

ARTICLES

GENETIC MARKERS FOR ALZHEIMER'S DISEASE

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ABSTRACT

This report aims to inform on the progression of research into the genetic factors involved in the development of Alzheimer's disease (AD). AD is a life-altering disease that affects millions of individuals from varying races and ethnic backgrounds¹. According to the National Institute on Aging, a faculty of the U.S. Department of Health and Human Services, AD has been ranked as the third leading cause of death in the United States, only behind cancer and heart failure. It is predicted that by 2050, approximately one in 45 Americans will be afflicted with the disease⁵.

Distinctive physical indications of the onset of AD include neuron loss, amyloid plaques and neurofibrillary tangles⁵. Onset is not frequent prior to 60 years of age but can be caused by one of two reasons. The first is a mutation in the amyloid precursor protein (APP) gene on chromosome 21. This gene is responsible for the regulation of the production of amyloid beta (A β) proteins, which are known to be abundant in the brains of AD patients. A mutation in the gene leads to an inappropriate regulation of this protein. The second, and more common cause is a result of an unidentified gene on chromosome 14 in AD patients². It has been confirmed that there is involvement of chromosome 19 in late onset AD (LOAD) as well¹. Most of the genes that are associated with the development of AD have yet to be identified, but the research is bringing society closer and closer to that goal everyday.

Ce rapport vise à fournir de l'information sur la progression de la recherche au sujet des facteurs génétiques impliqués dans le développement de la maladie d'Alzheimer (MA). La MA est une maladie bouleversant la vie de la personne et qui affecte des millions d'individus de diverses races et ethnicité¹. Selon l'Institut national sur le vieillissement, un corps professoral du département américain de la santé et des services sociaux, la MA a été classée comme la troisième cause de décès aux États-Unis, ne cédant le pas qu'au cancer et à l'insuffisance cardiaque. Il est prévu que d'ici l'an 2050, environ une personne sur 45 Américains sera affligée avec cette maladie⁵.

Des indications visuelles distinctives de l'apparition de la MA comprennent la perte des neurones, les plaques amyloïdes et des enchevêtrements neurofibrillaire⁵. L'apparition précoce n'est pas fréquente avant 60 ans, mais peut être causée par l'une des deux raisons. La première raison est une mutation dans le gène de la protéine précurseur de l'amyloïde (PPA) sur le chromosome 21. Ce gène est responsable de la régulation de la production de protéines bêta-amyloïde (A β), qui sont connues pour être abondant dans le cerveau des patients atteints de la MA. Une mutation dans le gène conduit à une régulation inappropriée de cette protéine. La seconde cause, et celle-là plus communes sont le résultat d'un gène inconnu sur le chromosome 14. Il a été confirmé qu'il y a aussi une participation du chromosome 19 dans l'apparition tardive de la MA (ATMA)¹. La plupart des gènes qui sont associés avec le développement de la MA n'ont pas encore été identifiés, mais la recherche rapproche la société de cet objectif de plus en plus tous les jours.

INTRODUCTION

Article 1: Gene Dose of Apolipoprotein E Type 4 Allele and the Risk of Alzheimer's disease in Late Onset Families¹

In a seminal paper in the field of AD genetics, Corder et al.¹, aimed to show that the APOE4 gene expression is related to an elevated risk as well as an earlier onset period of AD. The late onset variation of AD has been associated with the APOE4 allele on chromosome 19¹. The first aspect of this study aimed

to determine whether or not the aforementioned allele was in fact responsible for early onset AD. This was found to be the case.¹ Approximately 64% of AD late onset cases have at least one APOE4 allele.¹

The researchers subsequently studied the presence of this allele, and how expression affected the age of onset. It was found that each additional APOE4 allele constituted a younger onset age. From no APOE4 allele to only one, the drop in age was far

the drop in age was far more drastic than that of the difference between subjects with one APOE4 allele and two.

The allelic association found can be attributed to genetic linkage disequilibrium; two loci (chromosome locations) are situated close enough to each other that recombination is rare¹. As a result, these alleles can be passed through many generations in their original orientation.¹ It was reported that there is a genetic linkage between late onset AD and the loci residing near APOE.¹ It is important to recognize that while the presence and dosage of the APOE4 allele plays a role in determining age of onset for AD patients, it is not the determining factor for whether a person will develop the disease or not.

Article 2: Integrative Genomics Identifies APOE4 Effectors in AD²

The study by Rhinn et al.², written a decade after the Corder et al.¹ study describes in more detail the procedures used to determine that the APOE4 allele is associated with LOAD. In order to determine the pathways that result in LOAD in an unbiased fashion, differential co-expression analysis (DCA) was used. This method aims to differentiate between causative events (i.e. the events that cause the LOAD) and secondary changes, which are in fact a result of the causative events but appear to be the causative events. DCA can be used to identify regulatory mechanisms that affect LOAD and those that affect LOAD risk². Through this method, two key points were determined. The first was the identification of APBA2, ITM2B, FYN, RNF219, and SV2A as genes, that mediate the transcriptomic changes observed in APOE4 carriers as well as LOAD patients. Secondly, genome-wide association study (GWAS) data showed that common genetic variants within two of the mentioned genes, FYN and RNF219, are associated with LOAD. In order to determine whether the DCA node genes (above) function as regulators of amyloid precursor protein (APP), mouse neuroblastoma cells with human APP transgene were injected with APOE protein variants. Treatments with human APOE4 (not APOE2 or APOE3) increased the levels of A β plaque present, build-up of which predicts AD.

