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Neurocognitive and neurobehavioral characterization of two frequent forms of neurodevelopmental disorders: the DYRK1A and the Wiedemann–Steiner syndromes

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Abstract

DYRK1A and Wiedemann–Steiner syndromes (WSS) are two genetic conditions associated with neurodevelopmental disorders (NDDs). Although their clinical phenotype has been described, their behavioral phenotype has not systematically been studied using standardized assessment tools. To characterize the latter, we conducted a retrospective study, collecting data on developmental history, autism spectrum disorder (ASD), adaptive functioning, behavioral assessments, and sensory processing of individuals with these syndromes ($n = 14;21$). In addition, we analyzed information collected from families ($n = 20;20$) using the GenIDA database, an international patient-driven data collection aiming to better characterize natural history of genetic forms of NDDs. In the retrospective study, individuals with DYRK1A syndrome showed lower adaptive behavior scores compared to those with WSS, whose scores showed greater heterogeneity. An ASD diagnosis was established for 57% (8/14) of individuals with DYRK1A syndrome and 24% (5/21) of those with WSS. Language and communication were severely impaired in individuals with DYRK1A syndrome, which was also evident from GenIDA data, whereas in WSS patients, exploration of behavioral phenotypes revealed the importance of anxiety symptomatology and ADHD signs, also flagged in GenIDA. This study, describing the behavioral and sensorial profiles of individuals with WSS and DYRK1A syndrome, highlighted some specificities important to be considered for patients' management.

KEYWORDS
ADHD, anxiety, autism spectrum disorder, behavioral phenotype, communication, DYRK1A, KMT2A, Wiedemann–Steiner syndrome

1 | INTRODUCTION

DYRK1A syndrome (or MRD7 for Mental Retardation autosomal dominant 7, MIM#614104) is an autosomal dominant genetic syndrome caused by loss-of-function mutations in the *DYRK1A* (Dual-specificity tyrosine phosphorylation regulated kinase 1A) gene located in the Down syndrome critical region on chromosome 21 (21q22.13). This syndrome is associated with global developmental delay, consistent moderate to severe intellectual disability (ID), developmental language impairment, epilepsy, gait disorders,

feeding difficulties, microcephaly, epilepsy, brain MRI abnormalities, growth retardation and peculiar facial gestalt.[1–9] Wiedemann–Steiner syndrome (WSS, MIM#605130) is an autosomal dominant genetic syndrome caused by mutations in the *KMT2A* (Lysine methyltransferase 2A) gene located on chromosome 11 (11q23.3). Patients with this syndrome have variable mild to severe ID, associated with hypotonia, hypertrichosis, short stature, congenital malformations (cardiac, bone, brain, ophthalmologic) and facial dysmorphia.[10–14]

The *DYRK1A* and *KMT2A* genes are among the most frequently mutated genes found in syndromic neurodevelopmental disorders (NDDs)[15,16] and are considered to be associated with both ID and autism spectrum disorder (ASD).[9,11,17,18] As *DYRK1A* is found more frequently mutated in cohorts of individuals with ASD[19–24] than *KMT2A*,[22,25] *DYRK1A* is more considered as a gene involved in ID and ASD,[17,19] whereas *KMT2A* is rather considered a gene involved in ID.[11]

Clinical manifestations of these two syndromes are now widely known, but behavioral and neurocognitive profiles have not been precisely described and even less in a standardized way. In the DYRK1A syndrome, simple case reports or cohort analysis have highlighted the presence of ASD, attention deficit disorder with or without hyperactivity (ADHD), anxiety disorders and stereotyped behaviors, with variable frequencies.[1,4,6–9,17] This is also the case in WSS, where descriptive studies have reported the presence of ASD, ADHD, anxiety disorders and aggressive behavior in individuals.[11,12,14,18]

