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Aging in Rare Intellectual Disability Syndromes

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This review highlights several methodological challenges involved in research on aging, health, and mortality in adults with rare intellectual disability syndromes. Few studies have been performed in this area, with research obstacles that include: the ascertainment of older adults with genetic versus clinical diagnoses; likelihood that adults will not receive adequate health care and referrals to genetic specialists; cohort differences related to generational and treatment effects; and increased mortality and selective survival biases. Even so, aging in Prader-Willi and Williams syndromes are reviewed as they reveal new insights into the phenotypic expression and treatment options for older adults with these disorders. The review ends with recommendations for future research that takes better advantage of genetic advances, changes in adult phenotypes, and ties across syndrome-specific research silos. Although aging in rare neurodevelopmental disorders is barely on the research landscape, the field stands to learn much from these older adults. Dev Disabil Res Rev 2013;18:75–83.

Key words: aging; intellectual disability; Prader-Willi syndrome; Williams syndrome; adult intervention

Scant data exist on the healthy or typical aging processes of adults with intellectual disabilities and rare genetic disorders. Healthy aging aside, even the life expectancies or causes of death have yet to be rigorously studied in adults with most rare syndromes. In contrast to these conditions, aging in Down syndrome has been relatively well studied, especially as it relates to high rates of Alzheimer's disease in this population (see Zigman, this issue).

This article first identifies several inter-related reasons for the paucity of published research on aging or adulthood in rare intellectual disability syndromes. Two syndromes are then briefly reviewed that exemplify the inherent challenges in studying aging in these groups, and how both phenotypic complexities and the aging process complicate this work. Last, recommendations are made for future work on aging in rare syndromes. These ideas build on accomplishments to date, but also require new ways of thinking for the scientific and professional communities who study and serve individuals with these rare disorders.

Why Hasn't Aging in Rare Intellectual Disability Syndromes Been Studied?

Note that this question specifically targets aging and not other features of rare neurodevelopmental disorders. Indeed, in a thorough analysis of which neurodevelopmental disorders get researched and why, Bishop [2010] found that, when prevalence is taken into account, the number of publications on rare conditions far exceeds those for more common neurodevelopmental disorders, primarily because rare disorders often have more severe clinical manifestations. These findings are virtually identical in the field of neurology, where severity as opposed to prevalence was also associated with increased numbers of publications on rare, life-threatening neurological diseases [Al-Shahi et al., 2001].

Thus, severe neurodevelopmental disorders are indeed studied, typically by geneticists, neuroscientists, and pediatricians [Bishop, 2010]. The bulk of this work, however, is focused on affected infants and children, or the genetic and neurobiological mechanisms that underpin these severe conditions. A lifespan approach has yet to be used, leaving it unknown how, when, or why the aging process impacts the health or quality of life of older adults with these disorders and their families.

Ascertainment of Adults

A major obstacle to aging research in rare intellectual disability syndromes is the ascertainment of properly diagnosed adults with these disorders. Beyond low prevalence rates, work with these adults is impeded by diagnostic obstacles in adults versus children, the recent availability of many genetic tests, and reduced life expectancies.

Child versus adult identification. Relative to young children, adults are less likely to be screened, detected, or diagnosed with rare genetic syndromes. Many rare genetic disorders are increasingly identified in infancy or early

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childhood, and there is a general consensus across disorders that the average age of diagnosis is getting younger over time.

This trend is attributed to increased awareness and knowledge of these disorders in the medical community, especially during infancy. A severely hypotonic newborn with a poor sucking reflex, for example, should automatically trigger suspicion of Prader-Willi syndrome in contemporary, well-trained medical geneticists or pediatricians [Cassidy and Driscoll, 2009]. Even if not identified in infancy, children with developmental delays typically have a safety net of pediatric care, early intervention, and special education services. This safety net increases the likelihood that, at some point in their childhood, they will be properly screened or diagnosed.

This safety net, however, dissolves as youth age out of pediatric care and leave school and special education services, usually between 18 and 21 years old. Indeed, services for adults versus children with intellectual disabilities are typically fragmented, scattered across multiple funding agencies, and less readily navigated or accessible to families. In the U.S. alone, an estimated 2.4 million adults with intellectual disabilities are on waiting lists for services [National Council on Disability, 2005].

