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Dementia in Rare Genetic Neurodevelopmental Disorders

A Systematic Literature Review

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Abstract

Background and Objectives

Knowledge of young-onset Alzheimer disease in adults with Down syndrome has greatly improved clinical care. However, little is known about dementia in rare genetic neurodevelopmental disorders (RGNDs). In this review, a comprehensive overview is provided of reports on dementia and cognitive/adaptive trajectories in adults with RGNDs.

Methods

A systematic literature review was conducted in Embase, Medline ALL, and PsycINFO on December 6, 2022. The protocol was registered in PROSPERO (CRD42021223041). Search terms for dementia, cognitive and adaptive functioning, and RGNDs were combined using generic terms and the Orphanet database. Study characteristics and descriptive data on genetic diagnosis, clinical and neuropathologic features, comorbidities, and diagnostic methods were extracted using a modified version of the Cochrane Data Extraction Template.

Results

The literature search yielded 40 publications (17 cohorts, 23 case studies) describing dementia and/or cognitive or adaptive trajectories in adults with 14 different RGNDs. Dementia was reported in 49 individuals (5 cohorts, 20 cases) with a mean age at onset of 44.4 years. Diagnostics were not disclosed for half of the reported individuals (n = 25/49, 51.0%). A total of 44 different psychodiagnostic instruments were used. MRI was the most reported additional investigation (n = 12/49, 24.5%). Comorbid disorders most frequently associated with cognitive/adaptive decline were epilepsy, psychotic disorders, and movement disorders.

Discussion

Currently available literature shows limited information on aging in RGNDs, with relatively many reports of young-onset dementia. Longitudinal data may provide insights into converging neurodevelopmental degenerative pathways. We provide recommendations to optimize dementia screening, diagnosis, and research.

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Glossary

AD = Alzheimer disease; **ASM** = antiseizure medication; **DS** = Down syndrome; **FSIQ** = full-scale IQ; **FXTAS** = fragile X–associated tremor/ataxia syndrome; **ID** = intellectual disability; **NPA** = neuropsychological assessment; **RGNDs** = rare genetic neurodevelopmental disorders; **TSC** = tuberous sclerosis complex.

Introduction

Rare genetic neurodevelopmental disorders (RGNDs) are characterized by a variety of neurologic and psychiatric symptoms, often involving intellectual disability (ID) and somatic comorbidity in various organ systems. By the European definition, diseases are rare when affecting fewer than 1 in 2,000.[1] Although individually rare, together RGNDs are estimated to affect 1%–3% of the total population and millions of people globally.[1] Improvement of health care has resulted in increasing life expectancy for this patient population, revealing age-related diseases such as dementia.

It is well-known that Down syndrome (DS), a common cause of ID, is associated with young-onset Alzheimer dementia due to the triplication of the amyloid precursor protein gene located on chromosome 21. This knowledge has resulted in targeted screening and diagnostic recommendations,[2] greatly improving overall care for adults with DS. In the general population with ID (not caused by DS), varying prevalence rates of dementia have been reported, ranging from rates similar to the general population[3-5] to rates up to 4 times higher,[6-14] with both late[3,4] and young onset (younger than 65 years).[11,14] Higher dementia prevalences with young onset would be plausible in ID due to a lower premorbid cognitive reserve.[15] In addition to genetic risk factors, comorbid disorders in RGNDs may also contribute to accelerated cognitive decline. Epilepsy, for instance, occurs in 20%–30% of individuals with ID, and age at onset, seizure type, duration of disease, and chronic use of antiseizure medication (ASM) have been associated with cognitive decline.[16] Other common comorbidities associated with cognitive decline include psychosis, schizophrenia,[17] and mood disorders.[18] Diagnostic manuals state that to meet dementia criteria, cognitive decline cannot be *better explained by another mental disorder*. In patients with RGNDs, diagnosis may be more challenging because (reversible) psychiatric disorders may be causative or co-occurring and difficult to distinguish from dementia. Other diagnostic challenges in those with RGNDs include limited availability and validity of neuropsychological instruments,[19] invasiveness of additional medical investigations, and limited guidance for cognitive monitoring of genetic conditions other than DS.

Hence, many questions remain regarding epidemiology, phenomenology, determinants, and mechanisms of dementia in RGNDs. This knowledge is necessary to improve care by identifying care gaps and targets for prevention, screening, diagnosis, monitoring, and treatment. In this study, we aim to provide a systematic review of knowledge on dementia, cognitive/adaptive trajectories, and associated factors in adults with RGNDs.

Methods

We followed and used the template of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist (Figure 1).[20] The methodologic framework was published in advance in PROSPERO International Prospective Register of Systematic Reviews (CRD42021223041).

