

Successful Aging in a 70-Year-Old Man With Down Syndrome: A Case Study

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Abstract

The authors present a case study of a 70-year-old man with Down syndrome (“Mr. C.”) who they followed for 16 years and who does not exhibit declines in cognitive or functional capacities indicative of dementia, despite having well-documented, complete trisomy 21. The authors describe the age-associated changes that occurred over 16 years as well as provide detailed information regarding Mr. C.’s health and genetic status. To further emphasize Mr. C.’s successful aging, the authors compared his longitudinal performance profile with that of 2 peers of comparable level of intellectual functioning: 1 similar-aged man with clinical Alzheimer’s disease and a younger man who was healthy. The authors present potential explanations for the phenotypic variability observed in individuals with Down syndrome.

DOI: 10.1352/2008.46:215–228

Trisomy 21 (Down syndrome) is the most prevalent chromosomal abnormality associated with intellectual disability (National Institute of Child Health & Human Development, 2006; also see Jenkins & Velinov, 2001, for a review). It is estimated to occur in approximately 1 in every 733 live births and in all racial and socioeconomic groups (U.S. Centers for Disease Control and Prevention, 2006). Down syndrome is caused by complete or partial triplication of human chromosome 21 and affects multiple body systems. It is associated with a constellation of phenotypic characteristics, including distinctive facial and physical features, intellectual disability with cognitive strengths and weaknesses, health problems, earlier-onset Alzheimer’s disease, and shortened life expectancy (e.g., Baird & Sadovnick, 1987; Roizen, 2001; see Dykens, Hodapp, & Finucane, 2000, for a review). Down syndrome also has some features that are associated with precocious aging (Devenny et al., 2005). It is important that almost every aspect of the phenotype associated with Down syndrome shows high degrees of variability in terms of both occurrence and degree of severity. For example, although individuals with Down syndrome generally function in the mild to moderate range of intellectual disability (with IQ scores in the 50s), IQ levels vary widely (Connolly, 1978).

Similar to adults in the general population, adults with intellectual disability, both with and without

Down syndrome, have benefited from advances in medical care, nutritional practices, and public health policies that occurred during the 20th century, resulting in a dramatic extension of their life expectancy (see Silverman, Zigman, Kim, Krinsky-McHale, & Wisniewski, 1998). Yang, Rasmussen, and Friedman (2002) determined that life expectancy among people with Down syndrome has been increasing, on average, 1.7 years per year over the past 14 years (from 25 years in 1983 to 49 years in 1997). In the current birth cohort, over 55% of individuals with Down syndrome are expected to survive into their 50s (Strauss & Eymann, 1996), and 13.5% may still be alive at 68 years old (Baird & Sadovnick, 1988, 1989). However, although the lifespan of individuals with Down syndrome has dramatically increased in recent years, these individuals are still at increased age-specific mortality risk compared with both individuals with intellectual disability from other etiologies and the general population without intellectual disability (e.g., Glasson et al., 2003).

Adults with Down syndrome are also at increased risk for developing earlier-onset Alzheimer’s disease (K. Wisniewski, Wisniewski, & Wen, 1985; Zigman, Schupf, Sersen, & Silverman, 1996; see Mann, 1993, for review). The high risk for Alzheimer’s disease has been attributed, at least in part, to the triplication and overexpression of the gene coding for amyloid precursor protein (APP), which

is located on chromosome 21 and seems to contribute to the deposition of β -amyloid protein in diffuse and neuritic plaques (Hof et al., 1995; Hyman, West, Rebeck, Lai, & Mann, 1995; Rumble et al., 1989). The formation and deposition of plaques follow an age-dependent pattern in which most of the β -amyloid remain nonfibrillized (diffuse) and does not result in neuronal degeneration or loss of function until about the end of the 4th decade of life (H. M. Wisniewski, Wegiel, & Popovitch, 1994). From the 5th decade on, the proportion of fibrillar (neuritic) plaques accelerates with each decade (H. M. Wisniewski, Wegiel, & Popovitch, 1994; T. Wisniewski et al., 1995).

It is intriguing that not all adults with Down syndrome develop clinical dementia at ages when the presence of large numbers of neuritic plaques is presumed to exist (Chicoine, McGuire, Hebein, & Gilly, 1994; Devenny et al., 1996; Oliver, Crayton, Holland, Hall, & Bradbury, 1998; Zigman et al., 1996). Even in those individuals who develop dementia, there is wide variation in the age at onset (Lai & Williams, 1989; Prasher & Krishnan, 1993). Individual differences in vulnerability then, must exist, but the factors contributing to these differences are still largely unknown (Silverman et al., 1998).

Adults with Down syndrome show age-associated changes in cognitive abilities that mirror the changes observed in older adults without intellectual disability (e.g., Devenny et al., 1996; Devenny, Krinsky-McHale, Sersen, & Silverman, 2000; Haxby, 1989; Oliver et al., 1998; Vicari, Nocentini, & Caltagirone, 1995). Specifically, longitudinal studies have found declines with age in episodic memory and new learning (Devenny et al., 1996, 2000; Haxby & Shapiro, 1992; Oliver et al., 1998), and cross-sectional studies have reported poorer performance by older adults with Down syndrome on measures of memory, learning, language, visuospatial abilities, aspects of attentional control, and speed of information processing compared with older adults with other forms of intellectual disability (e.g., Burt et al., 2005; Devenny & Zimmerli, 1996; Fromage & Anglade, 2002; Haxby, 1989; Thase, Tigner, Smeltzer, & Liss, 1984; Vicari, Nocentini, & Caltagirone, 1995). Declines in adaptive behavior with age have also been observed in this population (Rasmussen & Sobsey, 1994; Zigman et al., 1996). Many health problems increase in prevalence with age, including vision impairments, hearing loss, thyroid dysfunction, and depression (e.g., Buchanan, 1990; Castane, Boada-Rovira, & Hernandez-Ruiz,

2004; Evenhuis, 1995; Evenhuis, Theunissen, Denkers, Verschuure, & Kemme, 2001; Krinsky-McHale et al., 2001; Prasher, 1995a, 1995b; also see Merrick, Kandel, & Morad, 2003, for a review on health issues in adults with Down syndrome). The consensus that has emerged from studies investigating these behavioral and medical aspects of aging in adults with Down syndrome is that these age-related problems occur earlier than is characteristic of the general population but typically not before the age of 50 years (Devenny & Krinsky-McHale, 1998; Holland, Hon, Huppert, Stevens, & Watson, 1998; Zigman, Schupf, Lubin, & Silverman, 1987; cf. Burt et al., 1995).

There have been several early reports of individuals with Down syndrome living beyond their expected age (Demissie, Ayres, & Briggs, 1988; Dupont, Vaeth, Videbeck, 1986; Forssman & Åkesson, 1965; Jancar, 1989), but the characteristics of these long-lived individuals have not been well described. Recently, Chicoine and McGuire (1997) presented a case study of an 83-year-old woman with Down syndrome and reported that she showed, “no physical deterioration, no memory loss, and no loss of skills” and that, “she had been relatively healthy all her life” (p. 477). Chromosome analysis indicated that she had mosaic Down syndrome (25/75 cells with trisomy 21) rather than typical trisomy 21. In addition, Prasher et al. (1998) reported on a 78-year-old woman who did not have dementia when she died and who had a partial trisomy of the long arm of chromosome 21 in the area of the APP gene [46,XX,rec(21)dup q,inv(21) (p12q22.1)]. At autopsy, there was no evidence of the neuropathology suggestive of Alzheimer’s disease.

