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Behavioral and cognitive functioning in individuals with Cantú syndrome

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Abstract

Cantú syndrome (CS) is caused by pathogenic variants in *ABCC9* and *KCNJ8* encoding the regulatory and pore-forming subunits of ATP-sensitive potassium (K_{ATP}) channels. CS is characterized by congenital hypertrichosis, distinctive facial features, peripheral edema, and cardiac and neurodevelopmental abnormalities. Behavioral and cognitive issues have been self-reported by some CS individuals, but results of formal standardized investigations have not been published. To assess the cognitive profile, social functioning, and psychiatric symptoms in a large group of CS subjects systematically in a cross-sectional manner, we invited 35 individuals (1–69 years) with confirmed *ABCC9* variants and their relatives to complete various commonly applied standardized age-related questionnaires, including the Kaufman brief intelligence test 2, the social responsiveness scale-2, and the Achenbach system of empirically based assessment. The majority of CS individuals demonstrated average verbal and nonverbal intelligence compared to the general population. Fifteen percent of cases showed social functioning strongly associated with a clinical diagnosis of autism spectrum disorder. Both externalizing and internalizing problems were also present in this cohort. In particular, anxiety, anxiety or attention deficit hyperactivity disorder, and autism spectrum behaviors were predominantly observed in the younger subjects in the cohort (≥25%), but this percentage decreased markedly in adults.

KEYWORDS
autism, behavior, Cantú syndrome, DSM V, intelligence, psychiatric symptoms

1 | INTRODUCTION

Cantú syndrome (CS, OMIM #239850) is a rare autosomal dominant genetic disorder that affects multiple organ systems with about 150 published cases worldwide. Individuals with CS have cardiac abnormalities, including an enlarged heart, pericardial effusion, blood pressure abnormalities, and structural abnormalities, such as vessel (patent ductus arteriosus [PDA]) and heart valve defects. Additionally, CS subjects have noncardiac manifestations that include large size at birth, hypertrichosis (thick/abundant scalp hair and excess body hair), distinctive facial features, skeletal abnormalities, peripheral edema, tortuous blood vessels in the brain, and neurodevelopmental abnormalities including hypotonia, motor delays, and exercise intolerance (Grange et al., 2006; Grange et al., 2019; Leon Guerrero et al., 2016; Roessler et al., 2020). CS is caused by gain-of-function (GoF) pathogenic variants in *ABCC9* and, less commonly, in *KCNJ8*, which encode the regulatory (SUR2) and pore-forming (Kir6.1) subunits, respectively, of ATP-sensitive potassium (K_{ATP}) channels (Brownstein et al., 2013; Cooper et al., 2014; Harakalova et al., 2012; McClenaghan et al., 2017; van Bon et al., 2012). The majority of cases harbor de novo variants.

Most individuals with CS have normal intellect, although some show mild learning disabilities and/or developmental delay in early childhood, including delays in speech development and motor skills most likely due to hypotonia (Grange et al., 2019). Whereas most publications have focused on the description of the clinical effects of CS, detailed knowledge on the behavioral phenotype, (e.g., cognitive and language disorders, social changes) associated with the disorder is currently lacking. In the past, a few clinical reports have suggested behavioral abnormalities in individual CS subjects based on self-reported symptoms like anxiety or attention deficit hyperactivity disorder and autism spectrum features (Grange et al., 2019; Grange et al., 2020; Scurr et al., 2011). However, social and/or psychological concerns related to CS have not been reported in detail.

The observation and evaluation of behavior are not straightforward since not all patients with the same syndrome have the same behavioral traits, and there may be a broad spectrum of severity. Thus, the aim of this study was to characterize social and cognitive phenotypes involved in CS in (1) a large patient cohort including all ages and a balanced gender-ratio and (2) using a standardized and comparable manner. By applying the same questionnaires in all patients, we are able to compare results between individuals from the same age groups and rule out incomparability based on the application of different or inaccurate tests done by third parties. This is the first study to assess behavior and cognitive profile as well as social functioning in CS individuals systematically instead of relying on self-reported behavioral issues by patients. Using quantitative measures designed with specific focus on verbal and nonverbal intelligence, social behavior, autistic traits, and psychiatric symptoms, we aim to provide a more detailed characterization of such deficits in this cohort. Further characterization of behavioral features associated with CS might contribute to targeted behavioral interventions, will enable us to anticipate behavioral problems, and offer additional information on CS associated phenotypes during the genetic counseling process.

1.1 | Subjects and methods

1.1.1 | Study participants

All data reported here were collected after getting the consent of the patient or the parents or legal guardians for individuals younger than 18 years old.

Participants included 35 individuals (14 males; 21 females) aged 1–69 years. Due to age-dependency, not every questionnaire was administered to all subjects. All participants had been molecularly diagnosed with CS either by Sanger-sequencing of the *ABCC9* gene or whole exome or genome sequencing. All study participants are part of the International Cantú Syndrome Registry (ICSR) and have been reported previously at least once (Grange et al., 2019). Patient demographics are provided in Table 1. Questionnaires were filled in during specialized annual Cantú syndrome research clinics at the Utrecht University Medical Center in the Netherlands ($n = 13$) and Washington University in St. Louis, Missouri, USA ($n = 22$).