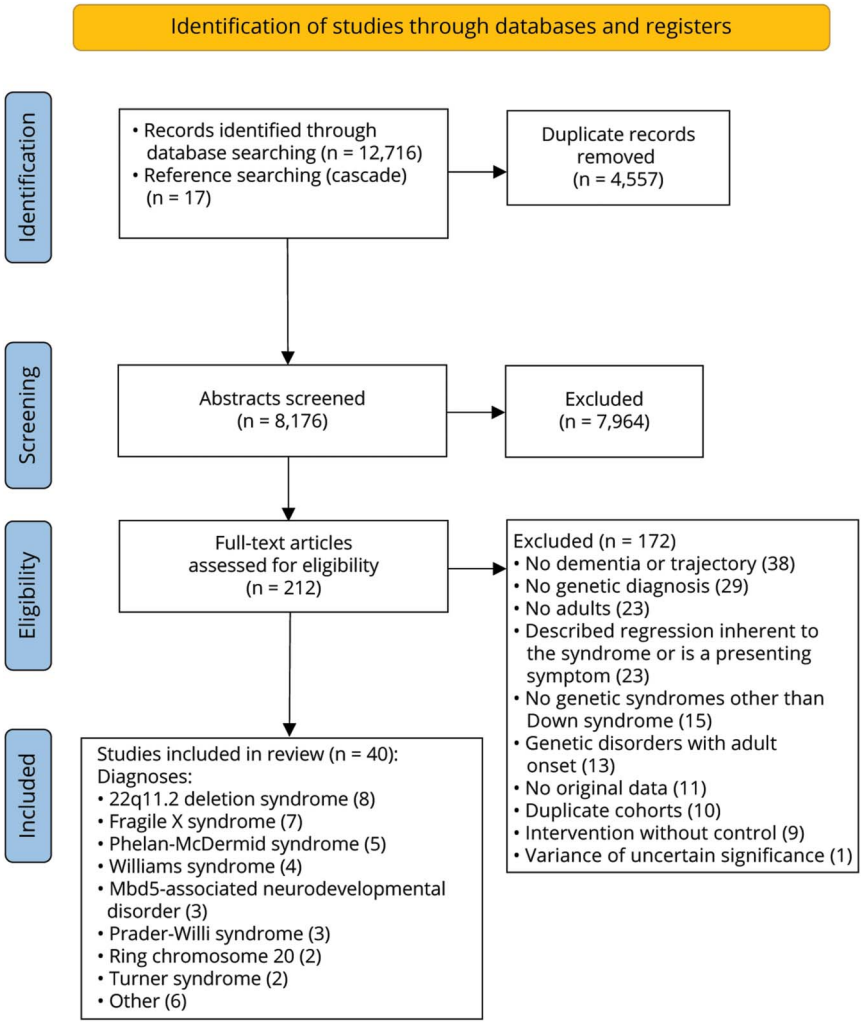
Eligibility

Inclusion criteria consisted of all peer-reviewed studies in adults with molecularly confirmed RGNDs that reported on dementia and/or cognitive/adaptive functioning. Cognitive functioning is defined as the performance of mental processes such as memory and perception, whereas adaptive functioning refers to everyday tasks required for a person to fulfill typical roles in society, such as self-help, domestic skills, and communication.[21] Dementia was defined as a significant decline from a prior level of cognitive and adaptive functioning. Studies reporting on cognitive/adaptive functioning required a longitudinal design or cross-sectional design that reported results for different age groups. Trajectories spanning both childhood and adulthood were excluded when participants were underaged during the majority of the interval. We defined RGNDs according to the Orphanet database as rare disorders with a genetic etiology affecting the nervous system in early development.[22] Genetic disorders with adult onset, gene variants of uncertain significance, and Down syndrome (prevalence > 1:2000) were excluded. To target aging rather than developmental processes, we also excluded RGNDs in which cognitive decline is a presenting symptom, such as childhood dementias and neurometabolic disorders (see eTable 1 for an overview of excluded disorders).

Search Strategy, Study Selection, Risk of Bias, and Quality Assessment

A literature search was performed in Embase, Medline ALL (Ovid), and PsycINFO (Ovid) on December 6, 2022, with the assistance of clinical research librarians (J.D. and M.F.M.E.). The search included (1) terms on dementia and cognitive or adaptive functioning and (2) terms regarding RGNDs including all rare genetic and chromosomal disorders from the Genetic and Rare Disease Information Center of the NIH (search terms in eTable 2). Additional articles were identified by citation tracking (n = 17). Authors were approached for adult-specific data in 8 cohorts that included

Figure 1 PRISMA Flowchart



both children and adults, which was provided by 1 author (acknowledgements). Three adults in 2 children cohorts were included as case studies because information on their cognitive trajectories was provided.

Rayyan, an application for systematic reviews, was used for title and abstract screening.[23] All titles and abstracts were screened for relevance by 4 reviewers (A.M.v.E., L.t.H., M.v.S., and H.K.). A 10% subsample was screened for interrater reliability using the Cohen Kappa statistic to determine consistency between raters. Full-text articles were screened by 2 reviewers, where data were extracted and abstracted by one reviewer and checked by a second reviewer (M.v.S., H.K.). Discrepancies were discussed until consensus was reached. For quality appraisal, the Newcastle-Ottawa scale that allows the appraisal of the methodologic qualities of nonrandomized studies was used.[24]

Data Extraction and Abstraction

We extracted study characteristics and descriptive data using a modified version of the Cochrane Consumers and Communication Review Group's Data Extraction Template.[25] Data were extracted and abstracted on general information (first author, year of publication, and study design), patient characteristics (age, sex, level of ID, and premorbid intelligence quotient), genetics (genetic diagnosis, relevant coexisting diagnoses, and molecular test results), cognitive/adaptive trajectories, dementia features (prevalence, age at onset, etiology, neuropathology, and diagnostics), medication, epilepsy characteristics (seizure type and age at onset), other comorbidity, and use of psychodiagnostic instruments (Figure 2).

Standard Protocol Approvals, Registrations, and Patient Consents

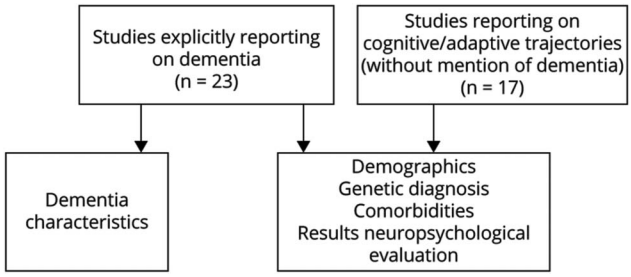
Data Availability

Any data not published within the manuscript will be shared upon request.

Results

Of 12,733 identified citations, 40 studies met the inclusion criteria (see eReferences e1–e40 and eTables 3–4), describing

Figure 2 Overview of Study Selection and Data Extraction



dementia (n = 23, 57.5%) or cognitive or adaptive trajectories without dementia diagnosis (n = 17, 42.5%) in adults with RGNDs (flowchart Figure 1) (view eTables 5 and 6 for all included trajectories, including stable or improving). A total of 17 cohorts (6 prospective, 7 retrospective, and 4 cross-sectional) and 23 case studies were identified, reporting on a total of 3,089 individuals with 14 different genetically confirmed RGNDs. The cohorts comprised 12 convenience samples from care facilities or (inter)national consortia, 2 population-based studies, 2 retrospective chart reviews, and 1 voluntarily sample from an online community.