For both syndromes, individual behaviors described in the literature are rarely based on validated questionnaires and standardized tools. It is therefore likely that the behavioral abnormalities reported in these syndromes are under or overestimated. To our knowledge, only two studies have focused on autistic symptomatology in patients with DYRK1A syndrome using standardized diagnostic tools (Autism Diagnosis Observation Schedule-Module 2 [ADOS-2] and Autism Diagnostic Interview-Revised version [ADI-R]),[4,17] but none has specifically explored in parallel the extended behavioral phenotype of the syndrome (specific search for ADHD, anxiety disorders, maladaptive behaviors or sensory disorders) using standardized tools. Similarly, only one study on six patients only has assessed to date the behavioral phenotype of WSS using recommended tools.[18]

This study was designed to accurately determine and compare the behavioral phenotype of the DYRK1A syndrome and WSS. The evaluation was carried out in a standardized manner using adapted and validated tools focusing on the patients' adaptive behavioral profiles, autistic characteristics, ADHD symptomatology, anxiety disorders, maladaptive behaviors, and sensory disorders. These results were cross-checked with those reported for the two syndromes in the GenIDA caregiver-based patient registry, which aims to provide a better characterization of the clinical manifestations and natural history of genetic forms of neurodevelopmental disorders through the completion of an online structured medical questionnaire by caregivers of an affected person.

2 | METHODS

2.1 | Retrospective study

2.1.1 | Patient recruitment

This study includes 14 individuals carrying a pathogenic variant in *DYRK1A*, 13 of whom have already been published by Courraud et al[9] and Bronicki et al,[1] as well as 21 individuals with a pathogenic variant in *KMT2A*, 7 of whom have already been published by Baer et al[11] (Table S1). Behavioral phenotype of patients already published had never been studied using standardized and validated tools. All *KMT2A* variants were de novo, as well as almost all *DYRK1A* variants, excepted for patient P9, for whom familial segregation was not available (Table S1). All these patients were recruited thanks to collaborations between geneticists from different French University Hospitals and *via* the respective support groups for French families. This study was conducted in compliance with ethical standards: the ethics committee of the Strasbourg University Hospitals approved this study (CE-2021-41) and a non-objection form to participate in this research was signed by the parents of the participants. We retrospectively collected data related to developmental history, ASD diagnosis, adaptive functioning, complementary behavioral assessments, and sensory profile of patients. Tests used for each domain are specified below.

2.1.2 | Autism Diagnostic Interview-Revised

The timeline of developmental milestones (i.e., age of first words, first sentences, and age of acquisition of walking) was obtained via the Autism Diagnostic Interview-Revised questionnaire (ADI-R). The ADI-R[26] was used to determine the presence of ASD in patients. It is a standardized semi-structured interview commonly used for the diagnosis of ASD (in verbal and nonverbal individuals), based on DSM-IV criteria. The ADI-R items explore three domains: qualitative abnormalities in reciprocal social interactions (Domain A), qualitative abnormalities in communication (Domain B), and restricted, repetitive, and stereotyped behaviors patterns (Domain C). Each item can be scored from 0 to 3: a score of "0" means that the behavior was not present, a score of "2" or "3" should be assigned when the abnormality was present, and a score of "1" means that the subject exhibited abnormal behavior, but not severe enough to warrant a score of "2." The ADI-R supports a diagnosis of ASD when scores in all three domains (A, B, and C) are above cut-off scores. This instrument has high sensitivity and specificity for identifying ASD in a variety of groups, including children with developmental disabilities, although sensitivity and specificity are lower in children under the developmental age of 2 years.[26] We used the French validation of the ADI-R.[27] The ADI-R also allowed us to define each patient's overall language level through item 30 (functional use of spontaneous, echolalic or stereotyped language, which in everyday life includes sentences of three words or more with at least occasional verbs, and which are understandable to others): if the score on this item was "1" or "2," the subject was considered nonverbal.

2.1.3 | Social Communication Questionnaire

The severity of ASD symptoms was assessed using the Social Communication Questionnaire (SCQ)[28] in French.[29] This questionnaire consists in 40 items (based on the ADI-R questions) to be answered by yes (presence = 1 point) or no (absence = 0 point). These items are grouped into three domains as in the ADI-R. A total score above 15 is indicative of an ASD. The SCQ has good concurrent validity with the ADI-R.[26] The SCQ in its Current Behavior form used in this study explores the individual's behavior over the past 3 months.

