Received: 10 August 2018 | Revised: 24 December 2018 | Accepted: 31 December 2018

DOI: 10.1111/gbb.12553

Genes, Brain and Behavior

ORIGINAL ARTICLE

Exploring the behavioral and cognitive phenotype of KBG syndrome

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KBG syndrome is a neurodevelopmental disorder, caused by dominant mutations in *ANKRD11*, that is characterized by developmental delay/intellectual disability, mild craniofacial dysmorphisms, and short stature. Behavior and cognition have hardly been studied, but anecdotal evidence suggests higher frequencies of ADHD-symptoms and social-emotional impairments. In this study, the behavioral and cognitive profile of KBG syndrome will be investigated in order to examine if and how cognitive deficits contribute to behavioral difficulties. A total of 18 patients with KBG syndrome and a control group consisting of 17 patients with other genetic disorders with comparable intelligence levels, completed neuropsychological assessment. Age-appropriate tasks were selected, covering overall intelligence, attention, memory, executive functioning, social cognition and visuoconstruction. Results were compared using Cohen's d effect sizes. As to behavior, fewer difficulties in social functioning and slightly more attentional problems, hyperactivity, oppositional defiant behavior and conduct problems were found in the KBG syndrome group. Regarding cognitive functioning, inspection of the observed differences shows that patients with KBG syndrome showed lower scores on sustained attention, cognitive flexibility, and visuoconstruction. In contrast, the KBG syndrome group demonstrated higher scores on visual memory, social cognition and emotion recognition. The cognitive profile of KBG syndrome in this sample indicates problems in attention and executive functioning that may underlie the behavior profile which primarily comprises impulsive behavior. Contrary to expectations based on previous (case) reports, no deficits were found in social cognitive functioning. These findings are important for counseling purposes, for tailored education planning, and for the development of personalized intervention.

KEYWORDS

ANKRD11, attention, behavior, cognition, contextual neuropsychology, executive functioning, genetics, KBG syndrome, neurodevelopmental disorder, visuoconstruction

1 | INTRODUCTION

KBG syndrome (KBGS; OMIM #148050) is an autosomal dominant neurodevelopmental disorder which was first described by Hermann in 1975 and was named after the surname initials of the three families he reported.[1] The syndrome is caused by heterozygous mutations in *ANKRD11* (OMIM #611192).[2] It seems likely that haploinsufficiency is responsible for the clinical phenotype, as complete heterozygous deletions of *ANKRD11* have been found causative. However, recent findings suggest that the pathogenesis of a heterozygous *ANKRD11* mutant may also involve another mechanism, as abnormal ANKRD11 protein accumulation was observed probably caused by dimerization of mutant and with wild-type ANKRD11.[3] Although KBGS was hardly recognized until a few years ago, a tremendous increase in molecularly

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confirmed cases has been achieved after the introduction of genome-wide sequencing technologies. So far, 218 patients have been reported and described worldwide.[2–8] Intriguingly, *ANKRD11* was identified as the most frequently mutated gene (incidence of 39) in a cohort of 4293 patients with neurodevelopmental disorders that were diagnosed based on whole-exome-sequencing, establishing KBG syndrome as one of the most prevalent dominant neurodevelopmental syndromes.[9]

With regard to the somatic phenotypic presentation, KBGS is mainly characterized by mild craniofacial dysmorphisms, macrodontia of upper central permanent incisors, short stature and skeletal anomalies. Other recognized features include cardiac abnormalities, partial hearing loss and a persistent/large fontanel.[4–7] As to neurological findings, abnormal electroencephalogram (EEG) patterns both with and without epileptic seizures are often described.[5,6,10,11] Types of seizures include tonic–clonic, complex partial, and absence variants and the EEG consists mostly of non-specific slowing. Reports of neuroimaging show various usually mild anomalies as small cerebelli, hypoplasia of the cerebellar vermis, enlargement of the ventricles, partial agenesis of the corpus callosum, and white matter anomalies around the ventricles and near the gray-white junction in both hemispheres.[5–8,10–12]

Behavioral functioning in KBGS has primarily been described in terms of diagnostic classifications. Series of case-studies have reported anecdotal evidence for attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), anxiety, as well as aggression or compulsive behavior.[4–8,10,13] The majority of studies that included behavioral classifications did not clarify whether these classifications were solely based on observations, or based on an extensive diagnostic procedure. In order to substantiate the findings regarding the psychopathology in patients with KBGS, behavioral functioning needs to be objectified by means of multiple diagnostic instruments, such as behavior questionnaires, clinical interviews and systematic observations.

