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ORIGINAL ARTICLE

Lessons from two series by physicians and caregivers' self-reported data in *DDX3X*-related disorders

Valentin Ruault[1,2] | Pauline Burger[3] | Johanna Gradels-Hauguel[4] | Nathalie Ruiz[1,2] | Xtraordinaire[5] | Rami Abou Jamra[6] | Alexandra Afenjar[7] | Yves Alembik[8] | Jean-Luc Alessandri[9] | Stéphanie Arpin[10] | Giulia Barcia[11] | Šárka Bendová[12] | Ange-Line Bruel[13,14] | Perrine Charles[15] | Nicolas Chatron[16,17] | Maya Chopra[18,19] | Solène Conrad[20] | Valérie Cormier Daire[11] | Auriane Cospain[21] | Christine Coubes[1,2] | Juliette Coursimault[22] | Andrée Delahaye-Duriez[23,24,25] | Martine Doco[20,26] | William Dufour[16] | Benjamin Durand[8] | Camille Engel[27] | Laurence Faivre[13,28] | Fanny Ferroul[9] | Mélanie Fradin[21,29] | Hélène Frenkiel[5] | Carlo Fusco[30] | Livia Garavelli[31] | Aurore Garde[13,28] | Bénédicte Gerard[8] | David Germanaud[32,33] | Louise Goujon[32,33] | Aurélie Gouronc[8] | Emmanuelle Ginglinger[34] | Alice Goldenberg[22] | Miroslava Hancarova[12] | Markéta Havlovicová[12] | Delphine Heron[35] | Bertrand Isidor[20] | Nolwenn Jean Marçais[21] | Boris Keren[36] | Margarete Koch-Hogrebe[37] | Paul Kuentz[14,27] | Victoria Lamure[24] | Anne-Sophie Lebre[26,38] | François Lecoquierre[22] | Natacha Lehman[1,2] | Gaetan Lesca[16,17] | Stanislas Lyonnet[11,39] | Delphine Martin[5] | Cyril Mignot[36] | Teresa M. Neuhann[40] | Gaël Nicolas[22] | Mathilde Nizon[20] | Florence Petit[41] | Christophe Philippe[13,14] | Amélie Piton[8] | Marzia Pollazzon[31] | Darina Prchalová[12] | Audrey Putoux[16,42] | Marlène Rio[11] | Sophie Rondeau[11] | Massimiliano Rossi[16,42] | Quentin Sabbagh[1,2] | Pascale Saugier-Veber[22] | Ariane Schmetz[37] | Julie Steffann[11] | Christel Thauvin-Robinet[13,14,28] | Annick Toutain[10] | Frederic Tran Mau Them[13,14] | Gabriele Trimarchi[31] | Marie Vincent[20] | Markéta Vlčková[12] | Dagmar Wieczorek[37] | Marjolaine Willems[1,2] | Kevin Yauy[1,2] | Michaela Zelinová[12] | Alban Ziegler[43] | GENIDA Project[3] | Boris Chaumette[4,44,45] | Bekim Sadikovic[46,47] | Jean-Louis Mandel[3,48] | David Geneviève[1,2]

ERN Ithaca members: Valentin Ruault, Nathalie Ruiz, Šárka Bendová, Ange-Line Bruel, Auriane Cospain, Christine Coubes, William Dufour, Laurence Faivre, Mélanie Fradin, Carlo Fusco, Livia Garavelli, Aurore Garde, David Germanaud, Louise Goujon, Miroslava Hancarova, Markéta Havlovicová, Nolwenn Jean Marçais, Margarete Koch-Hogrebe, Natacha Lehman, Gaetan Lesca, Florence Petit, Christophe Philippe, Marzia Pollazzon, Darina Prchalová, Audrey Putoux, Massimiliano Rossi, Quentin Sabbagh, Ariane Schmetz, Christel Thauvin-Robinet, Frederic Tran Mau Them, Gabriele Trimarchi, Markéta Vlčková, Dagmar Wieczorek, Marjolaine Willems, Kevin Yauy, Michaela Zelinová, David Geneviève are members of the European Reference Network on Rare Congenital Malformations and Rare Intellectual Disability ERN-ITHACA [EU Framework Partnership Agreement ID: 3HP-HP-FPA ERN-01-2016/739516].

