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Prenatal Diagnosis and Genetic Etiology of Fetal Polycystic Kidney Disease: A Single-Center Retrospective Study of 147 Cases in Yunnan Province, Southwest China

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Abstract

Background

Fetal polycystic kidney disease (FPDK) is a common ultrasound finding, but its genetic causes vary widely, and data from Yunnan Province are scarce. We aimed to fill this gap by systematically testing a large local cohort.

Methods

We reviewed 147 FPDK cases seen at our center in Yunnan between 2020 and 2024. All had karyotyping and CNV-seq as first-line tests. Families who tested negative on both were offered trio whole-exome sequencing (trio-WES). Outcomes came from medical records or phone calls.

Results

Karyotyping detected 18 chromosomal abnormalities (12.2%) mostly trisomy 21 (n = 10), trisomy 13 (n = 3), trisomy 18 (n = 1), 45,X (n = 1), and 47,XXY (n = 1) plus two structural rearrangements. CNV-seq identified isolated pathogenic CNVs in 14 cases (9.5%), ten of which (71.4%) were 17q12 deletions involving HNF1B. Among 32 families who went on to trio-WES, we identified diagnostic single gene variants in 19 (59.4% of those tested, 12.9% overall). The main culprits were *PKD1* (n = 6), *PKHD1* (n = 4), *BBS2* (n = 2), and one each of *BBS7*, *TMEM67*, *TMEM237*, *NEK8*, *VHL*, *HNF1B*, *HDAC8*, *CELSR1*, *BUB1B*, and *GRIN1*. All told, we found a genetic cause in 51 of 147 cases (34.7%). Of these, 44 families (86.3%) chose to terminate.

Conclusions

In this Yunnan cohort, trisomy 21, 17q12 deletion, and *PKHD1*/*PKD1* mutations were the leading causes. A two-step approach parallel karyotyping and CNV-seq first, then trio-WES for negatives greatly improves detection and gives families essential information for decision-making. These results offer much needed regional data for prenatal counseling in Yunnan and surrounding areas.

BACKGROUND

Fetal polycystic kidney disease (FPDK) shows up fairly often on mid-pregnancy ultrasound. Depending on whose numbers you look at, it affects somewhere between 1 in 1,000 and 1 in 5,000 pregnancies [1]. The ultrasound appearance can be quite varied: one kidney or both may be enlarged, the tissue may look brighter than usual, the usual boundary between cortex and medulla may disappear, or you might see small cysts. These signs could mean anything from a minor developmental quirk to a syndrome that involves multiple organ systems [2].

The genetics of FPDK are surprisingly broad. A decade or two ago, most clinicians thought of just two possibilities: ARPKD (recessive, from *PKHD1* mutations) and ADPKD (dominant, usually *PKD1* or *PKD2*) [3]. But with better genetic tools, we now recognize a much longer list of conditions that can present this way before birth ciliopathies like Bardet-Biedl, Meckel, Joubert, and Fraser syndromes, plus chromosome disorders such as trisomies 21, 13, and 18 [4,5].

In recent years, copy number variants especially the 17q12 deletion that knocks out one copy of *HNF1B* have emerged as a major player in fetal kidney disease, often appearing as bright kidneys on ultrasound [6,7]. But here's the thing: most of what we know comes from Western populations or small Asian series. For Yunnan Province a region in Southwest China with substantial ethnic diversity we simply don't have a clear picture. And as far as we can tell, no one has put a combined testing strategy to the test in a large group of patients from this area.

Why should anyone care? Because the outlook for the baby depends entirely on what's causing the problem. ARPKD is often fatal around birth or leads to kidney failure in early childhood. ADPKD, on the other hand, may not cause issues until adulthood [8]. Syndromic ciliopathies usually bring severe problems outside the kidneys and a grim prognosis. So knowing the genetic cause helps families grapple with tough choices whether to continue the pregnancy, how to plan delivery and newborn care, and what the chances are of it happening again in a future pregnancy.

With all this in mind, we went back and looked at 147 fetuses diagnosed with FPDK over five years at Yunnan Provincial First People's Hospital, a major referral center in Kunming, Yunnan Province, Southwest China. We used a two-layer strategy: everyone got karyotyping and CNV-seq done in parallel as the first pass; those who came up negative on both went on to trio whole-exome sequencing (trio-WES). We

wanted to know: (1) how many cases this approach could solve; (2) what the genetic landscape looks like in Yunnan; and (3) whether genetic testing actually helps with counseling and management decisions.