The transition period from adolescence to young adulthood is also a time when health and mental health disparities worsen [Krahn et al., 2006]. In contrast to those without disabilities, adults with intellectual disabilities are less likely to have routine medical visits, or to be regularly screened or treated by their physicians for any number of concerns, ranging from elevated cholesterol to changes in weight, vision, hearing, behavior or mood. They are also less likely to be referred to specialists for diagnostic evaluations regarding the underlying cause for their disability. In this context, physicians may not think to send their adult patients for genetic testing for a childhood onset "developmental disorder" [Tyler, 1998]. In medical school curricula, intellectual disabilities typically come under the purview of pediatrics or genetics, not adult or geriatric medicine [Perkins and Moran, 2010].

Beyond diminished professional awareness of developmental disorders in adulthood, parents may also be less invested in pursuing a genetic diagnosis in their child's later versus earlier years. Many parents of adult children with intellectual disabilities harbor the view that pursuing a genetic or other diagnosis would not be of any great benefit. Some parents also feel that a genetic diagnosis would not substantially alter what they do to support their child -- "We went through all of that early on, she is who she is", "What good would it do?" Other parents, however, who receive diagnoses for their adult children are grateful for finally having "an answer" and for the new sources of information and support offered through syndrome-specific advocacy groups. A correct diagnosis can also positively impact how some adults with disabilities view themselves and their strengths, challenges, or life circumstances [Tyler, 1998].

Recent discoveries and availability of genetic testing. A second complication is that many rare conditions have only recently been discovered, and glaring cohort effects exist in these populations. Although Langdon Down first identified Down syndrome some 160 years ago, Lejeune first identified trisomy 21 as its cause only 53 years ago. Similarly, many rare intellectual disability syndromes were first described phenotypically, and syndrome diagnoses were initially made using clinical criteria. Only later were the genetic causes of these syndromes discovered, many in the last 20 years. Table 1 demonstrates this traditional time sequence for several rare syndromes, from the clinical characterizations of syndromes to the discovery of their genetic causes.

Table 1 also includes age projections for various cohorts of affected individuals, based on the year when the genetic etiologies of these syndromes were first published in the literature up to the present time. Obviously, individuals were diagnosed using clinical criteria prior to these genetic discoveries, and today's clinically diagnosed adults may or may not ever receive confirmatory genetic testing. Thus, if researchers wanted to now study older adults with rare syndromes, their sample may or may not have received confirmatory genetic testing. These samples also would not have received the same syndrome-specific interventions as their younger counterparts.

In contrast, if researchers wanted to minimize cohort effects by only recruiting individuals who received genetic testing early in life and thus received similar interventions, they would be studying a younger sample. For example, Table 1 indicates that if individuals were genetically diagnosed with Williams syndrome between birth and 10 years of age, they would now be 19 to 29 years old. While Table 1 is an imperfect guide, as many older adults are also genetically diagnosed, it does demonstrate the temporal complexity of aging research in rare disorders.

The diagnostic odyssey of some individuals and families also demonstrates the complex interplay among time, age and specific genetic breakthroughs. For example, it is not uncommon for older individuals with clinical diagnoses of Prader-Willi syndrome to be "undiagnosed" once they receive genetic testing and a thorough medical history. Being undiagnosed may be a highly emotionally experience for families, and many continue to seek information and support through syndrome-specific parent advocacy groups.

On the flip side, anecdotes abound of adults who were first diagnosed with a genetic disorder much later in life, often due to chance or serendipity. One parent approached a family in the airport, spontaneously pointed out the similarities between their sons, and asked the unaware couple if they are also a Williams syndrome family. An immobile, morbidly obese man was lifted by crane from his apartment window, and, with the ensuing media coverage, came to the attention of Prader-Willi syndrome advocates. A newly assigned legal guardian for two institutionalized adults was especially drawn to her new charge with the broad smile and frequent laughter. She mentioned him to her husband in medical school who recalled a lecture on genomic imprinting. After reading his history, she insisted that this institutionalized adult be tested for Angelman syndrome.

Although we are often left wondering how these "classic" individuals could have possibly been missed, these chance encounters are profoundly life changing. Over time, and with increased awareness of rare conditions, fewer stories may be told about how some older adults, by chance or circumstance, ultimately receive diagnoses. These stories also make it clear that some older adults may never get diagnosed, which also confounds current research.