Individuals

Cohorts

In 17 cohorts, a total of 3,056 individuals were included, of whom 1,496 were female (49.0%, excluding 1 cohort in which sex was unknown). The average age at last assessment was 33.7 (range 19–52) years. At baseline, a mean full-scale IQ (FSIQ) score was reported in 13 cohorts with a mean of 64.6 (range 43.7–77.2).

Case Studies

In 23 case studies, a total of 32 individuals were described, of whom 17 were female (53.1%, sex of 1 case unknown). The average age was 46.5 (range 18–77) years. ID was absent in 6 cases (18.8%), unspecified in 6 (18.8%), and confirmed in 20 (62.5%), further specified in 18 as borderline (n = 2), mild (n = 7), moderate (n = 5), and severe ID (n = 4). At baseline, FSIQ was reported in 9 cases with a mean of 70.2 (range 38–114) and a developmental age in 6 cases with a mean of 5.6 (range 3–9) years, corresponding to moderate ID. No family histories of dementia were reported, aside from relatives affected by the same RGND.[e14,e18,e24,e25]

Dementia in RGNDs

Prevalence

Dementia was reported in 5/17 (29.4%) cohort studies and in 20/32 (62.5%) separate case reports, describing a total of 49 individuals with 12 different RGNDs (Table 1). Two possible cases with dementia and 1 probable case with dementia were reported in a small population-based cohort of Prader-Willi syndrome (n = 3, 16.7%),[e40] based on neuropsychological assessments. In a 22q11.2 deletion syndrome cohort from a psychiatric outpatient clinic,[e9] 3 individuals had dementia (n = 3, 9.1%) (shown as separate cases) and 18 others showed both cognitive and adaptive decline without a formal diagnosis of dementia (n = 18, 54.5%). Dementia was also reported in small cohorts with Williams syndrome (n = 3, 13.6%)[e28] and Dravet syndrome (n = 1, 4.5%) from care facilities,[e7] but the certainty and method of diagnoses were not discussed. Medical records of a sample of fragile X syndrome,[e33] referred for clinical or research evaluations, reported *cognitive decline or dementia* (n = 6, 9.7%), but no further details were provided, and it is unclear whether all individuals had been screened. In a national registry–based cohort of 1,349 individuals with neurofibromatosis type 1,[e17] medical records were screened for *dementia-related encounters*, such as a dementia-related hospital visit, ICD-10 code, or purchase of antidementia drugs. A prevalence of 1.2% dementia-related encounters was reported, with increased risks of dementia (HR = 1.67), Alzheimer disease (AD) (HR = 2.88), and dementia-related death (RR = 2.42).

Etiology

The assumed etiology was specified in 9/23 studies that reported on dementia (39.1%). A clinical impression of AD was reported in 3 individuals of a Prader-Willi cohort and a separate case study, all women aged 40–58 years with the maternal uniparental disomy subtype and a history of psychosis, although authors did not clarify how this impression was substantiated.[e30,e40] An 18-year-old man with Phelan-McDermid syndrome and late-onset psychiatric features and sleep disturbances was diagnosed with bipolar disorder and possible AD, which was substantiated by CSF concentrations of low Aβ, low total tau, and normal phosphorylated tau protein.[e38] The AD diagnosis in neurofibromatosis type 1 were likely formal because these were retrieved by ICD-10 codes, but diagnostic details were not provided.[e17] A cohort study in Williams syndrome reported on 3 cases of vascular dementia, with no further details.[e28] Four men with fragile X syndrome[e12,e22,e25,e26] met criteria for fragile X–associated tremor/ataxia syndrome (FXTAS) because of the onset of parkinsonism and dementia along with findings of elevated FMR1 mRNA levels[e22,e26] and intranuclear inclusions characteristic of FXTAS pathology.[e25] In 3 of these individuals, this was explained by a *size* mosaic form of fragile X syndrome, defined as those with both premutation and full mutation cells. The fourth man had a fully unmethylated, full mutation.[e25] A probable diagnosis of a behavioral variant of frontotemporal dementia was reported in a 52-year-old man with a subclinical form of tuberous sclerosis complex,[e24] based on behavioral changes, neuropsychological profile, and MRI findings.

Age at Onset

The identified individuals with dementia had a mean age at onset of 44.4 (range 16–71, median 40) years, of whom 21/49 (42.9%) had young-onset dementia (younger than 65 years). No association with young-onset dementia was found in neurofibromatosis type 1, in which the average age at *first*

Table 1 Reports of Dementia in Rare Genetic Neurodevelopmental Disorders

RGND	Dementia prevalence	Sex f/m	(Mean) Age at onset	(Mean) Age at diagnosis	Diagnostic method	Diagnostic results of cases with dementia	Terminology as per the author	Suggested dementia etiology
Cohort studies reporting on dementia (5)								
Prader-Willi syndrome	3/18 16.6%	3/0	53, 40, 40	55, 45, 41	NPA	CAMDEX-DS impaired (1), WAIS decline (1), clinical impression only (1)	Dementia	Alzheimer disease
Williams syndrome	3/22 13.6%	n/a	n/a	n/a	Unknown	n/a	Dementia	Vascular dementia
Fragile X syndrome	6/62 9.7%	n/a	n/a	n/a	Unknown	n/a	Cognitive decline or dementia	n/a
Dravet syndrome	1/22 4.5%	0/1	n/a	55	NPA, MRI, EEG, autopsy	Cerebellar atrophy, periventricular white matter loss, myelin loss in medulla and cervical spinal cord	Dementia	Epileptic encephalopathy
Neurofibromatosis type 1	16/1.349 1.2%	8/8	n/a	74.2 (9.0)[b]	Unknown	n/a	Dementia	Alzheimer disease, vascular dementia, other
Case studies reporting on dementia (20)								
RGND	Sex	Age at onset	Age at diagnosis	Areas of decline	Diagnostic method	Diagnostic results	Terminology as per the author	Suggested dementia etiology
22q11.2 deletion syndrome	M	36	52	Memory, orientation, behavior, speech, adaptive function	NPA	8 y: IQ 75-80 36 y: IQ <45 44 y: IQ 26 52 y: IQ 21	Dementia	n/a
	M	n/a	38	Cognition, adaptive function	NPA	18 y: mild ID 29 y: mild/moderate ID 36 y: severe ID	Dementia	n/a
	F	23	29	Cognition, adaptive function, social skills	NPA	22 y: DA 6.4 25 y: mild ID 28 y: DA 4.8 30 y: DA 2.4	Dementia	n/a
3q29 deletion syndrome	F	56	57	Language, memory	NPA	56 y: FSIQ 62 MMSE 23/30 MoCA 11/30	Dementia	n/a
Cardiofaciocutaneous syndrome	M	Early 30s	39	Memory, EF, speech, adaptive function, motor	NPA, CT	15 y: WRAT2 3/3 38 y: BNA-R results all impaired	Dementia	n/a
Fragile X syndrome	M	69	77	Cognition, motor	NPA, MRI, autopsy	60 y: FSIQ 67 71 y: MMSE 25/30 74 y: MMSE 22/30	Progressive neurodegenerative syndrome	FXTAS, Parkinson disease dementia, Alzheimer disease
	M	64	70	Cognition, EF, disorientation, motor, mood, sleep	NPA, MRI	68 y: MMSE 10/30	Late onset neurologic symptoms consistent with the diagnosis of FXTAS	FXTAS

