

Supplementary Table 2: AD-DS neuropathological studies¹⁻¹⁷

Reference	Number of Cases in study (age range)	Aβ amorphous plaque Earliest case (years) (number of cases)	Aβ dense-cored plaque Earliest case (years) (number of cases)	Cerebral amyloid angiopathy Earliest case (years) (number of cases)	Neurofibrillary tangles Earliest case (years) (number of cases)
Burger and Vogel 1973	13 (12-65 years)	NR	17 (11/13)	NR	38 (8/13)
Ball and Nuttall 1980	5 (21-62 years)	NR	21 (5/5)	NR	21 (5/5)
Roper and Williams 1980	20 (30-64 years)	NR	30 (20/20)	NR	30 (20/20)
Whalley 1982	10 (13-58 years)	NR	53 (7/10)	NR	53 (7/10)
Wisniewski et al 1985a	7 (47-65 years)	NR	47(7/7)	NR	47 (7/7)
Wisniewski et al 1985b	100 (0-80 years)	NR	11-20 years* (56/100)	NR	11-20* (56/100)
Mann et al 1986	12 (31-65 years)	37 (11/12)	37 (11/12)	NR	37 (11/12)
Godridge et al 1987	5 (34-64 years)	NR	52 (4/5)	NR	52 (3/5)
Mann and Esiri 1989	13 (13-50 years)	31 (12/13)	37 (11/13)	NR	37 (11/13)
Motte and Willams 1989	15 (25-59 years)	25 (13/14)	48 (8/14)	48 (6/15)	48 (8/15)
Murphy et al 1990	6 (19-64 years)	19 (6/6)	19 (3/6)	NR	56 (2/6)
Lemere et al 1996	29 (3-73 years)	12 (20/29)	15 (17/29)	46 (6/29)	29 (16/29)
Iwatsubo et al 1995	16 (31-64 years)	31 (16/16)	44 (13/16)	31 (16/16)	NR
Leverenz and Raskind 1998	42 (4 days – 38 years)	8 (18/42)	28(3/42)	NR	28 (3/42)
Hirayama et al 2003	20 (21 weeks gestation – 60 years)	32 (9/20)	32 (9/20)	NR	NR
Head et al 2003	15 (5 months -67 years)	31 (14/15)	31 (14/15)	NR	37(13/15)
Margallo-Lana et al 2007	16 (43-76years)	NR	43 (16/16)	NR	44 (15/16)

* Age range only not age of first case
NR – not reported

Reference List

1. Ball,M.J. & Nuttall,K. Neurofibrillary Tangles, Granulovacuolar Degeneration, and Neuron Loss in Down Syndrome - Quantitative Comparison with Alzheimer Dementia. *Annals of Neurology* **7**, 462-465 (1980).
2. Burger,P.C. & Vogel,F.S. Development of Pathologic-Changes of Alzheimers Disease and Senile Dementia in Patients with Downs-Syndrome. *American Journal of Pathology* **73**, 457-476 (1973).
3. Godridge,H., Reynolds,G.P., Czudek,C., Calcutt,N.A., & Benton,M. Alzheimer-Like Neurotransmitter Deficits in Adult Downs-Syndrome Brain-Tissue. *Journal of Neurology Neurosurgery and Psychiatry* **50**, 775-778 (1987).
4. Head,E. *et al.* Parallel compensatory and pathological events associated with Tau pathology in middle aged individuals with Down Syndrome. *Journal of Neuropathology and Experimental Neurology* **62**, 917-926 (2003).
5. Hirayama,A., Horikoshi,Y., Maeda,M., Ito,M., & Takashima,S. Characteristic developmental expression of amyloid beta 40, 42 and 43 in patients with Down syndrome. *Brain & Development* **25**, 180-185 (2003).

6. Iwatsubo,T., Mann,D.M.A., Odaka,A., Suzuki,N., & Ihara,Y. Amyloid-Beta Protein (A-Beta) Deposition - A-Beta-42(43) Precedes A-Beta-40 in Down-Syndrome. *Annals of Neurology* **37**, 294-299 (1995).
7. Lemere,C.A. *et al.* Sequence of deposition of heterogeneous amyloid beta-peptides and APO E in Down syndrome: Implications for initial events in amyloid plaque formation. *Neurobiology of Disease* **3**, 16-32 (1996).
8. Leverenz,J.B. & Raskind,M.A. Early amyloid deposition in the medial temporal lobe of young Down syndrome patients: A regional quantitative analysis. *Experimental Neurology* **150**, 296-304 (1998).
9. Mann,D.M.A., Yates,P.O., Marcyniuk,B., & Ravindra,C.R. The Topography of Plaques and Tangles in Downs-Syndrome Patients of Different Ages. *Neuropathology and Applied Neurobiology* **12**, 447-457 (1986).
10. Mann,D.M.A. & Esiri,M.M. The Pattern of Acquisition of Plaques and Tangles in the Brains of Patients Under 50 Years of Age with Downs-Syndrome. *Journal of the Neurological Sciences* **89**, 169-179 (1989).
11. Margallo-Lana,M.L. *et al.* Fifteen-year follow-up of 92 hospitalized adults with Down's syndrome: incidence of cognitive decline, its relationship to age and neuropathology. *Journal of Intellectual Disability Research* **51**, 463-477 (2007).
12. Motte,J. & Williams,R.S. Age-Related-Changes in the Density and Morphology of Plaques and Neurofibrillary Tangles in Down Syndrome Brain. *Acta Neuropathologica* **77**, 535-546 (1989).
13. Murphy,G.M. *et al.* Antigenic Profile of Plaques and Neurofibrillary Tangles in the Amygdala in Downs-Syndrome - A Comparison with Alzheimers-Disease. *Brain Research* **537**, 102-108 (1990).
14. Ropper,A.H. & Williams,R.S. Relationship Between Plaques, Tangles, and Dementia in Down Syndrome. *Neurology* **30**, 639-644 (1980).
15. Whalley,L.J. The Dementia of Downs-Syndrome and Its Relevance to Etiological Studies of Alzheimers-Disease. *Annals of the New York Academy of Sciences* **396**, 39-53 (1982).
16. Wisniewski,K.E., Dalton,A.J., Mclachlan,D.R.C., Wen,G.Y., & Wisniewski,H.M. Alzheimers-Disease in Downs-Syndrome - Clinicopathologic Studies. *Neurology* **35**, 957-961 (1985).
17. Wisniewski,K.E., Wisniewski,H.M., & Wen,G.Y. Occurrence of Neuropathological Changes and Dementia of Alzheimers-Disease in Down Syndrome. *Annals of Neurology* **17**, 278-282 (1985).