In summary, many individuals with rare genetic disorders became adults long before their syndrome was either phenotypically or genetically identified. Several factors conspire to makes it less likely that these adults will now be routinely screened for syndrome diagnoses. These include the

Table 1. Dates of Clinical and Genetic Identification of Selected Rare Syndromes, Lag Between the Two, and Prevalence and Age Projections

Clinical Identification of Syndrome	Genetic Cause of Syndrome	Years Lag	Prevalence Estimates	Current Age if Genetically Diagnosed Between Birth and 10 years
1961, Williams-Beuren syndrome	1993, Ewart et al; deletion at 7q11.23 in most cases	32	1:7,500 to 1:15,000	19 to 29 years
1956, Prader-Labhart-Willi syndrome	1981, Ledbetter et al, deletion at 15q11-q13 in many but not all cases 1983, Butler et al, deletion is paternal in origin 1989, Nicholls et al, genomic imprinting and mUPD	23 for deletion 33 for mUPD	1:15,000 to 1:25,000	23 to 33 years
1965, Angelman syndrome	1987, Magenis et al, maternal deletion at 15q11-q13 in many cases 1997, Kishino et al, 1997, Matsuura et al. both show UBE3A/E6-AP mutations cause Angelman syndrome	22 for deletion, 32 for UBE3A	1:10,000 to 1:40,000	15 to 25 years
1966, Rett syndrome	1999 Amir et al, MECP2 mutations at Xq28 cause Rett syndrome	33	1:10,000 to 1:22,000	13 to 23 years
1933, Cornelia de Lange syndrome	2004, Kranz et al, NIPBL mutations at 5p13.1 in most cases 2007, Deardoff et al, SMC1A, SMC3 mutations in 5%	71	1:10,000 to 1:30,000	8 to 18 years
1963, Rubinstein- Taybi syndrome	1995, Petrij et al, CREBBP mutations at 16p13.3 in most cases 2005, Roelfsema et al, EP300 mutations at 22q13 in 5%	32	1:100,000	17 to 27 years
1963, Cri du Chat syndrome	1963, Lejeune, partial deletion identified 1994, Overhauser et al, deletion at 5p15.3 for cat cry; at 5p15.2 for other clinical features	31	1:37,000 to 1:50,000	18 to 28 years
1982, Smith-Magenis syndrome	1986, Smith et al, mutations at 17p11.2 2005, Girirajan et al, RAI1 gene as causal	23	1:15,000 to 1:25,000	26 to 36 years

relative newness of genetic tests for rare disorders; variable parent or professional awareness of them; fewer perceived benefits in pursuing genetic testing in adults versus children; and more fragmented services and persistent health care disparities in the adult intellectual disability population, increasing the likelihood that these adults will be "missed."

Reduced life expectancies. An additional complication in aging research relates to the risks for a reduced life span in individuals with rare disorders. Such risks include an earlier age of death, premature or accelerated aging, or increased rates of sudden death; life expectancy also generally diminishes as the level of disability becomes more severe [Patja, 2000].

On the one hand, the population of older adults with intellectual disabilities is increasing (see Coppus, this issue). This growing population seems due to increased longevity and to larger numbers of infants who receive early life-saving treatments and grow into adulthood. Consider, for example, newborns with Down syndrome, who are now thought to have average life expectancies of 58–60 years [Bittles and Glasson, 2004]. For the first time ever, these adult children with Down syndrome are projected to outlive their parents—and both parents and offspring may experience physical declines at or about the same time [Hodapp et al., in press].

On the other hand, virtually no reliable data exist on the life expectancies of people with any number of rare genetic disorders. In the absence of data, researchers often surmise that individuals with rare syndromes have a "normal life expectancy," and then typically note the age of the oldest known affected individual. It is not clear, however, if these authors are referring to a normal life expectancy relative to the general population, or to others with similar levels of intellectual impairments or medical fragilities. As such, while Table 2 summarizes syndrome-specific factors that may diminish life expectancy in specific rare disorders, life expectancy is not included. Table 2 also includes causes of death noted in the literature. While not exhaustive, Table 2 demonstrates the divergent, complex medical and phenotypic factors that need to be taken into account when calculating life expectancy.

