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RESEARCH

Genetic Abnormalities in Neurodevelopmental Disorders with Multidimensional Impairment

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Abstract

Objectives: Many children with neurodevelopmental disorders (NDD) show complex, multidimensional impairments meeting criteria for multiple NDD, yet remain "diagnostically homeless" as DSM-5 lacks a Multidimensional Impairment (MDI) category. We investigated the prevalence of genetic abnormalities in such complex NDD cases. Methods:Between 2017 and 2019, we diagnosed MDI in 666 patients. Among them, 122 (18%) underwent genetic assessment (DNA microarrays, karyotype, gene panels, FISH, FMR1 testing, exome/genome sequencing). We used univariate analyses and clustering to explore associations between clinical dimensions and genetic findings. Results: Genetic abnormalities were identified in 78 patients. Of these:

(1) 41 had known abnormalities usually linked to complex NDD (e.g., del22q11.2);
(2) 16 had mutations associated with severe ASD/ID (e.g., *GRIA3* on Xq25);
(3) 11 showed novel abnormalities not previously linked to NDD (e.g., duplication Xq21.1 including *POU3F4*);
(4) 10 had variants of uncertain significance.

Depending on classification, prevalence ranged from 47% (57/122, definite or predisposition) to 64% (78/122, including uncertain/possible pathogenic variants). Neither clinical dimensions nor severity clusters were associated with the presence of genetic abnormalities. Conclusion:Despite a referral bias toward severe cases, the high rate of genetic findings in this cohort underscores the need for more systematic genetic testing in complex NDD with multidimensional impairment.

Keywords Neurodevelopmental disorders · Copy number variations · Genome sequencing · Phenotype · Psychometrics

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Introduction

Both the DSM-5 and ICD-11 have maintained a categorical approach to Neurodevelopmental Disorders (NDDs), even if some specifiers have been included for some diagnoses (e.g., autism spectrum disorder, ASD). Besides intellectual disability (ID) and ASD, NDDs also include communication and learning disorders, attention deficit hyperactivity disorder (ADHD), Tourette syndrome, and Developmental Coordination Disorder (DCD) (Weisbrot & Carlson 2021). NDDs are highly comorbid with each other (Germanò et al. 2010; Moll et al. 2014; Pham & Riviere 2015). For example, ASD often cooccurs with ID or ADHD; and communication disorder with learning disorders (Xavier & Cohen 2020). To encompass the relevance of comorbidity, several diagnosis proposals have been made, such as deficit in attention motricity and perception (DAMP) in Sweden (Gillberg 2003), multiple complex developmental disorder (MCDD) in the US, or developmental disharmony in France, the last two proposals being related (Xavier et al. 2011). Unfortunately, these attempts to categorize patients into new diagnoses have often associated the presence of psychiatric symptoms, which excludes many patients because complex neurodevelopmental disorders have very heterogeneous presentations. Some complex cases show dysfunction in several developmental milestones in the areas of communication, motor and visual-spatial skills, attention, memory, inhibition, emotion regulation, reading, writing, or math. These cases have been called "diagnostically homeless" in the DSM (Frazier & Carlson 2005) but deserve, in our opinion, their own study. These complex NDDs have a clear adaptive impact, but the trajectory of these patients is generally more favorable and more accessible to interventions than patients with ID or ASD, which are generally two diagnoses of exclusion (American Psychiatric Association, s. d.). We therefore propose a multidimensional approach to neurodevelopment to better address this question.

The concept of multi-dimensionally impaired (MDI) disorder originated from a study conducted by the NIMH on a cohort of patients with childhood-onset schizophrenia (Kumra et al. 1998). Nearly one-third of the patients did not meet the criteria for schizophrenia. These children had many symptoms, including a propensity to have hallucinations and transient delusions under stress. Other cohorts have been studied, such as Buitelaar's and Van Der Gaag's in Holland, who also performed a lot of research in this area (Buitelaar & van der Gaag 1998; van der Gaag et al. 1995; van der Gaag et al. 2005). The group of patients is hard to study, as it is difficult to agree on what symptoms to include. These patients very frequently presented with language and memory disorders, visual-spatial disorders, and disorders of emotion regulation or social cognition. More recently, in a study carried out in our department, 41% of $n = 88$ patients with early-onset schizophrenia (schizophrenia syndrome beginning before the age of 18 years old) had at least one learning disorder, including 16% with language disorders; 74% had an NDD, whatever its comorbidity (Giannitelli et al. 2019). The two concepts are therefore not mutually exclusive, and a strong association between certain disorders seems to exist. The developmental trajectories of these so-called MDI patients are less severe than those in ASD or ID, and, unlike patients with schizophrenia, they never exhibit formal thought disorders (Giannitelli et al. 2019; Kumra et al. 1998).

A modern concept of MDI would encompass a dimensionally exhaustive approach and concern patients with at least two communication and/or developmental disorders. MDI is poorly studied per se in the literature (Xavier & Cohen 2020). Here we will refer to Complex NDD to describe these patients with at least two domains of neurodevelopment impacted, but who do not meet the full criteria of an official DSM-5 diagnosis of ID or ASD. Like other NDDs, different etiological factors can be found, such as macroscopic brain anomalies, obstetrical causes, postnatal factors (traumatic, infectious, toxic), and genetic vulnerability (Zarrei et al. 2019). An interesting genetic syndrome for the concept is 22q11.2 deletion, whose variable phenotype includes many different NDDs (DCD, visual spatial dysfunction, ADHD) that appear highly comorbid (McDonald-McGinn et al. 2015) and less frequently ID, (early onset) schizophrenia, and ASD (Zinkstok et al. 2019).

Regarding the genetics of NDDs, most of the variants identified in the GWAS studies are common variants with minor effects, not sufficient by themselves to explain a significant part of the vulnerability (Gialluisi et al. 2021; Mountford et al. 2021). The variants with higher penetrance are often rare Copy Number Variants (CNVs) or Single Nucleotide Variants (SNVs) (Gialluisi et al. 2021; Mosca et al. 2016). These are often phenotypically non-specific, found in other NDDs such as ID, schizophrenia, ASD (Zarrei et al. 2019), and also in certain neurological disorders such as epilepsy (Borlot et al. 2017; Vissers et al. 2016). These are therefore variants with *incomplete penetrance and variable expressivity*. Known variants in NDDs concern genes mostly expressed in brain tissues and are generally involved in mechanisms of either neurogenesis, neuronal migration, synaptogenesis, neuronal plasticity, pruning, or neurotransmission (Tordjman et al. 2018). Some CNVs impacting these genes and/or mechanisms could potentially contribute to the etiology of multiple NDDs (Zarrei et al. 2019).

Here, we aimed to establish the prevalence of genetic variants found in a single-center cohort of complex NDD patients evaluated in a tertiary university hospital and to investigate whether the existence of a genetic abnormality

was associated with greater severity in one or more specific domains of development.

