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Assessment of Adaptive Functioning and the Impact of Seizures in KBG Syndrome

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ABSTRACT

This study aimed to examine the adaptive functioning status and the impact of epileptic seizures on neurocognitive outcomes in KBG syndrome, a rare genetic neurodevelopmental disorder characterized by pathogenic variants in *ANKRD11*. A single clinician interviewed individuals and families with genetically confirmed cases of KBG syndrome. Trained professionals also conducted assessments using the Vineland–3 Adaptive Behavior Scales. The assessment covered the domains of communication, daily living skills, socialization, and maladaptive behaviors, and then compared individuals with and without epilepsy. Further comparisons were made with data from interviews and participants' medical records. Thirty-nine individuals (22 males, 17 females) with KBG syndrome, confirmed through genetic analysis, were interviewed via videoconferencing, followed by Vineland–3 assessment by trained raters. Individuals with KBG syndrome came from 36 unique families spanning 11 countries. While the KBG cohort displayed lower overall adaptive behavior composite scores compared with the average population, several members displayed standard scores at or higher than average, as well as higher scores compared with those with the neurodevelopmental disorder Ogden syndrome. Within the KBG cohort, males consistently scored lower than females across all domains, but none of these categories reached statistical significance. While the group with epilepsy exhibited overall lower scores than the nonseizure group in every category, statistical significance was only reached in the written communication subdomain. Our research provides insights that can aid in epilepsy screening and inform assessment strategies for neurocognitive functioning in those with this condition. The cohort performed overall higher than expected, with outliers existing in both directions. Although our results suggest that seizures might influence the trajectory of KBG syndrome, the approaching but overall absence of statistical significance between study groups underscores the need for a more extensive cohort to discern subtle variations in functioning.

1 | Introduction

KBG syndrome is a neurodevelopmental disorder characterized by mutations in the ankyrin repeat domain 11 gene (*ANKRD11*) or microdeletions that affect *ANKRD11* on chromosome 16q24.3 (Herrmann et al. 1975; Goldenberg et al. 2016; Novara et al. 2017; Gnazzo et al. 2020; Ockeloen et al. 2015; Loberti et al. 2022). While the precise functional role of ANKRD11 in the brain remains unclear, variants in this gene have been associated with cognitive and neurological anomalies. These include a range of seizures such as focal and generalized seizures, tonic–clonic and absence seizures, myoclonic seizures, and unclassified

sleep-related seizures (Buijsse et al. 2023). Some KBG syndrome individuals may exhibit electroencephalogram (EEG) abnormalities without clinically evident seizures (Swols, Foster, and Tekin 2017). EEG abnormalities, with or without seizures, have been reported in about 50% of affected individuals (Skjei, Martin, and Slavotinek 2007), suggesting increased susceptibility to epilepsy. This suggests that those with KBG syndrome are more susceptible to epilepsy, which occurs in a significant percentage of cases (Murphy et al. 2022), although epilepsy is not formally recognized as a defining characteristic of this condition.

It is suggested that epilepsy syndromes in general, often characterized as "epileptic encephalopathies," can trigger developmental regression or be linked to a poorer prognosis upon onset of seizures (Camfield and Camfield 2019). Similarly, other genetic neurodevelopmental conditions such as Rett syndrome display a high incidence of epilepsy associated with more severe developmental disabilities (Operto et al. 2019). While KBG syndrome does not specifically fall under this category, the phenotypic presentation shares similarities with many of these conditions. Understanding these broader patterns can provide valuable insight as the impact of seizures on cognitive outcomes has been a significant focus of research (Berg, Loddenkemper, and Baca 2014; Kwan and Sander 2004). Often, individuals with early-onset or prolonged epilepsy experience cognitive impairments, including disruptions in memory, attention, processing speed, and executive functioning (Auvin 2022; Novak, Vizjak, and Rakusa 2022). The type and location of seizures can also influence the extent of cognitive impairment. Previous studies have hypothesized a potential link between early onset of seizures and a more severe form of KBG syndrome (Guo et al. 2022).

