Université de Montréal

Profil neurocomportemental d'individus porteurs de variants pathogènes dans le gène *CHD3*

Par

Anca Stefania Ionescu, BSc

Département de psychologie

Faculté des arts et des sciences

Essai doctoral présenté en vue de l'obtention du grade de Doctorat en psychologie (D.Psy.), option neuropsychologie clinique

Août 2023

Résumé

Le syndrome de Snijders Blok-Campeau (SNIBCPS), un trouble neurodéveloppemental décrit pour la première fois en 2018, est causé par des variants pathogènes hétérozygotes du gène CHD3. La protéine codée par le gène *CHD3* joue un rôle crucial dans le développement du système nerveux des embryons. Certains traits phénotypiques généraux ont été associés à ce syndrome. Notamment, des retards neurodéveloppementaux globaux tels que des déficiences intellectuelles, un retard dans l'acquisition de la parole, des particularités physiques telles que des traits faciaux caractéristiques et une macrocéphalie. Cette étude vise à évaluer les enfants et les adolescents atteints de ce syndrome et de les comparer à deux populations cliniques, une d'individus avec le Syndrome du X Fragile (SXF) et une autre d'individus avec le trouble du spectre de l'autisme (TSA). Ainsi, nous présentons le profil neurocomportemental de 41 personnes présentant des variants dans le gène CHD3 et le comparons à une cohorte de 49 personnes présentant un TSA et à une cohorte de 33 personnes présentant le SXF. Des déficits cliniques profonds ont été constatés dans le fonctionnement adaptatif, les capacités de communication et le fonctionnement sensorimoteur chez la plupart des participants. Des similitudes entre les cohortes du SXF et du SNIBCPS ont été dévoilées, caractérisées par des niveaux diminués de comportement adaptatif, de compétences de socialisation et de capacités de communication. En revanche, nous soulignons une socialisation relativement élevée et des problèmes émotionnels/comportementaux minimes au sein de l'échantillon, ce qui suggère des forces potentielles inhérentes à ce syndrome. Nous avons identifié un comportement d'évitement social nettement réduit chez les SNIBCPS par rapport au FXS, soulignant un trait distinctif et nouveau, nécessitant une exploration approfondie. Cette étude enrichit la rare littérature sur le SNIBCPS en délimitant le spectre phénotypique neurocomportemental du SNIBCPS et en ouvrant la voie à des comparaisons avec des troubles neurodéveloppementaux cliniquement apparentés.

Mots-clés : Syndrome Snijders Blok-Campeau, CHD3, troubles neurodéveloppementaux, épigénétique

Abstract

Snijders Blok-Campeau syndrome (SNIBCPS), a neurodevelopmental disorder first described in 2018, is caused by heterozygous pathogenic variants in CHD3. Its encoded protein plays a crucial role in the development of the nervous system of embryos. Whereas broadly defined phenotypic traits have been identified (i.e. global neurodevelopmental delays such as intellectual disabilities and delayed speech acquisition, and physical features such as characteristic facial features and macrocephaly), the phenotypic spectrum has not been further assessed. We present the neurobehavioral profile of 41 individuals with variants in CHD3 and compare it to the ones of Autism Spectrum Disorder (ASD) and Fragile X syndrome (FXS) cohorts. Profound clinical deficits were found in adaptive functioning, communication skills and sensorimotor functioning in most participants. We highlight relatively strong socialization and minimal emotional/behavioural issues within the sample, suggesting potential strengths inherent to this syndrome. We identified a markedly reduced social avoidance behaviour in SNIBCPS relative to the FXS, underscoring a distinctive and novel trait demanding thorough exploration. Similarities between FXS and SNIBCPS cohorts were unveiled, characterized by diminished levels of adaptive behaviour, socialization skills, and communication abilities. This study enriches the scarce SNIBCPS literature by delineating the neurobehavioral phenotypic spectrum of SNIBCPS and by innovating comparisons with clinically akin neurodevelopmental disorders.

Keywords: Snijders Blok-Campeau syndrome, CHD3, neurodevelopmental disorders, clinical epigenetics

Table des matières

Listes des tableaux

Listes des figures

Liste des sigles et des abréviations

ABAS-II: Adaptive Behaviour Assessment System, Second Edition

ABC-C: Aberrant Behavior Checklist for Community

ABC: Adaptive Behavior Composite

ADHD: Attention-Deficit/Hyperactivity Disorder

ADOS-2: Autism Diagnostic Observation Schedule, Second Edition

ASD : Autism Spectrum Disorder

ASQ-3: Ages & Stages Questionnaires, Third Edition

ASR: Adult Self-Report

CAARS – S:L : Conners' Adult ADHD Rating Scales, Self Report

CAS: Childhood Apraxia of Speech

CBCL: Children Behaviour Checklist

CGG: Cytosine-Guanine-Guanine

CHD3: Chromodomain Helicase DNA-binding 3 gene

CHD3: Chromodomain Helicase DNA-binding 3 protein

DCD: Developmental Coordination Disorder

DCDQ: Developmental Coordination Disorder Questionnaire

DNM: *De novo* Mutation

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition

DSM-V: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

FXS: Fragile X Syndrome

GAC: General Adaptive Composite

GI: Conners-3 Global Index Total

ID: Intellectual Disability

NDD: Neurodevelopmental Disorder

NuRD: Nucleosome Remodeling and Deacetylase

REDCap: Research Electronic Data Capture

SNIBCPS: Snijders Blok-Campeau Syndrome

SRS-II: Social Responsiveness Scale, Second Edition

Remerciements

J’aimerais prendre un moment pour remercier toutes les personnes qui ont contribué de près ou de loin à ce projet. Tout d’abord, je tiens à remercier mes cosuperviseurs, Sarah Lippé et Philippe Campeau, qui ont cru en moi dès notre première rencontre en décembre 2019. Merci de m’avoir fait confiance avec un projet si passionnant. Je vous suis reconnaissante de votre accompagnement tout au long de mon cheminement professionnel et académique. J’aimerais également remercier les membres du laboratoire Neuroscience of Early Development et du laboratoire de Dr. Campeau pour les échanges stimulants à travers les années.

Un merci particulier à Etienne Maes et à Victoria Veas, mes grands amis, pour leur soutien précieux tout au long de mon parcours universitaire. Votre appui a été important autant au niveau du partage de connaissances en recherche, qu’au niveau de votre capacité à célébrer à mes côtés.

Je suis infiniment reconnaissante envers mes parents, qui m’ont accueillie les bras ouverts dans les hauts comme dans les bas. Votre soutien autant financier que moral m’a permis de m’investir complètement dans mes apprentissages et d’en ressortir enrichie à plusieurs niveaux. J’ai su persévérer grâce à vos encouragements et à vos conseils.

Enfin, j’aimerais remercier mes collègues, Mélissa, Marianne, Alexis, Agathe, Frédérique, Catherine H.-A., Kim, Rachel, Sarah et Sacha. Je garde précieusement en mémoire nos fins de semaine au chalet, nos Zooms COVID-19, nos 5 à 7, nos brunchs, nos soupers de Noël, notre soirée bowling et notre semaine au Mexique.

Avant-propos

L'article empirique faisant l'objet de cet essai doctoral est présenté dans les prochaines pages du document. Il sera soumis à la revue **European Journal of Human Genetics** sous forme d'**Article** à l'automne 2023. L'article est précédé par une brève mise en contexte théorique pour une meilleure compréhension de la problématique.

Introduction

Position du problème

The literature of the Snijders Blok-Campeau syndrome (SNIBCPS) emerged in 2018 following the identification of *CHD3* variants in 35 patients, marking this as a novel neurodevelopmental disorder. Despite ongoing efforts from the scientific community to define SNIBCPS, the scarcity of cases presents a significant challenge. With an estimated global count of around 150 cases and limited available literature, many fundamental features of the syndrome remain to be more precisely defined, emphasizing the need for a deeper comprehension of the behavioral attributes exhibited by affected individuals. A strategic approach in the characterization of such novel rare disorder is the comparison of such ill-defined profiles with well-established ones of similar syndromes such as Fragile X syndrome (FXS), and with a syndrome with a well-established profile, such as autism spectrum disorder (ASD).

