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Symptom of Autism Versus Confirmed Diagnosis in Cystic Kidney Disease: A Multi- Method Assessment Combining Screening and In-Depth Diagnostics

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Abstract

Background

Hereditary cystic kidney diseases (CysKDs) are increasingly recognized as multisystem disorders with neurodevelopmental involvement. Previous studies have reported elevated symptoms of autism spectrum disorder (ASD) in specific CysKDs, but whether these elevations correspond to confirmed ASD diagnoses remains unclear.

Method

We assessed social-communication difficulties and broader autistic symptom burden in a multicenter cohort of 100 individuals aged 1–24 years with genetically confirmed CysKDs, including Bardet–Biedl syndrome (BBS; n = 37), *HNF1B* deletions (*n* = 24), intragenic *HNF1B* pathogenetic variants (*n* = 7), and other rare CysKDs. All participants underwent standardized questionnaire-based phenotyping; a subsample of 21 additionally received in-depth ASD diagnostics using ADOS-2 and ADI-R.

Results

Individuals with *HNF1B* deletions showed greater symptoms of ASD burden than those with intragenic variants, including more pronounced impairments in social responsiveness (p = .041, d = 1.01) and social communication (p = .040, d = 0.71). Exploratory analyses further showed greater social-responsiveness difficulties in BBS and *HNF1B* deletion groups compared with other CysKDs, $F(2,87) = 6.44$, p = .003. Importantly, elevated screening-based symptom burden did not uniformly correspond to a confirmed ASD diagnosis in the in-depth diagnostic subsample. ADOS-2 severity did not differ significantly between BBS (*n* = 11) and *HNF1B* deletions (*n* = 9).

Conclusions

These findings confirm substantial symptoms of ASD burden in BBS and *HNF1B*-associated disease but demonstrate that screening elevations should not be equated with ASD diagnosis. Comprehensive diagnostic assessment is therefore warranted following positive screening

Background

Hereditary cystic kidney diseases (CysKDs) comprise a heterogeneous group of rare disorders characterized by renal cyst formation and variable progression to chronic kidney disease or kidney failure (1). Advances in genetic diagnostics have identified numerous disease-causing genes (2, 3). Beyond their renal manifestations, many CysKDs are now recognized as multisystem disorders affecting a wide range of organs, including the liver, pancreas, eyes, central nervous system, and the reproductive tract (4, 5). Consequently, increasing attention has been directed toward extra-renal manifestations that substantially influence long-term health outcomes and quality of life (6). Among these, neurodevelopmental impairment, like neurodevelopmental disorders (NDDs) have emerged as an important but still insufficiently characterized aspect of several genetic CysKDs (7).

NDDs comprise a group of childhood-onset conditions resulting from altered brain development and affecting cognition, behavior, communication, motor function, and social interaction with high level of overlap between these disorders and their constituent symptoms. (8). NDDs, including autism spectrum disorder (ASD), intellectual disability, attention-deficit/hyperactivity disorder (ADHD), and developmental delay, have been reported across several hereditary CysKDs (7, 9). ASD is characterized by persistent and early starting deficits in social communication and interaction in combination with restricted, repetitive patterns of behavior(10) alongside with behavioral and emotional problems. The heterogeneity and overlap with many other mental disorders make diagnostic assessment difficult. For these reasons, it is important to distinguish between symptoms of ASD in the sense of a dimensional - as a gradual continuum - manifestation of individual symptoms that occur in many mental and developmental disorders — and the categorical assessment of whether ASD is present or whether the diagnostic criteria are not met, as a yes/no determination. Particularly high frequencies of symptoms of ASD have been described in ciliopathies such as Bardet–Biedl and Joubert syndrome (11, 12, 9), whereas evidence also suggests neurodevelopmental involvement in *HNF1B* -associated disease (13). However, available evidence is largely based on case reports and small disease-specific cohorts, and standardized in-depth assessments of ASD across different CysKDs remain scarce (14).

