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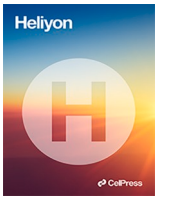

Compound heterozygous *WDR19* variants associated with nephronophthisis, Caroli disease, refractory epilepsy and congenital bilateral central blindness: Case report

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ABSTRACT

The *WDR19* gene has been reported to be involved in nephronophthisis-related ciliopathies such as isolated nephronophthisis 13 (NPHP13), Sensenbrenner syndrome, Jeune syndrome, Senior-Loken syndrome, Caroli disease, retinitis pigmentosa and Asthenoteratospermia. In the present study, we provided the detailed clinical characteristics and genetic analysis of a patient with four variants in *WDR19* and *TG*, reviewed a comprehensive mutation analysis in the *WDR19*-related ciliopathies, discussed the relationship between genotype and phenotype, and compared the allele frequencies (AFs) of *WDR19* variants depending on the ethnic background. We used whole-exome sequencing (WES) combined with bioinformatics analysis to investigate the genetic variants of a 3-year-old boy with common features of *WDR19*-associated NPHP13 and Caroli disease, bilateral central blindness, refractory epilepsy, and elevated thyroid stimulating hormone. A novel splice-donor variant, c.98+1G > C, and a recurrent missense variant, c.3533G > A, were identified in the *WDR19* gene. We used effective mRNA analysis to verify the effects on pre-mRNA processing and to assess the pathogenicity of the splice-site variant. The patient also harbored compound heterozygous variants of the *TG* gene (c.4889A > G, c.274+2T > G). Of note, using a review of an in-house database, we identified four additional likely pathogenic *WDR19* variants and estimated the overall AF of *WDR19* mutations to be 0.0025 in the southern Chinese population. Our findings have expanded the allelic spectrum of mutations in the *WDR19* gene and broadened the clinical phenotype spectrum of *WDR19*-related ciliopathies. The results have also provided new insights into the clinical heterogeneity of the disorder, which would be useful in accurate genetic counseling for affected individuals and carrier screening in a general population.

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1. Introduction

The cilium is an antenna-like structure that protrudes from the surface of most vertebrate cells. Dysfunction of this organelle is associated with ciliopathies, which are a group of genetic disorders that are involved in a wide range of symptoms [1]. Major organ systems affected by ciliopathies are the kidneys, retina, nervous system and skeletal system [2].

The *WDR19* (WD repeat-containing protein 19, MIM#608151) gene encodes the intraflagellar transport component, IFT144, and has been reported to be the causative gene of nephronophthisis-related ciliopathies such as isolated nephronophthisis (NPHP), Sensenbrenner syndrome, Jeune syndrome, Senior-Loken syndrome and retinitis pigmentosa [2–7]. Patients with *WDR19* mutations typically display nephronophthisis or cystic kidney disease, as a renal phenotype, and have various extrarenal manifestations, such as multiple dental anomalies [2], retinitis pigmentosa [3], skeletal or other organ disorders [4], and Caroli disease [5,7]. A homozygous *WDR19* mutation leading to disorganization of sperm flagella microtubules and nonsyndromic asthenoteratospermia has also been reported [8].

So far, more than 70 cases with *WDR19*-related ciliopathies have been diagnosed worldwide (Table 1). In addition to large fragment deletions, over 100 pathogenic or likely pathogenic *WDR19* variants have been identified in these patients or listed in the ClinVar database (Table S1). Herein, we investigated a male patient from a healthy Chinese family who harbored compound heterozygous variants in the *WDR19* and *TG* genes. The patient presented with *WDR19*-related NPHP13, Caroli disease, bilateral central blindness, elevated thyroid stimulating hormone, global developmental delay, and refractory epilepsy. To the best of our knowledge, this study is the first to report an association between *WDR19*-related conditions and epilepsy. We identified a novel variant in the patient and also identified four additional likely pathogenic *WDR19* variants by reviewing the detected variants from the in-house database (Table S2). We estimated the total AF of the pathogenic and likely pathogenic *WDR19* variants in our cohort to be almost 0.0025. Our study broadened the possible clinical phenotype and known mutation spectrum of *WDR19*.