In this study, we evaluate cognitive outcomes in individuals with KBG syndrome, both with and without seizures, using the Vineland Adaptive Behavior Scales, Third Edition (Vineland–3) (Sparrow, Cicchetti, and Saulnier 2016; Msall and Tremont 1999). This tool is a standardized formal assessment used to measure adaptive behavior in the diagnosis of intellectual and developmental disabilities or delays. This study's objective is to determine whether seizure prevalence affects the neurocognitive outcome in individuals with KBG syndrome. We aim to explore potential phenotype correlations through analysis of communication, socialization, and daily living skills, focusing on how these aspects may be influenced by the presence of epilepsy.

2 | Methods

2.1 | Participants

Thirty-nine individuals (22 males, 17 females) with KBG syndrome, confirmed through genetic analysis, were interviewed via videoconferencing (Zoom version 5.2.0) by a single physician board certified in child and adolescent psychiatry (G.J.L.). These individuals belonged to 36 unique families spanning 11 countries: Argentina, Australia, Canada, Ecuador, Germany, Lebanon, Mexico, Portugal, Spain, the United Kingdom, and the United States. The majority of our cohort (53.8%) was of United States origin. Before the initial interviews, medical records including genetic reports, and facial/whole-body photographs were collected from participants. Videoconferencing occurred in two phases: preliminary data collection (G.J.L.) and Vineland–3 adaptive behavior assessment (K.P.S., L.G., E.Y., J.P.). All sessions spanned from one to 4 h and were conducted in English, with a translator used for one family whose primary language was Spanish. The primary language for 10 families was English, whereas other families were multilingual. With prior consent, interviews were recorded and archived for subsequent analyses.

Twenty-two individuals in our cohort have not been previously published in the literature (KBG-GJL-001 to KBG-GJL-005, KBG-GJL-007 to KBG-GJL-013, KBG-GJL-016, KBG-GJL-018 to KBG-GJL-020, KBG-GJL-023 to KBG-GJL-025, and KBG-GJL-029, KBG-GJL-039, and KBG-GJL-040). Four affected individuals (KBG-GJL-007, KBG-GJL-010, KBG-GJL-032, and KBG-GJL-042) had one or more children who also possessed a confirmed KBG diagnosis. At least one child of each of these four participants was part of the assessed cohort.

2.2 | Data Collection

Phase 1: Initial videoconferences were held over 20 months from February 2021 to October 2022. Families were recruited through a KBG syndrome Facebook group or referrals of other families with known members possessing KBG syndrome. ANKRD11 variants were annotated to the NM_013275.5 transcript in GrCh37/hg19. The severity of developmental delay and level of functioning was assessed by the physician through patient interaction, paternal/maternal reports, and cross-referencing existing medical records. Metrics were systematically documented, encompassing speech and motor delays, behavioral issues, and neurological abnormalities, including seizures. The type and onset of epilepsy, along with comprehensive details about the treatment, such as the specific medications used, were recorded. Medical records pertaining to epileptic events in relevant individuals were thoroughly reviewed. Any abnormalities detected through neuroimaging, such as MRI and EEG, were noted, and families were requested to provide copies of these records. Furthermore, additional neurological features, such as abnormal pain thresholds and altered tactile sensations, were also documented, as well as other features such as anatomical abnormalities or complications during birth.

Phase 2: Adaptive behavior was assessed using the Vineland–3, administered through teleconferences from September 2022 to January 2023 using a small group of trained raters (K.P.S., L.G., E.Y., J.P.). Each assessment involved a semi-structured interview with a parent or primary caregiver knowledgeable about the daily behaviors of the individual with KBG syndrome. The scores obtained from the Vineland–3 for those with KBG syndrome were compared with those of the general population and individuals with another genetic neurodevelopmental disorder, Ogden syndrome, characterized by pathogenic variants in the NAA10 and NAA15 genes (Makwana et al. 2024; Lyon et al. 2023). Our research team has a history in Ogden syndrome research, with one of the authors (G.J.L.) first publishing on this condition in 2011. This experience has enabled us to conduct Ogden syndrome studies involving the Vineland–3 in a consistent manner with our study's methodology, allowing for validity in comparing our results. Although KBG syndrome and Ogden

syndrome are distinct genetic disorders, they share a multitude of phenotypic and genetic characteristics that warrant comparison. Both conditions are linked to specific genetic mutations impacting neurodevelopment and often but not always present with cognitive or intellectual disabilities. Individuals with KBG syndrome and those with Ogden syndrome may also exhibit similar behavior challenges and adaptive functioning issues, allowing for meaningful exploration of adaptive behavior outcomes by the Vineland–3 (Makwana et al. 2024).