As such, a comprehensive analysis of the neurobehavioral profile of SNIBCPS individuals, alongside comparisons with similar clinical populations, is essential to provide a more in-depth comprehension of the neurobehavioral challenges and the strengths within this cohort and to contextualize them within the spectrum of neurodevelopmental disorders.

Article

Neurobehavioral profile of individuals with pathogenic variants in *CHD3*

Anca Ionescu[1,2], Mélodie Proteau-Lemieux[1,2], Inga S Knoth[2], Keely Vachon[3], Kerri Whitlock[3], Hazel Maridith Barlanhan Biag[4], Sébastien Jacquemont[1,2], François Bolduc[3], Randi J Hagerman[4], David Hessl[4], Andrea Schneider[4], Leonard Abbeduto[4], Evdokia Anagnostou[5], Julia Frei[6] , Lucia Capano[7], Philippe M Campeau[1,2*] and Sarah Lippé[1,2*]

[1]University of Montreal, Montreal, Quebec, Canada
[2]Research Center of the Sainte-Justine University Hospital, Montreal, Quebec, Canada
[3]University of Alberta, Canada
[4]MIND Institute of the University of California, Davis, United States
[5]Holland Bloorview Research Center, Toronto, Ontario, Canada
[6]McMaster University of Ottawa, Ontario, Canada
[7]Queen's University of Kingston, Ontario, Canada

***Correspondence**

Sarah Lippé
sarah.lippe@umontreal.ca

Philippe Campeau
p.campeau@umontreal.ca

Keywords: Snijders Blok-Campeau syndrome, CHD3, neurodevelopmental disorders, clinical epigenetics

1. Introduction

Neurodevelopmental syndromes characterized by global developmental delays and intellectual deficiencies affect around 1.5% of the worldwide population (1). Our understanding of the genetics of neurodevelopmental disorders (NDDs) has rapidly advanced over the past few years. Next-generation sequencing platforms have greatly accelerated the discovery of neurodevelopmental genes and have facilitated the exploration of understudied variant classes, such as *de novo* mutations. *De novo* mutations (DNMs) in developmentally important genes are enriched in the genomes of individuals with severe, undiagnosed developmental disorders (2). More specifically, a national study identified 94 genes most frequently associated with deleterious *de novo* mutations in developmental disorders (2). Among these genes is Chromodomain Helicase DNA-binding 3 (*CHD3,* OMIM #602120), for which *de novo* heterozygous pathogenic variants were described in 2018 as causing a neurodevelopmental disorder later coined Snijders Blok-Campeau syndrome (SNIBCPS, OMIM # 618205). *CHD3*, located on 17p13.1, plays a crucial role in the development of the embryo's nervous system though its encoded protein CHD3. Along with CHD4 and CHD5, CHD3 is a chromatin remodeler embedded in the nucleosome remodeling and deacetylase (NuRD) complex. This complex epigenetic regulator of gene expression uses histone deacetylase activity and ATP-dependent nucleosome remodeling activity to regulate chromatin structure, gene transcription, and DNA repair (3,4). CHD3 aids heterochromatin formation and remodeling through both gene activation and repression, which consequently plays a role in neural cells' pluripotency and lineage commitment (5,6). The chromatin remodeling activity of NuRD-associated CHD proteins is critical during corticogenesis, exhibiting a well-organized sequential expression pattern (4,5). As CHD4 helps in the generation and proliferation of neural progenitors/neurons, CHD5 regulates early neural migration (4,5). Finally, CHD3 regulates the late migration of neurons and cortical layer specification (4,5). More specifically, CHD3 has been shown to control timing of upper-layer neuron specification. In *Chd3*-knockdown mice, deeper layer markers were more likely to be expressed whereas upper layer

markers Brn2 and Cux1 were significantly lower (5). The laminar localization of neurons and diverse cytoarchitecture provides a framework for efficient information processing, as distinct neuron types and layers collaborate to carry out specialized computational tasks (4,7). Consequently, perturbations in processes of cortical migration, generation, differentiation and wiring of cortical projections can profoundly impact cognitive functions, resulting in intellectual deficits and other cognitive delays (8). The precise orchestration of these developmental events is crucial for the establishment of robust brain structures and neural organization across the brain. Disruptions in these processes can lead to alterations in cognitive function and behaviour.

As a result, SNIBCPS can lead to symptoms affecting multiple organ systems. Reported clinical characteristics include physical phenotypic characteristics such as macrocephaly, facial dysmorphisms, genital anomalies, joint laxity and vision abnormalities as well as developmental and neuropsychological ones such as infantile hypotonia, speech-related problems, borderline to severe intellectual disability (ID), autistic features, and motor delays (9).

Characterization of neuropsychological profiles is based on comparison of the affected population with neurotypical population. For novel rare disorders, parallels with other clinical populations may enlighten such characterisation. Given the estimated prevalence of autistic traits, intellectual disability, and speech delays in SNIBCPS, comparing this syndrome to well-established conditions primarily characterized by these traits provides a framework for classification. SNIBCPS shares significant speech delays and intellectual disability with Fragile X syndrome (FXS), a common cause of inherited intellectual disability. Contrasting SNIBCPS with ASD offers an opportunity for a nuanced examination, aligning SNIBCPS's documented ASD traits with those of a robust syndrome exhibiting similar characteristics but with minimal or no intellectual disability, specifically in this study’s ASD sample. Therefore, the

parallels and divergences uncovered through these comparisons will position this novel syndrome within well-established neurodevelopmental conditions.

Despite the limited global cases (unofficial est. 150), the present report describes the neurobehavioral profile of 41 individuals with variants in the *CHD3* to establish the phenotypic spectrum associated with SNIBCPS. In addition, we compared the SNIBCPS group to clinical groups of FXS and ASD, examining their neurobehavioral profiles across adaptive, socioemotional, and behavioral domains. To date, this study is the first to focus on a deeper analysis of the neurobehavioral profile of the SNIBCPS population and to compare such profile with other clinical populations. This knowledge is of utmost importance for healthcare professionals, individuals affected by the condition, and their families, as it plays a vital role in guiding clinical management, providing accurate counseling, and facilitating prognosis.

2. Subjects and Methods

2.1. Participants

Forty-one participants with reported deleterious *CHD3* pathogenic or likely pathogenic variant were recruited for the study via referral, direct contact with CHU Sainte-Justine medical geneticist Dr. Philippe Campeau, and via family associations. Each participant or legal caregiver was able to complete at least one questionnaire based on an appropriate level of understanding of the English language. Two participants required the use of a German interpreter during the Vineland-3 assessment. As such, analyses for each questionnaire were conducted with variable sample sizes with respect to their chronological age and available norms (see Table 1 and 2 for supplemental description). We included two additional clinical cohorts of 49 idiopathic ASD and 33 FXS participants from our lab's database, using Vineland-3 and ABC-C-FXS questionnaire data. The FXS cohort underwent genetic screening and were diagnosed with the full mutation (i.e. presence of more than 200 repetitions of CGG (cytosine-guanine-guanine)). The ASD cohort was evaluated by clinicians and met the DSM-5 criteria for ASD. The diagnosis was also supported by the ADOS-2. Participants had no other genetic condition. No

exclusion criteria were considered during recruitment of the SNIBCPS cohort due to the rarity of cases. Comorbid diagnoses and medication intake are present among the cohorts. The study was reviewed and approved by the Research Ethics Committee of the CHU Sainte-Justine and was carried out according to the declaration of Helsinki. Parents were asked to electronically fill out questionnaires about the behavior of their children via a Research Electronic Data Capture (REDCap) weblink and via e-mail. Procedures were explained in detail before obtaining informed consent from participants or legal caregivers and assent from participants.