For Affiliation refer page on 6

Correspondence
David Geneviève, Montpellier University, INSERM Unit 1183, Arnaud de Villeneuve, 371 bd du doyen gaston giraud, 34295 Montpellier Cedex 5, France.
Email: d-genevieve@chu-montpellier.fr

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Abstract

Introduction and Methods: We report two series of individuals with *DDX3X* variations, one (48 individuals) from physicians and one (44 individuals) from caregivers.

Results: These two series include several symptoms in common, with fairly similar distribution, which suggests that caregivers' data are close to physicians' data. For example, both series identified early childhood symptoms that were not previously described: feeding difficulties, mean walking age, and age at first words.

Discussion: Each of the two datasets provides complementary knowledge. We confirmed that symptoms are similar to those in the literature and provides more details on feeding difficulties. Caregivers considered that the symptom attention-deficit/hyperactivity disorder were most worrisome. Both series also reported sleep disturbance. Recently, anxiety has been reported in individuals with *DDX3X* variants. We strongly suggest that attention-deficit/hyperactivity disorder, anxiety, and sleep disorders need to be treated.

KEYWORDS
ADHD, caregivers, *DDX3X*, developmental milestones

1 | INTRODUCTION

De novo pathogenic or likely pathogenic variants (PV and LPV) in dead-box helicase 3 X-linked (*DDX3X*, MIM *300160; #300958) have been reported in 1% to 3% of females with intellectual disability (ID) (Snijders Blok et al., 2015; Wang et al., 2018) and occasionally males with ID. *DDX3X* maps to Xp11.4 and escapes X-inactivation (Garieri et al., 2018). DDX3X plays an important role in RNA metabolism such as export, translation, or pre-RNA splicing (Kukhanova et al., 2020).

Clinical manifestations of *DDX3X*-related disorders (*DDX3X*-RD) include ID, hypotonia, and behavioral problems such as autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), and hyperactivity, self-injurious behavior, poor impulse control or aggression in females (Chanes et al., 2019; Dikow et al., 2017; Lennox et al., 2020; Scala et al., 2019; Snijders Blok et al., 2015; Wang et al., 2018) and males (Kellaris et al., 2018; Nicola et al., 2019). ID ranges from mild to severe (Snijders Blok et al., 2015). Individuals with *DDX3X* PV or LPV can also have vision problems, congenital heart anomalies or epilepsy. Language delay is common: 51% of females are nonverbal at age 5 (Lennox et al., 2020).

This study aimed to better delineate the clinical presentation of individuals with *DDX3X*-RD by describing the clinical phenotype of 48 previously unpublished individuals with *DDX3X* PV or LPV from a physician's point of view ("series 1"). The second part of this study was to describe parents' and caregivers' self-reported characteristics and life quality data via the GENIDA questionnaire for a series of 44 individuals ("series 2," some individuals in common with the first series), with the help of patient associations. We searched for similarities and discrepancies but also additional data between physician-reported and caregiver self-reported data.

2 | MATERIALS AND METHODS

2.1 | Data collection

Two different series were recruited. In the first series ("series 1"), physicians collected clinical data for 48 females enrolled mainly via the Xtraordinaire association and by contacting medical geneticists directly from genetics centers in Europe (Group DI France, AnDDI-Rares [http://anddi-rares.org/], ERN ITHACA [https://ern-ithaca.eu/] networks). Individuals with *DDX3X* PV or LPV were identified by exome sequencing. Clinical data were systematically collected by use of a standardized form sent to collaborators.

The second series includes 44 individuals ("series 2", Supplementary Figure S1) on whose behalf a caregiver participated in the GenIDA study (https://genida.unistra.fr/). GenIDA is an international participatory research project that aims to better characterize the clinical manifestations and natural histories of rare genetic forms of ID and/or ASD (Burger et al., 2023). Families answer to a structured

questionnaire that investigates cognitive as well as behavioral aspects, neurological manifestations of the disease, and core physiological functions of the affected individual. We describe the results of GenIDA for *DDX3X*. Because the GenIDA questionnaire is anonymized, one cannot know how many individuals are common to both series.

2.2 | Statistical analyses

For calculating the frequency of features, we excluded individuals for whom that feature was coded as "unknown" in the clinical form. Data are reported with numbers or median (interquartile range and range) and mean.