Continued

Table 1 Reports of Dementia in Rare Genetic Neurodevelopmental Disorders *(continued)*

RGND	Dementia prevalence	Sex f/m	(Mean) Age at onset	(Mean) Age at diagnosis	Diagnostic method	Diagnostic results of cases with dementia	Terminology as per the author	Suggested dementia etiology
	M	Late 50s	65	Memory, orientation, motor	NPA, MRI	53 y: FSIQ 71 65 y: FSIQ 52 MMSE 7/30 severe global atrophy, ventriculomegaly, and WM intensities	Significant dementia	FXTAS
	M	71	77	Cognition, motor	NPA, MRI	60 y: FSIQ 67 71 y: MMSE 25/30 subcortical WM disease and dilated ventricles 77 y: MMSE 13/30	Progressive cognitive decline/ neurodegeneration	FXTAS
Mbd5-associated neurodevelopmental disorder	F	n/a	60	Cognition	NPA, MRI	36 y: DA 9; 0 56 y: DA 5; 1–6; 11 60 y: DA 3; 8-5; 3 pronounced folia of the cerebellar vermis	Early-onset dementia	n/a
	F	46	48	Cognition, behavior, speech	NPA, MRI, LP, FDG-PET, blood tests	46 y: MMSE 29/30 48 y: Bilateral frontotemporal and parietal lobe hypometabolism in FDG-PET, MRI, and CSF unremarkable	Mild dementia	n/a
	M	Unknown	44[a]	Cognition, behavior	n/a	n/a	Early-onset dementia	n/a
Phelan-McDermid syndrome	F	30	33	Adaptive function, motor, speech	MRI	No abnormalities in MRI	Progressive process in the CNS/early debut of dementia	n/a
	M	16	18	Mood, motor, attention, speech	MRI, LP, blood tests	Low amyloid beta (479 mg/L), low total tau (82 ng/L), normal phosphorylated tau (24 mg/L) protein in LP	Early dementia	Alzheimer disease
	F	43	47[a]	Motor, cognition	MRI	n/a	Severe progressive neuro-degeneration	n/a
	F	39	40[a]	Motor, speech	MRI	n/a	Severe progressive neuro-degeneration	n/a
Prader-Willi syndrome	F	n/a	72	Memory, adaptive behavior	NPA	56 y:DA 6; 6 59 y: DA 4; 4	Early dementia	n/a
	F	40	58	Cognition, motor, adaptive behavior	NPA, CT	53 y: DA 1; 2–4; 10, SRZ total 5 58 y: DA 0; 8-1; 9, SRZ total 3, DSDS total 33	Dementia	n/a
Tuberous sclerosis complex	M	n/a	52	Behavior, mood, language, EF, visual episodic memory, processing speed	NPA, MRI	Atrophy and white matter lesions in temporal and frontal lobes	Dementia	Behavioral variant frontotemporal dementia
Turner syndrome	F	n/a	59	Memory, orientation	Tomography, X-ray skull, blood tests	Generalized atrophy	Presenile dementia	n/a

Abbreviations: BNA-R = Behavioral Neurology Assessment; CT = computed tomography; DA = developmental age; DSDS = Dementia Scale for Down syndrome; EF = executive functioning; f/m = female/male; FSIQ = Full-Scale Intelligence Quotient; FXTAS = Fragile-X–associated tremor ataxia syndrome; LP = lumbar puncture; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; NPA = neuropsychological assessment; SRZ = the social competence rating scale for persons with an intellectual disability; WAIS = Wechsler Adult Intelligence Scale; WM = white matter; WRAT-2 = Wide-Range Achievement Test.
[a] Separate case reports of adults in children cohorts.
[b] Average age at first dementia encounter.

dementia encounter (see above) was 74.2 (range 65.2–83.2) years or in the mosaicism cases of fragile X syndrome with dementia onset in the sixth or seventh decade.

Behavioral and Psychological Symptoms

Reported behavioral and psychological symptoms of dementia included most often changes in mood (10/49, 20.4%), aggression (9/49, 18.4%), and obsessive-compulsive behavior (5/49, 10.2%) (eTable 7). In a Williams syndrome cohort, common symptoms of dementia were explicitly mentioned, including weight change, change in appetite, onset of or increase in physical aggression, and reduced quantity of speech.[e28] A subgroup of patients with 22q11.2 deletion syndrome and significant intellectual decline displayed more symptoms of depressive and psychotic disorders than those without cognitive decline, memory and concentration problems, restlessness, sleep problems, and anhedonia.[e9]

Dementia Diagnosis

Diagnostic methods were rarely specified in cohort studies; in total, not for half of the reported individuals (n = 25/49, 51.0%). In the others, cognitive decline was substantiated by neuropsychological assessment (NPA) in most (n = 18/49, 36.7%). Language (n = 8) and memory (n = 7) were cognitive domains affected most often. In none of the cases with Phelan-McDermid (n = 4), NPA was reported, although authors presumed dementia or neurodegeneration. Additional medical examinations included the following: MRI (n = 12/49, 24.5%), blood tests (n = 3/49, 6.1%), lumbar puncture (n = 2/49, 4.1%), computed tomography (n = 2/49, 4.1%), autopsy (n = 2/49, 4.1%), PET (n 1/49, 2.0%), X-ray scan (1/49, 2.0%), and electroencephalography (n = 1/49, 2.0%).

