



Genetics and epigenetics of Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is a highly prevalent condition that predominantly affects older adults. AD is a complex multifactorial disorder with a number of genetic, epigenetic and environmental factors which ultimately lead to premature neuronal death. Predictive and susceptibility genes play a role in AD. Early-onset familial AD is a rare autosomal dominant disorder. Genome-wide association studies have identified many potential susceptibility genes for late-onset AD, but the clinical relevance of many of these susceptibility genes is unclear. The genetic variation by susceptibility genes plays a crucial role in determining the risk of late-onset AD, as well as the onset of the disease, the course of the AD and the therapeutic response of patients to conventional drugs for AD. The newer understanding of the epigenetics in AD has also been highlighted. Recent advances in genetics, epigenetics and pharmacogenetics of AD pose new challenges to the future management of AD.

INTRODUCTION

Alzheimer's disease (AD) and related dementias represent a major health problem throughout the world and is a cause of disability in the older people. Dementia causes progressive deterioration of cognition and function, a wide range of challenging behavioural disturbances, and ultimately death. The prevalence of AD increases exponentially from approximately 2% at the age of 60–65 years to more than 30%–35% in people older than 80 years. It doubles for every 5-year increase in age in both sexes, after the age of 65.¹ In 2010, 35.6 million people in the world had dementia, and this number is projected to double by 2030.² Current treatments for AD are limited and the few treatments that exist have generally modest effectiveness.

β -Amyloid, inflammation, oxidative and vascular damage all appear to play a role in the neurodegeneration of AD.^{3–5} In an autopsy study, 33% of patients with AD had evidence of brain infarcts and thus cerebrovascular disease is considered a risk factor for AD.⁶ The pathology of AD is characterised by an accumulation of misfolded protein, oxidative damage and inflammatory changes that result in region-specific loss of synaptic connections and neuronal cell death.⁷ β -Amyloid has been found in the brain of normal older people and in AD patients, and so its role in late-onset Alzheimer's disease (LOAD) is not clear.⁸ Some researchers also argue that plaque burden does not correlate with cognitive impairment in AD.⁹ The recent failure of several treatments based on the amyloid hypothesis has generated interest in reassessing the fundamental pathophysiological processes that lead to AD.¹⁰ These findings suggest pathology

other than what can be explained by the amyloid hypothesis may be contributing to the development of AD.

AD is the common type of dementia and is seen in 50%–70% of all people with dementia in Western countries.¹¹ In AD, neurodegeneration has been linked to the phenotypic expression of more than 200 genes.¹¹ The recent dramatic advances in genetics and epigenetics research will refine the understanding of pathophysiology of dementias and has the potential to lead to future treatments for these neurodegenerative conditions. The completion of the human genome project and subsequent major advances (eg, completion of the HapMap and technological advances making genome-wide association studies (GWAS) feasible, see Glossary) have led to an explosion of information about the genetics and epigenetics of many diseases including the dementias over the past few years.¹² It is important for clinicians to have some understanding of these recent advances because they may soon have an impact on clinical practice (eg, diagnostic testing, therapeutic advances). It is difficult for clinicians to keep up-to-date in this rapidly evolving area due to limited training on methodology of genetics research. The objectives of this paper are to outline the current understanding of genetics and epigenetics that contribute to the development of AD and the implications for treatments and care of those with this form of dementia.

GENETICS OF AD

Multiple genetic defects, involving either predictive (mutational) or susceptibility (risk) genes, have been linked to the development of AD. Mutations in the predictive genes linked to AD render the individuals who carry them very likely in developing AD at some point in their lives. In contrast, susceptibility genes do not reliably cause the disease but increase an individual's susceptibility or predisposition to developing AD. The genetics of AD supports a dichotomous model, with early- and late-onset variants, based on the age of the affected individuals when symptoms first appear (cut-off age is 65). Despite several genetic mutations found in AD, more than 95% of cases are sporadic. As Mastroeni *et al* pointed out, mutations in predictive genes account only for a very small proportion of AD cases (about 5%)^{13 14} and are mainly responsible for the early onset variant of AD. On the other hand, the likelihood of developing late onset AD seems to be linked to the interplay between environmental factors and a number of susceptibility genes, of which apolipoprotein E (APOE) gene has the most impact. It is one of the few diseases in which a single susceptibility gene, namely APOE, gives rise to a substantial sporadic risk.¹⁵