Cognitive functioning is closely related to behavioral functioning. Because deficits in cognitive functioning contribute to symptoms of behavior disorders, clarification of the underlying cognitive deficits is essential for understanding these disorders (eg, [14,15]). Insight into the cognitive profile enables explanation of specific learning difficulties in patients with behavior disorders and may also provide directions for daily living, education planning and treatment of these patients. Moreover, identification of cognitive deficits may further unravel the specific contribution of *ANKRD11* and its corresponding protein to nervous system functioning and in particular to cognition. However, virtually no studies are available that focus on cognitive functioning in KBGS. The few studies that do address cognitive functioning in KBGS are limited to case descriptions, mentioning evidence of intellectual disability (ID), delayed speech and delayed motor development.[5,6,8,11] Two descriptive case studies, comprising a total of four patients with KBGS, presented additional problems in memory, executive and visuospatial functioning.[13,16]

We recently explored cognitive abilities focusing on the strengths and weaknesses in intelligence profiles in a larger cohort of patients with KBGS and compared these to patients with other genetic syndromes. Our results showed intelligence levels that vary from a moderate ID to average levels of intelligence, with a majority of patients showing mild ID.[17] Furthermore, results of this study denoted comparable intelligence profiles in patients with KBGS and patient controls, indicating that the cognitive profile of KBGS did not include specific weaknesses in speed of information processing or working memory performance.[17] However, as the main cognitive domains measured by the Wechsler scales are fluid and crystallized intelligence, working memory, visual processing and processing speed, and it does not provide specific measures of, for instance, long-term memory and social cognition,[18,19] examination of these domains is needed to further delineate a cognitive profile in KBGS. Therefore the purpose of this study is to thoroughly investigate both the behavioral and cognitive profile in KBGS.

The majority of studies regarding cognitive profiling of genetic syndromes directly compares patients' performance to normative means or results of a healthy control group, both usually representing individuals with an average level of intelligence.[20] Because patients with genetic syndromes often have mild to moderate ID and achieved lower levels of education compared to the general population, such comparison goes with a high risk of overestimation of cognitive deficits in these patients, because they will probably deviate on all domains of cognitive functioning compared to individuals with an average level of intellectual functioning. This risk of overestimation of cognitive deficits emphasizes the need to additionally compare cognitive performance of patients with the genetic syndrome to performances of individuals with a similar intelligence level, to enable identification of a unique cognitive profile related to this syndrome. In this study we perform both comparisons.

To examine how potential cognitive deficits may contribute to the behavioral difficulties in KBGS, we will explore both the behavioral and cognitive profile in KBGS. Given the findings of the previously described case studies on behavioral functioning in KBGS, symptoms from the ADHD and ASD spectrum may be expected, as well as anxiety, aggressive and compulsive behavior. Furthermore, based on previous case descriptions regarding cognitive functioning, specific deficits in memory, executive functioning and visuoconstruction are expected. To objectify these expected problems in KBGS, an extended neuropsychological test battery that includes objective and subjective measures as well as systematic observations, will be administered in a representative group of patients with KBGS. Performances in this group will be compared to both normative means and to performance of an appropriate control group, consisting of patients with genetic syndromes other than KBGS, who also had ID and developmental delay (DD).

2 | MATERIALS AND METHODS

2.1 | Participants

Forty-six participants took part in this study, including 21 patients with a confirmed mutation in the *ANKRD11* gene (KBGS group) and 25 patient genetic controls (PGC group). The latter included a mixed group of patients with a variety of other genetic syndromes, who also had ID/DD. Nearly every Dutch patient known with KBGS at the time

of data collection (2015) participated in this study. The data was collected simultaneously for the present study and a previous study on intellectual profiles in KBGS.[17] All participants were approached by a clinical geneticist (T.K. or C.W.O.) at the Department of Human Genetics of the Radboud University Nijmegen Medical Centre, The Netherlands. The study was approved by the Central Committee on Research Involving Human Subjects region Arnhem-Nijmegen (NL43187.091.13). Participation was on a voluntary basis and written informed consent was obtained from all participants or their legal representatives.

Patients under 6 years of age, patients with an auditory or visual handicap, or patients who were not able to speak, sit in a chair, use a pencil or execute more than two-thirds of the cognitive tasks, were excluded from this study. Based on these criteria, three patients with KBGS and eight potential participants for the control group were excluded from the study. This exclusion resulted in a group of 18 participants with KBGS (7 males) and 17 PGC (11 males), with a mean chronological age of respectively 18.7 (SD = 15.8, range 6-66) and 14.6 (SD = 5.6, range 6-25) years. There was no significant group difference regarding chronological age ($t(33) = 1.02$, $P = 0.32$, $d = 0.35$). The general level of intellectual functioning and developmental age did not differ between participants with KBGS and PGC (respectively $t(33) = -0.45$, $P = 0.65$, $d = 0.16$ and $t(27) = 0.13$, $P = 0.90$, $d = 0.05$). Intelligence was measured by age appropriate Wechsler scales (KBGS group: $M = 65$, range 45-99) and adaptive functioning was measured by a Dutch extended interview version of the Vineland Adaptive Behavior Scales (KBGS group: $M = 7$ years of age, range 3-12 years of age).