In summary, by virtue of the genetic abnormality defining Down syndrome, individuals with this condition present with a unique aging profile, and, in certain areas of cognitive and adaptive functioning, they appear to age precociously. Interpretation of these findings is complicated by the high risk for earlier-onset Alzheimer’s disease, and there is high interindividual variability in the expression and age of onset of changes in functioning. Because increased longevity for individuals with Down syndrome is a relatively recent phenomenon, far too little is known about their adult development.

In this article, we present a case study of a 70-year-old man with Down syndrome, “Mr. C.,” who we have followed for the past 16 years. We describe his age-associated cognitive and functional changes over the years of his participation in our study as well as

detailed information regarding his health and genetic status. Of particular interest is the fact that Mr. C., despite having well-documented complete trisomy 21, has not experienced a decline in memory function or in performance of activities of daily living that might be suggestive of dementia, making him the oldest participant in our 20-year longitudinal study who does not exhibit clinical Alzheimer's disease.

Method

Genetic Assessments

To verify the diagnosis of Down syndrome for Mr. C., we collected samples of nonfasting blood, with informed consent, for chromosomal and DNA analysis. Karyotyping was performed by standard methods using phytohemagglutinin-stimulated peripheral blood lymphocytes (as reported in Jenkins et al., 1983, 1996; Jeziorowska et al., 1992). Interphase fluorescence in situ hybridization (FISH) was used to determine whether Mr. C. was subject to low-level mosaicism for trisomy 21. In addition, we carried out high-resolution, genome-wide analysis of DNA copy number on Affymetrix (Affymetrix, Santa Clara, CA) 250K *NspI* single nucleotide polymorphism (SNP) arrays, with probe synthesis, and data analysis by normalization and model-based expression using the dChip software package (Li & Wong, 2001). Genotyping for apolipoprotein E (APOE) was performed by using the method of Hixson and Vernier (1990).

Cognitive and Functional Assessments

Mr. C. is a participant in a longitudinal study examining the changes in functioning associated with aging in adults with intellectual disability (see, e.g., Devenny et al., 1996; Silverman et al., 2004). He entered the study in 1990 at the age of 53 years, and we have evaluated him every 12 to 18 months since that time, providing 11 separate assessments as of 2006. Assessments have included direct cognitive testing (including measures of mental status, general cognitive abilities, verbal skills, visuospatial organization, new learning, fine-motor coordination, and memory), review of current and past medical history, and structured informant interviews regarding behavior (functional and maladaptive). Table 1 summarizes the tests evaluated for this article and the domains assessed. Details of the tests administered are presented elsewhere (e.g., Devenny et al., 1996; Krinsky-McHale, Devenny, & Silverman, 2002; Silverman et

al., 2004). All testing was done individually either at Mr. C's day program or his residence.

Dementia Status

The nondemented status of Mr. C. was established based on in-depth evaluations of cognitive, functional, and health status conducted repeatedly over many years during case consensus conferences. Procedures for determining status were consistent with guidelines recommended by the American Association on Mental Retardation (now the American Association on Intellectual and Developmental Disabilities [AAIDD])–International Association for the Scientific Study of Intellectual Disability (AAMR-IASSID) Working Group for the Establishment for the Criteria for the Diagnosis of Dementia in Individuals with Developmental Disability (Aylward, Burt, Thorpe, Lai, & Dalton, 1995; Burt & Aylward, 2000). The details of the case consensus conferences are also provided elsewhere (Silverman et al., 2004; Zigman et al., 2004).

Results

Genetic Testing

Confirmatory cytogenetic analysis conducted on Mr. C.'s entry into this study showed a karyotype with a complete triplication of chromosome 21, the most prevalent Down syndrome karyotype. Furthermore, using FISH on 1,000 cells, all but 1 cell had three chromosome 21 signals, which effectively ruled out significant low-level mosaicism. To investigate a partial trisomy due, for example, to unbalanced translocation involving chromosome 21 or trisomy with an internally deleted segment of chromosome 21, we carried out high-resolution, genome-wide analysis of DNA copy number using Affymetrix 250K *NspI* SNP arrays. This approach measures DNA copy number using 250,000 markers that are roughly evenly spaced across the genome, thereby providing the ability to detect both whole-chromosome aneuploidies and subchromosomal amplifications and deletions. Figure 1 compares the DNA copy number from Mr. C. (Lane 3), illustrating chromosomes 17, 19, 21, and X, with DNA. The other lanes provide comparisons with other individuals for those respective chromosomes.

The sensitivity of this method is validated by the detection of a small deletion on chromosome arm 17p for 1 of these individuals (Lane 2). Also as shown in Figure 1, the difference between males and females can be easily seen for the X-chromosome

Table 1 Summary of the Selected Tests Reviewed and the Domains Assessed

Test administered	Domain assessed	Brief description
Informant-based measures		
Adaptive Behavior Scale (Part I) ^a	Adaptive behavior	A broadly based assessment of functional abilities. Items on Part I of the ABS measure 10 domains related to self-care and socialization. Maximum score = 280.
Reiss Screen ^b	Mental health problems	Screens for possible depression, psychosis, and behavior problems. Caregivers rate 38 symptoms of psychiatric behavior as being “no problem,” “problem,” or “major problem” for the individual in question. Maximum score = 76.
Dementia Scale for Down Syndrome ^{c,d}	Functional declines associated with Alzheimer’s disease	Includes questions related to activities of daily living and typical behaviors indicative of decline associated with Alzheimer’s disease in individuals with Down syndrome. It also provides information about severity of dementia or rate of deterioration. Maximum score = 60.
Direct testing measures		
IBR Evaluation of Mental Status ^e	Mental status	Brief omnibus measure conceptually based on a mental status examination commonly used to evaluate dementia in the general population without intellectual disability (see Folstein, Folstein, & McHugh, 1975). Consists of questions to determine orientation to person, place, time, the naming of colors and objects, rote memory, and fine-motor praxis. Maximum score = 74.
Selective Reminding Test ^f	Episodic memory	Test consists of the verbal presentation of 8 items within a single category followed by 6 trials of free recall. After the first trial, only those items not recalled on the immediately preceding trial is re-presented for learning on the next trial. Maximum score is the total number of items recalled over the 6 trials = 48.
Block Design Sub-test ^g and Extended Block Design Test ^h	Visuospatial organization	Task involves reproducing visual patterns from models made with red and white Kohs blocks. Each trial has a time limit and the score is the number of designs completed successfully. Bonus points are given for more complicated designs based on how much earlier the design is correctly reproduced. Maximum score = 78.

^aNihira, Foster, Shellhaas, and Leland (1974). ^bReiss Screen for Maladaptive Behavior (Reiss, 1994). ^cGedye (1995). ^dA high score on this measure indicates that more features of dementia were present. ^eH. M. Wisniewski & Hill (1985). ^fKrinsky-McHale et al. (2002). ^gWechsler (1974). ^hHaxby (1989).

dosage, accurately reflecting the presence of two copies for the only female compared with the single copy for males. It is important that no deletions were detected in Mr. C.’s DNA, and Lane 3 shows a uniform increase in DNA copy number for chromosome 21 (within the range of signal variation of this method), thereby verifying the cytogenetic finding of simple trisomy 21. Of course, analyses were conducted only

on one type for Mr. C.’s tissue (lymphocytes) and, therefore, results cannot be generalized to brain or other tissues with absolute certainty, but complete trisomy seems very likely.

