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Cognitive and Adaptive Functioning of CTNNB1 Syndrome Patients: A Comparison With Autism Spectrum Disorder and Cerebral Palsy

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Keywords: adaptive functioning | autism spectrum disorder | cerebral palsy | CTNNB1 syndrome | neuropsychological profile

ABSTRACT

Background: The CTNNB1 syndrome is a neurodevelopmental disorder considered an ultra-rare disease, first discovered in 2012. Given its comorbidity of symptoms with more prevalent diseases, such as ASD or CP, many CTNNB1 syndrome patients had previously received those diagnosis. Therefore, the aim of this study is to establish differences on the cognitive and adaptive functioning of the CTNNB1 syndrome compared with ASD and CP.

Methods: A total of 55 paediatric patients—25 CTNNB1 syndrome, 17 ASD and 13 PC—were assessed with an extensive protocol for neuropsychological domains through in-person assessments and online meetings for the parent-reported questionnaire.

Results: No cognitive differences were found among verbal tasks between groups, even though CTNNB1 syndrome patients obtained significantly lower scores in visuospatial and logical tasks. Regarding adaptive functioning, ASD patients outperformed the CTNNB1 syndrome group in most domains, whereas CP patients did not differ as much, obtaining only lower scores in gross motor ability. Externalizing problems were more prevalent in the CTNNB1 syndrome group compared with the control groups. Also, correlations indicated improvement of cognitive and adaptive functioning over the years for the CTNNB1 syndrome patients.

Conclusions: This is the first study to compare the cognitive and adaptive functioning of CTNNB1 syndrome patients with control diseases and detect significant difference. Although intellectual disability is one of the main manifestations of the CTNNB1 syndrome, patients performed better on verbal cognitive tasks than in visuospatial and logical thinking exercises, while adaptive functioning performances did not differ from control groups.

1 | Introduction

The CTNNB1 syndrome was first discovered in 2012 by de Ligt et al. (2012) and later described to be a neurodevelopmental disorder caused by de novo heterozygous variants in the *CTNNB1* gene (Kuechler et al. 2015). The most frequent clinical manifestations are intellectual disability (ID), speech disorders, craniofacial anomalies and microcephaly, ophthalmic disorders, motor difficulties, behaviour problems and autistic spectrum disorder (ASD) symptoms (Dubruc et al. 2014; Miroševič et al. 2022; Sudnawa et al. 2024; Tucci et al. 2014). However, the CTNNB1 syndrome phenotype is still not well defined as the main focus on the scarce literature has typically been genetic matters and description of symptoms, leaving behind the study of the cognitive and psychological profile (Pallarès-Sastre et al. 2025).

From a genetic perspective, the *CTNNB1* gene is responsible for encoding the β-catenin protein, from exon two to 15. This protein is a key factor for the development of the nervous system, mainly for two reasons; it is central to the Wnt/β-catenin signalling pathway and it is involved in the morphogenesis of epithelial and nervous tissue, in particular as part of the adherens junctions between cells (Valenta et al. 2012). Cell–cell junctions have a decisive influence on the mechanical properties of tissues and are also essential for neuronal synapses and synaptic plasticity, the basis of memory and learning. Therefore, β-catenin would be essential for memory consolidation in the hippocampus (Fortress et al. 2013). Several studies have demonstrated the role of this protein in the emotional learning process and declarative memory (Maguschak and Ressler 2012). Additionally, it has been implicated in visuospatial memory, which is encoded but not consolidated or stored (Tabatadze et al. 2012), indicating a possible deficit in the hippocampus due to non-optimal levels of β-catenin (Tucci et al. 2014). However, these deficits have not yet been observed in CTNNB1 syndrome patients.

Some CTNNB1 syndrome patients had initially received a diagnosis of cerebral palsy (CP) or ASD (Dixon et al. 2016; Ji et al. 2023; Kayumi et al. 2022; Kharbanda et al. 2017; Kuechler et al. 2015; Lee et al. 2023; Lesnyak et al. 2024; Onesimo et al. 2023; Rossetti et al. 2020; Sudnawa et al. 2024; Yan et al. 2022; Zuluaga et al. 2022), as they share many clinical manifestations with CTNNB1 syndrome. Whole-exome sequencing (WES) has been used as a method of gene discovery in large series of patients with ASD and CP, among others, and it has identified many novel and ultra-rare diseases which are underrepresented in clinical genomic research (Kayumi et al. 2022; Lee et al. 2023; Retterer et al. 2016). Current studies indicate that one-quarter of CP is caused by a genetic variant (Chopra et al. 2022), and clinical genomic investigations are still being overlooked by attributing symptoms to prenatal o perinatal brain injury. More specifically, genetic testing is particularly recommended in those CP patients that show ASD symptoms and ID with no apparent causative factor related to CP (Basu et al. 2024; Miroševič et al. 2022). Moreover, these advanced technologies have allowed the discovery of de novo mutations in ASD cohorts (Krupp et al. 2017). More specifically, Dong et al. (2016) showed that loss-of-function of *CTNNB1* gene in mice led to behaviours similar to autism such as impaired object recognition, social interaction and repetitive behaviours. These findings have led to the identification of the the *CTNNB1* gene as a risk gene for autism (Zhuang et al. 2023). In fact, some CTNNB1 syndrome patients obtain scores that indicate autistic-like behaviours in screening scales for autism (Sudnawa et al. 2024; Verhoeven et al. 2020).

To date, only Sudnawa et al. (2024) have conducted extensive in-person neuropsychological assessments to study the cognitive profile of CTNNB1 syndrome patients. Other studies provide only overall total scores without detailing performance in specific cognitive domains (Dashti et al. 2022; Lee et al. 2023; Verhoeven et al. 2020; Wang et al. 2019), while some do not specify the instruments used for assessment (Bulot et al. 2022; Ho et al. 2022; Lee et al. 2022; Paparella et al. 2022; Pipo-Deveza et al. 2018; Tucci et al. 2014).

Considering the scarcity of literature in the research of the CTNNB1 syndrome, this article aims to compare the cognitive and adaptive functioning of CTNNB1 syndrome to similar diseases, such as ASD and CP patients. Specifically, verbal, nonverbal and visuospatial domains will be assessed, as well as communication ability, daily living skills, socialization, motor functioning and behavioural problems.

2 | Methods

2.1 | Participants and Procedure

The sample consisted of 55 paediatric patients divided into three groups: a CTNNB1 syndrome group ($n=25$; $M_{age}=10.59$; $SD_{age}=4.25$; age range = 2.04–17 years), an ASD group ($n=17$, $M_{age}=8.71$; $SD_{age}=3.65$; age range = 4.05–17.01 years) and a CP group ($n=13$; $M_{age}=7.26$; $SD_{age}=4.09$; age range = 3.06–15.1 years).

The CTNNB1 syndrome group was recruited from the CTNNB1 Spanish Association (Asociación CTNNB1 España) between November 2023 and June 2024. All patients had undergone genetic testing that confirmed the diagnosis and were able to participate in in-person assessments, which were carried out by neuropsychologist who travelled across the country during family meetings. Cognitive assessments were not available for one participant. Genetic variants are included in Table 1. The inclusion criteria were as follows: (a) to have a genetic diagnosis of CTNNB1 syndrome, (b) to have signed the informed consents prior to participation and (c) to have Spanish as one of the primary languages.