Methods

Study Design

In 2016, we established a secure computerized database of genetic data as part of the National Referral Center for Psychiatric Rare Diseases, authorized by the Commission Nationale Informatique et Liberté. We conducted a retrospective study on clinical records from 2017 to 2019 in the child and adolescent psychiatry department of Sorbonne University and Pitié Salpêtrière Hospital, APHP, Paris. Complex NDD cases were evaluated using both categorical and dimensional approaches (e.g., intelligence, language, motor coordination, executive functions).

Inclusion/Exclusion Criteria

The study included inpatients and outpatients under 18 years old with two or more developmental disorders (e.g., communication disorder, learning disorder, ADHD, coordination disorder), with no characterized ASD (F84.x), genetic testing including at least a DNA chip, and a medical evaluation in the department (Fig. 1). Exclusion criteria included ID (global IQ < 70, except for some cases of borderline heterogeneous IQ with most indices above 70), missing genetic or clinical data, and evaluations outside the study period.

Patients' Identification

Physicians identified included patients from their lists, and ICD-10 coding records were used to verify diagnoses. We used the following codes: F80.x, F81.x, F82.x, F83.x, F90.x. Autistic traits without characterized ASD have been assessed when appropriate. Diagnoses related to pervasive developmental disorders were not included if they were better understood as forms of depressive disorders, but emotional regulation was still evaluated dimensionally. Inpatients and outpatients from general and specialized consultations (e.g., National Referral Center for Psychiatric Rare Diseases, Referral Center for Developmental Learning Disorders) were included.

The diagram flow is shown in Fig. 2. We identified 666 patients over the years 2017 to 2019 with a diagnosis of complex NDD in the database of the child and adolescent psychiatry department. Among them, 140 accepted and received genetic explorations. The proposal for genetic exploration was based on the psychiatrists' experience with these tests, and the criteria for performing genetic testing

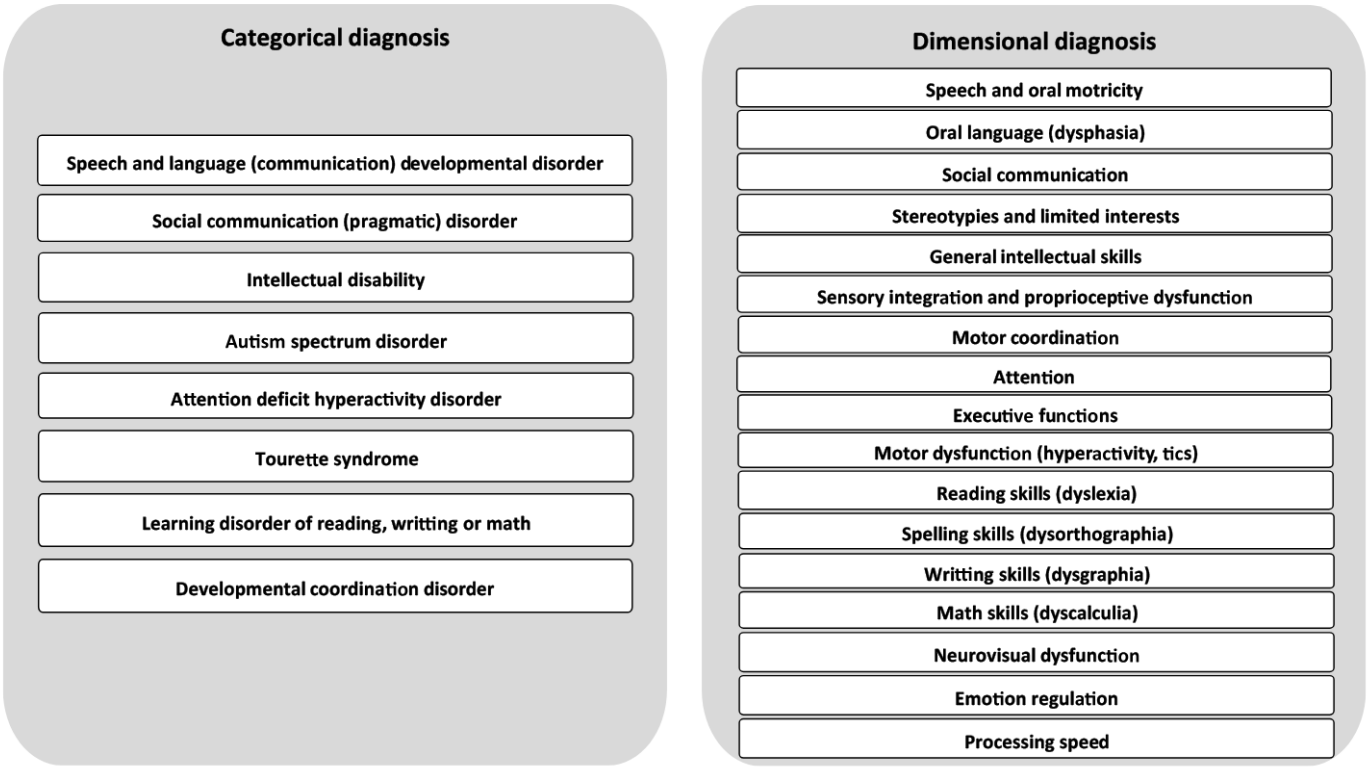

Fig. 1 Neurodevelopmental dimensions and transversal categorical diagnoses evaluated in our cohort of multidimensionally impaired patients with or without responsible genetic diagnosis