We examined Mr. C.’s APOE genotype because it is a genetic marker that may predict age-specific and overall risk for Alzheimer’s disease and longevity in both the general population without intellec-

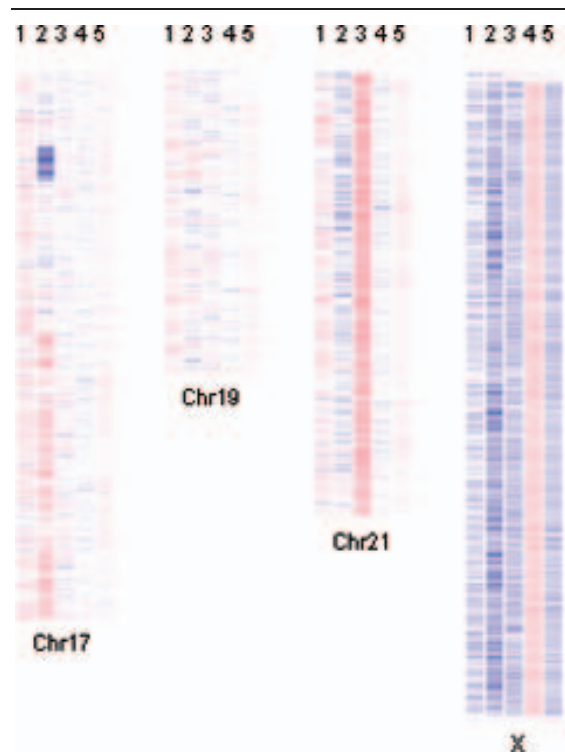


Figure 1 SNP array analysis (Affymetrix 250K Nspl), showing simple trisomy 21 in Mr. C.'s peripheral blood leukocyte DNA. The five vertical lanes for each illustrated chromosome show the DNA copy number of individual markers arranged by physical position from one end (p-telomere) to the other (q-telomere). Blue indicates a single marker copy, pink indicates two copies, and red indicates three copies. Mr. C.'s chromosomes are illustrated in Lane 3, whereas Lanes 1, 2, and 5 are comparisons from men and Lane 4 from a woman. (Lane 4 in the X-chromosome view shows a woman, with the expected two-fold increase in X-chromosome copy number [XX], relative to the other samples from men [XY]). Also note the detection of a microdeletion on chromosome 17 for the comparison case in Lane 2, illustrating the sensitivity of these procedures.

tual disability (see Christensen, Johnson, & Vaupel, 2006, for a review) and in individuals with Down syndrome (Deb et al., 2000; Schupf et al., 1996; Tyrrell et al., 1998). Mr. C.'s observed genotype of 3/3 is the most common allelic expression and would not be considered a contributing factor to either decreased risk for Alzheimer's disease or increased longevity.

Social and Family History

Mr. C. was born in 1936 and was the first-born child following what was reported as an uncomplicated pregnancy and delivery. He was diagnosed with Down syndrome subsequent to his release from the hospital. According to his medical records, his developmental milestones were delayed and he displayed aggressive, tantrum-like behavior. On the advice of the family physician, Mr. C. was placed in an institution for persons with intellectual disabilities in 1941 at the age of 5 years, and over the next 36 years he resided in three different institutions. However, Mr. C. was reported to spend 4 months out of every year in his family home, "the two coldest and the two hottest months," according to his sister (personal communication, December 18, 2006). With the philosophical and societal shift away from large, congregate-care settings that occurred during the 1970s, Mr. C. returned home to live with his parents at the age of 41 and remained with them for the next 12 years. Mr. C. then moved to a supervised community residence and then to an even less restrictive residence 2 years later. At present, he lives with three other men and has support available 24 hr a day. His father died when he was 55 years old and his mother died when he was 63. (Age at death was 82 for his father and 89 for his mother.) According to clinical records, his parents were very involved in his life, even during the 36 years of institutionalization. His surviving younger sister is 67 years old. She reported that the family would visit Mr. C. every Sunday during these years. She remains active in his life, visiting him frequently. There are no reports of Alzheimer's disease or dementia from other causes among his family members.

Mr. C. regularly attends a sheltered workshop 5 days a week for 5 hr per day. He is cognitively capable of traveling to and from this program independently, which requires taking city buses, and did so for many years. However, due to recurrent falling, he now uses a van made available to individuals with disabilities. His work is described as slow but very neat. There is no indication in his records that Mr. C. received a formal education. He is able to write his name and can add coins up to \$1, although he cannot make correct change.

Mr. C. is independent in most areas of activities of daily living, requires little help in organizing his leisure time, and actively participates in his religious community. He is able to choose his clothes and dress independently and has some basic cooking skills, but

he requires assistance with laundry, other household chores, medication administration, medical appointments, and community inclusion. Staff at his residence indicated that he is an avid music lover and likes to play cards. He enjoys going out into the community for walks and patronizing local stores. He is generally described as outgoing and friendly.

Medical Status

Mr. C. is 5'2" tall and his weight has fluctuated over recent years from a low of 141 pounds approximately 6 years ago to his present weight of 164 pounds.

Cardiovascular system. Mr. C. does not have a congenital heart defect. His records indicated that his blood pressure and pulse rate have been normal and stable over the years that we have known him. His cholesterol levels have remained within normal limits, and in 2006 his total cholesterol level was 171 mg/dL (normal reference range <200 mg/dL), high-density lipoprotein = 48 mg/dL (referred to as *good cholesterol*; normal reference range ≥ 40 mg/dL), low-density lipoprotein = 102 mg/dL (referred to as *bad cholesterol*; normal reference range <130; see Zigman, Schupf, Jenkins, Urv, Tycko, & Silverman, 2007, for a discussion of the relation between total cholesterol levels and increased risk of Alzheimer's disease in adults with Down syndrome).

Endocrine. Mr. C. has normal thyroid functioning despite the fact that hypothyroidism is a prevalent condition among adults with Down syndrome (Rooney & Walsh, 1997; Rubello et al., 1995). Over the last 7 years, his thyroid-stimulating hormone (TSH) level, triiodothyronine (T3), and thyroxine (T4) values have remained within normal limits, and no other concerns relevant to endocrine system function were noted in comprehensive reviews of clinical records.

Sensory. Mr. C.'s vision has always been poor and he has worn corrective lenses all his adult life. He is myopic and is reported to have a right eye esotropia (inward eye turn). In 1987, at the age of 51 years, he was declared legally blind. At the age of 63, he underwent cataract extraction with corneal lens implantation in both eyes, and at the age of 65 he had a right-eye corneal transplant. He was also diagnosed with glaucoma at the approximate age of 65. (Treatment for glaucoma has consisted of brimonidine eye drops [Alphagan; Allergan, Irvine, CA], which is an alpha-2 adrenergic agonist.) In 2004, when he was 67, he was diagnosed with age-related macular degeneration. There was

no indication in his medical records of either the specific form of macular degeneration (e.g., nonexudative or exudative forms) or the treatment he is receiving for this condition, if any.

Mr. C.'s hearing has deteriorated significantly over the last few years. A recent evaluation indicated that he has a moderate to severe mixed hearing loss in the right ear and a moderate to profound mixed hearing loss in his left ear. However, he prefers not to wear hearing aids. Recent cognitive testing has been done with the aid of an amplification device, which he tolerates.

Cognitive Status

History. At 16 years of age, Mr. C. had a full-scale IQ score of 40 on the Wechsler Intelligence Scale for Children (WISC; Wechsler, 1949, 1974), an indication that he was functioning at the moderate level of intellectual disability. Subsequent retesting from the mid-1980s through 2001 showed variability, with full-scale Wechsler IQ scores ranging from a low of 52 in 1984 to a high of 60 in 1998 and 2001. The discrepancy in IQ scores with repeated administration cannot be explained. Mr. C. is described as a verbal individual who communicates his wants and needs to staff effectively and without hesitation.

