



Novel *CTNNB1* Gene Variants in Spanish *CTNNB1* Syndrome Patients: Clinical and Psychological Manifestations

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Abstract

CTNNB1 Syndrome is a neurodevelopmental disorder caused by de novo pathogenic variants characterized by global cognitive impairment, microcephaly, speech and motor delay, abnormal muscle tone, ophthalmologic impairments, behaviour problems and autistic spectrum disorder (ASD) symptoms. The aim of this study is to carry out a thorough clinical and psychological characterization of Spanish *CTNNB1* syndrome patients. We used standard clinical assessment instruments and an ad hoc questionnaire to measure motor functioning, neurodevelopmental milestones, sleep problems, daily life activities, behavioural problems, communication and speech impairments, eating disorders and autistic features in 25 participants with *CTNNB1* syndrome (15 females, 10 males; mean age 7.1 ± 4.1). Main clinical manifestations reported were microcephaly, motor impairment, sight problems, sleep disturbances and sensorial problems. Attainment of developmental milestones indicated motoric, language and daily living skills to be generally delayed. All participants had adaptative skills below their chronological age, even though verbal individuals had better functioning compared to nonverbal. Regarding behaviour impairments, *CTNNB1* syndrome patients scored significantly high at internalizing and externalizing behavioural problems. Additionally, about 60% presented symptoms of ASD. Our findings have important implications for the psychotherapeutic and clinical approaches of *CTNNB1* syndrome patients. We show the importance of early stimulation, given that an early attainment of developmental milestones is related to a current better function of many clinical variables. Moreover, previous underrated symptoms such as sleep problems, impaired adaptative skills and high rates of behavioural symptoms should be taken into consideration due to the harmful impact that have on every day life.

Keywords *CTNNB1* syndrome · Developmental delay · Motor impairments · Behavioural problems · Autism spectrum disorder · Rare disease

CTNNB1 syndrome is a neurodevelopment disorder caused by de novo heterozygous pathogenic variants in the *CTNNB1* gene (Kuechler et al., 2015). It is a rare disease due to its low prevalence, described for the first time by de Ligt et al. (2012) who postulated *CTNNB1* to be a novel

intellectual-disability gene that caused a variety of clinical manifestations, including general developmental delay, intellectual disability (ID), speech disorders, learning and memory disturbances, craniofacial anomalies and microcephaly, ophthalmic disorders, motor difficulties, behaviour problems

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and autistic spectrum disorder (ASD) symptoms (de Ligt et al., 2012; Dubruc et al., 2014; Kuechler et al., 2015; Tucci et al., 2014). *CTNNB1* encodes β -catenin, a protein essential in cell growth and development which regulates intercellular contacts and gene transcription (Shang et al., 2017; Xu & Kimelman, 2007). Germline *CTNNB1* mutations distribute along the entire *CTNNB1* gene, with a predominance of nonsense substitutions and small insertions and deletions that introduce premature termination codons in the *CTNNB1* coding sequence (Kayumi et al., 2022). This generates, in many cases, truncated β -catenin proteoforms expected to result into loss-of-function or altered functional properties.

Patients affected with CTNNB1 syndrome present a great phenotypic variety, whereby the main clinical manifestations are expressed with varying degrees of severity among individuals. The most common features are facial dysmorphism (98%), eye abnormalities (93%), muscle tone (92%), speech difficulties (89%), microcephaly (74%), walking inability (40%) and behavioural problems (Mirošević et al., 2022). Therefore, CTNNB1 syndrome affects essential developmental aspects such as global cognition, motor functioning, language acquisition and behavioural problems. However, only in few cases standardised methods have been used to assess these clinical phenotypes, which makes it difficult to compare results from different studies.

CTNNB1 syndrome is a recently described disease, diagnosed through genetic screening (Nagy et al., 2024), which shows resemblance with other pathologies such as autism (Dong et al., 2016) and cerebral palsy (Jin et al., 2020). Due to the lack of specific assessment protocols for CTNNB1 syndrome, the present study has based the design of the methodology on analogous diseases such as autism (Caputo et al., 2018; Pry et al., 2011), fragile X syndrome (Caravella & Roberts, 2017; Grefer et al., 2016; Hogan et al., 2017), Williams syndrome (Braga et al., 2018), FOXP1 disorder (Braden et al., 2021; Trelles et al., 2021) and cerebral palsy (Ballester-Palné et al., 2016; Romeo et al., 2014; Skjeldal et al., 2008; Weber et al., 2016).

Sudnawa and colleagues carried out a clinical characterization from caregiver-reports and in-person assessments from 32 individuals with CTNNB1 syndrome (Sudnawa et al., 2024). To our knowledge, this has been the only study up to date that has evaluated patients on the basis of an extensive protocol, using standardised and specific tests for the needs of CTNNB1 patients. Although this investigation provides advances in this field, deeper characterization of the clinical and psychological manifestations of these patients is a current necessity.

The aim of our study was to carry out an extensive and thorough assessment of clinical and psychological manifestations in Spanish patients with CTNNB1 syndrome. A specific assessment protocol has been designed to

study essential aspects of the neurodevelopment of CTNNB1 syndrome patients, including motor functioning, neurodevelopmental milestones, sleep problems, daily life activities, behavioural problems, communication and speech impairments, eating disorders and autistic features.

Method

Patients

A total of 25 Spanish CTNNB1 patients (15 females, 10 males; mean age 7.1 ± 4.1 ; age range 2.03–17.02; median: 6.08) participated in the study, even though most tests were answered by the parents. Participants were recruited through the CTNNB1 Spanish Association (Asociación CTNNB1 España) between November 2023 and April 2024. Clinical and genetic information was systematically collected after written informed consent.

The inclusion criteria were as follows: (a) to be the progenitor of a diagnosed child with CTNNB1 syndrome by a genetic test, (b) to have the informed consent prior to the participation, (c) to have Spanish as one of the primary languages and (d) to have the Spanish nationality. Study exclusion criteria were: (a) not to have a genetic diagnosis that indicates CTNNB1 syndrome and (b) to have other diagnosis not secondary to CTNNB1 syndrome.

All study procedures were in line with the Declaration of Helsinki, complying with all relevant ethical regulations and the protocol was approved by the Ethics Committee of the University of Deusto (ETK-24/23-24).

Instruments

Sociodemographic data and clinical information were collected through an ad hoc neurodevelopmental questionnaire. Tests adapted in Spanish were the following.