For a description of the specific genetic aberrations and medical characteristics of the participants, see Supplementary Table S1 (KBG) and Table S2 (PGC). Regarding brain development and functioning in participants with KBGS, three patients had a history of absences during early childhood; all conditions were currently in remission. Results from neuroimaging reports in medical records, present for eight participants with KBGS, did not show any structural anomalies. An exception was one patient with minor anomalies in the left cerebellum, probably as a result of complications during delivery. As for psychopharmacotherapy, four of the patients received methylphenidate, one patient received risperidone and one patient received a combination of both types of medications. Four participants with KBGS were first-degree relatives (mother, her two daughters and her grandson). All participants with KBGS, except one, already took part in the previous study for intelligence profiling in KBGS by the same research group,[17] and for six of these participants, the molecular and phenotypical characteristics have previously been reported.[4] The PGC group included a convenience sample of patients displaying various medical anomalies, dysmorphic features, and a delayed motor/communicative development or ID, possibly accompanied by behavioral difficulties, who were referred on suspicion of a genetic diagnosis to the specialized outpatient clinic of the department of clinical genetics.

2.2 | Materials and procedure

Participants were visited at their homes by researcher LvD, psychologist, accompanied by a research assistant. Two visits of approximately 4 hours were necessary to complete the assessment for each participant, in which breaks were provided based on the individual needs of each participant. Directly after each assessment, systematic observations of the participants were notated, with emphasis on behavioral, attentional, executive and social functioning. For reasons of conformity, a checklist based on the Test Observation Form[21] was used to scrutinize specific observational criteria such as attention span during the assessment, motor restlessness and the quality of eye contact.

Behavioral measures included Dutch versions of multiple widely used, gold-standard, and age appropriate behavior questionnaires to examine the frequency and nature of behavioral difficulties and social functioning as reported by primary caregivers (Child Behavior Checklist, CBCL, 6-18 years of age; Strengths and Difficulties Questionnaire, SDQ, 4-17 years of age; Children's Social Behavior Questionnaire, CSBQ, 4-18 years of age).

Cognitive measures included instruments that target the specific cognitive domains of attention, memory, executive functioning, social cognition and visuoconstruction. All tests have sufficient norms, are well validated, and also commonly used in a variety of international neuropsychological studies. Attention was measured by the D2 sustained attention test (from 9 years of age), a variant of the continuous performance test. Measures of cognitive flexibility and planning included the Intra/Extradimensional shifting task (IED, Cambridge Neuropsychological Test Automated Battery, CANTAB, Cambridge Cognition, Cambridge, UK), Key search task and Zoo map task (both part of the Behavioral Assessment of the Dysexecutive Syndrome battery, BADS/Behavioral Assessment of the Dysexecutive Syndrome battery for Children, BADS-C). The Dysexecutive Questionnaire (DEX), Dysexecutive Questionnaire for Children (DEX-C, 8-16 years of age) and Behavior Inventory of Executive Functioning (BRIEF, 5-18 years of age) were used to measure the experience of executive functioning in everyday life, as perceived by the primary caregivers of the participants. Memory was assessed by the Rey Auditory Verbal Learning Test (RAVLT), Rey Auditory Verbal Learning Test for Children (RAVLT-C, 6-12 years of age), Paired Associates Learning test (PAL) and Pattern Recognition Memory test (PRM). Using the CANTAB, both measures of visual episodic memory and learning (PAL) and visual recognition memory (PRM) were obtained. Social cognition was measured by performance on the Dutch Theory of Mind test Revised (TOM-test R, from 4 years of age), and an emotion recognition task (ERT, from 8 of age). Visual and motor abilities including spatial and organizational components were measured by both the Beery-Buktenica Developmental Test of Visual-Motor Integration (Beery VMI, from 2 years of age) and the Rey-Osterrieth Complex Figure Test (Rey CFT, from 8 years of age). A more extensive description of the tests and their references is included in Table S3. Both children and adults were included in this study in order to maximize the number of participants. Therefore we used different versions of the Wechsler scales, DEX and RAVLT in children and adults.

2.3 | Statistical analysis

First, a comparison was made between participants with KBGS and the norm group (healthy individuals). To this end, raw questionnaire scores and cognitive test performance scores for all individual participants with KBGS were, directly or via the transformation of T-scores, transformed into standardized scores. However, instead of standardizing with the KBGS group mean and SD, we used the norm group mean and SD. The norm group refers to descriptive statistics in the test manuals of the behavioral and cognitive tests. Additionally, for the standardization of the score of each individual KBGS participant we used the norm group means and SD that matched the age of the participant (and if available also its gender and education level). This will result in means that are not zero, while normally standardized variables have a mean of zero and a SD of one.