2.2. Questionnaires

Data for the SNIBCPS cohort was gathered from ten standardized questionnaires. 1) An in-house questionnaire was used to collect demographic information, pathogenic variant and overall developmental skills. Three global adaptive functioning questionnaires were used: 2) *The Ages & Stages Questionnaires, Third Edition* (ASQ-3) measures developmental progress determined by cut-off scores on five areas: *Communication*, *Gross Motor*, *Fine Motor*, *Problem Solving* and *Personal Social* (10). 3) *Adaptive Behaviour Assessment System-Second edition* (ABAS-II) was used to assess adaptive functioning (11). Three composites were calculated to obtain the adaptive domains: *Conceptual*, *Social* and *Practical*. A *General adaptive composite* (*GAC*) was also calculated. Standardized scores (mean=100 and SD=15) were obtained from a chronological age normative sample. Higher scores indicate better adaptive functioning. 4) The *Vineland Adaptive Behavior Scale – Third Edition Comprehensive Interview Form (Vineland-3)* was conducted by videoconference to estimate the level of support required by our clinical population in daily life. The Vineland-3 is known to be the leading instrument for supporting the diagnosis of intellectual and developmental disabilities (12). Three composites were calculated to obtain the adaptive domains: *Communication*, *Daily Living Skills*, and *Socialization*. An *adaptive behavior composite* (*ABC*) was also calculated. The Vineland-3 and the ABAS-II follow the same standardized method (mean=100 and SD=15). Two questionnaires and other

pertinent adaptive domains were used to screen and assess sensorimotor functioning: 5) *The Developmental Coordination Disorder Questionnaire* (DCDQ) was used to screen for Developmental Coordination Disorder (DCD) based on DSM-IV criteria based on cut-off scores. Lower scores indicate greater indication of DCD (13). 6) *Sensory Profile 2 & Adolescent/Adult Sensory Profile* were used to assess sensory processing patterns. Scores from four sensory profiles and processing domains were categorized based on an age normative sample. Greater or lower scores indicated a processing pattern more or less similar to the majority (14,15). Four questionnaires were used to screen social, emotional, and behavioural difficulties: 7) The revised version of the *Aberrant Behavior Checklist for Community* (ABC-C; 16) specifically developed for the FXS population, was used. In this version, social avoidance, which is highly associated with ASD and FXS, was added as a sixth subscale. The ABC-C is a questionnaire especially designed for populations with ID measuring different types of problematic behaviour, such as lethargy and inappropriate speech. We used the ABC-C norms based on a FXS sample to obtain Z scores (mean=0 and SD=2) for each subscale for each clinical group (16). 8) The *Social Responsiveness Scale – Second Edition* (SRS-II) has been used to assess the presence and severity of autistic traits (17–19). Norms were based on a normative sample and T-scores (mean=50 and SD= 10) were calculated. Higher scores indicate greater autistic symptomatology. 9) The *Conners 3rd Edition* (Conners 3) or the *Conners' Adult ADHD Rating Scales–Self Report* (CAARS – S:L for older participants) was used to assess attention-deficit/hyperactivity disorder (ADHD) and its most common comorbid disorders (20). T-scores (mean=50 and SD= 10) were calculated for six domains: *Conners-3 Global Index Total* (GI), *Learning Problems*, *DSM-V ADHD Inattentive*, *DSM-V ADHD Hyperactive-Impulsive*, *DSM-V Conduct Disorder* and *DSM-V Oppositional Defiant Disorders*. Higher scores indicate more ADHD symptoms. 10) *Children Behaviour Checklist* (CBCL) or *Adult Self-Report* (ASR for older participants) measure general behavioral and emotional issues as well as providing an overview on psychopathology (21–24). Standardized scores were obtained from chronological age CBCL/ASR

normative samples. Higher scores indicate more psychopathology symptoms.

2.3. Statistical analysis

Statistical analyses were performed using SPSS Statistics, version 23 (IBM Corp., Armonk, NY, USA) for comparisons between the study' three clinical cohorts of interest using ABC-C-FXS and Vineland-3 questionnaire data. Data distribution was verified using histograms as well as skewness / kurtosis criteria (values within -1 and 1 were considered acceptable) and z-scores. The significance level for statistical tests was set to 5% ($p = 0.05$). Comparisons between groups were performed using Kruskal-Wallis H tests. Significant differences were investigated using post-hoc pairwise comparisons with Bonferroni-correction. Descriptive analyses were conducted for the SNIBCPS cohort across all ten questionnaires. Total scores or general scales are presented, except in cases where only subscales are available (e.g., Sensory Profile 2, ASQ-3, Conners/CAARS, and only the social scale for ABAS-II 0-5 y.o.), or when subscales are used for between-group comparisons (ABC-C-FXS and Vineland-3). Results are presented based on percentages and ratios (number of affected individuals/total number of respondents for that scale or subscale).

3. Results

3.1. SNIBCPS cohort and other clinical cohorts

Forty-one participants with reported deleterious *CHD3* pathogenic variants were part of our SNIBCPS cohort. The average age of our cohort is 9.8 years, with the youngest patient being 2 months, and the oldest being 47 years old. The FXS cohort's average age is 11.55, ranging from 7 to 20 years old and the ASD cohort's average age is 12.04, ranging from 4 to 17 years old. Age differences were found between the groups. As such, only participants falling between the range of 3 years old and 20 years old were selected to conduct between-group statistical analyses. Table 1 provides more general demographics on the SNIBCPS and other clinical cohorts in the study whereas Tables 3 and 4 provides demographics for the clinical populations included in the between-groups statistical analyses for ABC-

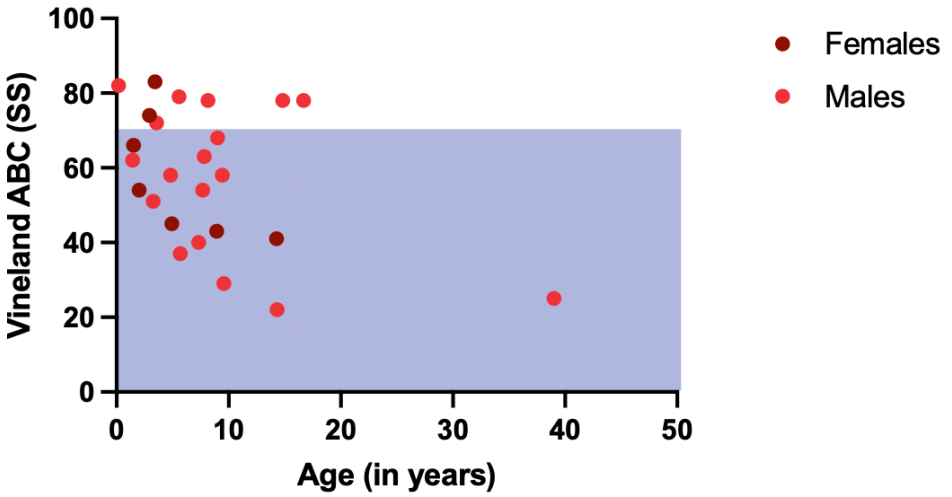
C-FXS and Vineland-3, as well as p-values for age differences. Table 2 provides demographics for the SNIBCPS individuals included in the descriptive analyses for each questionnaire.