Early-onset AD

This AD variant occurs before 65 years of age and represents only about 5% of all cases of AD. A significant proportion of early-onset AD is caused by autosomal dominant, fully penetrant mutations in one of three genes, namely, the gene encoding the amyloid β precursor protein (APP) on chromosome 21,¹⁶ presenilin 1 (PSEN1) on chromosome 14¹⁷ or presenilin 2 (PSEN2) on chromosome 1.¹⁸ The most common mutation is found in PSEN 1 (40%–70% of all cases of early onset AD), which encodes a protein implicated in the cleavage of the APP to β -amyloid. Mutations in PSEN1 or PSEN2 were found to increase the ratio of the toxic β -amyloid 42 to the benign β -amyloid 40.¹⁹ Overexpression of the APP gene increases plaque formation by promoting synthesis of β -amyloid in its most pathogenic form, β -amyloid 42.¹⁹ The gene encoding APP is found on chromosome 21. Therefore, adults with trisomy 21 (Down's syndrome) are at a high risk of developing the characteristic neuropathological hallmarks of AD if they survive beyond age 40. The extra dose of the APP gene in trisomy 21 leads to increased production of APP and therefore to an excess of cerebral amyloid as compared with normal people, which likely explains the propensity to develop early-onset AD in individuals afflicted with this genetic disorder.²⁰ Dominantly Inherited Alzheimer Network, an international partnership of leading scientists, aims to study families carrying genetic mutations that causes early-onset AD, and is currently conducting active research likely to shed some light onto the pathophysiology of this rare but inherited form of dementia.

Late-onset AD

Susceptibility genes contribute to AD predisposition, and therefore the presence of specific mutations within them increases the likelihood of developing the disease (phenotypic expression of AD). Susceptibility genes may each add quantitatively to an individual's personal risk. GWAS have reported many candidate susceptibility genes. Single nucleotide polymorphisms (SNPs) in many susceptibility genes are associated with the risk of AD, but each one contributes only a small amount to the risk of the disease. The disease risk associated with the APOE4 allele has been consistently replicated and reproduced. The AlzGene database provides a comprehensive, unbiased and regularly updated field synopsis of genetic association studies performed in AD.²¹ According to the AlzGene database, the top 10 genes showing the strongest association with AD are APOE, BIN1, CLU, ABCA7 (ATP-binding cassette transporter), CR1, PICALM, membrane spanning 4-domains subfamily (MS4A6A), CD33, MS4A4E and CD2-associated protein (CD2AP).²² As previously stated, the gene encoding APOE, which was discovered more than 15 years ago, contributes the largest disease risk.

Apolipoprotein E

The best established gene known to influence late-onset of AD is the gene encoding APOE on chromosome 19. The APOE gene has three alleles APOE2, APOE3 and APOE4. The APOE4 allele has the strongest association with AD. Whereas only 24%–30% of the general Caucasian population carries at least one APOE4 allele, 40%–65% of AD patients have at least one copy of the APOE4 gene. Interestingly, there is also a dose effect with carriers of two APOE4 alleles (homozygous APOE4/APOE4 state) having a higher risk than carriers of a single APOE4 allele of developing AD.²³ However, many LOAD patients have no APOE4 allele, whereas individuals carrying the APOE4 allele may never develop AD, suggesting that there are additional factors modulating the influence of the APOE4 allele in causing the development of AD, such as the contribution of other susceptibility genes and environmental factors. Nevertheless, the presence of APOE4 allele represents the most important risk factor for LOAD after age. An increasing body of evidence shows that the APOE proteins function in the clearance of amyloid, by cross linking with the β -amyloid and thus reducing its circulating concentration in the blood, a process which seems to be less efficient in the presence of the APOE4 variant.^{24–25} Cholesterol metabolism has been implicated in AD pathogenesis,²⁶ which might represent another facet of the APOE's role in AD pathogenesis, given the well-established function of APOE in lipid metabolism and lipoprotein dynamics.²⁷

As mentioned above, apart from APOE, there are many other, less influential, susceptibility genes linked to increased risk of developing AD. The roles of a few of them have been established and confirmed by several recent GWAS, genetic case-control studies and meta-analyses (see Replicated LOAD susceptibility genes section, below), whereas the role of some others is still controversial (see Non-replicated LOAD susceptibility genes section, below).