Next, this study hypothesized that a SV2A inhibitor called levetiracetam (used to treat seizure

disorders) could also be used to correct APOE4 related alteration in APP processing. It was found that levetiracetam drastically decreased excess A β levels. This determined that SV2a is necessary for the APOE4-facilitated induction of APP processing. Since it was determined that DCA genes function as regulators for APP, it is sound to suggest that variants at these gene loci may control the association of APOE4 with LOAD (i.e. risk or age-of-onset)².

In conclusion, it was established that APOE4 is linked to heightened A β brain accumulation, which in turn results in accelerated cognitive deterioration. However, since not all APOE4 carriers develop LOAD, it is apparent that there are other factors involved in its development. Additionally, levetiracetam was demonstrated to rekindle cognition in individuals with mild cognitive deficiency². When tested in mice however, in the absence of human APOE4, the levetiracetam did not affect APP processing.

Article 3: Cardiovascular disease contributes to AD: Evidence from large-scale Genome-Wide Association Studies³

In previous reports, AD risk pathways were investigated by analyzing individual GWAS datasets in isolation. In this study, Liu et al. propose that multiple GWAS be investigated simultaneously in order to identify new AD risk pathways.

In the analysis, Liu et al.³ replicated previous GWAS findings, including AD risk genes such as TOMM40, PVRL2, APOE, CLU, CR1, PICALM, MS4A6A, MS4A2, ABCA7, and EXOC3L2. Furthermore, novel AD susceptibility genes were identified with the most significant belonging to the APOE family of genes. The latter was to be expected since as discussed in the previous articles, the APOE gene has been found to be the most prevalent risk factor for LOAD. Previous studies have shown that there is an involvement of pathways related to metabolism, the immune system, signaling molecules and interaction, and neurodegenerative diseases in AD risk. There are four significant pathways linked to cardiovascular disease (CVD), three of which are also linked to AD. Although not certain, this study suggests that the associations between CVD and AD pathways are related to shared genetic factors.

Article 4: Meta-Analysis of 74,046 Individuals Identifies 11 new Susceptibility Loci for AD⁴

Lambert et al.⁴ describe the largest meta-analysis (combining datasets from previous GWAS) that currently exists of genetic factors associated with AD risk. The authors successfully determined 11 new possible loci that play a role in AD risk. Previously, there were nine identified loci associated with late-onset AD. The search for additional loci however, requires a larger sample size in order for meta-analyses to be conducted with apt statistical power.

In this study, the first stage of meta-analysis was completed using four conglomerates, with quality control being conducted for the genetic variants. Those that did not pass the control were excluded from the analysis.

As aforementioned, the APOE locus is a critical region in predicted LOAD. In addition to this locus, 14 other regions had significant associations. Nine of these were previously identified as susceptibility factors, but five are representative of newly discovered associated loci. An example is SORLI. Of these newly associated loci, it is apparent that these may or may not be causative genes. In addition to the already identified genes, the most significant new association is the HLA-DRB5-DRB1 region. Interestingly, this is a region commonly associated with two other neurodegenerative disorders; multiple sclerosis and Parkinson's disease. The study was inconclusive on which gene(s) were responsible for the signal from this region. The second strongest signal was associated with the SORLI gene, a critical region related to an increased risk of autosomal dominant and sporadic forms of AD⁴. The third and fourth most significant loci identified are PTK2B and SLC25A4, respectively. The latter of the two is commonly involved in iris, hair, and skin colour variation in humans as well as neural development. Another significant locus that was identified was near MEF2C. Mutations here commonly result in severe mental deficiency, epilepsy, and cerebral malformation.

This study is a clear example of the ever-developing research behind AD-oriented genetics. The fact that through this one study 11 additional potential loci associated with the development of AD have been

identified exemplifies the accelerating world of research, and moves us closer and closer towards understanding the genetic factors contributing to AD risk.

CONCLUSION

As humans, we strive to have a clear understanding of everything we encounter. We are passionately curious by nature – an excellent quality since it has enabled our lives to advance farther than any other species. Our lives consist of a string of experiences, which aid us in living the remainder of our lives. The past guides the present. What happens, though, when there is no past? What happens when there is no recollection of what you ate for dinner yesterday, or what you had for breakfast this morning? Life is no longer simple at that point. This uncertainty is the reality of individuals living with AD. The key to making the lives of those afflicted easier, is understanding what lies beneath the symptoms. This knowledge comes from ongoing research.

This paper outlined four independently completed research papers, each assessing various loci that are potentially responsible for the development of AD. Conclusively, it is apparent that the single most important region identified is APOE41-4. The mutation at this location is present in all patients with LOAD. However, it is also known that not all individuals who have a mutation within this locus develop AD. This incomplete penetrance is indicative of the fact that there is more than one cause for this disease. As of 2013, at least 25 critical loci have been identified that contribute to AD risk. By identifying the genetic origins of the disease, prevention can become a reality. The medical world is developing into one of preventative medicine rather than curative. This transition is only possible if we have a clear understanding of what it is we are trying to prevent, and how to specifically go about it. The aforementioned research projects, and the likes of them, move us closer to our goal of being able to detect and prevent AD.

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