Comorbidity

Epilepsy

In a cohort of adults with neurofibromatosis type 1, epilepsy was more frequent in individuals with dementia.[e17] In a fragile X cohort, lower intelligence was reported in 1 individual with increased seizure frequency at follow-up.[e27] In a family with ring chromosome 20 syndrome, younger age at seizure onset (5 and 7 years) was associated with worse cognitive trajectories.[e14] In 2 siblings with Phelan-McDermid syndrome, cognition declined progressively after adult-onset epilepsy and psychosis.[e18] In a cohort of late-diagnosed adults with Dravet syndrome with and without *SCN1A* mutations (n = 22), cognitive decline was partially reversible after seizure control in 2 individuals (after as long as 60 years of drug-resistant epilepsy), with neuropathologic research ruling out neurodegeneration.[e7]

Movement Disorders

FXTAS with dementia was reported in all cases with mosaic fragile X mentioned earlier, Parkinson disease with cognitive decline in 4/44 (9.1%) male individuals with full fragile X mutations,[e33] cerebellar atrophy and parkinsonism with cognitive decline in 9/9 (100%) individuals with Dravet syndrome,[e7] and gait abnormalities with onset of psychiatric illness and functional regression in 7/38 (18.4%) individuals with Phelan-McDermid syndrome.[e19]

Psychotic Disorders

In 22q11.2 deletion syndrome, (a history of) psychotic episodes and schizophrenia were associated with cognitive decline in 5 partially overlapping cohorts[e2,e8,e9,e23,e39] and in 6 separate cases.[e10] In 4/5 cohorts, psychosis onset occurred in adolescence (mean cohort age 21.3 years), and cognitive decline preceded psychosis onset. In 1 Prader-Willi cohort, a history of psychosis was considered a primary risk factor of young-onset dementia,[e40] with 1 patient meeting criteria for *at least mild dementia* after a psychotic episode. In 2 separate case reports of mosaic Turner syndrome with schizophrenia, neuroimaging indicated significant cerebral atrophy.[e3,e21]

Cardiovascular Disorders

For older individuals with neurofibromatosis type 1, there was no significant association between hypertension and dementia.[e17] In the cohort with Williams syndrome,[e28] abundant cardiovascular comorbidity was reported including hypertension (77%), congenital heart defects (45%), and a history of transient ischemic attacks (23%); however, the presence of cardiovascular comorbidity in the 3 identified cases with dementia was not specified.

Medication

One retrospective observational study in 22q11.2 deletion syndrome suggested positive correlates between selective serotonin reuptake inhibitors (SSRIs) and IQ measures, hippocampal volume, and cortical thickness.[e23] A positive cognitive effect of the ASM valproate was suggested in Dravet syndrome (see earlier).[e7]

Neuropsychological Assessment

Across all included studies, a variety of 44 different psychodiagnostic instruments were reported in 10 RGNDs and 28 studies (Table 2). Cognition was most often assessed with versions of the Wechsler Adult Intelligence Scale (in 13 studies), Wechsler Intelligence Scale for Children (in 8 studies), or the screener Mini-Mental State Examination (in 7 studies). Adaptive functioning was most often assessed with the Vineland Adaptive Behavior Scales (in 5 studies).

Quality Assessment

Results regarding study quality, as assessed by the Newcastle-Ottawa scale, are listed in eTable 3. Summarized, most cohort studies were rated to have some limitations in quality by missing stars in at least 1 criterion. The main information missing related to representativeness, mostly due to missing information on unexposure, nonresponse bias, or high percentages lost to follow-up.

Discussion

This study provides the first systematic review of cognitive and adaptive trajectories of adults with RGNDs, focusing on dementia. With now more than 1,700 known ID-related

Table 2 Use of Psychodiagnostic Instruments in Rare Genetic Neurodevelopmental Disorders

RGND	Studies (N)	Cognitive functioning (in N studies)	Adaptive functioning (in N studies)	Other (in N studies)
22q11.2 deletion syndrome	8	WISC-III/IV/R (6) WAIS–III/IV (6) WPPSI (2) Conners CPT-2 or 3 (1) CVLT (1) DMR (1) GDS (1) GIT (1) IQCODE (1) PPVT (1) Visual span test (1) WCST (1) WIAT-II (1)	ABCL (2) VABS (2)	Pennsylvania emotion recognition test (1)
Fragile X syndrome	6	MMSE (4) WAIS-III/R (3) ACE-R (1) Color form sorting test (1) FAB (1) FRWT (1) GBT (1) LIPS (1) Merrill-Palmer test (1) Stanford-Binet test (1) WASI (1) WCST (1) WMS-III (1)	W-ADL (1)	n/a
Williams syndrome	4	WAIS-III/IV (2) BPVS (1) BSID-II (1) Buschke's SRT(1) EOWPVT (1) LIPS (1) Snodgrass' picture fragment completion (1) WISC-R (1) WPPSI (1)	VABS (1)	PPS-LD (1)
Prader-Willi syndrome	2	CAMDEX-DS (1) DSDS (1) Merill-Palmer test (1) Stanford-Binet (1)	SRZ (1) VABS (1)	n/a
Mbd5-associated neurodevelopmental disorder	2	WISC-III (1) MMSE (1) FAB (1) Verbal fluency animals (1)	VABS-Z (1)	SEO-R (1)
Ring chromosome 20 syndrome	2	WAIS (2)	n/a	n/a
Cardiofaciocutaneous syndrome	1	BNA-R (1) CDR (1) WRAT-2 (1)	n/a	n/a
Dravet syndrome	1	MMSE (1)	n/a	n/a
Phelan-McDermid syndrome	1	ITPA (1) Merill-Palmer test (1) WPPSI-R (1)	n/a	n/a
3q29 deletion syndrome	1	MMSE (1) MoCA (1)	n/a	n/a

