<i>ABCA7</i>	ATP-binding cassette subfamily A member 7	19p13.3	~20%	Lipid metabolism; cellular signaling
<i>CD2AP</i>	CD2-associated protein	6p12.3	~10%	Cellular signaling
<i>EPHA1</i>	EPH receptor A1	7q34	~10%	Cellular signaling; innate immunity
<i>MS4A6A/MS4A4E</i>	Membrane-spanning 4-domains, subfamily A, members 6A and 4E	11q12.1	~10%	Cellular signaling
<i>ATXN1</i>	Ataxin 1	6p22.3	NA	Production of A β

GENETICS OF LATE-ONSET AD: MISSING HERITABILITY AND *ADAM10*

The GWAS approach involves genotyping common ancestral polymorphisms that usually occur in >5% of the general population. The risk effects exerted by the GWAS-derived genes discussed above are tiny, that is they confer only an ~0.10- to 0.15-fold increase or decrease in AD risk in carriers versus noncarriers of the associated alleles, as compared with a four- to 15-fold increase in AD risk owing to the inheritance of *APOE* ϵ 4. A substantial proportion of the genetic variance of LOAD remains unexplained by the currently known susceptibility genes.

The “missing heritability” of complex and heterogeneous disease has been coined the “dark matter” of GWASs because we know it exists but cannot yet observe it (Manolio et al. 2009). The “dark matter” may be explained by common variants that are not included on existing microarrays, copy number variants

including genomic insertion/deletions and rearrangements, and rare sequence variants. With regard to rare variants conferring large effects on risk for LOAD, we recently reported two rare LOAD mutations in the *ADAM10* gene that caused AD at an average age of 70 years in seven of 1000 LOAD families tested (Kim et al. 2009).

ADAM10 encodes the major α -secretase in the brain. This enzyme cleaves within the A β domain of APP to preclude the formation of β -amyloid. The two novel *ADAM10* LOAD mutations, Q170H and R181G, are located in the prodomain region, and dramatically impair the ability of ADAM10 to carry out α -secretase cleavage of APP both in vitro (Kim et al. 2008) and in vivo (unpublished observation). Thus, the two LOAD-associated mutations in *ADAM10* would appear to be strong candidates for the first rare, highly penetrant pathogenic mutations to be genetically associated with late-onset AD (Kim et al. 2009). This study then becomes the first (and

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to date, only) to challenge the rare mutation–rare disease (EO-FAD)/common variant–common disease (LOAD) paradigm that postulates that LOAD is only associated with common variants, (e.g., *APOE* ϵ 4).

The two LOAD mutations in *ADAM10* also argue that, in addition to GWASs, resequencing, for example, using novel high-throughput (“next-generation”) technologies and whole-genome or exome sequencing, will be necessary to search for additional rare variants causing LOAD. Along these lines, large-scale resequencing has been employed to create a comprehensive array of all rare mutations in the human genome, known as the “1000 Genomes project” (<http://www.1000genomes.org/>). This database will aid immensely in determining whether rare mutations found in disease cases are novel and pathogenic. Ultimately, the validation of bona fide pathogenic mutations will require comprehensive functional studies in in vitro systems, in vivo animal models, and clinical samples.

SUMMARY

Our understanding of the etiology and pathogenesis of AD can be arguably be divided into two eras: before and after the identification of the AD genes. The past three decades of genetic research in AD have revolutionized our understanding of the causes of AD and accelerated the discovery and development of novel therapeutics aimed at the treatment and prevention of AD (Tanzi and Bertram 2005). The modern era of AD research guided by genetics began in the 1980s and 1990s with genetic linkage studies and positional cloning efforts that led to the identification of the three EO-FAD genes: *APP*, *PSEN1*, and *PSEN2*. The late-onset AD gene *APOE* was discovered using a similar strategy, but was ultimately validated by genetic association studies. Genetic association studies remain the most common method for identifying novel LOAD genes and are most often employed in the form of large-scale GWASs that screen the entire human genome for novel disease loci. Recently, our family-based and others’ case–control GWASs (reviewed in Bertram et al. 2009,

2010) led to the elucidation of novel susceptibility variants, all of which confer only small effects on risk. Moreover, up to 50% the heritability of AD remains unexplained by the known genes and AD candidate loci that have been derived from GWASs.

Our initial understanding of the etiology of AD began with the identification of rare causal mutations in the three EO-FAD genes. More recently, we discovered two rare pathogenic mutations in *ADAM10* that impair ADAM10 enzyme activity and lead to AD by 70 years old with high penetrance (Kim et al. 2009). Based on the roughly 200 EO-FAD gene mutations and two *ADAM10* LOAD mutations, it will be important to search for additional rare sequence variants in other genes that predispose to AD. Ultimately, the insights into the etiology and pathogenesis of AD garnered from genetic studies of AD will continue to enhance our understanding of the pathological mechanisms leading to AD. Moreover, these findings will aid in the development of novel therapeutic strategies for preventing, stopping and even reversing AD.

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