Among ciliopathies, Bardet–Biedl syndrome (BBS) represents one of the most extensively studied conditions with respect to neurodevelopmental involvement. Beyond its cardinal features of retinal dystrophy, obesity, polydactyly, and renal anomalies, BBS has repeatedly been associated with intellectual disability, developmental delay, and symptoms of ASD (15, 11). Based on parent-report screening scales, Barnett et al. (11) found symptoms of ASD in approximately one third of patients with BBS, and Kerr et al. (16) found elevated symptoms of ASD in the majority (77%), independent of intellectual disability, which was diagnosed in only 20–25% of the cohort. However, these findings rely exclusively on screening instruments rather than standardized, in-depth ASD diagnostic assessment, limiting conclusions about the phenotypic overlap between BBS and ASD with respect to symptom burden versus formal diagnosis (15, 16).

Among hereditary CysKDs, *HNF1B* -associated disease has received particular attention due to its broad phenotypic spectrum (17). Heterozygous intragenic variants or whole-gene deletions caused by the recurrent 17q12 microdeletion cause a multisystem disorder characterized by congenital anomalies of the kidney and urinary tract, renal cysts, diabetes, pancreatic hypoplasia, electrolyte disturbances, genital tract malformations, and a variable progression to

chronic kidney disease (18, 19). Increasing evidence also links *HNF1B* -associated disease to NDDs, including ASD, intellectual disability, developmental delay, and learning difficulties (7, 20).

Most evidence originates from retrospective studies, case reports, or 17q12 microdeletion cohorts, whereas assessment of intragenic variants remains scarce, leaving unresolved whether abnormalities reflect *HNF1B* haploinsufficiency or loss of additional genes within the deleted region. Moreno-De-Luca et al. (21) found the 1.4-Mb 17q12 deletion enriched among patients with ASD, intellectual disability, and schizophrenia relative to controls. Based on clinical chart diagnoses, NDDs were reported in up to 40% of deletion carriers versus none with intragenic variants (22), and clinically ascertained neurological/psychiatric complications occurred exclusively in deletion carriers in a Japanese cohort (5/14 vs. 0/19, p = .0071; (23)). Clinically diagnosed ASD rates among deletion carriers range from 5.7% in a nephrology-ascertained cohort (14) to 75% in a small, prenatally ascertained cohort (n = 4; (24)), though nephrology ascertained cohorts report milder phenotypes (1/26, (25); 1/12, (26)). These discrepancies reflect heterogeneous ascertainment and reliance on clinical diagnosis rather than standardized, in-depth assessment, leaving the true *HNF1B* -related neurodevelopmental phenotype insufficiently defined.

Given this heterogeneity, we conducted a comprehensive, cross-diagnostic characterization of neurodevelopmental symptoms across genetic CysKDs, with a targeted comparison within *HNF1B* -associated disease. The study comprised two parts: a screening phase assessing overall behavioral and emotional problem burden, ADHD symptoms, functioning, and ASD symptoms across a large CysKD sample, followed by comprehensive, standardized ASD diagnostic assessment in participants with elevated ASD symptoms. Exploratory group comparisons (given small subgroup sizes) tested two hypotheses: that symptoms of ASD are more pronounced in *HNF1B* deletions than intragenic variants, and that patients with BBS and *HNF1B* deletions show more pronounced symptoms of ASD than other rare CysKD diagnoses.

Methods

Participants and Procedure

A total of 100 participants (60 male, 40 female; aged 1–24 years, M = 10.23, SD = 5.26) with genetically confirmed CysKD were recruited between June 2020 and December 2025 across six pediatric nephrology sites in Germany (Essen, Hannover, Heidelberg, Cologne, Marburg, Münster), in collaboration with an ASD outpatient clinic (Marburg), as part of the NEOCYST consortium ((27); ; ethics approval: University of Marburg, #71/20). Questionnaires were administered via mail, initially due to COVID-19 restrictions (diagnostic group sizes in Table 1). Participants exceeding predefined screening cut-offs for ASD (SCQ > 11; SRS ≥ 60; M-CHAT: ≥ 3 of 23 items or ≥ 2 critical items) were invited for comprehensive assessment at the Marburg outpatient clinic. Of 174 patients approached, nine could not be reached, seven were excluded for insufficient language proficiency, 13 declined, 45 did not return questionnaires after initial consent, and one had inconclusive genetic testing, yielding a final sample of 100.

Measures

Screening Questionnaires

If available, normed questionnaires were used, comparing an individual's score to that of a large healthy reference population of the same age and sex. Scores are expressed as standardized values, with higher values indicating a greater deviation from the norm.