Subsequently, behavioral difficulties and cognitive test performances of participants with KBGS were compared to those of the PGC, to reveal a specific behavioral and cognitive profile for participants with KBGS when taking their ID into account. Reports on all questionnaires and performances on all above-described tests of attention, memory, executive functioning, social cognition and visuoconstruction were compared between both groups using Cohen's d. Although a generalized linear model would have been the preferable choice for this design, this was not feasible with a lack of power due to the relatively small sample size compared to the large number of dependent variables. Instead, Cohen's d effect sizes, the standardized mean difference between the two groups, were calculated for all differences in performance on cognitive tests between both groups.[22,23] Raw test scores for each questionnaire and cognitive test were used for the calculation of Cohen's d, except for the Wechsler scales, for which the total intelligence coefficients were used (calculated as described in the respective test manuals[24,25]). Cohen's d is sensitive to outliers, therefore the presence of outliers (> 3 SD) has been inspected. If outliers were present, both Cohen's d with and without inclusion of the outliers were reported in the result section.

3 | RESULTS

3.1 | Behavioral functioning—questionnaires

Table 1 displays the comparison between perceived behavioral problems and social-emotional functioning compared to the norm group. Compared to the norm group, a higher number of problems are reported in the KBG group for all social-emotional and behavioral functioning. The means for the total problems range between 1.05 (CBCL) and 2.21 (SDQ), with the most substantial deviations (>1.5 SD) present in behavior problem subscales related to attention/ADHD associated problems and social problems (>1 SD).

Table 2 displays the comparison of the KBGS and PGC group. No relevant differences, as reflected by small effect sizes, were indicated for the reported number of behavioral problems (SDQ, KBGS: M = 16.56, SD = 5.00, PGC: M = 16.55, SD = 5.39; d = 0.002; CBCL, KBGS: M = 40.63, SD = 11.26, PGC: M = 47.56, SD = 24.68; d = − 0.38; CSBQ, KBGS: M = 33.11, SD = 15.72, PGC: M = 37.56, SD = 14.34; d = − 0.31). Furthermore, fewer problems in participants with KBGS were also reported on the subscales of the SDQ and CBCL related to social, affective and somatic functioning. Finally, in the KBGS group, there was a somewhat higher number of problems in attention (CBCL-syndrome scale: attention problems: KBGS: M = 9.88, SD = 2.80; PGC: M = 9.33, SD = 2.83; d = 0.20) and hyperactivity (SDQ: KBGS: M = 6.44, SD = 2.92; PGC: M = 5.55, SD = 3.42; d = 0.29) as well as oppositional defiant behavior (CBCL-Diagnostic Statistical Manual scale: oppositional defiant problems: KBGS: M = 3.25, SD = 2.71; PGC: M = 2.89, SD = 3.30; d = 0.43) and conduct problems (CBCL—Diagnostic Statistical Manual scale: conduct problems: KBGS: M = 2.25, SD = 3.37; PGC: M = 2.11, SD = 1.76; d = 0.29).

3.2 | Behavioral functioning—observations

During the assessments, participants with KBGS generally displayed a cheerful attitude. Compared to the PGC group, participants in the KBGS group acted more confident and displayed a tendency to brag/-boast. A flat affect and signs of tiredness were also more frequently present in participants with KBGS compared to PGC. Participants with KBGS displayed *fewer* internalizing symptoms, such as being anxious, worrying, being dependent on the examiner, or showing a lack of self-confidence, compared to PGC. Almost all participants with KBGS were initially motivated for the tasks, but were quickly under- or over stimulated and displayed both performance anxiety and a low frustration tolerance. Assessment was therefore adapted by providing more breaks in between tasks and the use of rewards for good performances. Hyperactive/restless behaviors were shown by one-third of the participants with KBGS, especially the young boys, and this behavior expanded when task demands increased. Hyperactive behaviors included not being able to sit still (walking, frequent movement on a chair or with extremities), impatience during test instructions and excessive talking. Furthermore, participants with KBGS worked more quickly and made more errors compared to the PGC.

3.3 | Cognitive functioning—cognitive tests

For the comparison with healthy controls, Table 1 presents the mean differences (Z-scores) between participants with KBGS and the available norm groups for all cognitive tests. As expected, participants with KBGS show a substantially weaker performance on all test of cognitive functioning, with Z-scores ranging between - 0.79 and - 2.33. In line with these results, there is also a higher number of perceived/subjective cognitive problems, as reported by primary caregivers of the participants (BRIEF: Z = 0.52; DEX: Z = 1.17).