Sleep Problems

Sleep Disturbances Scale for Children (Pagerols et al., 2023). This scale provides an overall measure of sleep disturbances to be used in clinical screenings and research. Consists of 26 Likert-type items and is divided in 5 subdomains: disorders of initiating and maintaining sleep, sleep breathing disorders, disorders of arousal, sleep–Wake transition disorders, disorders of excessive somnolence and sleep hyperthyroidism. A score of 39 or higher indicates global sleep disorder and the tests has a Cronbach's alpha value of 0.71 (Pagerols et al., 2023).

Ability to Eat

Eating and Drinking Ability Classification System (EDACS) (Sellers et al., 2013). The purpose of this scale is to classify how individuals, originally for cerebral palsy patients, eat and drink in everyday life into a five levels scale. The focus is on the functional activities related to eating, therefore the distinctions between the different levels are based upon the ability to eat; from eating and drinking safely to unable to do so. The original instrument showed almost perfect interrater reliability (Tschrren et al., 2018).

Communication

Viking Speech Scale (VSS) (Lindsay et al., 2013). The aim of this scale is to classify children's speech production, specifically taking into consideration to what extent their speech is understandable. It has four level options; from not affected speech to not understandable speech. In this study, we have asked the parents to choose the most accurate level on the basis of their knowledge of the child. Test–retest reliability of the original version of the test was substantial to almost perfect for the health care professionals ($k > 0.68$) (Pennington et al., 2013).

Communication Function Classification System (CFCS) (Keith & Arellano, 2012). This test provides five levels to describe every day's communication performance, originally to assess individuals with cerebral palsy although it is currently being used for any disability. In this case, classification on the CFCS has been made by the parents, who are familiar with the ability of their child to establish a conversation in which the role of the sender and the receiver of information is being exchanged. The test–retest reliability of the original version was 0.82 (Hidecker et al., 2011).

Motor Function

Manual Ability Classification System for Children with Cerebral Palsy (MACS and mini-MACS) (Barrón, 2010; Barrón & Palomino, 2013). These tests describe how children usually use their hands to handle objects in their day to day life. MACS is the original form of the test and evaluates children from 4 to 18 years old, whether mini-MACS is an adaptation assessed to children from 1 to 4 years of age. Caregivers/Parents have to determine which of the five possible levels describes best the overall ability of their child to handle objects. The original version of the instrument has good validity and reliability; the intraclass correlation coefficient between therapist was 0.97 and between parents and therapist was 0.96 (Eliasson et al., 2006).

Gross Motor Function Measure 88 (GMFM88) (Ferre-Fernández et al., 2020). The GMFM88 is commonly

used in the evaluation of gross motor function in children with cerebral palsy and it consists of 5 dimensions: lying and rolling, sitting, crawling and kneeling, standing and walking, running and jumping. Scores range from 0 to 3 and a percentage of each subdomain is obtained, from which the final percentage is calculated. The instrument has a Cronbach's alpha value of 0.90 (Ferre-Fernández et al., 2020).

Neurodevelopment

Vineland Adaptive Behavior Scales-3 (Sparrow et al., 2016). The Vineland-3 is an individually administered measure of adaptive behaviour and everyday functioning of an individual with intellectual and developmental disabilities. The parent/caregiver form is a questionnaire-type instrument that is completed by the parent, on the basis of their knowledge of the child. It has five main domains; communication (COM), daily living skills (DLS), socialization (SOC), motor skills and maladaptive behaviour, each composed by subdomains. A raw score is obtained from each subdomain, from which a V-scale score is calculated considering the age of the examinee. Scores less than 70 are considered impaired (70–79 borderline; 80–89 below average; 90+ average). The test has a Cronbach's alpha value of 0.98 (Sparrow et al., 2016).

Autism

Form B of the Social Communication Questionnaire (SCQ) (Pereña & Santamaría, 2005). This test is a parent-report questionnaire that evaluates three principal aspects of ASD: social relating, communication and range of interests. The purpose is to identify if the child has compatible symptomatology with ASD. Consists of 40 yes or no items and a score higher than 15 indicates possible compatibility with ASD symptoms. The instrument has high reliability, with a reported alpha of 0.90 (Pereña & Santamaría, 2005).

Childhood Autism Rating Scale (CARS) (García-Villamizar, 1992). The aim of this behavioural rating test is to determine the presence and severity of ASD symptoms. There are 15 items, each with a possible score from 1 to 5, therefore total scores can range from 15 to 60. The Cronbach's Alpha coefficient of the instrument is 0.89 (García-Villamizar, 1992).

Procedure

Recruitment began by contacting the CTNNB1 Spanish Association, who shared the research with the families. After acceptance, a brief online meeting was conducted to explain the three parts of the research. The first part consisted of an online questionnaire that included self-administered

tests through the software *Qualtrics*. The following section was an online interview with an examiner to address the neurodevelopmental information and the tests that required an in-person administration. Finally, parents were requested to ask their child's physiotherapist to assess the GMFM88 with prior consent of the professional.

Data Analyses

The statistical program SPSS (Statistical Package for Social Sciences) version 28.0 was used to perform the analyses. To study the normal distribution of the sample, a Shapiro–Wilk analysis was made, indicating a non-normal distribution for most of the variables. However, because of the small sample size, non-parametric analyses were exclusively carried out. Descriptive statistics were performed for all measures and, to compare different variables, raw scores were converted into *Z* scores. Further analysis consisted of Mann–Whitney *U* test for group comparison, Spearman *Rho* for correlations between variables and, lastly, Wilcoxon *W* for intrasubject analyses. The level of significance was established at a *p* value of 0.05.

Results

Gene Variants Found in the Sample

Our series is composed of 25 patients with genetic alterations in the *CTNNT1* gene. All *CTNNT1* mutations were de novo mutations present in heterozygosis. Most of the alterations were small insertions or deletions causing frameshift, single-nucleotide substitutions causing nonsense mutations, and splicing mutations, distributed along the entire *CTNNT1* nucleotide sequence. To the best of our knowledge, we have identified 13 novel *CTNNT1* mutations: two nonsense mutations, eight small insertions or deletions causing frameshift, two splicing mutations, and one in-frame small deletion. In addition, some mutations from our series are recurrent in *CTNNT1* syndrome patients. No missense mutations were found (Table 1 and Fig. 1).

Clinical Findings

Clinical characteristics and neurodevelopment features of patients are summarized in Fig. 2 and Supplementary information 1.