1.1.2 | Data collection

Data were collected using three standardized questionnaires: The Kaufman brief intelligence test 2 (KBIT-2) (Kaufman & Kaufman, 2004), the social responsiveness scale—second edition (SRS-2) (Constantino & Gruber, 2012), and the Achenbach system of empirically based assessment (ASEBA) (Achenbach & Rescorla, 2001, 2003). All questionnaires were available in the native language of the patient or informant. Detailed information about each applied questionnaire can be found in the Supplementary Methods.

Since not all questionnaires were introduced during the same CS research clinic and some individuals were not able to attend every annual clinic, not every form has been completed by every participating subject. The KBIT-2 was exclusively administered to 13 subjects from the CS cohort at Washington University in St. Louis. SRS-2 and ASEBA questionnaires were completed by nearly the entire study cohort including patients from both research sites (30/35). Four of 30 subjects (CS0003, CS0030, CS0037, and CS2004) did not complete both questionnaires, resulting in differences in total numbers between both tests (Figure 1).

Additionally, a few subjects filled in the questionnaires over the span of multiple CS research clinics, hence their age deviates between the different assessments. Table 1 shows the type of questionnaires that have been completed by every participating individual per study site and the age at the time of examination.

1.1.3 | Data analysis

Descriptive statistics were applied to describe the data. Standard error of mean was calculated using Prism (GraphPad).

No statistical tests have been performed due to low patient numbers.

TABLE 1 Patient *ABCC9* variants and general features ($n = 35$)

Patient	Gender	cDNA variant	Protein alteration	De novo status	Race/ ethnic background	(Self-)reported behavioral abnormalities	Special education during school	Highest degree	SRS-2 (age [years])[a]	ASEBA (age [years])[a]	KBIT2 (age [years])[a]	Previous publication
CS0001	M	c.3460 C>T	p.Arg1154Trp	de novo	C	ADHD, mood swings	+	High school	+ (16)	+ (18)	+ (15)	1, 4
CS0002[b]	F	c.3461 G>A	p.Arg1154Gln	Inherited from affected mother	C	Depression	–	High school	+ (21)	+ (21)	+ (20)	1, 2, 3
CS0003[b]	F	c.3461 G>A	p.Arg1154Gln	Inherited from affected mother	C	–	+	College	na	+ (29)	na	1, 2, 3
CS0004[b]	F	c.3461 G>A	p.Arg1154Gln	de novo	C	–	+	College	+ (52)	+ (52)	+ (49)	1, 2, 3, 4
CS0005	F	c.3460 C>T	p.Arg1154Trp	de novo	C	Depression	+	College	+ (21)	+ (21)	+ (20)	1, 4, 5
CS0006	M	c.3014 A>T	p.His1005Leu	de novo	C	ADHD, ASD, OCD	+	Attends school	+ (17)	+ (17)	+ (15)	1, 4
CS0007[b]	F	c.3346 C>T	p.Arg1116Cys	de novo	C	Mood swings, depression	–	College	na	na	+ (34)	1, 4
CS0009[b]	M	c.3346 C>T	p.Arg1116Cys	Inherited from affected mother	C	–	+	Attends school	na	na	+ (9)	1, 4
CS0010[b]	M	c.3346 C>T	p.Arg1116Cys	Inherited from affected mother	C	ASD	+	Attends school	na	na	+ (8)	1, 4
CS0011	M	c.3347 G>A	p.Arg1116His	de novo	C	–	+	Attends school	+ (11)	+ (11)	na	1, 4, 5
CS0013	M	c.4469 T>A	p.Va1490Glu	de novo	C/H	–	–	–	+ (4)	+ (4)	na	1, 5
CS0015	M	c.3796 G>A	p.Val1266Met	de novo	C	ADHD, mood swings, OCD	–	–	na	na	+ (5)	1
CS0016	F	c.2378 A > T	p.Asp793Val	de novo	C	–	–	–	+ (3)	+ (3)	na	1, 5
CS0017	F	c.3014 A>T	p.His1005Leu	de novo	C/H	–	–	–	+ (3)	+ (3)	na	1, 5
CS0020	M	c.3461 G>A	p.Arg1154Gln	de novo	C	ASD, mood swings, OCD, anxiety	+	Attends college	+ (20)	+ (20)	+ (18)	1
CS0021[b]	F	c.881 G>A	p.Gly294Glu	Inherited from affected mother	C	Depression, anxiety, mood swings	+	College	+ (46)	+ (46)	+ (45)	1
CS0022[b]	F	c.881 G>A	p.Gly294Glu	de novo	C	Depression	–	College	na	na	+ (69)	1
CS0024	M	c.4040 G>T	p.Arg1347Leu	de novo	C	Anxiety	–	Attends school	+ (5)	+ (7)	na	1, 5
CS0028	F	c.3605 C>T	p.Thr1202Met	de novo	C/H	ADHD, mood swings, anxiety	–	–	+ (5)	+ (5)	na	1

TABLE 1 (Continued)