Participants in the clinical control groups were recruited through APNABI Autismo Bizkaia for the ASD group and Aspace Bizkaia for the CP group. The study was presented to the associations and, after they agreed to participate, they recruited the sample matching the age and gender of the CTNNB1 syndrome participants. Before the recruitment, both associations were instructed to include only eligible participants with a ruled-out genetic mutation in their diagnoses or, in case of CP participants, those with a known cause of their clinical symptoms. Both groups were selected based on the inclusion criteria mentioned earlier, except for point (a), being replaced by a diagnosis of ASD or CP respectively. The specific causes of CP included in the sample were the following: ischaemic hypoxia ($n=1$), perinatal asphyxia ($n=1$), cytomegalovirus encephalopathy ($n=1$), prematurity ($n=2$), intrapartum anoxia ($n=1$), hypoxic–ischemic encephalopathy ($n=5$), spastic tetraparesis

TABLE 1 | Genetic variants from the CTNNB1 syndrome group.

Case	Genetic alteration	Nucleotide change	Exon (Intron)	Amino acid change	Domain
P1	Nonsense	c.1981C > T	13	p.(Arg661*)	Arm 12
P2	del 3p22.1	—	—	—	—
P3	Nonsense	c.577C > T	5	p.(Gln193*)	Arm 2
P4	Frameshift	c.1213delC	9	p.(Leu405Phefs*10)	Arm 7
P5	Frameshift	c.1923dupA	12	p.(Glu642Argfs*6)	Arm 12
P6	Nonsense	c.881 T > A	6	p.(Leu294*)	Arm 4
P7	Nonsense	c.1420C > T	9	p.(Arg474*)	Arm 8
P8	Frameshift	c.974_984del	7	p. (Val325Glufs*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
P12	Frameshift	c.964dupC	7	p.(Gln322Profs*31)	Arm 5
P13	Large deletion	c.(936 + 1_937–1)_(*1106_?)del	7–15	—	—
P14	Frameshift	c.137dupT	3	p.(Ser47Glufs*3)	N-term
P15	Frameshift	c.1930delC	12	p.(Leu644Phefs*35)	Arm 12
P16	Splicing	c.2137 + 2 T > C	(14)	—	C-term
P17	Splicing	c.1082-1G > C	(7)	—	Arm 6
P18	In-frame deletion	c.1298_1306del	9	p.(Lys433_Lys435del)	Arm 7
P19	Nonsense	c.1014G > A	7	p.(Trp338*)	Arm 5
P20	Frameshift	c.661delC	5	p.(Leu221Phefs*21)	Arm 2
P21	Frameshift	c.137dupT	3	p.(Ser47Glufs*3)	N-term
P22	Frameshift	c.1925_1926del	12	p.(Glu642Valfs*5)	Arm 12
P23	Nonsense	c.268C > T	4	p.(Arg90*)	N-term
P24	Splicing	c.2076 + 1G > A	(13)	—	C-term
P25	Nonsense	c.904C > T	6	p.(Gln302*)	Arm 4

($n = 1$) and cerebral infraction ($n = 1$). There was no specific genetic or developmental diagnosis associated with the clinical profiles of participants in the ASD group.

All in-person cognitive assessments were divided in two parts of half an hour each to guarantee the patient's attention during their performance. The parent-reported questionnaire was administered via an online meeting with the neuropsychologist.

2.2 | Instruments

2.2.1 | Peabody Picture Vocabulary Test, Third Edition (PPVT-3) (Dunn et al. 2010)

This test assesses receptive language ability and is a screening tool for verbal skills. Each item contains four simple black-and-white illustrations, and the examinee must select the picture that best matches the word said by the examiner. The test consists of 17 sets of 12 items arranged in order of increasing difficulty. Its reliability ranges from 0.80 and 0.99.

2.2.2 | Wechsler Nonverbal Scale of Ability (WNV) (Wechsler and Naglieri 2011)

This test is a non-verbal measure that assesses the cognitive development of children with language impairment, autism or hearing problems. Although it includes six subtests, only the following were assessed in this study. First, the Matrices subtest assesses perceptual reasoning through simultaneous processes ($\alpha = 0.85$). Moreover, Object assembly subtest measures perceptual organization and reasoning ($\alpha = 0.75$). Finally, the Recognition subtest assesses immediate memory without the need of expressive language ($\alpha = 0.73$). Both Matrices and Recognition tests conclude once the examinee scores four consecutive zeros, whereas the Recognition test ends after two consecutive zeros.

2.2.3 | Comprehension of Instructions (CI) From the NEPSY-II (Korkman et al. 2007)

This subtest assesses the ability to receive, process and execute oral instructions of increasing syntactic complexity. After the oral instruction, the examinee must point to the appropriate stimulus. Even though the subtest is for children aged three to 16 years and 11 months, it can also be administered to older kids with neurodevelopmental disorders and intellectual disability. The test consists of 33 items and it finishes once the examinee scores seven consecutives zeros. The instrument has good reliability, with a Cronbach's alpha value of 0.79.

2.2.4 | The Boston Naming Test (BNT) (Kaplan et al. 2005)

This instrument assesses lexical ability using illustrations arranged in order of increasing difficulty. In case the examinee is unable to name the image, the examiner provides phonemic or phonetic clues and, as a last resort, multiple-choice options. The test has a Cronbach's alpha value of 0.55.

2.2.5 | Spatio-Temporal Orientation and Sequencing Paradigm (STOSP) (Based on Mastrogiuseppe et al. (2019) Experiment)

This ad hoc paradigm assesses visuospatial episodic memory by reproducing the location of objects, considering the place, the order and the selection of the correct object. The materials used include a large board with four small, randomly placed boxes glued to it, six play dough figures, two *Landmarks* and a smaller board with only two boxes for the practice. This paradigm consists of two parts, each divided into two sections. In the first section of each part, after the examiner demonstrates the sequence of events, the examinee must reproduce the same sequence consecutively. After 5 min of completing another task, the examinee is asked to repeat the sequence without seeing the examiner's example, thus completing the second section. As mention before, this procedure has to be repeated approximately 10 min after the first part is completed. However, this second part includes the use of *Landmarks*, which will be placed on top of the boxes where objects will be hidden. Before starting the second part, on another practice board, the two *Landmarks* will be associated with the object that will later be placed in the box where the *Landmark* is positioned. This paradigm is based on the theory of spatial organization of the brain (Doeller et al. 2008; Lee and Spelke 2010) and the role of β-catenin in the consolidation of spatial memory according to animal research (Lee et al. 2017). Specifically, the cognitive ability to learn and remember object placement relative to environmental boundaries, based on geometric shape, has been linked to hippocampal activation and emerges during development, independent of experience. In contrast, learning and remembering of *Landmark*-related locations is linked to dorsal striatal activation and is supported by different learning mechanisms (Doeller et al. 2008; Ferrara and Landau 2015). Further instructions for the test assessment can be found at Data S1. This test was exclusively assessed to the CTNNB1 syndrome group.

