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Genetics and dementia: Risk factors, diagnosis, and management

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Abstract New developments in molecular genetics have improved our understanding on a number of neurodegenerative dementias considerably, especially Alzheimer's disease and frontotemporal dementia. However, this explosion of information can be overwhelming to clinicians, making it difficult to integrate into regular clinical practice. In this article, we briefly reviewed our current understanding regarding causative genetic mutations and genetic risk factors on the major forms of dementia, which provided the background information for discussion in the Third Canadian Consensus Conference on the Diagnosis and Treatment of Dementia. The principles of genetic counselling were applied. Guidelines and recommendations on the application of genetics in the assessment, diagnosis, and management of patients and families with dementia were summarized.

Keywords: Genetic counselling; Alzheimer's disease; Frontotemporal dementia; *APOE*; *PSEN1*; *PSEN2*; *MAPT*; *PGRN*

1. Background

Advances in genetics, especially with completion of the human genome project, have improved our understanding of the pathogenesis of many diseases, including Alzheimer's disease (AD) and other types of dementia [1–4]. With the increase in public awareness, dementia patients and family members as well as the general public now often request genetic testing as part of their assessment of risk of dementia, even in the absence of treatments known to slow or prevent disease progression [5–7]. It is thus expected that these requests will increase over time when such treatments become realities. The clinician must understand the role of genetic risk factors to provide accurate information to their patients and to refer them to genetics clinics when appropriate. Canadian sites can be found at http://ccmg.medical.org/clinical.html (accessed March 3, 2006). Here we review the current literature on the genetic risk factors for dementia, summarize the current knowledge, and provide evidence-based recommendations to clinicians.

2. Methods

We initially retrieved 1721 articles by a PubMed search on genetic risk factors for AD and other dementias from January 1996 up to and including December 2005. Relevant articles before 1996 have been summarized elsewhere in meta-analyses and reviews [8,9]. We further conducted a review of all the genes listed in the ALZGENE website (accessed February 14, 2006) [10] and articles from bibliographies of selected studies. Authors' files were also scanned. For genetic association studies, we only considered those with large sample sizes (>300 cases and >300 controls), with well-defined clinical diagnostic criteria and with findings consistently replicated in four or more independent samples. Because we came to the conclusion that *APOE* is the only genetic risk factor that has been consistently replicated to date, we further examined studies on *APOE* and its interaction with other risk factors in relation to AD. We also looked at single gene mutations studies, because within specific families they are known to be causal and thus represent risk factors for unaffected biologic relatives of demented individuals carrying the specific mutation.

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Table 1
Genes confirmed to be associated with dementia mentioned in this article

Disease	Chromosome	Gene	Penetrance	Frequency of Mutation in Families	Mutation	Pathology
EOAD	21q21	*APP*	Full penetrance	About 18% of familial early-onset AD	Missense mutations around Aβ portion of APP	Increases $A\beta_{42}$ production from APP processing
EOAD	14q24.3	*PSEN1*	Full penetrance	Represent up to 78% of familial early-onset AD	Mostly missense mutations	Promotes cleavage at γ-secretase site and increases Aβ production and accumulation
EOAD	1q31.42	*PSEN2*	Incomplete penetrance	Rare, ~4% of familial early-onset AD	Missense mutations	Promotes cleavage at β-secretase site leading to increased Aβ production and accumulation
CADASIL	19p13	*NOTCH3*	Full penetrance	400 families described worldwide, but probably under-recognized	95% are missense mutations	Functional consequences of mutation still unclear; probably affects protein conformation of Notch3 product
FTDP-17	17	*MAPT*	Full penetrance	10% to 30% of familial FTD, 5% of all FTD	Missense and splice site mutations	Increase ratio of 4-repeat tau to 3-repeat tau
FTLD-U	17	*PGRN*	High penetrance	23% of familial FTD, 5% of all FTD	Missense, splice site, and promoter region mutations	Leads to null mutations with haploinsufficiency
Disease	Chromosome	Gene	Penetrance	Allele frequency in population	Mutation	Pathology
LOAD	19q13.2	*APOE*	Risk factor, but neither necessary nor sufficient to cause disease	e2, ~10%, e3, ~75%, e4, ~15%	e4 genotype, heterozygous increases odds by ~3 and homozygous by ~9	Acts as a molecular chaperone to promote Aβ accumulation and senile plaque formation

Abbreviations: EOAD, early-onset AD; LOAD, late-onset AD; FTDP-17, FTD with parkinsonism linked to chromosome 17.

3. Results

3.1. Causative mutations for dementia

3.1.1. Alzheimer's disease

Through linkage analysis of affected pedigrees (positional cloning), mutations in three genes have been found to cause early-onset familial AD (Table 1) [1,11]. The first gene identified was the amyloid precursor protein gene (*APP*) on chromosome 21 [12–16]. Although the physiologic function of the amyloid precursor protein (APP) remains unclear, the post-translational processing of APP is clearly involved in the pathogenesis of AD [17,18]. APP is a membrane bound protein that can undergo a series of endoproteolytic cleavages by enzymes known as secretases. When cleaved by α-secretase in the middle of the Aβ domain within APP, a soluble fragment of the protein is released, and there is no accumulation of the peptide; whereas when it is cleaved at the β and γ sites, the Aβ peptide is released, which can undergo further conformational change into an insoluble form that aggregates in senile plaques [19–21]. *APP* mutations that are causal for early-onset familial AD all promote cleavage at the β or γ sites, leading to an overproduction of the Aβ peptide[20]. Two other genes with mutations that cause early-onset familial AD are presenilin 1 (*PSEN1*) and presenilin 2 (*PSEN2*), which are located on chromosomes 14 and 1, respectively [22,23]. Current evidence suggests that both *PSEN1* and *PSEN2* play an important role in the γ-secretase complex, and mutations in these genes lead to an excessive cleavage at the γ site leading to excessive production and accumulation of Aβ [17,19]. Taken together, the three causal genes identified to date for AD provide strong support for the amyloid cascade hypothesis, in which the accumulation of Aβ peptide into senile neuritic plaques is central to the pathogenesis of AD.

To date, although well-documented families exist in