Austin Aging Research

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Editorial

The Inheritance of a Normal Apo E Allele, Apo E3 or Apo E2 May Contribute to Diminished Incidence of Alzheimer's Disease Related Dementia and to Longevity

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Received: March 09, 2016; **Accepted:** March 22, 2017; **Published:** March 30, 2017

Abstract

Background: A major proportion of dementia results from Alzheimer's Disease (AD). The highest risk factor for AD is aging. In addition, there are other risk factors such as being a female, head trauma injury and Apo E4 allele. Apo E4 can increase the risk by 3-4 fold based on whether it is 1 copy or both copies. With 35 million Americans in the age group of 55-75 and 20% of them likely to be positive for the Apo E4 allele, a very significant number are progressing to AD. Several Americans who have had head trauma injury and have the Apo E4 allele are likely to have a worst case scenario upon reaching the age range of 55-70. FDA approved treatment becomes ineffective at later stages of AD and marginally effective at preventing progression from early stages. The recent failure of clinical trials for new AD treatment, conducted by giant pharmaceutical companies Merck and Lily brings the need for innovative ideas to the forefront with an urgency of now. The astronomical cost expected to rise in caring for AD approaching and the baby boomers likely to increase the incidence of AD, a recommendation due to ample rationale for screening for the Apo E allele is made here and the approach to determining the Apo E allele in an individual is discussed.

Approach: The affordable cost of determining Single Nucleotide Polymorphism (SNPs) in several genes that can predict predisposition to diseases has become possible due to 23 and Me. The Apo E gene SNP can be valuable to determine persons with the Apo E4 alelle can lead to identifying candidates for early interventions against AD. If Apo E4 is found then a 6 step standardized procedure developed for human DNA isolation and sequencing to determine the inheritance of Apo E allele status can be carried out to confirm the presence of Apo E4. Results from a study of a 97 year old father and his 61 year old son by both the 23 and me and standardized procedure were identical for the pair with Apo E3 allele, indicating that the ease of knowing the Apo E status has significantly improved.

Conclusion: The longer living individual with no dementia or memory loss had a normal Apo E allele. Those who do not have the Apo E4 have the relief of knowing they are at a significantly lower risk of developing AD and dementia resulting from it. Those who are found to have the Apo E4 allele have the option to adopt intervention strategies of slowing the progression of AD.

Introduction

According to the Alzheimer's Association 2016 Alzheimer's Disease (AD) facts and figures, more than 5 million Americans are living with AD. One in every 3 seniors die due to AD and AD is the 6th leading cause of death in the USA. Of the 5.4 million Americans with AD, an estimated 5.2 million people are age 65 and older, and approximately 200,000 individuals are under age 65 (early onset AD). One in nine people age 65 and older has AD. It has been very well established that head trauma injury and individuals with Apo E4 allele have a 3 fold higher probability of progressing to AD [1-4]. Besides Apo E4, family history of AD due other genetic predisposition to AD is well known and associated with extracellular deposition of amyloid protein [5,6]. The amyloid protein (Abeta1-42) and plaques in the brain and cerebral vasculature of AD patients is the hallmark of AD [7]. There is a strong association between the Apo E4 allele with greater complement activation and a higher risk for AD [8,9]. There is also evidence that in aging brains in non-Apo E4 brains too there is increased complement activation [10], underscoring the key role complement plays in AD pathogenesis.

The use of a complement inhibitor could therefore benefit persons with Apo E4 allele and the aging population in general [11]. Several drugs currently in the pipeline target the neurodegenerative effects of beta-amyloid accumulation [12]; however, most of these drugs have either proven ineffective in trials or have other significant problems. Thus, despite the hundreds of millions dollars spent by large pharmaceutical companies on clinical trials and on acquiring the R&D pipelines of small biotech companies with promising products, physicians and sections of the pharmaceutical and biotech

Citation: Kotwal GJ. The Inheritance of a Normal Apo E Allele, Apo E3 or Apo E2 May Contribute to Diminished Incidence of Alzheimer's Disease Related Dementia and to Longevity. Austin Aging Res. 2017; 1(1): 1003.

industry still await the discovery of new and more effective options to prevent or slow the progression of AD.

Information drawn from the fields of molecular biology, genetics, and histopathology paints a highly complex picture of the pathological features associated with AD [7,13-15]. Amyloid protein expression and plaque deposition are associated with activation of several pro-inflammatory mediators, especially complement components [11]. These pro-inflammatory mediators cause damage on their own, and also work in synergy with each other, ultimately leading to neurodegeneration. Over time, as the disease progresses, the damaging effects of complement components overpower their beneficial effects [16]. One might wonder if complement pathways, as distinct from other pro-inflammatory pathways, might be novel targets for blocking the progression of AD.

The affordable cost of determining small nuclear polymorphism in the Apo E gene a universal screening of all persons with the Apo E4 alelle can lead to identifying candidates for early interventions such as reduction of excess weight, triglycerides, cholesterol, sugar and carbohydrate intake, through physical and mental exercises and proper nutrition. Diet rich in antioxidants, flavanoids, polyphenols, vitamins, omega fatty acids, higher proportion of polyunsaturated fats having proven neuroprotective benefits could contribute to slowing the progression of AD [8]. An additional early intervention that has shown promise in very recent preclinical studies by our group in transgenic mice with human AD implicated genes, amyloid precursor protein and presenilin is the modulation of complement mediated CNS inflammation by vaccinia virus complement control protein. A combination of such multiple choices along with approved drugs for early stage AD treatment can provide a potential to prevent the onset of AD to a later stage accompanied by an improved quality of life. The current understanding of Apo E genotyping is that you are looking for either cysteine or arginine at positions 112 and 158, which correspond to SNP positions rs429358 and rs7412, respectively. . If the DNA being tested is homozygous T/T at position rs429358 and homozygous C/C at rs7412 it encodes for Cys at 112 and Arg at 158, then it is homozygous for the E3 allele. E3 allele is considered normal and not predisposed to AD.