2. Case presentation

2.1. Clinical description

The proband was a 3-year-old Chinese boy who was the first child born to healthy and non-consanguineous parents. There was no family history of kidney disease. Prenatal ultrasound examinations during pregnancy revealed slightly enhanced parenchymal echoes and enlarged kidneys on both sides. The patient was born at term (40 weeks) by cesarean section. The birth height was 51 cm, weight was 3720 g and the Apgar score was 10-10-10 in 1-5-10 min, respectively. He contracted pneumonia at 2 weeks of age. Three weeks after birth, he was admitted to our hospital due to shortness of breath and poor appetite. Physical examination on admission revealed weight loss (3170 g), dehydration, and hypotonia. The boy was given respiratory support through continuous positive airway pressure systems. The blood biochemical examination indicated elevated serum creatinine (218.00 μmol/L), high plasma urea (32.78 mmol/L), hyperkalemia (5.7 mmol/L), hyperchloremia (113.6 mmol/L), elevated aspartate aminotransferase (85 U/L), elevated alanine aminotransferase (107 U/L) and elevated γ-glutamyl transpeptidase (465 U/L). Blood gas analysis revealed anemia (Hb 81 g/L) and severe metabolic acidosis (pH = 7.0 and HCO_3^- = 8.4 mmol/L). And cardiac ultrasound examination revealed a patent foramen ovale. His renal ultrasound demonstrated increased renal echogenicity. Intracranial magnetic resonance imaging showed no definite structural abnormalities, while abdominal magnetic resonance imaging showed dilatation of the intrahepatic bile ducts in the left lobe of the liver (3.6 mm). At this time, he showed proteinuria and decreased urine. He then developed anuria and was diagnosed with stage 3, severe acute kidney injury. Peritoneal dialysis was then performed. At the age of 4 weeks, the child showed hypernatremia and involuntary movements of the eyes. Although 24-h ambulatory electroencephalogram (EEG) monitoring found abnormal electrical activity in the brain, no epilepsy was determined. He stayed in the neonatal intensive care unit (NICU) for 2 weeks, and was discharged with a body weight of 3730 g. One week after discharge, the child developed pneumonia again and was readmitted. Since then, he has suffered from frequent infections. He presented with elevated thyroid stimulating hormone (14.86 uIU/mL) and slightly low free thyroid hormone levels (10.49 pmol/L) at 7 weeks of age. One week later, the diagnosis of epilepsy was made and treatment with valproic acid began. His kidney, liver and pancreatic cysts, plus focal dilatation of the intrahepatic bile ducts, were found at 2 months of age and were consistent with NPHP13 and Caroli disease (Fig. 1A and B). Digital radiography of both knees showed no definite structural abnormalities (Fig. 1C). The right hand showed a temporary calcified zone at the distal end of the metacarpals. Some of the metacarpals and phalanges were short and broad, which may have been caused by loss of calcium and phosphorus (Fig. 1D). At this time, his serum alkaline phosphatase level was normal (258 U/L), but he presented with decreased calcium concentrations (1.84 mmol/L) and Vitamin D deficiency (14.08 ng/mL). He also showed elevated γ-glutamyl transpeptidase concentrations (1528 U/L) and severe liver injury at this stage. At the age of 10 months, he progressed into end-stage renal disease (ESRD) and hemodialysis was initiated. At 22 months of age, he received a renal transplantation. Over the next year and a half, he suffered from numerous infections, which included four bouts of pneumonia and two bouts of sepsis.

The child was also diagnosed with bilateral central blindness of normal eyes, normal fundus, normal pupillary light reflex and normal retina. He could raise his head at 6 months, turn over at 8 months, sit independently at 12 months but, to date, he cannot walk by himself and is unable to speak. At 3 years old, his height and weight were 86 cm (−3 SD) and 10.6 kg (−2.6 SD, respectively). This study was reviewed and approved by the medical ethics committee of Maternal and Child Health Hospital of Guangxi Zhuang Autonomous Region with a reference number of 2020-1/15. Written informed consent was obtained from the parents of the patient.

Table 1
Clinical characteristics and genetic information of patients with *WDR19*-associated disorders have been described in the literature.

Reference	Patient	Ethnicity	Gender	Mutation 1	Mutation 2	Diagnostics	Other symptoms
Bredrup et al. 2011 PMID: 22019273	Family 1 II-1	Norwegian	F	c.2129T > C(p.Leu710Ser)	c.3307C > T(p.Arg1103Ter)	Sensenbrenner	Multiple dental anomalies, renal transplantation, diopathic bone marrow hypoplasia, reduced lung capacity, retinitis pigmentosa, nephronophthisis-like nephropathy, tapetoretinal dystrophy, hypertension, skin laxity
	Family 1 II-2	Norwegian	M	c.2129T > C(p.Leu710Ser)	c.3307C > T(p.Arg1103Ter)	Sensenbrenner	Multiple dental anomalies, developmental dysplasia of both hips, craniosynostosis of the sagittal suture, retinitis pigmentosa, hyperechoic kidneys without clinical or biological signs of renal, skin laxity disease, rod-cone dystrophy
	Family 2 II-1	Dutch	F	c.20T > C(p.Leu7Pro)	c.20T > C(p.Leu7Pro)	Jeune syndromes	Small kidneys, renal transplants, short fingers, short foot, chronic renal disease and several eye abnormalities
	Family 3 II-1	Moroccan	M	c.1034T > G(p.Val345Gly)	c.3068dupA(p.Tyr1023Ter)	Nephronophthisis13	Small kidneys, interstitial fibrosis with atrophic tubules and 50% sclerotic glomeruli
	Family 3 II-3, 5	Moroccan	F	c.1034T > G(p.Val345Gly)	c.3068dupA(p.Tyr1023Ter)	Nephronophthisis13	Small kidneys
	Family 3 II-6	Moroccan	F	c.1034T > G(p.Val345Gly)	c.3068dupA(p.Tyr1023Ter)	Renal disease	Mild features of renal disease
Halbritter et al. 2013 PMID: 23559409	A2556-21/22	Egyptian	/	c.682C > T(p.Gln228Ter)	c.3703G > A(p.Glu1235Lys)	Nephronophthisis13	Caroli disease
	A4436 -22	Omani	/	c.3533 G > A(p.Arg1178Gln)	c.3533 G > A(p.Arg1178Gln)	Nephronophthisis13	Polydactyly, retinal dystrophy, Caroli disease
	A3241-21	American	/	c.3533 G > A(p.Arg1178Gln)	c.3565+1G > A	Nephronophthisis13	Cortical blindness, pancreatic cysts, hepatic cysts
	F754 -22	American	/	c.781dupA(p.Thr261Asnfs*13)	/	Nephronophthisis13	None
Coussa et al.2013 PMID: 23683095	MOGL1764	French-Canadian	M	c.2129T > C(p.Leu710Ser)	c.2129T > C(p.Leu710Ser)	Retinitis pigmentosa	Mild cognitive impairement, bilateral congenital subclinical renal cysts
	MOGL3157	French-Canadian	F	c.2129T > C(p.Leu710Ser)(hom)	c.1477G > C(p.Asp493His)	Retinitis pigmentosa	None
	F1229	Spanish	/	c.641dupT(p.Leu214Phefs*5)	c.1477G > C(p.Asp493His)	Senior-Loken syndrome	Nephronophthisis, growth retardation
	F889	Turkish	/	c.203T > A(p.Val68Asp)	c.407-2A > G	Senior-Loken syndrome	Nephronophthisis
	F713	Canadian	/	c.88G > C(p.Ala30Pro)	/	Senior-Loken syndrome	Nephronophthisis, bilateral hip dysplasia, ventricular septum defect
	A2335	Canadian	/	c.326G > A(p.Gly109Glu)	/	Senior-Loken syndrome	Nephronophthisis, vesicoureteral reflux, proteinuria, gestational polyhydramnios, intellectual disability
	A4395	Canadian	/	c.781dupA(p.Thr261Asnfs*13)	/	Senior-Loken syndrome	Nephronophthisis, Jeune asphyxiating thoracic dystrophy, night blindness, brachydactyly, scoliosis
Fehrenbach et al. 2014 PMID: 24504730		Philippine	F	c.1483G > C(p.Gly495Arg)	c.1483G > C(p.Gly495Arg)	Jeune and Sensenbrenner syndromes	Hypotonia, facial dysmorphism, mild psychomotor development retardation, short stature, mild skeletal anomalies, strabism, deafness, hepatosplenomegaly, end-stage renal failure
Lee et al. 2015 PMID: 25726036	I-1	Korean	M	c.3533 G > A(p.Arg1178Gln)	c.3703G > A(p.Glu1235Lys)	Nephronophthisis13	Caroli
	I-2	Korean	F	c.3533 G > A(p.Arg1178Gln)	c.3703G > A(p.Glu1235Lys)	Nephronophthisis13	Caroli
	I-3	Korean	F	c.3533 G > A(p.Arg1178Gln)	c.3703G > A(p.Glu1235Lys)	Nephronophthisis13	Caroli