Patient	Gender	cDNA variant	Protein alteration	De novo status	Race/ ethnic background	(Self-)reported behavioral abnormalities	Special education during school	Highest degree	SRS-2 (age [years])[a]	ASEBA (age [years])[a]	KBIT2 (age [years])[a]	Previous publication
CS0030	F	c.4480 G>A	p.Ala1494Thr	de novo	C/H	Mood swings, depression	–	Graduate school	+ (40)	na	na	1
CS0035	F	c.3704 C>T	p.Ser1235Phe	de novo	C	–	–	College	+ (58)	+ (58)	+ (58)	1
CS0037	F	c.3056 C>A	p.Thr1019Lys	de novo	C	–	–	–	+ (1)	+ (1)	na	1
CS2001	F	c.1295 C>T	p.Pro432Leu	de novo	C	na	–	Attends school	+ (11)	+ (11)	na	1, 5, 6
CS2002[b]	M	c.1433 C>T	p.Ala478Val	de novo	C	na	+	High school	+ (39)	+ (39)	na	1, 7
CS2003[b]	M	c.1433 C>T	p.Ala478Val	Inherited from affected father	C	na	–	–	+ (3)	+ (3)	na	1, 5, 7
CS2004	M	c.178 C>T	p.His60Tyr	de novo	C	na	–	Attends school	+ (12)	+ (12)	na	1, 5
CS2005	F	c.3460 C>T	p.Arg1154Trp	de novo	C	na	–	Attends school	+ (17)	+ (17)	na	1, 5
CS2006	F	c.3461 G>A	p.Arg1154Gln	de novo	C	na	–	–	+ (5)	+ (5)	na	
CS2008	F	c.3345 C>G	p.Arg.1116Gly	de novo	C	na	+	Attends school	+ (15)	+ (15)	na	1, 5
CS2009	F	c.3461 G>A	p.Arg1154Gln	de novo	C	na	–	High school	+ (22)	+ (22)	na	1, 5
CS2010	F	c.3460 C>T	p.Arg1154Trp	de novo	C	na	–	Attends school	+ (17)	+ (17)	na	1, 5
CS2011[b]	F	c.3345 G>A	p.Arg1116His	de novo	C	na	–	Graduate school	+ (45)	+ (45)	na	1, 5, 6, 7
CS2012[b]	M	c.3345 G>A	p.Arg1116His	Inherited from affected mother	C	na	+	Attends school	+ (10)	+ (10)	na	1, 6, 7
CS2013	F	c.3460 C>T	p.Arg1154Trp	de novo	C	na	–	Attends school	+ (10)	+ (10)	na	1, 5, 6
CS2014	M	c.3461 G>A	p.Arg1154Gln	de novo	C	na	–	–	+ (3)	+ (3)	na	1, 5

Note: Due to age-dependency of the applied questionnaires, not every measure was administered to every individual. Additionally, sometimes questionnaires have been filled in at various ages of the patient. Therefore, we report a separate age for every administered questionnaire per patient. Patient identification numbers CS0001–CS0037 refer to US cohort, CS2001–CS2014 refer to Dutch cohort. 1: Grange et al. (2019), 2: Grange et al. (2006), 3: van Bon et al. (2012), 4: Leon Guerrero et al. (2016)), 5: Roessler et al. (2020), 6: Harakalova et al. (2012), 7: Roessler et al. (2018).

Abbreviations: ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; C, Caucasian; H, Hispanic; na, not assessed; OCD, obsessive–compulsive disorder; (+), present/assessed; (–), not present.

[a]Questionnaires have been filled in at various ages of the patient.

[b]Kindreds are grouped together: CS0002/CS0003/CS0004, CS0007/CS0009/CS0010, CS0021/CS0022, CS2002/CS2003, CS2011/CS2012.