Longitudinal assessments. To emphasize Mr. C.'s successful aging profile, we present his data beside those of 2 other individuals with Down syndrome, a 63-year-old man ("Mr. P.") with Alzheimer's disease and a 57 year-old healthy man ("Mr. M."). Briefly, both Mr. P. and Mr. M. began participating in the study in 1985 when they were 43 and 37 years of age, respectively. At their entry into the study, both men were considered healthy, in that they were not suspected of declines in everyday functioning by their caregivers. In 2001, at the age of 59, Mr. P. received a diagnosis of Alzheimer's disease by a community physician and was classified with dementia based on our research findings of progressive declines in cognition and everyday function. A differential diagnosis of Alzheimer's disease was given using exclusionary criteria consistent with the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV;* American Psychiatric Association, 1994) and the *International Classification of Diseases and Related Health Problems (ICD-10;* World Health Organization, 1992). Mr. M. remains healthy, and his unimpaired status has been confirmed at case conferences. The IQs of both individuals (established at a younger age) were comparable with Mr. C.'s when they entered the

study, but, of course, Mr. P. would now test lower due to dementia. We selected these 2 individuals after examination of the database revealed extensive longitudinal information regarding their cognitive, behavioral, and medical status, spanning over 20 years of their participation in the study, more than was available on other participants in the study. This was especially true of Mr. P., where we have extensive data both preceding and subsequent to his Alzheimer's disease diagnosis.

Dementia evaluations. Mr. C.'s performance on the IBR (Institute for Basic Research) Evaluation of Mental Status (Silverman et al., 2004; H. M. Wisniewski & Hill, 1985) has been stable over the 16 years of testing with scores in the mid- to high 60s out of a possible score of 74 (see Figure 2). He continues to be well oriented to person, place, and time, but he has always shown weakness in the subscales of concentration (involving reciting the alphabet and counting forward and backward) and fine-motor coordination (involving the writing/copying of letters and numbers and drawing geometric shapes). These difficulties may reflect his lack of formal education and are unlikely to be effects of aging. A pattern of stability was also observed in the longitudinal performance of Mr. M.; his scores were typically in the low 70s. Our previous research has found scores on this test to be stable over repeated evaluations (Devenny et al., 1996). This is in contrast to the performance of Mr. P., who has shown a progressive decline in mental status over the years of testing. Prior to his diagnosis of Alzheimer's disease, he scored in the mid- to high 60s; however, at the last assessment he was no longer able to do the task.

Results of repeated administration of the Dementia Scale for Down Syndrome (DSDS; Gedye, 1995) indicated that Mr. C. did not meet the criteria for dementia on this scale. Mr. M. also did not meet the criteria. As documented by the DSDS, Mr. P. has shown the features of progressive dementia. According to responses given by an informant who has known him for many years, as of 2005, he had progressed to the late stages of dementia.

Adaptive and maladaptive behavior. Mr. C.'s scores over the last 6 years on the American Association on Mental Deficiency (now the American Association on Intellectual and Developmental Disabilities) Adaptive Behavior Scale (Part I; Nihira, Foster, Shellhaas, & Leland, 1974; Zigman et al., 1996, 2004) have been stable and have not indicated any evidence of progressive impairments in

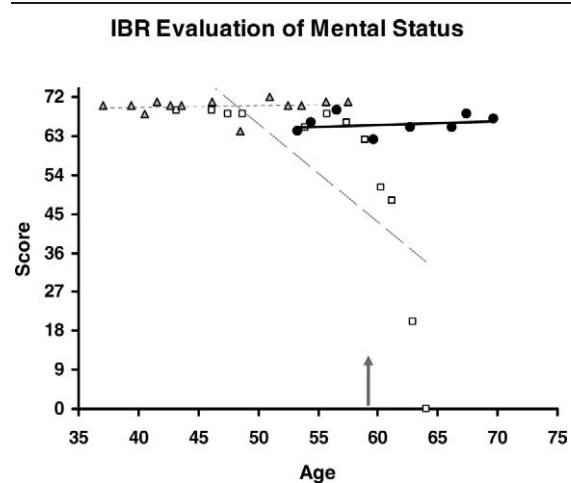


Figure 2 Longitudinal performance with regression lines for Mr. C. (filled circles, solid line), Mr. M. (gray triangles, short dashes), and Mr. P. (open squares, long dashes) on the IBR Evaluation of Mental Status Exam. The red arrow indicates the session that was closest to Mr. P.'s diagnosis.

adaptive behavior suggestive of dementia. Mr. M.'s scores have also been relatively stable. This is in contrast to Mr. P., who has shown a generally progressive decline in adaptive functioning.

Results from the Reiss Screen for Maladaptive Behavior (Reiss, 1994; Urv, Zigman, & Silverman, in press) indicated that Mr. C. has few behavior problems. The staff at his residence has consistently reported that he will occasionally engage in lying and stealing and has the habits of twisting the truth, teasing others, and using foul language when upset. However, these concerns have been longstanding characteristics and are unlikely to be associated with any substantial change in functioning. Mr. M. has shown no consistent behavior problems over time. The staff at Mr. P.'s residence has consistently reported that he exhibits several maladaptive behaviors, but the type and severity of these have become of increasing concern with the progression of dementia. Since diagnosis Mr. P. reportedly has become aggressive, anxious, hostile, impulsive, and inattentive. He also reportedly has exhibited confused thinking, temper tantrums, and sleep problems.

Cognitive assessment. Mr. C. has shown an unusual level of variability in performance on a task of episodic memory, the Selective Reminding Task (Devenny et al., 1996; Krinsky-McHale et al., 2002), even meeting the provisional criterion for the classi-

fication of Alzheimer's disease of a 20% decline from his highest score of 38 (achieved at the age of 57) on several test sessions (see Krinsky-McHale et al., 2002, for a discussion of the provisional criteria). These fluctuations in performance do not appear to be related to either medical conditions or life events, and the cause remains unclear to date. However, on the latest test, Mr. C. obtained a total recall score of 36, the second highest score since his entry into the study, and a regression line of his performance over time indicated minimal change over the last 16 years (Figure 3). The slope of a regression line for Mr. M.'s performance, who is substantially younger, was similar to that of Mr. C. (examination of group data typically reveals small age-associated declines in recall [see Devenny et al., 1996; Krinsky-McHale et al., 2002]; however, we have also observed stable performance over time with individual performance data). The longitudinal performance profiles of Mr. C. and Mr. M. contrast to that of their peer with a diagnosis of Alzheimer's disease, Mr. P., whose recall score has declined substantially over the past 12 years (Figure 3).

In terms of visuospatial organization, Mr. C. has shown some age-associated decline on the Block Design subtest from the Wechsler Intelligence Scale for Children—Revised (Wechsler, 1974) and the Extended Block Design Test (Haxby, 1989), as has Mr. M. However, this is in sharp contrast to Mr. P., who has shown a much steeper decline in performance. Again, Mr. P.'s initial performance was comparable with the other two men, but he no longer can do this task.