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Table 1 (*continued*)

Reference	Patient	Ethnicity	Gender	Mutation 1	Mutation 2	Diagnostics	Other symptoms
	II-1	Korean	M	c.3533 G > A(p.Arg1178Gln)	c.1483G > T(p.Gly495Cys)	Nephronophthisis13	Caroli, retinitis pigmentosa
	III-1	Korean	M	c.3533 G > A(p.Arg1178Gln)	c.1853T > C(p.Leu618Pro)	Nephronophthisis13	Caroli, pancreatic cysts
	IV-1	Korean	F	c.3533 G > A(p.Arg1178Gln)	c.3533 G > A(p.Arg1178Gln)	Nephronophthisis13	Dysplastic kidney, Caroli disease
Park et al. 2015 PMID: 26260382	7	Korean	/	c.1307A > C(p.His436Leu)	c.3533 G > A(p.Arg1178Gln)	Nephronophthisis13	None
	8	Korean	/	c.3262-2A > G	c.3703G > A(p.Glu1235Lys)	Nephronophthisis13	None
	9	Korean	/	c.189_190ins3 (p.63_64insAla)	c.962-2A > G	Nephronophthisis13	None
	10	Korean	/	c.3533 G > A(p.Arg1178Gln)	c.3533 G > A(p.Arg1178Gln)	Nephronophthisis13	None
	11	Korean	/	c.3533 G > A(p.Arg1178Gln)	c.3533 G > A(p.Arg1178Gln)	Nephronophthisis13	None
Westerfield et al. 2015 PMID: 26275793	11	/	/	c.275T > G(p.Leu92Ter)	c.880G > A(p.Gly294Arg)	Short-rib thoracic dysplasia type 5	Skeletal anomalies, edema, echogenic kidneys, and possible ventricular septal defect
Patel et al. 2016 PMID: 26355662	12DG1471	Saudi Arabian	/	c.2777G > T(p.Ser926Ile)	/	Non-syndromic retinitis pigmentosa	Retinitis pigmentosa, Rod cone dystrophy
Braun et al. 2016 PMID: 26489029	A4436	Arabian	/	c.3533 G > A(p.Arg1178Gln)	c.3533 G > A(p.Arg1178Gln)	Nephronophthisis	None
	F1036	East Africa	/	c.14T > C(p.Phe5Ser)	c.3565+1G > A	Nephronophthisis	None
Daoud et al. 2016 PMID: 27241786	11	Canadian	M	c.1600G > T(p.Glu534Ter)	c.2129T > C(p.Leu710Ser)	Cranioectodermal dysplasia	None
Zhang et al. 2016 PMID: 27596865	BLM071	Hispanic	F	c.3533 G > A(p.Arg1178Gln)	c.2561A > C(p.Lys854Thr)	Non-syndromic retinitis pigmentosa	No other symptoms
Shaheen et al. 2016 PMID: 27894351	13DG1415	/	/	c.2585T > C(p.Leu862Pro)	c.2585T > C(p.Leu862Pro)	Cranioectodermal dysplasia	Renal failure, cleft lip and palate, dysmorphic facies, short-bifid nose, small teeth, short extremities, Caroli disease, liver and renal cysts, pituitary hypoplasia, ectopic neurohypophysis, metaphyseal dysplasia and acromelia
Yoshikawa et al., 2017 PMID: 28621010	Patient 1	Japanese	F	c.956delA(p.Asn319Ilefs*16)	c.3533 G > A(p.Arg1178Gln)	Sensenbrenner	Dolichocephaly, narrow thorax, and brachydactyly, intrahepatic bile ducts with central dot signs, retinal dystrophy, subdural hygroma, and psychomotor retardation.
	Patient 2	Japanese	F	c.2645+1G > T	c.3533 G > A(p.Arg1178Gln)	Sensenbrenner	Dolichocephaly, narrow thorax, polydactyly, and short stature, congenital pancreatic cysts, retinal dystrophy, hydrocephalus, and psychomotor retardation
Zhang et al., 2018 PMID: 29068549	R00-304	Caucasian	/	c.3565+1G > A	c.817A > G(p.Asn273Asp)	Asphyxiating thoracic dystrophy	None
	R01-210A	Caucasian	/	c.781dupA(p.Thr261Asnfs*13)	c.880G > A(p.Gly294Arg)	Asphyxiating thoracic dystrophy	None
	R04-526A	Caucasian	/	c.3484-2A > C	c.475G > A(p.Asp159Asn)	Short-rib polydactyly syndromes IV	None