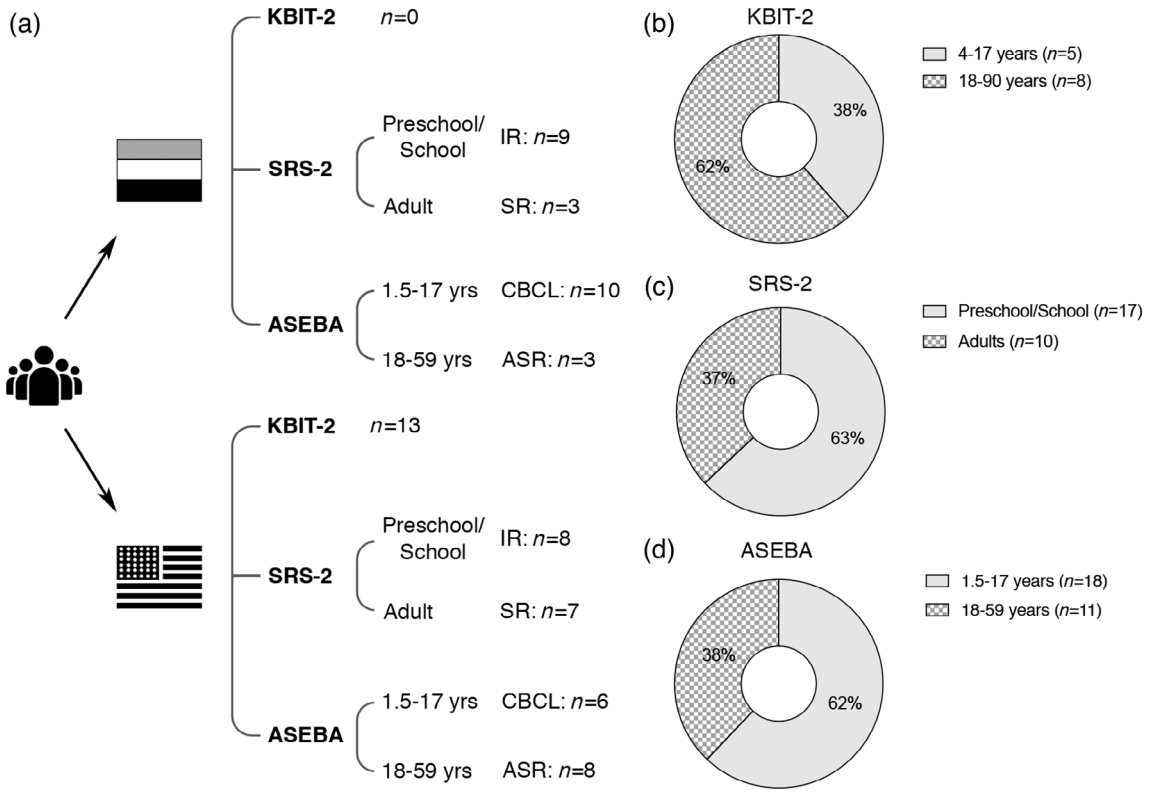

FIGURE 1 (a) Overview indicating the number of completed KBIT-2, SRS-2, and ASEBA questionnaires (and their subtypes) in both participating countries. (b–d) Distribution of age-related groups and questionnaire subtypes in this study. ASR, adult self-report; CBCL, children behavior checklist; IR, informant report; SR, self-report

2 | RESULTS

We assessed behavioral and intellectual functioning in 35 CS subjects, 14 males and 21 females, with an age range of 1–69 years. All individuals had confirmed genetic variants in *ABCC9*; in 27 of 35 cases, this variant was de novo. Information regarding genotype, general features, and previously self-reported behavioral abnormalities of all subjects is provided in Table 1. All individuals are part of the ICSR (Grange et al., 2019) and thus have been published at least once before. Patient study numbers applied in this study are linked to the ICSR published by Grange et al., which documents clinical features of each patient in detail (Grange et al., 2019). All subjects participated in this study through a specialized Cantú syndrome research clinic in the Netherlands or the United States. All participants were Caucasian and the majority identified as non-Spanish/Hispanic/Latino (31/35, 89%), reflecting the location of the participating sites.

2.1 | Reported psychiatric syndromes (total $n = 22$)

Information regarding already established behavioral abnormalities is not complete in this cohort. Data are available for all cases assessed at Washington University in St. Louis (22/35, 63%) (Table 1). Mood swings are reported in 7 of 22 (32%) subjects and depression in 6 of 22 (27%). Four out of 22 (18%) subjects are reported to have ADHD. Autism or autism spectrum disorder (ASD) and obsessive–compulsive disorder (OCD) are self-reported in 3 of 22 (14%) individuals. These features occur separately or in combination (Table 1).

2.2 | Intelligence (total $n = 13$)

To measure verbal and nonverbal intelligence in CS, 13 subjects seen at Washington University were administered the KBIT-2. Information on mean standard scores (SS) and associated clinical range can be seen in Table 2. Two out of 13 (15%) assessed subjects scored an IQ composite SS below average, 2 of 13 (15%) subjects showed a nonverbal SS below average, and 1 of 13 (7.5%) individuals revealed a verbal SS below average. As a group, the CS cohort presented with intellectual abilities only 0.5 SD below the general population mean (IQ composite SS: 93.46 ± 2.95). In order to compensate for the wide age range present in our cohort assessed by KBIT-2 (5–69 years), participating individuals were divided into two groups according to age for further analysis: (1) 4–17 years ($n = 5$) and (2) 18–90 years ($n = 8$). When comparing both groups, the mean IQ composite SS was considerably lower, but still within an average range, in CS children (89.40 ± 3.60) compared to adults (96.00 ± 4.14). This results from a decreased nonverbal SS in younger individuals (4–17 years: 85.00 ± 6.94; 18–90 years: 94.13 ± 4.63), which is 1 SD below the general population mean. Verbal intelligence was presented in a similar range between age groups. Notably, no gender-related differences were observed in the assessed cohort.

TABLE 2 Descriptive statistics for KBIT-2 standard scores in 4 to 17-year-old ($n = 5$) and 18 to 90-year-old ($n = 8$) individuals with Cantù syndrome

	4–17 years ($n = 5$)						18–90 years ($n = 8$)					
		Descriptive category						Descriptive category				
KBIT-2 components	Mean (± SEM)	Lower extreme	Below average	Average	Above average	Upper extreme	Mean (± SEM)	Lower extreme	Below average	Average	Above average	Upper extreme
Age	9.80 (±2.18)						39.13 (±6.79)					
Verbal SS	96.40 (±3.74)	0%	0%	100% 5/5	0%	0%	97.63 (±3.72)	0%	12.5% 1/8	87.5% 7/8	0%	0%
Nonverbal SS	85.00 (±6.94)	20% 1/5	0%	80% 4/5	0%	0%	94.13 (±4.63)	0%	12.5% 1/8	87.5% 7/8	0%	0%
IQ Composite SS	**89.40 (±3.60)**	**0%**	**20% 1/5**	**80% 4/5**	**0%**	**0%**	**96.00 (±4.14)**	**0%**	**12.5% 1/8**	**87.5% 7/8**	**0%**	**0%**

Note: Range: Lower extreme (SS ≤69), below average (SS 70–84), average (SS 85–115), above average (SS 116–130), upper extreme (SS ≥131). The values are bold as they represent the overall score, all other values in the table make up this score.