2.1.4 | Vineland Adaptive Behavior Scales

The Vineland Adaptive Behavior Scales in its second edition (VABS-II; interview form)[30] was used to assess adaptive behavior in individuals. It was designed to measure adaptive functioning in four domains: communication, daily living skills, socialization, and motor skills (for this last domain, only for children under 7 years of age). Adaptative level is defined according to standard scores (low between 20 and 70, moderately low between 71 and 85, adequate between 86 and 114, moderately high between 115 and 129, and high between 130 and 160). We used the French validation of the VABS-II.[31]

2.1.5 | Aberrant Behavior Checklist

Non-ASD behavioral problems were studied using the Aberrant Behavior Checklist (ABC),[32] a 58-item rating scale used to identify the presence of maladaptive behavior in five categories: irritability; lethargy/social withdrawal; stereotypy; hyperactivity/noncompliance and inappropriate speech. Each item is scored from 0 (not a problem at all) to 3 (a very significant problem), with a higher score indicating a more severe problem. This scale was designed for people with developmental disabilities[32] and has previously been used in people with genetic syndromes.[33]

2.1.6 | Screen for Child Anxiety Related Emotional Disorders

Anxiety was assessed using the Screen for Child Anxiety Related Emotional Disorders scale (SCARED) for parents[34] validated in French.[35] It is a 41-item questionnaire investigating five anxiety disorders: generalized anxiety disorder, panic disorder, separation anxiety disorder, social anxiety disorder and significant school avoidance. A total score of 25 or more indicates an anxiety disorder.

2.1.7 | Conners' Parent Rating Scale

To assess symptoms of inattention, distractibility, impulsivity and hyperactivity, the 48-item Conners' Parent Rating Scale (CPRS)[36] was used. The score of this scale (ADHD index) is considered in favor of ADHD when above 15.

2.1.8 | Sensory processing

Sensory processing was assessed using the short sensory profile (SSP).[37] The SSP is a 38-item questionnaire exploring seven sensory domains: tactile sensitivity, taste/smell sensitivity, movement sensitivity, underresponsiveness/seeks sensation, auditory filtering, low energy/weak, and visual/auditory sensitivity. All items are scored on a 1–5 scale (i.e., ranging from 1–always to 5–never). Based on the score in each domain and the final score, the degree of sensory impairment of the individual is considered a typical performance, a probable difference, or a definite difference.

2.2 | GenIDA collection and parental testimonies

GenIDA is an international patient- and parent-driven data collection initiated in 2016 and available online (https://genida.unistra.fr/) approved by the French ethics committee. It aims to better characterize the clinical manifestations and natural history of genetic forms of ID by building gene- or CNV-specific patient cohorts and collecting information useful for the care management of affected individuals, through a structured online questionnaire completed by caregivers, usually parents. GenIDA provides new insights into the phenotype and natural history of genetic forms of ID, as the questions address physical parameters, cognitive aspects, behavioral aspects, the presence or absence of neurological manifestations or problems in important physiological functions. In June 2022, GenIDA comprises 1533 well-documented patient records for different genetic forms of ID (41% in France, 21% in the United States, 10% in the United Kingdom, 4% in the Netherlands, etc.) and already includes 20 well-documented records for individuals with DYRK1A syndrome and 20 as well for WSS that we used for our study. Wordclouds were generated from parental testimonies using Wordcloud package in R after removing of stop and uninformative words (adverbs, helping verbs, etc.).

2.3 | Statistical analysis

We used the JAMOVI 1.8.4 software (Jamovi project)[38] to perform the statistical analyses in this work. Participants were matched on age and gender. We used Fisher's exact test for qualitative variables and the Mann–Whitney *U* test for quantitative variables. *p*-values lower than .05 were considered significant.

