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The Link between Alzheimer's Disease and Down Syndrome. A Historical Perspective

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Approximately 40–80% of persons with Down syndrome (DS) develop Alzheimer's disease (AD)-like dementia by the fifth to sixth decade of life [1], a much younger age than is typically seen in sporadic AD [2–4]. The onset of dementia symptoms in DS parallels the development of classic brain neuropathological lesions *(i.e.,* amyloid plaques) similar to that evident in AD. Both disorders appears to have a similar genetic linkage, which is supported by the triplication of the gene that codes for amyloid beta (A4) precursor protein (APP) in persons with DS [5] and an extra copy of the *APP* gene causes familial AD in persons without DS [6]. Despite an overlap in the genetics of these disorders, the clinical presentation of dementia differs between persons with DS and AD. Whereas 'forgetfulness' is a typical symptom of early-phase dementia for persons in the general population, behavioral problems and personality changes are early signs of dementia for persons with DS [4, 7]. There are indications that amyloid burden begins in the frontal cortex before spreading to other brain regions in those with DS-AD, something that is not always the case in sporadic AD [8] suggesting pathological variances between these disorders. These differences beg the question: Are the genetic and neuropathological commonalities found in DS- and AD-related dementia an associated similarity or do these disorders share a common pathogenesis? To address this query, we briefly review the clinical, histopathological, and genetic research supporting a putative link between dementia in DS and AD.

The nineteenth century physicians Esquirol (1838) [9] and Seguin (1846) [10] first published descriptions of individuals with DS while working to improve the social and educational conditions of individuals living in mental institutions. However, it was John Langdon Down a distinguished 19th century British physician who was serving a ten-year appointment as Medical Superintendent of Earlswood Asylum, England, and characterized the more salient physical, cognitive, and behavioral features underlying a specific phenotype, which today bears his name [11]. In an 1866 essay, he reported the phenotypic features of this cohort of people as possessing a constellation of physical, intellectual, language, and motor

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CONFLICT OF INTEREST

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impairments that were distinctively different from other individuals with intellectual disabilities [12]. He stated that, “when placed side by side, it is difficult to believe these specimens compared are not children of the same parents.” Down and his son Reginald later described atypical palmar creases in the hands of individuals with DS. These observations had personal connotations since Reginald’s oldest son, a well-loved and happy boy who lived with the family until his death at the age of 65, had DS. Down’s grandson lived at home indicating the family’s commitment to improving the medical, social, and educational experience of persons with DS, since most individuals with DS at this time were institutionalized. Down was simultaneously striving to develop comprehensive educational programs comprised of physical exercise, sensory stimulation, and dramatic play for individuals with DS. These programs encouraged training of professionals that today would be classified as physical, occupational, speech, and play therapists.

Awareness of DS was gradually increasing in the late 1800s. For example, within two years after Down’s initial publication, Shuttleworth (1866) and Tanner and Meadows (1879) mentioned the condition of DS in medical texts [13]. Fraser and Mitchell (1876) conducted a study consisting of 62 individuals with DS who experienced functional decline in adulthood [14], specifically noting, “death was attributed to nothing more than general decay- a sort of precipitated senility.” Some investigators referred to DS as a form of progeria (see *e.g.,* [15]). During this time period, researchers were becoming increasingly interested in the pathobiology of brain diseases. In 1892, Blocq and Marinescu used silver staining to describe abnormal extracellular plaques in post mortem brain tissue obtained from two elderly patients with senility [16], a finding that was recapitulated six years later by Emil Reich and later by Oskar Fischer [17]. Alois Alzheimer, a German psychiatrist and neuroanatomist, used the Bielschowsky’s silver staining method to examine the brain of a 51-year old patient named Augusta Deter. Deter had presented to Alzheimer with signs of paranoia, memory loss to the degree that she could no longer find her way around the house, and strong changes in personality, which involved intense jealousy of her husband. Following institutionalization, Deter’s condition deteriorated to the point that she became incontinent, apathetic, and bedridden, dying five years later at the age of 56. At autopsy, Alzheimer noted brain atrophy, prominent neuronal loss, and dense, thick bundles of neurofibrils and intricate tangles, which resembled the skeletons of degenerated neurons whose nuclei and cytoplasm were no longer present. He presented his findings on November 4, 1906 in Tubingen, to the South-West German Society of Alienists, a professional association dedicated to understanding the legal aspects of psychiatry. During the meeting, Alzheimer emphasized the co-occurrence of dementia, plaques, and tangles--hallmark features that appeared to be associated with the death of neurons and shrinkage of the AD brain. In 1910, Emil Kraepelin, suggested that this triad of signs and symptoms should be placed under the umbrella nomenclature “Alzheimer’s disease”.