Mean age of *CTNNT1* syndrome diagnosis was 4.2 ± 3.4 although it widely varied across participants; older cases were diagnosed later than younger ones. The most common medical finding was microcephaly (24/25; 96%), followed by motor impairments. Sight problems were also prevalent among cases (21/25; 84%), of which strabismus (16/25;

64%) farsightedness (10/25; 40%) and stigmatism (5/25; 20%) were present. Related to sensorial problems, loud noises sensitivity was commonly described (20/25; 80%), as also was scarce pain sensitivity (20/25; 80%). On the other hand, current or previous persistent sleep problems were also a noticeable issue (17/25; 68%), for which 11 took prescribed medication. Moreover, 16 participants scored above the cut-off point for sleep problems at the Sleep disturbances Scale for children (64%), with an overall mean score of 46.3 ± 14.9 . More specifically, disorders of initiating and maintaining sleep and sleep–wake transition were the most affected aspects [see Supplementary Information 1]. On another note, 16 parents reported some type of facial dysmorphisms (64%) and 15 had lower than normal weight or height currently or in the past (60%). Lastly, eating problems were present in 10 out of 25 individuals (40%), such as difficulties when swallowing or poor appetite. In the same line, individuals scored a mean score on the EDACS scale of 1.4 ± 0.8 out of five, indicating a general ability to eat and drink safely, except for a few cases [see Supplementary Information].

Pregnancy and New-Born Period

Information on pregnancy matters and new-born period was obtained from the ad hoc questionnaire, which was carried out by an interview with the caregivers and a revision of medical records (see Supplementary Information 1). Mothers' mean age of pregnancy was 34.2 ± 3.1 years old, while parents' mean age was 35.72 ± 4.44 , and 10 out of 25 experienced issues during their pregnancy (40%), being the most prevalent preeclampsic risk and fetal growth restriction. Both mean gestation period and mean new-born weight were within the average parameters and four participants required incubator. Regarding new-born activity, 13 out of 25 parents described their child to be less active (52%) and 10 out of 25 as crankier (40%). Moreover, feeding problems were also present during the new-born period, being the most prevalent stomach cramps (16/25; 64%), suction difficulties (14/25; 56%) and difficulty in gaining weight (10/25; 40%). Other relevant findings were the significant correlations between activity problems during the new-born period and the age at which participants started using two-words sentences ($Rho = 0.521$; $p = 0.047$), indicating more difficulties in achieving this speaking ability if activity problems were present at the first period of life.

Attainment of Developmental Milestones

Age range in which participants reached milestones was notably wide, however, it was delayed in most cases. Figure 3 shows a comparison between the normative mean age of achievement of the most significant milestones

Table 1 *CTNNB1* variants from our series

Case	Genetic alteration	Nucleotide change	Exon (Intron)	Amino acid change	Domain ^a	Relative frequency ^b	Database ^c
P1	Nonsense	c.1981C>T	13	p.(Arg661*)	Arm 12	2.34	HGMD,ClinVar
P2	del 3p22.1	–	–	–	–	–	–
P3	Nonsense	c.577C>T	5	p.(Gln193*)	Arm 2	0.26	HGMD
P4	Frameshift	c.1213delC	9	p.(Leu405Phefs*10)	Arm 7	–	–
P5	Frameshift	c.1923dupA	12	p.(Glu642Argfs*6)	Arm 12	0.78	HGMD,ClinVar
P6	Nonsense	c.881 T>A	6	p.(Leu294*)	Arm 4	–	–
P7	Nonsense	c.1420C>T	9	p.(Arg474*)	Arm 8	5.2	HGMD,ClinVar
P8	Frameshift	c.974_984del	7	p.(Val325Gluufs*23)	Arm 5	–	–
P9	Frameshift	c.1588insC	10	p.(Gln530Profs*42)	Arm 9	–	–
P10	Frameshift	c.1563delC	10	p.(Ala522Glnfs*15)	Arm 9	–	–
P11	Nonsense	c.999C>A	7	p.(Tyr333*)	Arm 5	6.77	HGMD,ClinVar
P12	Frameshift	c.964dupC	7	p.(Gln322Profs*31)	Arm 5	–	–
P13	Large deletion	c.(936+1_937-1)_([*] 1106_?)del	–	–	–	–	–
P14	Frameshift	c.137dupT	3	p.(Ser47Gluufs*3)	N-term	–	–
P15	Frameshift	c.1930delC	12	p.(Leu644Phefs*35)	Arm 12	0.26	HGMD
P16	Splicing	c.2137+2 T>C	(14)	–	C-term	–	–
P17	Splicing	c.1082-1G>C	(7)	–	Arm 6	–	HGMD,ClinVar
P18	In-frame deletion	c.1298_1306del	9	p.(Lys433_Lys435del)	Arm 7	–	–
P19	Nonsense	c.1014G>A	7	p.(Trp338*)	Arm 5	0.26	HGMD,ClinVar
P20	Frameshift	c.661delC	5	p.(Leu221Phefs*21)	Arm 2	–	–
P21	Frameshift	c.137dupT	3	p.(Ser47Gluufs*3)	N-term	–	–
P22	Frameshift	c.1925_1926del	12	p.(Glu642Valfs*5)	Arm 12	3.12	HGMD,ClinVar
P23	Nonsense	c.268C>T	4	p.(Arg90*)	N-term	2.6	HGMD,ClinVar
P24	Splicing	c.2076+1G>A	(13)	–	C-term	–	–
P25	Nonsense	c.904C>T	6	p.(Gln302*)	Arm 4	–	–

HGMD human gene mutation database

^aArm: armadillo repeat; N-term: N-terminal extension; C-term: C-terminal extension

^bRelative frequency of the variants in *CTNNB1* syndrome patients, according to the analysis of Kayumi et al. (2022), from 384 *CTNNB1* syndrome cases