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Table 1 (*continued*)

Reference	Patient	Ethnicity	Gender	Mutation 1	Mutation 2	Diagnostics	Other symptoms
	R05-449C	Caucasian	/	c.3800G > A(p.Cys1267Tyr)	c.817A > G(p.Asn273Asp)	Asphyxiating thoracic dystrophy	None
	R09-396A	African American	/	c.3716+1G > A	c.746T > C(p.Phe249Ser)	Asphyxiating thoracic dystrophy	None
	R15-017A	Pacific Islander	/	c.1483G > C(p.Gly495Arg)	c.2563C > T(p.Gln855Ter)	Asphyxiating thoracic dystrophy	None
Ryan et al., 2018 PMID: 29121203	NPH1848	French/ Japanese	F	EXON 1-4 DEL	c.3533 G > A(p.Arg1178Gln)	Mainzer-Saldino Syndrome	Congenital Leber amaurosis, cystic liver and pancreas, bone dysplasia, cone-shaped epiphyse, thoracic distension, hyperechogenic kidneys with small cysts, moderate dilation of the intra-renal cavities and left ureter, end-stage renal disease, cardiomegaly, brain ventricle dilations and ciliary dyskinesia with concomitant airway infections
Stone et al., 2018 PMID: 28559085	498	/	M	c.2129T > C(p.Leu710Ser)	c.3066_3067delAT(p.Tyr1023Serfs*18)	Retinal dystrophy	None
	825	/	M	c.1031A > G(p.His344Arg)	c.1454G > T(p.Ser485Ile)	Stargardt disease	None
Fuster-García et al., 2019 PMID: 31725169	FRP-539	Spanish	M	c.1983-2A > T	c.2782A > T(p.Ile928Phe)	Usher-Like Phenotypes	Retinitis pigmentosa, nyctalopia; visual field constriction, cataracts, funduscopy revealed mild thinning of the peripheral vessels, presence of peripheral bone-spicule pigments
Dharmadhikari et al., 2019 PMID: 31101064	WC5	/	/	c.3703G > A (p.Glu1235Lys)	exons 10–13 deletion	Nephronophthisis	None
Shamseldin et al., 2020 PMID: 32055034	19DG1441	Saudi Arabian	/	c.2777G > T(p.Ser926Ile)	/	Nonsyndromic Stargardt disease	None
Surl et al., 2020 PMID: 32165824	P36	Korean	F	c.3533 G > A(p.Arg1178Gln)	c.3533 G > A(p.Arg1178Gln)	Senior-Loken syndrome	Nephronophthisis and Caroli disease
	P37	Korean	M	c.3533 G > A(p.Arg1178Gln)	c.3533 G > A(p.Arg1178Gln)	Senior-Loken syndrome	Severe mental retardation and mild hypotonia, bilateral T2 hyperintense signal in the putamen
Ni et al., 2020 PMID: 32323121	/	Chinese	M	c.3811A > G(p.Lys1271Glu)	c.3811A > G(p.Lys1271Glu)	Asthenoteratospermia	No other symptoms
Montolío-Marzo et al., 2020 PMID: 33002628	/	Spanish	M	c.1442A > G(p.His481Arg)	c.2741C > A(p.Ala914Asp)	Mainzer-Saldino syndrome	Nyctalopia, right eye nystagmus, trigonocephaly, growth retardation, dorsal-lumbar kyphoscoliosis and cone shaped epiphysis, cystic nephropathy, enlarged intrahepatic biliary ducts, left ventricle hypertrophy, renal artery stenosis
Zampaglione et al., 2020 PMID: 32037395	121–047	/	/	c.3374C > T(p.Ala1125Val)	c.3515G > A(p.Gly1172Glu)	Retinal degeneration	None
	121–244	/	/	c.89_90insTACT(p.Val31Thrfs*6)	c.2785C > T(p.Arg929Cys)	Retinal degeneration	None
Hammarsjö et al., 2021 PMID: 33875766	18	Swedish	M	c.56 T > G(p.Phe19Cys)	c.3868_3871del(p.Thr1290Cysfs*14)	Asphyxiating thoracic dystrophy and short-rib polydactyly syndrome	Nephronophthisis
	19	Swedish	F	c.974 T > C(p.Leu325Ser)	c.3758 G > A(p.Cys1253Tyr)	Asphyxiating thoracic dystrophy and short-rib polydactyly syndrome	Nephronophthisis, dolichocephaly, speech delay

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Table 1 (*continued*)