Approach to Determining Apo E Allele Status

In order to obtain the Apo E status, one could send a saliva sample to a company called 23andMe and the results that would be obtained would provide information of about 100 different genes that who have different alternative forms called alleles and the read out will indicate the possibility of acquiring AD in comparison to the normal possibility. Alternatively, the following steps are recommended to determine the Apo E status.

DNA Isolation Using Oragene® Self-Collection Kit Was Performed According to the Protocol Provided By the Dnagenotek

"Laboratory protocol for manual purification of DNA from whole sample". Document PD-PR-015, Issue 10. DNA Genotek Inc. 2015.

http://www.dnagenotek.com/ROW/pdf/PD-PR-015.pdf

There are products from other companies that could provide the same quality of DNA.

SNP sequencing from SeqWright (http://www.seqwright.com)

Description of Services Assay development and validation with many pre-validated genes already available. PCR amplification is carried out using the primers shown below and an amplicon product of the size of 243bp is purified. Bi-directional DNA sequencing on ABI 3730xl DNA sequencers.

Primer	Sequence	Amplicon
S1203863.KBC-CP3	TAAGCTTGGCACG GCTGTCCAAGGA	243bp
S1203863.KBC-CP4	A C A G A A T T C G C C C C G G C C T G G T A CACTGCCA	

The sequence of the Amplicon is as follows

T A A G C T T G G C A C G G C T G T C C A A G G A G C T G C AGGCGGCGCAGGCCCGGCTG

GGCGCGGACATGGAGGACGTGTGCGGCCGCCTGGTG CAGTACCGCGGCGA

GGTGCAGGCCATGCTCGGCCAGAGCACCGAGGAGCTG CGGGTGCGCCTCG

C C T C C C A C C T G C G C A A G C T G C G T A A G C G G C T C CTCCGCG ATGCCGATGAC

CTGCAGAAGCGCCTGGCAGTGTACCAGGCCGGGG CGAATTCTGT

Mutation profiling & sequence variation reporting

An email as follows is received from SeqWright along with the data; I have attached the sequencing results for S1203863.KBC. I have included the raw chromatograms, an alignment of the sequencing reads for each sample with the reference PCR amplicon, a consensus for each sample, and a genotype report in Excel format. The current understanding of Apo E genotyping is that you are looking for either cysteine or arginine at positions 112 and 158, which correspond to SNP positions rs429358 and rs7412, respectively. All three samples for this project were identical. They are all homozygous T/T at position rs429358 and homozygous C/C at rs7412. This encodes for Cys at 112 and Arg at 158, so the samples are all homozygous for the E3 allele.

Potential Benefit of Knowing Apo E Status

Saliva to DNA sequence of the Apo E allele in an individual is now possible using the commercially available protocols from any Human DNA isolation kits. Some lab. Work in order to perform the DNA isolation and to quantitate the DNA and check the quality followed by obtaining the PCR product of the exon corresponding to the Apo E and then sequencing and alignment of sequences. If the sequence reveals an Apo E4 allele; it is not the end of the world. It just means the outlook to life has to change to ensure preparedness to possibly living a life with diminishing short term and long term memory. There are also possible ways to slow the progress of AD and the accompanying memory loss, diminished cognition, vascular dementia, mitochondrial dysfunction, anxiety etc. One of the ways to slow the progression is by maintaining a healthy lifestyle with striving to have normal lipid profile [6], blood pressure ideally below 130/80, body mass index and glucose profiles within normal levels through high fiber low fat no sugar diet and maximum physical activity. Specifically balanced nutrition through consumption of a variety of

vegetables, herbs and spices during breakfast, lunch and dinner along with protein rich foods and mineral and vitamin supplementation

Concluding Remarks

Whenever the topic of getting Apo E allele being tested has been discussed by the author, with participants of conferences in which this approach for testing the Apo E allele status has been presented, listeners are skeptical about getting tested for Apo E, and for good reason. Discovering that one has the Apo E4 allele, but then having no recourse to deal with the impending possibility of progression to AD is beyond frightening, especially as the development of suitable neuroprotective agents for the treatment of AD is still far from reality and ongong recent trials have failed. There are new concepts being explored such as the blocking of complement mediated inflammation in central nervous system diseases [11,17-27].

Acknowledgement

Parts of this work were published as abstract of talks presented at The International Conference on developmental translation and Clinical Pharmacogenomics held at the Patel Center for global solutions, University of Florida, Tampa, USA in September 2011, Apo E, Apo E Receptors & Neurodegeneration Symposium in Lexington, KY, USA, June 2014, The second International conference on Geriatrics and Gerontology in Toronto, Canada August 2015, The 13th International Congress of Human Genetics, Kytoto, Japan, April 2016 and BITs 4th International Congress of Geriatrics and Gerontology, Kaoshiung, Taiwan, 2016.

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