Abbreviations: ACE = Addenbrooke's Cognitive Examination; BNA = Behavioral Neurologic Assessment; BPVS = British Picture Vocabulary Scale; BSID = Bayley Scales of Infant Development; CAMDEX-DS = Cambridge Examination for Mental Disorders of Older People with Down Syndrome and Others with ID; CDR = Clinical Dementia Rating Scale; Conners CPT = Continuous Performance Test; CVLT = California Verbal Learning Test; DMR = Dementia Questionnaire for Persons with Mental Retardation; DSDS = Dementia Scale for Down Syndrome; EOWPVT = Expressive One-Word Picture Vocabulary Test; FAB = frontal assessment battery; FRWT = Face Recognition of Warrington Test; GBT = Grober and Buschke Test; GDS = Gordon Diagnostic System; GIT = Groninger Intelligence Test; ITPA = Illinois Test of Psycholinguistic Abilities; IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly; LIPS = Leiter International Performance Scale; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; PPS-LD = Present Psychiatric State–Learning Disabilities assessment; PPVT = Peabody Picture Vocabulary Test; RGND = rare genetic neurodevelopmental disorder; SEO-R = Dutch Scale for Emotional Development in people with ID; SRT = selective reminding task; SRZ = The Dutch Social Functioning Scale for ID; VABS = Vineland Adaptive Behavior Scale; W-ADL = Waisman Activities of Daily Living scale; WAIS = Wechsler Adult Intelligence Scale; WASI = Wechsler Abbreviated Scale of Intelligence; WCST = Wisconsin Card Sorting Test; WIAT = Wechsler Individual Achievement Test; WISC = Wechsler Intelligence Scale for Children; WMS-III = Wechsler Memory Scale; WRAT = Wide-Range Achievement Test.

genetic disorders,[26] the current yield of 40 reports in 14 different RGNDs reveals a gap in understanding and reporting of cognitive aging in this population.

In total, dementia was reported in 49 individuals with 12 genetic syndromes and with various dementia etiologies, diagnostic certainties, and diagnostic methods. Given the rarity of the disorders, cohorts were often small in size and sampled from convenience sources such as consortia or care facilities, making prevalence rates unsuitable for generalization. An exception was one large national registry study of individuals with neurofibromatosis type 1, providing the most robust evidence on elevated hazard risks for all types of dementia and AD. This is probably due to neurofibromatosis type 1 being less rare, and with a relative mild neurocognitive phenotype facilitating dementia diagnosis, underlining a diagnostic care gap in more rare and severe RGNDs.

The presumed dementia etiology was specified in few articles. In Prader-Willi syndrome, the presumed young-onset AD in 4 female individuals is consistent with previously reported neuropathologic features. All these individuals had uniparental disomy, which has been associated with psychosis risk[27] and may also increase susceptibility of young-onset AD in Prader-Willi syndrome. Another factor might be female sex because decreasing sex hormones during menopause have been associated with both schizophrenia spectrum disorders[28] and AD[29] The role of sex hormones might be particularly crucial in Prader-Willi syndrome because hypogonadism and early menopause are common.[30] A possible case of AD in Phelan-McDermid syndrome fits the phenotype of regression in adolescents with Phelan-McDermid syndrome following psychiatric episodes[31] and is the first to report CSF biomarkers indicative of AD. Of note are the reported clinical and neuropathologic findings of FXTAS in cases with mosaic or unmethylated full *FMR1* mutations in fragile X syndrome, considering that FXTAS was historically considered to be exclusive to the premutation carriers. While dementia in FXTAS is reported to share features with AD and APP-upregulation,[32] both neuropathologic[33] and neuropsychological[34] FXTAS characteristics primarily resemble a white matter dementia. The psychiatric manifestations in a man with tuberous sclerosis complex (TSC) were reported to resemble the behavioral variant of frontotemporal dementia (bvFTD), consistent with recent neuropathologic findings of an aging-associated *TSC tauopathy*,[35,36] in which the mTOR pathway hyperactivation and elevated phosphorylated tau aggregates are associated with premature neurodegeneration. Because psychiatric manifestations are part of TSC-associated neuropsychiatric disorders,[37] this underlines the necessity of systematic monitoring of the behavioral adult phenotypes to identify new-onset disorders.

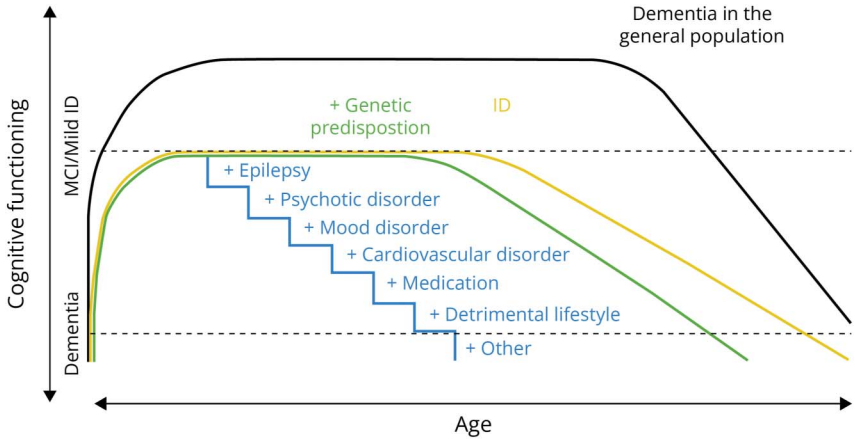
This review shows that dementia can have a young age at onset in individuals with some but not all RGNDs. The identified high prevalence rate of young-onset dementia in this review (42.9%) is very likely subject to publication bias but still noteworthy considering the global age-standardized prevalence of young-onset dementia (<1%). In a recent review on causes of young-onset dementia,[38] several rare genetic disorders were identified, illustrating that increased understanding of young-onset dementia from a genetic point of view is pivotal. The current findings suggest that in addition to DS, other genetic neurodevelopmental disorders predispose to young-onset dementia as well. This is concordant with accumulating evidence of overlapping genes, proteins, and pathways involved in both abnormal neurodevelopment and neurodegeneration,[39,40] providing a context of a neurodevelopmental-degenerative continuum rather than dichotomous separation.