METHODS

Study population

We included 147 singletons diagnosed with FPDK on mid-trimester ultrasound (18–24 weeks) at Yunnan Provincial First People's Hospital from January 2020 through December 2024. This hospital is the main prenatal referral center for Yunnan Province and surrounding areas in Southwest China, serving a population of over 40 million. We used ISUOG criteria for diagnosis: one or both kidneys enlarged (> 95th percentile for gestational age), increased echogenicity, and/or multiple small cysts [9]. We left out cases where sample quality wasn't good enough for genetic testing. The ethics committee signed off on the study (approval No. KHLL2022-KY017), and all families gave written consent.

Sample collection

Fetal samples came from amniocentesis (18–22 weeks) or cordocentesis (23–28 weeks). Parental blood was drawn whenever possible.

First-tier tests: Karyotyping and CNV-seq (in parallel)

Everyone got G-banded karyotyping and CNV-seq at the same time as the first step. Karyotyping followed standard protocols, with results reported per ISCN 2020. For CNV-seq, we extracted DNA from fetal samples and did low pass whole genome sequencing on an Illumina platform. We focused on CNVs larger than 100 kb and classified them using ACMG guidelines [10].

Second-tier test: Trio whole-exome sequencing

We offered trio-WES to families whose first-tier tests were both clear (normal karyotype and no CNVs of concern). We captured exomes with KAPA HyperExome or equivalent kits and sequenced on an Illumina NovaSeq 6000. We filtered and annotated variants, then classified them for pathogenicity per ACMG/AMP 2015 [11]. Suspected disease causing variants were confirmed by Sanger sequencing and family segregation.

Follow up

We got pregnancy outcomes (termination, live birth, or miscarriage) from medical records or by calling families.

Statistical analysis

We stuck to descriptive statistics for diagnostic yields. No fancy comparisons just counts and percentages.

RESULTS

Overall diagnostic yield

Altogether, we established a definite or likely genetic diagnosis in 51 of 147 cases (34.7%) (Fig. 1). The first-tier tests, performed in parallel, identified abnormalities in 32 cases: karyotyping detected 18 chromosomal abnormalities (12.2%), including aneuploidies and structural rearrangements; and CNV-seq detected isolated pathogenic/likely pathogenic microdeletions/microduplications (CNVs) in 14 cases (9.5%). Trio-WES, performed in 32 families with negative first-tier results, identified 19 diagnostic single-gene variants (59.4% of those tested, 12.9% overall). Figure 2 shows the breakdown of genetic etiologies.

Negative findings

Even after the full workup, 96 of 147 cases (65.3%) remained without a genetic diagnosis. Breaking this down further: karyotyping was negative in 129 cases (87.8%); CNV-seq was negative in 133 cases (90.5%). Among the 32 families who underwent trio-WES, 9 (28.1%) had no pathogenic, likely pathogenic, or clinically meaningful VUS; another 4 (12.5%) had VUS that we did not consider diagnostically significant.

Chromosomal abnormalities

Karyotyping detected 18 chromosomal abnormalities (Table 1), of which 17 were aneuploidies—trisomy 21 (n = 10), trisomy 13 (n = 3), trisomy 18 (n = 1), 45,X (n = 1), and 47,XXY (n = 1) and two were structural rearrangements: 46,XX,del(4)(q21) and 46,XN,add(9)(p24). These

abnormalities were also identifiable by CNV-seq, All aneuploidy cases had additional extrarenal ultrasound findings.

Table 1
Chromosomal abnormalities identified in 147 fetuses with FPDK (n = 19)