Abbreviations: SEM, standard error mean; SS, standard score.

2.3 | ASD-associated features (total $n = 27$)

To assess whether CS subjects reveal criteria for ASD, participating Dutch and US subjects or their relatives were invited to complete the social responsiveness scale-2 (Constantino & Gruber, 2012). For a more detailed analysis, the subjects were divided into two age-related groups according to the specific SRS-2 questionnaire they had to fill in: (1) Preschool- and school-age (2.5–17 years, $n = 17$) and (2) adult (≥18 years, $n = 10$). Mean SRS-2 T-scores and the percentage of individuals who received T-scores in the mild, moderate, or severe range for each group are reported in Table 3.

Out of the 27 CS cases who provided a completed questionnaire, three subjects (11%) had SRS-2 total scores in the mild range, indicating mild interference with everyday social interactions, and four (15%) were in the severe range, which is strongly associated with a clinical diagnosis of ASD. Notably, all seven subjects belong to the younger age group. The remaining 20 cases all scored within a normal range (74%). Interestingly, the number of CS cases with an SRS-2 total score falling in the range of ASD systematically decreased with age (preschool-age: 63%; school-age: 22%; adults: 0%).

In addition, 7 of 17 (41%) CS individuals originating from the younger age group revealed social communication indices (SCI) in the clinically significant range. In contrast, only 1 of 10 (10%) individuals from the older age group showed an SCI in the clinically severe range. Similarly, restricted interests and repetitive behavior indices (RRBI) were in the clinically significant range for 8 of 17 (47%) younger CS cases, whereas merely 3 of 10 (20%) older subjects revealed a clinically significant RRBI.

Interestingly, ASD-associated features seem predominantly present in younger male CS cases in this cohort. Boys aged 2.5–17 years revealed a mean total score in the mild range (64.50 ± 6.01, $n = 8$), while female individuals in the same age group were represented in the normal range (52.00 ± 5.34, $n = 9$). No gender-related difference was observed in the older age group. Notably, both individuals who self-reported a diagnosis of ASD revealed total scores in the severe range.

2.4 | Behavioral and emotional functioning (total $n = 29$)

ASEBA assesses competencies, strengths, adaptive functioning, and behavioral, emotional, and social problems from age 1.5 to 59 years. Twenty-nine CS subjects or their relatives completed specific age-appropriate ASEBA questionnaires. To assess the entire CS cohort, the subjects were again sorted into two age-related groups according to the specific ASEBA questionnaire they were asked to complete: (1) 1.5–17 years ($n = 18$) and (2) 18–59 years ($n = 11$). In each assessed category, we indicate a mean T-score and the percentage of individuals who received T-scores in the borderline clinical and clinical range (Tables 4-6). For all groups, the questionnaire was divided into two parts: One assessing social competencies (only available for children from 6 to 17 years and adults) and the other assessing behavior problems.

TABLE 3 Social responsiveness derived from SRS-2 in 2.5 to 17-year-old ($n = 17$) and above 18-year-old ($n = 10$) individuals with Cantù syndrome

	Preschool/school-age: 2.5–17 years ($n = 17$)				Adults: ≥ 18 years ($n = 10$)			
Social category	**Mean (± SEM)**	**Mild**	**Moderate**	**Severe**	**Mean (± SEM)**	**Mild**	**Moderate**	**Severe**
Age	9.059 (± 1.38)				36.40 (± 4.53)			
SCI	58.75 (± 8.81)	17.6% 3/17	0%	23.5% 4/17	50.50 (± 3.55)	0%	0%	10% 1/10
Social awareness	56.00 (± 3.48)	0%	17.6% 3/17	11.8% 2/17	49.40 (± 2.31)	10% 1/10	0%	0%
Social cognition	53.71 (± 3.58)	0%	11.8% 2/17	11.8% 2/17	52.10 (± 3.22)	0%	0%	10% 1/10
Social communication	57.59 (± 4.42)	5.8% 1/17	11.8% 2/17	23.5% 4/17	551.10 (± 3.35)	0%	0%	10% 1/10
Social motivation	56.65 (± 3.21)	11.8% 2/17	5.8% 1/17	11.8% 2/17	58.90 (± 3.53)	20% 2/10	10% 1/10	10% 1/10
RRBI	60.00 (±4.13)	5.8% 1/17	17.6% 3/17	23.5% 4/17	54.90 (± 3.80)	10% 1/10	0%	10% 1/10
SRS-2 overall score	**57.88 (± 4.17))**	**17.6% 3/17**	**0%**	**23.5% 4/17**	**48.90 (± 1.45)**	**0%**	**0%**	**0%**

Note: For simplicity, results from preschool- and school-aged CS individuals have been pooled. SCI is sum of awareness, cognition, communication, and motivation subscales. Range: within normal limits (T-score ≤59), mild range (T-score 60–65), moderate range (T-score 66–75), severe range (T-score ≥76). The values are bold as they represent the overall score, all other values in the table make up this score.
Abbreviations: RRBI, restricted interests and repetitive behaviors index; SCI, social communication index; SEM, standard error mean.