There was one family, possessing the identifier KBG-Family-24 and consisting of a mother and her two sons, also previously published (Guo et al. 2022), who was initially included in all analyses but was then later removed (with all analyses performed again) due to having a variant of uncertain significance (VUS) (consisting of a Val586Met missense mutation). Exome reanalysis of this trio is underway, in search for any other possible cause of the condition in that family.

2.3 | Data Analysis

The Vineland–3 evaluates adaptive behavior in three major domains: communication, daily living skills, and socialization, each with a normative mean of 100 and a standard deviation of 15. These domains are further divided into subdomains. In addition to the three main domains, the Vineland provides an option for additional assessment through the maladaptive behavior domain, which focuses on internalizing behaviors such as anxiety and depression as well as externalizing behaviors such as hyperactivity and disruptive behavior. Subscores from each domain contribute to the overall adaptive behavior composite (ABC) score, reflecting the individual's overall comprehensive adaptive functioning. A representation of the Vineland's domain and subdomain breakdown is provided in Figure S1.

Vineland–3 data were analyzed using Prism GraphPad (version 9.5.1). Descriptive statistics, including mean, standard deviation, and range were computed for each of the three core domains and the ABC score. Independent two-tailed *t*-tests were used to compare differences across domain and ABC scores. Separate analyses for sex were completed with an *F*-test. Simple linear regression was used to assess the effects of age on ABC score. Comparative analysis was conducted using one-sample *t*-tests for epilepsy versus no seizures. Effect sizes were calculated to determine the practical significance of any observed differences.

3 | Results

The locations of ANKRD11 variants are depicted in Figure 1, with demographic information and descriptions of specific mutations displayed as Tables S1 and S2, respectively. Seventeen individuals had de novo variants while 17 had unknown modes of inheritance. Mutations in three individuals were maternally inherited while two were paternally inherited. When analyzing types of mutations, 23 possessed frameshift mutations, 11 had nonsense mutations, 1 had a missense mutation, and the remaining 4 had copy number variants involving deletions of the gene. Mutations were classified per the American College of Medical Genetics and Genomics (ACMG) criteria for the interpretation of sequence variants (Richards et al. 2015). All participants analyzed were either class one pathogenic ($n = 36$) or class two likely pathogenic ($n = 3$).

3.1 | Cohort Analysis

While the cohort displayed a lower mean in ABC scores compared with the average population standard mean of 100, several members displayed scores at or higher than average, as well as higher scores compared with those with Ogden syndrome and closer to those with NAA15-related neurodevelopmental syndrome (Lyon et al. 2023; Cheng et al. 2019, 2018) (Figure S2). KBG syndrome females had a higher mean ABC score when compared with males, analyses by *t*-test revealed no statistically significant difference. Additional comparisons by sex were made including ABC scores based on age. This graphical representation of ABC scores showed consistent values with a marginally positive trend, presenting a slightly negative slope for males versus a slightly positive slope for females. This stratification by both sex and age did not reach statistical significance when compared (Figure S2).

Mean domain scores were similar to ABC scores, averaging around a score of 70 (Figure 2). Specific domain score means and *p* values are listed in Table S3. Within the KBG cohort, males consistently scored lower than females across all categories, but none of the domains reached statistical significance.

3.2 | Epilepsy Analysis

Participants with epilepsy are further detailed in Table S4. Most epileptic patients experienced generalized tonic–clonic seizures, with absence seizures being the second most prevalent. When comparing the age of onset of seizures and whether initial age had

