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Genetic Basis of Alzheimer's Disease

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Alzheimer's disease is a progressive neurodegenerative disorder and is the most common cause of dementia in elderly people. There are four different genetic loci associated with inherited susceptibility to Alzheimer's disease. The four genes to be identified in association with inherited susceptibility to Alzheimer's disease are amyloid precursor protein, apolipoprotein E epsilon 4, presenilin 1 and presenilin 2. The mutations or polymorphisms in these genes cause excessive cerebral accumulation of the amyloid beta-protein and subsequent neuronal and glial pathology in brain parts which are important for memory and cognition. Other miscellaneous genes involved in Alzheimer's disease are interleukin-1 alpha, interleukin-6, interleukin-10, tumor necrosis factor-alpha, cystatin C, neprilysin, angiotensin converting enzyme, BACE 1, cathepsin D and brain-derived neurotrophic factor.

Alzheimer 's disease (AD) is a neurodegenerative disorder with a complex etiology and pathogenesis. It is the most common cause of dementia seen among the elderly. Two major neuro-pathological features of AD include generalized deposition of amyloid β in the form of senile plaques and aggregation of abnormally phosphorylated tau protein into neurofibrillary tangles[1,2]. Neurofibrillary tangles consist largely of a type of protein wrapped into bundles. These proteins are called tau proteins which are chemically altered by being abnormally phosphorylated and twisted together.

It has been suggested that heredity may play a part in the development of AD. In research on families in which the disease (called as early onset familial AD) has frequently occurred before the age of 50, is caused by mutations in amyloid precursor protein (APP) gene (present on chromosome 21), Presenilin 1 gene (present on chromosome 14) and Presenilin 2 gene (present on chromosome 1). Mutations in these genes, however, account for less than 5% of the total number of AD cases. The remaining 95% of AD patients are mostly sporadic late-onset cases, and caused by the major susceptibility gene called as apolipoprotein E gene, which is present on chromosome 19[3]. Mutations or polymorphisms in these genes cause excessive cerebral accumulation of the amyloid beta-protein and subsequent neuronal and glial pathology in brain regions important for memory and cognition[4].

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AMYLOID PRECURSOR PROTEIN (APP) GENE

Amyloid precursor protein, abbreviated as APP, is necessary for normal brain function. Research has shown that APP protects brain cells from injury and insult. Amyloid β (Aβ) -peptide (40 to 42 amino acids long) is generated proteolytically from the APP, which is widely expressed by neurons throughout the brain in normal individuals as well as in those with AD. APP is encoded in humans by a gene on chromosome 21.

Expression, metabolism and functions of APP:

APP was identified from the original isolation and sequencing of its Aβ fragment in the meningovascular amy-

loid of AD[5]. APP is a polypeptide having 770 amino acids. This 770 amino acid form and the slightly shorter 751 residue are the most common isoforms expressed in non-neuronal cells. Neurons express these as well as a more abundant 695 residue isoform. Very small deposits of nonfibrillar (diffuse) Aβ have been detected in some non-neural tissues, including skin, spleen and intestine[6]. The reasons for this striking anatomic variation in Aβ deposition could include both the high rate of Aβ production by neurons and potential differences in the fate of Aβ following its release from neural versus non-neural cells–for example, an adverse balance between degradation and aggregation of the peptide in the brain.

Proteolytic processing of APP:

APP is cleaved by a group of proteases called secretases to generate derivatives of APP, which are secreted in human plasma, cerebrospinal fluid (CSF) and cultured cells[7]. The cleavage of APP molecules by α-secretase(s) appears to be a highly regulated event in both neural and non-neural cells. For example, activation of certain kinases such as protein kinase C by stimulating various cell-surface receptors (e.g. muscarinic receptors) linked to this kinase and to phospholipase C results in a substantial increase in the secretion of APPs–α[8]. In most cells, a minority of total APP molecules undergoes α-secretase cleavage, so that an increase in this scission would still leave many APP polypeptides that could be subjected to the alternative cleavages (made by β- and γ-secretases) that lead to Aβ formation. The APP mutations have been shown to increase the secretion of Aβ into the extracellular fluid, particularly that of the $A\beta_{42}$ forms[9].

Generation of amyloid β-protein:

Aβ was found to be constitutively secreted by normal, healthy cells in culture and could actually be detected as a circulating peptide in both the plasma and cerebrospinal fluid (CSF) of normal humans and lower mammals[10,11]. The discovery of normal Aβ production by cells carries implications for the normal proteolytic processing of transmembrane proteins in general and for the role of Aβ production in AD in particular. APP is cleaved sequentially by β- and γ-secretases, whereas p3 (a smaller 3-kd fragment) is created when APP is cleaved sequentially by α- and γ-secretases.

