Loss-of-function mutation in *DDX53* associated with hereditary spastic paraplegia-like disorder

Xiangshu Yuan, Ya Wang, Xiyuan Li, Sheng Zhong, Danyi Zhou, Xianlong Lin, Maofeng Wang 3, * , Yanling Yang 2, * , Hezhi Fang 1, *

1 Key Laboratory of Laboratory Medicine, Ministry of Education, Zhejiang Provincial Key Laboratory of Medical Genetics, School of Laboratory Medicine and Life sciences, Wenzhou Medical University, Wenzhou 325035, Zhejiang, China;

2 Department of Pediatrics, Peking University First Hospital, Beijing 100034, China;

3 Department of Biomedical Sciences Laboratory, Affiliated Dongyang Hospital of Wenzhou Medical University, Dongyang, Zhejiang, China.

* Correspondence: fangh@wmu.edu.cn (Hezhi Fang); organic.acid@vip.126.com (Yanling Yang); wzmcwmf@163.com (Maofeng Wang)

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Supplementary Table 1. Biochemistry data of the patient

Age at	14 y	15.9 y	16.1 y	16.2 y	16.4 y	16.9 y	17.1 y	24.2 y	25.8 y	Biological reference interval (unit)
Total Protein（TP）		80.0				77.6				65-85（g/L）
Albumin（ALB）		48.3				48.0		50		40-55（g/L）
Alkaline Phosphatase（ALP）		134				107		71		45-125（IU/L）
Total Bilirubin（TBIL）		12.8				4.6				1.7-20（μmol/L）
Direct Bilirubin（DBIL）		0.71				0.28				0-6（μmol/L）
Cholinesterase（PCHE）		12717				12576				4300-13200（mg/L）
Prealbumin (PA)		307.1				333.4				170-420（mg/L）
Creatinine（CREA*）	69	62.00				80.00				44-133（μmol/L）
Uric Acid（UA*）		354				489				150-420（μmol/L）
Urea（UREA*）		3.63				5.22				1.8-7.1（mmol/L）
Glucose（GLU*）	9.30↑	5.5		6.91↑	5.55	6.21↑				3.61-6.11（mmol/L）
Ca（CA*）		2.42				2.40				2.12-2.75（mmol/L）
P（P*）		1.52				1.54		-		0.96-1.62（mmol/L）
Mg（MG）		1.06				1.01		-		0.8-1.2（mmol/L）
K（K*）	3.89	4.57		4.30		4.22		-		3.5-5.3（mmol/L）
Na（NA*）	145.90	139.00		137.00		142.80		-		137-147（mmol/L）
Cl（CL*）	100.2	100.3		101.00		103.0		-		99-110（mmol/L）
Bicarbonate（CO2）	27.10	30.20				24.60		-		22-30（mmol/L）
Ammonia（NH3）	79↑	34				19.42		-		18-72（μmol/L）
Total Bile Acid（TBA）		1.50				5.60		-		0-10（μmol/L）
Lactic Acid（L-LAC）	2.8↑					2.2↑		-		0.5-2（mmol/L）
β- Hydroxybutyric	0.01	0.02				0.12		-		0.03-0.3（mmol/L）
Pyruvate（PYRUV）	160↑	51				139↑		-		30-100（μmol/L）
Lactic Acid（L-LAC）/ Pyruvate（PYRUV）	17.5↑					15.8↑				10:1
Triglyceride（TG*）		1.9↑		2.78↑	5.5↑	3.22↑		-		0.56-1.7（mmol/L）
Total Cholesterol		5.97↑		6.0↑	5.42↑	5.62↑		-		3.4-5.2（mmol/L）
High Density Lipoprotein（HDL-C）		1.04		1.30		1.04		-		0.9-1.4（mmol/L）
Low Density Lipoprotein（LDL-C）		4.11↑		4.09↑		3.92↑		-		2.1-3.1（mmol/L）

Supplementary Table 2. Population-based analysis of DDX53 variants

Variant	Number	Allele Frequency＜ 0.01%	Allele Frequency （0.01%-1%）	Allele Frequency＞ 1%	Homozygote Frequency>0
Missense	261	236	21	4	7
Frameshift /nonsense	11	11	0	0	0
Deletion	2	0	2	0	0
	274	247	23	4	7

Note: The data regarding missense, frameshift, and nonsense variants were obtained from the gnomAD v2.2.1 Database. The data related to deletion variants were retrieved from gnomAD SVs 2.2.1.

