

10<sup>th</sup> World Congress on

# ALZHEIMER'S DISEASE & DEMENTIA

May 30-31, 2018 Osaka, Japan

## Genetics and epidemiological studies of dementia of alzheimer's type among Arab populations

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**Objective:** To study the genetic and environmental risk factors and the prevalence of Dementia of the Alzheimer Type (DAT) among the elderly in an Arab community in Israel.

**Material & Method:** Epidemiological and genetic studies of dementia have rarely been reported in an Arab population. Alzheimer disease (AD [MIM #104300]) is a progressive, neurodegenerative disease characterized clinically by gradual loss of memory and pathologically by neurofibrillary tangles and amyloid plaques in the brain. We have observed an unusually high prevalence of dementia of the Alzheimer type in Wadi Ara, an inbred Arab community in northern Israel comprising <850 persons over the age of 60 years. Apolipoprotein E (APOE-  $\epsilon$ 4), has been established as a strong susceptibility marker that accounts for nearly 30% of the risk in late-onset AD.

**Result:** Remarkably, in our study DAT is not associated with APOE, because the frequency of the  $\epsilon$ 4 allele is very low in both nondemented (2.4%) and demented elders (3.6%). We also map chromosomal loci contributing to DAT susceptibility; we conducted a 10 cM scan in a series of twenty cases and twenty controls selected from one hamula. Markers from 18 chromosomal regions showed significant allelic association with DAT ( $P < 0.05$ ). Locations on chromosomes 2, 9 and 10 remained significant after testing additional affected and non-demented individuals. Significant associations were also observed for markers on chromosome 12 which overlap with a locus implicated in previous genome scans. Additionally, several lines of evidence support for a role of angiotensin converting enzyme (ACE) in Alzheimer Disease (AD). Most genetic studies have focused on an Alu insertion/deletion (I/D) polymorphism in the ACE gene (DCP1) and have yielded conflicting results. We evaluated the association between 15 (SNPs) in DCP1, including the I/D variant and AD in a sample of 92 patients with AD and 166 non-demented controls from an inbred Israeli Arab community. Although there was no evidence for association between AD and I/D, we observed significant association with SNPs rs4343 ( $P = 0.00001$ ) and rs4351 ( $P = 0.01$ ).

**Conclusion:** In Wadi Ara, the high prevalence may be due to a founder effect enhanced by consanguinity which make this population attractive for investigating DAT susceptibility recessive genes. Thus, a specific disease susceptibility allele may be overrepresented in cognitively impaired subjects compared with cognitively healthy residents. Other two main conclusions can be drawn from the genome-wide linkage and Linkage Disequilibrium (LD) studies. Firstly, multiple genes are involved in DAT. Secondly, there is a high level of consistency among linkage and association studies regarding the general location of putative AD genes. However, the general location of putative AD genes on a given chromosome covers a broad region which may contain several genes.

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