2.2.6 | Vineland Adaptive Behaviour Scales, Third Edition (Vineland-III) (Sparrow et al. 2016)

The parent/caregiver form is a questionnaire-based instrument completed by the parent, assessing a child's abilities across five domains: communications (COM), daily living skills (DLS), socialization (SOC), motor skills and maladaptive behaviour, which includes internalizing and externalizing behaviours, as well as Section C, also known as critical items. A raw score is obtained from each subdomain, from which a V-scale score is calculated based on the examinee's age. The test has a Cronbach's alpha value of 0.98.

2.3 | Data Analysis

The statistical program used to carry out the analyses was SPSS (Statistical Package for Social Sciences) version 28.0. Descriptive statistics were performed for all measures, along with conversion of raw score to Z scores in order to compare variables. Differences in performance between groups were assessed through a Kruskal–Wallis multivariate analysis of variance (MANOVA), together with LDS test as a post hoc analysis. The effect size was expressed based on the partial eta squared indicator. For intra-subject differences a Wilcoxon signed-rank test was performed. Correlations were conducted between age and cognitive and adaptive functioning variables. The level of significance was established at a p value of 0.05.

3 | Results

No significant differences in age or gender were found among the CTNNB1 syndrome, CP and ASD groups, as indicated by the Kruskal–Wallis and chi-squared tests, respectively ($H = 5.627$, $p = 0.06$; $\chi^2 = 1.447$, $p = 0.485$).

Table 2 shows differences between the CTNNB1 syndrome, CP and ASD groups in cognitive and adaptive functioning performances. Regarding cognitive performance, the data revealed statistically significant differences in all three subtests of the WNV (Figure 1). However, as the BNT test was only administered to participants with expressive language (CTNNB1 syndrome = 17; CP = 5; ASD = 17), a Kruskal–Wallis analysis found no differences among groups ($H = 0.37$; $p = 0.504$). Adaptive behaviour was assessed using the Vineland-III. No significant differences were found among groups in the COM and SOC domains, except for the DLS. Conversely, specific domains within COM, SOC and DLS, showed statistical differences. Gross and fine motor performance, as well as the three subdomains from the maladaptive scales differed among groups.

In order to detect which groups exhibited differences, post hoc analyses were carried out (Table 3). The LDS analysis indicated significant differences primarily between the CTNNB1 syndrome and ASD groups, with the CTNNB1 syndrome group performing worse on all cognitive tests, except for the CI. In contrast, the CTNNB1 syndrome and the CP groups only showed differences in Matrices and Recognition subtests from the WNV. Regarding adaptive functioning, significant differences were mainly observed between the CTNNB1 syndrome and the ASD

TABLE 2 | Differences between CTNNB1 syndrome patients and the CP and ASD group on their performance in neuropsychological and adaptive functioning tests.

	CTNNB1 syndrome	CP	ASD	MANOVA		Effect size
	M (SD)	M (SD)	M (SD)	*F*	*p*	η^2_p
Cognition						
PPVT-3	42.12 (28.31)	57.38 (25.88)	66 (36.48)	3.180	0.05	—
CI	11.21 (4.52)	13.38 (6.13)	14.82 (7.72)	1.832	0.170	—
Matrices	5.46 (4.11)	11.54 (3.38)	16.06 (5.83)	27.365	<0.001**	0.518
Object assembly	4.58 (5.23)	4 (6.12)	24.41 (12.32)	33.945	<0.001**	0.571
Recognition	7.79 (4.69)	12.23 (3.94)	13.47 (4.76)	8.798	<0.001**	0.257
Adaptive functioning						
COM_Vineland-III	24.08 (10.85)	21.92 (10.32)	27.76 (8.14)	1.357	0.266	—
Receptive	56.32 (10.48)	64 (7.12)	56.35 (10.16)	3.102	0.053*	0.107
Expressive	50.08 (29.82)	49.08 (29.96)	64.24 (23.06)	1.586	0.215	—
Written	12.88 (13.72)	17.31 (10.95)	34.35 (19.99)	10.198	<0.001**	0.282
DLS_Vineland-III	18.48 (6.94)	15.54 (9.94)	24.59 (3.66)	6.801	0.002*	0.207
Personal	38.40 (22.25)	33.62 (20.79)	63.53 (22.85)	8.807	<0.001**	0.253
Domestic	5.64 (10.52)	4.31 (3.88)	10 (9.66)	1.727	0.188	—
Community	10.84 (9.82)	22.23 (8.75)	26.88 (20.48)	7.434	0.001*	0.222
SOC_Vineland-III	23.88 (9.1)	23.92 (11.79)	25.06 (8.5)	0.086	0.918	—
Interpersonal relationship	41.76 (9.59)	46.92 (13.37)	41.82 (16.04)	0.805	0.453	—
Play and leisure	20.04 (12.49)	32.62 (18.41)	31.59 (20.29)	3.563	0.035*	0.121
Coping skills	17.48 (7.86)	24.38 (9.68)	23.24 (16.95)	1.959	0.151	—
Gross motor	41.72 (18.54)	23.62 (23.62)	72.71 (14.16)	27.278	<0.001**	0.512
Fine motor	32.24 (10.02)	25.69 (14.04)	51.18 (13.41)	19.143	<0.001**	0.424
Internalizing problems	7.88 (3.73)	6.23 (4.76)	10.53 (5.06)	3.695	0.032*	0.124
Externalizing problems	7.92 (3.81)	2.69 (2.29)	4.94 (2.04)	13.632	<0.001**	0.344
Section C	9.32 (3.75)	4.46 (3.48)	10.29 (5.07)	8.243	<0.001**	0.241
Total vineland	62.16 (14.25)	56.77 (17.32)	65.76 (7.19)	1.670	0.198	—

Note: Section C is a sum of critical items covering more severe maladaptive behaviours.
Abbreviations: CI: Comprehension of Instructions; COM: communication v-scale; DLS: daily living skills v-scale; F: MANOVA; M: mean; PPVT-3: Peabody Picture Vocabulary Test; SD: standard deviation; SOC: socialization v-scale; η^2_p: partial eta squared.
*$p < 0.05$.
**$p < 0.001$.

groups, with the ASD group obtaining higher scores. Differences were found only in the DLS domain, in particular in the Personal and Community subdomains. Although the other domains did not differ among groups, subdomains such as Written, Play and Leisure and Gross and Fine motor showed better performance for the ASD group. The CTNNB1 syndrome group exhibited higher prevalence of externalizing problems compared with the ASD group. In contrast, fewer differences were observed between the CTNNB1 syndrome and CP groups. However, the CP group obtained lower scores in the Receptive, Community and Play and Leisure subdomains from the Vineland-III. Additionally, the CP group demonstrated worse Gross motor functioning compared with the CTNNB1 syndrome group. Significant differences were also found in externalizing problems and Section C, with the CTNNB1 syndrome group exhibiting a higher prevalence of critical maladaptive symptoms. Finally, no significant differences were found among groups in the total composite score of the Vineland-III.