Without reliable life expectancy data, it is hard to determine the extent to which studies on aging in rare conditions are confounded by selective survival biases. This term refers to the idea that those who live longer differ from those who do not [Widaman et al., 1994], specifically that they are healthier than those who have died. As a result, survivors may not be

Table 2. Variables Associated With Ill Health, Reduced Life Expectancy, and Causes of Death in Selected Rare Syndromes

Syndrome	Factors That May Lead to Adult Ill Health, Reduced Life Expectancy, and Common Causes of Death
Angelman syndrome	Severe epilepsy; dysphagia; ataxic gait and falling; immobility; severe scoliosis; aspiration; sudden deaths related to infections, seizures and complications of anesthesia; attraction to water and accidental drowning (Clayton-Smith and Laan, 2003)
Rett Syndrome	Dyspraxia; reduced mobility; hand stereotypies and mouthing; seizures; breathing disturbances; impaired sleep; scoliosis; poor growth and wasting; malnutrition; aspiration pneumonia (Percy, 2008)
Williams syndrome	Cardiovascular, endocrine and renal disease; hypertension; sensorineural hearing loss; elevated anxiety, phobias; risks for social exploitation; diabetes; joint contractures; hyperreflexia; cardiovascular disease major cause of death (Pober, 2010)
Prader-Willi syndrome	High rates of obesity; Type II diabetes; cardiovascular disease; hormonal deficiencies; sleep apnea and daytime sleepiness; leg ulcerations and edema; fractures; temperature instability; high pain threshold; psychosis primarily in mUPD; respiratory infections; gastric rupture and necrosis; accidental choking; complications of obesity major cause of death in adults (Cassidy and Driscoll, 2009)
Cri du Chat syndrome	Upper respiratory infections; larynx anomalies; cardiac, muscular or skeletal problems; hyperactivity; self-injury-head banging and self-biting; increased fragility and death in infants with unbalanced translocations or severe organ involvement (Maindri et al, 2006)
Rubinstein-Taybi syndrome	Gastroesphogeal reflux; feeding difficulties; constipation; hypotonia; congenital heart disease; renal anomalies; problems with anesthesia; ophthalmologic and orthopedic problems; benign and malignant tumors; leukemia and lymphoma; immune dysfunction (Wliey et al, 2003)
Smith-Magenis syndrome	Inverted circadian rhythm of melatonin and sleep disturbances; elevated cholesterol and triglycerides, ocular problems; hearing loss; velopharyngeal insufficiency; scoliosis; self-injury-inserting objects into bodily orifices and nail yanking; peripheral neuropathy (Shelley and Robertson, 2005)
Cornelia de Lange syndrome	Limb, digital and dental abnormalities; feeding (chewing, swallowing) and gastrointestinal problems (reflux, vomiting); respiratory infections; severe hearing loss; ophthalmologic problems; hyperactivity; self-injury (Jackson et al, 1993)

representative of the entire syndromic population. Inherent in any study of aging, selective survival biases may prove particularly striking in rare intellectual disability disorders, especially given the severity of their physical, sensory, neural and other medical problems. Such complexities underscore the need to examine rates of survival and healthy aging in prospective, longitudinal studies with young and older adults with rare genetic disorders.

Aging in Specific Syndromes

Several genetic syndromes demonstrate the methodological twists and challenges involved in research on aging and adults with rare disorders. Here, however, two syndromes were selected for review because each boasts at least some literature on adulthood, and each illustrates one or more of the methodological problems in conducting aging research described above.

Prader-Willi Syndrome

Prader-Willi syndrome is caused by lack of paternally derived imprinted material at 15q11-13, either through paternal deletions or maternal uniparental disomy (mUPD; two imprinted chromosomes derived from the mother). Affected individuals typically show: mild to moderate intellectual disabilities; hyperphagia and risks of obesity; growth hormone deficiency; excessive daytime sleepiness; and restricted, repetitive behaviors. Prader-Willi syndrome aptly demonstrates issues related to mortality and selective survival biases, cohort effects, and differences in adult outcomes based on molecular genetic subtypes.

Mortality: Rates and causes. Unlike other rare conditions, Prader-Willi syndrome features several population-based studies that estimate death rates and causes of death. Whittington and colleagues (2001) found a 3% death rate for PWS as a whole, with a substantially higher death rate of 7% in adults over 30 years. Similarly, Einfeld et al. [2006] found that, relative to others with similar levels of intellectual disabilities, those with Prader-Willi syndrome were 6.1 times more likely to die in adulthood.

Causes of death are also well described in these adults. Whereas children with Prader-Willi syndrome are more apt to die from respiratory infections, death in adults is typically associated with complications of obesity, including diabetes, cardiovascular disease, and cardiorespiratory failure [Butler, et al., 2002; Einfeld et al., 2006]. Gastric perforations and necrosis have also been reported, especially in slim but previously obese adults who have occasions to binge eat [Stevenson et al., 2007]. Across children and adults, temperature instability, a high pain threshold, inability to vomit, and limited abilities to verbalize pain may mask serious underlying infections, hormonal deficiencies or diseases. These factors are believed to underpin at least some cases of sudden death in Prader-Willi syndrome [for a review, see Lee, 2006]. Other deaths are related to accidental drowning or choking, especially when individuals are sneaking food. Taken together, those adults with Prader-Willi syndrome who have survived to older ages (e.g., their 60's) likely differ in their health status than those who have already died.