^cHGMD, Human Gene Mutation Professional Database (Stenson et al., 2020); ClinVar, NCBI ClinVar database (Landrum et al., 2024). To the best of our knowledge, the variants of this report that are not indicated as annotated in the databases are novel variants, with the exception of P2 (del 3p.22.1). None of the listed variants is annotated in gnomAD database

during the firsts years of life compared to the mean age of the *CTNNB1* syndrome sample. Related to motor milestones, only four participants took their firsts steps prior to 18 months (16%), an additional 10 individuals took their first steps before or during their 36 months of age (56%), seven started walking between 36 and 60 months of age (84%), while the remaining four still could not walk independently, but it should be taken into account that case 11 and 19 had not yet reached 60 months of age. Moreover, the vast majority of cases were able to walk independently after a few months of taking their first steps but for two cases (case 2 and 23) that were only able to walk less than 10 steps on their own. On the other hand, language milestones were also delayed; three individuals

started babbling before or during their seven months of age (12%) and seven participants used their first word by 24 months of age (28%). At the time of evaluation, 15 individuals were able to speak with two-words sentences (60%), achieving this milestone at the mean age of 49.6 ± 27.2 months of age and 13 started using three-words sentences at 57.5 ± 29 months of age (52%). However, case 20 was still too young to have reached this last milestone. Furthermore, 10 out of 25 participants had bowel control (40%) achieved at the mean age of 6.3 ± 2.95 years old, even though two only during the day, whereas bladder control was already achieved by eight out of 25 participants (32%), at the mean age of 5.88 ± 3.23 years old. It is important to note that sphincter control ability indicated

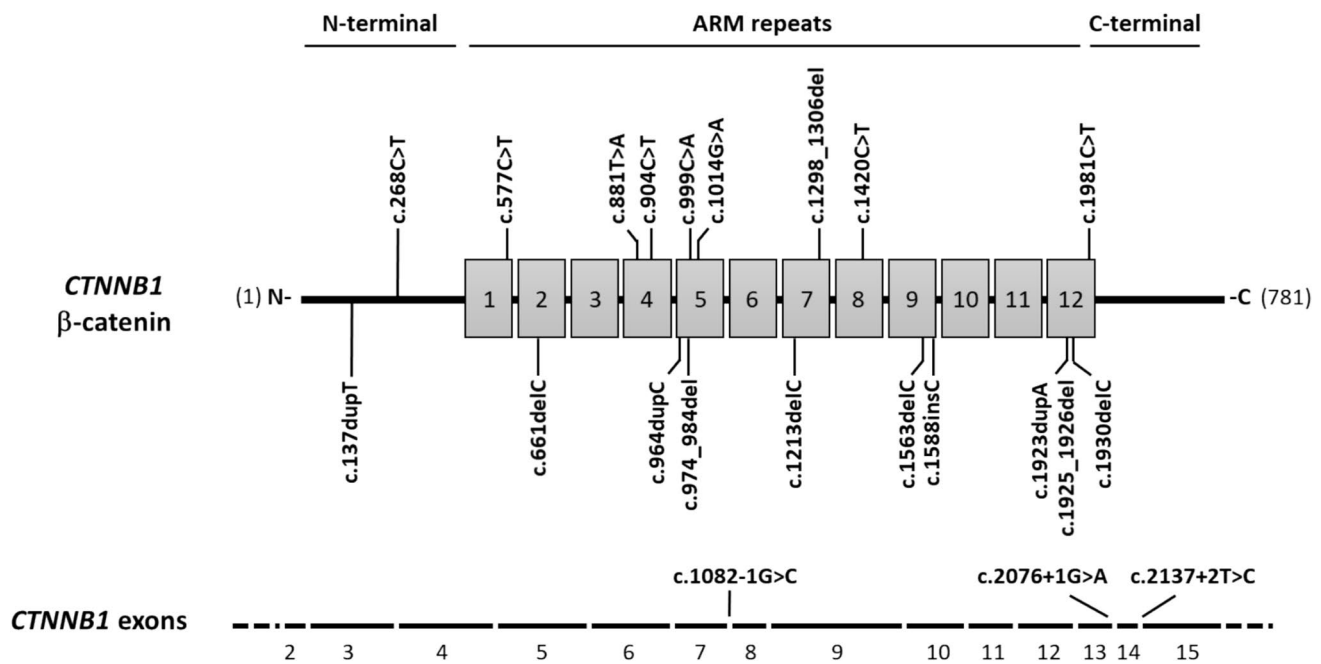
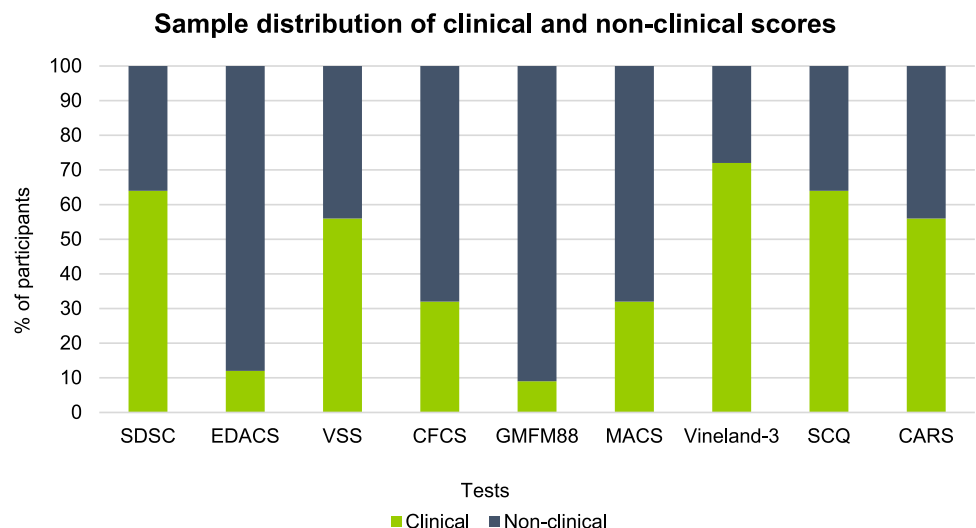


Fig. 1 Gene variants found in the CTNNB1 syndrome Spanish patients' series. Schematic depiction of the identity and distribution of CTNNB1 mutations from the patients analysed in this study. The upper depiction shows the domain organization of β-catenin protein (Xing et al., 2008). The grey boxes represent armadillo (ARM) repeats (amino acids 151–666), and the flexible N-terminal (amino acids 1–150) and C-terminal (amino acids 667–781) extensions are indicated. Mutations are indicated following the HGVS nucleotide

nomenclature. Single nucleotide substitutions generating premature termination codons, and one 9-nucleotide in-frame deletion are indicated on the top. Small nucleotide insertions or deletions causing frameshifts followed by premature termination codons are indicated in the bottom. The lower depiction shows the exon organization of CTNNB1 gene, with indication of the splicing mutations identified. See Table 1 for further details

Fig. 2 Summary of sample distribution of clinical and non-clinical scores of the tests used. Clinical cut-off scores for each test were the following: SDSC > 39; EDACS ≥ 3; VSS ≥ 3; CFCS ≥ 4; GMFM88 > 50%; MACS ≥ 3; Vineland-3 < 70; SCQ ≥ 15; CARS ≥ 30



better performance on some clinical variables related to motor and language abilities, eating efficacy, daily living skills and gross motor functioning (Table 2). Age also significantly correlated with bladder and bowel control ($Rho = 0.550$; $p = 0.004$), therefore indicating an achievement of this milestone over time.

