Supplemental Figures and Tables

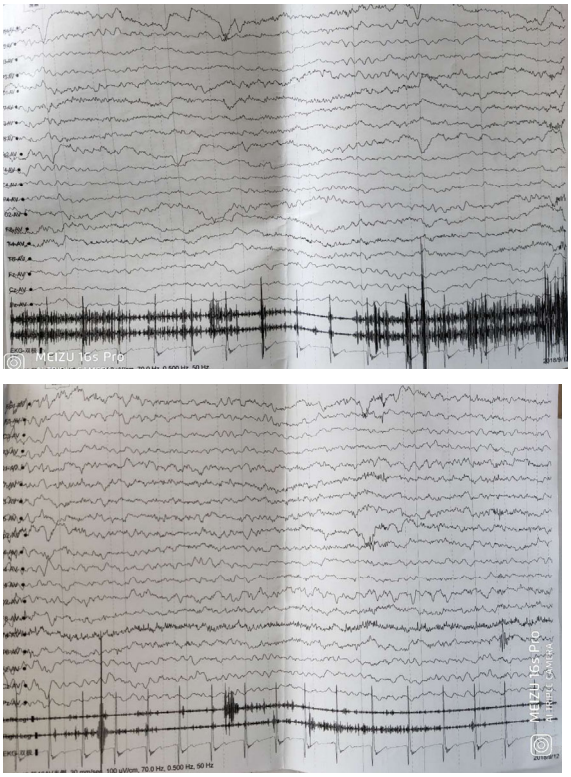

Figure S1. Electroencephalogram (EEG) of patient at six years old.

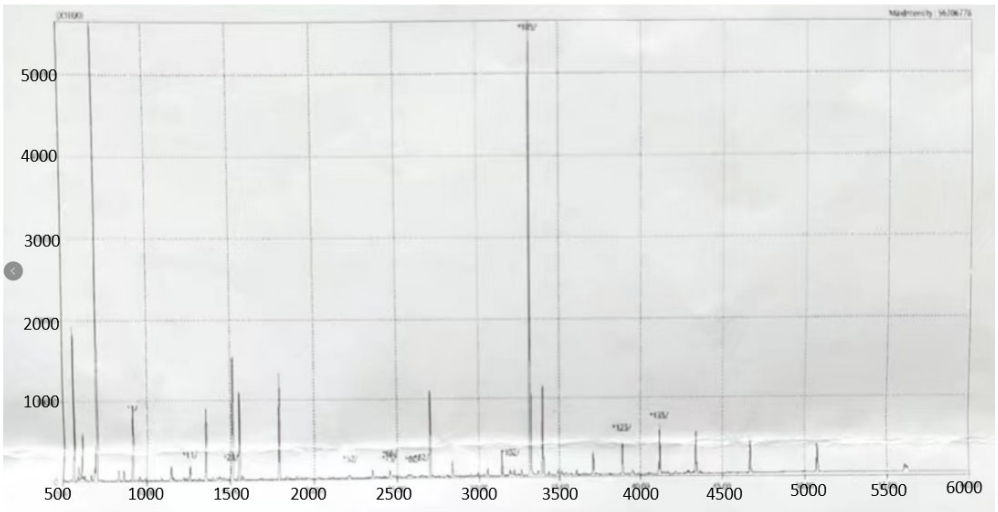

Figure S2. Chromatogram for the organic acids at three year of age.

Table S1. Clinical and genetic characteristics of patients carrying GTPBP3 variants.