3.2. Global Adaptive Functioning of the SNIBCPS Population and Comparison with Similar Clinical Populations

An analysis of the total sample of the Vineland-3 completed questionnaires for the SNIBCPS population revealed that about two-thirds of participants (64%; 16/25) exhibiting profound global impairment in adaptive functioning (less than 2 SD) and one-third of them (32%; 8/25) showed borderline global impairment (between 1 SD and 2 SD) as reflected by the ABC standard scores (Figure 1). The Vineland-3 reveals Low Adaptive Level of Daily Living Skills in the SNIBCPS population with almost three quarters of participants (72%; 18/25) falling below 2 SD. Similarly, the ABAS-II revealed GAC scores in the Extremely Low range in almost all participants aged between 5 and 21 years old (90%; 18/20). The preschool-aged individuals (0–5 y.o.) showed significantly delayed developmental milestones as more than two-thirds (67%; 10/15) fell below the cut-off on at least one developmental category of the ASQ-3.

Figure 1. Vineland Adaptive Behaviour Composite Standard Scores.

The normative area is 100 +/- 15. The shaded area presents the clinical range (below 2 SD) interpreted as the Low Adaptive Level.



When compared to other clinical populations, such as FXS and ASD groups, a Kruskal-Wallis H test showed that there was a statistically significant difference in the Vineland-3 ABC standard score between the groups, $H = 20.774$, $p < 0.001$, with a mean rank ABC standard score of 39.18 for SNIBCPS, 34.19 for FXS and 61.78 for ASD. Post-hoc pairwise comparisons using Bonferroni-correction revealed higher adaptive functioning in ASD when compared to FXS ($p < 0.001$) and to SNIBCPS ($p = 0.013$). FXS and SNIBCPS groups were not significantly different ($p = 1.000$; Figure 2A).

Similarly, the same statistically significant difference was found between standard scores of the Daily Living subdomain of these clinical populations. A Kruskal-Wallis H test showed that there was a statistically significant difference in the Vineland-3 Daily Living subdomain standard score between the groups, $H = 13.765$, $p = 0.001$, with a mean rank Daily Living subdomain standard score of 36.41 for SNIBCPS, 39.40 for FXS and 59.44 for ASD. Post-hoc pairwise comparisons using Bonferroni-correction revealed higher daily living skills in ASD when compared to FXS ($p = 0.006$) and to SNIBCPS ($p = 0.011$). FXS and SNIBCPS groups were not significantly different ($p = 1.000$; Figure 2B).

In general, global adaptive functioning and daily living skills of the SNIBCPS population show clinically significant impairments, which are comparable with the ones of the FXS population.

3.3. Communication Level of the SNIBCPS Population and its Comparison with Similar Clinical Populations

More than two-thirds (67%; 10/15) of the preschool SNIBCPS population were clinically delayed on the Communication domain of the ASQ-3. Almost three-quarters of the participants (72%; 18/25) show a Low Adaptive level and almost one-quarter (28%; 7/25) of them show a Moderate Adaptive Level on Vineland-3 Communication domain. No SNIBCPS participant showed normotypical communication skills (0% within the norms).

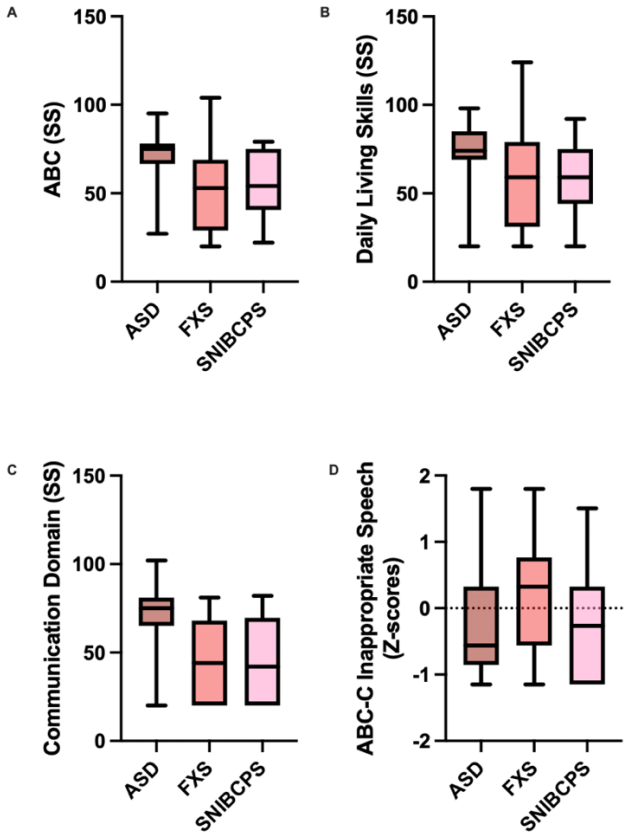
When compared to other clinical populations, such as FXS and ASD groups, a Kruskal-Wallis H test showed that there was a statistically significant difference in the Vineland-3 Communication subdomain standard score between the groups, $H = 28.730$, $p < 0.001$, with a mean rank Communication subdomain standard score of 36.18 for SNIBCPS, 32.21 for FXS and 64.07 for ASD. Post-hoc pairwise comparisons using Bonferroni-correction revealed higher communication skills in ASD when compared to FXS ($p < 0.001$) and to SNIBCPS ($p = 0.001$). FXS and SNIBCPS groups were not significantly different ($p = 1.000$; Figure 2C).

There was a statistically significant difference in Inappropriate speech scores on the ABC-C-FX questionnaire between the groups, $H = 9.365$, $p = 0.009$, with a mean rank Inappropriate speech score of 51.44 for SNIBCPS, 70.84 for FXS and 51.13 for ASD. Post-hoc pairwise comparisons using Bonferroni-correction revealed higher inappropriate speech in FXS when compared to ASD ($p = 0.015$) and to SNIBCPS ($p = 0.062$). ASD and SNIBCPS groups were not significantly different ($p = 1.000$; Figure 2D).

Overall, FXS and SNIBCPS groups showed comparable communication skills with FXS showing higher inappropriateness of speech than SNIBCPS. However, careful interpretation of these findings is warranted, as the FXS sample included individuals with a minimum speech production threshold of three

words, while no specific speech ability criteria were specified during the recruitment of SNIBCPS participants.

Figure 2. Comparisons of (A) ABC Standard Scores (B) Daily Living Skills Standard Scores (C) Communication Standard Scores (D) Inappropriate Speech Z-Scores between ASD, FXS and SNIBCPS populations.



3.4. Sensorimotor Functioning in the SNIBCPS Population

The Gross Motor domain was the domain which the SNIBCPS preschool population showed the greatest developmental delay on the ASQ-3 with almost all participants (87%; 13/15) falling below the cut-off score. The Fine Motor domain was also severely impaired in these individuals as two-thirds (66%; 10/15) of the sample fell below the cut-off score. Similarly, DCDQ results revealing clinically significant impairments in the SNIBCPS sample suggested suspected DCD in all participants. Likewise, almost two-

thirds (62%; 13/21) of the population show a Low Adaptive Level in the Motor domain of the Vineland-3.

The SNIBCPS population's Sensory Profile results revealed extremely low registration of the sensory cues (43% ; 12/28 ; below 2 SD) and normotypical sensation avoidance (61% ; 17/28 ; within 1 SD). Overall, the SNIBCPS population were characterized as missing sensory input (both sensory detection and processing) at a higher rate than the norm without actively moving away from the sensory input in their environment. Interestingly, several patients in the two initially published cohorts of SNIBCPS had pain insensitivity. Body position processing was the subdomain showing the most impairment in the younger participants (below 14 years old), with 61% (14/23) falling in the clinical range.

3.5. Screening for the Social, Emotional and Behavioral domains in the SNIBCPS population and Comparison with Similar Clinical Populations

3.5.1. Socialization Level of the SNIBCPS population and Comparison with Similar Clinical Populations.

The preschool SNIBCPS population showed clinically significant delays in the Personal Social domain of the ASQ-3 (73%; 11/15) and the Social domain of the ABAS-II (60%; 9/15). Despite such results in the preschool population, the Socialization domain of the Vineland-3 showed the highest adaptive functioning (i.e. smallest number of participants falling in the clinical range). In fact, about half of the participants showed Low Adaptive Levels of Socialization skills (less than 2 SD; 52%; 13/25) whereas the other half showed either Moderate Adaptive Levels (between 1 SD and 2 SD ; 44% ; 11/25) or Adequate Adaptive Levels (4%; 1/25).