Cohort effects: Growth hormone treatment. In light of their growth hormone deficiencies, growth hormone replacement therapy is now an FDA-approved best practice for children with Prader-Willi syndrome. Numerous studies show that growth hormone treatment improves linear height, agility, muscle mass and strength in children [e.g., Carrel et al., 1999], and also results in earlier ages of sitting unassisted or walking. Growth hormone treatment may also enhance learning in treated infants due to their increased arousal, energy and attention [Meyers et al., 2006].

The majority of older adults with Prader-Willi syndrome, however, have not had benefit of this treatment, and FDA approval for it was limited to the pediatric population. This discrepancy introduces possible cohort differences related to both generational effects and the use of a new treatment in younger but not older individuals.

Even so, preliminary data suggest that adults on growth hormone show improved endocrine profiles, body composition, and responses to cognitive

tasks that tap mental speed, flexibility, reaction time, and motor performance [Hoybe et al., 2005; Mogul et al., 2008]. Further growth hormone studies are needed on adults, but, in the meantime, children and youth growing up today on growth hormone are likely to differ from today's adults who have not had the benefit of this treatment.

Aging: Behavioral, psychiatric and weight concerns. Behavioral problems are significant in Prader-Willi syndrome and include: repetitive, compulsive behaviors; insistence on sameness; tantrums or outbursts (especially with changes in routine); skin-picking; food-seeking; aggression and tantrums; irritability; emotional lability, and hoarding [e.g., Soni et al., 2002; Dykens and Roof, 2008; Sinnema et al., 2011].

The trajectories of these behavior problems in adulthood remain unclear. Some persist or even worsen in adulthood, especially hoarding and collecting non-food items, skin-picking, irritability, food-seeking and mood swings [Ogura et al., 2008]. Dykens [2004] noted a peak of externalizing behavior problems (e.g., aggression, impulsivity) in young adulthood, with fewer such behaviors in older adults aged 40 and higher.

Different trajectories of behavioral or psychiatric problems likely exist across the major genetic subtypes of this syndrome [Dykens and Roof, 2008]. Adults with larger, Type I deletions at 15q11-13 may show increased withdrawal and passivity over time, and a slowing in cognitive or adaptive performance. Conversely, those with smaller, Type II deletions seem to have relatively persistent behavior problems, while adults with mUPD show higher rates of disruptive, bizarre behaviors, and thought disturbance. Many adults experience significant depression, while those with mUPD versus deletions are also more prone to psychosis, with or without a depressive component [Soni et al., 2002; Dykens et al., 2012]. Increased rates of psychosis in mUPD are thought to relate to the overexpression of maternally imprinted genes in this genetic subtype. Longitudinal studies of these psychiatric concerns have yet to be published, leaving it unknown if they remit with early treatment, re-emerge at stressful times, or contribute to ill health later in adulthood.

Weight loss in adulthood may be associated with improved physical health but not necessarily mental health. Relative to overweight or obese adults, those with lower BMIs show more distress, tearfulness, confusion, restlessness, screaming, excitation, repetitive movements, and anxiety [Dykens, 2004; Sinnema et al., 2011]. These findings may relate to hormonal changes or to the inherent stress of maintaining weight loss and a low calorie diet when one is "always hungry, never full" (National Prader-Willi Syndrome Association motto.)

Adult interventions and quality of life issues. Although many adults co-reside with their parents, dedicated Prader-Willi syndrome group homes have been very successful in helping individuals lose weight and gain social and coping skills. Almost all adults need psychiatric or behavioral interventions, reduced calorie diets, supervision around food, and daily physical activity or exercise. Employment for adults is hard because employers need to provide food supervision or a food-secure work environment.

More so than others with disabilities, both men and women with Prader-Willi syndrome seem drawn to taking care of pets or children. This desire to caretake may relate to aberrant plasma or CSF levels of levels oxytocin [e.g., Martin et al., 1998]. Adults with Prader-Willi syndrome also gravitate to word find and jigsaw puzzles, and many perform them quite proficiently, on par or exceeding chronological age-matched controls [Dykens, 2002; Verdine et al., 2008]. Recreational use of electronic or computer games may confer some cognitive advantage to adults, but increased computer or TV screen time is also associated with higher BMIs in adults with Prader-Willi syndrome [Dykens, 2012].