Overall Behavioral and Emotional Problem Burden was assessed using the Achenbach System of Empirically Based Assessment (ASEBA; (28); German version: (29)): the parent-report Child Behavior Checklist (CBCL 1.5–5, 6–18), the informant-based Adult Behavior Checklist (ABCL), and the self-report Adult Self-Report (ASR, ages 18–59). All instruments yield age- and gender-normed T-scores for internalizing, externalizing, and total problems, plus syndrome scales; T-scores of 60–63 indicate borderline clinical, and ≥ 64 clinically significant problems.

ADHD Symptoms were assessed with age-appropriate Conners Scales: the Conners 3 Short Form – Parent Version for ages 6–18 ((30); German adaptation: (31)), and the Conners' Adult ADHD Rating Scales – Short Version (CAARS; self- and observer-report) for ages over 18 (CAARS; (32); German adaptation: (33)). Both yield normed T-scores; 60–64 borderline, 65–69 = elevated, ≥ 70 = clinically significant.

Functional Impairment was assessed using the parent-report Weiss Functional Impairment Rating Scale (WFIRS; (34)), administered in age-appropriate versions for preschool (2–5 years) and school-age/adolescent (6–17 years) participants, covering multiple domains of daily functioning. A domain was considered impaired if one item was rated 3 or two items rated 2, operationalizing the DSM-5 requirement of impairment across at least two domains or settings (34).

Symptoms of ASD were screened using three instruments. The Fragebogen zur sozialen Kommunikation **(**FSK; (35); German adaptation of the SCQ, (36) is a categorical, DSM-5-based parent-report questionnaire (ages 4–24 in this study) covering reciprocal social interaction, communication, and restricted/repetitive behaviors, with raw scores ≥ 15 indicating clinically significant traits. The Social Responsiveness Scale (SRS; (37); German adaptation: (38); SRS-A for adults: (39)) is a dimensional measure yielding T-scores overall and for five subscales (social awareness, cognition, communication, motivation, restricted interests/repetitive behavior); T-scores ≥ 60 indicate clinically relevant symptoms. Early ASD signs in toddlers (16–30 months) were screened with the Modified Checklist for Autism in Toddlers (M-CHAT; (40, 41)), 23 dichotomous items with elevated risk indicated by ≥ 3 failed items overall or ≥ 2 failed key items.

Comprehensive ASD diagnostic assessment-methods

A clinical best-estimate ASD diagnosis was confirmed or excluded following gold-standard guidelines, integrating standardized cognitive assessment, the semi-structured Autism Diagnostic Observation Schedule-2 (ADOS-2), the caregiver interview Autism Diagnostic Interview–Revised (ADI-R), and comorbidity assessment (see below).

Cognitive functioning was assessed using age-appropriate German Wechsler scales: WPPSI-IV (2:6–5:11; (42)), WISC-V (6:0–16:11; (43)), and WAIS-IV (≥ 17; (44)), yielding age-normed IQ scores; intellectual disability was classified per DSM-IV criteria.

The ADOS-2 ((45); German: (46)) is a semi-structured observation assessing communication, social interaction, and restricted/repetitive behaviors across modules. As different modules were used depending on language level and age, Calibrated Severity Scores (CSS; (47), range 1–10) ensured comparability across modules, in addition to algorithm cut-offs distinguishing ASD from typical development. CSS scores were interpreted as: 1–3 minimal, 4–5 mild, 6–7 moderate, 8–10 high severity (47).

The ADI-R ((48); German: (49)) is a structured caregiver interview on developmental history and current symptoms, with algorithm cut-offs of ≥ 10 (social interaction), ≥ 8 verbal/≥7 nonverbal (communication), and ≥ 3 (restricted/repetitive behaviors); meeting thresholds across all domains indicated ASD.

Psychiatric comorbidity was assessed with the Kinder-DIPS (50), a DSM-IV/ICD-10-based structured interview covering anxiety, mood, somatoform, and externalizing disorders.