When compared to global adaptive scores (ABC), almost all participants (84%; 21/25) showed higher mean standard score of the Socialization domain relative to the global score (M = 5.44; SD = 6.52).

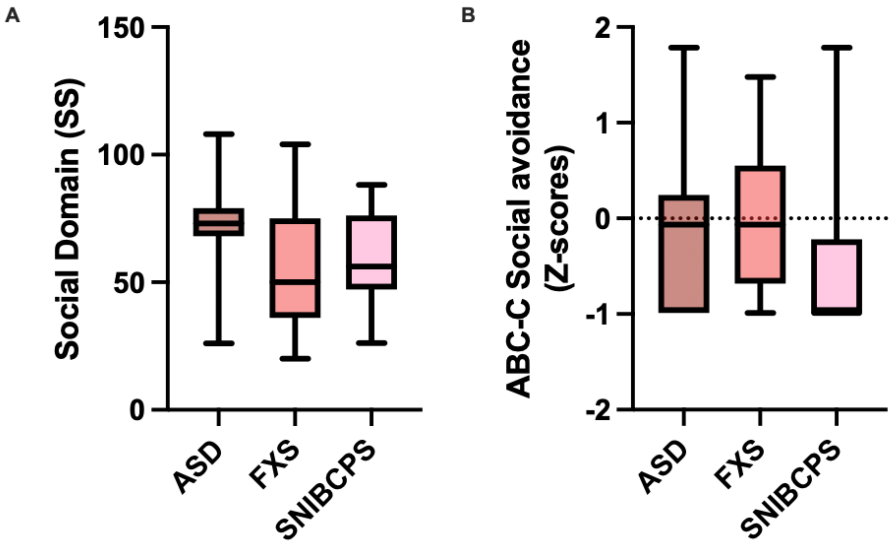
Further investigation within the domain revealed the Interpersonal Relationship Subdomain as the one with the highest number of participants falling within the norm (20%; 5/25).

When compared with other clinical populations, such as FXS and ASD groups, a Kruskal-Wallis H test showed that there was a statistically significant difference in the Vineland-3 Socialization subdomain standard score between the groups, $H = 13.765$, $p = 0.001$, with a mean rank Socialization subdomain standard score of 42.32 for SNIBCPS, 36.97 for FXS and 58.93 for ASD. Post-hoc pairwise comparisons using Bonferroni-correction revealed higher social skills in ASD when compared to FXS ($p = 0.002$). SNIBCPS group did not significantly differ from FXS ($p = 1.000$) nor ASD groups ($p = 0.108$; Figure 6).

There was a statistically significant difference in social avoidance scores on the ABC-C-FX questionnaire between the groups, $H = 6.868$, $p = 0.032$, with a mean rank social avoidance score of 42.56 for SNIBCPS, 62.64 for FXS and 60.82 for ASD. Post-hoc pairwise comparisons using Bonferroni-correction revealed lower social avoidance scores in SNIBCPS when compared to FXS ($p = 0.041$). Without the Bonferroni correction, social avoidance scores of SNIBCPS group also showed a tendency to differ from the ones of the ASD group ($p = 0.023$). ASD did not significantly differ from SNIBCPS ($p = 0.070$) nor from FXS ($p = 1.000$; Figure 7).

Overall, the SNIBCPS population showed comparable socialization skills to the FXS and the ASD populations and tended to exhibit lower social avoidance behaviour than these groups.

Figure 3. Comparisons of (A) Socialization Standard Scores (B) Social avoidance Z-Scores between ASD, FXS and SNIBCPS populations.



3.5.2. Screening for ASD traits in the SNIBCPS population.

Variable results on the SRS-2 were observed within the SNIBCPS sample; about one-quarter of the population fell within each of the four ranges (8/33 in the Normal range, 9/33 in the Mild range, 10/33 in the Moderate range and 7/33 in the Severe range of deficiencies in social interaction).

The preschool population seemed to exhibit less social impairment. In fact, two-thirds of the preschool population (4/6; 67%) fell within typical limits and no individual showed severe deficiencies in social interaction.

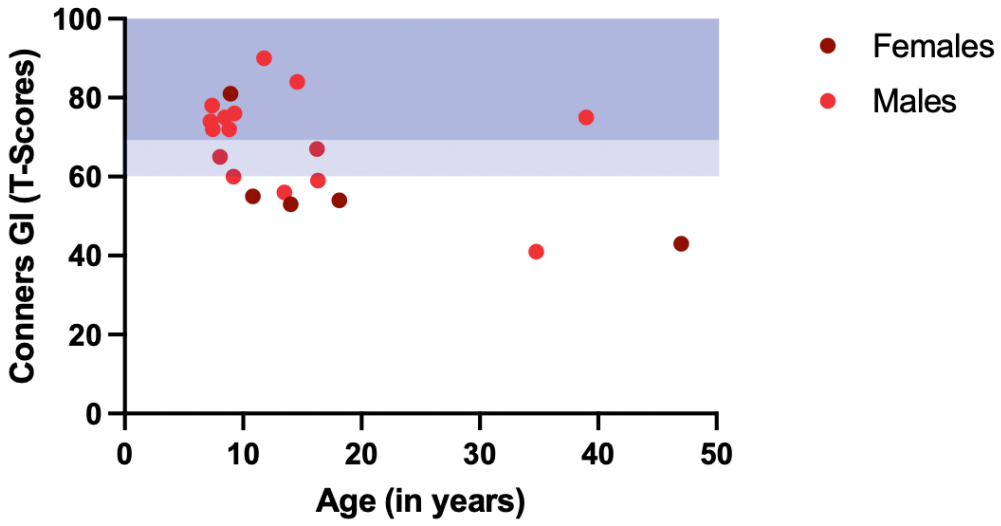
3.5.3. Screening for ADHD traits in the SNIBCPS population.

Half of the population (50%; 10/20) showed clinical levels of behavioural, academic, and emotional issues associated with ADHD as reflected by Conners-3 Global Index Total (GI) scores of the Conners-3 questionnaire (Figure 8). Both DSM-V ADHD Inattentive and DSM-V ADHD Hyperactive-Impulsive symptomatology of ADHD were observed as significant areas of concern in the SNIBCPS population (45%; 9/20 and 55%; 11/20, respectively). The academic area was indicated as a significant area of concern in two-thirds of the younger population (18 and below; 65%; 11/17). Most of the population

scores within the norm in the DSM-V Conduct Disorder (88%; 15/17) and DSM-V Oppositional Defiant Disorders (82%; 14/17) scales on the Conners-3 questionnaire.

Figure 4. Conners-3 Global Index Total (GI) T-Scores.

The normative area is 50 +/- 10. The light shaded area presents the borderline range ("Elevated" and "High Average" area of concern; between 1 and 2 SD). The dark shaded area presents the clinical range "Very Elevated" area of concern; above 2 SD).



3.5.4. Emotional functioning and Psychopathology in the SNIBCPS population and Comparison with Similar Clinical Populations.

About two-thirds (65%; 24/37) of the SNIBCPS population showed CBCL/ ASR Total scores within the norm. About one-quarter (24%; 9/37) of the SNIBCPS population were in the clinical range.

When compared with other clinical populations, such as FXS and ASD groups, a Kruskal-Wallis Test found no significant differences were found among the groups for the ABC-C composite score ($H = 3.10$, $p = .21$, $df = 2$), the hyperactivity subscale ($H = 5.77$, $p = .06$, $df = 2$), irritability subscale ($H = 1.37$, $p = .50$, $df = 2$), lethargy subscale ($H = 1.88$, $p = .39$, $df = 2$), and stereotypy subscale ($H = 1.02$, $p = .60$, $df = 2$).