No significant differences were found in the spatio-temporal orientation and sequencing paradigm when comparing the use of *Landmarks* versus no *Landmarks*, both in short-term memory ($W = 37.5$; $p = 0.073$) and long-term memory ($W = 58$; $p = 0.379$).

Finally, age positively correlated with neuropsychological performances within the CTNNB1 syndrome group, in exception

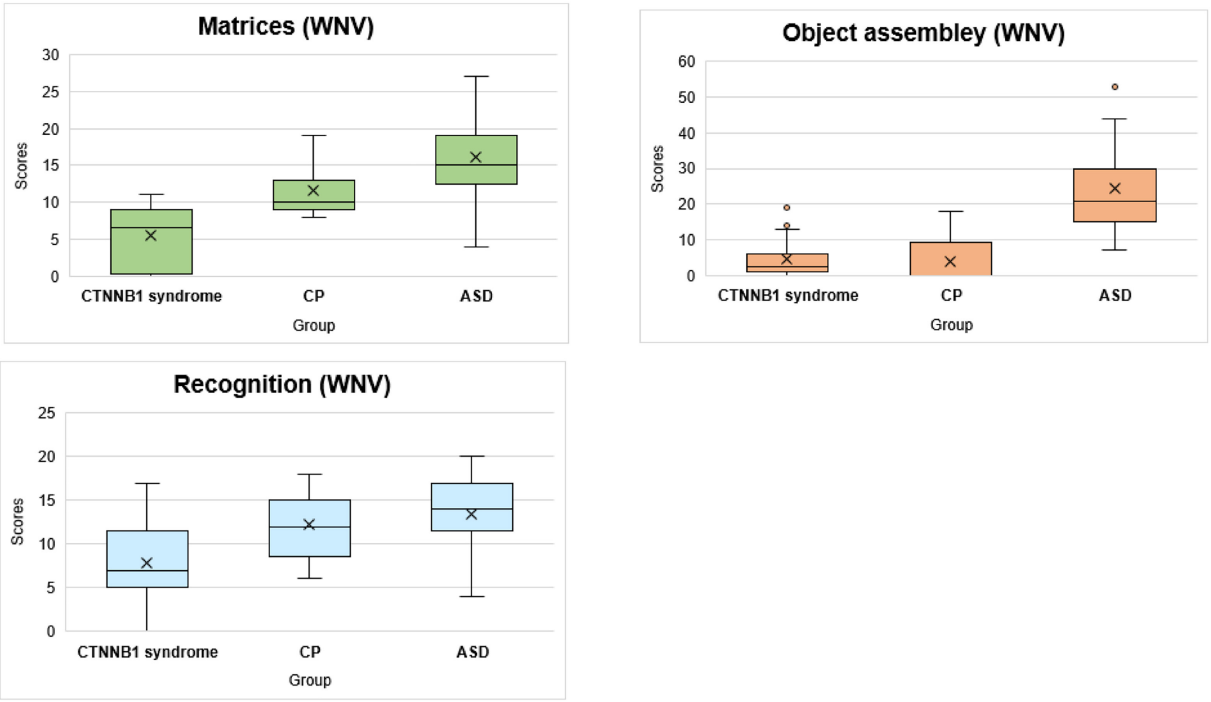

FIGURE 1 | Violin plots of neuropsychological performance among groups.

for the PPVT-3 test. Regarding adaptive functioning, subdomains such as Written, Personal, Domestic, Community and Fine motor from the Vineland-III positively correlated with age, indicating improvement over time (Table 4).

4 | Discussion

To our knowledge, this is the first study to assess cognitive and adaptive functioning in CTNNB1 syndrome patients and compare results with control groups (Pallarès-Sastre et al. 2025). A total of 25 CTNNB1 syndrome, 13 CP and 17 ASD patients were evaluated using a comprehensive battery of neuropsychological tests, as well as a parent-reported questionnaire. The results showed distinct cognitive and psychological profiles associated with each disease, although some overlapping symptoms were observed.

4.1 | Cognitive Functioning

Concerning the neuropsychological profile of CTNNB1 syndrome patients compared with the control groups, no significant differences were found in verbal-related tests, such as the receptive and expressive vocabulary knowledge or comprehension and execution of instructions. However, specific analyses comparing the CTNNB1 syndrome and ASD groups indicated that the CTNNB1 syndrome group obtained worse scores in receptive vocabulary. This finding suggests that children with intellectual disabilities may have limited access to various learning experiences, particularly communicative experiences that promote vocabulary acquisition (Ballester-Plané et al. 2016; Strauss et al. 2006). In contrast, CTNNB1 syndrome patients scored significantly lower than both control groups in the non-verbal tasks from the WNV, aligning with previous research (Sudnawa et al. 2024). Specifically, 26.7% of the sample performed within the average range for the verbal domain, while only 6.7% achieved normative scores in the non-verbal reasoning domain, most spatial cluster scores were the lowest (Sudnawa et al. 2024). These findings highlight the discrepancy in CTNNB1 syndrome patients' cognitive abilities, with stronger verbal performance compared with non-verbal spatial tasks. Such differences may relate to the two forms of intelligence first introduced by Cattell in 1943. The better performance in verbal tasks reflects knowledge integration, also known as crystallized intelligence, in comparison to spatial or logic tasks which do not depend on learning experience and concerns fluid intelligence. Nevertheless, Sudnawa et al. (2024) noted that visual impairments in CTNNB1 syndrome patients might have interfered with test performance, potentially skewing cognitive assessments. Fine motor impairment may have also biased the results, which could explain the lack of differences in the assembly test between the CTNNB1 syndrome and CP groups, unlike other non-verbal tasks where the CP group performed better. From a developmental perspective, limitations in movement, exploration and communication could have consequences for cognitive functioning (Stadskleiv et al. 2017). In contrast, several studies have corroborated the use of the PPVT-3 and some subscales from the WNV for CP patients even with greater motor impairment (Ballester-Plané et al. 2016).

Existing literature on CTNNB1 syndrome described general ID among patients with varying degrees of impairment, establishing this feature as one of the main clinical manifestations of the syndrome. Nonetheless, the vast majority did not use standardized methods to assess the cognitive profiles and just a few provided general scores without interpretation of results (Pallarès-Sastre et al. 2025).

TABLE 3 | Post hoc results of cognitive and adaptive functioning performance between groups.