Discussion

Mr. C. is a man with Down syndrome who aged successfully through his 60s, a relatively uncommon occurrence in this population. At Age 70, he is the oldest of hundreds of participants in our longitudinal study of aging in adults with Down syndrome who has not shown signs or symptoms of clinical dementia. (There have been individuals in our study older than Mr. C., but none without some indications of dementia by Age 70.) Whereas previously published case studies concerning longevity in this population have described individuals who were older than Mr. C., to our knowledge, ours is the first study to include extensive prospective and longitudinal data on cognitive and behavioral functioning in addition to detailed genetic analyses. Most important, several previous case reports that focused on successful aging of adults with Down

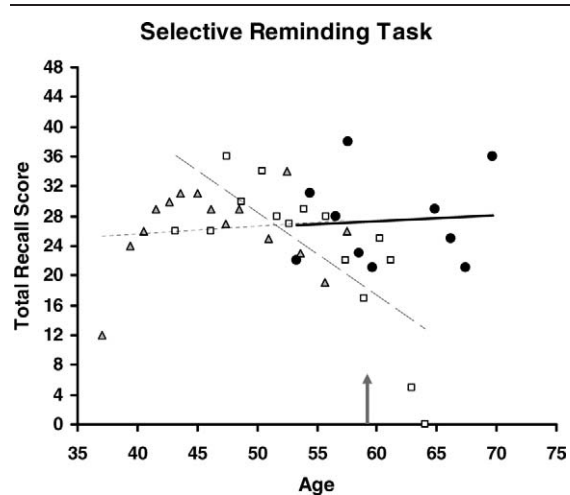


Figure 3 Longitudinal performance with regression lines for Mr. C. (filled circles, solid line), Mr. M. (gray triangles, short dashes), and Mr. P. (open squares, long dashes) on the Selective Reminding Task. The red arrow indicates the session that was closest to Mr. P.'s diagnosis.

syndrome reported atypical genotypes, whereas Mr. C. has complete trisomy 21.

Mr. C.'s neuropsychological profile showed that, although he has not exhibited decline in episodic memory associated with frank dementia, he has been experiencing age-associated changes in cognition, as evidenced by a gradual decline in visuospatial abilities. To emphasize Mr. C.'s successful aging profile, his longitudinal performance was compared with 2 peers, a younger healthy man (Mr. M.) and a similar-aged peer with clinical Alzheimer's disease (Mr. P.). On all of the measures presented, the trajectory of age-associated change was similar for Mr. C. and Mr. M. This was in sharp contrast to the profile of Mr. P., who showed steep declines on all the performance measures over the more recent years of his participation (and who is now untestable with our cognitive assessment battery). We first started testing Mr. C. when he was 53 years old, already a relatively advanced age for his cohort with Down syndrome. It is not possible to know if his performance on our measures would have been better when he was a younger adult, and future studies of extended duration are needed to clarify patterns of cognitive development throughout adulthood.

We looked at several plausible genetic and environmental explanations for Mr. C.'s successful aging. Cytogenetic and FISH analyses showed a kar-

yotype with a complete triplication of chromosome 21 and the absence of mosaicism (even at a low level). Additional analyses using SNP arrays showed a uniform increase in DNA copy number, verifying the cytogenetic findings and showing that all of chromosome 21 was present in three copies. Of course, it is possible that even higher resolution analyses might detect very small regions of chromosome 21 that were not triplicated, but at this point, microdeletions in the third copy of Mr. C.'s chromosome 21 seem unlikely.

We also examined Mr. C.'s APOE genotype because of its strong association with risk of Alzheimer's disease. There are three common variants of the APOE gene encoded for by three alleles, $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$. The $\epsilon 2$ allele reduces risk of Alzheimer's disease in individuals with Down syndrome (Deb et al., 2000; Lai et al., 1999; Schupf et al., 1996, 1998; Tyrell et al., 1998), and the $\epsilon 4$ allele is associated with higher risk (Schupf et al., 1996). Mr. C. has the "neutral" genotype of 3/3, so his APOE status should not be a contributing factor to either his decreased risk for Alzheimer's disease or increased longevity.

We also examined Mr. C.'s medical and family history. He was described as experiencing relatively good health for most of his life. There is no indication in his medical records of a congenital heart defect or hypothyroidism, two common disorders among individuals with Down syndrome. His cholesterol levels also have consistently been in the normal range. It seems relevant to note that both parents lived into their 80s and were reported to be dementia free at the time of their deaths, so he may be fortunate in that he inherited a "good constitution."

Environmental enrichment did not seem to contribute in a major way to Mr. C.'s longevity. He was institutionalized for much of his childhood and early-adult life during an era when these facilities typically had extremely poor living conditions that were unlikely to nurture developmental growth, although it is possible that the negative effects of institutionalization were ameliorated by the active involvement of his family during these years.

What other factors might explain Mr. C.'s individual phenotype? Several potential explanations could be based on genetic factors and variations in gene expression with trisomy 21 (see Antonarakis & Epstein, 2006; Antonarakis, Lyle, Dermitzakis, Raymond, & Deutsch, 2004; Cheung et al., 2003; Morley et al., 2004; Sultan et al., 2007). (*Gene expression* refers to the process by which a gene's DNA is used to produce proteins that influence the structure and

function of cells within our bodies.) As noted earlier, Down syndrome results from the triplication of chromosome 21, and this could result in the systematic overexpression of all its constituent genes. However, variability in this overexpression can occur and may be partially responsible for individual differences in phenotypic presentation among affected individuals (Antonarakis & Epstein, 2006; Antonarakis et al., 2004; Sultan et al., 2007). That is, for different genes on chromosome 21, the effects of trisomy may be dosage compensated to differing degrees across individuals, and recent findings have also indicated that gene overexpression can vary with cell type and may change with cell senescence (Li et al., 2006). In addition, for some organ systems, some cells may not actually have the trisomy 21, depending on the timing of the nondisjunction event that originally resulted in Down syndrome, and there could be variations in genotype among tissues originating from different germ layers. All these factors may be contributing to Mr. C.'s specific phenotype (see de Arruda Cardoso Smith et al., 2004) and future studies of atypical cases will be needed to clarify if and how these types of mechanisms influence life span development. Although cytogenetic and SNP array data clearly indicated no mosaicism in Mr. C.'s blood cells (lymphocytes, specifically), additional testing on tissue closer embryologically to the brain (e.g., skin) could be very informative (Jenkins & Velinov, 2001; Kingsbury, Yung, Peterson, Westra, & Chun, 2006).

The specific genes that are implicated in the phenotypic features of Down syndrome are still generally unknown (Antonarakis et al., 2004; Li et al., 2006). Recent research has identified a region on the chromosome proximal to 21q22.3 that contains critical genes (Rahmani et al., 2005). However, Korenberg et al. (1994) examined individuals with partial trisomy 21 and found evidence suggesting a significant contribution of genes outside this Down syndrome-critical region (also see Olson et al., 2007). Interactions either among genes on chromosome 21 or among those on chromosome 21 and others also have been hypothesized as contributing to phenotypic variability (see Antonarakis & Epstein, 2006; Korenberg et al., 2004) and nongenetic factors such as learning and experience cannot be ignored (Jenkins & Velinov, 2001; Korenberg et al., 2004).

The processes regulating aging and dementia are extraordinarily complex, and it is unlikely that a single mechanism can fully explain the spectra of change and stability that occur with successful and unsuccessful aging in individuals with Down syndrome. As

more information is discovered about the genes on chromosome 21, their products, the impact of the occurrence of an extra copy of chromosome 21 on the rest of the genome, and the effects of nongenetic factors, researchers will achieve a better understanding of the underlying factors and mechanisms that contribute to all aspects of phenotypic variability associated with Down syndrome (see Jenkins & Velinov, 2001). This will lead potentially to better strategies for minimizing disability and for promoting successful aging to an even greater degree than has been seen over the last several decades.