We use Fisher's exact test to compare the features in common between the two series.

3 | RESULTS

3.1 | Phenotype ("series 1")

Series 1 clinical data were collected for 43 individuals with a *DDX3X* LPV/PV, with ages ranging from 4 to 65 years. ID was the most common feature (28/31 individuals). The mean walking age was 27.5 months and the age at first word was 26.5 months (Figure 1a, Table 1 and Supplementary Table S1). Physicians noted feeding difficulties (18/39, 46%), such as gastroesophageal reflux disease and especially hyperphagia, which are lifelong issues for *DDX3X*-RD individuals and need to be medically evaluated. ADHD was also common (14/32, 44%). Hearing issues were not reported in this series. Other neurological findings included hypotonia for 28/38 individuals (74%), coordination troubles for 23/36 (64%), and movement disorders for 6/34 (18%). Epilepsy was reported in 9/41 (22%) individuals, which agrees with the literature. ASD was reported in only 9/39 (23%) individuals, fewer than previously described. Neuroblastoma was described in 3 individuals in the literature (Lennox et al., 2020), and we found 1 individual with neuroblastoma diagnosed at 6 months.

3.2 | Caregivers self-reported series ("series 2")

Clinical and daily life data were available for 44. Data collected for these patient via GenIDA project are summarized in Supplementary Table S2. From parents' and caregivers' point of view, the main problem of quality of life is ADHD, which concerned 26/42 (62%) individuals. ID was reported in 23/35 (66%) individuals; some individuals are under 6 years old, so ID might not have been diagnosed yet. Self-reported developmental milestones agreed with series 1 data: mean sitting age 12.9 months, standing 19.9 months, walking 26.3 months, first word 27.2 months, also with a large range (Figure 1b, Table 1).

Hyperopia and strabismus are frequent symptoms in *DDX3X*-RD (both 18/44 individuals; 41%). Myopia is reported in 3 individuals and cataracts in 1. Seromucous otitis is reported in a few individuals (8/44; 18%); symptoms disappeared with grommets insertion. As for series 1,

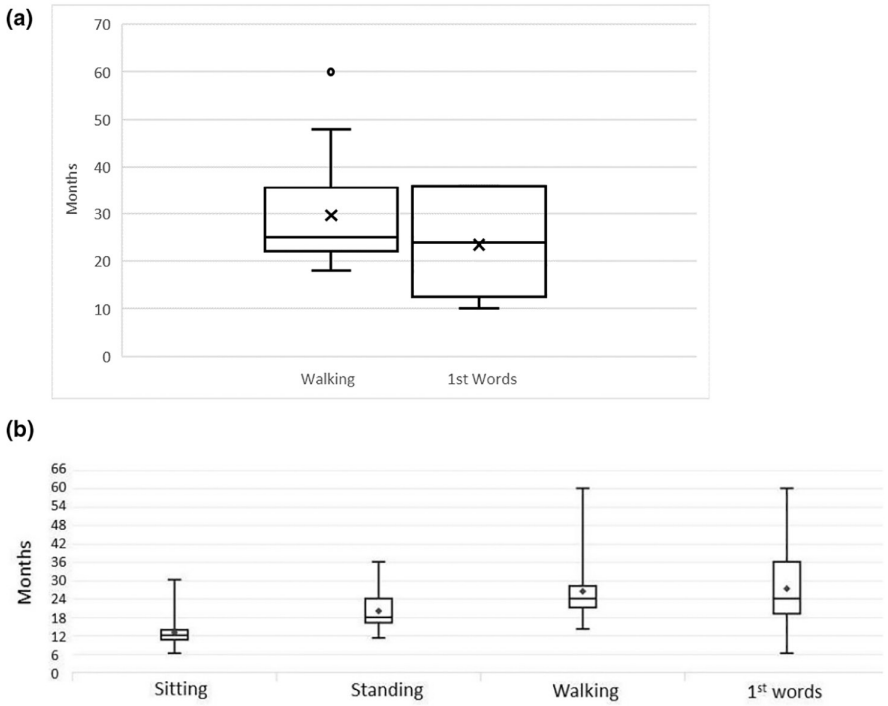

FIGURE 1 Box plots of (a) physician-reported developmental milestones and (b) parent and caregiver-reported developmental milestones. Data are median (horizontal bars), 1st and 3rd quartiles (box edges), and range (whiskers). (Figure generated from GENIDA).