Replicated LOAD susceptibility genes

Several susceptibility genes for LOAD were replicated by further independent follow-up studies to have associations with AD (see table 1 for pathogenetic effects associated with several replicated susceptibility genes). Three of the best known such genes are PICALM, a gene encoding for the phosphatidyl inositol-binding clathrin assembly protein, the CLU gene encoding clusterin (also known as apolipoprotein J) and the CR1 gene encoding a complement receptor 1.^{28–30} CR1 is the main receptor of the complement C3b protein, a key inflammatory protein that is activated in AD.^{31–32} Clusterin is involved in β -amyloid aggregation, fibrillation and clearance, regulation of brain lipid metabolism and the inhibition of neuronal apoptosis.^{33–34} PICALM plays a role in synaptic transmission and removal of apoptotic cells.³⁵ APOE and PICALM interact synergistically and

Table 1 Common mechanisms linked with predictive and replicated and some non-replicated susceptibility genes for AD pathogenesis

Type of AD/pathogenetics	Predictive genes	Susceptibility genes	
		Replicated genes	Some non-replicated genes
EOAD: β -amyloid linked genes	APP, PSEN1, PSEN 2		
LOAD: β -amyloid linked genes		APOE, CLU, PICALM, CR1, BIN1, GAB2	A2M, IDE, ACE, ubiquilin 1, SORL1
Immune and inflammatory system linked genes		CLU, CR1, ABCA 7, CD33, EPHA1	IL-1
Cell membrane and synapse linked genes		PICALM, BIN1, CD33, CD2AP	
Cholesterol and vascular linked genes		APOE, CLU, ABCA 7	ACE

ABCA 7, ATP-binding cassette transporter; AD, Alzheimer's disease; APOE, apolipoprotein E; APP, amyloid β precursor protein; BIN1, bridging integrator 1; CD2AP, CD2-associated protein; EOAD, early-onset AD; EPHA1, ephrin receptor A1; GAB2, glycine-rich protein-associated binding protein 2; IL-1, interleukin 1; LOAD, late-onset AD; PSEN1, presenilin 1; PSEN2, presenilin 2; SORL1, sortilin-related receptor.

increase the risk of AD.³⁰ Another recent meta-analysis has confirmed that CR1, CLU and PICALM as AD risk loci and has also revealed interactions with APOE genotypes.³⁰

Other genes which have been replicated are described below. CD33, sialic acid-binding immunoglobulin like lectin and ephrin receptor A1 (EPHA1) exert their effects on the immune system. CD33 also has an effect on synaptic membrane transmission.³⁶ The gene coding for glycine-rich protein-associated binding protein 2 (GAB2) has been associated with amyloid peptide protein synthesis by interacting with APOE ε4 carriers and thus increasing the risk.^{37–38} Recent meta-analysis of GWAS also showed variants at CD33 and EPHA1 as well as MS4A4/MS4A6E and CD2AP to be associated with LOAD.³⁶ CD2AP regulates the actin cytoskeleton and is involved in the regulation of receptor mediated endocytosis. Bridging integrator 1 and ABCA7 are also replicated LOAD genes, involved in the four pathways (amyloid protein synthesis, immune system function, lipid metabolism and membrane synaptic transmission) leading to AD^{22–39} (see table 1). The genes in the MS4A cluster are located on chromosome 11 and encode proteins with at least four potential transmembrane domains, but their specific functions have not yet been well characterised.

Non-replicated LOAD susceptibility genes

Some of the other susceptibility genes have modest effect with reported OR of about 1.2.⁴⁰ Among these lower risk susceptible genes, the ones coding for sortilin-related receptor (SORL1),⁴¹ death-associated protein kinase 1,⁴² ubiquilin 1⁴³ and ATP-binding cassette transporter I, subfamily A⁴⁴ on chromosome 9, and low-density lipoprotein receptor related protein 6 on chromosome 12,⁴⁵ are all associated with potentially relevant biological mechanisms. The genetic variant SORL1 is associated with APP trafficking,⁴⁶ while the death-associated protein kinase 1 variant is observed with neuronal apoptosis,⁴² and ubiquilin 1 is related to the accumulation of presenilin proteins⁴³ (see table 2).