3 | RESULTS

3.1 | General description of the two groups: individuals with DYRK1A syndrome and with WSS

The ages of individuals participating to the retrospective study at the time of evaluation ranged from 3.5 to 28.5 years (mean age 10.8 years) for individuals with WSS, not significantly different from

those of individuals with DYRK1A syndrome (5.6–35.8 years, mean age 12.9 years; Table 1). The gender distribution did not differ between the two groups (57% males, 43% females; Table 1). Motor development was not significatively different in terms of severity in the two groups, with a similar proportion of individuals presenting motor delay (85% and 80%, respectively) with a similar mean age for walking acquisition (25.8 months for DYRK1A syndrome and 21.6 months for WSS; Table 1). Language impairments were stronger in individuals with DYRK1A syndrome ($p = 0.001$), as found in all 14 individuals of this group, with most patients considered as nonverbal at the time of testing ($n = 10/14$, 71%). On the contrary, most individuals with WSS are considered as verbal ($n = 18/21$, 86%) with 15 individuals who had correct language for their age, while three used short sentences or age-inappropriate language; one patient had not yet acquired language and two used less than 50 words (Table 1). VABS-II scores showed that adaptive skills in the three domains studied were broadly homogeneous in the DYRK1A group, with standard scores ranging from 20 to 43 in communication, 20 to 50 in daily living skills and 20 to 51 in socialization (Table 1, Figure 1). All patients had scores below 70 in the three domains and thus showed impaired adaptive behaviors. For the WSS group, adaptive skills in the three domains were more heterogeneous as they ranged from 20 to 97 or 98 (Table 1, Figure 1). In total, we observed that adaptive functioning was significantly higher in the WSS group than in the DYRK1A syndrome group for the three domains (Table 1, Figure 1) but with a larger degree of heterogeneity.

3.2 | Language impairments

Nonverbal individuals were overrepresented in the DYRK1A group ($n = 10$, 71%; Table 1). According to the type of language, no

TABLE 1 Clinical, developmental, and adaptive characteristics of individuals with DYRK1A syndrome and WSS

	DYRK1A ($n = 14$)		WSS ($n = 21$)			
	Mean	SD	Mean	SD	Statistical test	*p*-value[a]
Age (in years)	12.9	(8.0)	10.8	(5.8)	$U = 124$	0.45
Sex						
Male (*n*; %)	8; 57	-	12; 57	-	Fisher's exact test	1.00
Language						
Language delay (*n*; %)	14; 100	-	15; 71	-	Fisher's exact test	0.061
Nonverbal (*n*; %)	10; 71	-	3; 14	-	Fisher's exact test	**0.001**
Motor development						
Motor delay (*n*; %)	12; 85	-	16; 80	-	Fisher's exact test	1.00
Age for walking acquisition (in months)	25.8	(12.2)	21.6	(5.1)	$U = 127$	0.66
VABS-II						
Communication	24.1	(7.8)	52.9	(23.4)	$U = 42.5$	**< 0.001**
Daily living skills	28.8	(10.9)	57.2	(25.9)	$U = 53.5$	**0.002**
Socialization	29.6	(10.0)	54.4	(25.4)	$U = 56.5$	**0.002**

Abbreviations: SD, standard deviation; *U*, Mann–Whitney test, VABS-II, Vineland Adaptive Behavior Scales.
[a]Significant *p*-values are in bold.