References

- American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: Author.
- Antonarakis, S. E., & Epstein, C. J. (2006). The challenge of Down syndrome. *Trends in Molecular Medicine*, *12*, 473–479.
- Antonarakis, S. E., Lyle, R., Dermitzakis, E. T., Raymond, A., & Deutsch, S. (2004). Chromosome 21 and Down syndrome: From genomics to pathophysiology. *Nature Review. Genetics*, *5*, 725–738.
- Aylward, E. H., Burt, D. B., Thorpe, L. U., Lai, F., & Dalton, A. J. (1995). *Diagnosis of dementia in individuals with intellectual disability*. Washington, DC: American Association on Mental Retardation.
- Baird, P. A., & Sadovnick, A. D. (1987). Life expectancy in Down syndrome. *The Journal of Pediatrics*, *110*, 849–854.
- Baird, P. A., & Sadovnick, A. D. (1988). Life expectancy in Down syndrome adults. *The Lancet*, *2*, 1354–1356.
- Baird, P. A., & Sadovnick, A. D. (1989). Life tables for Down syndrome. *Human Genetics*, *82*, 291–292.
- Buchanan, L. H. (1990). Early onset of presbycusis in Down syndrome. *Scandinavian Audiology*, *19*, 103–110.
- Burt, D., & Aylward, E. (2000). Test battery for the diagnosis on dementia in individuals with intellectual disability. *Journal of Intellectual Disability Research*, *44*, 262–270.
- Burt, D. B., Loveland, K. A., Chen, Y., Chuang, A., Lewis, K. R., & Cherry, L. (1995). Aging in adults with Down syndrome: Report from a longitudinal study. *American Journal on Mental Retardation*, *100*, 262–270.
- Burt, D. B., Primeaux-Hart, S., Loveland, K. A., Cleveland, L. A., Lewis, K. R., Lesser, J., & Pearson, P. L. (2005). Aging adults with intellectual disabilities. *American Journal on Mental Retardation*, *110*, 268–284.
- Castane, M., Boada-Rovira, M., & Hernandez-Ruiz, I. (2004). Eye conditions as features of Down's syndrome in patients over 40 years of age. *Revista de Neurologia*, *39*, 1017–1021.
- Cheung, V. G., Conlin, L. K., Weber, T. M., Arcaro, M., Jen, K. Y., Morley, M., & Spielman, R. S. (2003). Natural variation in human gene expression assessed in lymphoblastoid cells. *Nature Genetics*, *33*, 422–425.
- Chicoine, B., & McGuire, D. (1997). Longevity in a woman with Down syndrome: A case study. *Mental Retardation*, *35*, 477–479.
- Chicoine, B., McGuire, D., Hebein, S., & Gilly, D. (1994). Development of a clinic for adults with Down syndrome. *Mental Retardation*, *32*, 100–106.
- Christensen, K., Johnson, T. E., & Vaupel, J. W. (2006). The quest for genetic determinants of human longevity: Challenges and insights. *Nature Review. Genetics*, *7*, 436–448.
- Connolly J. A. (1978). Intelligence levels on Down's syndrome children. *American Journal of Mental Deficiency*, *83*, 193–196.
- de Arruda Cardoso Smith, M., Borsatto-Galera, B., Feller, R. I., Gonçalves, A., Oyama, R. S. K., Segato, R., Chen, E., Griz Carvalheira, G. M., Clemente Filho, A. S., Rodríguez Burbano, R., & Marques Payão, S. L. (2004). Telomeres on chromosome 21 and aging in lymphocytes and gingival fibroblasts from individuals with Down syndrome. *Journal of Oral Science*, *46*, 171–177.
- Deb, S., Braganza, J., Norton, N., Williams, H., Kehoe, P. G., Williams, J., & Owen, M. J. (2000). APOE epsilon 4 influences the manifestation of Alzheimer's disease in adults with Down's syndrome. *Journal of Psychiatric Research*, *176*, 468–472.
- Demissie, A., Ayres, R. C., & Briggs, R. (1988). Old age in Down syndrome's syndrome. *Journal of the Royal Society of Medicine*, *81*, 740.
- Devenny, D. A., & Krinsky-McHale, S. J. (1998). Age-associated differences in cognitive abilities in adults with Down syndrome. *Topics in Geriatric Rehabilitation*, *13*, 65–72.
- Devenny, D. A., Krinsky-McHale, S. J., Sersen, E., & Silverman, W. P. (2000). Sequence of cognitive decline in dementia in adults with Down

- syndrome. *Journal of Intellectual Disability Research*, 44, 654–665.
- Devenny, D. A., Silverman, W. P., Hill, A. L., Jenkins, E., Sersen, E. A., & Wisniewski, K. E. (1996). Normal ageing in adults with Down's syndrome: A longitudinal study. *Journal of Intellectual Disability Research*, 40, 208–221.
- Devenny, D. A., Wegiel, J., Schupf, N., Jenkins, E., Zigman, W., Krinsky-McHale, S. J., & Silverman, W. P. (2005). Dementia of the Alzheimer's type and accelerated aging in Down syndrome. *Science SAGE KE*. Retrieved from <http://sageke.sciencemag.org/cgi/content/full/sageke>
- Devenny, D. A., & Zimmerli, E. J. (1996, March). *Age-associated changes in non-verbal abilities in adults with Down syndrome*. Presentation at the 27th Annual Gatlinburg Conference on Research and Theory in Mental Retardation and Developmental Disabilities, Gatlinburg, TN.
- Dupont, A., Vaeth, M., & Videbeck, P. (1986). Mortality and life expectancy in Down's syndrome in Denmark. *Journal of Mental Deficiency Research*, 30, 111–120.
- Dykens, E. M., Hodapp, R. M., & Finucane, B. M. (2000). *Genetics and mental retardation syndromes*. Baltimore: Brookes.
- Evenhuis, H. M. (1995). Medical aspects of ageing in a population with intellectual disability: 1. Visual impairment. *Journal of Intellectual Disability Research*, 39, 19–25.
- Evenhuis, H. M., Theunissen, M., Denkers, I., Verschuure, H., & Kemme, H. (2001). Prevalence of visual and hearing impairment in a Dutch institutionalized population with intellectual disability. *Journal of Intellectual Disability Research*, 45, 457–464.
- Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, 12, 189–198.
- Forssman, H., & Åkesson, H. O. (1965). Mortality in patients with Down's syndrome. *Journal of Mental Deficiency Research*, 9, 146–149.
- Fromage, B., & Anglade, P. (2002). The aging of Down's syndrome subjects. *Encephale*, 28, 212–216.
- Gedy, A. (1995). *Dementia Scale for Down Syndrome manual*. Vancouver, Canada: Author.
- Glasson, E. J., Sullivan, S. G., Hussain, R., Pette-son, B. A., Montgomery, P. D., & Bittles, A. H. (2003). Comparative survival advantage of males with Down syndrome. *American Journal of Human Biology*, 15, 192–195.
- Haxby, J. V. (1989). Neuropsychological evaluations of adults with Down's syndrome: Patterns of selective impairment in non-demented old adults. *Journal of Mental Deficiency Research*, 33, 193–210.
- Haxby, J. V., & Shapiro, M. B. (1992). Longitudinal study of neuropsychological function in older adults with Down syndrome. In L. Nadel & C. J. Epstein (Eds.), *Down syndrome and Alzheimer disease* (pp. 35–50). New York: Wiley-Liss.
- Hixson, J. E., & Vernier, D. T. (1990). Restriction isotyping of human apolipoprotein E by gene amplification and cleavage with HhaI. *Journal of Lipid Research*, 31, 545–548.
- Hof, P. R., Bouras, C., Perl, D. P., Sparks, I., Mehta, N., & Morrison, J. H. (1995). Age-related distribution of neuropathologic changes in the cerebral cortex of patients with Down's syndrome. *Archives of Neurology*, 52, 379–391.
- Holland, A. J., Hon, J., Huppert, F. A., Stevens, F., & Watson, P. (1998). Population-based study of the prevalence and presentation of dementia in adults with Down's syndrome. *British Journal of Psychiatry*, 172, 493–498.
- Hyman, B. T., West, H. L., Rebeck, G. W., Lai, F., & Mann, D. M. A. (1995). Neuropathological changes in Down's syndrome hippocampal formation. *Archives of Neurology*, 52, 373–378.
- Jancar, J. (1989). Old age in Down's syndrome [Letter]. *Journal of the Royal Society of Medicine*, 82, 317–318.
- Jenkins, E. C., Duncan, C. J., Wright, C. E., Wilbur, L., Wisniewski, K., Sklower, S. L., French, J. H., Jones, C., Rucquoi, J., & Brown, W. T. (1983). Atypical Down syndrome and partial trisomy. *Clinical Genetics*, 24, 97–101.
- Jenkins, E. C., Schupf, N., Genovese, M., Ye, L., Kappell, D., Canto, B., Harris, M., Devenny, D., Lee, J. H., & Brown, W. T. (1996). Older individuals with Down syndrome exhibit increased loss of chromosomes [Abstract]. Abstract presented at the annual meeting of the American Society of Human Genetics. *American Journal of Human Genetics*, 59, A121 (Abstract 670).
- Jenkins, E. C., & Velinov, M. T. (2001). Down syndrome and the human genome. *Down Syndrome Quarterly*, 6(4), 1–12.
- Jeziorowska, A., Houck, Jr., G. E., Yao, X.-L., Sklower-Brooks, S. L., Wisniewski, K. E., Jenkins, E. C., & Wisniewski, H. M. (1992). Re-

