Lessons from two series by physicians and caregivers' self-reported data, and DNA methylation profile in DDX3X-Related Disorders

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Brief Communication

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Abstract

We report two series of individuals with *DDX3X* variations, one (48 individuals) from physicians and one (44 individuals) from caregivers. 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. Each of the two datasets provide complementary knowledge. We confirmed that symptoms are similar to those in the literature and provide more details on feeding difficulties. Caregivers considered that the symptom attention-deficit/hyperactivity disorder was 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. In addition, we demonstrate preliminary evidence of a mild genome-wide DNA methylation profile in patients carrying mutations in *DDX3X*.

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 1–3% of females with intellectual disability (ID)[1,2] and occasionally males with ID. *DDX3X* maps to Xp11.4 and escapes X-inactivation[3]. DDX3X plays an important role in RNA metabolism such as export, translation or pre-RNA splicing[4].

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[1,2, 5–8] and males[9,10]. ID range from mild to severe[1]. Individuals with *DDX3X* PV or LPV can also have vision problems, congenital heart anomalies or epilepsy. Language delay is common: 51% of females are non-verbal at age 5[5].

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the clinical presentation of individuals with *DDX3X*-RD by describing the clinical phenotype of 48 previously unpublished individuals with *DDX3X* PV or LPV from a physician's point of view ("series 1"). A 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 but also additional data between physician-reported and caregiver self-reported data. We also aimed to assess evidence for a genome-wide DNA methylation profile in *DDX3X*-RD with DNA collected in series 1.

Materials And Methods

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 Fig. 1) 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[17]. 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.

Sample collection

For each individual from series 1, we required a 0.5-µg DNA sample obtained from peripheral blood, with information about the individual’s sex and age at the time of sampling.

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.

DNA methylation analysis

We performed DNA methylation analysis of 12 female samples (supplementary data).

Results

Phenotype and episignature (“series 1”)

Series 1 clinical data were collected for 43 individuals with a *DDX3X* LPV/PV, with age ranging from 4 to 65 years. ID was the most common feature (28/31 individuals). Mean walking age was 27.5 months and age at first word 26.5 months (Fig. 1A, Table 1 and Supplementary Table 1). 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[5], and we found 1 individual with neuroblastoma diagnosed at 6 months.

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"	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	35/38	106/106
Hypotonia	28/38	5/43	29/38	54/93
Spasticity	8/36	n.a.	17/38	5/93
Movement disorder	6/34	31/44		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	n.a.	n.a.
Walking age (mean month)	27.5	26.3	n.a.	n.a.
Feeding difficulties	18/39	13/43	n.a.	n.a.
Gastro-esophageal 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	n.a.	n.a.
Refractory problems	20/39	21/44	13/38	n.a.
Deafness	0/38	0/44	3/38	n.a.
Autism spectrum disorders	9/39	6/35	20/38	n.a.
Behavioral anomalies	22/35	27/42		n.a.
ADHD	14/32	26/42		n.a.
Seizures and/or epilepsy	9/41	11/44	6/38	17/93

ADHD: attention-deficit/hyperactivity disorder

	This study "series 1"	GENIDA cohort "series 2"	Snijders Blok et al. 2015	Lennox et al. 2020
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	n.a.	3/107
ADHD: attention-deficit/hyperactivity disorder				

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 2. 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 (Fig. 1B, Table 1).

Hyperopia and strabismus are frequent symptoms in *DDX3X*-RD (both 18/44 individuals; 41%). Myopia is reported in 3 individuals and cataract in 1. Seromucous otitis is reported in a few individuals (8/44; 18%); symptoms disappeared with grommets insertion. As for series 1, sleeping disorders are reported in series 2, in 14/44 (32%) individuals; some required treatment. Constipation is frequent, in 18/44 (41%) individuals.

Epigenetic signature

DNA methylation analysis gave evidence of a mild genome-wide DNA methylation profile in peripheral blood of patients with *DDX3X* mutations. However, this methylation difference is not sufficiently robust to derive a sensitive and specific biomarker at this time (Supplementary Fig. 2).

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 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. 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[12], meta-cognitive therapies, dialectical behavioral therapies, mindfulness-based interventions and cognitive remediation[13,14], 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%)[15,16]. Sleep disturbance need 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[16] and could interfere with ADHD and with 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.

The diagnosis of *DDX3X*-RD is established when identifying a heterozygous PV or LPV in *DDX3X* by molecular testing, However, one of the remaining challenges for the diagnosis is the reclassification of variants of unknown significance, which can be complex and time-consuming. A growing number of genetic conditions have demonstrated evidence of genome-wide DNA methylation profiles detectible in peripheral blood. Many profiles have been developed as highly sensitive and specific biomarkers called episignatures. An important clinical utility of DNA methylation episignatures is the ability to reclassify

genetic variants of unknown clinical significance to provide insights into the molecular pathophysiology of the “episignature disorders”[11].