Statistical analyses

Analyses comprised a screening part (*N* = 100) and an in-depth ASD diagnostic assessment (*N* = 21). Screening data met normality assumptions (Shapiro–Wilk, all $p > .05$); group differences in SRS/SCQ scores between *HNF1B* deletions and intragenic variants were tested with one-tailed Welch's t-tests (Cohen's d; Benjamini-Hochberg corrected), and, given the predominance of BBS cases, exploratory comparisons among BBS, *HNF1B* deletions, and other CysKD diagnoses used one-way ANOVAs with pairwise Welch's t-tests (Benjamini-Hochberg corrected). In-depth ASD results (ADOS-2, ADI-R) were reported descriptively for BBS, *HNF1B* deletion, and nephronophthisis subgroups; as normality was violated, BBS-vs- *HNF1B* differences in CSS and comorbidity count were tested with two-tailed Mann-Whitney U tests (effect size *r*), and proportion with ≥ 1 comorbid diagnosis with Fisher's exact test (OR, 95% CI). The nephronophthisis group (*n* = 1) was described descriptively only.

Results

Descriptive Data Analysis

Table 1 presents the descriptive statistics for demographic and somatic variables in the analysis.

Table 1
Demographic and Clinical Characteristics by Diagnostic Group

Cystic kidney disease	N	Female, n (%)	Age (years)	eGFR (mL/min/1.73 m²)	BMI SDS	Dialysis (*n*, %)	KTx (*n*, %)
Bardet–Biedl syndrome	37	12 (32.4%)	9.8 (± 5.6)	89.2 (± 29.6)	2.4 (± 1.3)	-	1 (4%)
HNF1B nephropathy	31	13 (41.9%)	10.1 (± 6.2)	99.2 (± 36.4)	0.3 (± 1.6)	1 (4.3%)	4 (17.4%)
Deletion	24	9 (37.5%)	9.7 (± 6)	107.9 (± 34.6)	0.3 (± 1.7)	1 (5.9%)	2 (11.8%)
Variants	7	4 (57.1%)	11.3 (± 7.1)	66.5 (± 23.6)	0.4 (± 1.4)	-	2 (33.3%)
Ciliopathies	24	9 (37.5%)	12.1 (4)	73.3 (50.7)	-1.7 (1.7)	7 (41.2%)	7 (41.2%)
Recessive cystic kidney diseases	8	6 (75%)	9.9 (± 2.5)	57.9 (± 41.9)	-1.4 (± 1.3)	1 (33.3%)	2 (66.7%)
Total cohort	100	40 (40%)	10.2 (5.3)	81.1 (41.2)	0.5 (2.2)	9 (13.2%)	14 (20.6%)

Note. Values are presented as *M* (*SD*) unless otherwise indicated. *N* = number of participants; *n* = number of participants with available data; eGFR = estimated glomerular filtration rate, patients with dialysis or kidney transplantation excluded; BMI-SDS = body mass index standard deviation score; KTx = kidney transplant, ; *HNF1B* = hepatocyte nuclear factor 1 beta; Ciliopathies: Nephronophthisis, Joubert syndrome, COACH syndrome, Recessive cystic kidney diseases: autosomal recessive polycystic kidney disease, Polycystic Kidney and Hepatic Disease 1. [a]One patient lost to follow up

Screening Results

As shown in Table 2, average scores for overall behavioral and emotional problem burden (CBCL Total) and ADHD symptoms were generally within the normative range across groups, with two exceptions: in BBS, internalizing problems (e.g., anxiety, withdrawal) and the overall scores of overall behavioral and emotional problem burden fell within the borderline range (T = 60–63), and mean inattention scores in *HNF1B* nephropathy reached clinical significance (*M* = 65.42, *SD* = 5.20). However, group averages can mask individual variation: at the individual level, clinically elevated scores were common — affecting roughly one-third of participants for emotional/behavioral problems overall, and over 40% for inattention symptoms (*HNF1B* nephropathy) or peer-relationship difficulties (BBS) (Supplementary Table S2).