Reference	Patient	Ethnicity	Gender	Mutation 1	Mutation 2	Diagnostics	Other symptoms
	21	Swedish	F	c.1623C > G(p.Tyr541Ter)	c.3533 G > A(p.Arg1178Gln)	Cranioectodermal dysplasia	Macrocephaly, dolichocephaly, sparse hair, Nephronophthisis, cystic liver
Alawi et al., 2021 PMID: 34354814	P18	Omani	M	c.3533 G > A(p.Arg1178Gln)	c.3533 G > A(p.Arg1178Gln)	Senior-Løken syndrome	Nephronophthisis, hypertension, developmental delay and retinal dystrophy
Kim et al., 2021 PMID: 33946315	172–223	Korean	/	c.2645+1G > T	c.1613G > T(p.Gly538Val)	Senior-Løken syndrome	Retinitis pigmentosa
Quinaux et al., 2021 PMID: 33606107	Patient #4	French	M	c.373_375dup(p.Asn125dup)	c.2269C > T(p.Gln757Ter)	Sensenbrenner syndrome	Increased nuchal translucency, hypotonia, dysmorphisms, scaphocephaly, craniosynostosis, psychomotor delay, severe growth retardation, nail dysplasia, chronic kidney disease, hypoplastic kidneys, nystagmus, hypermetropia
Kaynar et al., 2021 PMID: 35937515	/	Turkish	F	c.991G > T(p.Gly331Cys)	c.991G > T(p.Gly331Cys)	Complement 1q nephropathy	Proteinuria, focal segmental glomerulosclerosis, patient's sister with focal segmental glomerulosclerosis
Keyser et al., 2022 PMID: 35362211	/	Mexican-Irish	F	c.742G > A(p.Gly248Ser)	c.617T > C(p.Leu206Pro)	Multi-malformations	Restrictive and obstructive lung disease, short rib thoracic dysplasia, end-stage renal disease, developmental delay, hepatic fibrosis, and severe recurrent pancreatitis, motor delay, hypotonia, brachydactyly, short stature
Sakakibara et al., 2022 PMID: 35140360	SC237	Japanese	F	c.956delA(p.Asn319Ilefs*16)	c.3533 G > A(p.Arg1178Gln)	Nephropathy	Renal cysts, high echog enecity, abnormal corticomedullary differentiation
	SC255	Japanese	F	c.2645+1G > T	c.3533 G > A(p.Arg1178Gln)	Nephropathy	Renal cysts, high echogenecity, abnormal corticomedullary differentiation, kidney enlargement, glomerulo screlosis, tubuloin terstitial damage
	SC825	Japanese	F	c.3262-2A > G	c.3533 G > A(p.Arg1178Gln)	Nephropathy	Renal cysts
Capra et al., 2023 PMID: 36833411	Case 1	Caucasian	M	c.3470A > G (p.Tyr1157Cys)	c.3470A > G (p.Tyr1157Cys)	Multi-malformations	Chronic renal failure, polycystic kidney disease, polycystic liver disease, delayed psychomotor development, motor delay, intellectual disability, trigonocephaly, microcephaly, short stature, skin syndactyly of the II and III fingers and toes, abnormality of the ocular region.
Sajovic et al., 2023 PMID: 36833218	/	Slovenian	M	c.1454G > T(p.Ser485Ile)	Exon 29 del	Stargardt disease	No other symptoms

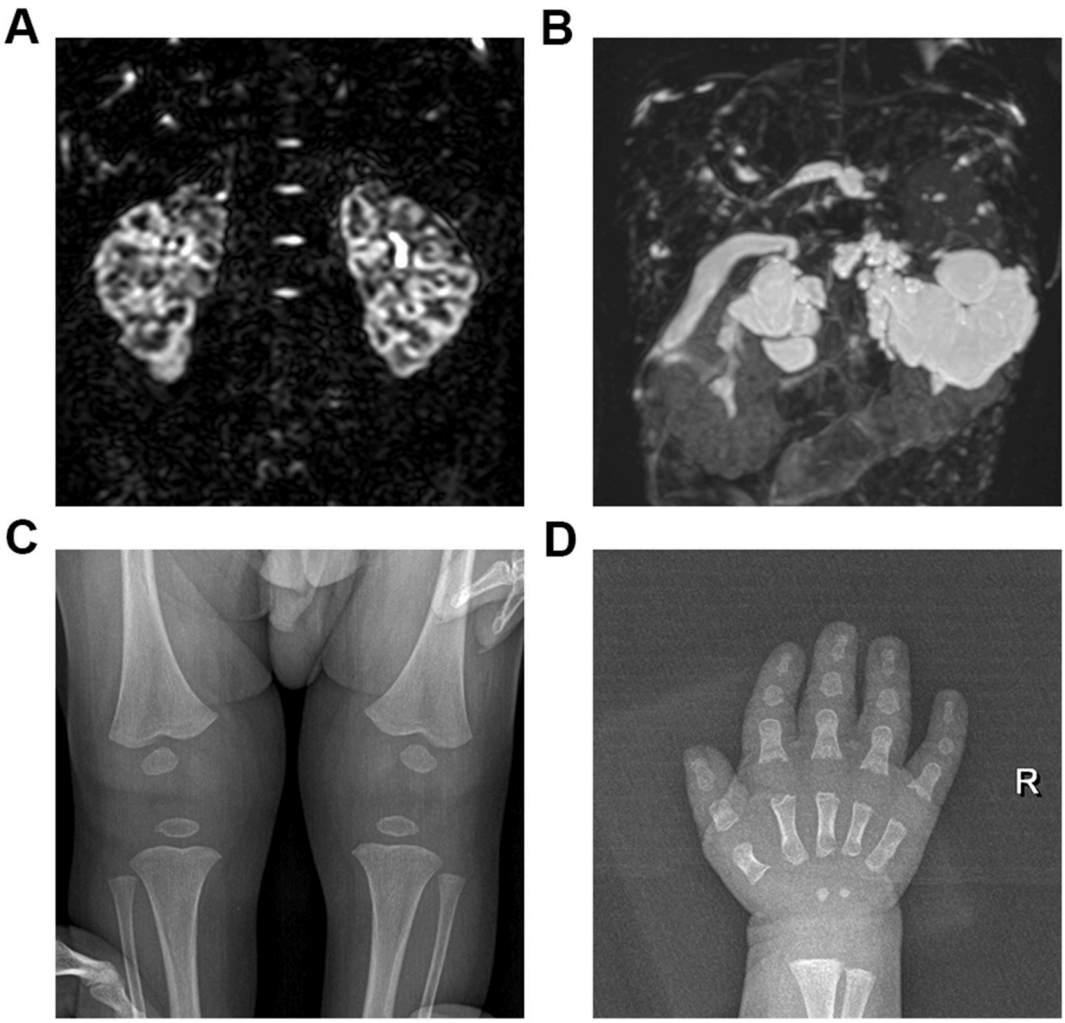

Fig. 1. Phenotype of the kidneys and images of the extrarenal manifestations of the patient. (A) Abdominal magnetic resonance imaging demonstrated bilateral kidneys were enlarged with diffuse microcysts. (B) Liver and pancreas cysts, and focal dilatation of the intrahepatic bile ducts. (C) Digital radiography of both knees showed no definite structural abnormalities. (D) X-ray revealed the temporary calcified zone at the distal end of the metacarpals, metacarpals and phalanges were short and broad.