	CTNNB1 syndrome vs. CP		CTNNB1 syndrome vs. ASD		ASD vs. CP	
	Mean differences (SD)	*p*	Mean differences (SD)	*p*	Mean differences (SD)	*p*
Cognition						
PPVT-3	−0.48 (0.33)	0.154	−0.75 (0.30)	0.017*	0.27 (0.35)	0.448
CI	−0.35 (0.34)	0.302	−0.59 (0.312)	0.66	0.23 (0.36)	0.522
Matrices	−0.94 (0.24)	< 0.001**	−1.64 (0.22)	< 0.001**	0.69 (0.26)	0.010*
Object assembly	0.05 (0.23)	0.84	−1.59 (0.21)	< 0.001**	1.64 (0.24)	< 0.001**
Recognition	−0.86 (0.3)	0.007*	−1.09 (0.28)	< 0.001**	0.24 (0.32)	0.463
Adaptive functioning						
COM_Vineland-III	0.22 (0.34)	0.530	−0.37 (0.31)	0.245	0.58 (0.37)	0.118
Receptive	−0.76 (0.31)	0.025*	−0.003 (0.30)	0.991	−0.76 (0.35)	0.037*
Expressive	0.04 (0.34)	0.917	−0.50 (0.31)	0.11	0.54 (0.36)	0.147
Written	−0.25 (0.29)	0.405	−1.20 (0.27)	< 0.001**	0.955 (0.32)	0.004*
DLS_Vineland-III	0.38 (0.31)	0.225	−0.79 (0.29)	0.008*	1.17 (0.33)	< 0.001**
Personal	0.19 (0.30)	0.530	−1.00 (0.28)	< 0.001**	1.19 (0.32)	< 0.001**
Domestic	0.14 (0.34)	0.671	−0.47 (0.31)	0.135	0.62 (0.36)	0.096
Community	−0.74 (0.31)	0.020*	−1.04 (0.28)	< 0.001**	0.30 (0.033)	0.365
SOC_Vineland-III	−0.004 (0.35)	0.990	−0.12 (0.32)	0.698	0.12 (0.37)	0.750
Interpersonal relationship	−0.41 (0.34)	0.242	−0.01 (0.32)	0.987	−0.40 (0.37)	0.283
Play and leisure	−0.72 (0.37)	0.031*	−0.66 (0.30)	0.032*	−0.06 (0.35)	0.867
Coping skills	−0.58 (0.34)	0.092	−0.48 (0.31)	0.126	−0.09 (0.36)	0.792
Gross motor	0.69 (0.24)	0.007*	−1.18 (0.22)	< 0.001**	1.87 (0.26)	< 0.001**
Fine motor	0.42 (0.26)	0.121	−1.21 (0.24)	< 0.001**	1.62 (0.28)	< 0.001**
Internalizing problems	0.35 (0.33)	0.281	−0.57 (0.29)	0.062	0.93 (0.35)	0.011*
Externalizing problems	1.42 (0.28)	< 0.001**	0.81 (0.26)	0.003*	0.61 (0.30)	0.049*
Section C	1.04 (0.30)	< 0.001**	−0.21 (0.28)	0.458	1.25 (0.33)	< 0.001**
Total vineland	0.39 (0.34)	0.244	−0.27 (0.31)	0.395	0.66 (0.36)	0.074

Note: Section C is a sum of critical items covering more severe maladaptive behaviours.
Abbreviations: CI: Comprehension of Instructions; COM: communication v-scale; DLS: daily living skills v-scale; PPVT-3: Peabody Picture Vocabulary Test; SOC: socialization v-scale.
*$p < 0.05$.
**$p < 0.001$.

4.2 | Adaptive Functioning

Adaptive functioning reflects the ability to perform or respond to daily activities. The current study used the parent/caregiver form of the Vineland-III to assess such matter. Significant differences among groups were only found in the DLS subdomain, even though specific analyses found differences mostly when comparing the CTNNB1 syndrome to the ASD group, with the latter group outperforming the former in some subdomains. In particular, the Written subdomain was significantly better, but neither the Receptive or the Expressive subdomains differed among groups, which highlights the heterogeneity of receptive and expressive language ability in both conditions. The DLS domain, as well as the Personal and Community subdomains, were significantly better, indicating greater autonomy in personal care and appropriate behaviour in public spaces. Within the SOC domain, only the Play and leisure subdomain showed better performance in the ASD group, suggesting that both groups exhibit similar challenges in social interactions (Skoufou 2019). In fact, such differences could

TABLE 4 | Age correlations with neuropsychological and adaptive functioning tests.

	CTNNB1 syndrome		CP		ASD	
	Rho	***p***	***Rho***	***p***	***Rho***	***p***
PPVT-3	0.268	0.206	−0.033	0.915	0.628	0.007*
CI	0.434	0.034*	−0.117	0.703	0.541	0.025*
Matrices	0.428	0.037*	−0.011	0.971	0.588	0.013*
Object assembly	0.565	0.004*	0.138	0.653	0.646	0.005*
Recognition	0.547	0.006*	−0.011	0.971	0.599	0.011*
BNT	0.0552	0.022*	0.600	0.285	0.679	0.003*
Receptive	0.294	0.154	0.177	0.564	0.714	0.001*
Expressive	0.041	0.846	−0.775	0.002*	0.681	0.003*
Written	0.400	0.048*	−0.317	0.291	0.840	<0.001**
Personal	0.598	0.002*	−0.369	0.214	0.901	<0.001**
Domestic	0.456	0.020*	−0.153	0.135	0.445	0.073
Community	0.433	0.031*	−0.218	0.475	0.746	<0.001**
Interpersonal relationship	0.027	0.897	−0.645	0.017*	0.520	0.032*
Play and leisure	−0.196	0.347	−0.580	0.038*	0.436	0.081
Coping skills	−0.042	0.843	−0.338	0.258	0.687	0.002*
Gross motor	0.285	0.167	−0.432	0.141	0.534	0.027*
Fine motor	0.487	0.014*	−0.259	0.393	0.709	0.001*
Internalizing problems	0.072	0.731	−0.061	0.843	0.197	0.449
Externalizing problems	−0.177	0.397	0.053	0.863	−0.132	0.613
Section C	0.096	0.648	0.566	0.044*	0.185	0.476

Note: Section C is a sum of critical items covering more severe maladaptive behaviours.
Abbreviations: BNT: Boston Naming Test; CI: Comprehension of Instructions; PPVT-3: Peabody Picture Vocabulary Test.
*$p < 0.05$.
**$p < 0.001$.

be explained by the superior motor and cognitive abilities of the ASD group. Lastly, Gross motor and Fine motor skills also significantly differed, with the ASD group performing better, potentially marking one of the most distinctive symptoms between groups. This suggests that CTNNB1 syndrome patients require greater assistance or accommodations for daily tasks compared with ASD patients.

When comparing CTNNB1 syndrome and CP patients, fewer differences were observed in adaptive functioning. The only subdomains that differed were Receptive, Community and Play and leisure, where the CP group showed better performance. In contrast, the CP group exhibited significantly poorer Gross Motor functioning compared with CTNNB1 syndrome patients. In areas where motor functioning was crucial, such as writing, some daily living skills or even establishing interpersonal relationships, no differences were found between groups, indicating limitations in both groups (van Gorp et al. 2019). However, in subdomains relying more on cognitive abilities and appropriate behaviour, the CP group demonstrated better adaptive functioning.

Despite these findings, no significant differences were found in the Total Vineland-III score, suggesting that no substantial differences in overall adaptive functioning exist between CTNNB1 syndrome, ASD and CP.

Maladaptive behaviour scales from the Vineland-III indicated differences regarding externalizing problems, so that the CTNNB1 syndrome group exhibited higher prevalence of symptoms compared with the control groups. Additionally, CTNNB1 syndrome patients displayed more severe maladaptive behaviours (Section C) compared with the CP group.