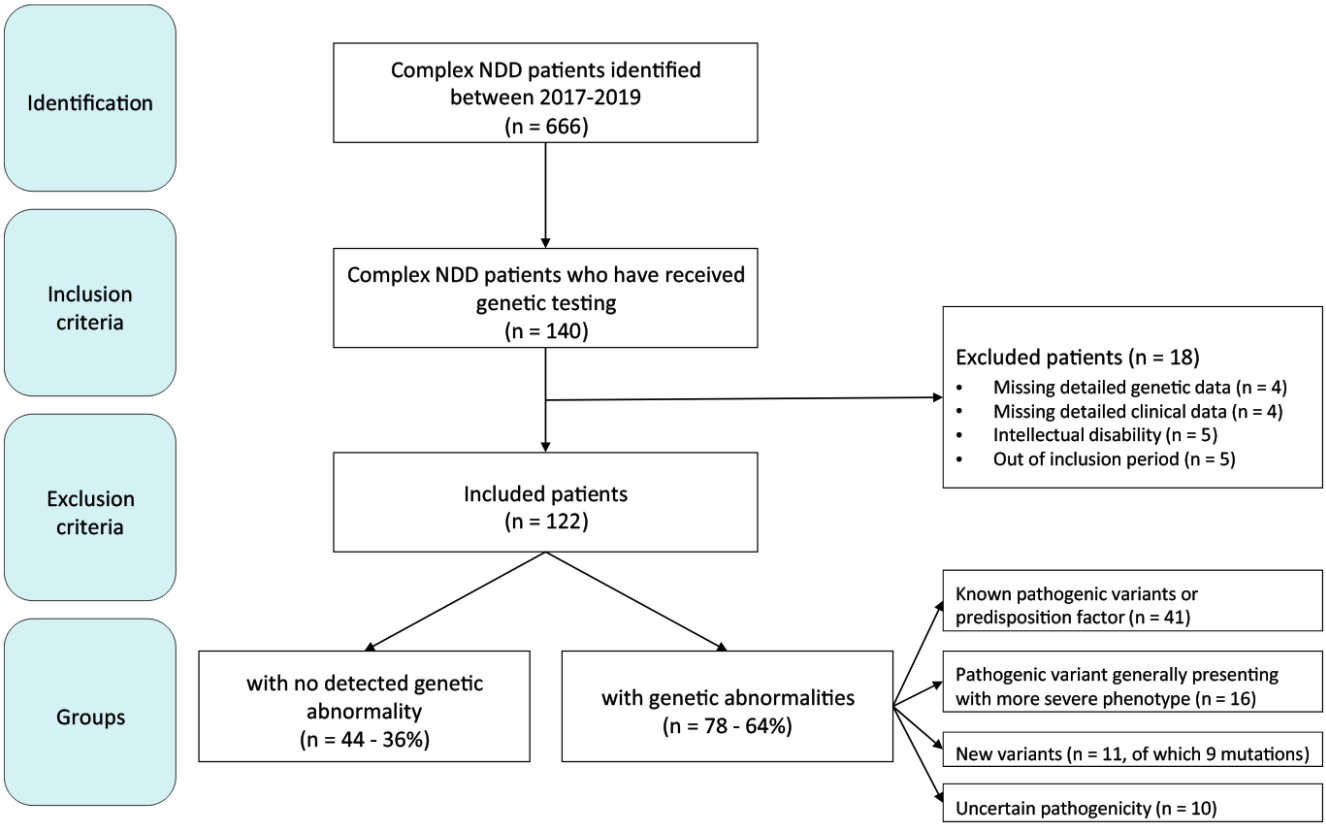

Fig. 2 Flow chart of the study evaluating the proportion of complex NDD patients multidimensionally impaired in our center with or without a genetic diagnosis responsible for their symptoms

was not standardized in the cohort. Among the 140 patients, we excluded $n=4$ (3%) patients for whom genetic data were not available in detail, $n=4$ (3%) patients for whom clinical data were not available either, $n=5$ (4%) patients who presented a diagnosis of ID or ASD, and finally $n=5$ (4%) patients who did not actually correspond to the designated evaluation period.

Clinical Data Collection

Complex NDD clinical forms were designed and filled out by the referring physicians who knew these patients and evaluated the different dimensions of development with a Likert scale ranging from 0 to 3. All assessments were reviewed by a single investigator, and double scoring was performed during data extraction. We first collected the categorical diagnoses of the various NDD, associated pathologies, and the malformative aspects when these were informed.

The different dimensions of neurodevelopment were evaluated using a dimensional approach. Based on specific testing that can be scored in Z-score, percentiles, or standard deviations from norms, we normalized scoring using the method developed by Demouy et al. (l., 2011) for the language domain. Each domain and subdomain (e.g., visual spatial quotient for intelligence, or orofacial motor development for motor development) were evaluated using a scale from 0 to 3 points. We scored the dimensions with 0 points when they were considered normal for a patient. We scored the domain with 1 point when patients had difficulties but no trouble (SD ranging from − 1 to − 2 excluded, or below the 15th percentile). We scored the domain with 2 points when patients had a dysfunction involving the given domain (SD ranging from − 2 to − 3 excluded, or below the 5th percentile). Finally, we scored the domain with 3 points when patients had severe dysfunction involving the domain (SD below − 3, or score below the 1 st percentile).

Patients with borderline intelligence, i.e., an IQ around 70 or slightly below, could be included if the indices were heterogeneous and at least one domain of competence was above 70. When there was a discrepancy between the patient's clinic and the scores obtained in the assessments, an expert opinion was sought from a doctor at the referral center of developmental language and learning disorders to determine the severity of the various dimensions (JM, DC, CG, IZ, AdF). Some mild cases with social interaction dysfunction (social (pragmatic) communication disorder sometimes misdiagnosed with autistic traits) were included if formal ASD diagnosis was not consensual between experts or contradictory between assessments (e.g., Autism Diagnostic Interview and Autism Diagnostic Observation Schedule that

are commonly used in the department). Finally, when quantitative testing was missing to justify the severity, clinical and school data could be used with a lesser degree of certainty (except in the case of a total absence of difficulty, side 0).

Clinically, 8% of the participants had autistic traits ($N=10$), 16% had social pragmatics disorder ($N=19$), 80% of patients had developmental coordination disorder ($N=98$), 62% had ADHD ($N=76$), 70% had oral language disorder ($N=85$), 92% had learning disorder ($N=111$, including 63% dyslexia, 46% dyscalculia, 64% dysorthographia and 66% dysgraphia) (table S1, supplementary materials, any known malformative or somatic comorbidity are described).

Hypothesis

Our main hypothesis is that there is a high prevalence of rare genetic variants (known and often pleiotropic variants, or new variants requiring better description) in the population of patients with complex NDD. We also hypothesize that the presence of genetic variants is correlated with greater severity in a dimensional analysis, in particular a more impacted motor dimension.

Genetic Data Collection

Molecular genetic assessments were performed in the genetic department of our hospital genetic test selection based on clinical suspicion (mostly early onset disorders, malformative features, abnormalities in the physical examination, comorbidities and resistant disorders. More recently, DNA chips are performed for more patients with NDD referred to the hospital). Other assessments were performed depending on available resources and recommendations from the genetics department at the time. Prior to any genetic analysis, both parents' acceptances are needed and information prior to blood puncture is the rule. 91% of patients received a DNA microarray ($N=111$). The samples for DNA microarray were processed on OmniExpress 24 arrays (Illumina) with the Infinium HTS protocol. Images were acquired with the HiScan system (Illumina). Log ratios were determined with the GenomeStudio 2.0.5 software and the genotyping module (Illumina). CNVs were called with the cnvPartition 3.1.6 plugin (Illumina) and annotated with the Bench Lab software (Agilent). Patients who did not have a microarray received either a karyotype and a more focused gene panel or FISH (abnormal return). 13% of patients received targeted FMR1 gene exploration for abnormal triplet repeats ($N=16$). Finally, 23% of the cohort received further exploration by exome or whole genome sequencing ($N=28$).

To examine variants prevalence among the cohort, we used the following filters to classify these variants:

- The American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG-AMP) system for variant classification was used by the genetic department to report class 3 to 5 variants in the cohort, using population data, computational and predictive data, functional data, segregation or de novo data, and allelic data (Richards et al. 2015).
- Localization of Copy Number Variants (CNV) among the genome using genome browser (https://genome.ucsc.edu/cgi-bin/hgGateway). Identification of included genes.
- Previous publications research for variants of the same region or gene using the OMIM database (https://www.omim.org/) and the ClinVar database (https://www.ncbi.nlm.nih.gov/clinvar/)
- For new mutations or variants usually described in other diseases: we used the GeneCard (https://www.genecards.org/) database to classify the patient's mutation.