2.4.1 | Social and professional functioning

Children (6–17 years) were assessed on competencies in terms of the child's functioning in activities, social relationships, and school, whereas adults (18–59 years) were assessed on adaptive functioning for academic performance and favorable characteristics including friends, spouse/partner, family, job, and education (Table 5). The mean total competence scores for Group 1 (40.47 ± 3.10) and the mean adaptive functioning score for Group 2 (47.73 ± 2.16) were in the normal range. In detail, all individuals who were 6 years of age or older were (or had been) attending mainstream education schools and 11 of 21 (52%) required or had required special education services. Three of 10 (30%) subjects currently attending school had to repeat at least one grade and 4 of 10 (40%) were reported to perform below average. Eight out of 12 (67%) eligible subjects attended or had attended college after obtaining their high school degree, with two individuals receiving a graduate degree (Table 1). For adults, 7 of 12 (58%) had a paid job at the time of assessment.

2.4.2 | Behavioral symptoms

The list of items for psychiatric symptoms provides scores for eight empirical scales or syndromes, and for 2 second-order factors (internalizing disorders and externalizing disorders), in addition to the total score (Table 5). A total problem score in the clinically affected range was found in 8 of 29 (28%) subjects. Internalizing problems (emotional disorders) in the clinical range were present in 10 of 29 (34%) individuals and clinically recognizable externalizing problems (disruptive disorders) were observed in 6 of 29 (21%) subjects. The following specific problem clusters contained four or more clinical cases: "anxious/depressed" (4 of 29, 14%), "somatic complaints" (5 of 29, 17%), and "attention problems" (6 of 29, 21%).

When comparing psychiatric symptoms in male and female CS subjects from both age-specific groups, younger male cases revealed a mean total (66.25 ± 5.54, $n = 8$) and internalizing problem score (67.50 ± 5.12) in the clinically affected range, whereas females presented in the normal range (internalizing problems: 54.30 ± 4.47; total score: 51.50 ± 3.82, $n = 10$). No gender-related differences were observed in the older age-associated group.

Additionally, a list of DSM-oriented scales derived through expert consensus is provided (Table 6). We observed that 9 of 29 (31%) subjects qualified for one or more (up to six) DSM diagnoses with six cases originating from the younger age group. Moreover, we found that ≥17% of younger CS cases had T-scores in the clinically affected range on "depressive problems," "anxiety problems," and "ADHD problems" on the DSM-oriented scale with another 10%–15% scoring in the borderline range. These percentages decreased markedly in adults (clinically affected range: <10%).

When comparing psychiatric symptoms and DSM-oriented problems between various family members with CS (familial cases, $n = 12$), a high variability was observed, confirming the known intra-familial variability of CS-associated features (Grange et al., 2019; Roessler et al., 2018).

3 | DISCUSSION

In this study, we investigated the presence and type of behavioral, social, and intellectual abnormalities in a large cohort of individuals with Cantú syndrome.

TABLE 4 Social and professional functioning derived from ASEBA in 6 to 17-year-old ($n = 10$) and 18 to 59-year-old ($n = 11$) individuals with Cantù syndrome

	6–17 years ($n = 10$)				18–59 years ($n = 11$)		
Social/professional category	**Mean (± SEM)**	**BR (%)**	**CR (%)**	**Social/professional category**	**Mean (± SEM)**	**BR (%)**	**CR (%)**
Age	12.70 (± 1.13)			Age	33.733 (± 4.42)		
Activities	40.67 (± 2.54)	0%	11% 1/9	Friends	43.45 (± 2.69)	0%	9% 1/11
Social	45.00 (± 2.78)	0%	10% 1/10	Spouse/Partner	49.00 (± 3.82)	14% 1/7	0%
School	38.00 (± 3.34)	25% 2/8	25% 2/8	Family	48.45 (± 2.01)	0%	0%
Total competence score	**40.47 (± 3.05)**	**14% 1//7**	**14% 1//7**	Job	52.38 (± 2.04)	0%	0%
				Education	52.00 (± 8.00)	0%	0%
				Personal strengths	50.64 (±1.78)	0%	0%
				Adaptive functioning score	**47.73 (± 2.16)**	**9% 1/11**	**0%**

Note: For simplicity, only social/professional categories related to main findings of the study are shown. Range: Borderline range (BR) for syndrome scale, T-score 30–35; clinical range (CR) for syndrome scale, T-score ≤ 30. The values are bold as they represent the overall score, all other values in the table make up this score.
Abbreviations: BR, borderline range; CR, clinical range; na, not assessed; SEM, Standard error mean.

TABLE 5 Psychiatric symptoms derived from ASEBA in 1.5 to 17-year-old ($n = 18$) and 18 to 59-year-old ($n = 11$) individuals with Cantù syndrome

