Alzheimer’s Disease and Down Syndrome: Developing a National Tissue Repository

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With the recent Notice of Change in Funding Mechanism for Human Tissue Banks (NOT-MH-12-020), the NIH has emphasized the need for widespread availability of high quality human brain tissue stored with a linked IT system and database. The well-recognized need for the careful collection of tissues that include good controls and a variety of disease states also highlights the limitations of animal models in faithfully replicating the spectrum of defects in human neurological diseases. The ultimate goal of such a repository is to obtain a detailed understanding of the defects in the disease to be able to target and correct them. An important question today is how to develop appropriate medication paradigms for individuals with Down syndrome (DS) and Down syndrome related dementia (DSD). According to the Center for Disease Control (CDC), there are 6,000 babies born with DS every year in the US, and the incidence of DS is 1 in 691 births, an increase from the previously recorded 1 in 733 births. Individuals with DSD do not respond as well to Alzheimer’s disease (AD) medications, and some AD medications may be contraindicated in DSD, due to gastric or cardiac consequences of the trisomy [1]. DS is caused by a complete or segmental chromosome 21 trisomy, resulting in variable intellectual ability at birth, and progressive memory loss and neurodegeneration with age. Most research in DS neuropathology has focused on development of the central nervous system, but age-related changes are important, in view of the increased life span observed in DS over the last few decades [2]. DS leads to pathological hallmarks of Alzheimer’s disease (AD) by 40 or 50 years of age, coupled with an increased risk of early onset dementia [2]. One of the major pathways explored in the pathogenesis of AD is processing of the amyloid precursor protein, APP [3]. Located on chromosome 21, APP is triplicated in DS, and amyloid-beta deposition is frequently profound in these individuals, even in early childhood or adolescence [4]. Thus, while familial causes of AD are rare, and idiopathic AD is difficult to model, DS represents a relatively homogenous population with relevant animal models that can serve to explore biological pathways involved in both AD and in DSD [5]. The high predictability with which individuals with DS acquire AD neuropathology and clinical dementia makes this population important to study.

Because individuals with DS often exhibit deficits in cardiac and metabolic systems, cholinesterase (AChE) inhibitors prescribed to AD patients may be contraindicated in some people with DSD [1]. In addition, a recent multi-site study on the use of donepezil in individuals with DS [6], revealed variable efficacy, suggestive of phenotypic variability of DSD. On the other hand, a recent Japanese study reported improvement in activities of daily living in DS individuals maintained on the AChE inhibitor donepezil [7]. Another promising AD drug, memantine, a glutamate NMDA receptor antagonist, was recently reported to have very modest, if any, effects on a cohort of DS individuals with dementia [8]. The investigators concluded that there is a striking absence of data showing cognitive improvement in DSD individuals with pharmacotherapies, and that memantine does not hold promise for future treatment of DSD. These studies suggest that novel or modified medications should be developed for DSD, since individuals with this disorder appear not to respond as well to existing AD medications, despite strong experimental evidence in a DS mouse model for successful treatment with memantine [5]. Consequently, despite the value of the available animal models, some factors remain human disease-specific, with resources required for understanding human disease processes. Therefore, we propose the establishment of a national Down syndrome repository for brain tissue from cognitively characterized individuals with, and without, DSD. The availability of brain tissue from DSD cases will lead to collaborative studies to examine the neurobiological similarities and differences between people with DSD and AD, to better understand the underlying pathology. These findings will provide data as to why individuals with DS and dementia are relatively unresponsive to AD medication, allow for the examination of biological mechanisms for the disease process leading to dementia in DS individuals, and to the development of novel treatment approaches for DSD.

While there are several studies in the literature showing neuropathological changes in the DSD versus AD brain [9,10], a concerted effort has not been made to establish a national repository for clinically, neuropsychologically and neuropathologically well characterized DSD subjects including cognitive data. One year ago, a request for information (RFI) came out from the NIH asking for information regarding “Acquisition, Processing, Storage, and Distribution of Human Brain and Other Tissues to Advance Understanding and Treatment of Down Syndrome” (see NOT-HD-11-001). The request was issued by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). The Brain and Tissue Bank for Developmental Disorders at the University of Maryland (Dr. H. Ronald Zielke, director), has been classified as an NICHD repository for DS brains, but cognitive information is generally not available for these specimens. A nationally integrated collection program should be established, to provide researchers with tissue from multiple brain regions for both histological and molecular analysis, which can be correlated with cognitive decline and common biomarkers for AD. Because of the rapid increase in life expectancy in DS individuals [2],

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the time has come to initiate a national collaborative effort to develop and coordinate a brain donation program for clinical molecular and pathological research into the processes underlying the biology of DS.

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References