Understanding the link between Down syndrome and Alzheimer's disease: developing preventative treatments

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Defeat Dementia in DS
www.DementiaInDS.com
Trisomy 21 reported by Lejeune 1959

Sequencing of Chr. 21

APP gene

The Amyloid Cascade Hypothesis
Selkoe 1991

Clinical

Pittsburgh Compound-B (PiB), Klunk et al 2004

A human stem cell model of early AD pathology in DS
Yichen Shi et al 2012

Landt et al 2013
The age-specific risk of dementia in people with DS

Defeat Dementia in Down Syndrome
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% affected

35-40 41-45 46-50 51-55 56-60 >60

Age (years)

Lai & Williams, 1989
Visser et al., 1997
Lai et al., 1999
Holland et al., 1998

Schupf, N et al; BJP 2002;180:405-410
Understanding Alzheimer’s disease: the amyloid cascade hypothesis

Proposed by Selkoe (1991), and extended by Hardy and Higgins (1992), the amyloid cascade hypothesis has been the basis for the majority of research into AD (Hardy 2009)

Down Syndrome – trisomy 21

Aβ cleavage

Excessive Aβ

Formation of oligomers

Formation of protofibrills and fibrills

Sequestered into plaques

Synaptic dysfunction?

Neuronal cell death?

pTau accumulation and NFT formation?

Cell death

Synaptic dysfunction, neuronal cell death

Alzheimer’s disease

Memory changes, loss of skills etc characteristic of dementia

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The use of neuroimaging

MRI
Structure

PET
Amyloid

What is the relationship between brain amyloid accumulation, the loss of brain tissue and the development of dementia (Alzheimer’s disease)?
Age and brain amyloid binding in adults with DS

There was a significant positive correlation between age and BP_{ND} values in frontal, parietal and temporal cortices, $r(40) = .741$, $p<0.01$
Early findings
Differences in cortical thickness between amyloid negative DS and amyloid positive DS in comparison to people without DS - importance of amyloid (Aβ)

R-hemisphere of Aβ negative DS vs Controls  R-hemisphere of Aβ positive DS vs Controls
Looking ahead

Neuropathology versus age in Down's syndrome

(approximated from Mann et al., 1989)
Challenges...

• Can we be certain that amyloid deposition starting early in life is leading to Alzheimer-like changes?

• What other factors in people with DS are modifying this risk for AD and what are the implication for treatment?

• Can we develop safe interventions and how do we test whether or not they prevent AD in people with DS years later?
Thank you...

• For the invitation to be part of this very special event

• To the UK DS Association and to people with Down syndrome and their families for their participation in research

• To many colleagues for their expertise and to funding organisations for financial support for research from across the world