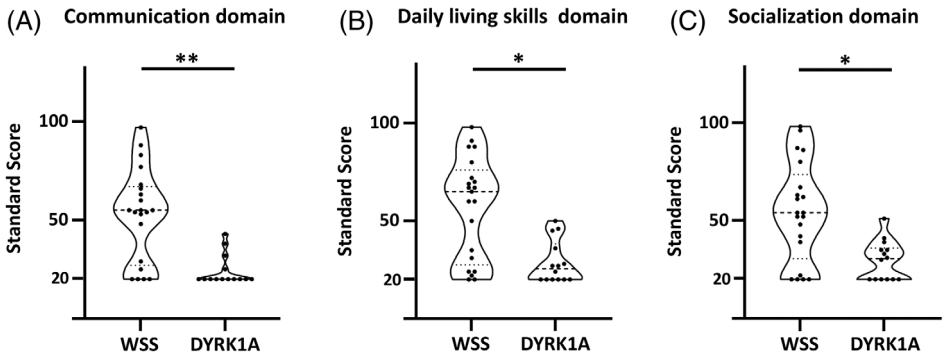

FIGURE 1 VABS-II standard scores in three domains: communication, daily living skills, and socialization. Adaptive skills measured by the Vineland Adaptive Behavior Scales II. The standard score is reported for the DYRK1A group (right) and the WSS group (left). Violin plots representing the average standard score in (A) communication, (B) daily living skills and (C) socialization for individuals with DYRK1A syndrome ($n = 14$) and WSS ($n = 21$). The standard scores were significantly lower in the DYRK1A group. *p-value <0.01; **p-value < 0.001.

individual use adapted language for current age, two speak using short sentences with verbs, 11 speak using less than 50 words and one has not yet acquired word. Moreover, five patients communicate using sign language or the Makaton method[39] and three used the Picture Exchange Communication System (PECS).[40] Consistent with this finding, the VABS-II communication subscore was also lower in this group (Table 1). In addition to the data from the retrospective study, communication and speech impairments also emerged as the main problem according to the caregivers' answers in the GenIDA database (Figure S1A). In detail, families reported that 50% of children do not speak and only 10% do speak in correct and complete sentences in DYRK1A syndrome. The remaining individuals have language abilities ranging from only a few words to the use of incorrect sentences (Figure S1B). They use various alternative means of communication, mostly gestures, sounds, pictures and sign language (Figure S1C) and in the vast majority (88.2%), the understanding was better than the expression (Figure S1D) as illustrated by some sentences extracted from the parents' testimonies (Figure S1E).

3.3 | Autistic features

Individuals with DYRK1A syndrome showed significantly higher ADI-R scores than individuals with WSS in the three subdomains: communication, socialization, and restricted/repetitive behaviors, as well as higher total SCQ score (Table 2), suggesting a higher autistic symptomatology in DYRK1A individuals. More than a half ($n = 8/14$, 57%) of the individuals with DYRK1A syndrome reached the ASD

TABLE 2 Mean scores, standard deviation, and maximum and minimum scores for the ADI-R and SCQ tests

	DYRK1A ($n = 14$)		WSS ($n = 21$)		Comparison	
	Mean (SD)	Range	Mean (SD)	Range	Mann–Whitney *U* test	*p*-value[a]
ADI-R						
Communication	14.6 (6.7)	*7–24*	7.1 (5.1)	1–21	54.0	**0.002**
Social interaction	9.4 (3.1)	*5–13*	7.0 (3.9)	1–14	86.5	**0.042**
Restricted/repetitive behaviors	4.6 (1.7)	*1–7*	2.9 (1.8)	0–6	76.0	**0.016**
SCQ						
Total score	16.8 (5.9)	*8–29*	10.5 (5.33)	2–22	59.5	**0.003**

Abbreviations: ADI-R, Autism Diagnostic Interview-Revised; SCQ, Social Communication Questionnaire; SD, standard deviation.
[a]Significant *p*-values are in bold.

TABLE 3 Mean scores, standard deviation, and maximum and minimum scores for the ABC, CPRS and SCARED tests