Table 2 presents the mean raw scores and effect sizes for the cognitive tests and questionnaires of the KBGS and the PGC group. There is a slightly weaker performance in sustained attentional functioning in KBGS compared to PGC (KBGS: M = 96.14, SD = 30.67; PGC: M = 102.63, SD = 40.15; d = − 0.19). Participants with KBGS display a different strategy compared to PGC on the sustained attention test. A description of the performance style is presented in Table 3. In general, participants with KBGS show inhibition problems; they tend to work faster than PGC, that is, process a higher number of stimuli within the same time span (KBGS: M = 327.07, SD = 83.14;

TABLE 1 Questionnaire and test scores KBGS group compared to norm scores

			N	SD
Behavior	Questionnaires	CSBQ[a]	9	1.77
		SDQ	8	2.21
		Emotional symptoms	8	0.55
		Conduct problems	8	0.76
		Hyperactivity/inattention	8	1.66
		Peer relations	8	1.12
		CBCL[a]	8	1.05
		SS: Anxious/depressed	8	0.64
		SS: Withdrawn/depressed	8	0.68
		SS: Somatic complaints	8	0.58
		SS: Social problems	8	1.40
		SS: Thought problems	8	0.31
		SS: Attention problems	8	1.73
		SS: Rule-breaking behavior	8	0.43
		SS: Aggressive behavior	8	0.85
		DOS: Depressive problems	8	0.53
		DOS: Anxiety problems	8	0.98
		DOS: Somatic problems	8	0.55
		DOS: Attention deficit/hyperactivity problems	8	1.56
		DOS: Oppositional defiant problems	8	0.71
		DOS: Conduct problems	8	0.46
Cognition	Tests	WAIS-IV/WISC-III[a]	18	−2.33
		D2 sustained attention test[a,b]	13	−0.98
		Key search[a]	13	−0.79
		Zoo map 1[a]	13	−0.85
		Zoo map 2[a]	13	−1.21
		RAVLT immediate recall[a,e]	18	−0.94
		ToM test R[a,e]	18	−1.18
		ERT[a,c]	11	−0.91
		Beery VMI[a]	16	−1.97
		Rey CFT[a]	14	−2.20
	Questionnaires	BRIEF[a,b]	9	0.52
		DEX/DEX-C[d]	11	1.17

Abbreviation: SS, syndrome scales, DOS, DSM-oriented scales.
Normative means were corrected for the following:
[a] Age.
[b] Gender.
[c] Years of education.
[d] Normative means were different for children and adults.

PGC: *M* = 287.00, SD = 102, 65; *d* = − 0.44), but make a substantially higher number of errors (KBGS: *M* = 42.14, SD = 37.68; PGC: *M* = 17.69, SD = 14.45; *d* = − 0.91).

Furthermore, mixed results are found within the domain of executive functioning. Participants with KBGS perform weaker on a test that measures shifting and flexibility (IED: KBGS: *M* = 6.78, SD = 2.51; PGC: *M* = 7.73, SD = 1.39; *d* = − 0.47) whereas there are no relevant differences, as reflected by small effect sizes, for the performance on tasks that measure the ability to plan and maintain overview (Key Search: KBGS: *M* = 4.71, SD = 4.57; PGC: *M* = 3.94, SD = 4.32; *d* = 0.18; Zoo map 1: KBGS: *M* = −1.12, SD = 6.44; PGC: *M* = −0.65, SD = 5.44; *d* = − 0.08). Compared to PGC, participants with KBGS seem to benefit more when structure is externally provided in a planning test (Zoo map 2: KBGS: *M* = 4.65, SD = 4.97; PGC: *M* = 3.35, SD = 5.45; *d* = 0.26). As for the level of experienced problems in executive functioning in everyday life, results indicate no relevant differences in the number of problems between both participant groups (BRIEF: KBGS: *M* = 140.33, SD = 22.27; PGC: *M* = 144.22, SD = 23.22; *d* = − 0.18; DEX: KBGS: *M* = 34.91, SD = 14.49; PGC: *M* = 34.50, SD = 12.05; *d* = 0.03).

Moreover, mixed results are also found for memory functioning. Participants with KBGS display a trend of a higher performance for the visual memory tasks (PRM: KBGS: *M* = 10.50, SD = 1.25; PGC: *M* = 9.67, SD = 2.02; *d* = 0.52; PAL: KBGS: *M* = 7.22, SD = 1.56; PGC: *M* = 6.73, SD = 1.62; *d* = 0.32; PRM performance without outlier *d* = 0.65) and the delayed recall of the semantic memory task (RAVLT: KBGS: *M* = 7.17, SD = 4.64; PGC: *M* = 6.13, SD = 3.61; *d* = 0.26). The performance on the direct recall of the semantic