2.2. Genetic analysis

WES analysis revealed compound heterozygous variants, c.98+1G > C and c.3533G > A (p.Arg1178Gln), in the *WDR19* gene (NM_025132.3) of our patient (Fig. 2). The paternally inherited missense substitution is a known pathogenic variant that has been recurrently reported in patients with nephronophthisis, polydactyly, Caroli disease and retinal dystrophy (Table 1). The p.Arg1178Gln mutant was predicted to be tolerated by SIFT, but it was predicted to be disease-causing or damage by other in silico tools (Table S3). The maternally inherited splice-site variant is absent from all publicly available databases. This transversion may disrupt the highly conserved GT dinucleotide sequence of the splice junction (Table S3). To investigate its effect on mRNA processing, we extracted mRNA from leukocytes of the proband and agarose gel electrophoresis of reverse-transcribed cDNA amplification products revealed a shortened band (Fig. 3A). Sanger sequencing of the PCR products confirmed the presence of a truncated transcript skipping exon 2 (Fig. 3B). According to the ACMG/AMP guidelines, it was classified as pathogenic (PVS1+PM2_supporting + PM3) [9].

WES data from this patient also showed compound heterozygous variants, c.274+2T > G and c.4889A > G (p.Tyr1630Cys), in the *TG* gene (Fig. 2). The maternally inherited splice-site variant is listed in the dbSNP database, annotation rs1398373161, but it is not found in ClinVar. The transversion in the canonical splice donor site may break the GT dinucleotide sequence at the splice donor site (Table S3) and it can be classified as likely pathogenic according to the ACMG/AMP guidelines (PVS1+PM2_supporting). The paternally inherited missense variant is not listed in any publicly available databases and it was assessed to be detrimental for the protein function by all the prediction software (Table S3). The substitution can be classified as a variant of uncertain significant (VUS) (PM2_supporting + PM3).

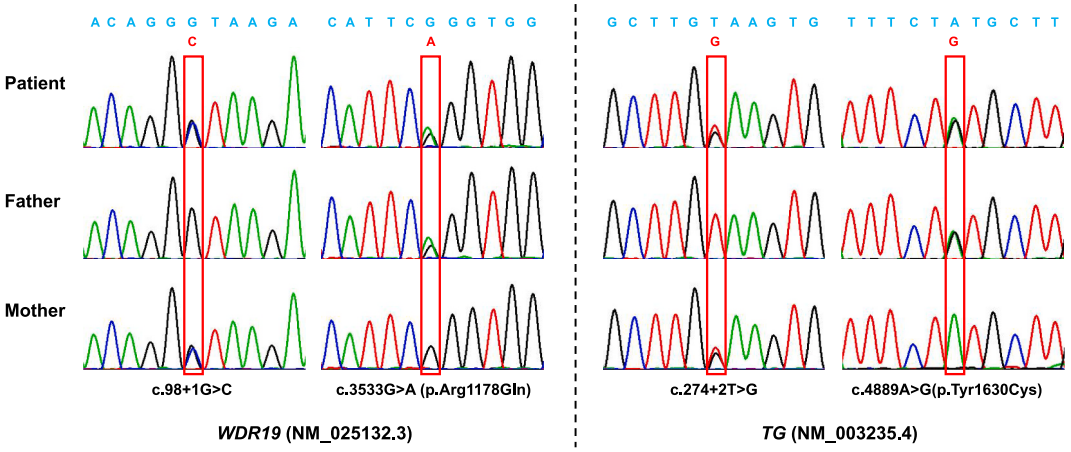

Fig. 2. Results of genetic testing of the patient and his parents. The patient had compound heterozygous mutations in *WDR19* and *TG*. The red frames represent the variant sites.

2.3. Analysis of local mutation frequency

To assess the local mutation frequency of the *WDR19* gene, we analyzed all previously identified variants in the in-house database (n = 6886). After filtering-out the intronic variants and variants with AF ≥1%, 77 variants were selected for further analysis (Table S2). According to the ACMG/AMP variant interpretation guidelines, five variants were evaluated as pathogenic (one novel and four reported) and seven were likely pathogenic (four novel and three reported). The overall AF was approximately 0.0025 in our cohort. In addition, we identified two missense variants, c.1993G > C (p.Ala665Pro) and c.3895G > C (p.Ala1299Pro), of the *WDR19* gene in a fetus who presented with short limbs, skin edema and intrauterine growth retardation. The c.1993G > C variant is present in population databases (rs753976268, ExAC, 0.01%) and it is listed in ClinVar (RCV001998324) as a VUS. The c.3895G > C variant is absent from the general population databases. Both transversions had high REVEL scores (0.88 and 0.83, respectively) and were predicted to be deleterious. Unfortunately, genetic testing of the parents was not possible and both variants were considered to be VUS, according to the ACMG/AMP guidelines.

3. Discussion

The *WDR19* gene is located on chromosome 4p15-4p11 and consists of 36 coding exons. It encodes a 1342 amino acid protein, IFT144, and contains six WD40 repeats, three TPR repeats, one COG5290 and one double zinc ribbon (DZR) domain (https://www.ncbi.nlm.nih.gov/protein/).