	DYRK1A ($n = 14$)		WSS ($n = 21$)		Comparison	
	Mean (SD)	Range	Mean (SD)	Range	Mann–Whitney *U* test	*p*-value[a]
ABC						
Total score	44.5 (23.3)	10–84	48.8 (30.1)	9–113	139.5	0.814
Irritability	9.3 (7.2)	0–23	14.4 (11)	0–40	105.0	0.161
Lethargy	13.8 (9.8)	0–32	5.3 (6.9)	0–23	69.0	**0.009**
Stereotypy	6.9 (2.5)	3–11	5.6 (5.6)	0–20	94.5	0.078
Hyperactivity	12.6 (7.5)	1–26	18.9 (11.1)	4–42	96.5	0.092
Inappropriate speech	1.9 (1.8)	0–5	4.7 (3.1)	0–11	64.0	**0.005**
CPRS						
ADHD index	8.8 (4.2)	4–17	13.4 (6.6)	0–26	80.5	**0.026**
SCARED						
Total score	15.6 (10.1)	3–37	22.3 (11.9)	3–45	94.0	0.077
GAD	4.1 (3.8)	0–15	7.4 (3.9)	1–16	69.0	**0.009**
Social anxiety disorder	4.0 (3.4)	0–11	3.4 (3.4)	0–12	129.5	0.563
Panic disorder	3.8 (3.3)	0–9	4.5 (3.9)	0–13	124.0	0.443
Separation anxiety disorder	3.3 (2.3)	0–8	5.6 (3.1)	0–11	79.0	**0.022**
School avoidance	0.4 (0.6)	0–2	1.4 (1.7)	0–6	87.0	**0.030**

Abbreviations: ABC, Aberrant Behavior Checklist; ADHD, Attention Deficit Hyperactivity Disorder; CPRS, Conners' Parent Rating Scale; GAD, generalized anxiety disorder; SCARED, Screen for Child Anxiety Related Emotional Disorders; SD, standard deviation.
[a]Significant *p*-values are in bold.

measured with ADI-R, including three individuals (21%) with an SCQ score suggesting severe autism (score SCQ ≥22). In comparison, five individuals with WSS ($n = 5/21$, 24%) received an ASD diagnosis with the ADI-R, among them two (9.5%) had a SCQ score in favor of severe autism. The ABC scale was used to measure the maladaptive autistic behaviors. The total score, and more especially the score measuring the intensity of the stereotypic behavior, did not differ between the two groups. Individuals from the DYRK1A group had a significantly higher score on the "lethargy/social withdrawal" subscale ($p = 0.009$). They also showed a significantly lower score on the "inappropriate speech" subscale ($p = 0.005$; Table 3).

3.4 | ADHD and anxiety symptoms

Individuals with WSS had a significantly higher ADHD index score on the CPRS than individuals with DYRK1A syndrome suggesting a significant higher ADHD symptomatology in WSS ($p = 0.026$; Table 3). In total, eight individuals with WSS (38%) obtained a score on the CPRS in favor of a diagnosis of ADHD, compared to only two individuals with DYRK1A syndrome (14%). Anxiety symptomatology measured by the SCARED did not differ between the two groups in terms of total score, but when comparing subscores, individuals in the WSS group had significantly higher scores for generalized anxiety disorder, separation anxiety, and school avoidance than those in the DYRK1A group (Table 3). Eight individuals (38%) from the WSS group obtained a SCARED total score suggesting an anxiety disorder. Among the various forms of anxiety reported, generalized anxiety disorder ($n = 8$), panic anxiety disorder ($n = 5$), separation anxiety disorder ($n = 12$), social anxiety disorder ($n = 4$) and significant school avoidance ($n = 3$) were mentioned. In comparison, only three individuals with DYRK1A syndrome (21%) had a SCARED total score in favor of an anxiety disorder. ADHD and anxiety are among the problems that are reported in GenIDA by parents of individuals with WSS as primarily affecting their children's daily quality of life (Figure S2A). Families reported that a large majority of individuals with WSS (95.5%) have behavioral problems (Figure S2B), including attention deficit, anxiety, and phobia, but also low frustration tolerance, obsessive behavior or aggressive behavior (Figure S2C).

3.5 | Sensory profiles

The SSP score did not differ between the two groups. Six individuals with DYRK1A syndrome (43%) and seven with WSS (33%) showed definite difference in the total sensory profile score. No specific profile emerged. In both groups, significant lack of energy in daily life (DYRK1A $n = 11$, WSS $n = 11$) was prominent.