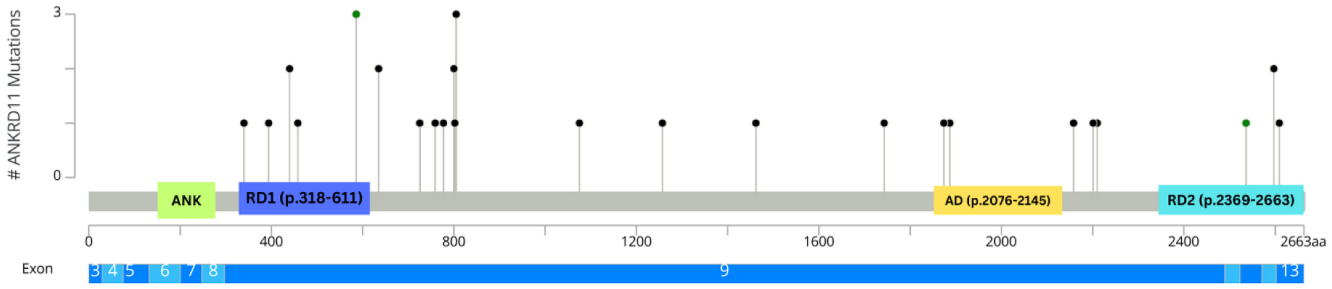

FIGURE 1 | KBG Syndrome Cohort Mutations Map. The coding exons for ANKRD11 are depicted to scale. This figure was made using https://www.cbiportal.org/mutation_mapper. aa = Amino acid.

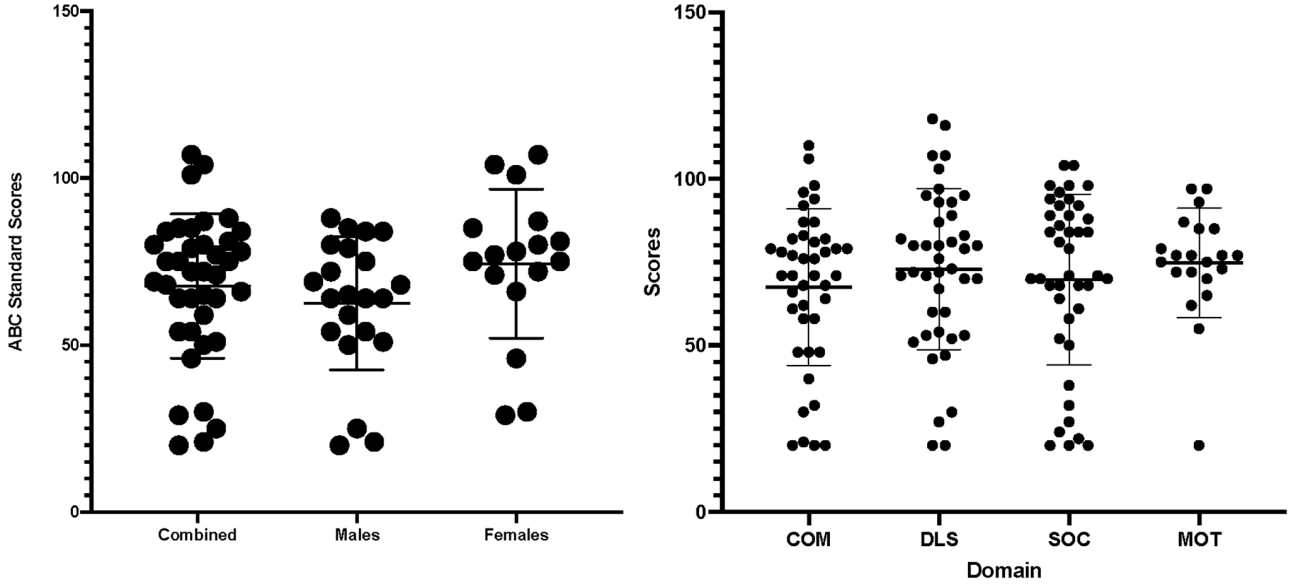

FIGURE 2 | ABC standard and domain scores of KBG cohort. Left graph displays ABC standard scores for KBG syndrome cohort including stratification between sexes with no significant difference. Right graph displays domain scores. Means and *p* values are listed in Table S3. COM = communication, DLS = daily living skills, MOT = motor, SOC = socialization.

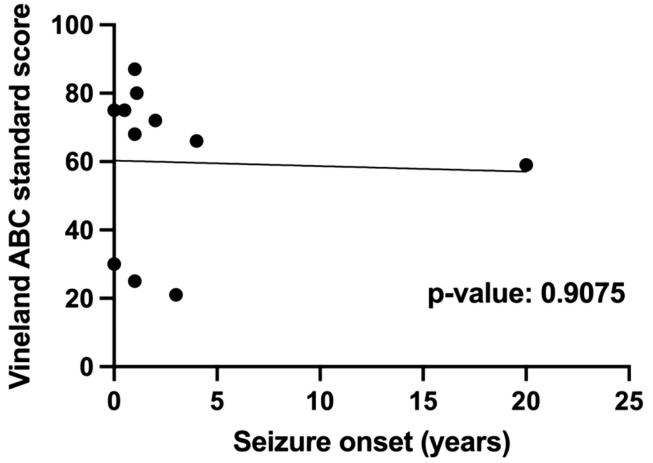

FIGURE 3 | Vineland–3 score versus seizure onset. Comparison of ABC standard scores and domain scores for participants compared with seizure onset. No statistical significance was achieved.