Both in cell culture and in normal human CSF and plasma, $A\beta_{40}$ peptides are far more abundant than $A\beta_{42}$ peptides, constituting roughly 90% of total secreted Aβ[12]. This marked disparity in basal concentrations of the two peptides underscores the strong aggregation properties of $A\beta_{42}$, which despite its minor levels, accumulates first in the form of diffuse plaques in AD and aged normal brains. The two cleavages after residues 40 and 42 can be differentially blocked by certain protease inhibitors, suggesting that there are two different proteases or at least two rather distinct proteolytic activities of one enzyme[13]. $A\beta_{42}$ is the most abundant form in endoplasmic reticulum-rich fractions, whereas $A\beta_{42}$ and $A\beta_{40}$ are readily detectable in Golgi-rich fractions[14].

Metabolism, deposition and cytotoxic effects of Aβ:

In most cell types, Aβ is quantitatively released from cells into the extracellular fluid, with much smaller amounts of total Aβ detectable intracellularly. Nonetheless, some Aβ, particularly $A\beta_{42}$, has been detected inside cells, including in neuronal cell lines[14,15]. The normal presence of Aβ in human extracellular fluids, including plasma, CSF, and urine, and the accumulation of extracellular Aβ in the form of innumerable diffuse and compacted plaques in aged and AD brain tissue suggest that much of the activity and metabolism of Aβ occurs in the extracellular space. In contrast, there has been very little evidence for the accumulation of Aβ inside cells in AD brain tissue.

One possible fate of Aβ is that it is taken up again by cells following its secretion and the degraded intracellularly, presumably in the endosomal/lysosomal system[16,17]. Another possible route of clearance would be by proteolytic degradation in the extracellular space. Protease activities are capable of degrading synthetic $A\beta_{40}$ and $A\beta_{42}$ peptides *in vitro*[18]. One protease is insulin-degrading enzyme which is a metalloprotease that is capable of degrading insulin, glucagon, and other small peptides in a variety of tissues and has been detected in human CSF and in normal and AD brain tissue[19]. There is currently very little information about other specific proteases that degrade Aβ endogenously under normal or pathological circumstances. Both $A\beta_{40}$ and $A\beta_{42}$ have a tendency to self-assemble into oligomers and polymers based on their hydrophobic properties. The $A\beta_{42}$ species, however, with its two extra nonpolar residues, has a particularly strong tendency to aggregate rapidly into insoluble oligomeric/polymeric material[20]. The first morphological form in which Aβ is detectable in AD or normal aged brain tissue is as the material comprising diffuse plaques. The Aβ in these initial plaque-liked deposits is particulate and insoluble in aqueous buffer[21]. Studies of Aβ deposition in transgenic mice over expressing mutant human APP suggest that $A\beta_{42}$ accumulates to high levels in first soluble and then insoluble forms prior to the appearance of diffuse plaques[22]. It is likely that

once soluble monomers exceed a certain concentration, oligomers begin to form, presumably with the help of other molecules such as pathological chaperones that can promote aggregation but do not necessarily become part of the aggregates. One example of such an aggregation-mediating molecule may be heparin sulfate proteoglycan, which is present in diffuse as well as compacted plaques[23,24].

With regard to biological activities of Aβ itself, there has been some evidence that Aβ in either soluble or particulate form at low concentrations may have neurotrophic functions and may support neuron attachment and neurite outgrowth[25,26]. Rodents in general do not convert as many of their APP molecules to Aβ peptides as compared to humans[27], so it could be that constitutive Aβ production has salutary function only in higher mammals (dogs, monkeys, humans) that are also prone to excessive Aβ accumulation with age. Aβ could exert direct neurotoxicity, could potentiate minor neurotoxic events that occur during normal cerebral metabolism in aged humans, and/or could act initially by proinflammatory mechanisms (i.e., stimulating local microglia and astrocytes to release various cytokines and acute phase proteins). The various cytotoxic mechanisms of Aβ aggregates include altered calcium homeostasis[28], a decrease in acetylcholine release[29], free radical generation and an increase of reactive oxygen species and acetylcholinesterase activity[30,31], various forms of peroxidative injury[32]. Antibodies against beta-amyloid plaques can slow cognitive decline in patients with AD[33]. Neprilysin is a rate-limiting peptidase, which participates in Aβ degradation in brain. The up-regulation of neprilysin activity would be a relevant strategy for therapy and prevention through reduction of the Aβ levels[34,35].

PRESENILIN 1 AND 2 GENES

The presenilin 1 and 2 are two closely related genes whose implication in familial AD (FAD) is well known. Presenilin 1 gene has been found to be present on chromosome 14[36,37]. This is principally localized to endoplasmic reticulum and Golgi compartments. Shortly after presenilin 1 was cloned, a highly homologous second gene, termed presenilin 2 and located on chromosome 1 was identified as the cause of early-onset familial AD[38,39]. APP and presenilins can participate in protein complexes detectable in the endoplasmic reticulum and Golgi compartments[40] in which mutations in presenilin 1 and presenilin 2 have been shown to elevate $A\beta_{42}$ levels in the blood, cerebrospinal fluid, and brain[41]. The AD brain is under significant oxidative stress, including protein oxidation and lipid peroxidation. Mutations in APP and presenilin 1 induce brain oxidative stress, thereby causing long-term pathological cascade of AD[42].