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Table 2

Summary of Psychological Questionnaire Scores by Diagnostic Group

Cystic kidney disease	IQ	Overall Behavioral /Emotional Problem Burden (ASEBA)			ADHD Symptoms (Conners 3 P/CAARS (O))					
		Externalizing Problems	Internalizing Problems	Total Problems	Inattention	Hyperactivity/ Impulsivity	Learning Problems	Executive Functioning	Aggression	Peer Relatio
Bardet–Biedl syndrome	56.43 (14.64)	52.81 (7.8)	60.17 (8.47)†	60.03 (9.33) †	61.48 (5.42) †	53.48 (7.09)	62.33 (9.04) †	57.29 (9.27)	55.71 (8.57)	63.67 (7.02)
HNF1B nephropathy	82.07 (17.04)	52.55 (13.83)	53.87 (15.73)	56.1 (15.69)	65.42 (5.2) †	60.21 (8.83) †	62.79 (7.73) †	61.16 (8.1)	57.89 (9.87)	63.16 (8.13)
deletion	82.25 (19.16)	53.75 (13.89)	55.58 (16.92)	58.04 (15.69)	66.4 (4.85) ††	61.4 (7.98) †	64.13 (7.85) †	62.07 (7.82) †	58.4 (9.39)	64.27 (8.39)
Variants	81.33 (3.51)	48.43 (13.82)	48 (9.35)	49.43 (14.82)	61.75 (5.44)	55.75 (11.7)	57.75 (5.32)	57.75 (9.39)	56 (12.88)	59 (6.2
Ciliopathies	101.67 (18.99)	50.87 (10.93)	57.61 (14.98)	56.61 (15.02)	60 (9.27)	55.59 (10.95)	59.41 (10.69)	56.06 (8.23)	56.24 (7.94)	58 (8.8
Recessive cystic kidney diseases	89 (NA)	52.5 (8.26)	53.88 (11.91)	55.12 (13.3)	57.25 (9.04)	56 (11.21)	53.75 (10.53)	54.75 (8.4)	52 (5.68)	54.12 (6.45)
Total cohort	**80.17 (22.37)**	**52.24 (10.66)**	**57.06 (13.09)**	**57.58 (13.23)**	**61.72 (7.39)**	**56.31 (9.42)**	**60.65 (9.57)**	**57.78 (8.68)**	**56.03 (8.53)**	**60.86 (8.36)**

Note. Values are presented as *M* (*SD*); † Values in the borderline range, †† elevated values, ; ‡ value above SRS Cut off. **ASEBA** = Achenbach System of Empi **Conners 3 P/CAARS (O)** = Conners 3 Parent Rating Scale for children and adolescents and Conners' Adult ADHD Rating Scales (Observer version) for adult Communication Questionnaire; **SRS** = Social Responsiveness Scale; **M-CHAT** = Modified Checklist for Autism in Toddlers. Ciliopathies: Nephronophthisis, Jo syndrome, Recessive cystic kidney diseases: autosomal recessive polycystic kidney disease, Polycystic Kidney and Hepatic Disease 1.

Hypothesis I: Symptoms of ASD are more pronounced in HNF1B deletions than intragenic HNF1B variants

As hypothesized, patients with *HNF1B* deletions showed significantly more pronounced dimensional symptoms of ASD (SRS; *M* = 72.2, *SD* = 11.62) than those with intragenic variants (*M* = 59.3, *SD* = 15.82), *t*(8.39) = 1.98, *p* = .041 (one-tailed), *d* = 1.01, and more pronounced categorical symptoms of ASD in screening measurements SCQ; *M* = 11.74, *SD* = 6.32 vs. *M* = 7.67, *SD* = 2.80), *t*(19.8) = 2.20, *p* = .040 (one-tailed), *d* = 0.71, see Table 2.

Hypotheses II: Patients with BBS and HNF1B deletions show more pronounced symptoms of ASD than patients with other rare CysKD diagnoses.

Comparing BBS, HNF1B deletions, and pooled "other CysKD" diagnoses revealed significant group differences in dimensional symptoms of ASD (SRS), F(2, 87) = 6.44, p = .003, with elevated means in BBS (M = 71.22, SD = 11.89) and HNF1B deletions (M = 72.20, SD = 11.62) versus other CysKD (M = 60.95, SD = 16.41). Post-hoc tests confirmed higher scores for both BBS and HNF1B deletions versus other CysKD (both adjusted p = .006), with no difference between BBS and HNF1B deletions (adjusted p = .771). Categorical symptoms of ASD SCQ) did not differ significantly between groups, F(2, 85) = 1.94, p = .150.