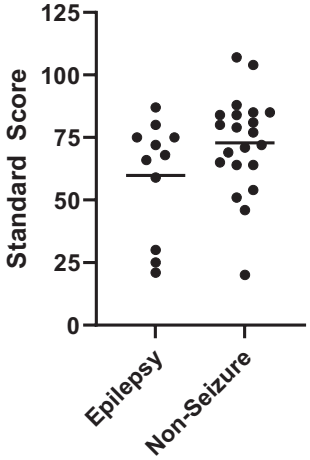

FIGURE 4 | ABC standard score of epilepsy versus nonseizure groups. The ABC score encompasses an individual's overall adaptive functioning; the standard mean for a person without intellectual or developmental disabilities is 100 with a standard deviation of 15. The mean ABC standard score in the KBG epilepsy group is 59.82 and the mean of the nonseizure group is 72.86 with a *p* value of 0.105.

any influence on adaptive scores, no statistically significant differences were indicated (Figure 3). Seven interviewed individuals in our cohort reported one or more possible or potential seizures that did not clearly exhibit epilepsy descriptions and were not diagnosed by a clinician. This includes participant KBG-GJL-014 whose mother reported occasional "zoning out" for short periods, possibly suggesting absence seizures, but was not certain or confirmed. KBG-GJL-007 mentioned a memory of a possible seizure in childhood but was also unsure of its nature. All seven individuals who experienced a single, unconfirmed seizure or had suspected but undiagnosed seizures did not fulfill epilepsy criteria and were excluded from the following seizure analysis. They were not included in either the epilepsy group ($n = 11$) or the "nonseizure" group ($n = 21$) given the questionable history.

Anecdotally, per primary caregivers, several participants (4 of the 11) indicated a level of developmental regression following the onset of seizures. However, when comparing the means of ABC standard scores, no statistical significance was found between those with and without epilepsy (Figure 4). Analysis of mean scores in the Vineland domains also revealed no statistical significance (Figure 5).

Each of the domains was further assessed by subdomain, with the subdomain of written communication showing a statistically significant difference between epilepsy groups. The scores for communication subdomains are presented in Figure 6. The remaining subdomains of daily living skills and socialization as well as maladaptive behavior scores did not exhibit statistical significance between groups, as represented in Figure S3.

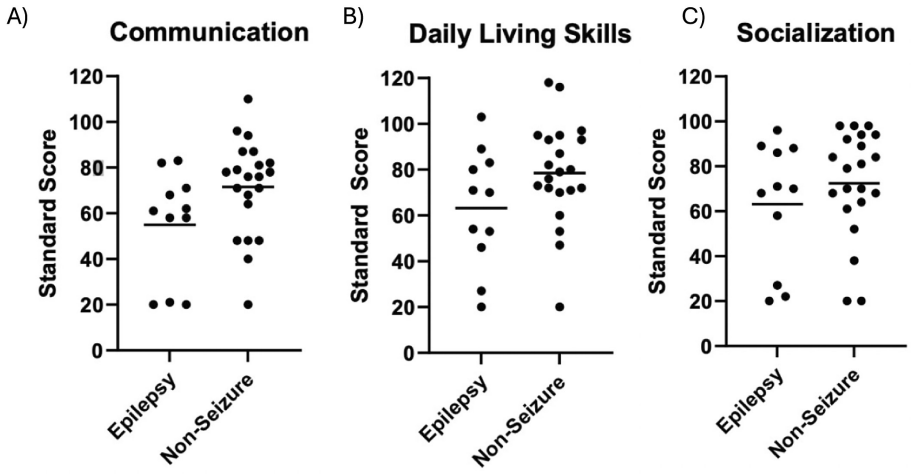

FIGURE 5 | Domain scores of epilepsy versus nonseizure groups. The three major domains, the standard mean for a person without intellectual or developmental disabilities is 100 with a standard deviation of 15. (A) Mean communication domain standard scores were 54.91 for the epilepsy group and 69.68 for the nonseizure group with a p value of 0.051. (B) Mean daily living skills domain standard scores were 63.27 for the epilepsy group and 75.36 for the nonseizure group with a p value of 0.093. (C) Mean socialization domain standard scores were 63.18 for the epilepsy group and 69.82 for the nonseizure group with a p value of 0.331.