APOLIPOPROTEIN E (APOE) GENE

Apolipoprotein E is a lipoprotein, or a protein connected to a fat[43]. Apolipoprotein E is a major component of specific lipoproteins called very low-density lipoproteins. In general, apoE is involved in triglyceride, phospholipid, and cholesterol transport in and out of cells[44]. It facilitates cholesterol removal from the plasma and cerebrospinal fluid[43,45]. In the peripheral nervous system, it has been shown to help in the mobilization and redistribution of cholesterol in repair, growth, and maintenance of myelin and neuronal membranes during development and injury[44,46].

There are the three common isoforms or alleles of human apoE gene namely epsilon 2, epsilon 3, and epsilon 4[46,47]. Epsilon 4 is associated with larger, less dense lipoproteins more so than epsilon 3, and is therefore associated with total cholesterol levels[48]. ApoE epsilon 4 allele is associated with familial and late-onset sporadic AD[43,45,49]. This gene is located on chromosome 19[45,47,48]. AD patients with the epsilon 4 allele were found to have an increased formation of senile plaques compared to AD patients without the e4 allele[50]. The association of apoE epsilon 4 allele and AD holds true for both sexes, but there are reports that suggests a higher frequency of epsilon 4 alleles in women compared to men[51]. The higher susceptibility of women could be due to independent factors such as estrogen[43,52]. ApoE expression is influenced by estrogen and estrogen therapy may not benefit women bearing an apoE epsilon4 allele. An allele dependent modulation of estrogen induced regulation of apoE might be involved in the increased risk for AD in women bearing an epsilon4 allele[53].

Inheritance of the infrequent ApoE epsilon 2 allele appears to confer a decreased risk of developing AD compared to that seen in humans harboring the common epsilon 3 allele[54]. The molecular mechanisms by which the ApoE epsilon 4 protein (which lacks cysteines and therefore cannot undergo intramolecular or intermolecular disulfide cross-linking) increases the likelihood of AD, whereas ApoE3 and ApoE2 proteins (which contain cysteines) do not, remains unclear. Patients of AD with two epsilon 4 alleles have a significantly higher number and density of Aβ deposits in their cerebral cortex than subjects with no epsilon 4 alleles, whereas subjects with one epsilon 4 allele tend to fall in between[55,56]. ApoE epsilon 4 allele was associated with a four fold increase in the risk of disease, and transferrin C2 allele was significantly associated with

AD only in epsilon 4 negative subjects[57]. ApoE also plays an important role in the proper function of the cholinergic system, which relies heavily on the availability of lipids to synthesize acetylcholine, in the neurons[43]. Acetylcholine production is significantly reduced among AD patients carrying the epsilon 4 allele[43,58].

MISCELLANEOUS GENES

Clinical and immunopathological evidence suggest that production of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), is increased in the brains of people with AD[59]. Moreover, association studies suggest a possible involvement of cytokine-related genes in the susceptibility to sporadic AD. There is a significant involvement of interleukin-1 alpha, interleukin-6 and interleukin-10 genes in susceptibility to AD[60-62]. TNF-alpha gene polymorphisms have been reported to be associated with AD in Caucasian populations. No interaction effect of apoE and TNF-α genotypes was found, but both acted as important risk factors for AD[63]. There is association of a cystatin C gene polymorphism with late-onset AD[64]. Neprilysin gene is associated with susceptibility to late-onset AD[65]. A polymorphism in the angiotensin 1-converting enzyme gene is associated with damage to cerebral white matter in AD[66]. β-site APP-cleaving enzyme 1 (BACE1) is the major beta-secretase to cleave the beta-amyloid precursor protein to generate beta-amyloid. Oxidative stress has been shown to affect Aβ generation in the AD pathogenesis. Up-regulation of BACE 1 gene transcription by oxidative stress may contribute to the pathogenesis of AD[67]. Cathepsin D gene contributes to familial AD[68]. Variations in two single-nucleotide polymorphisms within the brain-derived neurotrophic factor gene have been associated with AD[69].

CONCLUSION

There are four principal genes involved in the development of AD and linkage analysis of other families makes it clear that additional genetic risk factors are involved. Three of the known genes – APP on chromosome 21, presenilin 1 on chromosome 14, and presenilin 2 on chromosome 1 can be said to be causative agents of early-onset AD in the respective families in which mutations in these genes occur. In each of these three cases, there is a strong evidence that the mechanism involves altered APP catabolism to generate increased amounts of Aβ peptides, particularly the highly amyloidogenic 42 residue form. In case of the ApoE gene present on chromosome 19, its epsilon 4 allele is a major genetic risk for the development of late-onset AD, and inheritance of this is consistently associated with excessive cerebral deposition of Aβ40.

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