In brief, longitudinal studies are needed in Prader-Willi syndrome that identify shifts in behavior, hyperphagia, symptoms of depression or psychosis, and everyday activities in relation to genetic subtypes and shared trajectories with other disability groups. Neuroimaging studies of older adults may also provide new insights into the neuropathology of this syndrome.

Williams Syndrome

Due to a hemizogous deletion of approximately 24 genes on chromosome 7p11.23, Williams syndrome involves cardiovascular, endocrine and renal problems, and a distinctive cognitive, linguistic, and social phenotype [see Martens et al., 2008 for a review]. The behavioral phenotype includes pronounced weaknesses in visuospatial construction and relative strengths in auditory short-term memory, face processing and expressive language, especially vocabulary. Despite an appealing, engaging style, people with Williams syndrome generally show hypersociability, which actually leads to difficulties navigating social situations or forming friendships [Elison et al., 2010], and increased rates of exploitation by others. Most phenotypic work has focused on children, yet several changes in adulthood deserve further study.

Accelerated or premature aging. Converging data suggest that adults with Williams syndrome undergo a moderately premature or accelerated aging process. Cognitively, overall IQ scores appear stable over time [e.g., Howlin et al., 2009], but markedly poorer performances were reported in older versus younger Williams syndrome adults in tasks tapping explicit, but not implicit, memory [Krinsky-McHale et al., 2004]. Though seemingly rare, dementia has been observed in some older adults [Pober, 2010].

Many age-related medical conditions in Williams syndrome begin much earlier than expected, in late adolescence or young adulthood. These include premature graying of the hair, diverticulosis, diabetes mellitus, hypertension, and sensorineural hearing loss [Pober, 2010]. Some of the syndrome's cardiac problems may also worsen in adults. With advancing age, adults are also prone to joint contractures and hyperreflexia, and they often become even more unsteady with such motoric tasks as stepping up or down stairs. These clinical observations underscore the need for studies that track neural and hormonal changes in adults, and how they interact with genetic risk factors (e.g., APOE4) known to accelerate aging in general.

Aging: Psychiatric and behavioral concerns. Williams syndrome is characterized by high rates of inattention, anxiety and fears [Dankner and Dykens, in press]. ADHD is seen in up to 65% of children with Williams syndrome [e.g., Leyfer et al., 2009], and diminished hyperactivity but persistent distractibility and inattention is noted in the vast majority of adults [Elison et al., 2010]. Persistent inattention is associated with problems with disengaging attention, as seen in an intense focus on faces, and in a prolonged attentional blink, or difficulty detecting a second visual target when it is presented in close temporal proximity to an initial target [Lense et al., 2011].

Regarding anxiety, up to 90% of individuals with Williams syndrome

have multiple fears and approximately 35–80% meet diagnostic criteria for specific phobias [Dykens, 2003; Leyfer et al., 2009]. Generalized and anticipatory anxiety is also common, with 18–43% meeting criteria for generalized anxiety disorders [Dykens, 2003; Woodruff-Borden et al., 2010].

Anxiety symptoms appear to worsen or persist with advancing age in Williams syndrome. Relative to children or youth, Dykens [2003] found that adults, especially women, had the highest rate of specific fears. In particular, these adults seemed to acquire new and more age-appropriate fears (e.g., the future, uncertainty, world events), without the expected abatement of fears seen in children (e.g., the dark, spooky things, animals). Similarly, Woodruff-Borden et al. [2010] found that adolescents versus children had higher rates of generalized anxiety disorders, and they also developed new phobias while maintaining prior ones. These trends are consistent with Chernicke et al. [2004], who found moderate to severe anxiety disorders in 73% of adult patients with Williams syndrome.

Adult interventions and quality of life issues. Generalized anxiety disorders, fears and phobias detract considerably from the overall quality of life for adults with Williams syndrome, as does their strong and often unsuccessful efforts to have enduring friendships. Not surprisingly, anxiolytic drugs are commonly given to these adults [Pober, 2010], though no studies have yet evaluated the effectiveness of psychotropic agents alone or combined with cognitive-behavioral, group, or other therapies. Group-based, mindfulness- based stress reduction was found to be helpful in adults with Williams syndrome, as measured by their self-ratings, biomarkers of anxiety and stress, and generalization of breathing techniques outside of sessions [Miodrag et al., 2012].