Leo Davidoff also employed the Bielschowsky staining method to visualize significant atrophy of the cortex and cerebellum, simplicity of gyri, paucity of neuronal number in frontal, temporal and parietal cortices (particularly layer 3), as well as degeneration of the periventricular area in the DS brain. Davidoff, a fellow at the Peter Bent Brigham Hospital in Boston, examined postmortem brain tissue from 10 individuals with DS ages 7 months to 42 years, obtained from Professor A. Jacob’s collection in Staats-krankenanstalt, a psychiatric

teaching hospital in Hamburg Germany. Davidoff concluded that the brains of individuals DS were prone to significant neuronal degeneration in the cortical layers and used words like *agenesis, aplaysia,* and *paragenesis* to describe these differences [18].

Davidoff's observation of neurodegenerative alterations were in conjunction with Fraser and Mitchell's report of "precipitated senility" in adults with DS. Friedrich Struwe [19] later descripted isolated and perivascular plaques pathognomonic features of AD in brains of individuals with DS. Characterization of these aging adults was especially valuable given that the average life expectancy in 1929 was 9 years of age [20]. Bertrand and Koffas (1946) reproduced these findings and described amyloid plaques in the DS brain [21]. Seminal work of Jervis (1948) definitively linked the co-occurrence of dementia, brain atrophy, plaques, and tangles in DS [22]. Four years later, Verhaart and Jelgersma (1952) published a case study of a 56-year-old female with DS who met diagnostic criteria for AD [23], which further substantiated clinical and pathological AD-like features in the DS population. Together, these findings established a link between the two disorders wherein the neuropathologi- cal hallmarks of dementia *(e.g.,* plaques and tangles) came to be associated with both DS and AD.

Although in 1959, the French geneticist and pediatrician Jérôme Lejeune, discovered the genetic basis for DS [24], suggestions of a genetic hypothesis for DS that had been proffered earlier by Waardenburg [25] and Davenport [26] based upon a higher incidence with increasing maternal age and among siblings. A chromosomal analysis designed to test the genetic hypothesis concluded that neither triploidy or aneuploidy was a cause [27]. A later report demonstrated that the normal human karyotype was comprised of 46 chromosomes [28], whereas Lejeune visualized 47 chromosomes in persons with DS, suggesting a genetic basis for the disorder [24, 29]. Rapid confirmation of extra chromosome 21 material [30] by Fraccaro and colleagues [31] soon followed giving rise to an alternative name for DS, "trisomy 21." Notably, Lejeune's discovery was the first instance wherein a defect in intellectual development was linked to chromosomal abnormalities. Based upon an increased rate of DS births in the families of those with AD a familial linkage was suggested between DS and AD [32]. The next step in understanding the molecular pathogenesis came in 1984 when plaque rich samples from the brains of patients with AD were purified and investigators sequenced a protein, later named amyloid beta (A|3) [33]. Three years later several groups published studies that linked the gene for the APP to a locus on the proximal portion of the long arm of chromosome 21 [34, 35]. Korenberg narrowed the location of *APP* to chromosome 21 [36] and Alison Goate (1991) identified a missense mutation in *APP* and linked the mutation to a familial form of AD [37].

These findings raise the question of whether overexpression of *APP* might play a role in the occurrence of AD neuropathology in people with DS. Prasher and colleagues [38] presented a case study of a 78-year-old woman with partial trisomy 21 who failed to show cerebral atrophy and AD-type dementia according to *in vivo* imaging. Notably, the woman's short- and long-term memory, concentration and attention, language, and visuospatial skills remained unchanged until the time of her death. Moreover, she was mobile, continent, able to read and write, and cared for herself with supervision. Following her death, brain autopsy revealed that the frontal and temporal cortex, hippocampus, amygdala, locus coeruleus, basal

nucleus of Meynert, and raphe nuclei showed little evidence of degeneration. Her karyotype revealed that she had a partial trisomy of the long arm of chromosome 21 (46, XX, rec(21)dup q, inv(21)(p12;q22.1). Thus, the woman's elongated lifespan, lack of neuropathology, and failure to develop dementia suggested that genes outside the DS critical region and proximal to 21q22.1 to 21qter were critical to AD-like pathology in DS, even though the facial and behavioral phenotype of DS was present.