- assessment of a chromosome 12Q+ marker by fluorescent in situ hybridization (FISH). *Clinical Genetics*, 42, 124–128.
- Kingsbury, M. A., Yung, Y. C., Peterson, S. E., Westra, J. W., & Chun, J. (2006). Aneuploidy in the normal and diseased brain. *Cellular and Molecular Life Sciences*, 63, 2626–2641.
- Korenberg, J. R., Chen, X.-N., Schipper, R., Sun, Z., Gonsky, R., Gerwehr, S., Carpenter, N., Daumer, C., Dignan, P., Distèche, Graham, Jr., J. M., Hugdins, L., McGillivray, B., Miyazaki, K., Ogasawara, N., Park, J. P., Pagon, R., Puschel, S., Sack, G., Say, B., Schuffenhauer, S., Soukup, S., & Yamanaka, T. (1994). Down syndrome phenotypes: The consequences of chromosomal imbalance. *Proceeding of the National Academy of Sciences*, 91, 4997–5001.
- Krinsky-McHale, S. J., Abramov, I., Devenny, D. A., Gordon, J., Oley, N., & Tannazzo, T. (2001, March). *Visual deficits in adults with Down syndrome*. Paper presented at the 34th annual Gatlinburg conference on Research and Theory in Mental Retardation and Developmental Disabilities, Charleston, SC.
- Krinsky-McHale, S. J., Devenny, D. A., & Silverman, W. P. (2002). Changes in explicit memory associated with early dementia in adults with Down syndrome. *Journal of Intellectual Disability Research*, 46, 98–108.
- Lai, F., Kammann, E., Rebeck, G. W., Anderson, A., Chen, Y., & Nixon, R. A. (1999). APOE genotype and gender effects on Alzheimer disease in 100 adults with Down syndrome. *Neurology*, 53, 331–336.
- Lai, F., & Williams, R. S. (1989). A prospective study of Alzheimer disease in Down syndrome. *Archives of Neurology*, 46, 849–853.
- Li, C. M., Guo, M., Salas, M., Schupf, N., Silverman, W., Zigman, W. B., Husain, S., Warburton, D., Thaker, H., & Tycko, B. (2006). Cell type-specific over-expression of chromosome 21 genes in fibroblasts and fetal hearts with trisomy 21. *BMC Medical Genetics*, 15, 7–24.
- Li, C., & Wong, W. H. (2001). Model-based analysis of oligonucleotide arrays: Expression index computation and outlier detection. *Proceedings of the American Academy of Science*, 98, 31–36.
- Mann, D. M. A. (1993). Association between Alzheimer disease and Down syndrome: Neuropathological observation. In J. M. Berg, K. Karlinsky, & A. J. Holland (Eds.), *Alzheimer's disease, Down syndrome and their relationship* (pp. 711–792). Oxford, United Kingdom: Oxford University Press.
- Merrick, J., Kandel, I., & Morad, M. (2003). Health needs of adults with intellectual disability relevant for the family physician. *The Scientific World Journal*, 3, 937–945.
- Morley, M., Molony, C. M., Weber, T. M., Devlin, J. L., Ewens, K. G., Spielman, R. S., & Cheung, V. G. (2004). Genetic analysis of genome-wide variation in human gene expression. *Nature*, 430, 743–747.
- National Institute of Child Health & Human Development. (1997). *Facts about Down syndrome* [Brochure]. Retrieved November 27, 2006, from http://www.nichd.nih.gov/publications/pubs_details.cfm?from=&pubs_id=24
- Nihira, K., Foster, R., Shellhaas, M., & Leland, H. (1974). *AAMD Adaptive Behavior Scale*. Washington, DC: American Association on Mental Deficiency.
- Oliver, C., Crayton, L., Holland, A., Hall, S., & Bradbury, J. (1998). A four-year prospective study of age-related cognitive change in adults with Down syndrome. *Psychological Medicine*, 28, 1365–1377.
- Olson, L. E., Roper, R. J., Sengstaken, C. L., Peterson, E. A., Aquino, V., Galdzicki, Z., Siarey, R., Pletnikov, M., Moran, T. H., & Reeves, R. H. (2007). Trisomy for the Down syndrome 'critical region' is necessary but not sufficient for brain phenotypes of trisomic mice. *Human Molecular Genetics*, 16, 774–782.
- Prasher, V. P. (1995a). Age-specific prevalence thyroid dysfunction and depressive symptomatology in adults with Down syndrome and dementia. *International Journal of Geriatric Psychiatry*, 110, 25–31.
- Prasher, V. P. (1995b). Epilepsy and associated effects on adaptive behavior in adults with Down syndrome. *Seizure*, 4, 53–56.
- Prasher, V. P., Farrer, M. J., Kessling, A. M., Fisher, E. M. C., West, R. J., Barber, P. C., & Butler, A. C. (1998). Molecular mapping of Alzheimer-type dementia in Down's syndrome. *Annals of Neurology*, 43, 380–383.
- Prasher, V. P., & Krishnan, V. H. R. (1993). Age of onset and duration of dementia in people with Down syndrome: Integration of 98 reported cases in the literature. *International Journal of Geriatric Psychiatry*, 8, 915–922.
- Rahmani, Z., Blouin, J.-L., Créau-Goldberg, N., Watkins, P. C., Mattei, J.-F., Poissonnier, M., et