Language Abilities

Individuals' score on the VSS and the CFCS were used to assess expressive and communication performance [see Supplementary Information 1]. Mean score on the VSS was 2.8 ± 1 , indicating imprecise speech but understandable

Fig. 3 Comparison of developmental milestones between normative data and CTNNB1 syndrome individuals. Normative mean age is from the Haizea-Llevant growth chart (Gobierno, 2005).

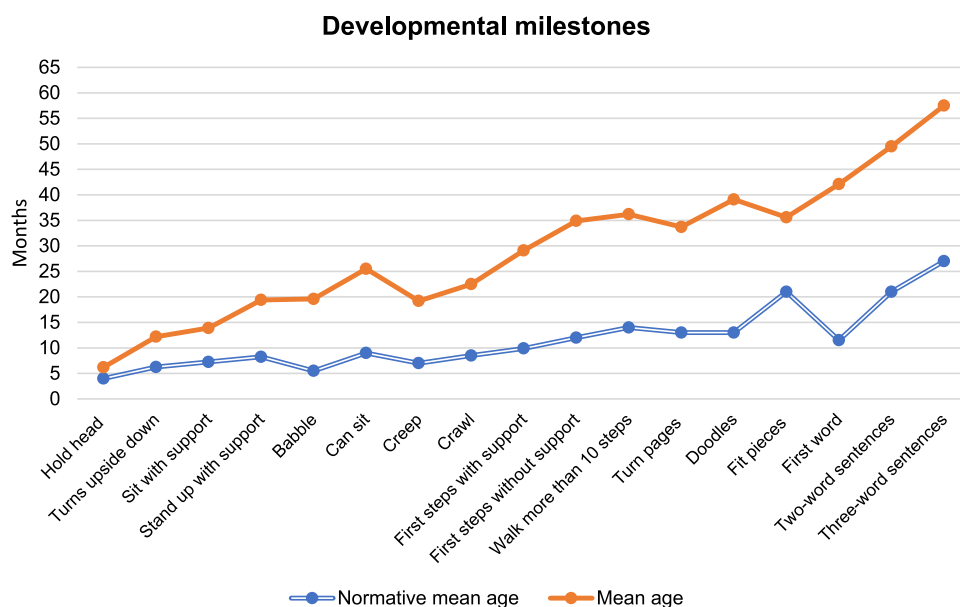


Table 2 Correlations sphincter control ability and clinical variables

	Bowel and bladder control	
	<i>Rho</i>	<i>p</i>
Receptive (V-III)	0.459	0.021
Written (V-III)	0.548	0.005
Personal (V-III)	0.806	0.001
Domestic (V-III)	0.605	0.001
Community (V-III)	0.470	0.018
Gross motor (V-III)	0.473	0.017
Fine motor (V-III)	0.578	0.002
MACS and mini-MACS	-0.447	0.025
EDACS	-0.445	0.026
Total score GMFM88	0.558	0.007

GMFV-III gross motor functioning measure 88, V-III vineland-III

by strangers, while CFCS mean score was 2.6 ± 1.3 and suggested that individuals could act as the sender and the receiver in a conversation, with familiar and unfamiliar partners but may need extra time. The main form of communication varied across participants; eight out of 25 expressed themselves verbally (32%), another eight participants with signs or pictograms (32%) and the remaining nine used both systems (36%). However, all but two cases reported articulation problems. Moreover, significant correlations were found between age of the first word and VSS ($Rho = 0.676$; $p = 0.001$) and the CFCS ($Rho = 0.457$; $p = 0.022$), indicating that the later they started talking there were more speech production and functional difficulties. Current age did not correlate with Receptive or Expressive Vineland-3 scores, which highlights the variability among cases regardless of the age, although it did correlate with the Written

Vineland-3 score ($Rho = 0.408$; $p = 0.043$). Another significant finding was the correlation between taking the first steps without support and the VSS ($Rho = 0.448$; $p = 0.041$), indicating a better language production if they started walking earlier in life.

Motor Impairments

The most prevalent motor symptoms were spasticity presented currently or in the past (22/25; 88%), mainly affecting the legs, and hypotonia at the current age or previously (23/25; 92%), specifically in the core. In this line of evidence, 17 out of 25 used Dynamic Ankle Foot Orthosis (DAFO) or support to walk (68%). Regarding fine motor skills, 22 out of 25 showed some difficulties performing tasks with the hands (88%), although mean score of the MACS and mini-MACS was 2.2 ± 0.6 , indicating a general ability to manipulate most objects, but with reduced quality or speed, whereas mean GMFM88 total score was 71.13 ± 15.84 and could only be assessed to 22 participants [see Supplementary Information 1]. Another relevant finding was the negative association between Gross Motor from the Vineland-3 with taking firsts steps with support ($Rho = -0.559$; $p = 0.005$) and without support ($Rho = -0.438$; $p = 0.047$), so that participants had current better performances at gross motor activities if they started walking early on. In the same lines, GMFM88 total score significantly correlated with taking first steps with support ($Rho = -0.462$; $p = 0.035$). Moreover, walking more than 10 steps independently significantly correlated with total score from the Sleep Disturbance Scale ($Rho = -0.498$; $p = 0.030$), indicating more sleep problems if the person started walking at an early stage.

Adaptive Functioning

The Vineland-3 scores indicated that no participants had an Adaptive Behaviour Composite (ABC) in the average range, even though there was wide variety among results (minimum score of 40 and maximum 88) [see Supplementary Information 1]. Mean subscale scores were the lowest for DLS, followed by SOC and COM. Moreover, age significantly correlated with all subdomains from DLS, specifically Personal ($Rho = 0.594$; $p = 0.002$), Domestic ($Rho = 0.450$; $p = 0.024$) and Community ($Rho = 0.428$; $p = 0.033$), as well as Fine Motor skills ($Rho = 0.479$; $p = 0.016$) from the Vineland-3, therefore indicating an improvement over time. Another relevant finding was the negative association between total score of the Vineland-3 and age of first word ($Rho = -0.631$; $p = 0.001$), so that participants had more adaptive and functional skills if they started talking early on. Moreover, GMF88 total score significantly correlated with Personal ($Rho = 0.498$; $p = 0.018$), Domestic ($Rho = 0.529$; $p = 0.011$), Gross Motor ($Rho = 0.829$; $p < 0.001$), Fine Motor ($Rho = 0.437$; $p = 0.042$) and Section B from the Vineland-3.

