Journal of
Alzheimer's Disease & Parkinsonism

Block et al., J Alzheimers Dis Parkinsonism 2014, 4:2
DOI: 10.4172/2161-0460.1000138

Research Article Open Access

Abnormal Protein Profiles in Hippocampus of Mouse Models of Down Syndrome: Similarities with Alzheimer's Disease

Aaron Block[1], A. Ranjitha Dhanasekaran[1], Md. Mahiuddin Ahmed[1] and Katheleen J Gardiner[1,2]*

[1]*Department of Pediatrics, Linda Crnic Institute for Down Syndrome, University of Colorado Denver, Colorado, USA*
[2]*Department of Biochemistry and Molecular Genetics, Human Medical Genetics and Genomics, and Neuroscience Programs, University of Colorado Denver, Colorado, USA*

Abstract

Down syndrome (DS) is caused by an extra copy of the long arm of human chromosome 21 (HSA21) and the increased expression, due to dosage, of HSA21 encoded genes. In addition to intellectual disability, all individuals with DS develop the neuropathology of Alzheimer's Disease (AD) by age 30-40. The amyloid precursor protein gene, APP, that is mutated or duplicated in some familial AD (FAD), is encoded by HSA21, over expressed in DS, and a candidate for causing AD in DS. However, only half of those with DS will develop the AD-like dementia by age 50-60, suggesting that additional HSA21 genes may modulate the effects of APP triplication, and/or protect the DS brain from early onset progression to dementia in spite of neuropathology. In sporadic AD and mouse models of FAD, abnormal levels of a diverse set of proteins, including receptors, scaffold proteins, kinases, phosphatases and cytokines, have been documented, but nothing is known about their possible roles in AD in DS. Here, we compare expression of 26 AD-related proteins in hippocampus of four mouse models of DS, the Ts65Dn, Tc1, Dp (10)1Yey and Dp (17)1Yey, that together provided trisomy of partially overlapping subsets of all HSA21 genes or mouse orthologs. In the Dp(10)1Yey, that is trisomic for HSA21 orthologs mapping to mouse chromosome 10, twelve of 26 AD-related proteins were elevated, while in the Tc1, Dp(17)1Yey and the popular Ts65Dn, six, four and two differed from littermate controls. These data suggest that genes mapping to the HSA21 orthologous regions of mouse chromosomes 10 and 17 contribute to protein perturbations in the DS brain, and possibly AD in DS. Considering the different phenotypic features of the four DS mouse models further suggests that some protein abnormalities may be compensatory and protective for brain function and/or that learning and memory deficits may be age-dependent.

Keywords: Alzheimer's disease; Down syndrome; Trisomy; Age-dependent deficits; Mouse chromosome 10

Introduction

Familial Alzheimer's Disease (FAD) is rare, accounting for fewer than 5% of all cases of AD, and is characterized by early onset, at <60 years of age. Mutations causing FAD have been identified in three genes, the amyloid precursor protein, APP, and the presenilin genes 1 and 2, PSEN1 and PSEN2 [1,2]. Duplications of the genomic region containing the APP gene have also been identified in FAD [3,4]. Sporadic AD (sAD) typically has a later age of onset and is common, estimated to affect as many as 45% of people by the age of 85. The genetic causes of sAD are not known, but are assumed to be complex, involving multiple genes. An allelic variant in the APOE 4 gene is well established as a risk for sAD, but variants affecting susceptibility for AD in many other genes have also been identified [1]. Most recently, incompletely penetrant mutations in the ADAM10 gene have been identified in some late onset families with AD [5].

Down syndrome (DS), trisomy of human chromosome 21 (HSA21), is caused by an extra copy of all or part of the long arm of HSA21 and the increased expression, due to dosage, of some subset of HSA21 encoded genes. In addition to intellectual disability, all individuals with DS develop a neuropathology by the age of 30-40 similar to that seen in AD and approximately 50% will eventually develop an AD-like dementia by the age of 50-60 [6,7]. Because the incidence of DS is approximately one in 750-1000 live births worldwide, with the population in the US alone estimated at approximately 300,000, AD in DS is a significant societal and medical issue [8]. The genetic cause of AD in DS may be a combination of genetic causes similar to those in FAD and sAD. The presence of the APP gene on human chromosome 21 (HSA21), and its consequent triplication and over expression in DS, is a clear candidate, similar to FAD. However, the fact that not all individuals with DS develop an early onset AD-like dementia, in contrast to FAD due to APP duplication [9], suggests that additional genes may modulate the effects of APP triplication, and/or protect the DS brain from early progression to dementia in spite of neuropathology.

FAD, sAD and AD in DS display common features of abnormal processing of the APP protein to neurotoxic Aβ peptides and their accumulation in neuritic plaques; hyperphosphorylation of the microtubule associated protein, Tau, and the formation of neuritic fibrils containing Tau; hyperactivation of glutamate receptors; and neuroinflammation [10-12]. To understand the potential causes of AD in DS at the molecular level, it is helpful to consider functional information regarding the genes of HSA21 and the protein abnormalities observed in brains of patients with AD and mouse models of AD.

HSA21 encodes 161 classical protein coding genes of diverse functions, plus approximately 45 genes encoding keratin associated proteins (some proportion of which may be pseudogenes), five microRNA genes, and more than 300 genes/gene structures of completely unknown functions [13]. Several HSA21 protein coding

***Corresponding author:** Katheleen Gardiner, Department of Pediatrics, Linda Crnic Institute for Down Syndrome, Human Medical Genetics and Genomics, and Neuroscience Programs, University of Colorado Denver, Mail Stop 8608, 12700 E 19th Avenue, Aurora, Colorado 80045, USA, Tel: 303-724-0572; Fax: 303-720-5741; E-mail: katheleen.gardiner@ucdenver.edu

Received December 20, 2013; **Accepted** January 22, 2014; **Published** February 03, 2014

Citation: Block A, Dhanasekaran AR, Ahmed MM, Gardiner KJ (2014) Abnormal Protein Profiles in Hippocampus of Mouse Models of Down Syndrome: Similarities with Alzheimer's Disease. J Alzheimers Dis Parkinsonism 4: 138. doi: 10.4172/2161-0460.1000138