Statistical Analysis

Statistical analyses were performed using R software 4.1.0, by resorting to bilateral tests with a significance level set to 5%. Quantitative variables were summarized using mean and standard deviation or alternatively median and Q1–Q3 interval, depending on the shape of the distribution. Qualitative variables were described by the number and percentage of occurrences. We first used univariate analysis to compare variables between patients with and without genetic abnormalities. We compared sociodemographic factors, performed genetic searches, categorical clinical diagnoses, and dimensional impairments. Depending on data distribution, we used both parametric and non-parametric tests for quantitative and qualitative variables.

Second, we then explored the data using a method of data reduction through clustering of the dimensional impairments. Clustering was based on the following variables that define complex NDD: Intelligence, Social interaction, Attention, Working memory, Cognitive speed, Other executive functions, Oral Language, Motor coordination, Reading, Writing, Mathematics, Neuro-visual, Emotion regulation. Prior to clustering, we first replaced the missing values with their predicted values using a non-parametric missing data imputation algorithm (missForest package). Secondly, we scaled the data to ensure maximum effectiveness of the algorithm. Finally, since there is always a risk of finding patterns in random data (i.e., non-meaningful clusters), we assessed the dataset for clustering tendency using visual analysis (seriation package). The clustering phase consisted of the comparison of three clustering algorithms: K-means clustering, partitioning around medoids (PAM), and hierarchical cluster analysis (HCA). We chose K-means clustering based on clustering stability using bootstrap resampling (fpc package, 1000 replications), silhouette plots, and by comparing

the distribution of clustering variables between clusters. The optimal number of clusters was assessed graphically (factoextra package) and found to be 2.

After K-means clustering, we compared the distribution of other variables of interest between the two clusters previously obtained. Comparisons involving quantitative variables were performed using either Welch t-test or Wilcoxon rank sum test, depending on tests' assumptions validity. Comparisons involving qualitative variables were performed using either chi-squared test or Fisher's exact test, depending on tests' assumptions validity.

Ethics

The data collection was conducted during the medical care of inpatients and outpatients. Parents of patients approved the collection of data. Study "MULTIDYSGEN" was approved by the local ethic committee of AP-HP as a MR004 (study number 20220602151048).

Results

Description and Prevalence of Genetic Features

Participants' clinical and sociodemographic characteristics are shown in Table 1. The mean age was 12.4 years at the time of evaluation, and there were 71% males. More than 80% of patients had pre-, neo-, and post-natal risk factors. The average gestational age was close to term, with 3.6% preterm birth ($n=5$, 100% of them being early preterm birth 32–34 weeks). The *settings* at birth were close to normal over the whole cohort with little variation. In particular, there was little intrauterine growth restriction and little growth retardation. Among the 122 included patients, 44 (36%) had no abnormal genetic finding on initial clinical test examination (DNA microarray (first-line), and when clinically indicated, FMR1 testing or karyotype), and the other 78 (64%) had an identified genetic abnormality (Table 1). Among these patients with identified genetic abnormalities, 41 had one or more well-known and well-described pathogenic or predisposition variants, and 16 had abnormalities that have been previously reported in a generally more severe phenotype of NDD such as ID and/or ASD. In addition, 11 patients presented abnormalities comprising 14 distinct variants that, to our knowledge, have not been previously described or whose molecular mechanisms deserve particular attention. This group included three patients each with a single SNV of interest, five patients each with a single CNV of interest, including three siblings carrying the same CNV, one patient with both a CNV and a balanced translocation, one patient with two distinct CNVs, and one patient with three CNVs in addition to a SNV of interest. Finally, 10 patients had abnormalities with uncertain pathogenicity (inherited CNV from NDD-parent or unknown parental status).

Table 1 Sociodemographic characteristics available in the ComplexNDD cohort ($N=122$)

Age at assessment: mean (SD)	12.4 (9.13)
Gender (female/male)	35 (29%)/87 (71%)
Gestational age at delivery: mean (SD)	38.66 (1.99)
Apgar score 1 mn (/10)	9.45 (1.44)
Apgar score 5 mn (/10)	9.94 (0.28)
Weight at birth (g): mean (SD)	3094.73 (700)
Height at birth (cm): mean (SD)	49.76 (5.69)
Head circumference (cm): mean (SD)	34.69 (2.41)
At least 1 prenatal risk factor	94 (84%)
At least 1 perinatal risk factor	96 (86%)
At least 1 neonatal risk factor	95 (84%)
Genetic abnormality diagnosed	78 (64%)
Karyotype performed	108 (91%)
DNA microarrays performed	111 (94%)
Gene panels or FISH performed	81 (86%)
FMR1 testing performed	16 (17%)
Whole exome or genome sequencing performed	28 (23%)
Tourette syndrome	2 (2%)
Autistic traits	10 (8%)
Social communication disorder	19 (16%)
Developmental coordination disorder	98 (80%)
ADHD	76 (62%)
Language and speech disorder	85 (70%)
Specific disorder of scholastic skills (≥ 1)	111 (92%)
Specific reading disorder	76 (63%)
Mathematics disorder	54 (46%)
Disorder of written expression	77 (64%)

According to French law and the methodology proposed when the database was collected, data about race, ethnicity, or religion were not collected for this study. *ADHD*, attention deficit hyperactivity disorder; *FISH*, fluorescence in situ hybridization; *IUGR*, intra-uterine growth restriction; *NDD*, neurodevelopmental disorder; *SD*, standard deviation.

Sociodemographic Characteristics and Genetic Testing Summary of the 122 Patients with Complex NDD

Tables 2, 3, 4, and 5 summarize the variants found in our cohort and for SNVs the genes involved. Among the most common variants (Table 2), we found variants in the 15q11-q13 region (e.g., Prader-Willi syndrome), variants in the 22q11.2 region, variants in the 1q21.1 region, sex chromosome anomalies (e.g., XXX or Turner Sd.), or mutations responsible for well-known genetic diseases such as neurofibromatosis, myotonic dystrophy type 1, or

Table 2 Genetic variants identified in the ComplexNDD cohort, group 1: known pathogenic variants or predisposition factors ($N=41$)