Many children and adults with Williams syndrome gravitate to either making music or listening to music, and their initial attractions to music may be associated with altered auditory processing and fascinations with sound [Lense and Dykens, 2011, Lense and Dykens, in press]. Using neural imaging and psychoacoustic tests, Wengenroth et al. [2010] found extreme holistic sound perception in Williams syndrome, seen in functional and structural leftward asymmetry of the auditory cortex. Their sample did not have musical training, yet showed brain morphology consistent with professional musicians. Although preliminary, findings suggest a neural template in Williams syndrome that is unusually receptive to sound and music.

Well-controlled studies identify positive therapeutic effects of music on decreased anxiety and enhanced well-being in people with developmental disabilities, medical or psychiatric problems, and healthy adults. Music making appears to have enhanced utility in adults with Williams syndrome as a means of appropriately connecting to others, quelling anxiety, building on strengths, and enriching everyday life.

Due to their persistent cardiac and other medical concerns, anxiety, fears, social vulnerabilities and risks for exploitation or abuse, the majority of adults with Willams syndrome live with their families or in closely supervised settings. Few adults are stably employed, yet most have high needs for engagement in meaningful daily and social activities. Future studies are sorely needed on interventions that improve health and anxiety, and optimize adaptive outcomes in adults with this syndrome.

RECOMMENDATIONS FOR FUTURE RESEARCH ON AGING IN RARE SYNDROMES

Take Advantage of Advances in Genetics

Technological advances hold much promise for changing how rare syndromes are identified. Historically, and as shown in Table 1, there was a time lag of 30 or more years between the initial description of a syndrome and subsequent discoveries about its underlying genetic cause. As the field evolved, some syndromes were both genetically and phenotypically described at the same time, as in the deletion at 17p11.2 and distinctive Smith-Magenis syndrome phenotype [Smith et al., 1982]. With such advances as high-throughput sequencing, genome wide association studies (GWAS) or copy number variation studies (CNVs), the one-way phenotype-to-genotype approach can instead become a two-way street. Genetic findings are prompting research on the phenotypic or clinical relevance of single nucleotide polymorphisms (SNPs), deletions, insertions, or duplications for many disorders, including intellectual disabilities [e.g., Qiao, 2010].

At this time, however, the evaluation of older adults with intellectual disabilities continues to rely on astute clinicians who use phenotypic clues from their patients to order appropriate diagnostic tests. As previously noted, this is less likely to happen in adults due to fragmented adult service systems, variable awareness of testing among clinicians, and less investment in pursuing evaluations in older versus younger groups.

Engage in Collaborative, Multi-Site Work

By definition, rare disorders require collaborations due to their low prevalence rates and investigators' needs for adequate sample sizes. The NIH supported Rare Disease Clinical Consortia provide one successful model for doing so, with two multi-site consortia focused on developmental disabilities: Urea Cycle Disorders; and Prader-Willi, Angelman and Rett syndromes. Increasingly, syndrome-specific parent and advocacy groups are recruiting their constituents into research registries, typically at their own expense and with input from their scientific advisory boards. These resources are a tremendous boon for researchers, albeit with the lingering concern that members of parent groups may not represent the entire population under study.

Other resources include broader types of registries or databases. ResearchMatch, for example, is a volunteer registry that encompasses virtually all diseases and is supported by the national network of 60 universities with NIH Clinical Translation Science Awards. The 14 NICHD-supported Intellectual and Developmental Disability Research Centers are already involved in registry and collaborative studies, and are uniquely well-positioned to grow and sustain studies of rare disorders. These resources and networks can powerfully accelerate research in rare disorders and need to be put to more widespread use.

Reconceptualize Dynamic Phenotypes Across the Lifespan

In most studies on rare intellectual disability disorders, adults are discussed in relation to life expectancy, ill health, or causes of death. Fuller descriptions are lacking on adult quality of life, learning, healthy aging, families, or social-adaptive functioning. This unevenness may reflect the more medical orientation in much of the adult rare disease literature, which has yet to be enriched by behavioral researchers from gerontology, geriatric psychiatry, psychology, or allied health fields. To the extent that behavioral

researchers study intellectual disabilities or rare syndromes, they typically focus on children.

Indeed, many researchers are drawn to the idea that syndromes are best studied in infancy or early childhood, when the earliest glimmerings of the phenotype emerge and presumably are more malleable. By definition, however, rare intellectual disability conditions are disorders of development, and we risk making erroneous conclusions about them by not adopting a developmental stance that encompasses changes across the life span [e.g., Scerif and Karmiloff-Smith, 2005].