TABLE 1 Physician- and parent and caregiver-reported clinical features of individuals in this study and 2 large series from the literature.

	This study "series 1"	GENIDA cohort "series 2"	Fisher's exact test between series 1 and 2	Snijders Blok et al. 2015	Lennox et al. 2020
Truncating variants	32/47	n.a.	–	20/38	53/104
Non-truncating variants	15/47	n.a.	–	18/38	51/104
Intellectual disability	28/31	23/35	0.020	35/38	106/106
Hypotonia	28/38	5/43	0.00000001	29/38	54/93
Spasticity	8/36	n.a.	–	17/38	5/93
Movement disorder	6/34	31/44	0.000003		n.a.
Coordination troubles	23/36	n.a.	–	n.a.	n.a.
Ataxia	15/35	n.a.	–	n.a.	n.a.
First words (mean month)	26.5	27.2	0.21	n.a.	n.a.
Walking age (mean month)	27.5	26.3	0.13	n.a.	n.a.
Feeding difficulties	18/39	13/43	0.17	n.a.	n.a.
Gastroesophageal reflux	12/38	n.a.	–	n.a.	n.a.
Hyperphagia	14/37	n.a.	–	n.a.	n.a.
Oral aversion	2/35	n.a.	–	n.a.	n.a.
Sleep disturbance	10/35	14/44	0.80	n.a.	n.a.
Refractory problems	20/39	21/44	0.83	13/38	n.a.
Deafness	0/38	0/44	1	3/38	n.a.
Autism spectrum disorders	9/39	6/35	0.57	20/38	n.a.
Behavioral anomalies	22/35	27/42	1		n.a.
ADHD	14/32	26/42	0.16		n.a.
Seizures and/or epilepsy	9/41	11/44	0.80	6/38	17/93
Pharmacoresistance?	0	n.a.	–	n.a.	n.a.
Scoliosis	5/37	n.a.	–	4/38	15/94
Vertebral malformations	1/28	n.a.	–	n.a.	n.a.
Hyperlaxity	17/34	n.a.	–	14/38	n.a.
Congenital heart defects	2/33	n.a.	–	n.a.	n.a.
Neonatal respiratory distress	2/33	n.a.	–	n.a.	n.a.
Laryngeal anomalies	1/29	n.a.	–	n.a.	n.a.
Anal abnormalities	2/33	n.a.	–	n.a.	n.a.
Sacral dimple	3/31	n.a.	–	n.a.	n.a.
Enuresis	5/28	n.a.	–	n.a.	n.a.
Precocious puberty	6/27	n.a.	–	5/38	11/94
Neuroblastoma	1/41	1/43	1	n.a.	3/107

Abbreviation: ADHD, attention-deficit/hyperactivity disorder.

sleeping disorders are reported in series 2, in 14/44 (32%) individuals; some required treatment. Constipation is frequent, in 18/44 (41%) individuals.

4 | DISCUSSION

DDX3X-RD is a rare monogenic disorder, with nearly 200 individuals reported in the literature.

In this study, we reported two different series of individuals expressing *DDX3X*-RD. We expanded the phenotype by describing 48 new individuals (5 without clinical data), thus providing novel clinical features to aid the clinical management of newly diagnosed individuals. We analyzed 44 caregivers' self-reported characteristics and quality of life data, providing crucial "everyday life" information.

For most clinical features in this series, the distribution was similar to that in the literature. A statistical difference

is only observed for hypotonia (28/38 vs. 5/43), movement disorder (6/34 vs. 31/44), and ID (28/31 vs. 23/35). We believe that these differences could be due to a difference in vocabulary between physicians and caregivers: hypotonia might be considered by caregivers only during the infancy and not considered when this symptom disappears, unlike doctors who describe this symptom even if transient. Regarding ID, we can speculate that the difference between the two series may be due to an age difference between the individuals in the two series (estimating the ID is more difficult for young people). We can also assume that parents are less inclined to use the term ID for their children. The difference in "Movement disorder" is more questionable, it might not have been observed by physicians, who only see his patient for a short time, or might be understood by caregivers as a behavioral disorder such as significant agitation as seen in attention disorders. Additional studies should be carried out to better describe and understand these discrepancies in description between physicians and caregivers.