Our study shows preliminary evidence of a mild genome-wide DNA methylation profile in *DDX3X*-RD. Ongoing efforts are focused on expanding the reference patient cohort to increase the sensitivity and specificity and develop an episignature classifier for *DDX3X*.

In conclusion, our study emphasizes the similarities between the data reported by physicians and that reported by caregivers. The major problem affecting the everyday life of relatives of caregivers is not always what physicians thought.

Declarations

DATA AVAILABILITY STATEMENT

All data are available in supplementary data and supplementary table 1 or on request to the corresponding author.

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AUTHOR CONTRIBUTION STATEMENT

VR collected data and wrote the article

PB collected data from serie 2 and take care of Genida project

JGH collected data from serie 1

NR collected data

X made the call for the project

RAJ collected data

AA collected data

YA collected data

JLA collected data

SA collected data

GB collected data

ALB collected data

PC collected data

MC collected data

SC collected data

VCD collected data

AC collected data

CC collected data

JC collected data

ADD collected data

MD collected data

WD collected data

BD collected data

CE collected data

LF collected data

FF collected data

MF collected data

HF collected data

CF collected data

LG collected data

AG collected data

BG collected data

DG collected data

LG collected data

AG collected data

EG collected data

AG collected data

MH collected data

MH collected data

DH collected data

BI collected data

NJM collected data

PK collected data

VL collected data

ASL collected data

FL collected data

NL collected data

GL collected data

SL collected data

DM collected data

CM collected data

TMN collected data

GN collected data

MN collected data

FP collected data

CP collected data

AP collected data

MP collected data

AP collected data

MR collected data

SR collected data

MR collected data

QS collected data and shipped dna samples

AS collected data

JS collected data

CT collected data

AT collected data

FTMT collected data

GT collected data

MV collected data

MV collected data

MW collected data

KY reviewed the project

MZ collected data

AZ collected data

G collected data from serie 2

BC collected data

BS collected data

JLM collected data from serie 2

DG supervised this work

All authors reviewed the manuscript

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.

The episignature study was approved by the Western University Research Ethics Board (REB 106302)

COMPETING INTERESTS

No competing interests to declare.

References

1. Snijders Blok L, Madsen E, Juusola J *et al.* Mutations in DDX3X Are a Common Cause of Unexplained Intellectual Disability with Gender-Specific Effects on Wnt Signaling. *Am J Hum Genet* 2015; **97**: 343–352.
2. Wang X, Posey JE, Rosenfeld JA *et al.* Phenotypic expansion in - a common cause of intellectual disability in females. *Ann Clin Transl Neurol* 2018; **5**: 1277–1285.
3. Garieri M, Stamoulis G, Blanc X *et al.* Extensive cellular heterogeneity of X inactivation revealed by single-cell allele-specific expression in human fibroblasts. *Proc Natl Acad Sci U S A* 2018; **115**: 13015–13020.
4. Kukhanova MK, Karpenko IL, Ivanov AV. DEAD-box RNA Helicase DDX3: Functional Properties and Development of DDX3 Inhibitors as Antiviral and Anticancer Drugs. *Molecules* 2020; **25**. doi:10.3390/molecules25041015.

5. Lennox AL, Hoye ML, Jiang R *et al.* Pathogenic DDX3X Mutations Impair RNA Metabolism and Neurogenesis during Fetal Cortical Development. *Neuron* 2020; **106**: 404–420.e8.
6. Dikow N, Granzow M, Graul-Neumann LM *et al.* DDX3X mutations in two girls with a phenotype overlapping Toriello-Carey syndrome. *Am J Med Genet A* 2017; **173**: 1369–1373.
7. Scala M, Torella A, Severino M *et al.* Three de novo DDX3X variants associated with distinctive brain developmental abnormalities and brain tumor in intellectually disabled females. *Eur J Hum Genet* 2019; **27**: 1254–1259.
8. Chanes NM, Wong J, Lacassie Y. Further delineation of DDX3X syndrome. *Clin Dysmorphol* 2019; **28**: 151–153.
9. Kellaris G, Khan K, Baig SM *et al.* A hypomorphic inherited pathogenic variant in DDX3X causes male intellectual disability with additional neurodevelopmental and neurodegenerative features. *Hum Genomics* 2018; **12**: 1–9.
10. Nicola P, Blackburn PR, Rasmussen KJ *et al.* De novo DDX3X missense variants in males appear viable and contribute to syndromic intellectual disability. *Am J Med Genet A* 2019; **179**: 570–578.
11. Peters TJ, Buckley MJ, Statham AL *et al.* De novo identification of differentially methylated regions in the human genome. *Epigenetics Chromatin* 2015; **8**: 6.
12. Weiss M, Murray C, Wasdell M, Greenfield B, Giles L, Hechtman L. A randomized controlled trial of CBT therapy for adults with ADHD with and without medication. *BMC Psychiatry* 2012; **12**: 30.
13. Nimmo-Smith V, Merwood A, Hank D *et al.* Non-pharmacological interventions for adult ADHD: a systematic review. *Psychol Med* 2020; **50**: 529–541.
14. Diamond A, Ling DS. Review of the Evidence on, and Fundamental Questions About, Efforts to Improve Executive Functions, Including Working Memory. Cognitive and Working Memory Training. 2019; : 143–431.
15. Tang L, Levy T, Guillory S *et al.* Prospective and detailed behavioral phenotyping in DDX3X syndrome. *Mol Autism* 2021; **12**: 36.
16. Ng-Cordell E, Kolesnik-Taylor A, O'Brien S, Astle D, Scerif G, Baker K. 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. 2022. doi:10.1007/s10803-022-05527-w.
17. Burger P, Colin F, Strehle A *et al.* GenIDA: an international participatory database to gain knowledge on health issues related to genetic forms of neurodevelopmental disorders. *J Neural Transm* 2023; **130**: 459–471.