	1.5–17 years ($n = 18$)			18–59 years ($n = 11$)		
Psychiatric symptoms	**Mean (± SEM)**	**BR (%)**	**CR (%)**	**Mean (± SEM)**	**BR (%)**	**CR (%)**
Age	8.50 (±1.31)			33.733 (± 4.42)		
Internalizing score	**60.17 (± 3.63)**	**0%**	**44.4% 8/18**	**54.64 (± 2.69)**	**0%**	**18.2% 2/11**
Anxious/depressed	60.00 (± 3.28)	22.2% 4/18	16.7% 3/18	54.18 (± 2.00)	0%	9.1% 1/11
Withdrawn/depressed	61.22 (± 3.28)	11.1% 2/18	16.7% 3/18	55.18 (± 1.87)	9.1% 1/11	0%
Somatic complaints	63.39 (± 2.88)	16.7% 3/18	16.7% 3/18	59.73 (± 2.50)	0%	18.2% 2/11
Externalizing score	**55.06 (± 4.05)**	**0%**	**33.3% 6/18**	**44.00 (± 2.53)**	**0%**	**0%**
Aggressive behavior	58.17 (± 3.18)	22.2% 4/18	11.1% 2/18	52.64 (± 1.25)	0%	0%
Attention problems	62.38 (± 3.15)	16.7% 3/18	27.8% 5/18	55.27 (± 2.32)	0%	9.1% 1/11
Total problem score	**58.17 (± 3.59)**	**5.6% 1/18**	**33.3% 6/18**	**51.09 (± 2.39)**	**0%**	**9.1% 1/11**

Note: For simplicity, only psychiatric symptoms related to main findings of the study are shown. Range: Borderline range (BR) for syndrome scale, T-score 65–70; clinical range (CR) for syndrome scale, T-score ≥ 70; BR for "internalizing, externalizing and total problems" scale, T-score 60–63; CR for "internalizing, externalizing and total problems" scale, T-score ≥ 64. The values are bold as they represent the overall score, all other values in the table make up this score.
Abbreviations: BR, borderline range; CR, clinical range; na, not assessed; SEM, standard error mean.

The majority of cases revealed average verbal and nonverbal intelligence, suggesting that both children and adults with CS, as a group, develop at a consistent rate relative to the KBIT-2 normative sample and no intellectual deficit was observed. The mean IQ composite SS of the described CS cohort was only 0.5 SD below the general population mean. Children and adolescents with CS revealed a decreased

TABLE 6 DSM-oriented scales derived from ASEBA in 1.5 to 17-year-old ($n = 18$) and 18 to 59-year-old ($n = 11$) individuals with Cantù syndrome

	1.5–17 years ($n = 18$)			18–59 years ($n = 11$)		
DSM-oriented scales	**Mean (±SEM)**	**BR**	**CR**	**Mean (±SEM)**	**BR**	**CR**
Depressive problems	63.11 (±3.10)	11.1% 2/18	16.7% 3/18	56.00 (±2.01)	18.2% 2/11	0%
Anxiety problems	61.94 (±3.48)	16.7% 3/18	33.3% 6/8	54.09 (±1.65)	9.1% 1/11	0%
AD/H problems	59.11 (±2.69)	11.1% 2/18	22.2% 4/18	55.18 (±2.22)	0%	9.1% 1/11
Somatic problems	Na			59.64 (±3.47)	9.1% 1/11	18.2% 2/11

Note: For simplicity, only DSM-oriented scales related to main findings of the study are shown. Range: Borderline range (BR) for DSM-oriented scale, T-score 65–70 (93rd to 97th percentile); clinical range (CR) for DSM-oriented scale, T-score ≥70 (percentiles of 98 and higher).
Abbreviations: AD/H, attention deficit/hyperactivity; BR, borderline range; CR, clinical range; na, not assessed; SEM, standard error mean.

nonverbal score that was 1 SD below the general population mean. Hence, minor deficits in reasoning and problem-solving with patterns and relationships, pictorial analogies, and categories could be observed in this group, potentially explaining the increased need for special education services observed in this CS cohort 11 of 21 (52%).

Moreover, this study was designed to measure strengths and weaknesses in social functioning of CS subjects by applying the SRS-2, often used to assess ASD-related features (Constantino & Gruber, 2012). Results suggest that especially younger individuals with CS (41%) have clinically recognizable difficulties with social behavior that may be indicative of ASD, in particular expressive social communication and the ability to pick up on social cues. The estimated prevalence of ASD in children in the general population is 1.5% (Developmental Disabilities Monitoring Network Surveillance Year Principal, Centers for Disease,, & Prevention, 2014). Similar deficits in social functioning were not observed in adult individuals with CS in this cohort.

Notably, it has been suggested that SRS scores are highly influenced by behavioral, non-ASD-related symptoms (Hus et al., 2013). Thus, SRS scores may also be interpreted as a subject's or informant's perception of the subject's overall level of impairment, which may not only be affected by ASD features, but also by developmental difficulties and behavioral problems. For instance, 6 of 8 (75%) assessed CS subjects aged 1–5 years were reported to have developmental delay (e.g., speech delay) requiring occupational, physical, and speech therapy, which potentially contributes to the difficulties in social functioning and therefore the yielded SRS-2 scores (Grange et al., 2019). Interestingly, CS cases in this age group revealed the highest percentage of individuals with a total SRS score in a clinically significant range (5 of 8, 62.5%), resulting from the mean T-score for 3 of 4 assessed treatment subscales falling in the mild range.

ASD-associated features were predominantly present in younger male CS cases in this cohort correlating with previous findings, which suggest that ASD is recognized four times more in males than females (Developmental Disabilities Monitoring Network Surveillance Year Principal et al., 2014).

Similarly, various psychiatric symptoms assessed by ASEBA questionnaires might show an age- and/or gender-related progression in this cohort. In particular, anxiety, ADHD, and depressive problems were observed in ≥17% of young individuals, whereas such symptoms seemed to lessen in older subjects. Interestingly, internalizing problems such as anxiety/depression and emotional reactiveness seemed to be predominantly present in male CS subjects prior to the age of 18 in our small sample, an aspect not reported before. However, sample sizes in these subgroups are very restricted and further research would be necessary to confirm the observed gender-specific differences in the assessed cohort.