Although the Vineland-III is widely used to assess adaptive functioning (Schoenmakers et al. 2024), several factors can bias results, including the presence of behavioural symptoms and availability of therapeutic interventions (Trelles et al. 2021). As socialization skills are partly dependent on language abilities, promoting communication interventions, such as gestures, sign language or assisted communicative devise, could improve social skills for non-verbal patients (Gentile et al. 2010).

4.3 | Symptomatology Course of CTNNB1 Syndrome

Age positively correlated with cognitive performance in CTNNB1 syndrome patients, in exception of the PPVT-3 test. These results suggest that cognitive improvements occur over time, even in tasks where CTNNB1 syndrome patients initially performed significantly lower than control groups, such as spatial and logical reasoning. In contrast, age did not correlate with Receptive or Expressive subdomains, nor with the PPVT-3, highlighting the heterogeneity of the language profile in CTNNB1 syndrome patients. Similarly, SOC's subdomains did not correlate with age, possibly because adolescent social behaviours require greater independence and autonomy, unlike early childhood socialization practices, which may be more aligned with CTNNB1 syndrome characteristics. On the contrary, all three subdomains from the DLS, as well as Fine motor, improved over time, emphasizing the importance of occupational therapy (Pallarès-Sastre et al. Unpublished manuscript). Currently, no published data track the developmental trajectory of CTNNB1 syndrome, making it unclear whether the developmental progression of the symptoms continue throughout life or if it inevitably stagnates at a pre-determined chronological or developmental age. Due to the syndrome's wide phenotypic variability, establishing a definitive stagnation age is unlikely. Providing useful and important baseline data is crucial for the development of future therapeutic trials that aim to reverse or minimize symptoms (Gentile et al. 2010).

4.4 | Visuospatial Impairments in CTNNB1 Syndrome

Although the spatio-temporal orientation and sequencing paradigm did not show differences between *Landmark*-based and non-*Landrmak* based navigation, evidence from the current study and Sudnawa et al. (2024) article suggest that CTNNB1 syndrome patients may have deficits in visuospatial tasks. This finding has already been proven in animal investigation; mouse models with β-catenin gene modification were able to learn to navigate using featural *Landmarks*, but did not improve their navigation by boundary geometry (Lee et al. 2017). The authors suggest that this visuospatial navigation deficit could be attributed to hippocampal dysfunction (Lee et al. 2017; Tucci et al. 2014). However, given that *Landmark*-learning is due to reinforcement learning (Doeller et al. 2008) and its neural activity is located at corpus striatum, the mice were able to learn the featural cues and navigate correctly. In the current study, perhaps the association between the *Landmark* and the location was not well established and needed more reinforcement. To date, no neuroimaging studies have yet examined hippocampal function in CTNNB1 syndrome patients.

4.5 | Limitations

Despite these novel findings, this study has several limitations to be considered in future research. The small sample size, as well as the wide age range of participants, may limit the generalization of results and the statistical power of the findings. However, this study includes the largest sample to date for in-person assessments of neuropsychological and psychological protocols and for comparing results with clinically comparable diseases. Regarding the instruments used, some neuropsychological tests are not entirely appropriate for the chronological age of the participants, however this study selected developmentally appropriate measures and used raw data for statistical analyses (Edgar et al. 2024). In addition, the effect of therapies on current cognitive and adaptive functioning scores was not considered, so future research should conduct longitudinal assessment to study the progression of the syndrome.

5 | Conclusions

In conclusion, this is the first study to compare the neuropsychological and adaptive functioning profile of CTNNB1 syndrome patients with control groups. Although CTNNB1 syndrome shares many symptoms and signs with ASD and CP, distinct differences were identified. Specifically, ASD patient may have generally better cognitive and adaptive functioning and no presence of motor symptoms. In contrast, CTNNB1 syndrome patients may present deficits in visuospatial and logical reasoning but better functioning in aspects of adaptive functioning as they may not have as much gross motor impairments as CP patients. Nonetheless, the severity of symptoms of all three diseases vary widely across patients, so individual characteristics should be considered. Also, a notable finding is the better level of performance in verbal cognitive tasks of the CTNNB1 syndrome group compared with non-verbal test related to logical and visuospatial performance, suggesting a deficit in the consolidation of information in the hippocampus. Thus, these findings should be considered when designing appropriate individualized psychotherapeutic approaches.

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Ethics Statement

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). Written informed consent was obtained from all parents or legal guardians of study participation.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author, M.P.S. The data are not publicly available due to private information from the participants.

References

Ballester-Plané, J., O. Laporta-Hoyos, A. Macaya, et al. 2016. "Measuring Intellectual Ability in Cerebral Palsy: The Comparison of Three Tests and Their Neuroimaging Correlates." *Research in Developmental Disabilities* 56: 83–98. https://doi.org/10.1016/j.ridd.2016.04.009.

Basu, A. P., K. Low, T. Ratnaike, and D. Rowitch. 2024. "Genetic Investigations in Cerebral Palsy." *Developmental Medicine and Child Neurology* 1–9: 177–185. https://doi.org/10.1111/dmcn.16080.

Bulot, V., F. Ramond, F. Mauguière, and L. Mazzola. 2022. "Startle Disease: An Overlooked Symptom of CTNNB1-Related Neurodevelopmental Disorder With Spastic Diplegia and Visual Defects." *Neurology Genetics* 8, no. 6: e200039. https://doi.org/10.1212/NXG.0000000000200039.

Chopra, M., D. L. Gable, J. Love-Nichols, et al. 2022. "Mendelian Etiologies Identified With Whole Exome Sequencing in Cerebral Palsy." *Annals of Clinical and Translational Neurology* 9, no. 2: 193–205. https://doi.org/10.1002/acn3.51506.

Dashti, S., S. Salehpour, M. R. Ghasemi, et al. 2022. "Identification of a Novel De Novo Mutation in the CTNNB1 Gene in an Iranian Patient With Intellectual Disability." *Neurological Sciences* 43, no. 4: 2859–2863. https://doi.org/10.1007/s10072-022-05904-4.

de Ligt, J., M. H. Willemsen, B. W. M. van Bon, et al. 2012. "Diagnostic Exome Sequencing in Persons With Severe Intellectual Disability." *New England Journal of Medicine* 367, no. 20: 1921–1929. https://doi.org/10.1056/NEJMoa1206524.

Dixon, M. W., M. S. Stem, J. L. Schuette, C. E. Keegan, and C. G. Besirli. 2016. "CTNNB1 Mutation Associated With Familial Exudative Vitreoretinopathy (FEVR) Phenotype." *Ophthalmic Genetics* 37, no. 4: 468–470. https://doi.org/10.3109/13816810.2015.1120318.

Doeller, C., J. A. King, and N. Burgess. 2008. "Parallel Striatal and Hippocampal Systems for Landmarks and Boundaries in Spatial Memory." *Proceedings of the National Academy of Sciences* 105, no. 15: 5915–5920. https://doi.org/10.1073/pnas.0801489105.