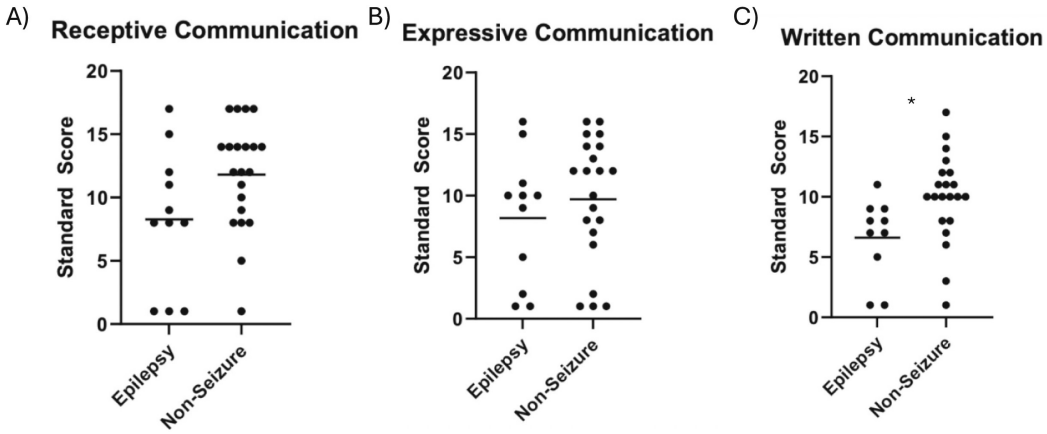

FIGURE 6 | Communication subdomain scores of epilepsy versus nonseizure groups. The communication domain is further subdivided into receptive, expressive, and written subdomains. The normative mean for each subdomain is 20 with a standard deviation of 3. (A) Mean receptive communication subdomain standard scores were 8.27 for the epilepsy group and 11.81 for the nonseizure group with a p value of 0.051. (B) Mean expressive communication subdomain standard scores were 8.18 for the epilepsy group and 9.71 for the nonseizure group with a p value of 0.430. (C) Mean written communication subdomain standard scores were 6.60 for the epilepsy group and 9.95 for the nonseizure group with a p value of 0.021. Written communication displayed statistical significance between groups, suggesting increased likelihood of those with KBG syndrome and epilepsy demonstrating worse ability to communicate through writing than those with KBG without epilepsy. $^*p < 0.05$.

We further analyzed five statistical outliers who had significantly lower ABC standard scores compared with the means. We discovered major shared characteristics between these individuals regarded obstetric and gynecological complications during childbirth. Of these five individuals with significantly lower Vineland scores, three have a diagnosis of epilepsy (KBG-GJL-003, KBG-GJL-34, and KBG-GJL-38) (Table S4). All five required emergency cesarean sections and three of the five were delivered prematurely.

One of the two outlier participants without epilepsy, KBG-GJL-014, was delivered at 29 weeks via cesarean section, resided in the neonatal intensive care unit (NICU) for 4 weeks, and remained hospitalized for 3 months due to aspiration and necrotizing enterocolitis. Her additional diagnoses include global developmental delays, migraines, hearing loss, and Crohn's disease. KBG-GJL-023 was delivered via emergency cesarean section at 33 weeks after shunts were placed for severe bilateral pleural effusions at 28 weeks. This was followed by a month-long stay in the NICU with six thoracentesis procedures for pleural fluid drainage. This individual's additional diagnoses include severe global developmental delays, autism, obsessive-compulsive disorder, and attention-deficit hyperactivity disorder.

