

Genetics and Molecular Biology of Alzheimer's Disease

Who will benefit from this information?

This talk will benefit scientists and clinicians who want to inform their approaches to imaging and diagnosis of Alzheimer's disease with the latest knowledge about the genetic and molecular mechanisms of disease risk.

How was a problem determined?

Alzheimer's disease is the most common form of dementia and is the only one of the top 10 causes of death in the USA lacking treatments that alter disease progression. It is a complex disease characterized by gradual onset and progression of memory loss combined with deficits in executive functioning, language, visuo-spatial abilities, personality, behavior and self-care. Alzheimer's disease can be divided into familial and late-onset. Familial Alzheimer's disease, which is the rare form of the disease, is characterized by autosomal dominant inheritance and usually has an early onset (<60years). Late-onset Alzheimer's disease is characterized by later onset (>60yrs) and complex patterns of inheritance. Both subtypes are defined by the same pathological features: neuronal loss and the presence of amyloid beta (A β) plaques and neurofibrillary tangles. It has been suggested that the aggregation of A β into insoluble plaques and the hyperphosphorylation and aggregation of tau into neurofibrillary tangles in the brain are central features of Alzheimer's disease (Hardy and Selkoe 2002). There is a clear genetic basis for Alzheimer's disease, with heritability estimated at 60-80% (Raiha, Kaprio et al. 1996; Gatz, Pedersen et al. 1997). Understanding the genetic basis of disease will provide important insights into disease pathology and potential diagnostic and therapeutic approaches.

Examples of how this issue has been addressed:

There has been considerable success in the identification of common alleles with small effects on risk for Alzheimer's disease using genome-wide association studies. In the past few years, variants in BIN1, CLU, ABCA7, CR1, PICALM, MS4A6A, CD33, MS4A4E and CD2AP have been shown to be associated with AD risk (Coon, Myers et al. 2007; Bertram, Lange et al. 2008; Li, Wetten et al. 2008; Beecham, Martin et al. 2009; Carrasquillo, Zou et al. 2009; Feulner, Laws et al. 2009; Harold, Abraham et al. 2009; Lambert, Heath et al. 2009; Jun, Naj et al. 2010; Seshadri, Fitzpatrick et al. 2010; Hollingworth, Harold et al. 2011; Naj, Jun et al. 2011). In addition, recent work using whole genome and whole exome datasets has identified rare variants with large protective (Jonsson, Atwal et al. 2012) and risk (Guerreiro, Wojtas et al. 2012; Jonsson, Stefansson et al. 2012) effects on Alzheimer's disease in *APP* and *TREM2*, respectively. These findings provide important insights into genes and biological pathways that alter risk for Alzheimer's disease.

What will learners be able to do differently because of this information?

Learners can use this information about the current knowledge of the genetic causes of Alzheimer's disease to inform their selection of imaging and other phenotypes for diagnosis and monitoring of Alzheimer's disease patients.

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