4. Discussion

Our study aimed to define the neurobehavioral phenotype of the SNIBCPS population and provide insights into the strengths and challenges of this developmental disorder through comparisons with similar clinical populations. In a new cohort of SNIBCPS participants aged between 2 months and 47 years old, 27 males and 14 females, we described levels of adaptive functioning and key behaviours. We found severe impairments in adaptive functioning, communication skills and gross and fine motor abilities, variable socialization skills with reduced engagement in active social "escaping" behaviours and mainly normotypical socioemotional functioning.

Furthermore, we contrasted the behavioral investigation of SNIBCPS participants to cohorts of 33 FXS participants and 49 ASD participants of similar age. We found comparable levels of adaptive functioning and communication skills to FXS, comparable socialization skills to the ASD and FXS and contrasting patterns in social avoidance to FXS.

4.1. Global adaptive functioning

Overall, the SNIBCPS population shows significant impairments in adaptive functioning as reflected by the Vineland-3, a widely used instrument for supporting the diagnosis of intellectual and developmental disabilities (Sparrow, Cicchetti, & Saulnier, 2016). While the formal diagnoses of ID and developmental delay were not feasible within the scope of our study, the results shed light on the challenges faced by this population in terms of independence and managing daily demands. Additionally, their level of support required for daily functioning is comparable with the one of FXS, a well-studied genetic neurodevelopmental syndrome.

4.2. Communication

The present study adds to the existing body of research by providing robust evidence that supports the presence of clinically impaired speech abilities in the examined population. Notably, none of the participants exhibited normotypical communication skills, thus highlighting the substantial nature of

speech delays within this cohort. The significant presence of speech delays in this cohort aligns with the consistent diagnosis of Childhood Apraxia of Speech (CAS) in the initial cohort, which led to the discovery of de novo mutations in *CHD3*, providing insights into the genetic basis of the SNIBCP syndrome. CAS represents a rare neurodevelopmental disorder characterized by impaired acquisition of synchronized sequences of mouth and facial movements essential for fluent speech. Notably, FOXP2, a transcription factor implicated in monogenic CAS variants, has emerged as a key player in CAS. Intriguingly, recent investigations have revealed the CHD3 protein as a notable interaction partner of FOXP2.

4.3. Sensorimotor functioning

This study refines previous findings by elucidating motor-based speech delays and hypotonia as fundamental characteristics within the SNIBCPS population. The preschool cohort exhibits notable impairments in gross and fine motor skills, underscoring early developmental motor deficits. Furthermore, consistent with additional investigations, a high prevalence of suspected DCD is evident across the entire age range studied (5-15 years), with most individuals displaying clinical adaptive motor levels. Complementary evidence from the Sensory Profile questionnaire substantiates hypotonia as a distinctive trait in the SNIBCPS population. Notably, the subdomain focused on body position processing, comprising proprioception-related items (e.g. “Seems to have weak muscles”, “Props to support self”, “Moves stiffly”, “Becomes tired when standing or holding the body in one position”), demonstrates the most pronounced impairments among individuals. Low scores on such items seems to drive low scores on the Registration domain, which states that this population misses sensory input at a higher rate than neurotypicals. Such difficulties in processing and detection of sensory input seem to be associated with disruptions of proprioceptive senses known to signal body shape, body position and movement, and muscle force (25). Disruptions in body signaling have also been reported in previous SNIBCPS cohorts with several individuals experiencing pain insensitivity. Existing literature postulates

compelling hypotheses highlighting the interplay between proprioception and pain, including the sensory-motor incongruity of pain and the gate control theory (26–28). Further investigation is warranted to unravel the intricate connections among proprioception, sensory processing, and pain within the SNIBCPS population. Intriguingly, our study reveals a paradoxical finding wherein most participants miss a substantial amount of sensory input while avoiding it at normal levels. Further investigation unveils that the items within the sensation avoidance domain primarily focus on the social-emotional aspects of sensory processing, aligning with our study's observation of mainly normotypical socioemotional functioning in the SNIBCPS population. These findings expand our knowledge of the sensory-motor impairments encountered by individuals in the SNIBCPS population.

4.4. Social behaviour

The considerable heterogeneity in research findings concerning the social skills of the SNIBCPS population has prompted a comprehensive exploration of this aspect. Despite initial suggestions by a French team regarding hypersociability as a clinical characteristic, no further studies have substantiated this claim to date (29). Sparse information on social skills stems from two previous cohorts, which only reported autistic-like traits in approximately one-third of the population based on clinical observations (9,30). In this study, we systematically investigate various facets of social skills, including social behaviour associated with ASD, social avoidance, and general socialization abilities. Such analysis does not pretend to provide evidence for the ill-defined hypersociability phenotype, but rather to gain a more profound understanding of the population's social interactions within their environment. Evidence on this population’s social functioning stands out from their clinical-level deficits found in other life domains. These individuals are the most adapted on the socialization domain. Their global adaptive scores seem to be driven by their socialization skills. More specifically, their interpersonal relationship skills (i.e their capacity in responding and relating to others) seem to impact their socialization abilities. Remarkably,

their social interactions seem to transcend the challenges posed by reduced motor abilities and significant speech delays.

Nevertheless, despite showing comparable socialization skills to the ASD and FXS populations on the Vineland-3, the SNIBCPS's general socialization skills seem to be unique and hard to define. The highly variable outcomes in assessing social behaviour associated with ASD suggest that the social interaction skills of the SNIBCPS population do not entirely resemble those observed in individuals with ASD. Similarly, SNIBCPS and FXS seems to exhibit contrasting patterns in social avoidance, a core characteristic of the FXS phenotype. Our results suggest that the SNIBCPS population is distinguishable by their reduced engagement in active social "escaping" behaviours when compared to the ASD and FXS populations. Although absence of social avoidance does not infer hypersociability, the study highlights the uniqueness of the SNIBCPS's social interaction. Further data needs to be gathered to corroborate such singularity.

4.5. Emotional functioning and psychopathology

To your knowledge, no other study has investigated socioemotional and behavioural issues with a psychopathological approach (i.e DSM-related scales) within the SNIBCPS population. Approximately half of the population exhibited clinical levels on scales associated with ADHD. Additionally, learning difficulties are revealed as an area of concern within most of the population, which is in concordance with previous evidence of intellectual disabilities (ID) and current findings of severely impaired global adaptive behaviour.

This study suggests that the SNIBCPS population does not exhibit apparent emotional and behavioural problems, which represents a noteworthy strength within this population. Most of the population does not exhibit actively disruptive behaviours associated with conduct or oppositional defiant disorders. Although such findings align with relatively high levels of socialization and absence of social avoidance

behaviours of our study, literature supports the opposite. In fact, rates of psychopathology are much higher for individuals with ID compared to the general population (31). The prevalence of psychiatric disturbances among young individuals with ID is found to be three to four times higher compared to children of average intelligence as 40 to 50% suffer from a psychiatric disorder (32,33). More specifically, disruptive and antisocial behaviours were more prevalent among young individuals with ID, while self-absorbed and social-relating problem behaviours were more common in those with more severe ID (32). Our study reveals evidence for both lower social avoidant and disruptive behaviours in the SNIBCPS group, contradicting current literature and revealing a unique characteristic of the syndrome. Further investigation regarding this population's psychiatric disorders is necessary to support low level of psychopathology as a core feature of the syndrome. Such evidence would alleviate negative impacts associated with psychopathology such as high levels of family stress and parental mental health problems (33–35).