Common behavioral and psychological dementia symptoms in RGNDs such as mood changes, aggression, and obsessive-compulsive behaviors are also well-recognized in the general population with ID. Behavioral and psychological symptoms vary between ID levels and are considered to be relevant dementia indicators in severe/profound ID particularly[41] because changes in cognition are more difficult to substantiate.[20] Considering the underrepresentation of severe/profound ID in this review, more research into dementia symptoms would particularly benefit this vulnerable subgroup.

Diagnostic methods were in accordance with current guidelines in 10 studies (20.4%), combining neuropsychological assessment and neuroimaging, although even this small number may be an overestimation because diagnostic methods for individuals in cohorts were rarely reported. In few occasions, other investigations to increase diagnostic certainty were reported, such as lumbar puncture (n = 2/49, 4.1%), PET (n = 1/49, 2.0%), or postmortem neuropathologic research (n = 1/49, 2.0%). In our clinical experience, these limited diagnostics reflect difficulties in performing lumbar puncture and imaging procedures, often necessitating sedation or anesthesia in a population in which anxiety disorders and medical phobias are common. It is notable that only 1 person with mild cognitive impairment was reported, raising the question whether early cognitive decline is underdiagnosed or misinterpreted as part of natural aging trajectories. Considering the impact of a dementia diagnosis and prognosis, and the limitations of neuropsychological instruments in ID (see *Neuropsychological assessment*), individuals and families should be offered additional investigations and postmortem neuropathologic confirmation to increase diagnostic accuracy.[42] Very promising for this patient population are the rapid developments of blood-based biomarkers for neurodegeneration and dementia, which are less invasive, less costly,[43] and recently recommended for prescreening purposes.[44]

In various RGNDs, associations between epilepsy characteristics and progressive cognitive decline were reported. Neuropsychological deficits are almost always reported in epilepsy, but the differential effects of seizures and the underlying neuronal abnormalities are unclear. A growing body of literature shows relations between epilepsy, mTOR pathways, tauopathy,[35,36,45] and neuronal activity–dependent

Figure 3 Aging Trajectories of Cognitive Functioning



ID = intellectual disability, MCI = mild cognitive impairment.

synaptic release of dementia biomarkers,[46,47] suggesting a link between neurodevelopmental disorders, epilepsy, and neurodegeneration. A developmental and epileptic encephalopathy is sometimes considered a (partly) reversible dementia, exemplified by the cohort with late-diagnosed Dravet adults in which some individuals improved cognitively even after decades of treatment resistance. This underlines the importance of epilepsy screening and adequate treatment with ASM. To integrate the epilepsy factors and other potential *second hits* in RGNDs, an adaption of the previously proposed *chronic accumulation model*[16] is depicted in Figure 3.

Coexistence of cognitive decline and movement disorders in RGNDs are in line with previous findings in RGNDs,[48] reporting cognitive decline or dementia in 16.6% of those with signs of parkinsonism. Our results show how neurodegeneration in some RGNDs may result in shared cognitive and motor symptomatology, which corresponds with secondary dementias known to certain neurodegenerative diseases, such as Parkinson disease, amyotrophic lateral sclerosis, and Huntington disease. This is important because some RGNDs are genetically predisposed to an elevated risk of parkinsonism, such as 22q11.2 deletion syndrome and those with pathogenic *RAB39b* variants.[48] Collaboration between neurologists and RGND experts will aid timely recognition and treatment of all neurodegenerative disorders, improving overall care.

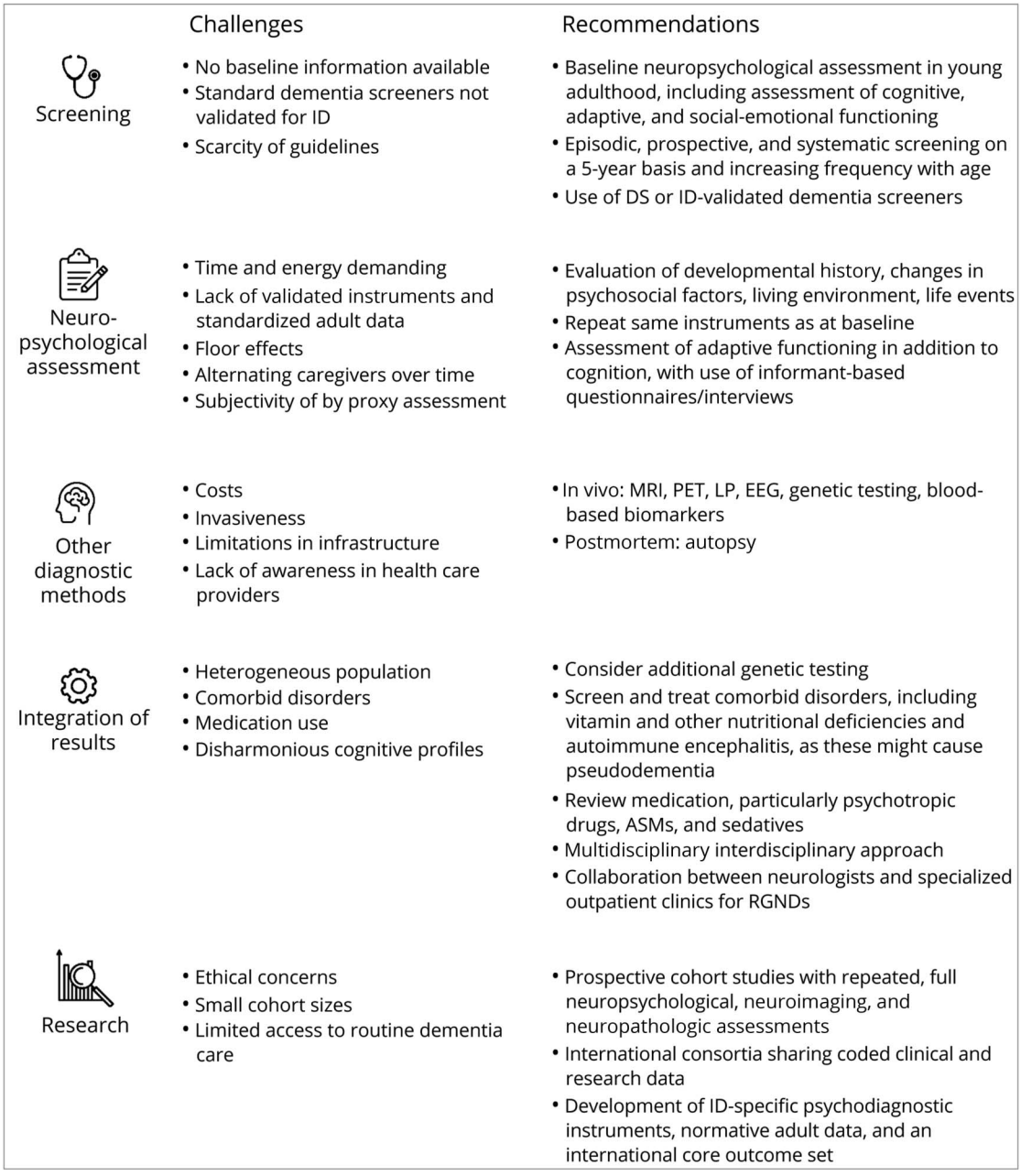
The abundance of reported associations between psychotic disorders and dementia/cognitive decline is not surprising because psychotic (*neuropsychiatric*) symptoms can occur in dementia, and cognitive symptoms and cognitive decline are a core symptom of schizophrenia. In the past, schizophrenia has long been considered a neurodegenerative disease (*dementia praecox*). Contrary to this neurodegenerative phenotype is the more modern neurodevelopmental model of schizophrenia, proposing that this abnormal neurodevelopmental trajectory is already established in gestation, long before clinical symptoms occur in early adult life. Our findings fit within a neurodevelopmental-degenerative-continuum[17] that proposes schizophrenia is a disorder with vulnerability throughout different life stages, observed as more *typical* schizophrenia trajectories with onset in adolescence in 22q11.2 deletion syndrome and as a chronic and progressive decline in older adults with RGNDs. This emphasizes that dementia should not be excluded from differential diagnostics in RGNDs suffering psychotic comorbidity.