Case	GA (weeks)	Sample	Maternal age	Renal US findings	Other US findings	Karyotype
1	20	Amnio	36	Bilateral increased echogenicity	Bilateral increased echogenicity, Ventriculomegaly, increased NF, absent nasal bone, echogenic bowel, polyhydramnios	47,XN,+21
2	18	Amnio	29	Mild bilateral increased echogenicity	IUGR, absent nasal bone	47,XN,+21
3	19	Amnio	38	Bilateral increased echogenicity	VSD, persistent LSVC, echogenic bowel	47,XX,+21
4	20	Amnio	29	Bilateral increased echogenicity	Absent nasal bone, pleural effusion, echogenic bowel, clubfoot	47,XY,+21
5	21	Amnio	22	Bilateral increased echogenicity	Increased NT, absent nasal bone, facial edema, ventriculomegaly, echogenic bowel	47,XX,+21
6	20	Amnio	25	Bilateral increased echogenicity	Increased NF, absent nasal bone, PRUV, echogenic liver, clubfoot	47,XY,+21
7	19	Amnio	26	Bilateral increased echogenicity	Choroid plexus cysts, absent nasal bone, LSVC, echogenic bowel	47,XY,+21
8	20	Amnio	33	Bilateral increased echogenicity	Echogenic bowel	47,XY,+21
9	21	Amnio	32	Mild bilateral increased echogenicity	Ventriculomegaly, hypertelorism, short nasal bone, arrhythmia, echogenic bowel	46,XX,del(4)(q21)
10	18	Amnio	31	Mild bilateral increased echogenicity	Third ventricle enlargement, single umbilical artery	45,X
11	18	Amnio	23	Mild right enlargement, increased echogenicity	Choroid plexus cysts, single umbilical artery	47,XN,+18
12	19	Amnio	32	Bilateral increased echogenicity, enlargement	Smooth cerebral cortex, micrognathia, cardiomegaly, thickened ventricles, polydactyly	47,XN,+13
13	21	Amnio	24	Left PKD, left ureteral dilation	None	46,XN,add(9)(p24)
14	18	Amnio	41	Mild bilateral parenchymal increased echogenicity	Choroid plexus cysts, increased NF (cystic hygroma)	47,XY,+21
15	19	Amnio	32	Bilateral increased echogenicity, pelvic separation	VSD, LSVC, postaxial polydactyly (hands and feet)	47,XY,+13
16	25	Amnio	34	Bilateral enlargement, increased echogenicity	Cerebellar vermis hypoplasia, LV echogenic focus, omphalocele	47,XY,+13
17	23	Amnio	29	Bilateral parenchymal increased echogenicity	Echogenic bowel, small amount of ascites	47,XY,+21
18	21	Amnio	26	Mild bilateral increased echogenicity ,|Echogenic bowel	Echogenic bowel	47,XXY

Abbreviations: GA, gestational age; Amnio, amniocentesis; Cord, cordocentesis; NF, nuchal fold; NT, nuchal translucency; IUGR, intrauterine growth restriction; VSD, ventricular septal defect; LSVC, persistent left superior vena cava; PRUV, persistent right umbilical vein; PKD, polycystic kidney disease; LV, left ventricle.

Isolated CNV abnormalities

CNV-seq picked up isolated pathogenic or likely pathogenic CNVs in 14 cases (9.5%) (Table 2) all with normal karyotypes. The 17q12 deletion was the runaway leader, accounting for 10 of 14 (71.4%). Deletion sizes ran from 1.44 to 1.55 Mb, all covering HNF1B. We also

spotted a 22q11.21 duplication, a 21q22 microdeletion, an Xq26.2 microdeletion (all likely pathogenic), and one 3p26.3 duplication (VUS). Parental testing showed five of these were de novo.

Table 2
PathogenicandlikelypathogenicCNVsidentifiedin147fetuseswithFPDK(n = 14)

Case	Age	GA	RenalUSfindings	Extrarenalfindings	CNVresult	Syndrome	Fetalsex	Pathogenicity	Inheritance
1	27	23	Bilateral parenchymal increased echogenicity	None	17q12 del 1.44Mb	RCAD	46,XY	P	De novo
2	27	24	Bilateral increased echogenicity	SUA	17q12 del 1.44Mb	RCAD	46,XX	P	Pat
3	22	25	Left MCDK	SUA	22q11.21 dup 2.95Mb	22q11 dup syndrome	46,XY	LP	Mat
4	34	26	Bilateral increased echogenicity	Gallbladder enlargement	17q12 del 1.5Mb	RCAD	46,XY	P	De novo
5	26	23	Bilateral increased echogenicity	Polyhydramnios	17q12 del 1.45Mb	RCAD	46,XY	P	Pat
6	22	23	Bilateral parenchymal increased echogenicity	Choroid plexus cysts	17q12 del 1.45Mb	RCAD	46,XX	P	Pat
7	29	24	Bilateral cortical increased echogenicity	None	17q12 del 1.45Mb	RCAD	46,XY	LP	De novo
8	28	24	Right renal dysplasia, mild left increased echogenicity	Aberrant right subclavian artery, SUA	21q22.2q22.3 del 6.65Mb	HPE1	46,XX	LP	De novo
9	27	25	Bilateral increased echogenicity	None	17q12 del 1.45Mb	RCAD	46,XY	P	De novo
10	25	19	Bilateral parenchymal increased echogenicity	Increased NT, hepatomegaly, echogenic bowel	del(X)(q26.2), 0.4Mb	/	46,XY	LP	Mat
11	23	25	Mild bilateral parenchymal increased echogenicity	None	17q12 del 1.45Mb	RCAD	46,XY	Pathogenic	Mat
12	22	23	Bilateral increased echogenicity	None	17q12 del 1.55Mb	RCAD	46,XX	LP	Mat
13	23	27	Bilateral parenchymal increased echogenicity	None	17q12 del 1.45Mb	RCAD	46,XY	P	Pat
14	31	21	Left MCDK	SUA, crossed pulmonary arteries	3p26.3 dup 1.6Mb	/	46,XY	VUS	Pat