Investigators are currently conducting meta-analyses of GWAS to synthesise evidence from multiple GWAS and settle inconsistencies.^{21–30} A systematic meta-analysis study unravelled additional AD susceptibility genes. More than 20 non-APOE related mutations have been shown to be associated with disease risk in this systematic meta-analysis.³⁰ Among these, there are mutations in the genes encoding ACE, β2-neuronal nicotinic acetylcholine receptor gene (CHRN2), cystatin C (CST3), oestrogen receptor1, glyceraldehydes-3-phosphate dehydrogenase, spermatogenic (GAPDHS), insulin-degrading enzyme, 5,10-methylene tetrahydrofolate reductase, nicastrin, prion protein and mitochondrial transcription factor A.²¹ Table 1 shows some of the non-replicated LOAD genes that have been

proposed to contribute to AD through different pathological pathways that are similar, but nonetheless distinct from the ones acted upon replicated LOAD genes. Some other non-replicated genes have been discussed under clinical associations in the next section. A major drawback of some of these epidemiological clinical studies is that they indicate merely statistical associations but cannot reveal the potential underlying biological mechanisms. Likewise, studies have failed to replicate all the genetic variants or SNPs of the SORL1 gene, indicating the sequence variation (allelic heterogeneity) in SORL1 with AD risk, adding to the complex puzzle of AD genetics.

However, some investigators have questioned the ultimate clinical utility of attempts to find genetic effects of diminishing importance in larger and larger GWAS. Pedersen has written: 'findings such as those reported by Seshadri *et al* reinforce the futility of using individual genetic risk profiling for AD beyond collecting information on age, sex, family history, and APOE status'.⁴⁷ Furthermore, independent replication of findings of many new susceptibility genes is still lacking.

Clinical associations with genetic variations in AD

Table 2 shows the clinical associations with genetic variations in AD. Individuals who have a family history of AD are at an increased risk of developing AD. Genetic studies have shown APOE, ACT and CHRNA 7 genes have been associated with the conversion of amnesic mild cognitive impairment to AD.⁴⁸ Age of onset of AD seems to be influenced by APOE with sporadic and familial LOAD.⁴⁹ Other genetic moderators for age of onset with sporadic AD include the genes for α 2 macroglobulin, low density lipoprotein receptor-related protein gene polymorphism and glutathione S-transferase.^{50–52} SORL1 (SNPs 19, 21, 23 and 25) has been shown to be associated with age of onset of AD in 349 Caucasian AD patients (HR 1.53; 95% CI 1.12 to 2.09, p=0.007).⁵³ A recent study found significant associations between age of onset of LOAD and piggy BAC transportable element derived 1 (p=0.04) as well as early B-cell factor 3 (p=0.03) genes.⁵⁴ Genetic factors may also play a role in the rate of cognitive decline. A study in AD patients who are homozygous for the APOE4 allele shows accelerated cognitive decline.⁵⁵ GAB2 (OR=0.78, p=0.007) and LOC 651924 (OR = 0.91, p=0.01) are also found to be risk modifiers like APOE.⁵⁴ Genes coding for interleukin 1 and insulin-degrading enzyme has been shown to influence the age of onset as well as disease progression.^{56–59} The genes that are associated with AD psychosis such as aggressive behaviour include the COMT gene, serotonin transporter 5- HTTLPR gene and the dopamine receptor genes DRD1 and DRD3.⁶⁰ Thus, behavioural and psychological symptoms associated with dementia could be partially heritable.

Among the risk genes, several studies have shown the clinical importance of the E4 variant of APOE susceptibility gene for sporadic AD, but cannot predict accurately who will develop AD. APOE4 has been associated with an earlier onset of the disease, accelerated cognitive decline and reduced efficacy to cholinesterase inhibitors (medications used to treat AD). With other susceptibility genes, this is the current evidence of the association of genetic mutations with clinical features. Further studies are needed to confirm these associations. The replicated and non-replicated genes identified in these studies tell only part of the story and it is very likely that currently unknown mechanisms are involved in AD pathogenesis. For more information on genes associated with amnesic MCI and its risk of conversion to AD, we must await the results of the ongoing REVEAL IV study.⁶¹

Table 2 Clinical characteristics associated with genetic variations in AD

Clinical characteristics	Genetic variants
Age of onset of AD	APOE4, A2M, LRP, glutathione S-transferase, IL-1, IDE, SORL1, PGBD1, EDF3
Accelerated cognitive decline	APOE4, IL-1, IDE
Aggressive behaviour	COMT gene, serotonin transporter 5-HTTLPR polymorphism, dopamine receptor genes (DRD1 and DRD3)
Poor response/more adverse effects to cholinesterase inhibitors	APOE4-4, PS2 genotype, CYP2D6 genetic variant, paroxonase 1 and butyrylcholinesterase (Buche-K) polymorphic variants

AD, Alzheimer's disease; APOE, apolipoprotein E; IL-1, interleukin 1; PGBD1, piggy BAC transportable element derived 1; SORL1, sortilin-related receptor.