One of the major symptoms is ADHD (14/32 individuals, 44%). This finding was confirmed by caregivers in series 2, who largely considered ADHD to be the major problem affecting their relatives' everyday life. Lifelong assessment of ADHD seems crucial for all individuals with *DDX3X*-RD and could lead to treatment, with medication (methylphenidate) or cognitive behavioral therapies (Weiss et al., 2012), meta-cognitive therapies, dialectical behavioral therapies, mindfulness-based interventions, and cognitive remediation (Diamond & Ling, 2019; Nimmo-Smith et al., 2020), which are efficacious for ADHD symptoms. It would be useful to evaluate if ADHD is more on the attentional or hyperactivity side.

Sleep disturbance was observed in 10/35 individuals from series 1 and 14/44 from series 2 (30%), also reported recently in 10/15 and 13/23 individuals with *DDX3X*-RD (60%) (Ng-Cordell et al., 2022; Tang et al., 2021). Sleep disturbance needs to be evaluated before assessment for ADHD, and might interfere with ADHD evaluation. Here again, lifelong assessment of sleep disturbance is crucial for all *DDX3X*-RD individuals and might lead to melatonin treatment for instance.

Even if not reported in this manuscript, we know anxiety is frequent in individuals with *DDX3X*-RD (Ng-Cordell et al., 2022) and could interfere with ADHD and sleep disturbance. We strongly suggest searching for and treating ADHD, anxiety, and sleep disturbance in individuals with *DDX3X*-RD because the caregivers' main complaint was ADHD.

For the first time, we report data on developmental milestones: the mean walking age was 27.5 months and the first word appeared at 26.5 months.

In conclusion, our study emphasizes the similarities between the data reported by physicians and that reported by caregivers.

AUTHOR CONTRIBUTIONS

Valentin Ruault, collected data and wrote the article; Pauline Burger, collected data from serie 2 and take care of Genida project; Johanna Gradels-Hauguel, collected data from serie 1; Nathalie Ruiz, collected data; Xtraordinaire, made the call for the project; Rami Abou Jamra, collected data; Alexandra Afenjar, collected data; Yves Alembik, collected data; Jean-Luc Alessandri, collected data; Stéphanie Arpin, collected data; Giulia Barcia, collected data; Ange-Line Bruel, collected data; Perrine Charles, collected data; Maya Chopra, collected data; Solène Conrad, collected data; Valérie Cormier Daire, collected data; Auriane Cospain, collected data; Christine Coubes, collected data; Juliette Coursimault, collected data; Andrée Delahaye-Duriez, collected data; Martine Doco, collected data; William Dufour, collected data; Benjamin Durand, collected data; Camille Engel, collected data; Laurence Faivre, collected data; Fanny Ferroul, collected data; Mélanie Fradin, collected data; Hélène Frenkiel, collected data; Carlo Fusco, collected data; Livia Garavelli, collected data; Aurore Garde, collected data; Bénédicte Gerard, collected data; David Germanaud, collected data; Louise Goujon, collected data; Aurélie Gouronc, collected data; Emmanuelle Ginglinger, collected data; Alice Goldenberg, collected data; Miroslava Hancarova, collected data; Markéta Havlovicová, collected data; Delphine Heron, collected data; Bertrand Isidor, collected data; Nolwenn Jean Marçais, collected data; Boris Keren, collected data; Victoria Lamure, collected data; Anne-Sophie Lebre, collected data; François Lecoquierre, collected data; Natacha Lehman, collected data; Gaetan Lesca, collected data; Stanislas Lyonnet, collected data; Delphine Martin, collected data; Cyril Mignot, collected data; Teresa M. Neuhann, collected data; Gaël Nicolas, collected data; Mathilde Nizon, collected data; Florence Petit, collected data; Christophe Philippe, collected data; Amélie Piton, collected data; Marzia Pollazzon, collected data; Audrey Putoux, collected data; Marlène Rio, collected data; Sophie Rondeau, collected data; Massimiliano Rossi, collected data; Quentin Sabbagh, collected data and shipped dna samples; Ariane Schmetz, collected data; Julie Steffann, collected data; Christel Thauvin-Robinet, collected data; Annick Toutain, collected data; Frederic Tran Mau Them, collected data; Gabriele Trimarchi, collected data; Marie Vincent, collected data; Markéta Vlčková, collected data; Marjolaine Willems, collected data; Kevin Yauy, reviewed the project; Michaela Zelinová, collected data; Alban Ziegler, collected data;

GENIDA Project, collected data from serie 2; Boris Chaumette, collected data; Bekim Sadikovic, collected data; Jean-Louis Mandel, collected data from serie 2; David Geneviève, supervised this work; all authors reviewed the manuscript.