Genomic localization (Chr, genes, or variant when known*)	Variant type	CNV size	Transmission	N subjects
1q (coordinates not available)	CNV, deletion	Unknown	De novo	1
1p13.3p11.2 (chr1: 107,335,538–121322377, GRCh37)	CNV, duplication	14 Mb	De novo	1
1q21.1 (chr1: 144,940,840–146290831, GRCh37, recurrent NDD loci)	CNV, duplication	1349 kb	De novo	1
1q32.1, *RBBP5* variant, c.980A > C: p.Glu327Ala, *VARS1* variant, c.518G > A: p.(Arg173Gln)	SNV	-	De novo	1
2p22.3 (coordinates not available)	CNV, deletion	132 kb	De novo	1
5p (coordinates not available)	Translocation	Unknown	De novo	1
7p22.1 (coordinates not available)	CNV, deletion	150 kb	Inherited (NDD + father)	1
9p24.3p24.2 (coordinates not available)	CNV, deletion	6100 kb	De novo	1
10q25.1 (chr10: 109,006,453–109856031, GRCh37)	CNV, duplication	849 kb	Inherited (NDD + father)	1
11q23.3, including *KMT2A* (Wiedemann Steiner syndrome)	CNV, deletion	Unknown	De novo	1
11q24.3q25 (chr11:130,703,906–13429260, GRCh37)	CNV, duplication	725 kb	Inherited (NDD + mother)	1
15q11.2 (coordinates not available)	CNV, deletion	400 kb		
12q13.12, *MLL2* variant, c.7140delG. c.7147*	SNV	-	Unknown	1
13q12.1, *GJB2* variant	SNV	-	De novo	2
15q11-q13 (Prader Willi syndrome)	CNV, deletion	6 Mb	De novo	1
15q11.2 (chr11:22,784,523–23,179,948, GRCh37)	CNV, duplication	Unknown	De novo	1
15q12 (coordinates not available)	CNV, duplication	Unknown	De novo	2
15q13.3, (coordinates not available, includes *CHRNA7)*	CNV, duplication	Unknown	Unknown	1
16p11.2 (chr16: 29,595,483–30,198,151, GRCh37, including *PRRT2* and *ALDOA,* recurrent NDD loci)	CNV, deletion	218 kb	De novo	2
16p13.3, *CREBBP* variant, (p.Arg1786His) (Rubinstein Taybi syndrome)	SNV	-	Inherited	1
17q11.2, *NF1* variant (neurofibromatosis type 1)	SNV	-	De novo	2
19q13.3, CTG extension in *DMPK* gene (Steinert disease type 1)	Triplet extension	-	De novo	3
22q11.2 (Di George syndrome)	CNV, deletion	3 Mb	De novo	7
22q11.2 (coordinates not available)	CNV, duplication	3 Mb	De novo	2
Sexual Chromosomes (Turner syndrome)	Aneuploidy	-	De novo	1
Sexual Chromosomes (XXX trisomy)	Aneuploidy	-	De novo	1
Sexual Chromosomes (47XYY)	Aneuploidy	-	De novo	2
Sexual Chromosomes (Fragile X syndrome)	Triplet extension	-	Amplification	1

Wiedemann-Steinert disease/syndrome. The 16 patients in "the second group" (Table 3) had anomalies described in the literature, generally in patients with more severe NDD such as ASD and ID. These included variants in the Xq25 region, partial trisomy 8p or 8q, or deletion 3q29. Finally, the third group of interest included 11 patients (Table 4) with 9 anomalies of interest undescribed or presenting a molecular mechanism of interest justifying further study (each case is detailed in supplementary materials). Finally, 10 patients had abnormalities that did not meet criteria of pathogenicity (e.g., no information about transmission and/or poorly known variant, clinical status of parent unknown for inherited variants, or incomplete genetic data) (Table 5).

In the population studied, genetic analyses are not routinely carried out in current practice. The tests were carried out in different genetic centers, and the data sent back to the prescribing psychiatrists were often partial and incomplete in the medical files. In some cases, only clinically relevant data were available. We have endeavored to gather as much detail as possible on the variants found, but the quality of the information remains highly heterogeneous. In view of the high prevalence of variants found in this population, this work supports the need for more systematic genetic testing in the future, which will enable us to better pinpoint pathological genetic anomalies and susceptibility factors.

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Table 3 Genetic variants identified in the ComplexNDD cohort, group 2: pathogenic variant generally presenting with more severe phenotype ($N=16$)

Genomic localization (Chr, genes, or variant when known*)	Variant type	CNV size	Transmission	N subjects
1q32.1, missense variant in *KDM5B*	SNV	-	Unknown	1
3q29 (coordinates not available, well-known locus for schizophrenia and NDD, includes candidate genes for schizophrenia)	CNV, deletion		De novo	1
5q31.2, missense variant in *ETF1*, c.380G > A,Chr5(GRCh37): g.137853272C > T, p.(Cys127Tyr)	SNV	-	De novo	1
6q25, (coordinates not available, includes *ARID1B)*	CNV, deletion	Unknown	De novo	1
10q23.31, *PTEN* variant (Cowden syndrome)	SNV	-	De novo	1
11q23.3, missense variant in *KMT2A*, c.10523 T > C: p.V3508A	SNV	-	Unknown	1
12q13.12, *TUBA1A* variant, c.349C > T p.Leu117Phe	SNV	-	De novo	2
14q32.33, missense variant in *PACS2*, chr14:g.105834449G > A, c.625G > A, p.Glu209Lys	SNV	-	De novo	1
15q24.2 (coordinates not available)	CNV, deletion	507 kb	De novo	1
16q24.3 (KBG Syndrome)	CNV, deletion	Unknown	De novo	2
16q12.1-q12.2 (chr16; 49,176,461–51,834,420, GRCh37, including *CBLN1*, *NKDI*, *ADCY7*, *TENT*	CNV, deletion	2.6 Mb	Unknown father status	1
17q12, (coordinates not available, includes *HNF1beta)*	CNV, deletion	1300 kb	De novo	1
Sexual Chromosome, Xq25, including *GRIA3*, c.1888G > A: p.Gly630Arg	SNV	-	Inherited (NDD + heterozygous mother)	2

Table 4 Genetic variants identified in the ComplexNDD cohort, group 3: novel variants of interest ($N=11$)

Genomic localization (Chr, genes, or variant when known*)	Variant type	CNV size	Transmission	N subjects
2p14, *PPP3R1* variant: c.354 T > A: p.(Asp118Glu)	SNV	-	De novo	1
2p16.3 (chr2: 48,697,682–48,910,133, GRCh37)	CNV, duplication	212 kb	De novo	1
2q13, (chr2: 110,852,875–110980346, GRCh37, including *NPHP1*)	CNV, duplication (homozygous)	127 kb	De novo	1
(chr1;2)(q43;p24)	Translocation (balanced)	Unknown	Inherited	
4q26 (chr4: 114,918,311–115,239,572, GRCh37, including *NDST4* intron 6/16)	CNV, duplication	321 kb	De novo	1
17q24.1q24.2 (chr17: 65,559,700–66494778, GRCh37, including *AXIN* 2 intron 1/10, *PRKCA* intron 1/16, *CEP112*, *APOH*)	CNV, duplication	915 kb	Inherited (NDD + mother)	
4q32.1q32 (chr4: 157,334,113–157,340,183, GRCh37, including *GRIA2*)	CNV, deletion	6 kb	De novo	1
1q21.2 (chr1: 142,536,083–144895977, GRCh37, including *PDE4DIP*)	CNV, duplication	2.3 Mb	Inherited (NDD + father)	1
7q22.1 (chr7: 101,599,027–101678460, GRCh37, including *CUX1*)	CNV, duplication	79 kb	De novo	
9p11.12 (chr9: 43,314,059–44271394, GRCh37, including *CNTNAP3B*)	CNV, deletion	957 kb	Inherited (NDD + father)	
12p13.33, *CACNA1C* variant, see Supplementary data 1	SNV	-	Inherited	
14q32.2, *BCL11B* variant c.2646_2649del: p.Asn884Thrfs*112	SNV	-	De novo	1
16p11.2, *GDPD3* variant, c.830G > A, g.30116320C > T,p.(Trp277*)	SNV	-	De novo	1
Xq21.1 (chrX: 82,161,602–82795961, GRCh37, including *POU3F4*)	CNV, duplication	634 kb	Inherited (NDD + mother)	3