EPIGENETICS OF AD

Emerging evidence from animal and human studies suggests that epigenetic mechanisms, which determine how and when genes are expressed, without altering the genetic code, contribute to AD. Epigenetic mechanisms, even though acting through reversible changes in gene transcription and expression, are increasingly recognised as being able to exert lasting changes in control over gene expression leading to the long-standing and progressive behavioural abnormalities characteristic of neurological and psychiatric disorders.⁶²

Many chronic neurological and psychiatric diseases may have at least a partial epigenetic aetiology.^{62–64} For example, AD genetics alone does not fully explain the pathogenesis of the disease.⁶⁴ Mutations in the genes encoding APP, PSEN1 and PSEN2 are known to induce the rare early-onset familial AD (see above). However, the vast majority of AD cases are LOAD in which the presence of the APOE4 allele has been shown to be only a risk factor rather than a determinant of disease. Therefore, epigenetic phenomena or environmental factors are likely to contribute to the development of LOAD.

Epigenetic changes, whether protective, benign or harmful, may help explain, in part, why some family members develop the disease while others do not. Monozygotic twin studies point out that young identical twin pairs are essentially indistinguishable in their genetic profiles, whereas substantial differences in epigenetics are seen in older twin pairs.⁶⁵ A large body of evidence suggests that gene–environment interactions play a significant role in the pathophysiology of different types of dementias through epigenetic mechanisms.^{66–67} Nutrients, toxins, environmental exposures and behaviours can activate or silence a gene without altering the genome (see ‘Genome–environmental interactions section, below’). The best understood epigenetic mechanisms through which the interplay between the genome and the environmental milieu influences the phenotype are DNA methylation and various histone modifications, which are discussed below.

DNA methylation

DNA methylation occurs through the covalent addition of a methyl group at the position 5 of cytosines, typically in the CpG dinucleotide context. In the human genome, clusters of CpG dinucleotides are found concentrated in regions called CpG islands, usually found in or close to gene promoter regions. Methylation of cytosines in these regions hinders the binding of transcription factors and is thus associated with gene silencing. Also, DNA methylation in other regions of the genome has been shown to promote chromosome stability. Whereas DNA methylation has a clear physiological significance, such as in the silencing of imprinted genes or X chromosome gene inactivation in women, it also plays a determining role in the pathophysiology of many diseases. Mastroeni *et al* showed epigenetic dysfunction in AD with decrements in DNA methylation in the entorhinal cortex, a region exhibiting substantial AD pathology.¹⁴ However, Silva *et al* reported significant hypermethylation of the HTERT gene and this resulted in increased expression rather than the usual silencing in histopathological studies in AD subjects.⁶⁸

Histone modification

Another epigenetic mechanism involves the reversible, post-translational modifications of histones, consisting of acetylation, methylation, phosphorylation, ADP-ribosylation, ubiquitylation or SUMOylation of specific amino acid residues of N-terminal histone tails.⁶⁹ Since histones play a prominent role in

DNA packaging, these modifications ultimately have a profound influence in the overall structure of the DNA, by favouring either an open, euchromatin state resulting in transcriptional activation or a closed, heterochromatin state resulting in gene silencing. Depending on which histone residue is affected, the same post-translational modification can have different effects. In general, however, histone acetylation activates gene transcription, whereas methylation causes gene silencing.

In support for a role of epigenetic mechanisms to the development of dementias, abnormal methylation pathways are detected in the brains of people afflicted with dementia. Furthermore, these changes are detectable much earlier than the pathological and clinical changes of dementia and therefore might implicate the epigenetic mechanism in the initiation phase of LOAD. The levels of S-adenosyl methionine, which is required for the methylation of both DNA and histones, are decreased in LOAD.⁷⁰ Furthermore, many studies identified epigenetic mechanisms acting on genes related to the β -amyloid pathway. It has been found, for example, that the gene encoding neprilysin, which is the major β -amyloid degrading enzyme and whose expression is decreased in both Alzheimer’s and ageing brains, is methylated under the very influence of β -amyloid itself.⁷¹ Therefore, epigenetic mechanisms forms a vicious cycle in which the production of β -amyloid induces silencing of the gene responsible for its removal result in more β -amyloid production.⁷¹ Another study, using different cell lines, suggests the regulation of the neprilysin gene by histone modifications rather than DNA methylation,⁷² emphasising the complexity of epigenetic mechanisms in the regulation and dysregulation of genes involved in the pathogenesis of AD. The role of histone modifications in the pathogenesis of human diseases associated with memory impairment, such as AD, is also suggested by the observation that overexpression of histone deacetylase 2 (HDAC 2) (which in mice neurons decreases synaptic plasticity and memory formation), whereas HDAC2 knockdown results in increased synapse number and memory facilitation.^{67–73} Various other epigenetic imprints have been associated with the AD disease and have been recently reviewed and catalogued elsewhere.^{66–67}