TABLE 2 Questionnaire and test scores—KBGS group vs PGC group

			KBG			PGC			Mean Difference [b]	Effect Size [c]
			N	M [a]	SD [a]	N	M [a]	SD [a]		
Behavior	Questionnaires	CSBQ	9	33.11	15.72	9	37.56	14.34	−4.45	−0.31
		Not optimally tuned to the social situation	9	11.00	5.70	9	7.11	5.25	3.89	0.75
		Reduced contact and social interest	9	4.44	4.10	9	6.22	5.07	−1.78	−0.41
		Orientation problems in time, place or activity	9	5.89	4.08	9	8.44	2.83	−2.55	−0.77
		Difficulties in understanding social information	9	6.78	4.27	9	9.11	2.15	−2.33	−0.73
		Stereotyped behavior	9	2.56	3.78	9	4.44	2.83	−1.88	−0.60
		Fear of and resistance to changes	9	2.44	1.74	9	2.33	2.40	0.11	0.06
		SDQ	9	16.56	5.00	11	16.55	5.39	0.01	0.002
		Emotional symptoms	9	2.78	0.97	11	3.73	3.47	−0.95	−0.38
		Conduct problems	9	2.00	1.58	11	1.91	1.81	0.09	0.06
		Hyperactivity/inattention	9	6.44	2.92	11	5.55	3.42	0.89	0.29
		Peer relations	9	2.56	3.21	11	4.64	2.20	−2.08	−0.81
		Prosocial behavior	9	6.33	2.00	11	6.55	2.81	−0.22	−0.09
		CBCL	8	40.63	11.26	9	47.56	24.68	−6.93	−0.38
		SS: Anxious/depressed	8	4.25	2.66	9	3.89	4.81	0.36	0.10
		SS: Withdrawn/depressed	8	2.25	2.38	9	3.67	3.94	−1.42	−0.46
		SS: Thought problems	8	1.50	0.53	9	4.67	4.24	−3.17	−0.08
		SS: Somatic complaints	8	1.75	1.39	9	2.22	2.44	−0.47	−0.25
		SS: Attention problems	8	9.88	2.80	9	9.33	2.83	0.55	0.20
		SS: Social problems	8	6.00	3.82	9	8.56	4.16	−2.56	−0.68
		SS: Rule-breaking behavior	8	1.75	2.38	9	1.78	1.30	−0.03	−0.02
		SS: Aggressive behavior	8	8.13	6.10	9	7.67	7.43	0.46	0.07
		DOS: Depressive problems	8	1.88	1.55	9	3.78	4.44	−1.9	−0.59
		DOS: Anxiety problems	8	3.13	2.30	9	3.56	2.74	−0.43	−0.18
		DOS: Somatic problems	8	1.00	0.93	9	1.56	1.67	−0.56	−0.59
		DOS: Attention deficit/hyperactivity problems	8	8.00	2.62	9	7.33	2.24	0.67	0.18
		DOS: Oppositional defiant problems	8	3.25	2.71	9	2.89	3.30	0.36	0.43
		DOS: Conduct problems	8	2.25	3.37	9	2.11	1.76	0.14	0.29
Cognition	Tests	WAIS-IV/WISC-III	18	65.06	13.26	17	67.12	13.58	−2.06	−0.16
		D2 sustained attention test	14	96.14	30.67	16	102.63	40.15	−6.49	−0.19
		IED	18	6.78	2.51	15	7.73	1.39	−0.95	−0.47
		Key search	17	4.71	4.57	17	3.94	4.32	0.77	0.18
		Zoo map 1	17	−1.12	6.44	17	−0.65	5.44	−0.47	−0.08
		Zoo map 2	17	4.65	4.97	17	3.35	5.45	1.3	0.26
		RAVLT immediate recall	18	33.11	13.74	17	36.59	12.03	−3.48	−0.28
		RAVLT delayed recall	18	7.17	4.64	16	6.13	3.61	1.04	0.26
		PRM	18	10.50	1.25	15	9.67	2.02	0.83	0.52
		PAL	18	7.22	1.56	15	6.73	1.62	0.49	0.32
		ToM test R	18	26.83	6.14	16	25.00	5.96	1.83	0.31
		ERT	14	48.71	10.10	14	43.93	9.08	4.78	0.52
		Beery VMI	16	17.44	4.10	15	19.40	5.34	−1.96	−0.43
		Beery visual	15	20.60	5.34	15	22.00	4.66	−1.4	−0.29
		Beery motor	16	19.94	4.85	15	21.67	5.43	−1.73	−0.35
		Rey CFT	15	14.17	8.89	15	17.73	9.31	−3.56	−0.41
	Questionnaires	BRIEF	9	140.33	22.27	9	144.22	23.22	−3.89	−0.18
		DEX/DEX-C	11	34.91	14.49	12	34.50	12.05	0.41	0.03

Abbreviation: SS, syndrome scales, DOS, DSM-oriented scales.

[a] Group means and standard deviations were calculated based on the raw performance scores.

[b] Group differences are expressed in mean differences (mean KBGS score minus mean PGC score) and effect sizes.

[c] Cohen's d effect sizes of 0.2, 0.5 and 0.8 represent respectively a small, medium and large effect [22].

TABLE 3 Results sustained attention test (d2)—KBGS group vs PGC group

Variable	KBG			PGC			Mean Difference [b]	Effect Size [c]
	N	M [a]	SD [a]	N	M [a]	SD [a]		
Number of items processed	14	327.07	83.14	16	287.00	102.65	40.07	–0.44
Number of errors	14	42.14	37.68	16	17.69	14.45	24.45	–0.91

[a] Group means and standard deviations are calculated based on the raw performance scores.
[b] Group differences are expressed in mean differences (mean KBGS score minus mean PGC score) and effect sizes.
[c] Cohen's d effect sizes of 0.2, 0.5 and 0.8 represent respectively a small, medium and large effect [22].

performance test is, however, slightly weaker in the KBGS group compared to the PGC group (RAVLT: KBGS: M = 33.11, SD = 13.74; PGC: M = 36.59, SD = 12.03; d = − 0.28).