AFFILIATIONS

[1]Genetic Department, Montpellier University, INSERM Unit 1183, Montpellier, France
[2]Reference Center for Rare Diseases Developmental Anomaly and Malformative Syndromes, Genetics Department, Montpellier Hospital, Montpellier, France
[3]Institute of Genetics and Molecular and Cellular Biology (IGBMC), Université de Strasbourg, INSERM U1258, CNRS UMR7104, Illkirch, France
[4]Center for Rare Psychiatric Disorders – GHU Paris Psychiatrie et Neurosciences – Paris – France APHP, GHU Sainte Anne, Paris, France
[5]Xtraordinaire Association, Paris, France
[6]Institute of Human Genetics, University of Leipzig Medical Center, Leipzig, Germany
[7]Département de Génétique Paris, Centre de Référence Malformations et maladies congénitales du cervelet et déficiences intellectuelles de causes rares, APHP, Sorbonne Université, Paris, France
[8]Service de Génétique Médicale, Institut de Génétique Médicale d'Alsace, Hôpitaux Universitaires de Strasbourg, Strasbourg, France
[9]CHU La Réunion, Service de génétique, Saint Denis, France
[10]Genetics Department, University Hospital, UMR1253 iBrain INSERM, University of Tours, Tours, France
[11]Service de Médecine Génomique des Maladies Rares, Hôpital Necker – Enfants Malades, Assistance Publique-Hôpitaux de Paris, Paris, France
[12]Department of Biology and Medical Genetics, Charles University Second Faculty of Medicine and University Hospital Motol, Prague, Czech Republic
[13]Unité Fonctionnelle Innovation en Diagnostic Génomique des maladies rares, CHU Dijon Bourgogne, Dijon, France
[14]UFR Des Sciences de Santé, INSERM-Université de Bourgogne UMR1231 GAD "Génétique des Anomalies du Développement", FHUTRANSLAD, Dijon, France
[15]APHP La Pitié Salpétrière, Paris, France
[16]Department of Medical Genetics, University Hospital of Lyon and Claude Bernard Lyon I University, Lyon, France
[17]Pathophysiology and Genetics of Neuron and Muscle (PNMG), UCBL, CNRS UMR5261 – INSERM U1315, Lyon, France
[18]Department of Neurology, Rosamund Stone Zander Translational Neuroscience Center, Boston Children's Hospital, Boston, Massachusetts, USA
[19]Genetic Department, Harvard Medical School, Boston, Massachusetts, USA
[20]Genetic Department, CHU Nantes, Service de Génétique, Nantes, France
[21]Genetic Department, CHU Rennes, Service de Génétique, CLAD Ouest CRDI, Rennes, France
[22]Department of Genetics and Reference Center for Developmental Disorders, University of Rouen Normandie, Inserm U1245, CHU Rouen, Rouen, France
[23]Medical Genomics and Clinical Genetics Unit, AP-HP, Hôpital Jean Verdier, Bondy, France
[24]Genetic Department, UFR SMBH, Université Sorbonne Paris Nord, Paris, France
[25]Genetic Department, Inserm 1141 NeuroDiderot, Paris, France
[26]Centre Hospitalier Universitaire de Reims, Pôle de Biologie Médicale et Pathologie, Service de Génétique, Reims, France
[27]Oncobiologie Génétique Bioinformatique, PC BIO, CHU Besançon, Besançon, France
[28]Centre de Génétique et Centre de référence maladies rares « Anomalies du Développement et Syndromes Malformatifs », FHU TRANSLAD, Hôpital d'Enfants, CHU Dijon, Dijon, France
[29]CH Saint Brieuc, Service de Génétique, Saint Brieux, France
[30]Child Neurology and Psychiatry Unit, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy
[31]Medical Genetics Unit, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy
[32]Genetic Department, CEA Paris-Saclay, NeuroSpin, Gif-sur-Yvette, France
[33]Département de Génétique, Centre de référence Déficiences intellectuelles de causes rares, Assistance publique-Hopitaux de Paris (AP-HP), Hopital Robert-Debré, Paris, France
[34]Génétique médicale GHRMSA, Hopital Emile Muller, Mulhouse, France
[35]APHP Trousseau, Paris, France
[36]Département de Génétique, Centre de Référence Déficiences Intellectuelles de Causes Rares, APHP Sorbonne Université, Paris, France
[37]Institute of Human Genetics, Medical Faculty, University Hospital Düsseldorf, Heinrich Heine University Düsseldorf, Düsseldorf, Germany
[38]Institute of Psychiatry and Neuroscience of Paris (IPNP), INSERM U1266, Université Paris Cité, Paris, France
[39]Laboratoire Embryologie et Génétique des Malformations, Université Paris Cité, INSERM, IHU Imagine – Institut des maladies génétiques, Paris, France
[40]Genetic Department, Medizinisch Genetisches Zentrum, Munich, Germany
[41]Genetic Department, CHU Lille, Clinique de Génétique Guy Fontaine, Lille, France
[42]INSERM U1028, CNRS UMR5292, Centre de Recherche en Neurosciences de Lyon, GENDEV Team, Université Claude Bernard Lyon 1, Bron, France
[43]Genetic Department, Service de Génétique, CHU d'Angers, Angers Cedex 9, France
[44]Institute of Psychiatry and Neuroscience of Paris, Université Paris Cité, INSERM U1266, Paris, France
[45]Department of Psychiatry, McGill University, Montreal, Quebec, Canada
[46]Department of Pathology and Laboratory Medicine, Western University, London, Ontario, Canada
[47]Verspeeten Clinical Genome Centre, London Health Sciences Centre, London, Ontario, Canada
[48]Genetic Department, University of Strasbourg Institute for Advanced Studies (USIAS), Strasbourg, France