Gene–environmental interactions

An exciting area of research focuses on the interaction between the genome and the environmental conditions that are mediated by epigenetic mechanisms leading to diseases such as AD later in life. It is becoming apparent that a variety of environmental stimuli, such as infections (bacteria, viruses), radioactivity, pesticides, hormones, smoking, heavy metals,⁷⁴ nutritional factors, and emotional and social factors feed onto epigenetic alterations of gene expression.^{69–75} This provides a potential mechanism through which the environment ultimately affects gene expression profiles of various cell types, including neural cells, leading to the characteristic abnormal transcriptomes associated with various diseases such as AD.

Apart from environmental factors, multiple modifiable vascular risk factors such as mid-life hypertension, hypercholesterolaemia, diabetes and smoking are seen to be contributing to AD risk;⁵ these factors either appear to accelerate or decelerate the time to develop dementia.⁷⁶ An interaction between APOE4 allele and cholesterol levels has been shown to increase the risk of AD.⁷⁷ A recent study showed subjects with a history of myocardial infarction or stroke; the progression of AD is influenced by the interaction between vascular factors and APOE4 carrier status.⁷⁸

Environmental factors can influence gene regulation in the long term; however, these perturbations do not have pathological

results until later in life in conditions such as AD.⁷⁹ Understanding the environmental conditions and the molecular basis of these changes can lead to the development of interventions to prevent adverse health effects. The good news is that epigenetic modifications such as DNA methylation and histone modifications are potentially reversible. Unlike mutant or defective genes, which are damaged permanently and, if found in the germ line, transmitted to future generations, methylated genes can be potentially demethylated via nutrients, drugs and lifestyle changes.⁷⁴ In animal studies, HDAC inhibitors can stimulate the recovery of learning and memory via chromatin remodelling.⁸⁰

An interesting example for the 'gene–environment' interaction is the impact of head trauma on AD onset and progression. Individuals carrying APOE4 alleles and having a history of head injury have a 10-fold increase in the risk of developing AD when compared with individuals with APOE4 but no history of head injury.⁸¹ Therefore, head injury may unmask the effect of

the APOE4 allele on amyloid deposition in the brain. It is not known whether epigenetic changes are at all responsible for the interplay between head trauma and the complex and poorly understood biological interactions leading to AD. Further research studies are needed to replicate this predicted interaction and also to understand the mechanisms underlying this interaction.

Relationship between biomarkers and genetic profile in AD

In Caucasians, hippocampal atrophy detected on MRI was associated with SNPs 22–26 of the SORL1 and has been confirmed in autopsy proven cases of AD.⁸² Brain activity differences are also seen in cognitively intact individuals who are at risk for LOAD based on their APOE status.⁸³ A recent meta-analysis also provided evidence that SNPs 19, 21, 23 and 25 produce variants of SORL1 that are associated with abnormal cerebrospinal fluid levels of A β 42 in 153 Caucasian AD patients ($p=0.003$).⁸⁴

Glossary

Genetics

The study of genes, heredity and variation in living organisms.

Epigenetics

The study of inherited changes in phenotype (appearance) or gene expression caused by mechanisms other than changes in the underlying DNA sequence.

Mutational or predictive genes

Mutational or predictive genes have a range of effects due to mutations (permanent changes in one or more specific genes). When the mutation is inherited, the chances of getting the disease are more likely. A mutational gene is a monogenic disorder and follows the Mendelian inheritance pattern.

Susceptibility or risk genes

Susceptibility or risk genes increase an individual's susceptibility or predisposition to a certain disease or disorder. It is a polygenic/complex disorder and the inheritance pattern is non-Mendelian, and so there is variable genetic risk associated with environmental factors. It alters the risk of disease development or its severity in many conditions such as cardiovascular disease, late onset Alzheimer's disease and depression through its complex interactions with the environment.

Allele

One of two or more versions of a genetic sequence at a particular location in the genome.