Related to behaviour, participants mean score for the Section A (19.16 ± 2.01) and Section B (19.2 ± 1.53) of the Vineland-3 were considered significantly above the average score, indicating presence of internalizing and externalizing problems respectively among the sample. Also, Section C allows for the detection of severe maladaptive behaviours, for which mean score was 9.3 ± 3.8 . Sections A and C positively correlated with the CARS score ($Rho = 0.548$; $p = 0.005$; $Rho = 0.398$; $p = 0.049$), but only Section A with the SCQ ($Rho = 0.500$; $p = 0.011$). Additionally, Sleep Disturbance Scale positively correlated with Section A ($Rho = 0.620$; $p < 0.001$) and Section C ($Rho = 0.431$; $p = 0.032$). On the other hand, Section B was negatively associated with VSS ($Rho = -0.411$; $p = 0.041$) and CFCS ($Rho = -0.451$; $p = 0.024$).

ASD Symptoms Measurement

Scores on the SCQ exceeded the autism cut offs for 16 participants (64%), whereas 14 (56%) scored above the autism cut-off point at the CARS [see Supplementary Information 1]. Out of these, 10 individuals obtained scores that indicated mild to moderate autism and the remaining four scored within the most severe autism range. Regarding subscales from the SCQ, the most prevalent symptoms were related to social relating problems, followed by communication difficulties and restricted range of interest, whereas the highest item scored at the CARS indicated resistance to routine change. More specifically, 73.3% of the female patients scored above the cut-off point for the SCQ and 53.3% also exceeded the cut-off score for the CARS. Total scores from the SCQ and the CARS

correlated moderately ($Rho = 0.69$; $p < 0.001$). There were significant differences between participants who scored above the cut-off point at SCQ in the Receptive Vineland-3 score (8.38 ± 4.22) and those without ASD symptoms (11.89 ± 1.69) ($U = 37.5$; $p = 0.049$), as well as in internalizing behaviours between participants with ASD symptoms (8.94 ± 3.55) and no ASD symptoms (6.0 ± 3.46) ($U = 110$; $p = 0.32$). In contrast, no differences were found in any of the motor functioning variables. Age at which participants achieved first word significantly correlated with the subdomain Social relating from the SCQ ($Rho = 0.411$; $p = 0.041$) and with Interpersonal relationship Vineland-3 score ($Rho = -0.491$; $p = 0.013$) which meant that participants with later expressive language abilities acquisition had more problems related to social interaction and interpersonal relationships. In agreement to this, a higher score at SCQ significantly correlated with a delay in starting to babble ($Rho = 0.502$; $p = 0.011$).

Expressive Language Analyses

For descriptive purposes, the sample was divided into two groups depending on their expressive language abilities; “Verbal” individuals were able to at least speak with two-words sentences, whereas “Minimally verbal” could only say single words or were non-verbal. To control possible age interferences, a Mann–Whitney U was carried out ($U = 64.5$; $p = 0.567$), which indicated no significant age differences among the two groups. To go into more depth on possible differences between expressive and receptive language abilities, we explored possible intra-subject differences between both subdomains of the Vineland-3 ($W = 115.5$; $p = 0.206$). Expressive and Receptive V-scale score are presented in Fig. 4 for each individual. Even though no differences were found between the Expressive and the Receptive subdomains among individuals, when the same analysis was done exclusively to the “Minimally verbal” cases, significant differences were found ($W = 0$; $p = 0.008$), showing better performance at the comprehensive language ability (7.1 ± 3.69) compared to the expressive (2.6 ± 2.46). In the same line, “Minimally verbal” individuals scored significantly higher in subdomains from the SCQ, specifically suggesting more difficulties in social relating and Communication difficulties. These types of analyses are based on those previously carried out by Burdeus-Olavarrieta et al. (2021).

Discussion

This study provides an in-depth characterization of the neurodevelopment, clinical and psychological profile of 25 Spanish patients diagnosed with CTNNB1 syndrome. The analytic approaches implemented in this article provide new insights into the clinical features of this