The genetic nature of DS, together with the relatively small size of human chromosome 21 (HSA21) would later encourage the complete sequencing of human chromosome 21. In 2000, Hattori [39] successfully sequenced the entire long arm of which revealed 225 genes (127 known genes, and 98 triplicated novel genes, and 59 pseudogenes). Later it was revealed that there are at least 364 genes on HSA21 [40]. According to these estimates, the genes included on HSA21 code for transcription factors, regulators and modulators, proteases and protease inhibitors, ubiquitin pathway, interferon and immune response, kinases, RNA processing, adhesion molecules, channels, receptors, and energy metabolism molecules. At least 130 of these genes encode proteins. The orthologues for these genes can be found on mouse chromosomes (MMU) 16, 17, and 10.

Attempting to recapitulate the genetic basis of DS, researchers generated mouse models for DS, a formidable task given that genes analogous for HSA21 are located on three separate mouse chromosomes *(i.e.,* MMU 16, 17, 10). Consequently, only portions of implicated genes were inserted into early mouse models. For example, the first mouse model generated in 1975 called Ts16 was derived by triplicating the entire MMU16 [41]. However, Ts16 mice die *in utero* making it impossible to determine effects of aging in these mice, even though seminal studies using cell lines generated from Ts21 mice were performed *(e.g.,* [42]). In 1993, in an attempt to circumvent these issues, Muriel Davisson generated a novel mouse model called Ts65Dn that had a partial trisomy of MMU16 extending from *Mrpl39* to *Znf295.* These mice exhibit many of the characteristics of human DS including basal forebrain cholinergic neuron dysregulation [43, 44]. Today this is the most commonly studied mouse model of DS [45]. Other mouse models include mice with triplication of smaller fragments of MMU16 (TslCje and TslRhr) or mice bearing an entire transgenic HSA21 (C21). To more authentically recapitulate the genetic basis of DS, Yu and colleagues (2007) generated mouse models with a triplication of all DS genes found on HSA21. As mentioned above, analogous genes for HSA21 are found on mouse chromosomes Mmu16, Mmu10, and Mmu17—prompting the generation of mice with triplication of combinations of these segments, termed Ts1Yey, Ts2Yey, Ts3Yey, and Ts1Yey/Ts2Yey/Ts3Yey, respectively [46]. These mice exhibit impairments including impaired spatial learning, contextual fear conditioning, and reduced hippocampal LTP [47].

The development of a human amyloid marker in the form of amyloid PET imaging using the Pittsburgh compound B (PiB) [48] appears to offer a promising advance towards better characterization of and treatment for amyloidopathies. Several groups used this method to investigate amyloid accumulation in the brain of adults with DS. Hartley and colleagues [49] reported imaging findings showing that more than a third of individuals with DS display a positive signal particularly in the anterior ventral striatum. Indeed, this brain region showed the earliest and most significant amyloid accumulation in people with DS. Other positive

brain regions included anterior cingulate, frontal cortex, lateral temporal cortex, parietal/precuneus cortex [49] similar to that reported for AD.

Although the neurobiology underlying DS remain unknown, mechanisms involving APP appear to play an important role. In a post mortem study of a person with segmental trisomy of HSA21, Prasher and colleagues (1998) first demonstrated the importance of the link between APP and dementia [38]. At autopsy, plaques and tangles were present in the brain of the affected individual, and yet absent were abnormalities in the LC and nucleus basalis of Meynert, suggesting that select neuropathology associated with DS- related dementia is associated, at least in part, with the *APP* gene. The APP gene is one of the 140 triplicated genes in Ts65Dn mice [50, 51]. Given their genetic background, Ts65Dn mice exhibit increased levels of full-length APP mRNA and protein in the cortex [52]. The up regulation of APP appears to play a role in regional degeneration of basal forebrain cholinergic neurons and cognitive decline [53–55]. We previously tested whether APP triplication in Ts65Dn mice was linked to failed transport of nerve growth factor (NGF) and basal forebrain cholinergic neuron degeneration. By using mice with either 2 or 3 copies of *APP*, we demonstrated that the deletion of an extra copy of *APP* led to significant improvement in BFCN morphology and increased axonal transport of NGF [56]. Similarly, sAPP acts synergis- tically with NGF in culture to potentiate neurotrophic and neuroprotective activities [57–59]. Clinical neuropathological studies have revealed deficits in NGF metabolism and its receptor expression in the cholinotrophic BFCN system in humans with DS, which overlap with that seen in AD [60–64] suggesting similar mechanistic processes.