Table 5 Genetic variants identified in the ComplexNDD cohort, group 4: uncertain pathogenicity* ($N=10$)

Genomic localization (Chr, genes, or variant when known*)	Variant type	CNV size	Transmission	N subjects
3q23.3	CNV, duplication	228 kb	Inherited (NDD- mother)	2
5p12-13.2	CNV, deletion	Unknown	Unknown	1
5p13.1 (chr5:41,901,991–41946529, GRCh37)	CNV, deletion	45 kb	Unknown	1
6q21, including *DDO*	CNV, deletion	12 kb	Inherited but unknown clinical status of parents	1
7q11.21, including *KCTD7*	CNV, duplication	424 kb	Unknown	1
8p and 8q partial trisomy (uncertain boundaries)	Aneuploidy	Unknown boundaries	Unknown	1
partial trisomy of chromosome 8, with insertion in chromosome 1	CNV, duplication-insertion	Unknown boundaries	Inherited (NDD- mother)	1
12q23.1	CNV, duplication	551 kb	Unknown (adoption)	1
13q	CNV, duplication	238 kb	Inherited (NDD- parent)	1

in the future, which will enable us to better pinpoint pathological genetic anomalies and susceptibility factors.

In the population studied, genetic analyses are not routinely carried out in current practice. The tests were carried out in different genetic centers, and the data sent back to the prescribing psychiatrists were often partial and incomplete in the medical files. In some cases, only clinically relevant data were available. We have endeavored to gather as much detail as possible on the variants found, but the quality of the information remains highly heterogeneous. In view of the high prevalence of variants found in this population, this work supports the need for more systematic genetic testing in the future, which will enable us to better pinpoint pathological genetic anomalies and susceptibility factors.

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Genetic variants identified in the Complex NDD cohort grouped by known pathogenic variants, more severe NDD variants, novel variants of interest, and variants with uncertain pathogenicity.

*Inherited CNV from NDD-parent or unknown parental status: here we consider incomplete penetrance or possible pathogenic variant if variant were de novo or inherited by undiagnosed parent.

We estimated the prevalence ranges of genetic abnormalities in our sample of complex NDD according to pathogenicity. Whether or not we accounted only for the pathogenic variants, the prevalence ranged between 47.5% ($N=58/122$), based on certain or probable pathogenicity, to 64% ($N=78/122$) based on uncertain and possible pathogenicity.

Group Comparison

Table 6 summarizes sociodemographic, perinatal risks, genetic assessments, and clinical characteristics of the 122 patients with complex NDD according to the presence of a genetic abnormality. The groups with and without identified genetic abnormalities were comparable in sex and age, as well as for obstetrical parameters, adaptation to extrauterine life, and prevalence of preterm births. In terms of clinical genetic testing, patients with identified abnormalities more often underwent second-line exome/genome sequencing after microarray (exome or genome sequencing 29.9% vs 11.4%, $p=0.02$), while investigation of an incomplete or full mutation of the FMR1 gene was more frequently performed as first-line exploration in the group that ultimately had no genetic abnormality (27% vs 10.5%, $p=0.038$).

Categorical NDD diagnosis distribution did not show any significant difference between groups, except for math disorder, which was more frequent in the group with genetic abnormalities (53.2 vs 31.7%, $p=0.025$). Similarly, the number of NDDs did not differ between the two groups. The dimensional analysis that included more clinical domains and a severity score by domain did not show any significant difference either. Mean severity was similar across domains and between groups. Similarly, the global severity, which added up the severity of each domain, was not different between the two groups.

ADHD, attention deficit hyperactivity disorder; *C section*, Caesarean section; *FISH*, fluorescence in situ hybridization; *IUGR*, intra-uterine growth restriction.

Table 6 Neurodevelopmental disorders with multidimensional impairment according to genetic abnormality

	Genetic abnormality (*N* = 78, unless specified)	**No abnormality (*N* = 44, unless specified)**	**Test**	***p*-value**
Sociodemographics				
Sex (F)	24 (30.8%)	11 (25%)	Chi^2	0.499
Age at testing (y)	13 (11.5)	11 (4.39)	*t*	0.720
Perinatal risks				
Prenatal risk factor(s)	59 (81.9%)	35 (87.5%)	Chi^2	0.443
Perinatal risk factor(s)	61 (84.7%)	35 (87.5%)	Chi^2	0.687
Pre-eclampsia	1 (1.4%)	2 (5%)	*F*	0.29
Eclampsia	None	None	-	-
Diabetes	3 (4.2%)	4 (10.3%)	*F*	0.239
IUGR	14 (19.7%)	7 (17.5%)	Chi^2	0.775
Breech presentation	3 (4.5%)	1 (2.6%)	*F*	1
C section	14 (21.5%)	10 (25.6%)	Chi^2	0.631
Gestational age (weeks of amenorrhea)	39 [38–40]	39 [37–40]	*W*	0.382
Apgar 1 mn (/10)	10 [9.75–10]	10 [10–10]	*W*	0.726
Apgar 5 mn (/10)	10 [10–10]	10 [10–10]	*W*	0.15
Birth weight (g)	3200 [2785–3500]	3040 [2730–3500]	*W*	0.508
Birth height (cm)	50 [48–51]	49.5 [48–51]	*W*	0.891
Head circumference (cm)	34 [33–35]	35 [34–36]	*W*	0.144
Neonatal risk factors	61 (83.6%)	34 (85%)	Chi^2	0.842
Hyperbilirubinemia	5 (6.9%)	3 (7.9%)	*F*	1
Birth defect	12 (16%)	5 (11.4%)	Chi^2	0.485
Molecular assessment				
Karyotype	34/62 (55%)	18/40 (45%)	*F*	0.010*
CGH array or ACPA	68/74 (91.9%)	43 (97.7%)	*F*	0.006*
Gene panel, or FISH	21/58 (36%)	9/36 (25%)	*F*	0.009*
FMR1	51 (89.5%)/6 (10.5%)	27 (73%)/10 (27%)	Chi^2	0.038*
Sequencing	24 (30.8%)	5 (11.4%)	Chi^2	0.02*
Neurodevelopmental disorders				
Tourette syndrome	1 (1.3%)	1 (2.3%)		1
Autistic traits	6 (7.8%)	4 (9.3%)		0.744
Social communication disorder	11 (14.1%)	8 (18.2%)		0.551
Developmental coordination disorder	60 (76.9%)	38 (86.4%)		0.208
ADHD	47 (60.3%)	29 (65.9%)		0.536
Language and speech disorder	53 (67.9%)	32 (72.7%)		0.581
Specific disorder of scholastic skills (≥ 1)	72 (93.5%)	39 (88.6%)		0.494
Specific reading disorder	46 (59.7%)	30 (68.2%)		0.355
Mathematics disorder	41 (53.2%)	13 (31.7%)		**0.025***
Disorder of written expression	50 (64.9%)	27 (61.4%)		0.694
Dimensional score				
Emotions' regulation	0 [0–1]	1 [0–2]		0.096
Intelligence	1 [0–1]	1 [0–1]		0.839
Attention	2 [1–2]	2 [0–2]		0.406
Working memory	1 [0–2]	1 [0–1]		0.184
Processing speed	1 [0–2]	1 [0–2]		0.791
Other exec. functions	1 [0–2]	1 [0–2]		0.517
Oral language	2 [1–3]	2 [1–3]		0.647
Written language	2 [1–3]	2 [2–3]		0.679
Global motricity	2 [1–3]	2 [2–3]		0.817
Writing skills	2 [1–3]	2 [1–3]		0.884