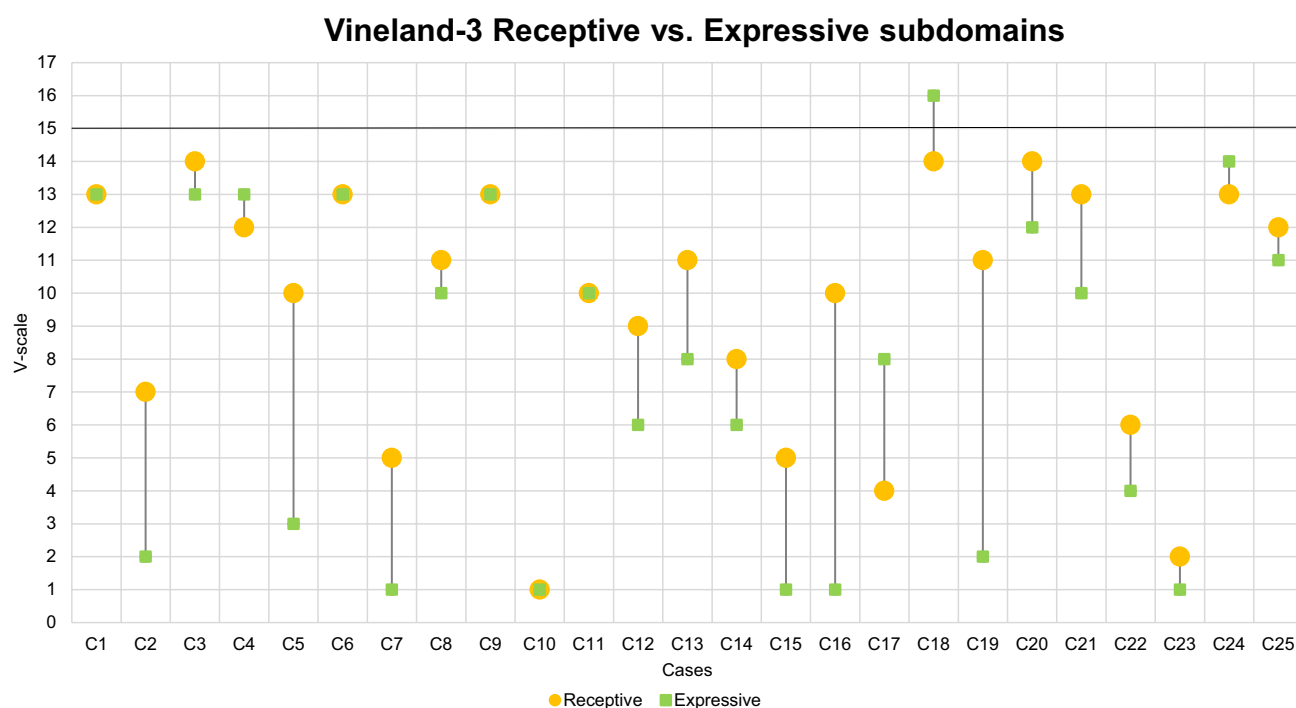


Fig. 4 Comparison of receptive and expressive scores from the Vineland-3. Scores of receptive and expressive subdomains from the Vineland-3 for each participant. V-Scale scores range from 1 to 24, being 15 the average score for that specific age group

syndrome, whose symptoms can overlap with other neurodevelopmental diseases. Findings from this study are consistent with previous reports, even though frequencies varied when compared to the most recent published articles; microcephaly and sensorial problems were higher than in most articles; motor impairment or delay, weight or height measurements and sight problems, specifically strabismus, displayed similar frequencies; whereas facial dysmorphism frequency was lower (Kayumi et al., 2022; Onesimo et al., 2023; Sinibaldi et al., 2023; Sudnawa et al., 2024; Yan et al., 2022). However, sensorial problems had not been reported as frequent as in this study (Sudnawa et al., 2024; Yan et al., 2022). Sleep problems were consistent with findings from Sudnawa and colleagues (2024), even though in our results the most prevalent sleep symptomatology was related to initiating and maintaining sleep. Eating and drinking ability was generally preserved, even though difficulties when swallowing or poor appetite were present. These results are in line with those from Onesimo et al. (2023), who concluded that CTNNB1 syndrome patients may have to deal with feeding challenges but, in most cases, would not compromise everyday life in a severe manner. Another significant finding from our study was sphincter control, which correlated with many clinical variables, indicating better performance if this milestone was achieved. While this finding was not previously described in CTNNB1 syndrome,

in other development diseases sphincter control has been found to be the strongest predictor of motor, cognitive, language and adaptive skills (Locatelli et al., 2021). The remaining correlations of clinical manifestations were not significant.

The age of the parents at conception was within the normal age range, although it is known that frequency of de novo mutations increases steadily with age of the father at conception (Goldman et al., 2019). The main pregnancy issues were related to fetal growth restriction and preeclamptic risk, whereas during the new-born period, activity and feeding problems were highlighted in accordance with previous studies (Kuechler et al., 2015; Onesimo et al., 2023; Verhoeven et al., 2020). The CTNNB1 mutations identified in our group of patients incorporate 13 novel CTNNB1 mutations, and include large and small deletions, small insertions, and nonsense and splicing mutations. As it has been reported for other CTNNB1 syndrome patient cohorts, missense mutations were not present in our cohort, highlighting the predominance in CTNNB1 syndrome of CTNNB1 variants generating unstable CTNNB1 mRNAs or truncated β -catenin proteins.

Attainment of developmental milestones indicated motoric, language and daily living skills to be generally delayed. The age range in which milestones were reached widely varied across patients, although in most cases

milestones were reached at mid childhood. This delayed pattern, also common in other neurodevelopmental disorders, should be taken into consideration since children may spontaneously develop a new skill, even when it is no longer expected (Thurm et al., 2016). Related to this, a repeated finding throughout the study was the fact that age did not positively correlate with almost any clinical manifestation, but age at which that milestone was reached correlated with current performance on that subject. Therefore, this finding suggests that patients who reach milestones within a normal age range are more likely to have current better performances compared to those who start later in life, even though correlations confirming that were moderate.

Language and communication varied widely across participants; 32% could express themselves verbally, 32% were non-verbal and used signs or pictograms and 36% used both systems. Thus, unlike other diseases, CTNNB1 syndrome individuals may not develop language abilities (Trelles et al., 2021) since, in addition, current age did not correlate with receptive or expressive abilities, although longitudinal studies would be needed to verify this hypothesis. Nevertheless, language delay and articulation problems were present in the vast majority of cases, a consistent finding according to the literature (Bulot et al., 2022; Dashti et al., 2022; Kharbanda et al., 2017; Panagiotou et al., 2017; Paparella et al., 2022; Rossetti et al., 2020; Sinibaldi et al., 2023; Spagnoli et al., 2022; Tucci et al., 2014; Yan et al., 2022). Contrary to previous studies, we did not find statistically significant differences between expressive and receptive language abilities (Mirošević et al., 2022). This consistent finding in the literature could be biased by the fact that many CTNNB1 syndrome patients are non-verbal, but still comprehend and follow instructions. In fact, there are significative differences between expressive and receptive language when intrasubject analysis was exclusively done for the non-verbal sample, but these differences are not significant when the verbal participants are considered. Therefore, it may be wrongly assumed that comprehension is more preserved than expression, although this assumption could be true for non-verbal CTNNB1 syndrome individuals. However, due to the small sample size and lack of onsite assessment it is not possible to obtain a clear conclusion. Additionally, analyses were carried out on the basis of expressive language ability, showing that non-verbal participants had more problems related to interpersonal relationships and communication. On the other hand, results showed that a better level at language production was associated to reaching motor milestones earlier in life, which is consistent with the established idea that language and motor skills are closely interrelated developmental areas, even for children with language impairments (Iverson & Braddock, 2010; Wang et al., 2014).

Related to motor difficulties, most individuals presented spasticity in the legs and hypotonic core, so that 68% needed support to walk, as reflected in literature (Dashti et al., 2022; Ji et al., 2023; Jin et al., 2020; Lee et al., 2022; Onesimo et al., 2023; Pipo-Deveza et al., 2018; Tucci et al., 2014; Verhoeven et al., 2020; Winczewska-Wiktor et al., 2016). Both fine and gross motor skills were impaired, even though Fine Motor score mean was higher than Gross Motor score from the Vineland-3, which goes in line with other studies that have suggested gross motor skills to be more affected than fine motor (Dubruc et al., 2014; Lee et al., 2023; Sudnawa et al., 2024). GMFM88 scores were similar to Pipo-Deveza et al. (2018), but higher compared to Sudnawa et al. (2024). Moreover, GMFM88 did not correlate with age, which is contradictory to previous findings (Sudnawa et al., 2024). In contrast, fine motor skills assessed with the MACS results indicated worst performance compared to Sudnawa et al. (2024), but better performance compared to a case study by Takezawa et al. (2018). Therefore, results reported so far are not consistent and require a more in-depth study of motor impairments with larger samples. Moreover, higher scores on the GMFM88 indicated better performances at many adaptive functions from the Vineland-3, and also with more externalising problems. This last finding was previously reported by Rodriguez et al. (2019) who stated that children with motor coordination difficulties showed more often emotional and behavioural problems.