This Special Issue provides an opportunity to emphasize the unique clinical and pathobiological relationship between AD and DS and how investment in research would mutually benefit our understanding of each disorder and provide much needed translational knowledge for the development of cross therapeutic drug targets. There are more than 400,000 individuals with DS in the USA today, and with a doubling of their life span (current average life span of 58 years of age) during the last couple of decades this population has a tripled risk for the development of AD. A number of drugs primarily developed for the treatment of cognitive dysfunction in AD have been tested in people with DS with different rates of success indicating a reciprocal relationship between AD and DS. This becomes even more important from the perspective of caregivers, since women who give birth to a child with DS when they are under the age of 35 exhibit a 5–6 times higher risk for AD themselves. When consulting the Alzheimer Association, it is evident that the double caregiver burden of simultaneously caring for a mother with AD and a sibling with DS-AD is difficult to bear, and this situation will grow as the life span of the DS population continues to increase.

The present Special Issue, summarizes the state of DS research with respect to clinical, pathobiology, genetics, potential treatment strategies and animal models of the disorder. Sabbagh and Edgin [65] review approaches to detect intellectual decline in DS individuals, including informant-based measures, dementia screening tools, and neuroimaging techniques and highlight the challenges for detecting decline in this group. Head and colleagues [66] describe some of the pathologies underlying DS, its relation to AD and evidence of potential compensatory responses in DS that may delay the onset of dementia

after the onset of AD pathology. Potter and coworkers [67] discuss the observation that trisomy 21 and other aneuploidy arise among neurons and peripheral cells in sporadic and familial AD suggesting that AD and DS are two sides of the same coin. Hamlett and associates [68] review potential treatment avenues regarding development of memory loss and AD neuropathology in DS mouse models, review age-related neuropathology, as well as findings from neuroimaging studies. The generation of appropriate DS mouse models that mimic neurodegeneration and memory loss in humans with DS are of value for the development of novel drug interventions. Phillips and colleagues [69] expound upon the similar pathology of the locus coeruleus norepinephrine (NE)-ergic neurons and their role in cognitive impairment in both AD and DS. These author's present data suggesting that rescue of NE-ergic system can attenuate neuropathology and cognitive decline in both disorders and that this system is a putative target for the treatment of AD and DS. Iulita and Cuello discuss the physiological role of NGF metabolism and its biological significance to the survival of basal forebrain cholinergic neurons in both AD and DS (see [64]), which may play a crucial role in aspects of cognitive decline in both disorders. Kelly and associates [70] provide evidence that prenatal dietary supplementation with choline provides a partial prophylaxis for hippocampal cholinergic related structural and functional deficits in the Ts65Dn mouse model of DS, which may extend to AD. In the final chapter of this special issue, Strupp and coworkers [71] review evidence supporting the use of maternal choline supplementation during pregnancy and lactation as a therapeutic strategy for the improvement of spatial cognition, attentional function, normalizing adult hippocampal neurogenesis and protection of basal forebrain cholinergic neurons in the Ts65Dn mouse model of DS. The authors suggest that a maternal diet with additional choline may serve as an effective and safe prenatal strategy for improving cognitive, affective, and neural functioning in DS. Clinical trials are needed to confirm the use of choline dietary supplementation as a treatment for DS.

This Special Issue hopes to encourage the investigation of the common molecular and cellular factors linking the clinical symptoms underlying AD and DS. Combining research findings from the AD and DS community may ultimately enhance our ability to understand the mechanisms driving the onset of dementia in both disorders. The high incidence of Alzheimer's dementia and pathology among people with DS makes it a target for early intervention, preventive measures and research that will possibly expedite the development of new therapies that would benefit individuals suffering from both neurological conditions.

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