Dong, F., J. Jiang, C. McSweeney, D. Zou, L. Liu, and Y. Mao. 2016. "Deletion of CTNNB1 in Inhibitory Circuitry Contributes to Autism-Associated Behavioral Defects." *Human Molecular Genetics*: ddw131. https://doi.org/10.1093/hmg/ddw131.

Dubruc, E., A. Putoux, A. Labalme, C. Rougeot, D. Sanlaville, and P. Edery. 2014. "A New Intellectual Disability Syndrome Caused by CTNNB1 Haploinsufficiency." *American Journal of Medical Genetics Part A* 146A, no. 6: 1571–1575. https://doi.org/10.1002/ajmg.a.36484.

Dunn, L. L. M., L. M. Dunn, and D. Arribas. 2010. *PPVT-III Peabody Test de Vocabulario en imágenes*. TEA.

Edgar, V. B., K. A. Dorsman, D. Horton, S. Messahel, and B. MacDonald. 2024. "Neuropsychological Assessment in Rare Pediatric Neurogenetic Disorders: Considerations for Cross-Cultural Clinical Research." *Child Neurology* 30, no. 6: 900–917. https://doi.org/10.1080/09297049.2023.2283939.

Ferrara, K., and B. Landau. 2015. "Geometric and Featural Systems, Separable and Combined: Evidence From Reorientation in People With Williams Syndrome." *Cognition* 144: 123–133. https://doi.org/10.1016/j.cognition.2015.07.010.

Fortress, A. M., S. L. Schram, J. J. Tuscher, and K. M. Frick. 2013. "Canonical Wnt Signaling Is Necessary for Object Recognition Memory Consolidation." *Journal of Neuroscience* 33, no. 31: 12619–12626. https://doi.org/10.1523/JNEUROSCI.0659–13.2013.

Gentile, J. K., W. H. Tan, L. T. Horowitz, et al. 2010. "A Neurodevelopmental Survey of Angelman Syndrome With Genotype-Phenotype Correlations." *Journal of Developmental & Behavioral Pediatrics* 31, no. 7: 592–601. https://doi.org/10.1097/DBP.0b013e3181ee408e./.

van Gorp, M. E., M. Roebroeck, M. van Eck, et al. 2019. "Childhood Factors Predict Participation of Young Adults With Cerebral Palsy in Domestic Life and Interpersonal Relationships: A Prospective Cohort Study." *Disability and Rehabilitation* 42, no. 22: 3162–3171. https://doi.org/10.1080/09638288.2019.1585971.

Ho, S., M. H. Tsang, J. L. Fung, et al. 2022. "CTNNB1-Related Neurodevelopmental Disorder in a Chinese Population: A Case Series." *American Journal of Medical Genetics. Part A* 188, no. 1: 130–137. https://doi.org/10.1002/ajmg.a.62504.

Ji, Y., Q. Xia, H. Zhang, et al. 2023. "Whole Exome Sequencing Identified Two Novel Truncation Mutations in the CTNNB1 Gene Associated With Neurodevelopmental Disorder, Language Dysfunction, and Microcephaly in Chinese Children." *Child Neurology Open* 10: 2329048X231184184. https://doi.org/10.1177/2329048X231184184.

Kaplan, E., H. Goodglass, and S. Weintraub. 2005. *Test de Vocabulario de Boston*. Panamericana.

Kayumi, S., L. A. Pérez-Jurado, M. Palomares, et al. 2022. "Genomic and Phenotypic Characterization of 404 Individuals With Neurodevelopmental Disorders Caused by CTNNB1 Variants." *Genetics in Medicine* 24, no. 11: 2351–2366. https://doi.org/10.1016/j.gim.2022.08.006.

Kharbanda, M., D. T. Pliz, S. Tomkins, et al. 2017. "Clinical Features Associated With CTNNB1 De Novo Loss of Function Mutations in ten Individuals." *European Journal of Medical Genetics* 60, no. 2: 130–135. https://doi.org/10.1016/j.ejmg.2016.11.008.

Korkman, M., U. Kirk, and S. Kemp. 2007. *NEPSY-II Evaluación Neuropsicológica Infantil*. Pearson Educación.

Krupp, D. R., R. A. Barnard, Y. Duffourd, et al. 2017. "Exonic Mosaic Mutations Contribute Risk for Autism Spectrum Disorder." *American Journal of Genetics* 101, no. 3: 369–390. https://doi.org/10.1016/j.ajhg.2017.07.016.

Kuechler, A., M. H. Willemsen, B. Albrecht, et al. 2015. "De Novo Mutations in Beta-Catenin (CTNNB1) Appear to Be a Frequent Cause of Intellectual Disability: Expanding the Mutational and Clinical Spectrum." *Human Genetics* 134, no. 1: 97–109. https://doi.org/10.1007/s00439-014-1498-1.

Lee, J., J. Yoo, S. Lee, and D. H. Jang. 2023. "CTNNB1-Related Neurodevelopmental Disorder Mimics Cerebral Palsy: Case Report." *Frontiers in Pediatrics* 11: 1201080. https://doi.org/10.3389/fped.2023.1201080.

Lee, S., S. S. Jang, S. Park, et al. 2022. "The Extended Clinical and Genetic Spectrum of CTNNB1-Related Neurodevelopmental Disorder." *Frontiers in Pediatrics* 10. https://doi.org/10.3389/fped.2022.960450.

Lee, S. A., and E. S. Spelke. 2010. "Two Systems of Spatial Representation Underlying Navigation." *Experimental Brain Research* 206, no. 2: 179–188. https://doi.org/10.1007/s00221-010-2349-5.

Lee, S. A., V. Tucci, and G. Vallortigara. 2017. "Spatial Impairment and Memory in Genetic Disorders: Insight From Mouse Models." *Brain Sciences* 7, no. 17: 1–8. https://doi.org/10.3390/brainsci7020017.

Lesnyak, O., F. Marini, P. Sokolnikova, et al. 2024. "Skeletal Abnormalities, Pediatric-Onset Severe Osteoporosis, and Multiple Fragility Fractures in a Patient With a Novel CTNNB1 De Novo Variant." *Bone Reports* 21: 101777. https://doi.org/10.1016/j.bonr.2024.101777.

Maguschak, K. A., and K. J. Ressler. 2012. "The Dynamic Role of Beta-Catenin in Synaptic Plasticity." *Neuropharmacology* 62, no. 1: 78–88. https://doi.org/10.1016/j.neuropharm.2011.08.032.

Mastrogiuseppe, M., N. Bertelsen, M. F. Bedeschi, and S. A. Lee. 2019. "The Spatiotemporal Organization of Episodic Memory and Its Disruption in a Neurodevelopmental Disorder." *Scientific Reports* 9: 1–12. https://doi.org/10.1038/s41598-019-53823-w.

Miroševič, Š., S. Khandelwal, P. Sušjan, et al. 2022. "Correlation Between Phenotype and Genotype in CTNNB1 Syndrome: A Systematic Review

of the Literature." *International Journal of Molecular Sciences* 23, no. 20: 12564. https://doi.org/10.3390/ijms232012564.