- al. (2005). Down syndrome critical region around D21S55 on proximal 21q22.3. *American Journal of Medical Genetics*, 37(S2), 98–103. Retrieved from <http://www3.interscience.wiley.com/cgi-bin/abstract/110515872/ABSTRACT?CRETRY=1&SRETRY=0>.
- Rasmussen, D. E., & Sobsey, D. (1994). Age, adaptive behavior and Alzheimer's disease in Down syndrome cross-sectional and longitudinal analyses. *American Journal on Mental Retardation*, 99, 151–165.
- Reiss, S. (1994). *Handbook of challenging behavior: Mental health aspects of mental retardation*. Worthington, OH: IDS Publishing.
- Roizen, N. J. (2001). Down syndrome: Progress in research. *Mental Retardation and Developmental Disabilities Research Reviews*, 7, 38–44.
- Rooney, S., & Walsh, E. (1997). Prevalence of abnormal thyroid function test in a Down's syndrome population. *Irish Journal of Medical Science*, 166, 80–82.
- Rubello, D., Pozzan, G. B., Casara, D., Girelli, M. E., Boccato, S., Rigon, F., Baccichetti, C., Piccolo, M., Betterle, C., & Busnardo, B. (1995). Natural course of subclinical hypothyroidism in Down's syndrome: Prospective study results and therapeutic considerations. *Journal of Endocrinological Investigation*, 18, 35–40.
- Rumble, B., Retallack, R., Hilbich, C., Simm, G., Multhaup, G., Martins, R., Hockey, A., Montgomery, P., Beyreuther, K., & Masters, C. L. (1989). Amyloid A4 protein and its precursor in Down's syndrome and Alzheimer's disease. *New England Journal of Medicine*, 320, 1446–1452.
- Schupf, N., Kapell, D., Lee, J. H., Zigman, W., Canto, B., Tycko, B., & Mayeux, R. (1996). Onset of dementia is associated with apolipoprotein E ϵ 4 in Down syndrome. *Annals of Neurology*, 40, 799–801.
- Schupf, N., Kapell, D., Nightingale, B., Rodriguez, A., Tycko, B., & Mayeux, R. (1998). Earlier onset of Alzheimer's disease in men with Down syndrome. *Neurology*, 50, 991–995.
- Silverman, W., Schupf, N., Zigman, W., Devenny, D., Miezieski, C., Schubert, R., & Ryan, R. (2004). Dementia in adults with mental retardation: Assessment at a single point in time. *American Journal on Mental Retardation*, 109, 111–125.
- Silverman, W., Zigman, W. B., Kim, H., Krinsky-McHale, S., & Wisniewski, H. M. (1998). Aging and dementia among adults with mental retardation and Down syndrome. *Topics in Geriatric Rehabilitation*, 13, 45–64.
- Strauss, D., & Eyman, R. (1996). Mortality of people with mental retardation in California with and without Down syndrome, 1986–1991. *American Journal on Mental Retardation*, 100, 643–653.
- Sultan, M., Piccini, I., Balzereit, D., Herwig, R., Saran, N. G., Lehrach, H., et al. (2007). Gene expression variation in Down's syndrome mice allows prioritization of candidate genes. *Genome Biology*, 8(5), R91.
- Thase, M. E., Tigner, R., Smeltzer, D. J., & Liss, L. (1984). Age related neuropsychological deficits in Down's syndrome. *Biological Psychiatry*, 19, 571–585.
- Tyrrell, J., Cosgrave, M., Hawi, Z., McPherson, J., O'Brien, C., McCalvert, J., McLaughlin, M., Lawlor, B., & Gill, M. (1998). A protective effect of apolipoprotein E ϵ 2 allele on dementia in Down's syndrome. *Biological Psychiatry*, 43, 397–400.
- Urv, T. K., Zigman, W. B., & Silverman, W. (in press). Maladaptive behaviors related to dementia status in adults with Down syndrome. *American Journal on Mental Retardation*.
- U.S. Centers for Disease Control and Prevention. (2006). Improved national prevalence estimates for 18 selected major birth defects—United States, 1999–2001. *Morbidity and Mortality Weekly Report*, 54(51&52), 1301–1305.
- Vicari, S., Nocentini, U., & Caltagirone, C. (1995). Neuropsychological diagnosis of aging in adults with Down syndrome. *Developmental Brain Dysfunction*, 7, 340–348.
- Wechsler, D. (1949). *Manual for the Wechsler Intelligence Scale for Children*. New York: The Psychological Corporation.
- Wechsler, D. (1974). *Wechsler Intelligence Scale for Children—Revised*. New York: The Psychological Corporation.
- Wisniewski, H. M., & Hill, A. L. (1985). Clinical aspects of dementia in mental retardation and developmental disabilities. In M. P. Janicki & H. M. Wisniewski (Eds.), *Aging and developmental disabilities* (pp. 195–207). Baltimore: Brookes.
- Wisniewski, H. M., Wegiel, J., & Popovitch, E. R. (1994). Age-associated development of diffuse and thioflavin-S-positive plaques in Down syn-

- drome. *Developmental Brain Dysfunction*, 7, 330–339.
- Wisniewski, K., Wisniewski, H. M., & Wen, G. Y. (1985). Occurrence of neuropathological changes and dementia of Alzheimer's disease in Down's syndrome. *Annals of Neurology*, 17, 278–282.
- Wisniewski, T., Morelli, L., Wegiel, J., Levy, E., Wisniewski, H. M., & Fragione, B. (1995). The influence of apolipoprotein E isotypes on Alzheimer's disease pathology in 40 cases of Down's syndrome. *Annals of Neurology*, 37, 136–138.
- World Health Organization. (1992). *International statistical classification of diseases and related health problems* (10th ed.). Geneva, Switzerland: Author.
- Yang, Q., Rasmussen, S. A., & Friedman, J. M. (2002). Mortality associated with Down's syndrome in the USA from 1983 to 1997: A population-based study. *The Lancet*, 359, 1019–1025.
- Zigman, W. B., Schupf, N., Devenny, D. A., Mizejeski, C., Ryan, R., Urv, T. K., Schubert, R., & Silverman, W. (2004). Incidence and prevalence of dementia in elderly adults with mental retardation without Down syndrome. *American Journal on Mental Retardation*, 109, 126–141.
- Zigman, W. B., Schupf, N., Jenkins, E. C., Urv, T. K., Tycko, B., & Silverman, W. (2007). Cholesterol level, statin use and Alzheimer's disease in adults with Down syndrome. *Neuroscience Letters*, 416, 279–284.
- Zigman, W. B., Schupf, N., Lubin, R. A., & Silverman, W. P. (1987). Premature regression of adults with Down syndrome. *American Journal of Mental Deficiency*, 92, 161–168.
- Zigman, W. B., Schupf, N., Sersen, E., & Silverman, W. (1996). Prevalence of dementia in adults with and without Down syndrome. *American Journal on Mental Retardation*, 100, 403–412.

Received 1/17/07, first decision 6/11/07, accepted 9/19/07.

Editor-in-Charge: Steven J. Taylor

We are grateful to Mr. C., Mr. M., and Mr. P.; their families; and the following agencies for their continued support and assistance with our research: Association

for the Help of Retarded Children of Manhattan, Guild for Exceptional Children, Federation Employment and Guidance Service, Inc. (FEGS), and the United Cerebral Palsy Association of New York State. We would like to thank Catherine Marino, Deborah Pang, Robert Ryan, and Marcia Dabbene, our project coordinators, for their invaluable contribution to this project over the years. We also thank Deirdre Conlon, Lisa Kullman, Tracy Listwan, Giovanna Palma, David Swift, Anna Trzeciak, and Sheelagh Vietze for their dedication and meticulous skills in conducting cognitive testing, informant interviews, and medical chart reviews. A special thank you goes to Mr. C.'s sister, who spent time with the first author reminiscing about Mr. C.'s life and providing details and stories that his charts could not.

This work was supported by funds from the New York State Office of Mental Retardation and Developmental Disabilities and National Institutes of Health Grants P01 HD35897 to Wayne Silverman and R01 AG14771 to Darlynn A. Devenny.

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