4 | DISCUSSION

In this study, we wanted to determine and compare the behavioral phenotype of the DYRK1A syndrome and WSS using standardized tools through a retrospective study of 14 patients with DYRK1A syndrome and 21 patients with WSS. In complement to these standardized measurements, we collected information from 40 families using the family driven GenIDA database, an international cohort of genetic forms of NDDs. Whereas individuals with WSS presented heterogenous adaptive behavior scores, individuals with DYRK1A syndrome had low adaptive behavior score. An ASD diagnosis was established for 57% ($n = 8/14$) of individuals with DYRK1A syndrome and 24% ($n = 5/21$) of individuals with WSS. Language was strongly impaired in individuals with DYRK1A syndrome; similar findings emerge from data collected via GenIDA. Exploration of behavioral phenotypes in the WSS group revealed the importance of anxiety symptomatology and signs of ADHD, also reported in GenIDA. Sensory disorders are reported in both groups, as basically known in individuals with ID.[41]

The comparison of adaptive behavior profiles in the two syndromes showed much greater heterogeneity in individuals with WSS than in individuals with DYRK1A syndrome. Our results are consistent with literature, as individuals with WSS present ID of varying severity ranging from mild to severe[11,13,42] while the majority of DYRK1A patients have moderate to severe ID.[4,9] Thus, genetic expressivity is much more variable in individuals with WSS, who may present mild or even no ID, illustrated by familial inheritance of some *KMT2A* pathogenic variations.[11] This was never reported for *DYRK1A* variants. However, we found no obvious genotype–phenotype correlation between the severity and the type or position of *KMT2A* variants which could explain the heterogeneity in the adaptive behavior profiles (Table S2).

The intensity of autistic symptomatology was significantly higher in the DYRK1A group, although the proportion of ASD was not significantly different between individuals with DYRK1A syndrome and WSS, which may be due to the small sample sizes studied. We found an ASD frequency of 57% ($n = 8/14$) in the DYRK1A group, that allows us to recommend a systematic assessment of ASD in individuals carrying pathogenic *DYRK1A* variants. A high frequency of ASD was also reported in studies already published about DYRK1A syndrome.[4,17] Of eight patients with *DYRK1A* variants evaluated using ADOS-2 and ADI-R, seven had an ASD diagnosis.[4] The largest DYRK1A sample studied to date, compiling previously published and newly identified cases ($n = 61$ individuals), reported 43% of ASD,[17] however ASD was formally assessed with ADI-R or ADOS-2 in only 10 patients (Table S3). A quarter of individuals with WSS were diagnosed with ASD in our study, a proportion similar to that of a recently published cohort of 104 individuals reporting ASD in 21.3% of the individuals.[14] These findings contrast with those of a cohort of 16 Chinese patients with WSS that reported ASD in only one of them.[12] Similarly, in a meta-analysis of 127 individuals, ASD was reported in less than 15% of them.[18] Chan et al reported a high proportion of ASD with five patients out of six having this diagnosis.[18] This last study was the only one to use standardized tools (ADOS-2 and ADI-R) (Table S3). The discrepancy of ASD frequency in WSS may be due to the lack of detailed information available on the modality of ASD diagnosis and/or the small number of patients included.

Our study showed that both syndromes are characterized by an overall developmental delay in both language and walking, with language much more impaired in individuals with DYRK1A syndrome, most of whom do not acquire functional language ($n = 10/14$). Language impairments (absent language, a few words, a few sentences) are reported in all the individuals with DYRK1A syndrome.[9] These severe language disorders constitute an important clinical feature and a specific item in the dedicated DYRK1A clinical score.[9] The importance of the use of alternative communication systems emerged both from the analysis of our cohort and from parental testimonies in GenIDA. Considering the frequency of language disorders and the homogenous adaptive profiles in individuals with DYRK1A syndrome, the use of alternative communication systems should be highly recommended. Concerning motor development, delay in walking acquisition did not differ between the two syndromes in our study. Mean age of walking was similar to those already reported: 21.6 months versus 23.9[11] or 20 months[14] in WSS, and 25.8 months versus 23 months[9] in DYRK1A syndrome.