Onesimo, R., E. Sforza, V. Trevisan, et al. 2023. "From Feeding Challenges to Oral-Motor Dyspraxia: A Comprehensive Description of 10 New Cases With CTNNB1 Syndrome." *Genes* 14, no. 10: 1–11. https://doi.org/10.3390/genes14101843.

Pallarès-Sastre, M., I. Amayra, R. Pulido, C. E. Nunes-Xavier, F. Cavaliere, and M. García. Unpublished manuscript. "Novel CTNNB1 Gene Variants in Spanish Syndrome Patients: Clinical and Psychological Manifestations.

Pallarès-Sastre, M., I. Amayra, M. Salgueiro, E. Villanueva-Viar, A. Lasa-Aranzasti, and M. García. 2025. "A Systematic Review of Cognitive and Behavioural Symptoms in CTNNB1 Syndrome." *Nueropsychology Review*: 1–24. https://doi.org/10.1007/s11065-025-09660-y.

Paparella, A., G. M. Squeo, E. Di Venere, et al. 2022. "Genome-Wide DNA Methylation Profiling and Exome Sequencing Resolved a Long-Time Misdiagnosed Case." *Journal of Human Genetics* 67, no. 9: 547–551. https://doi.org/10.1038/s10038-022-01043-y.

Pipo-Deveza, J., D. Fehlings, D. Chitayat, G. Yoon, H. Sroka, and I. Tein. 2018. "Rationale for Dopa-Responsive CTNNB1/β-Catenin Deficient Dystonia." *Movement Disorders* 33, no. 4: 656–657. https://doi.org/10.1002/mds.27320.

Retterer, K., J. Juusola, M. T. Cho, et al. 2016. "Clinical Application of Whole-Exome Sequencing Across Clinical Indications." *Genetics in Medicine* 18, no. 7: 696–704. https://doi.org/10.1038/gim.2015.148.

Rossetti, L. Z., M. R. Bekheirnia, A. M. Lewis, et al. 2020. "Missense Variants in CTNNB1 Can Be Associated With Vitreoretinopathy - Seven New Cases of CTNNB1 - Associated Neurodevelopmental Disorder Including a Previously Unreported Retinal Phenotype." *Molecular Genetics & Genomic Medicine* 9, no. 1: e1542. https://doi.org/10.1002/mgg3.1542.

Schoenmakers, D. H., I. van Beelen, M. M. Voermans, et al. 2024. "Adaptive Behaviour Assessed by Vineland-3 as Comprehensive Outcome Measure in Vanishing White Matter." *Annals of Clinical and Translational Neurology* 11, no. 3: 650–661. https://doi.org/10.1002/acn3.51985.

Skoufou, A. 2019. "Social Interaction of Preschool Children With Autism Spectrum Disorder (ASD) – Characteristics and Educational Approaches." *SSRG International Journal of Economics and Management Studies* 6, no. 6: 28–36. https://doi.org/10.14445/23939125/IJEMS-V6I6P105.

Sparrow, S. S., D. V. Cicchetti, and D. A. Balla. 2016. *Vineland 3*. Pearson: Spanish Parent/Caregiver Form Comprehensive Version.

Stadskleiv, K., R. Jahnsen, G. L. Andersen, and S. von Tetzchner. 2017. "Neuropsychological Profiles of Children With Cerebral Palsy." *Developmental Neurorehabilitation* 21, no. 2: 108–120. https://doi.org/10.1080/17518423.2017.1282054.

Strauss, E., O. Spreen, and E. M. S. Sherman. 2006. *A Compendium of Neuropsychological Tests; Administration, Norms and Commentary*. Vol. 3. Oxford University Press.

Sudnawa, K. K., A. Garber, R. Cohen, et al. 2024. "Clinical Phenotypic Spectrum of CTNNB1 Neurodevelopmental Disorder." *Clinical Genetics* 1–10: 523–532. https://doi.org/10.1111/cge.14487.

Tabatadze, N., C. Tomas, R. McGonigal, B. Lin, A. Schook, and A. Ruttenberg. 2012. "Wnt Transmembrane Signaling and Long-Term Spatial Memory." *National Institutes of Health* 22, no. 6: 1228–1241. https://doi.org/10.1002/hipo.20991.

Trelles, M. P., T. Levy, B. Lerman, et al. 2021. "Individuals With FOXP1 Syndrome Present With a Complex Neurobehavioral Profile With High Rates of ADHD, Anxiety, Repetitive Behaviors, and Sensory Symptoms." *Molecular Autism* 12, no. 1: 1–15. https://doi.org/10.1186/s13229-021-00469-z.

Tucci, V., T. Kleefstra, A. Hardy, et al. 2014. "Dominant β-Catenin Mutations Cause Intellectual Disability With Recognizable Syndromic Features." *Journal of Clinical Investigation* 124, no. 4: 1468–1482. https://doi.org/10.1172/JCI70372.

Valenta, T., G. Hausmann, and K. Basler. 2012. "The Many Faces and Functions of β-Catenin." *EMBO Journal* 31, no. 12: 2714–2736. https://doi.org/10.1038/emboj.2012.

Verhoeven, W. M. A., J. I. M. Egger, R. E. Jongbloed, et al. 2020. "A De Novo CTNNB1 Novel Splice Variant in an Adult Female With Severe Intellectual Disability." *International Medical Case Reports Journals* 13: 487–492. https://doi.org/10.2147/IMCRJ.S270487.

Wang, H., Y. Zhao, L. Yang, S. Han, and M. Qi. 2019. "Identification of a Novel Splice Mutation in CTNNB1 Gene in a Chinese Family With Both Severe Intellectual Disability and Serious Visual Defects." *Neurological Sciences* 40, no. 8: 1701–1704. https://doi.org/10.1007/s10072-019-03823-5.

Wechsler, D., and J. A. Naglieri. 2011. *Escala No Verbal de Aptitud Intelectual de Wechsler*. Pearson: Medida no verbal de la inteligencia general.

Yan, D., Y. Sun, N. Xu, Y. Yu, and Y. Zhan. 2022. "Genetic and Clinical Characteristics of 24 Mainland Chinese Patients With CTNNB1 Loss-of-Function Variants." *Molecular Genetics & Genomic Medicine* 10, no. 11: e2067. https://doi.org/10.1002/mgg3.2067.

Zhuang, W., T. Ye, W. Wang, W. Song, and T. Tan. 2023. "CTNNB1 in Neurodevelopmental Disorders." *Frontiers in Psychiatry* 14: 1143328. https://doi.org/10.3389/fpsyt.2023.1143328.

Zuluaga, L. M., S. C. Caballero, G. J. Vélez, J. D. Bravo, and J. H. Montoya. 2022. "CTNNB1 Gene Mutation Associated With Neurodevelopmental Disorder, Microcephaly, and Persistence of Bilateral Hyperplastic Primary Vitreous: A Case Report and Literature Review." *Archivos de la Sociedad Española de Oftalmología* 97, no. 1: 44–47. https://doi.org/10.1016/j.oftale.2020.11.018.

Supporting Information

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