Of the outliers with epilepsy, KBG-GJL-003 was delivered at full term via emergency cesarean section due to concerning fetal heart rate. Additional diagnoses include autism, attention-deficit hyperactivity disorder, global developmental delays, and epilepsy with tonic–clonic seizures diagnosed at 3 years of age. KBG-GJL-034 was born via emergency cesarean

section at 34 weeks with a prolonged hospital stay. Additional diagnoses of this individual include tonic–clonic seizures, autism, and global developmental delays. KBG-GJL-038 was delivered via emergency cesarean section at 40 weeks due to concerns about fetal heart rate. His diagnoses include global developmental delay, myoclonic epilepsy, autism, and significant speech regression. He is no longer verbal, despite knowing approximately 30 words at age four. His mother states that she has observed regression which she believes was likely involving his seizures.

4 | Discussion

The aggregate cohort exhibited a Vineland–3 performance measuring two standard deviations below the standard 100 mean, indicative of cognitive impairment relative to those not afflicted with KBG syndrome. However, these Vineland–3 scores revealed a comparatively less pronounced degree of impairment than expected. In contrast to those with Ogden syndrome (Makwana et al. 2024), those with KBG syndrome scored relatively higher across all categories, with a subset of KBG individuals achieving scores at or above the standard mean of 100 in all domains and subdomains. The KBG syndrome group demonstrated a nearly equivalent distribution of outliers both surpassing and falling below their mean ABC and domain scores compared with Ogden syndrome as well as compared with the general population. Additionally, analyses of scores by age suggest a sustained level of adaptive functioning across the KBG syndrome cohort, devoid of discernible regression or marked enhancement at any point in time. Noteworthy differentials emerged between sexes, with males exhibiting not statistically significant but overall lower scores across ABC scores, all domains, and all subdomains.

While no statistically significant variance in ABC scores was discerned between the epilepsy versus nonseizure groups, a negative trend was evident across ABC scores and each of the principal domains. An analysis of the subdomains in communication, daily living skills, and socialization revealed that the scores for written communication were significantly higher in individuals without epilepsy ($p = 0.021$). This is supported by previous evidence suggesting that those with KBG syndrome have especially significant impairments in communication (Lo-Castro et al. 2013). Although no significant difference in scores was found among the other domains, a negative trend was present with the nonseizure group scoring higher than the epilepsy group across all categories. Despite the consistent trend of superior performance among those without epilepsy, we theorize that the overall absence of statistical significance may imply a constraint imposed by sample size.

Our initial clinical suspicion regarding a dramatic effect of epilepsy on cognitive trajectory was not corroborated. However, one family, identified as KBG-Family-24, consisting of a mother and her two sons, all devoid of seizure occurrences, was initially considered for inclusion in our cohort, but it was ultimately determined that this family harbored a missense VUS with unclear indication as to whether their missense mutation was causing the phenotype in that family (see Section 2). Had these three individuals been incorporated into the cohort and categorized within the nonseizure group, statistical significance would have been observed across all domains as well as the overall ABC score. This statistical significance would have suggested the superior performance of the nonseizure group relative to the epilepsy group in functioning, but this reinforces that such analyses should really only be performed with cases that have Likely Pathogenic or Pathogenic variants, at least according to current ACMG criteria. Much larger populations with sequenced genomes or exomes, such as UK Biobank, could be investigated in the future to find a larger number of such individuals, in order to prove the more low to moderate effects of epilepsy on cognitive trajectories.

When considering the cohort of 39 participants, 18 required C-sections, much higher than the national average C-section rates in our participants' countries of origin, as we already reported (Kierzkowska et al. 2023). Given this finding, further research should study the possible effects of C-sections and perinatal complications on adaptive functioning, as this could potentially indicate the need for earlier neurocognitive assessment and intervention based on the methods or complications of a child's birth.

Although epilepsy is a well-described feature of KBG syndrome, the epilepsy phenotypes in our cohort were widely variable, ranging from focal to generalized seizures and from motor to nonconvulsive semiology (Auconi et al. 2023). The wide range of seizure categories in our epilepsy group resulted in very small samples if the epilepsy group was broken down by types of seizures experienced. The limited number of people experiencing each of the major seizure types serves as a major limitation for our study, as different seizure types and severities may alter neurocognitive outcomes in different ways. We recommend further research to delve more into the differences in seizure classification. Buijsse et al. (2023) discovered that those with simultaneous KBG and epilepsy diagnoses more often had moderate to severe intellectual disability compared with those without a history of epilepsy. Their finding is significant given that seizures occur in a large portion of the KBG syndrome population (up to 33%), with onset occurring during infancy through mid-teens and often recurring at or shortly after adolescence (Low et al. 2016). Moreover, previous studies have cited high rates of remission of seizures and discontinuation of antiepileptic medications in the KBG population up to 55% (28); however, within our cohort 9 of the 11 individuals with seizures remained on medication at the time of initial videoconferencing to control their seizure disorder.