The exploration of behavioral phenotypes (excluding ASD) associated with the two syndromes revealed more anxiety symptomatology and more signs of ADHD in the WSS group in our retrospective study. The SCARED results were consistent with an anxiety disorder in 38% ($n = 8/21$) of individuals with WSS. The largest cohort of WSS patients described to date did not mention any anxiety disorder[14] whereas a meta-analysis of 127 individuals reported anxiety symptoms in about 5% of individuals.[18] This discrepancy may be due to the lack of detailed information available on the tests used or not. The only study that assessed the behavioral phenotype using specific tests found anxiety symptoms in three out of six patients with WSS[18] (Table S3). Regarding DYRK1A syndrome, anxious behavior is reported in 21% ($n = 3/14$) of patients in our study and 27% ($n = 12/44$) in the study by Earl et al[17] without mention of the anxiety assessment modality (Table S3). In our study, anxiety symptomatology was otherwise greater in the WSS group than in the DYRK1A group. However, this difference could be misestimated by the fact that SCARED is better suited to populations of individuals with less severe ID. Nevertheless, a recent study has evidenced the relevance and validity of using this questionnaire in ID.[43] Moreover, some data from the literature[18] and parents' testimonies reported difficulties in emotional regulation for children with ID, an additional argument for an anxious symptomatology. In our study, ADHD symptomatology was more prominent in individuals with WSS. Hyperactivity is indeed a prominent behavioral manifestation of WSS, as it was found in 38% of individuals with WSS in our study, in up to 44.3% of individuals of the largest cohort,[14] and diagnosed in four out of six patients in the study by Chan et al,[18] whereas it was only reported in about 5% of individuals in the meta-analysis[18] (Table S3). Regarding DYRK1A syndrome, hyperactive behavior is reported in 33% of patients from the literature[17] and in 14% from our study. This behavioral feature had never been explored using standardized tools in DYRK1A syndrome before (Table S3).

Our study has potential clinic and therapeutic implications. As mentioned below, our results allow us to recommend a systematic assessment of ASD and the use of alternative communication supports (because of non-functional language) in individuals with pathogenic *DYRK1A* variants. In addition, our results highlight anxiety and ADHD problems in WSS. Systematic assessments of these disorders are therefore recommended. Further research on these two syndromes is now needed to test specific interventions and treatments. Our study is the first step toward personalized medicine in DYRK1A syndrome and WSS. Our standardized data are consistent with the data reported in GenIDA, allowing us to consider the reliability of the data collected from parents and demonstrating the complementarity of these two clinical and participatory approaches. Hence, studies such as GenIDA empower families who become real stakeholders in research in the field of rare diseases.

Our study presents nevertheless some limitations. First, the samples of individuals with DYRK1A syndrome and WSS included are relatively small. However, both syndromes are rare diseases and sample sizes are necessarily limited. Further research is needed to confirm our observations on larger groups and the use of participatory databases such as GenIDA could be very valuable. Furthermore, the assessments were based solely on parental reports. A multi-focal assessment involving professionals, for example, would be of special interest. A direct assessment of participants' ASD, using the ADOS for example,[44] would refine our clinical evaluation. For anxiety and ADHD, specific diagnostic interviews with parents that verified the respective DSM-5 criteria might be useful to complete the parental questionnaires we used.

5 | CONCLUSION

In conclusion, this study characterized the behavioral phenotype of DYRK1A and Wiedemann–Steiner syndromes. Individuals with DYRK1A syndrome exhibit more autistic symptomatology than individuals with WSS. Individuals with WSS exhibit a more heterogeneous profile of adaptive behaviors than individuals with DYRK1A syndrome, including higher anxiety symptomatology and more signs of ADHD. Moreover, this study is the first to combine detailed neurodevelopmental testing with parental views. Both appear to be necessary to tailor patient management in personalized medicine.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The ethics committee of the University Hospitals of Strasbourg approved this study (CE-2021-41) and a non-objection form to participate in this research was signed by the parents of the participants.

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