Results of comprehensive ASD diagnostic assessment

Characteristics of the BBS, *HNF1B* deletion, and nephronophthisis (*n* = 1, descriptive only) subgroups undergoing in-depth ASD assessment are in Table 3. An ASD diagnosis was established in 1/11 BBS (9.1%) and 2/9 *HNF1B* deletion patients (22.2%). As Shapiro-Wilk tests indicated non-normality, group differences were tested with Mann-Whitney U tests. ADOS-2 CSS did not differ significantly between BBS (*Mdn* = 4, IQR = 5) and *HNF1B* deletions (*Mdn* = 1, IQR = 0), *W* = 69, *p* = .122, though a moderate effect size (*r* = .36) suggests a possible difference given limited power (n_1 = 11, n_2 = 9).

At least one comorbid psychiatric diagnosis occurred in 3/11 BBS (27.3%) and 5/9 *HNF1B* deletion patients (55.6%); neither this difference (Fisher's exact test, *p* = .362, *OR* = 0.32, 95% *CI* [0.03, 2.67]) nor the number of comorbidities (*r* = .20) differed significantly. Comorbid diagnoses included, in BBS: mild intellectual disability (F70.0, *n* = 1), ADHD (F90.0, *n* = 2), oppositional defiant disorder (F91.3, *n* = 1), and other childhood emotional disorders (F93.8, *n* = 1); in *HNF1B* deletions: obsessive-compulsive disorder (F42.1, *n* = 1), intellectual disability (F70.0, *n* = 1), ADHD (F90.0, *n* = 1), separation anxiety disorder (F93.0, *n* = 1), unspecified emotional disorder (F93.9, *n* = 1), and nonorganic enuresis (F98.0, *n* = 1).

Table 3

Cystic kidney disease	*N*	Female, n (%)	Age (years)	IQ	ADOS-2 CSS	ADI-R			ASS Diagnosis *N* (%)	Psychiatric diagnoses *N* (%)
						Social Interaction	Communication	Restricted and Repetitive Behaviors		
Bardet–Biedl syndrome	11	4(36.4%)	10.08 (5.57)	59.83 (14.96)	4.09 (2.77)	10.5 (6.19)	7.3 (4.06)	3 (1.83)	1 (9.1%)	3 (27,3%)
HNF1B deletions	9	2 (22.2%)	12.44 (4.58)	79.78 (14.36)	2.44 (2.88	7.12 (8.94)	3.38 (4.5),	1.86 (2.04)	2 (22.2%)	5 (63,6%)
Nephronophthisis	1	0	9.08 (NA),	103 (NA),	2 (NA)	4 (NA)	4 (NA)	0 (NA)	-	-

Demographic, Cognitive, and Symptoms of ASD in the CysKD Subgroup Assessed with In-Depth ASD Diagnostics

Note

Values are presented as *M* (*SD*) unless otherwise indicated. *N* = number of participants; ; IQ = intelligence quotient; ADOS-2 = Autism Diagnostic Observation Schedule, Second Edition; CSS = Calibrated Severity Score; ADI-R = Autism Diagnostic Interview–Revised; SI = Social Interaction; C = Communication; RRB = Restricted and Repetitive Behaviors; **ASD** = autism spectrum disorder. NA = not applicable because only one participant was available. Psychiatric diagnoses refer to diagnoses other than ASD.

Discussion

This study examined symptoms of ASD across two levels of assessment — parent-report screening and standardized in-depth diagnostics — in a multicenter cohort of genetically confirmed CysKDs, with focus on *HNF1B*-associated disease. Overall behavioral and emotional problem burden and functional impairment were common overall, with internalizing problems most pronounced in BBS and clinically relevant inattention in *HNF1B* nephropathy. At the screening level, *HNF1B* deletions showed significantly more pronounced ASD symptoms than intragenic variants (large SRS, medium-to-large SCQ effect), and BBS showed comparably elevated SRS, but not SCQ, symptom burden. However, at the diagnostic level, ADOS-2 severity did not differ significantly between BBS and *HNF1B* deletions, and fewer BBS than *HNF1B* deletion patients received a categorical ASD diagnosis (9.1% vs. 22.2%) — a pattern discussed further below.

HNF1B Deletions versus Intragenic Variants

The more pronounced screening-level symptoms of ASD in *HNF1B* deletions relative to intragenic variants align with previous reports of greater neurodevelopmental burden associated with the 17q12 microdeletion, based largely on clinical chart diagnoses rather than standardized in-depth assessment (21, 23, 24, 22). In our own in-depth diagnostic subsample, the same direction emerged, with more *HNF1B* deletion than BBS patients receiving a categorical ASD diagnosis (22.2% vs. 9.1%); however, this rate is considerably lower than the 40–75% previously reported in deletion carriers, suggesting that the genotype effect, while likely present, may be less pronounced than earlier studies have suggested.