As for social cognitive functioning, a higher performance in the participants with KBGS compared to the PGC group is indicated for both social cognitive tests (ToM test R: KBGS: M = 26.83, SD = 6.14; PGC: M = 25.00, SD = 5.96; d = 0.31; ERT: KBGS: M = 48.71, SD = 10.10; PGC: M = 43.93, SD = 9.08; d = 0.52). Lastly, there are indications for weaknesses in visuoconstruction performance in the KBGS group (Beery VMI: KBGS: M = 17.44, SD = 4.10; PGC: M = 19.40, SD = 5.34; d = − 0.43; Rey CFT: KBGS: M =, SD =; PGC: M =, SD =; d = − 0.41). Weaknesses in performance were also found for visual perception and fine motor skills (Beery Visual: KBGS: M = 20.60, SD = 5.34; PGC: M = 22.00, SD = 4.66; d = − 0.29; Beery Motor: KBGS: M = 19.94, SD = 4.85; PGC: M = 21.67, SD = 5.43; d = − 0.35).

3.4 | Cognitive functioning—observations

Working speed during assessment appeared, in general, faster in participants with KBGS compared to the PGC group, with signs of impulsivity in two boys and one girl. Attention was easily drawn in most participants, but they differed in the level of distractibility. In females with KBGS, two girls had moments in which they responded remarkably slowly; it was unclear whether this was due to deficiencies in processing speed, attention or maybe even epileptic activity. All boys with KBGS, except for one relatively high functioning participant, were frequently distracted by both external and internal stimuli, and the degree of distractibility increased during the test assessment.

4 | DISCUSSION

To the authors' knowledge, this is the first systematic investigation of the behavioral and cognitive phenotype of KBGS using reliable and validated assessment instruments. Comparison of the KBGS cohort to the general population (normative means) as well as to the genetic patient control group, pointed to a behavioral profile that includes distractibility and impulsivity. As for cognitive functioning, comparison with normative means showed problems in all domains of cognitive functioning, which was expected considering the fact that the presence of an ID in participants with KBGS is not sufficiently taken into account in this comparison. Compared to the PGC group, relative weaknesses were found for sustained attention, shifting and visuoconstruction, and relative strengths were present in memory and social cognitive functioning.

Behavioral problems in patients with KBGS have in previous (descriptive) studies mainly been described in terms of ADHD.[5–7] In line with these previous observations of ADHD-like symptoms, a high level of distractibility, impulsivity and restless behavior was observed in the participants with KBGS in this study. A slightly higher number of these behavioral difficulties were also reported by caregivers of participants with KBGS compared to the PGC group. Regarding affective functioning, more externalizing behavior (emotion regulation problems, aggression as well as bragging/boasting) was observed in the group with KBGS compared to the PGC group as well as reported by caregivers of participants with KBGS (reflected in slightly more conducted problems and oppositional defiant behavior). In contrast, participants with KBGS displayed during test assessment fewer internalizing behaviors such as being anxious or worried, which fits the relatively fewer reported affective problems in the KBGS group compared to the PGC group. The first finding fits the case descriptions of temper tantrums and aggression in some patients with KBGS, whereas the latter contradicts the reports of anxious/shy behavior in similar studies.[4–7] ASD symptomatology has also been previously suggested in relation to KBGS.[4,6] In this study, caregivers of patients with KBGS indeed reported more social problems. However, when the reports of participants with KBGS were compared to an appropriate control group with a similar level of intellectual functioning (PGC), fewer problems in social behavior were mentioned. So there are indeed weaknesses in social behavior in patients with KBGS, but these problems are not considered an indication for ASD, but rather match the level of developmental functioning.

In line with the hypotheses regarding cognition in KBGS, weaknesses for both executive functioning and visuoconstruction were found in this study. More specific, comparison with the PGC group indicated weaknesses in sustained attention, inhibition (participants worked faster but made more errors) and cognitive flexibility. Participants with KBGS were, in contrast to the PGC group, not able to adjust their response speed to their capabilities, which resulted in a substantially higher number of errors in task performance. These inhibition problems may also underlie their weaker visuoconstruction performance. The visuoconstruction performance was not solely related to a deficit in fine motor skills, visual perception or visuomotor integration, but rather reflected an overall weakness in these skills. The relatively strong encoding of prominently visual (vs verbal) information in participants with KBGS also argues against specific deficits in visual processing. Interestingly, the insufficiencies in inhibition and shifting were not reflected in the subjective experience of executive functioning as reported by the primary caregivers. Although these kind of differences between subjective and objective findings are frequently found, it may in this case also indicate that that the cognitive

problems in participants with KBGS are not always visible for their caregivers, which makes it hard for them to take these weaknesses into account in daily living.