Table 6 (continued)

	Genetic abnormality ($N=78$, unless specified)	No abnormality ($N=44$, unless specified)	Test	p-value
Maths	2 [0–2]	1 [0–2]		0.261
Neuro-visual	2 [0.5–3]	2 [1–3]		0.86
Dysgraphia	50 (64.9%)	30 (68.2%)		0.717

To explore clinical domains using data reduction, we performed a K-means clustering based on neurodevelopmental severity domain scores, as we found high correlations between neurodevelopmental domains (see correlation matrix in figure S1, supplementary materials). The best solution comparing these different clustering algorithms was a 2-cluster solution using K-means clustering (see figure S2, supplementary materials). We found a less severe cluster-1 ($N=67$) on all neurodevelopmental domains except emotion regulation and a more severe cluster-2 ($N=55$). Mean pathological domains were 3 in cluster-1 compared to 6 in cluster-2. Table 7 summarizes sociodemographic, perinatal risks, genetic abnormalities, and dimensional clinical characteristics of the 122 patients with complex NDD according to clusters 1 and 2. As expected, all neurodevelopmental domains were more severe in cluster-2 than cluster-1. Similarly, in terms of ICD-10 diagnoses, we found a higher proportion of DCD, ADHD, language and speech disorder, and reading and math disorders in cluster-2 than cluster-1. No significant difference was found for sociodemographic and perinatal risks. Most importantly, the presence of genetic abnormalities was similar in cluster-2 and cluster-1.

Discussion

In the current categorical approach of both DSM-5 and ICD-10/11, our work had two aims: to establish the prevalence of genetic variants in complex NDD, and to investigate whether the existence of a detected genetic abnormality was associated with greater phenotypic severity. As expected, dimensional analysis of neurodevelopment of complex situations showed that our sample included patients with complex NDD highly comorbid for neurodevelopment dimensions and diagnoses. The first result is the particularly high prevalence of clinically relevant genetic abnormalities ranging from 47.5 to 64%. We are aware that the higher estimate may be inflated. Some of the variants identified may not be pathogenic. This is a retrospective study with incomplete data regarding the health status of parents and their genetic testing results (Lal et al. 2020). Also, some novel variants are of uncertain signification (e.g., class 3 CNV (Riggs et al. 2020)). Exome and genome sequencing were less frequently performed in the group without genetic abnormalities, which could possibly lead to reclassifying some of these to be the group with genetic abnormalities if they were evaluated by these methods. Contrarily, some findings defined as class 3 or 4 variants with missing data (such as parents not being tested, or variants not previously reported in databases) may be reclassified as "predisposition factors" in a multigenic model, or may even be considered benign or unrelated to the present condition. However, the lower estimate indicates a high prevalence of genetic abnormalities, yet under-recognized, in individuals with complex NDD. This suggests that clinical genetic testing should be performed in patients with complex NDD, at least with DNA chips, and sequencing when possible for individuals with no abnormality in DNA chips. Some transition models are already proposed, allowing the integration of genetic etiological information—starting with diagnostically proven CNVs—within the DSM-5 classification framework (Vorstman and Scherer 2021).

Regarding our second aim, K-means clustering based on our dimensional approach revealed 2 clusters, one more severe on all dimensions and one less severe. It is likely that in some other studies or sites, the more severe patients would be classified as "missed ID patients" or borderline intelligence (e.g., IQ < 85) and may question the definition of ID or the precision of tools, as their general cognitive level is sometimes close to the IQ threshold of ID. They also share some genetic risk factors with variable expression. However, as shown in Table 6, genetic findings did not differ between the two clusters, which is consistent with a syndromic and specific approach to complex NDD patients (Xavier and Cohen 2020). Many of the identified genetic abnormalities have previously been known in other isolated NDD, or often associated with syndromes that have been associated with ASD or ID. The role of polygenic effects of common variants may help to explain these results (Kim & State 2014). However, these phenotype data are missing since genetic samples were collected following clinical needs. In this retrospective study, genetic results were clinically reported by geneticists focusing on deleterious variants that can explain the clinical context, i.e., variants in genes expressed in the brain, or variants with an already known effect on brain development, neuronal migration, neurotransmission, or involved in more acute neurodevelopmental disorders. Genetic testing seems to be as important in this population as it is for ID or ASD patients, providing

Table 7 Neurodevelopmental disorders with multidimensional impairment according to clustering