The restricted sample size remains the most relevant limitation to our study, especially displayed given the drastic change in results when three participants (from KBG-Family-24) are added. This sample size weakens the power of our study and suggests that adding more participants to each group may have further stratified scores between epilepsy versus nonseizures. Furthermore, although all interviews were conducted in English (with one family utilizing a Spanish-to-English translator), it is important to note that the families' primary language was not inquired about and the frequency and context in which English is spoken may vary. Due to the oversight of not inquiring about the primary language, the potential multilingual nature of the participating families may vary. While all

families communicated with us in English during interviews, we lack data regarding the primary language spoken within their households. Some families may speak English more frequently while other multilingual households might use it equally with another language. This variability in language use could affect the Vineland responders' understanding of the interview questions, potentially influencing the results related to quality of life and adaptive function. Future studies should consider this linguistic diversity and its possible effects on data interpretation and participant comprehension.

Other severity proxies, such as seizure frequency and seizure type, would have helped draw more definitive conclusions regarding the impact of seizures on cognitive outcomes. However, our study was limited by sample size, which restricted our ability to collect comprehensive data on these factors. The potential impact of antiseizure medications on cognitive functioning served as a confounding variable and major consideration in our analysis. While we documented the seizure medications each participant has taken at least once in their lifetime, as shown in Table S4, we lack crucial information on the timing and frequency of their usage, as not all families remembered these details. Without knowing when the last dose was taken or how consistently these medications were administered, it is challenging to determine their influence on cognitive outcomes. Moreover, certain medications have been linked to varying degrees of cognitive impairment, further complicating our ability to draw definitive conclusions.

Additional limitations include the distribution of our cohort, as most of our participants were children and teenagers and few were adults. Sections of the Vineland are often recommended or restricted for certain ages, such as assessment of writing being typically recommended for only those over the age of three. Limitations related to the Vineland–3 administration include caregiver reporting bias and interrater variation, as respondents may not have full accuracy when describing the tasks that the KBG individual does daily. Regarding data collection, there were limited EEG files available for those diagnosed with seizures, which could provide further confirmation about the nature of seizures participants possessed.

5 | Conclusion

Our findings have shed light on the variation of cognitive phenotype presentations across KBG syndrome. While many individuals in our cohort experienced delays in the major Vineland domains and subdomains, others demonstrated normal functioning across these categories. When contrasted with other neurodevelopmental conditions such as Ogden syndrome, KBG syndrome exhibits an overall more favorable outcome, at least as observed in these initial cohorts, although there are some outliers with KBG syndrome who appear to be more severely affected. Furthermore, the observation that a significant proportion of individuals were delivered via C-section, including all outlier participants with the lowest Vineland scores across all categories, warrants further investigation. Regarding epilepsy, our analysis underscores the possibility of KBG seizure screening, as demonstrated by the observed disparities in cognitive functioning, particularly in written communication. We predict that the approaching but overall lack of statistical significance in ABC and domain scores is largely due to the low sample size of our study groups. Given these considerations, we emphasize the need for further screenings with Vineland–3 on a larger cohort. We acknowledge the importance of exploring the potential correlations between mutation type and seizure frequency. While the limited number of participants in our cohort precluded stratification based on mutation type, we recommend this as an additional detail to analyze in a larger cohort for future research. Performing behavioral assessments on a broader sample size of those with KBG syndrome could not only help us understand the influence of epilepsy but also provide valuable insight regarding this disorder's cognitive trajectory to inform both research and clinical practice.

Author Contributions

G.J. Lyon devised the initial study concept and performed all Phase 1 patient/family interviews. K.P. Sarino, L. Guo, and E. Yi further designed the study, performed the Vineland–3 behavior scales, analyzed the data, and wrote the manuscript, with revision by G.J. Lyon. All authors contributed to data collection and manuscript editing.

Acknowledgments

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Ethics Statement

Both oral and written patient consent were obtained for research and publication, with approval of protocol #7659 for the Jervis Clinic by the New York State Psychiatric Institute—Columbia University Department of Psychiatry Institutional Review Board. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.