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CONFLICT OF INTEREST STATEMENT

No competing interests to declare.

ETHICAL APPROVAL

Written consent was obtained from all individuals or their legal guardians. The study was performed in accordance with the ethical standards of our national research committee and with the Helsinki Declaration. Ethics approval was granted by Montpellier University Hospital Institutional Review Board (IRB-MTP_2020_06_202000531); ClinicalTrial.gov identifier: NCT04436588. Ethics approval for the GENIDA project was granted by the *Commission Nationale de l'Informatique et des Libertés* on 27/11/2015 (no. 1907912v0) and by the INSERM Institutional Review Board (CEEI-IRB00003888) on 15/11/2016 and 04/09/2019.

DATA AVAILABILITY STATEMENT

All data are available in supplementary data and supplementary Table S1 or on request to the corresponding author.

ORCID

Valentin Ruault https://orcid.org/0000-0003-0562-1706
Ange-Line Bruel https://orcid.org/0000-0002-0526-465X
Nicolas Chatron https://orcid.org/0000-0003-0538-0981
Auriane Cospain https://orcid.org/0000-0002-0007-4195
Laurence Faivre https://orcid.org/0000-0001-9770-444X
Hélène Frenkiel https://orcid.org/0009-0008-7648-4220
Louise Goujon https://orcid.org/0000-0003-2361-9909
Miroslava Hancarova https://orcid.org/0000-0001-6772-8862
Paul Kuentz https://orcid.org/0000-0003-2814-6303
Natacha Lehman https://orcid.org/0000-0002-3773-672X
Massimiliano Rossi https://orcid.org/0000-0002-5797-8152
Ariane Schmetz https://orcid.org/0000-0001-8220-7854
Frederic Tran Mau Them https://orcid.org/0000-0002-3795-9456
Markéta Vlčková https://orcid.org/0000-0002-1496-392X
Marjolaine Willems https://orcid.org/0000-0002-2959-0935
Alban Ziegler https://orcid.org/0000-0003-0287-3561

REFERENCES

Burger, P., Colin, F., Strehle, A., Mazzucotelli, T., Collot, N., Coutelle, R., Durand, B., Bouman, A., Landau Prat, D., Kleefstra, T., Parrend, P., Piton, A., Koolen, D. A., & Mandel, J. L. (2023). GenIDA: An international participatory database to gain knowledge on health issues related to genetic forms of neurodevelopmental disorders. *Journal of Neural Transmission*, *130*, 459–471.