Bardet–Biedl Syndrome as a Risk Group for Symptoms of ASD

The elevated screening-level symptoms of ASD in BBS align with earlier parent-report and case-series findings which reported screening-based rates of approximately 33% (CARS; 11) to 77% (ASRS; 16). No clear descriptive differences in ASD-related screening scores emerged across BBS gene subgroups (Supplementary Table S3), although subgroup sizes were too small to permit meaningful inferential comparisons. Elevation was evident for SRS but not SCQ scores, since SRS captures dimensional autistic traits while SCQ reflects categorical DSM-5 criteria. This pattern suggests broadly elevated symptoms that did not reach the threshold required to meet diagnostic criteria ((37, 35). However, when we applied standardized in-depth diagnostics (ADOS-2, ADI-R) rather than screening alone, only 1 of 11 BBS patients (9.1%) received a categorical ASD diagnosis — far below the screening-based rates reported previously, and below the rate observed here for *HNF1B* deletions. Part of this discrepancy may reflect item overlap between ASD screening measures and intellectual disability and/or emotional/behavioral problems, common in BBS; a companion analysis (Nittel et al., in preparation) suggests this overlap is most relevant in more cognitively impaired patients, while higher-functioning individuals show a distinguishable social-communication profile.

Strengths and Limitations

Strengths include a multicenter design addressing a clinicial relevant question in a group of patients with ultra-rare disorders (however, in total representing a relevant subset of young patients with chronic kidney disease), standardized questionnaires, and a subsample assessed with gold-standard ASD diagnostics (ADOS-2, ADI-R), combining confirmatory (*HNF1B*) and exploratory (BBS, other CysKD) analyses for a broader characterization of the neurodevelopmental phenotype across genetically heterogeneous CysKDs than previously available. However, recruitment targeted the *HNF1B* deletion- pathogenic variants comparison, and the resulting BBS overrepresentation means those findings remain hypothesis-generating. Several subgroups were small (intragenic variants, *n* = 7; ASD diagnostic subsample, *n* = 21; nephronophthisis, *n* = 1), limiting power and effect-size precision. The two-stage design (inviting only above-cut off participants to diagnostic assessment) and cross-sectional design limit generalizability and preclude conclusions about symptom trajectories.

Conclusions

This study provides evidence for a genotype-dependent neurodevelopmental phenotype in *HNF1B*-associated disease and identifies BBS as a CysKD subgroup with substantial screening-level symptoms of ASD. Critically, elevated screening scores did not consistently translate into confirmed diagnoses — most strikingly in BBS, where only 9.1% received a categorical diagnosis — underscoring that neurodevelopmental screening in CysKD should be paired with standardized diagnostic follow-up, and, tentatively, with ADHD-focused screening in *HNF1B* nephropathy, via collaboration between pediatric nephrology and child/adolescent psychiatry. As findings for BBS and *HNF1B* nephropathy stem from exploratory, uncorrected comparisons in small subgroups, they should be considered preliminary. Future studies should recruit larger samples of intragenic *HNF1B* variants and other underrepresented subgroups, adopt longitudinal designs, and extend in-depth ASD diagnostics to ciliopathies and recessive CysKD groups.

Declarations

Declarations

Ethics approval and consent to participate:

The study was approved by the Ethics Committee of the Faculty of Medicine, Philipps University Marburg (reference no. 71/20). Written informed consent was obtained from all participants and/or their parents or legal guardians prior to participation.

Consent for publication:

Not applicable.

Competing interests:

The authors declare that they have no competing interests.

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Author Contribution

C.M. N. wrote the manuscript text and prepared tables and figures. M.S. collected data. S.W., M.K. and I.K.-B. designed the study. All authors (J.K., K.B., M-C.) reviewed the manuscript.

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Data Availability

The datasets generated and analyzed during the current study are not publicly available due to the sensitive clinical and genetic information they contain but may be available from the corresponding author on reasonable request and subject to applicable data protection and ethical requirements.

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