The IFT144 protein is a member of intraflagellar transport (IFT) complex A, which is essential for cilia formation, maintenance, and function [4]. Previous reports have indicated that *WDR19* mutations, which include insertions, deletions, missense mutations, frame shifts and splicing alterations, caused a broad spectrum of ciliopathies, such as Jeune, Senior-Loken and Sensenbrenner syndromes, Caroli disease, retinitis pigmentosa, renal NPHP-like phenotypes, and asthenoteratospermia-induced infertility. Moreover, the *WDR19*

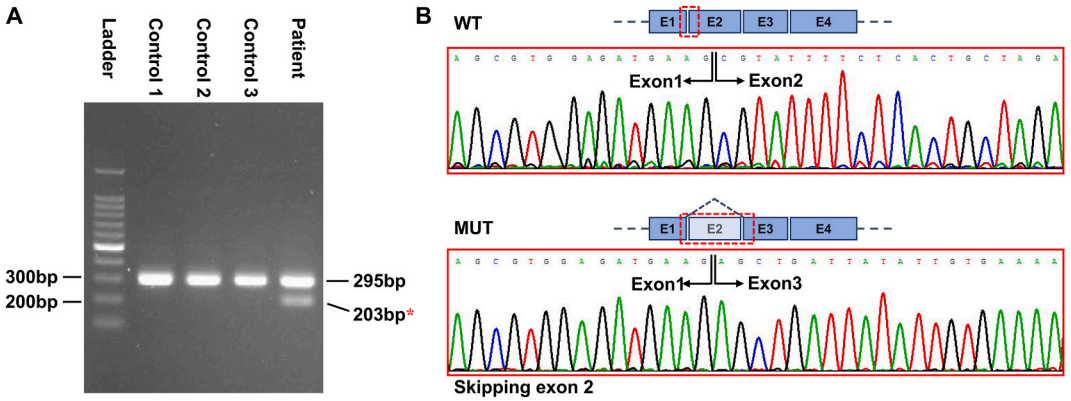

Fig. 3. Results of cDNA Sequencing in the patient. (A) RT-PCR products of WDR19 mRNA transcripts from patient and healthy control. Asterisk, the aberrant mRNA fragment. (B) The results of the cDNA sequencing showed that the truncated transcript lacked exon 2. WT, 295 bp; MUT, 203 bp.

gene has been reported to be associated with ataxia and cervical cancer [10,11]. In this study, the patient presented with nephronophthisis, Caroli disease, congenital bilateral central blindness, elevated thyroid stimulating hormone, global developmental delay and refractory epilepsy.

The clinical manifestations associated with *WDR19* mutations are diverse, with a wide range of severity in various ciliopathies. Bredrup et al. speculated that mutation type may be one of the factors affecting the presentation and clinical course of these disorders. They did not find combinations of two truncating mutations in the same family and, to date, all patients reported in the literature harbored either one missense mutation (or in-frame deletion/insertion) and one null mutation or two missense mutations (Table 1). This suggested that homozygous or compound heterozygous null mutations in the *WDR19* gene results in embryonic lethality. However, it is difficult to infer a causal relationship between genotypes and phenotypes as there is variability among individuals with the same mutations, even within the same family. Lee et al. reported six Korean patients that harbored a c.3533G > A mutation and presented with Caroli disease or hepatic cysts [6]. Interestingly, these symptoms were observed in our patient and may indicate a possible genotype-phenotype associated with hepatic involvement. The phenotypic variability in patients with *WDR19* mutations ranges from isolated nephronophthisis or non-syndromic retinitis pigmentosa to the embryonic lethal short-rib polydactyly. Nephronophthisis-like nephropathy is the most common manifestation in these patients. Most manifestations lead to inheritable end-stage renal disease during childhood or young adulthood and require renal transplantation therapy. However, cases with adult-onset non-nephrotic proteinuria have also been reported [12].

Our patient presented with early onset nephronophthisis-like nephropathy, metabolic acidosis and electrolyte disturbance. He also had liver cysts, renal cysts, pancreatic cysts, hepatic function damage and focal dilatation of the intrahepatic bile ducts. These symptoms have been observed in other patients but it is rare for an individual to present with all of the above features. Ocular abnormalities, such as retinitis pigmentosa and Stargardt disease, are the second most frequent features of the *WDR19*-associated ciliopathies. This is due to the *WDR19* mutations being associated with tapetoretinal degeneration in humans. However, our patient had congenital bilateral blindness with no retinal abnormalities. Central nervous system malformations and neurological deficits represents the severe extrarenal manifestation of the nephronophthisis-related ciliopathies clinical spectrum [13,14]. This may result in various neurological features including congenital bilateral blindness. In addition, our patient was diagnosed with refractory epilepsy, which has not been described in other patients with *WDR19* mutations. He was treated with valproic acid (sodium valproate oral solution, Debakin, 20 mg/kg/day, twice a day) for three years. The attempt to stop antiepileptic drug therapy was abandoned by serious seizures. Despite adherence to antiepileptic therapy, the child continued to experience seizures from time to time. Due to irregularly epileptic seizures, the relationship between abnormal physiological condition and epilepsy remains unclear. Guemez-Gamboa et al. presented that cilia persist in most mature neurons and glia of the brain [15]. Ciliopathies caused by defects in the structure and function of cilia may lead to abnormal discharge of brain neurons. For our patient, the complex clinical presentation makes it more difficult to identify the cause of refractory epilepsy. And our findings suggested that the *WDR19* gene may be involved in more biological processes and *WDR19* mutations may be associated with a broader phenotypic spectrum than previously reported.