Supplementary Table 3. DDX53 variants in patients worldwide

Database	Patient ID	Variation Location	Inheritance/Genotype	Mutation Type	Pathogenicity	Phenotypes
ClinVar	SCV000499891.1	Xp22.11(chrX:22960744_23019707)	Unknown / hemizygote	Deletion 58.964 KB	pathogenic	Developmental delay
ClinVar	SCV000174968.3	Xp22.11(chrX:22774924_23081201)	Unknown / hemizygote	Deletion 306.3 KB	Likely pathogenic	Developmental delay
ClinVar	SCV000500745.1	Xp22.11(chrX:23018417_23093129)	Unknown / hemizygote	Deletion 74.713 KB	Likely pathogenic	Developmental delay
ClinVar	SCV000178120.4	Xp22.11(chrX:22618623_23233979)	Unknown / hemizygote	Deletion 615.4 KB	-	Microcephaly/Vitreoretinopathy
ClinVar	SCV000177909.4	Xp22.11(chrX:22708737_23013878)	Unknown / hemizygote	Deletion 305.1 KB	-	Global developmental delay
Decipher	435888	Xp22.11(chrX:23000300_23075071)	Unknown / hemizygote	Deletion 74.77 KB	Likely pathogenic	Abnormal social behavior
Decipher	366498	Xp22.11(chrX:22942627_23075071)	Unknown / hemizygote	Deletion 132.44 KB	Uncertain	Autism spectrum disorders
Decipher	451712	Xp22.11(chrX:22942627_23121779)	Unknown / hemizygote	Deletion 179.15 KB	Uncertain	Intellectual disability
Decipher	288239	Xp22.11(chrX:22942131_23146318)	De novo (unconfirmed parentage)/ hemizygote	Deletion 204.19 KB	Uncertain	Delayed speech and language development/ Global developmental delay
Decipher	249968	Xp22.11(chrX:22709566_23165800)	Inherited from normal parent / hemizygote	Deletion 456.24 KB	Uncertain	Visual impairment/ Microcephaly/ Gait disturbance/ Intellectual disability
Decipher	349858	Xp22.11(chrX:22818207_23003550)	Maternally inherited/ hemizygote	Deletion 185.34 KB	Uncertain	-
Decipher	361042	Xp22.11(chrX:22975373_23283624)	Maternally inherited/ hemizygote	Deletion 308.25 KB	Uncertain	Hypoplastic left heart
Decipher	361037	Xp22.11(chrX:22915415_23103990)	Maternally inherited/ hemizygote	Deletion 188.58 KB	Uncertain	Atypical behavior/ Delayed speech and language development
Decipher	326597	Xp22.11(chrX:22797762_23052148)	Maternally inherited/ hemizygote	Deletion 254.39 KB	Uncertain	Delayed speech and language development / Global developmental delay
Decipher	281838	Xp22.11(chrX:22818207_23003550)	Maternally inherited/ hemizygote	Deletion 185.54 KB	Uncertain	Hypoplasia of the corpus callosum
HGMD	PMID 20531469	Xp22.11(chrX:22860224_22923580)	Maternally inherited/ hemizygote	Deletion 63 KB upstream gene	-	Autism spectrum disorders
HGMD	PMID 20531469	Xp22.11(chrX:22892380_23013494)	Maternally inherited / hemizygote	Deletion 121 KB	-	Autism spectrum disorders
HGMD	PMID 20531469	Xp22.11(chrX:22829183_23214712)	Maternally inherited / hemizygote	Deletion 385 KB	-	Autism spectrum disorders
HGMD	PMID 29127259	c.24G>A	Unknown / hemizygote	nonsense p.Trp8*	-	Steroid-resistant nephrotic syndrome
HGMD	PMID 31785789	c.772C>A	Unknown	Missense p.Gln258Lys	-	Neurodevelopmental disorders

Supplementary Table 4. proteins interacting with DDX53

	Interactors	Experimental Evidence Code	Quantititave scroce*	Interactors Evidence*
DDX53	DDX43	Affinity Capture-MS	CompPASS-Plus score0.998682	high
DDX53	DDX43	Affinity Capture-MS	CompPASS-Plus score 0.998226	high
DDX53	PPM1B	Co-fractionation-MS	Cofrac PPI score 0.082419	high
DDX53	CAPZB	Co-fractionation-MS	Cofrac PPI score 0.07618	high
DDX53	EGFR	Affinity Capture-Western	-	low
DDX53	HDAC2	Affinity Capture-Western	-	low

*****The CompPASS-Plus score (0-1): probability of high-confidence interaction. The Cofrac PPI score (0-1) reflects the association between interacting proteins.

*Interactors Evidence is based on the BioGRID database, incorporating evidence from published literature to determine the interaction score.

Supplementary Table 5. GO Analysis of DDX53

GO ID	Qualified GO term	Evidence*
GO:00001665	nucleotide binding	IEA
GO:00036765	nucleic acid binding	IEA
GO:000372335	enables RNA binding	IBA
GO:000372435	enables RNA helicase activity	IBA
GO:00043865	helicase activity	IEA
GO:000552435	enables ATP binding	IEA
GO:00167875	hydrolase activity	IEA
GO:001688735	enables ATP hydrolysis activity	IEA

*IBD (Inferred from Biological aspect of Descendant); IEA (Inferred from Electronic Annotation)