In contrast to previously described memory deficits in case studies on KBGS,[13,14] strengths in consolidation and retrieval of verbal information were found in participants with KBGS in the current sample. Encoding of verbal information was, in contrast to imprinting of visual information, relatively weak. These differences in memory functioning might be a result of the task properties in terms of triggering attention. The semantic test included the recurrent presentation of auditory stimuli, and the visual test included responding to visual stimuli on a tablet-computer. The latter might be perceived as a game, which could have positively affected the attention span.

This is the first study in which the (neuro)psychological phenotype of KBGS is extensively investigated in a substantial cohort of patients. Only a few studies[13,17] have focused on some aspects of cognitive functioning in individual patients with KBGS before, and studies with larger groups solely described cognitive and behavioral functioning in terms of observations and Diagnostic Statistical Manual classifications such as ID, ADHD or ASD.[4,6] Additionally, this study includes a suitable control group of patients with a similar level of intellectual functioning, which is essential to explore if syndrome specific cognitive deficits may underlie the observed behavioral phenotype. The inclusion of such a control group is often missing in other studies regarding cognition and behavior in genetic syndromes. Nonetheless, the results should also be interpreted in light of some limitations.

Although the cohort of this study is relatively large considering the prevalence of known patients with KBGS in the Netherlands, the sample size is still insufficient for regular statistical testing of significance. The exploration of the cognitive data by inspecting effect sizes is, however, a legitimate alternative to a multivariate analysis. Still, caution is warranted with respect to generalization of the reported findings. Future studies, obtaining data in multiple collaborating centers, could use the first results of this study as a starting point for further research regarding this topic. Finally, a relatively high amount of shared variance in cognitive tests complicates the differentiation between the participants with KBGS and PGC. The shared variance could be a result of floor effects; some of the cognitive tasks may have been too difficult for a part of the patient population. As there is still a lack of alternative cognitive tasks to reduce these floor effects, future cognitive research should always combine traditional cognitive assessment (measuring performance scores) with systematic observations (measuring performance processes).

Notwithstanding these limitations, the findings of this study support earlier indications for behavioral problems in patients with KBGS that include impulsivity, restless behavior, a high level of distractibility and impairments in emotion regulation. In psychiatric classificatory terms, this behavior is often referred to as ADHD and psychopharmacological treatment strategies in patients with KBGS include as yet both antipsychotics and psychostimulants. The effects of these drugs on behavioral symptoms, however, have not been studied in this specific population, warranting further research on the underlying neurobiological cause of the restless behavior. As to the potential underlying cognitive deficits, there are indications for problems in sustained attention, inhibition and shifting. Contrary to expectations based on previous (case) reports in which ASD symptomatology was described in some patients with KBGS, no disproportional deficits were found in social behavioral, nor social cognitive functioning in this study. Observations confirm that performances of patients with KBGS benefit from externally provided structure. Furthermore, patients should be actively involved in a task, to prevent them from getting distracted, which seems crucial for learning and development in KBGS.

In conclusion, the above described findings highlight the importance of in-depth evaluations of the neuropsychological profile of individual patients with KBGS (with a correction for the level of intelligence) both for counseling purposes, for tailoring education planning, and for the development of personalized treatment.

ACKNOWLEDGMENTS

The first author is a shared PhD-student of Vincent van Gogh Centre of Excellence for Neuropsychiatry and Radboud University Medical Centre Department of Clinical Genetics and the research is embedded within the collaborative research group 'Psychopathology and Genetics' of the aforementioned institutes. The authors would like to thank all participating patients and their caregivers for both their participation and hospitality during the data collection at their homes. The contribution of Wouter Oomens MSc, Mirthe Fransz MSc, Liz Driessen MSc, Laura Fornara MSc and Kelly Rutjes MSc in the data collection is gratefully acknowledged.

AUTHOR CONTRIBUTIONS

L.C.M.v.D., J.I.M.E., T.K. and E.W. designed and planned the study. L.C.M.v.D., A.G.B.R. and K.V. acquired the data, performed neuropsychological assessments. W.M.v.d.V. contributed to the analysis of the data and interpretation of the results. C.W.O. and T.K. diagnosed and recruited the patients and contributed to the interpretation of the genetic analyses. E.W. and J.I.M.E. contributed to the interpretation of the neuropsychological data. L.C.M.v.D., T.K., E.W. and J.I.M.E. drafted the manuscript. W.M.v.d.V. and C.W.O. critically reviewed the manuscript. All authors read and authorized the final version of the manuscript.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: van Dongen LCM, Wingbermühle E, van der Veld WM, et al. Exploring the behavioral and cognitive phenotype of KBG syndrome. *Genes, Brain and Behavior*. 2019; 18:e12553. https://doi.org/10.1111/gbb.12553