The patient had no ectodermal dysplasia or skeletal deformity but he suffered from severe developmental retardation. A variety of factors were thought to contribute to these clinical manifestations, including neurological deficits caused by genetic mutations, recurrent infections, metabolic abnormalities, and refractory epilepsy, etc. After kidney transplantation, our patient had a short period of rapid growth but this was interrupted by recurrent infections. This suggested that timely kidney transplantation is crucial for these patients, as well as post-transplant care and infection avoidance. Fortunately, after prenatal diagnosis, the family gave birth to a healthy boy.

The c.98+1G > C variant is a novel splice donor variant that may disrupt the canonical splice sites of the *WDR19* gene. Sequencing results of the cDNA from patient revealed the presence of an aberrant mRNA transcript lacking exon 2 (92bp), which led to a frameshift effect and triggered nonsense-mediated mRNA decay. Effective mRNA analysis is an important way to investigate the effect on pre-mRNA splicing. The recurrent missense variant, c.3533G > A, is listed in both the dbSNP database (rs79436363) and gnomAD, with a total AF of 0.00006347, an AF of 0.0003882 in the African population, an AF of 0.00003251 in the European population, an AF of 0.0001068 in the East Asian population but an AF of 0 in the South Asian population in gnomAD. It is noteworthy that the c.3533G > A variation was reported with a total AF of 0.00020 but was not detected in Han Chinese in Beijing and southern Han Chinese by the 1000 Genome project. The missense variant has a local AF of 0.0007 and is one of the most frequent *WDR19* mutations in the local population, which is helpful to identify the true frequency in the Asian population and different ethnic groups. To date, at least eight patients were homozygous for the missense transition, c.3533G > A, whereas 15 patients were compound heterozygotes for c.3533G > A and other variants that had previously been reported in patients with *WDR19*-related disorders (Table 1). And it meets the PM3_very strong criteria, according to the ACMG/AMP guidelines. Moreover, the transition had also been observed to segregate with disease in related individuals, who showed a similar phenotype of kidney and liver involvement (Table 1), and PP1 and PP4 evidences were also satisfied. For these reasons, the missense can be interpreted as pathogenic with evidence justifying PM2_supporting + PM3_very strong + PP1 + PP4 status. Lee et al. reported, by immunohistochemical study for WDR19 of the kidney biopsies, that diffuse intracytoplasmic localization with segmental areas of thick layers of staining at the apical membranes was noted in patients with the Arg1178Gln mutation, while the WDR19 protein was expressed in an orderly manner along the surface of luminal borders of the renal tubular epithelium in controls. Additional functional studies are required to elucidate the molecular mechanism regarding the deleterious effects of p.Arg1178Gln variant on WDR19 structure and/or function.

The *TG* gene encodes a protein with 2768 amino acids, which is exclusively synthesized in the thyroid gland and plays an essential role in the biosynthesis and storage of thyroid hormone. Homozygous or compound heterozygous mutations in the *TG* gene lead to permanent congenital hypothyroidism. Most patients with thyroid dyshormonogenesis presented with large goiters of elastic and soft consistency. The degree of thyroid dysfunction varies widely among patients with defective TG synthesis, however, these patients

usually have high levels of thyroid stimulating hormone with simultaneous low levels of free thyroid hormone [16]. And severe congenital hypothyroidism can result in growth retardation and permanent intellectual disability if not effectively treated in the early infancy. Although the missense variant, c.4889A > G, was classified as a VUS, in accordance with the ACMG/AMP guidelines, the compound heterozygous variants in the *TG* gene may be the pathogenic cause of the patient's elevated thyroid stimulating hormone level. The coexistence of two or more distinct genetic conditions in the same individual can lead to a more complex phenotype. The complexity makes such rare diseases more difficult to diagnose and treat for clinicians.

In our cohort, the total AF of *WDR19* mutations was approximately 0.0025. We speculated that many patients with *WDR19*-related disorders remain undiagnosed in Guangxi, as the predicted incidence of this disorder would be 6.25 per 1,000,000 people in southern China. However, the value may be an underestimate because some VUS may eventually be reclassified as pathogenic/likely pathogenic variants and a number of novel missense variants in the cohort were predicted to be deleterious, using in silico analyses. The two missense *WDR19* variants, c.1993G > C and c.3895G > C, were the most likely cause of the clinical symptoms of the fetus, although they can only be classified as VUS. This emphasizes the importance of regular data review and pedigree verification. So far, only one patient has been diagnosed with *WDR19*-related disorders in southern China, however, we recommend that the *WDR19* gene should be included in the local screening panel. The local AF of *WDR19* mutations was significantly higher than that in the gnomAD database (0.000279, Table S4). But the difference required careful interpretation, because this was a single-center study with a limited sample size and additional data from multi-center studies will be required to further investigate our findings.

In conclusion, we used whole exome sequencing and bioinformatics analysis to investigate a male patient with common features of *WDR19*-associated NPHP13 and Caroli disease but also had bilateral central blindness, refractory epilepsy and elevated thyroid stimulating hormone, and identified compound heterozygous mutations in *WDR19* and *TG* in this patient. We also identified four novel likely pathogenic variants and estimated the local AF of the *WDR19* mutations. Of note, we reviewed a comprehensive mutation analysis in the *WDR19*-related ciliopathies, discussed the relationship between genotype and phenotype, and compared AFs of *WDR19* variants in different ethnic groups. Our study expanded the genetic and clinical spectrum of *WDR19*-related ciliopathies and should increase awareness of this rare condition.

Data availability

Data will be made available on request.

CRediT authorship contribution statement

Xianglian Tang: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Sheng Yi:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Zailong Qin:** Writing – review & editing, Supervision, Methodology, Data curation. **Shang Yi:** Visualization, Software, Methodology, Formal analysis. **Junjie Chen:** Validation, Resources, Investigation, Data curation. **Qi Yang:** Resources, Investigation, Data curation. **Shanshan Li:** Visualization, Resources, Investigation, Data curation. **Jingsi Luo:** Writing – review & editing, Supervision, Resources, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e23257.

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