4.6. Limitations

The retrospective design of the study introduced several notable limitations. Firstly, no exclusion criteria were included, which means that the study lacked control over participant's use of medication and behavioural and educational interventions, potentially influencing behaviour ratings. However, excluding individuals who had received or were receiving treatment would have significantly reduced the sample size and led to a biased representation of the SNIBCPS population, thereby failing to encompass the broader population of affected individuals. Moreover, interpretation of results must be conducted with care as validity of standardized questionnaires can be highly influenced by different factors. For example, age and language ability can influence results on questionnaires assessing emotional and behavioural problems. Studies have shown that results tend to underestimate internalizing (i.e. broadly referring to symptoms of anxiety, depression and somatic symptoms), lethargy and irritability symptoms in children with language impairment relative to verbally fluent children and either

over- or underestimate behaviour problems in children under age 5 on the ABC-C (36,37). Additionally, diagnosis of neurodevelopmental disorders can also bias validity, which explains the use of clinical norms and comparisons between different clinical populations in this study. It is important to note that these comparisons analyses were based on different reference groups, namely differences between the clinical populations on the Vineland-3 are based on comparisons of the groups' raw scores to neurotypical norms whereas differences between the clinical populations on the ABC-C for FXS are based on comparisons of the groups' raw scores to FXS norms. Despite limiting interpretation of results, such analyses shed light on various similarities between FXS and SNIBCPS, namely regarding adaptive functioning, socialization skills and communication skills. Other parallels must be investigated between SNIBCPS and other similar neurodevelopmental disorders.

Notably, parent perception bias could have also influenced results. Future research should integrate expert assessments including formal evaluations conducted by medical professionals, neuropsychologists and therapists, a strategic approach to mitigate the impact of bias and attain a more precise depiction of the individuals' neurobehavioral profile. Future studies with larger sample sizes and additional measures (e.g., genetic analysis, IQ/neuropsychological assessments, MRI and EEG) would permit a more complete phenotypic profile of SNIBCPS, which in turn could be used to develop the sparse and unclear literature of the genotype-phenotype association within this population. Three families with inherited variants in *CHD3* participated in the study, which highlights the importance to investigate inheritance of *CHD3* variants and their phenotypic expressivity in the SNIBCPS. To date, only one study has explored the association with results pointing towards an overlap between de novo *CHD3* variants and inherited ones as well as variable expressivity between inherited *CHD3* variants and heterozygote parents (i.e midly or not affected; 34). On the one hand, the descriptive nature of our study aims to reveal core aspects of the syndrome to aid diagnosis and follow-up. On the other hand, generalisation of traits can impede personalized recommendations and interventions. Further efforts of analyzing variability within the

population, such as interfamily variability, could provide valuable information to clinicians and families for better personalized care.

5. Conclusion

In conclusion, this study presents an overview of the neurobehavioral profile observed in 41 individuals with a (likely) pathogenic variant in *CHD3*, known as the SNIBCP syndrome. Our findings reveal significant clinical impairments in adaptive functioning, communication skills and sensorimotor functioning among most of the population. We highlight relatively high socialization levels and low prevalence of emotional and behavioural problems in our sample, which is proposed as relative strengths of this syndrome. Phenotypic similarities and differences are reported between the FXS, ASD and SNIBCPS populations. Although the SNIBCPS and FXS groups show poor adaptive behaviour, socialization skills and communication skills, SNIBCPS exhibit significantly less socially avoidant behaviour, warranting further investigation into the unique social behaviour of this population. This overview provides valuable insights for affected individuals, parents, and healthcare professionals, enhancing our understanding of the typical phenotype of SNIBCPS and its comparison with clinically similar neurodevelopmental disorders.

References

1. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Lond Engl. 2018 Nov 10;392(10159):1789–858.
2. Deciphering Developmental Disorders Study. Prevalence and architecture of de novo mutations in developmental disorders. Nature. 2017 Feb;542(7642):433–8.
3. Chen Q, Chen X, He X, Wang L, Wang K, Qiu B. Aberrant structural and functional connectivity in the salience network and central executive network circuit in schizophrenia. Neurosci Lett. 2016 Aug;627:178–84.
4. Hoffmann A, Spengler D. Chromatin Remodeling Complex NuRD in Neurodevelopment and Neurodevelopmental Disorders. Front Genet. 2019;10:682.
5. Nitarska J, Smith JG, Sherlock WT, Hillege MMG, Nott A, Barshop WD, et al. A Functional Switch of NuRD Chromatin Remodeling Complex Subunits Regulates Mouse Cortical Development. Cell Rep. 2016 Nov 1;17(6):1683–98.
6. Pierson TM, Otero MG, Grand K, Choi A, Graham JM, Young JI, et al. The NuRD complex and macrocephaly associated neurodevelopmental disorders. Am J Med Genet C Semin Med Genet. 2019 Dec;181(4):548–56.
7. Guy J, Staiger JF. The Functioning of a Cortex without Layers. Front Neuroanat. 2017;11:54.
8. Rubenstein L, Siegle D, REIS S, Mccoach DB, Burton MJG. A Complex quest: The development and research of underachievement interventions for gifted students†‡. Psychol Sch. 2012 Aug 1;49.
9. Snijders Blok L, Rousseau J, Twist J, Ehresmann S, Takaku M, Venselaar H, et al. CHD3 helicase domain mutations cause a neurodevelopmental syndrome with macrocephaly and impaired speech and language. Nat Commun. 2018 Nov 5;9(1):4619.

10. Singh A, Yeh CJ, Boone Blanchard S. Ages and Stages Questionnaire: a global screening scale. Bol Méd Hosp Infant México. 2017 Jan;74(1):5–12.
11. Harrison, P.L., & Oakland, T. (2003), Adaptive Behavior Assessment System Second Edition, San Antonio, TX: The Psychological Corporation. - PDF Free Download.
12. Sparrow SS, Cicchetti DV, Saulnier CA. Vineland adaptive behavior scales, Third edition (Vineland-3). NCS Pearson. 2016;
13. Wilson BN, Crawford SG, Green D, Roberts G, Aylott A, Kaplan BJ. Psychometric Properties of the Revised Developmental Coordination Disorder Questionnaire. Phys Occup Ther Pediatr. 2009 Jan;29(2):182–202.
14. Dunn W. Sensory Profile, School Companion: User's Manual. Pearson Psychological Corporation; 2006.
15. Brown C, Dunn W. Adolescent/adult sensory profile. San Antonio, TX: Psychological Corporation; 2002.
16. Sansone SM, Widaman KF, Hall SS, Reiss AL, Lightbody A, Kaufmann WE, et al. Psychometric study of the Aberrant Behavior Checklist in Fragile X Syndrome and implications for targeted treatment. J Autism Dev Disord. 2012 Jul;42(7):1377–92.
17. Chan W, Smith LE, Hong J, Greenberg JS, Mailick MR. Validating the Social Responsiveness Scale for Adults with Autism. Autism Res Off J Int Soc Autism Res. 2017 Oct;10(10):1663–71.
18. Constantino JN, Gruber CP. Social Responsiveness Scale, Second Edition. Los Angeles, CA: Western Psychological Services; 2012.
19. Wilkinson LA. A Best Practice Guide to Assessment and Intervention for Autism Spectrum Disorder in Schools (2nd Edition). London & Philadelphia: Jessica Kingsley Publishers; 2017.
20. Conners KC. Conners 3rd Edition (Conners 3) | Pearson Assessment [Internet]. 2008 [cited 2021 Sep 27]. Available from:

https://www.pearsonclinical.co.uk/Psychology/ChildMentalHealth/ChildADDADHDBehaviour/Conners3rdEdition(Conners3)/Conners3rdEdition(Conners3).aspx