	Cluster 1 ($N = 67$)	Cluster 2 ($N = 55$)		p-value
Variables included in the K-means clustering				
Emotion regulation	0 [0–1.41]	1 [0–2]		0.247
Intelligence	0.08 [0–1]	1 [1–2]		< 0.001
Social interaction skills	0 [0–0]	0 [0–1]		0.002
Attention	1 [0–2]	2 [1.5–3]		< 0.001
Working memory	0 [0–1]	1.68 [1–2]		< 0.001
Processing speed	0.86 [0–1]	2 [1–2]		< 0.001
Other executive functions	1 [0–1.76]	2 [1–2.17]		< 0.001
Oral language	1.62 [0–3]	2 [2–3]		< 0.001
Written language	2 [1–3]	2.03 [2–3]		0.018
Global motricity	2 [1–2]	3 [2.5–3]		< 0.001
Writing skills	1 [0.5–2]	3 [2–3]		< 0.001
Maths	1 [0–1.44]	2 [1.64–2.74]		< 0.001
Neuro-visual	1 [0–2]	3 [2–3]		< 0.001
Number of spec dev. disorders	3 [2–5]	6 [5–7]		< 0.001
Global severity	13 [10–16]	22 [20–25]		< 0.001
Variables not included in the K-means clustering				
Sex (F/M)	22 (32.8%)/45 (67.2%)	13 (23.6%)/42 (76.4%)	Chi^2	0.264
Genetic (abnormal/normal)	45 (67.2%)/2 (32.8%)	33 (60%)/22 (40%)	Chi^2	0.412
Gestational age at delivery: mean (SD)	39 [38–40]	39 [38–40]	*W*	0.202
Apgar score 1 mn (/10)	10 [9–10]	10 [10–10]	*W*	0.237
Apgar score 5 mn (/10)	10 [10–10]	10 [10–10]	*W*	0.877
Weight at birth (g): mean (SD)	3160 [2732.5–3500]	3175 [2782.5–3500]	*W*	0.64
Height at birth (cm): mean (SD)	49 [47–51.25]	50 [48–51]	*W*	0.74
Head circumference (cm): mean (SD)	34 [33.5–35]	34 [33.5–36]	*W*	0.479
Prenatal risk factors	8 (12.7%)/55 (87.3%)	10 (20.4%)/39 (79.6%)	Chi^2	0.27
Perinatal risk factors	10 (15.9%)/53 (84.1%)	6 (12.2%)/43 (87.8%)	Chi^2	0.586
Neonatal risk factors	10 (15.9%)/53 (84.1%)	8 (16%)/42 (84%)	Chi^2	0.985
Breech presentation	57 (96.6%)/2 (3.4%)	44 (95.7%)/2 (4.3%)	*F*	1
C section	45 (77.6%)/13 (22.4%)	35 (76.1%)/11 (23.9%)	Chi^2	0.857
C section	45 (77.6%)/13 (22.4%)	35 (76.1%)/11 (23.9%)	Chi^2	0.857
Intensive care unit	57 (91.9%)/5 (8.1%)	46 (92%)/4 (8%)	*F*	1
Birth defect	10 (15.4%)/55 (84.6%)	7 (13%)/47 (87%)	Chi^2	0.707
Autistic traits	62 (95.4%)/3 (4.6%)	48 (87.3%)/7 (12.7%)	*F*	0.183
Social communication disorder	57 (85.1%)/10 (14.9%)	46 (83.6%)/9 (16.4%)	Chi^2	0.827
Developmental coordination disorder	23 (34.3%)/44 (65.7%)	1 (1.8%)/54 (98.2%)	Chi^2	< 0.001
ADHD	33 (49.3%)/34 (50.7%)	13 (23.6%)/42 (76.4%)	Chi^2	0.004
Language and speech disorder	29 (43.3%)/38 (56.7%)	8 (14.5%)/47 (85.5%)	Chi^2	0.001
Specific disorder of scholastic skills (≥1)	8 (12.1%)/58 (87.9%)	2 (3.6%)/53 (96.4%)	*F*	0.109
Specific reading disorder	31 (47%)/35 (53%)	14 (25.5%)/41 (74.5%)	Chi^2	0.015
Mathematics disorder	46 (70.8%)/19 (29.2%)	18 (34%)/35 (66%)	Chi^2	< 0.001
Disorder of written expression	28 (42.4%)/38 (57.6%)	16 (29.1%)/39 (70.9%)	Chi^2	0.129

etiological explanations for some patients in relatively similar proportions, and exploring interesting etiopathological perspectives for some others. We also expect a significant overlap between susceptibility factors given the variable expressivity of variants across these spectra.

We found no difference in the prevalence or severity of NDD in isolation according to the presence or absence of an identified genetic abnormality. The available data do not therefore allow us to conclude that a different positive molecular result may be predicted depending on whether a specific profile is found in these cognitive/developmental tests. The impact of genetics on more specific dimensions or clusters has not been established and warrants further prospective research (Chawner et al. 2019). Criteria for further

investigation (e.g., Next Generation Sequencing, or NGS) are to be determined in this population. In France, an NGS laboratory aims to conduct further investigations to determine the criteria for further investigations (e.g., NGS) (*Le territoire couvert par le laboratoire en médecine génomique SeqOIA*, s. d.).

Limitations

Our study reflects clinical practice in a tertiary care unit for both child and adolescent psychiatry and genetics. Of note, to date, there is no recommendation to conduct genetic testing in such patients in France. The high prevalence of genetic abnormalities in this sample makes the relevance of this reportclear. However, several limitations may affect the generalization of our results. First, we had some missing data in assessments of certain dimensions, in particular dyscalculia because of the limited availability of trained personnel and longer waiting times (Castaldi et al. 2020), and emotional dysregulation because of the retrospective clinical assessment (Benarous et al. 2014, 2020). Second, some dimensions regarding school learning have developmental limitations. School learning data were missing for patients who entered the study period at an early age (e.g., 6 years) as patients usually show non-significant deviation from the norm in reading, calculation, or writing at this age. Third, the dimensional assessment of DCD may have lacked precision in adolescents as many tools are saturated at this age (Albaret et al. 2018). Fourth, the cohort described in this study is not representative of all patients with complex NDD and is biased toward greater severity given the population recruited in our center (Cohen et al. 2021).

We do not know the proportion of patients who were offered genetic testing and what proportion refused. The lack of genetic testing may be due to a large list of factors, including lack of proposals (the criteria used by doctors in clinical practice are not well known and vary greatly from one doctor to another), absence of one parent that prevents any testing (acceptance of both parents is compulsory in France), other clinical needs (e.g., search for a school for children with special needs), and parents' or child's refusals. In addition, the selection of patients may have been biased because of the presence of dysmorphic faces or specific comorbidities, although the prevalence of birth defects in this population was low. Unfortunately, the database was made for those who accepted genetic testing, not for those who had the proposal. Therefore, the reason for genetic testing was not systematically specified in medical records, and there was some heterogeneity in the way doctors handled these tests and the criteria used. Patients with major obstetrical adverse events (such as preterm birth or eclampsia) are rare in this cohort and may not have been genetically tested, as obstetrical adverse events are considered pathogenic by themselves. On the other hand, some patients have been referred for consultation by genetics departments with whom we work in close collaboration. There is also heterogeneity in the practice of systematic genetic investigations between the practitioners (trained or not in this medicine) in our staff and between patients (e.g., not all patients with negative microarray genetic results had whole exome sequencing).

Perspectives

This study first highlights the need to evaluate neurodevelopment globally for NDD patients, exploring each domain of development, given the high comorbidity among and between NDD. It also strengthens the need to carry out clinical genetic investigations more systematically in complex NDD patients. The search for, identification, and analysis of novel variants, as well as the exploration of the mechanisms involved, are important in this population in order to identify more specific mechanisms. Secondly, given the frequency of complex NDD diagnoses in certain disorders related to neurodevelopmental pathologies such as schizophrenia, it would be interesting to evaluate the factors predicting entry into such disorders (including genetic factors, even if some of them in this cohort are already well known [e.g., 22q11.2 deletion]). Prospective studies are needed given the different ages at onset for those diagnoses. Larger multicentric studies including less severe patients should also be conducted to address the prevalence of genetic abnormalities in complex NDD patients (Chawner et al. 2020). Novel variants identified deserve specific further investigation to determine the pathogenicity by creating cohorts of patients to describe clinical characteristics and testing the impact of the variant. Finally, an evaluation of the patients' trajectory, in particular the effectiveness of treatments in compensating for the disabilities over a sufficiently long period, would allow a better understanding of the issues related to global treatment.

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Data Availability We established a secure computerized database of genetic data as part of the National Referral Center for Psychiatric Rare Diseases, authorized by the Commission Nationale Informatique et Liberté. The main genetic data and outcomes are provided as supplementary information files. Research data that support the findings are available on demand.

Declarations

Competing Interests The authors declare no competing interests.

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