Haplotype

A set of DNA variations (polymorphisms) that tend to be inherited together. A haplotype can refer to a combination of alleles or to a set of single nucleotide polymorphisms (SNPs) found on the same chromosome.

Genome-wide association studies (GWAS)

An approach used in genetics research to look for associations between many (typically hundreds of thousands) of specific genetic variations (most commonly, SNPs) and particular diseases or traits. GWAS have become feasible by recent technological advances, including the mapping of variability in the human genome in the HapMap project (<http://www.hapmap.org>) and advances in chip technology that allow genotyping of more than 100 000 SNPs per individual on a single chip. GWAS allow dissection of common complex conditions such as dementia. The proper interpretation of individual GWAS and meta-analysis of GWAS are a rapidly evolving area, as they require complex statistical analyses and there are sometimes inconsistent findings in different GWAS in different populations examining the same complex condition.

Complex condition

A multifactorial disease caused by the interaction of multiple genes and environmental factors. Alzheimer's disease and related dementias are examples of complex conditions.

Amyloid hypothesis

A proposal that the neurodegeneration seen in Alzheimer's disease is caused by the deposition of the peptide β -amyloid in plaques in brain tissue. According to the amyloid hypothesis, accumulation of β -amyloid in the brain is the primary influence driving Alzheimer's disease pathogenesis. The formation of neurofibrillary tangles containing τ protein is proposed to result from an imbalance between production and clearance of β -amyloid.

Autosomal dominant

In this disorder, the affected person will have a 50% chance of inheriting the mutated gene.

Sporadic disease

When a genetic disease occurs without a family history of genetic defects or occurs for the first time in a family due to new mutation, it is called a sporadic genetic disease.

PHARMACOGENETICS OF AD

Pharmacogenomics determines drug response and toxicity, and in the future, individual-specific drugs that are both safer and more effective for each patient are hoped to be developed in this field. The medications used in AD at present are cholinesterase inhibitors (donepezil, rivastigmine, galantamine) and NMDA receptor antagonists, such as memantine. There are clinically relevant genetic polymorphisms in drug metabolising enzyme like cytochrome P450s (CYPs). Fifteen per cent of the Caucasian population with AD are reported to be carriers of defective CYP2D6 polymorphic variants that are potentially responsible for therapeutic failures when receiving cholinesterase inhibitors and psychotropic drugs.^{85–86} However, cholinesterase inhibitor drugs show high efficacy in APOE4-negative patients.⁸⁷ Patients with a defective PS2 gene exon 5 (PS2⁺) always show a worse therapeutic response than PS2⁻ patients.⁸⁸ Paroxonase-1 is an arylesterase with many biological activities. Subjects carrying the R allele of the paroxonase-1 genotype are more likely to respond to cholinesterase inhibitors.⁸⁹ Butyrylcholinesterase (BuchE) genetic variants like wild type polymorphism showed lesser treatment responses in patients receiving cholinesterase inhibitors, but BuchE-K variant showed more frequent adverse events in rivastigmine treated patients.⁹⁰ NMDA receptor antagonists, such as memantine, are believed to protect neurons from glutamate-mediated excitotoxicity.⁹¹ Memantine has been indicated for use in severe dementia. So far, however, no genetic associations have been reported with this medication.

Many different genes interact to elicit a pharmacogenetic outcome in patients with AD. The response to AD medications could be due to interaction of genes involved in drug metabolism and genes associated with AD pathogenesis, and better understanding of AD genetics should help to design better medications in the future.

CLINICAL APPLICATIONS

Genetic testing and counselling could be recommended in families in which one of the specific mutations is suspected in early-onset AD. However, available genetic marker (APOE) in LOAD is not yet conclusive for diagnostic purposes. Genetic testing for

Main messages

- ▶ Alzheimer's disease (AD) is a complex multifactorial disorder with a number of genetic, epigenetic and environmental contributors that may ultimately leads to premature neuronal death.
- ▶ The genetic variation also plays an important role in determining the risk of late-onset AD as well as the clinical characteristics associated with the disease.
- ▶ The accumulation of genetic defects in AD may determine the onset of the disease, course of the disease and influence the therapeutic response of patients to conventional drugs.

the APOE ε4 allele cannot predict accurately who will develop the disease in LOAD. Genetic testing for AD and related dementias is not currently available in routine clinical practice for either high risk groups (eg, family members) or for population screening. Microarray technology has greatly facilitated genetic research and it is used in GWAS. Oligonucleotide (DNA) microarray analysis can test hundreds or even thousands of genes and mutations in parallel. This offers promise for more accurate and sensitive genetic testing in the future. Therapeutic response to cholinesterase inhibitors in AD is linked to the presence of APOE4, with the APOE4 carriers being poor responders to these medications. Furthermore, carriers of defective CYP2D polymorphic variants may affect the metabolism of cholinesterase inhibitors. To improve drug efficacy and safety, future clinical trials in dementia should include pharmacogenetics in drug development and into clinical practice. Pharmacogenetics is beginning to make its impact on the therapeutics of AD.