Phenotypic changes also occur in mid or late adulthood, and these developments may be just as informative for understanding gene expression or function, and how environments impact gene expression over time. Fragile X syndrome provides a convincing argument for the importance of lifespan studies. The fragile X tremor associated syndrome was only identified by studying older, premutation carriers, and data from these older adults led to hypotheses regarding the long-term effects of reduced fragile X protein (FMRP) expression levels, and resultant RNA toxicity, on tremors and other symptoms (see Hagerman, this issue).

Other syndromes may also reveal new insights into gene expression over time. In Prader-Willi syndrome, for example, some older adults are no longer hyperphagic, to the point where, unlike in their younger years, they can safely work in grocery stores and other food-related settings [Miller et al., 2011]. Despite their increased risks of psychiatric illness, those with mUPD may actually show significant gains in cognitive function in adulthood, especially in visual-spatial domains [Dykens, in preparation]. In Williams syndrome, anxiety and specific phobias appear to worsen with age, especially in women [Dykens, 2003]. In either case, it is unknown what combination of different environments, altered gene expression, and shifts in hormonal profiles or neural functioning contribute to these striking changes in the adult phenotype.

Intriguingly, the disability field's policies and practices may be an impediment to work on adult development and aging. Federally legislated mandates for special education services end at a time when many individuals with disabilities may actually be primed and ready to learn. Unlike their typical peers who attend college, engage in hobbies and lifelong learning, adults with intellectual disabilities have few outlets or expectations to continue their formal or informal education. Postsecondary programs for students with intellectual disabilities are spreading, but these are unlikely to accommodate those with rare or severe disabilities. Instruction typically ends after high school and studies have yet to identify the learning trajectories of specific cognitive skills in adults with intellectual disabilities. Indeed, a significant proportion of young adults with intellectual disabilities have nothing to do during the day [Taylor and Hodapp, 2012] and expectations seem low for their cognitive growth.

Yet these adults may be even more ready to learn. Certain medical problems such as seizures often stabilize after adolescence, and many of the behavioral problems that previously impeded learning are likely to have diminished or be better managed. It thus remains unknown if adults with rare or common disabilities show improvements in specific cognitive skills over time, and with intensive, targeted instruction. Important fluid reasoning skills can be improved in other at-risk groups [Mackey et al., 2011], raising the possibility that adults with intellectual disabilities may benefit from similar interventions.

Establish Bridges Across Syndrome-Specific Silos

Syndrome-specific advocacy and parent organizations fill a critical role in the field of rare neurodevelopmental disorders. They successfully disseminate information to parents and professionals, lobby and fundraise to support research, and create practice guidelines that better serve their population. These associations often attract core groups of dedicated researchers and clinicians to work with their families or serve on their advisory boards. In turn, these researchers come to be known by the syndrome they study, and one could argue that the complexity of rare disorders demands such a focused approach.

On the downside, these dedicated syndrome-specific groups work well within, but not necessarily across, disorders. These silos may not be conducive to new ways of thinking about common mechanisms or pathways that cut across syndromes with dramatically different phenotypes. As reviewed by van Bokhoven [2012], several functional relationships have now been identified between individual intellectual disability genes, as have common molecular and cellular pathways that involve synaptic plasticity, signaling pathways, and epigenetic genes. Indeed, several rare syndromes are specifically associated with altered epigenetic functioning, including fragile X, Rett, Prader-Willi, Rubinstein-Taybi, and Angelman syndromes [Day and Sweatt, 2011]. The search is thus well underway for converging networks that are associated with a variety of different causes of intellectual disabilities, as well as with certain psychiatric disorders that also show cognitive impairment.

Interestingly, Bishop [2010] found that the rate of growth in NIH research funding for neurodevelopmental disabilities was not solely explained by clinical severity, with steep funding increases for two highly prevalent conditions—autism spectrum disorders and ADHD. This funding trend highlights the need for a more unified intellectual disability community to speak with one voice regarding fiscal support for promising scientific breakthroughs that benefit all individuals with intellectual disabilities, both rare and common.

As shown in Prader-Willi and Williams syndromes, older adults are more challenging to study than their younger counterparts, with complexities involving temporal discrepancies in genetic or clinical diagnoses, increased mortality, and selective survival and cohort effects. Even so, older adults with rare disability syndromes stand to move the field forward in ways only gleaned from the passing of time.

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