Patient ID	Mutation type	Exon/ Intron	cDNA	Protein level	Inheritance	Gender	AO	Outcomes; cause of death	TTE	Brain MRI	Plasma lactate	Other phenotypes	Reference
Severe type													
#83904*,a	homozygote	Exon 1	c.32_33delinsGTG	p.Gln11Argfs*98	UNK	F	1 week	died 9 months; cardiac insufficiency with arrhythmia	DCM	UNK	20 mmol/L ↑	WPW; cardiogenic shock; metabolic acidosis	Kopajtich et al. (2014) [3]
#83905*,a	homozygote	Exon 1	c.32_33delinsGTG	p.Gln11Argfs*98	UNK	F	birth	died 10 days; cardiac insufficiency	DCM	UNK	UNK	WPW; cardiogenic shock; metabolic acidosis	Kopajtich et al. (2014) [3]
#81471	homozygote	Exon 4	c.424G>A	p.Glu142Lys	UNK	M	4 weeks	died 5 weeks; acidosis	HCM (concentric LVH)	hyperintensities in subthalamic nuclei	11 mmol/L ↑	weight loss; hypothermia; jaundice; recurrent apnea; metabolic acidosis	Kopajtich et al. (2014) [3]
#76671	homozygote	Intron 5	c.665-2delA	p.Ala222Gly; p.Asp223_Ser270del	UNK	M	birth	died 10 months; CHF	HCM (RVH)	bilateral hyperintensities in thalamus	5.2 mmol/L ↑	WPW; hypotonia; FTT; metabolic acidosis	Kopajtich et al. (2014) [3]
#75191	homozygote	Exon 8	c.1009G>C	p.Asp337His	UNK	F	birth	died 1 day; asystolia	HCM (apical RVH)	UNK	23 mmol/L ↑	Kussmaul breathing; stridor; hyporeactivit; poor feeding; hypotonia;	Kopajtich et al. (2014) [3]

												bradycardia	
#1	Compound heterozygote	Exon 4 Exon 4	c.413C>T c.509_510del	p.Ala138Val p.Gln170Glyfs*42	paternal maternal	M	17 h	died 5 days; CHF	normal	UNK	26 mmol/L ↑	hypothermia; stridor; hyporeactivit; respiratory failure; cardiogenic shock; metabolic acidosis	Yan HM et al. (2021) [4]
#72425	Compound heterozygote	Exon 4 Exon 6 Exon 7	c.484G>C c.673G>A c.964G>C	p.Ala162Pro p.Glu225Lys p.Ala322Pro	maternal paternal paternal	F	3.5 months	died 8 months; CHF	DCM	UNK	23.3 mmol/L ↑	poor feeding; FTT; hyporeactivity	Kopajtich et al. (2014) [3]
Mild type													
#75168*	homozygote	Exon 6	c.770C>A	p.Pro257His	UNK	F	2 years	alive 5 years	UNK	bilateral hyperintensities in thalamus and extending to the mesencephalon	>10 mmol/L ↑	developmental delay; epileptic seizures; intellectual disability	Kopajtich et al. (2014) [3]
Patient No.24	homozygote	Exon 7	c.836C>T	p.Pro279Leu	UNK	F	3 weeks	alive 10 years	normal	Delayed myelination	UNK	Mental motor retardation; epileptic seizure; hearing disability; thrombocytopenia	Eimas et al. (2019) [13]
#82790	Compound heterozygote	Exon 1	c.8G>T	p.Arg3Leu	UNK	F	1 year	alive 2 years	normal	bilateral hyperintensities	5.7~6.5 mmol/L	developmental delay; epileptic seizures;	Kopajtich et al.

		Exon 7	c.934_957del	p.Gly312_Val319del	UNK					in the putamen and weakly also in the anterior thalamus	↑	hypotonia	(2014) [3]
#3	Compound heterozygote	Exon 4 Exon 5	c.424G>A c.689A>C	p.Glu142Lys p.Gln230Pro	maternal paternal	F	1 year	alive 3 years	HCM (LVH)	bilateral lesions in brain stem, thalamus and dentate body of the cerebellum	4.26~16 mmol/L ↑	developmental delay; intellectual disability; fatigability	Yan HM et al. (2021) [4]
#66143	Compound heterozygote	Exon 4 Exon 7	c.476A>T c.964G>C	p.Glu159Val p.Ala322Pro	UNK UNK	M	2 years	alive 5 years	HCM	UNK	UNK (lactic acidosis)	sudden respiratory failure; CHF	Kopajtich et al. (2014) [3]
#2	Compound heterozygote	Exon 4 Exon 5	c.544G>T c.689A>C	p.Gly182* p.Gln230Pro	paternal maternal	F	1 year	alive 3 years	UNK	bilateral lesions in the midbrain, thalamus and dentate body of the cerebellum	7.7~14 mmol/L ↑	developmental delay; hypotonia	Yan HM et al. (2021) [4]
#C1	Compound heterozygote	Exon 5 Exon 8	c.689A>C c.1073delG	p.Gln230Pro p.Gly358Glufs*16	maternal paternal	F	3 years	alive 3 years	HCM (LVH)	abnormal symmetry signal of bilateral cortical spinal tract	29 mmol/L ↑	respiratory failure; myocardial damage; stroke-like syndrome	Yang Q et al. (2021) [15]
Our Patient	Compound heterozygote	Exon 5 Exon 7	c.689A>C c.1102dupC	p.Gln230Pro p.Arg368Profs*22	paternal maternal	M	3 days	alive 10 years	HCM (LVH)	abnormal signal of bilateral thalamus	3-11.6 mmol/L ↑	mental and motor retardation; selt-limitd epileptic seizures; abnormal visual	Our Patient