Figures

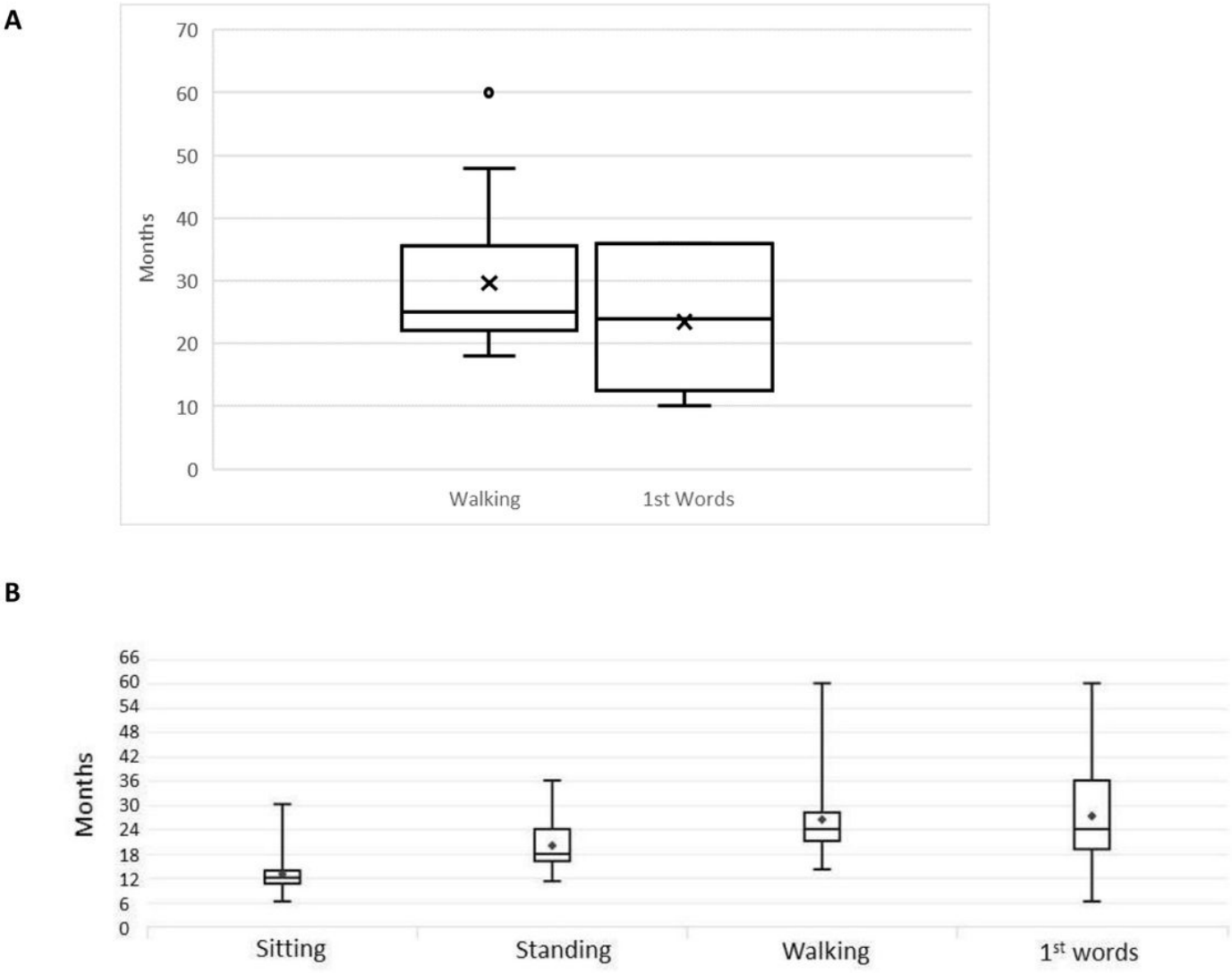

Figure 1

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).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- DDX3XRuaultSUPPLEMENTARYDATAfinal.docx
- Supplementarytable1allindividualsfinal.xlsx