21. Achenbach TM. The Child Behavior Checklist and related instruments. In: The use of psychological testing for treatment planning and outcomes assessment, 2nd ed. Mahwah, NJ, US: Lawrence Erlbaum Associates Publishers; 1999. p. 429–66.
22. Achenbach TM, Rescorla LA. Manual for the ASEBA School-Age Forms & Profiles. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families.; 2001.
23. Achenbach TM, Rescorla LA. Manual for the ASEBA Adult Forms & Profiles. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families.; 2003.
24. Dekker MC, Koot HM, Ende JVD, Verhulst FC. Emotional and behavioral problems in children and adolescents with and without intellectual disability. J Child Psychol Psychiatry. 2002 Nov;43(8):1087–98.
25. Proske U, Gandevia SC. The Proprioceptive Senses: Their Roles in Signaling Body Shape, Body Position and Movement, and Muscle Force. Physiol Rev. 2012 Oct;92(4):1651–97.
26. Melzack R, Wall PD. ON THE NATURE OF CUTANEOUS SENSORY MECHANISMS. Brain. 1962;85(2):331–56.
27. Sakai Y, Watanabe T, Wakao N, Matsui H, Osada N, Sugiura T, et al. Proprioception and Geriatric Low Back Pain. Spine Surg Relat Res. 2022 Sep 27;6(5):422–32.
28. Zampino C, Ficacci R, Checcacci M, Franciolini F, Catacuzzeno L. Pain Control by Proprioceptive and Exteroceptive Stimulation at the Trigeminal Level. Front Physiol. 2018 Aug 7;9:1037.
29. Coursimault J, Lecoquierre F, Saugier-Veber P, Drouin-Garraud V, Lechevallier J, Boland A, et al. Hypersociability associated with developmental delay, macrocephaly and facial dysmorphism points to CHD3 mutations. Eur J Med Genet. 2021 Apr;64(4):104166.

30. Drivas TG, Li D, Nair D, Alaimo JT, Alders M, Altmüller J, et al. A second cohort of CHD3 patients expands the molecular mechanisms known to cause Snijders Blok-Campeau syndrome. Eur J Hum Genet. 2020 Oct;28(10):1422–31.
31. Matson JL, Shoemaker ME. Psychopathology and intellectual disability: Curr Opin Psychiatry. 2011 Sep;24(5):367–71.
32. Einfeld SL, Tonge BJ. Population prevalence of psychopathology in children and adolescents with intellectual disability: II. Epidemiological findings. J Intellect Disabil Res JIDR. 1996 Apr;40 (Pt 2):99–109.
33. Hemmings C, Bouras N, editors. Special topics. In: Psychiatric and Behavioral Disorders in Intellectual and Developmental Disabilities [Internet]. 3rd ed. Cambridge University Press; 2015 [cited 2023 Jul 9]. p. 181–251. Available from: https://www.cambridge.org/core/product/identifier/9781107588714%23PTT-bp-4/type/book_part
34. Tonge BJ, Einfeld SL. Psychopathology and Intellectual Disability: The Australian Child to Adult Longitudinal Study. In: International Review of Research in Mental Retardation [Internet]. Elsevier; 2003 [cited 2023 Aug 13]. p. 61–91. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0074775003010024
35. Gardiner E, Iarocci G. Unhappy (and happy) in their own way: A developmental psychopathology perspective on quality of life for families living with developmental disability with and without autism. Res Dev Disabil. 2012 Nov;33(6):2177–92.
36. Fok M, Bal VH. Differences in profiles of emotional behavioral problems across instruments in verbal versus minimally verbal children with autism spectrum disorder. Autism Res. 2019;12(9):1367–75.
37. Schmidt JD, Huete JM, Fodstad JC, Chin MD, Kurtz PF. An Evaluation of the Aberrant Behavior Checklist for Children Under Age 5. Res Dev Disabil. 2013 Apr;34(4):1190–7.

38. van der Spek J, den Hoed J, Snijders Blok L, Dingemans AJM, Schijven D, Nellaker C, et al. Inherited variants in CHD3 show variable expressivity in Snijders Blok-Campeau syndrome. Genet Med Off J Am Coll Med Genet. 2022 Jun;24(6):1283–96.

Tables

Table 1. Demographics of the study populations.

	SNIBCPS	FXS	ASD
N	41	33	49
Males (n, %)	27 (65.85%)	29 (87.88%)	36 (73.47%)
Females (n, %)	14 (34.15%)	4 (12.12%)	13 (26.53%)
Age			
Mean±SD	9.86±10.04	11.55±6.36	12.04± 3.65
Range	0.17-47	7-20	4-17
Age category			
Preschool (0-4:11 y.o.)	15	0	0
School (5-18 y.o)	22	27	49
Adults (18+)	4	6	0

Table 2. Supplementary information on study questionnaires for the SNIBCPS cohort.

Questionnaire	Domains	Forms	N	Age range (YY:MM)
Vineland-3	ABC, Communication, Daily Living Skills, and Socialization domains	Comprehensive Interview Form (for ages 0-99)	25	0:02-39:02 y.o
ABAS-II	GAC for all ages and social domain for the 0-5 population	Parent (for ages 0-5) Parent (for ages 5-21)	15 20	0:02 – 4:11 5:01-19:04
ASQ-3	Communication, Gross Motor, Fine Motor, Problem Solving and Personal Social	Various forms (for ages one month to 5 ½ years)	15	0:02- 4:11
CBCL/ ASEBA ASR	Total score	Parent form (for ages 1-5)	18	1:02 – 47:06
		Parent form (for ages 6-18)	15	
		Self-Report (for ages 18+)	5	
SRS-2	Total score	Parent form (for ages 2.5-4.5)	6	2:07 - 47:06
		Parent form (for ages 4-18)	24	
		Parent form (for ages 18+)	5	

Conners-3/CAARS	Conners-3 Global Index Total (GI), Learning Problems, DSM-V ADHD Inattentive, DSM-V ADHD Hyperactive-Impulsive, DSM-V Conduct Disorder, DSM-V Oppositional Defiant Disorders Scales	Parent form (for ages 6-18)	17	7:02 - 47:06
	DSM-IV ADHD Inattentive, DSM-IV ADHD Hyperactive-Impulsive, ADHD Index	Self-Report – Screening version (for ages 18+)	3	
DCDQ	Total Score	Parent form (for ages 5-15)	16	7:02 – 15:09
Sensory Profile 2	Registration, Seeking, Sensitivity, Avoiding Quadrants and Auditory, Visual, Touch, Movement, Body Position, Oral,	Caregiver Questionnaire (for ages 3:0 to 14:11)	23	3:0 – 38:11

	Conduct, Social Emotional, Attentional Sections			
	Low registration, Sensation Seeking, Sensory Sensitivity and Sensory Avoiding	Adolescent/Adult Self Questionnaire (for ages 11 to 65+)	5	
ABC-C (revised for FXS population)	Composite score, Inappropriate Speech, Social avoidance, Hyperactivity, Irritability, Lethargy, Stereotypy	Parent Form (FXS norms available for ages 3-25)	29	3:00-19:04

Table 3. Supplemental demographics of the study populations included in the between-groups statistical analyses for the ABC-C-FX

	SNIBCPS	FXS	ASD
N	25	47	49
Males (n, %)	19 (76%)	35 (74.47%)	36 (73.47%)
Females (n, %)	6 (24%)	12 (25.53%)	13 (26.53%)
Age			
Mean±SD	9.2±4.48	12.79±4.47	12.80± 3.30
Range	3-19	5-20	6-17

p-values for age differences:

- ASD vs CHD3: $p = .001$
- FXS vs CHD3: $p = .002$
- ASD vs FXS: NS

Table 4. Supplemental demographics of the study populations included in the between-groups statistical analyses for the Vineland-3

	SNIBCPS	FXS	ASD
N	17	33	49
Males (n, %)	14 (82.35%)	29 (87.88%)	36 (73.47%)
Females (n, %)	3 (17.65%)	4 (12.12%)	13 (26.53%)
Age			
Mean±SD	8.24±3.78	13.39±4.27	12.80± 3.30
Range	3-13	7-13	6-17

***p-values for age differences*:**

- ASD vs CHD3: $p = .002$
- FXS vs CHD3: $p < .001$
- ASD vs FXS: NS