The results obtained from all applied questionnaires, KBIT-2, SRS-2, and ASEBA, suggest a potential age-dependency of assessed cognitive and behavioral features, which may decrease over time. However, the investigation of syndrome-specific age-related changes can involve multiple aspects. The timing of diagnosis and therefore potential patient bias need to be taken into consideration. As the genetic cause underlying CS has only been discovered recently (Harakalova et al., 2012), the majority of adult patients have been diagnosed within the last few years potentially explaining mild behavioral problems. In contrast, patients diagnosed early in life (age Group 1 in this study) are likely to have more severe symptoms. Hence, longitudinal studies of the same patients will be necessary to further examine the possibility of varying behavioral, cognitive, and emotional phenotypes across the lifespan of CS subjects.

Lastly, the improvement in symptoms over age might be explained by therapy services and special education interventions applied by these younger CS subjects.

Interpreting whether mildly impaired social functioning and observed psychiatric symptoms, especially in young CS individuals, is directly caused by CS-associated *ABCC9* variants and resulting K_{ATP} channel dysfunction or is rather influenced by social stimuli and resulting psychological and emotional distress due to CS symptoms (e.g., congenital hypertrichosis or distinctive facial features) is not straightforward. So far, no connection between *ABCC9* and ASD-related phenotypes has been observed. In order to further investigate and pinpoint the reason for the observed symptoms in this cohort, more

specific questionnaires and/or psychological analyses should be applied in the future. In addition, the majority of CS individuals in this cohort who presented with ASD and other psychological features (<5 years of age) are most likely too young to have enough self-awareness to be able to recognize that they look different compared to other children of their age, therefore most likely not causing changes in social functioning.

Recently, we described a novel *ABCC9*-related Intellectual disability Myopathy syndrome (AIMS) resulting from loss-of-function (LoF) mutations in *ABCC9*, in which patients exhibit mild to moderate intellectual disability, low IQ, and anxiety (Smeland et al., 2019). Neuronal K_{ATP} channels predominantly consist of Kir6.2 and SUR1 subunits; nevertheless, transcripts for all K_{ATP} channel subunits have been observed in multiple neuronal tissues (Liss & Roeper, 2001) and SUR2 is reported to be expressed in central and peripheral neurons (Kawano et al., 2009; Nelson et al., 2015; Zoga et al., 2010). However, so far it is not obvious how K_{ATP} channel dysfunction could lead to cognitive impairment or anxiety.

The potential presence of additional causal, but CS-independent variants in this cohort resulting in neurodevelopmental disorders such as ADHD or ASD cannot be ruled out. Psychiatric disorders are highly heritable and can be influenced by many single-nucleotide polymorphisms (Brikell et al., 2015; Tick et al., 2016). Hence, the presence of such symptoms should also be examined in unaffected family members of affected CS cases. Moreover, nongenetic influences should be considered; for instance, it is known that parents of children with congenital disorders tend to overprotect children, which can interfere with their otherwise normal development.

An additional drawback of this study is the varying numbers of participating subjects per applied questionnaire. Only CS subjects from one study site were assessed with the KBIT-2, potentially resulting in a selection bias because these results may not adequately reflect the entire CS population. This is less likely for results based on SRS-2 and ASEBA questionnaires, filled in by a pool of all known Dutch and randomly selected US cases.

Nevertheless, the results of this study contribute to increased awareness regarding the presence of social and psychiatric difficulties in CS subjects. Knowledge of behavioral phenotypes can help others to understand how a person interacts with their environment and how to adapt to the environment to suit their needs. Psychiatric symptoms such as anxiety are treatable with appropriate intervention (psychological and/or psychopharmacological). Even though no treatment has been shown to cure ASD or ADHD, interventions may reduce symptoms, improve cognitive ability and daily living skills, and maximize the ability of the individual to function and participate in the community (Shier et al., 2013; Weitlauf et al., 2014). Currently, there are no targeted therapies for CS available. Therefore, clinical management involves symptomatic treatments to address secondary complications. However, considerable effort is being invested in the development of a pharmacological treatment for CS subjects, focusing on the reversibility of clinical features such as cardiovascular anomalies, hypertrichosis, and edema (Ma et al., 2019; McClenaghan et al., 2020). If successful, such a therapy might also contribute to a decrease in the described behavioral symptoms.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Research clinic activities were coordinated by Helen I. Roessler, Kathleen Shields, Kristin P. Guilliams, Dorothy K. Grange, and Mieke M. van Haelst. Helen I. Roessler and Mieke M. van Haelst designed the study and formulated the research question. Evaluation and analysis of questionnaires were performed by Helen I. Roessler and Kathleen Shields. Helen I. Roessler wrote the initial manuscript draft and Mieke M. van Haelst reviewed and revised the manuscript. Lieke M. van der Heuvel, Kristin P. Guilliams, Nine V.A.M. Knoers, Gijs van Haaften, and Dorothy K. Grange critically reviewed the manuscript. Gijs van Haaften and Dorothy K. Grange provided funding acquisition.

DATA AVAILABILITY STATEMENT

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

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