At this point, there is no effective treatment for dementia, and genetic defects cannot be repaired. In addition, people testing positive for a particular genotype could face discrimination with health insurance. As a result, widespread genetic testing is not recommended and is used only as a research tool. Genetic counselling is necessary if two or more close relatives (parent, brother or sister) developed AD before 60 years. There are promising prospects for early detection of persons at risk for AD as well as optimised and personalised therapy by genetics analyses using already established and new AD biomarkers.

Genetic studies underway in Alzheimer's disease

- ▶ Dominantly inherited Alzheimer's Network is an international partnership to study families with a genetic mutation that causes early-onset Alzheimer's disease.
- ▶ The Alzheimer's Disease Genetics Study is gathering and analysing genetic and other information from 1000 or more families in the USA with two or more members who have late-onset Alzheimer's disease.
- ▶ The AlzGene database provides a comprehensive, unbiased and regularly updated field synopsis of genetic association studies performed in Alzheimer's disease.
- ▶ The Alzheimer's Disease Genetics Consortium is a collaborative work of geneticists who has collected samples from thousands of families around the world with members who do and do not have late-onset Alzheimer's disease and conduct genome-wide association studies.
- ▶ The National Cell Repository for Alzheimer's disease is a national resource where clinical information and DNA samples are stored and made available for analysis by qualified researchers.

CONCLUSIONS

Early-onset familial AD is a rare autosomal dominant disorder caused by highly penetrant mutations in APP and presenilin genes. Late-onset sporadic AD is a very common disorder affecting older adults where a number of susceptibility genes,

Current research questions

- ▶ Why some people who have memory problems only without functional decline (amnestic mild cognitive impairment) develop Alzheimer's disease (AD)?
- ▶ How does lifestyle and environmental risk factors interact with genetic factors and cause late-onset AD?
- ▶ If lifestyle factors are involved in AD, how many insults are required to produce the epigenetic changes in the brain?
- ▶ What preventive steps can be taken in order for the susceptibility genes becoming active and causing disease?

Key references

- ▶ **Pedersen NL.** Reaching the limits of genome-wide significance in Alzheimer's disease: back to the environment. *JAMA* 2010;**303**:1864–5.
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- ▶ **Cacabelos R.** Pharmacogenomics and therapeutic prospects in Alzheimer's disease. *Expert Opin Pharmacother* 2005;**6**:1967–87.
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epigenetic factors and environmental factors may all contribute to the development of the disease. It might turn out in the future that several susceptibility genes that are currently considered as (sporadic) AD risk genes will not maintain this status in the future, or that new AD sporadic risk genes will emerge. Behavioural and psychological symptoms of AD could be partially heritable. Discordance for AD among monozygotic twin pairs could be explained by epigenetic differences. Pharmacogenomic studies have shown some instances where prediction of therapeutic response to AD is genotype-specific. Research advances in AD help us understand the complex genetic makeup and environmental interactions, as well as their effects on the natural history of dementia. In the future, biomarkers, including genetic markers, will certainly be used as screening tools and predictors of subsequent disease as well as clinical characteristics of the disease. Disease-related genes and genes involved in drug metabolism may be responsible for drug efficacy and safety. Therapies may eventually be personalised based on advances in our understanding from genetic and epigenetic studies.

SELF-ASSESSMENT QUESTIONS (TRUE/FALSE; ANSWERS AFTER THE REFERENCES)

1. Early-onset AD is not an autosomal dominant disorder
2. Well established susceptibility gene in late-onset Alzheimer's disease is APOE4
3. COMT gene, serotonin transporter 5-HTTLPR polymorphism, dopamine receptor genes play a role in aggressive behaviour in AD
4. Carriers of defective CYP2D6 polymorphic variants alter the metabolism of cholinesterase inhibitors
5. Cholinesterase inhibitor drugs show high efficacy in APOE4 positive and PS2 positive patients

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ANSWERS

1. False
2. True
3. True
4. True
5. False