Chanes, N. M., Wong, J., & Lacassie, Y. (2019). Further delineation of DDX3X syndrome. *Clinical Dysmorphology*, *28*, 151–153.

Diamond, A., & Ling, D. S. (2019). Review of the evidence on, and fundamental questions about, efforts to improve executive functions, including working memory. *Cognitive and working memory Training*, *C8*, 143–431.

Dikow, N., Granzow, M., Graul-Neumann, L. M., & Granzow, M. (2017). DDX3X mutations in two girls with a phenotype overlapping Toriello-Carey syndrome. *American Journal of Medical Genetics. Part A*, *173*, 1369–1373.

Garieri, M., Stamoulis, G., Blanc, X., & Stamoulis, G. (2018). Extensive cellular heterogeneity of X inactivation revealed by single-cell allele-specific expression in human fibroblasts. *Proceedings of the National Academy of Sciences of the United States of America*, *115*, 13015–13020.

Kellaris, G., Khan, K., Baig, S. M., & Khan, K. (2018). A hypomorphic inherited pathogenic variant in DDX3X causes male intellectual disability with additional neurodevelopmental and neurodegenerative features. *Human Genomics*, *12*, 1–9.

Kukhanova, M. K., Karpenko, I. L., & Ivanov, A. V. (2020). DEAD-box RNA helicase DDX3: Functional properties and development of DDX3 inhibitors as antiviral and anticancer drugs. *Molecules*, *25*, 1015. doi:10.3390/molecules25041015

Lennox, A. L., Hoye, M. L., Jiang, R., & Hoye, M. L. (2020). Pathogenic DDX3X mutations impair RNA metabolism and neurogenesis during fetal cortical development. *Neuron*, *106*, 404–420.e8.

Ng-Cordell, E., Kolesnik-Taylor, A., O'Brien, S., Astle, D., Scerif, G., & Baker, K. (2022). Social and emotional characteristics of girls and young women with DDX3X-associated intellectual disability: A descriptive and comparative study. *Journal of Autism and Developmental Disorders*, *53*, 3208–3219. https://doi.org/10.1007/s10803-022-05527-w

Nicola, P., Blackburn, P. R., Rasmussen, K. J., & Blackburn, P. R. (2019). De novo DDX3X missense variants in males appear viable and contribute to syndromic intellectual disability. *American Journal of Medical Genetics. Part A*, *179*, 570–578.

Nimmo-Smith, V., Merwood, A., Hank, D., & Merwood, A. (2020). Non-pharmacological interventions for adult ADHD: A systematic review. *Psychological Medicine*, *50*, 529–541.

Scala, M., Torella, A., Severino, M., Morana, G., Castello, R., Accogli, A., Verrico, A., Vari, M. S., Cappuccio, G., Pinelli, M., & Vitiello, G. (2019). Three de novo DDX3X variants associated with distinctive brain developmental abnormalities and brain tumor in intellectually disabled females. *European Journal of Human Genetics*, *27*, 1254–1259.

Snijders Blok, L., Madsen, E., Juusola, J., & Madsen, E. (2015). Mutations in DDX3X are a common cause of unexplained intellectual disability with gender-specific effects on Wnt signaling. *American Journal of Human Genetics*, *97*, 343–352.

Tang, L., Levy, T., Guillory, S., & Levy, T. (2021). Prospective and detailed behavioral phenotyping in DDX3X syndrome. *Molecular Autism*, *12*, 36.

Wang, X., Posey, J. E., Rosenfeld, J. A., & Posey, J. E. (2018). Phenotypic expansion in - a common cause of intellectual disability in females. *Annals of Clinical Translational Neurology*, *5*, 1277–1285.

Weiss, M., Murray, C., Wasdell, M., Greenfield, B., Giles, L., & Hechtman, L. (2012). A randomized controlled trial of CBT therapy for adults with ADHD with and without medication. *BMC Psychiatry*, *12*, 30.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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