													development	
#C2	Compound heterozygote	Exon 5 Exon 9	c.689A>C c.1280delC	p.Gln230Pro p.Pro427Argfs*3	paternal maternal	F	9 years	alive 17 years	HCM (LVH)	UNK	5.53 mmol/L ↑	heart failure; intellectual developmental delay; abdominal pain; abdominal distention	Zhao XX et al. (2021) [14]
#49665*,b	Compound heterozygote	Exon 9 Exon 9	c.1291dupC c.1375G>A	p.Pro431Argfs*87 p.Glu459Lys	UNK UNK	M	10 years	alive 14 years	HCM (LVH)	Lactate peaks in parietal and precentral cortex	3~7 mmol/L ↑	mild intellectual disability; fatigability; limited vision; slight dyspnea with climbing stairs	Kopajtich et al. (2014) [3]
#36349*,b	Compound heterozygote	Exon 9 Exon 9	c.1291dupC c.1375G>A	p.Pro431Argfs*87 p.Glu459Lys	UNK UNK	M	UNK	alive 17 years	HCM	Lactate peaks in parietal and precentral cortex	UNK	mild intellectual disability; fatigability; limited vision; slight dyspnea with climbing stairs	Kopajtich et al. (2014) [3]

Abbreviations are as follows: AO, age of onset; TTE, transthoracic echocardiography; MRI, magnetic resonance imaging; UNK, unknown; CHF, congestive heart failure; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; LVH/RVH, left/right ventricular hypertrophy; WPW, Wolff-Par-kinson-White syndrome; FTT, failure to thrive.

NCBI reference sequence: NM_032620.4.

*They have consanguineous parents.

[a,b]These individuals are siblings.

Table S2. Distribution of homozygous missense variant in coding region of *GTPBP3* from COXPD23 patients and gnomAD across five structural domains.

DOMAIN		**GENERAL POPULATIONS** （HOMO）	**CLINICAL SAMPLES** （HOMO）
TRANSPORT PEPTIDE REGION	Number within this domain	57115	0
	Number outside this domain	66324	4
	Fisher's test		0.1292
N-TERMINAL REGION	Number within this domain	121670	1
	Number outside this domain	1769	3
	Fisher's test		<0.0001****
CENTRAL HELICAL DOMAIN 1	Number within this domain	1	0
	Number outside this domain	123438	4
	Fisher's test		>0.9999
TRME-TYPE G DOMAIN	Number within this domain	1768	3
	Number outside this domain	121671	1
	Fisher's test		<0.0001****
CENTRAL HELICAL DOMAIN 2	Number within this domain	1714	0
	Number outside this domain	121725	4
	Fisher's test		>0.9999

Table S3. Distribution of variants in GTPBP3 from severe types and mild types across five structural domains.

Domain		Total		LOFVs		Missense variants	
		severe types	mild types	severe types	mild types	severe types	mild types
Transport peptide region	Number within this domain	1	1	1	0	0	1
	Number outside this domain	8	13	2	5	6	8
	Fisher's test		**>0.9999**		**0.3750**		**>0.9999**
N-terminal region	Number within this domain	2	3	0	0	2	3
	Number outside this domain	7	11	3	5	4	6
	Fisher's test		**>0.9999**		**>0.9999**		**>0.9999**
Central helical domain 1	Number within this domain	3	4	1	2	2	2
	Number outside this domain	6	10	2	3	4	7
	Fisher's test		**>0.9999**		**>0.9999**		**>0.9999**
TrmE-type G domain	Number within this domain	4	3	2	1	2	2
	Number outside this domain	5	11	1	4	4	7
	Fisher's test		**0.3630**		**0.4643**		**>0.9999**
Central helical domain 2	Number within this domain	0	3	0	2	0	1
	Number outside this domain	9	11	3	3	6	8
	Fisher's test		**0.2530**		**0.4643**		**>0.9999**