Vascular dementia in Williams syndrome may be an example of how cardiovascular and lifestyle-related risk factors might predispose or protect individuals from specific dementia etiologies such as vascular dementia or AD. Treatment of hypertension and obesity along with diet and physical exercise should remain an area of improvement in all IDs and specifically in RGNDs predisposed to hyperphagia and cardiovascular risk.

The possible beneficial cognitive effects of SSRIs in 22q11.2 deletion syndrome and ASM in Dravet syndrome emphasize the importance of recognizing and treating states of pseudodementia caused by other disorders such as epilepsy or mood/anxiety disorders. A recent meta-analysis showed associations between some first-generation ASMs and greater dementia risk; however, verification by more prospective studies is warranted.[49]

A variety of 44 different psychodiagnostic instruments was reported with little uniformity within and between RGNDs, reflecting the challenges clinicians face in selecting appropriate instruments in this population (Figure 4) and the need for a core outcome set for ID and/or RGNDs. Age-appropriate instruments might result in floor effects,[19] while pediatric instruments lack normative data for adults. Recent reviews confirmed that only approximately half of applied instruments in ID are valid and reliable.[50,51] This review also shows that dementia screening was often initiated only when concerns emerged.

Figure 4 Challenges and Recommendations for Dementia Diagnostics and Research in Rare Genetic Neurodevelopmental Disorders



ASM = antiseizure medication; DS = Down syndrome; ID = intellectual disability; LP = lumbar puncture; RGND = rare genetic neurodevelopmental disorder.

Increasingly, recommendations are available for monitoring of cognitive functioning in RGNDs such as for 22q11.2 deletion syndrome, tuberous sclerosis complex,[37] and DS.[2] For the 1,700 RGNDs awaiting specific guidelines and for ID of unknown etiology, recommendations are proposed and summarized in Figure 4. Given that both dementia and most RGNDs are characterized by impairments in cognitive and adaptive functioning, longitudinal monitoring is necessary to substantiate decline from a previous level of functioning in individuals with RGNDs. Ideally, a baseline measurement should capture peak functioning in the adult life of an individual before onset of decline, typically from the age of 25 years. However, based on the very young onset of dementia in some of the identified RGNDs and even reports of decline in the second decade, we advise a broad, neuropsychological baseline measurement in all individuals with RGNDs starting in the beginning of adulthood and ideally before the transition to other daytime or living environments at approximately 18 years of age. From then on, this should be followed by a minimum of 5-yearly screening (increasing with age).[2] These

recommendations might raise concerns about validity and time consumption, but the DLD, DSQIID, and CAMDEX-DS are validated in the population with ID with a limited burden for informants.[50] More validation and systematic evaluation are necessary to develop an international core outcome set for longitudinal direct assessment.

Strengths of this systematic review include the comprehensive search strategy, the extensive data collection, the study quality assessment, and a multidisciplinary research team. Limitations include the retrospective nature and convenience sampling of most studies, the likelihood of publication bias, the fact that study populations were often small due to the rarity of the disorders, and that controls were often lacking. This is reflected by the limitations in study quality in some studies because samples were not always representative. Individuals of older age or with moderate to severe levels of ID were underreported, reflecting a care and research gap.

This review reveals diagnostic and reporting gaps in dementia and cognitive/adaptive trajectories in adults with RGNDs. Our findings underline that systematic longitudinal follow-up of cognitive and adaptive functioning, using validated instruments, from young adulthood is justified to improve diagnosis and anticipatory care. Future research is required to further investigate the neurodevelopmental-neurodegenerative continuum in RGNDs, including the prevalence, phenomenology, and pathophysiology of (young-onset) dementia. More insights into genetic and other risk factors will provide a basis for targeted screening, diagnostics, monitoring and guidelines, optimizing personalized care for this vulnerable patient population.

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Appendix *(continued)*

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