The Vineland-3 indicated that no participants functioned according to their chronological age, as in previous studies (Sudnawa et al., 2024; Verhoeven et al., 2020). As observed as individuals with ID and other neurodevelopmental diseases, despite the generalised difficulties with communication, our participants obtained the highest mean score in such domain (Burdeus-Olavarrieta et al., 2021). Additionally, verbal individuals had better performances at most areas of the Vineland-3, in exception of those domains that did not demand expressive language. Age positively correlated with all subscales from the DLS, as well as Fine Motor skills from the Vineland-3, indicating an improvement over time. Regarding behavioural problems, maladaptive behaviours scale from the Vineland-3 indicated high presence of externalising and internalizing problems, scoring above normal range at both sections. Sudnawa et al. (2024) reported internalizing problems to be more frequent than externalizing, contrary to what descriptive studies have reported (Ho et al., 2022; Mirošević et al., 2022). Additionally, there was also presence of more severe symptomatology, indicated by Section C of the Vineland-3. On the other hand, presence of maladaptive behaviours was also associated with sleep disturbances of the CTNNB1 syndrome sample, supported by the evidence that sleep problems and behavioural problems are associated in school

aged children (Bayes & Bullock, 2019). Moreover, the association between externalizing problems and language impairment has been widely reported by the literature. One of the most accepted theories is The Social Adaptation Model (Redmon & Rice, 1998), which implies that behaviour problems of language-impaired children reflect social adaptation to their language limitation (Maggio et al., 2014). Therefore, this finding brings into consideration the need to develop interventions not only for communicative purposes, but also to improve self-regulation.

Based on previous reports, ASD symptomatology was assessed. The majority of individuals scored above the cut-off point on both screening instruments of ASD. These results show higher frequencies of ASD symptoms compared to previous ones (Kayumi et al., 2022; Sudnawa et al., 2024; Yan et al., 2022). Most prevalent symptoms were related with reciprocal social interactions, followed by language and communication difficulties and restricted, repetitive and stereotyped behaviours and interests, as well as active resistance to changes in routine with anger or sadness response. Further comparative analyses were carried out on the basis of scoring above the cut-off point at the SCQ. Results showed that those patients with ASD symptoms had worst receptive skills and more internalizing behaviours, suggesting a more severe phenotype. However, even though autism-like behaviour has been reported as a common clinical manifestation and the *CTNNB1* gene had been previously reported as an ASD-associated gene (Zhuang et al., 2023), there is the need for larger descriptive and longitudinal analysis to evaluate the impact of ASD on daily functioning. Another significant finding was the high prevalence of autistic features in female patients, in contrast with the higher proportion of diagnosed male patients with ASD (Werling & Geschwind, 2013). Therefore, future investigations should compare CTNNB1 syndrome patients with matched age, sex and IQ idiopathic ASD patients and establish clinical and cognitive differences.

Regarding the limitations of the study, the first to be highlighted is the small sample size, which affects the data's statistical power and generalization of results. However, this study counts with one of the largest samples to date and it is the first to assess a wide cohort of Spanish CTNNB1 syndrome patients. Similarly, the distribution of gender across the sample is not equal since the number of women is higher. Moreover, the severity of symptoms and age range widely vary across the sample, which makes it difficult to draw a clear phenotypic profile. Future investigations with larger samples should carry out cluster analysis taking into consideration the genotype of participants, which could lead to genotype–phenotype correlations. On the other hand, data collection was obtained exclusively by the parents, so future investigations should include in-person assessments to the CTNNB1 syndrome individuals and focus on cognitive

functioning. In the same line, the instruments used are general for neurodevelopmental diseases and could leave aside relevant information specific to CTNNB1 syndrome, besides the fact that caregiver reports could be biased by the parent's subjective judgment. Additionally, the impact of therapies on current symptomatology has not been considered as it is a cross-sectional study, therefore future investigations should follow a longitudinal design to see the progression of the syndrome and use a unified protocol to compare results.

Conclusion

The current study adds to previous literature by conducting an in-depth analysis of clinical manifestations related to CTNNB1 syndrome, which typically includes speech and motor milestones acquisition delay, microcephaly, abnormal muscle tone, sight problems, various degrees of intellectual disability and previously underrated behavioural symptoms. Specifically, sleep problems, impaired adaptive skills, maladaptive behaviours and ASD symptoms can be sometimes overlooked by more noticeable problems such as motor or visual symptomatology, but have a major impact on the quality of life of the child and the caregiver. Also, given the relationship between early onset of motor and language milestones and the current level of performance, it is crucial that the CTNNB1 syndrome affected child benefits from early care therapies to stimulate the development of motor and language variables, even when the child is far outside of the normative chronological window for that milestones. Additionally, although CTNNB1 syndrome is characterised by specific and consistent clinical manifestations, the severity of these varies widely among individuals. This is consistent with analogous neurodevelopmental disorders such as autism or cerebral palsy. Future directions for research should include longitudinal data and use of specific measurement tools for in-person assessments to draw a clear picture of the phenotypic profile of CTNNB1 syndrome. Thus, these findings will help designing appropriate individualised psychotherapeutic approaches or pharmacological treatments.

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Author Contributions MPS drafted the manuscript, carried out the assessments, the data extraction and statistical analysis. IA participated

in the conceptualization and design of the study and revised the final manuscript. RP and CENX carried out the interpretation of the genetic variants and revised the final manuscript. SB and FC revised the manuscript for critically important intellectual content. MG participated in drafting the manuscript, carried out assessments and statistical analysis.

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Data Availability Dataset is available from the corresponding author on reasonable request and subsequent ethics review.

Declarations

Competing Interests The authors declare that they have no competing interests.

Ethical Approval Parents of all participants in this study provided informed consent prior to study participation. The protocol was approved by the Ethics Committee of the University of Deusto (ETK-24/23-24).

Consent for Publication Consent for publication was also obtained from all parents prior to the assessments.

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