Abbreviations: GA, gestational age; SUA, single umbilical artery; MCDK, multicystic dysplastic kidney; RCAD, renal cysts and diabetes syndrome; HPE1, holoprosencephaly 1; NT, nuchal translucency; VUS, variant of uncertain significance;P,pathogenic;LP,likely pathogenic;Pat,Paternal;VUS,variant of uncertain significance;Maternal ,Mat;De novo ,de novo mutation.

Trio-WES findings

We did trio-WES on 32 families whose first-round tests were clean. We found pathogenic or likely pathogenic single gene variants in 19 cases (59.4% of those tested, 12.9% overall), spread across 16 genes (Table 3). The top monogenic players were *PKD1* (n = 6, 31.6% of WES positive cases) and *PKHD1* (n = 4, 21.1%). Ciliopathies made up another 7 cases (36.8%): Bardet-Biedl (*BBS2*, n = 2; *BBS7*, n = 1), Meckel (*TMEM67*, n = 1), Joubert (T*MEM237*, n = 1), and Fraser (*FRAS1*, n = 1). We also ran into rarer things like Von Hippel-Lindau (*VHL*), Cornelia de Lange (*HDAC8*), and lymphatic malformation (*CELSR1*). Thirteen cases (40.6%) had VUS, including four where the clinical picture strongly pointed to pathogenicity despite the formal VUS label (*FRAS1*, *GREB1L*, *DCHS1*, *KMT2D*). Full clinical and molecular details for all 32 WES cases are in Supplementary Table S1.

Table 3
Genes with pathogenic/likely pathogenic variants identified by trio-WES

Gene	Associated disease (OMIM)	Inheritance	No. of cases (n = 32)	Pathogenicity classification
PKD1	ADPKD (173900)	AD	6	P
PKHD1	ARPKD (263200)	AR	4	Pathogenic/LP |
LRP5	PLD4 (617875)	AD	3	VUS
BBS2	Bardet-Biedl syndrome 2 (615981)	AR	2	Pathogenic/VUS
NEK8	PKD8 (620903) / RHPD2 (615415)	AD/AR	2	Pathogenic/LP/VUS
BBS7	Bardet-Biedl syndrome 7 (615984)	AR	1	Pathogenic
PKD2	ADPKD (613095)	AD	1	LP
TMEM67	Meckel syndrome 3 (607361)	AR	1	Pathogenic
TMEM237	Joubert syndrome 14 (614424)	AR	1	Pathogenic
VHL	Von Hippel-Lindau syndrome (193300)	AD	1	Pathogenic
HNF1B	RCAD (137920)	AD	1	Pathogenic
HDAC8	Cornelia de Lange syndrome 5 (300882)	XLD	1	LP
CELSR1	Lymphatic malformation 9 (619319)	AD	1	LP
BUB1B	MVA1 (257300)	AR	1	LP
GRIN1	IDAD8 (614254)	AD	1	LP
GREB1L	RHD3 (617805)	AD	1	VUS
DCHS1	Van Maldergem syndrome 1 (601390)	AR	1	VUS
KMT2D	Kabuki syndrome 1 (147920)	AD	1	VUS
FRAS1	Fraser syndrome 1 (219000)	AR	1	VUS

Abbreviations: LP, likely pathogenic; VUS, variant of uncertain significance; PLD4, polycystic liver disease 4; RHPD2, renal-hepatic-pancreatic dysplasia 2; RCAD, renal cysts and diabetes syndrome; MVA1, mosaic variegated aneuploidy syndrome 1; IDAD8, intellectual developmental disorder autosomal dominant 8; RHD3, renal hypoplasia/dysplasia 3.

Pregnancy outcomes

Of the 51 genetically confirmed pregnancies, 44 families (86.3%) chose to terminate. Nearly everyone with trisomy 21 (10/10), 17q12 deletion (9/10), ARPKD (4/4), or a severe syndromic ciliopathy (7/7) opted to end the pregnancy. In contrast, 4 of 6 families with *PKD1* mutations decided to go ahead mostly because ADPKD is an adult-onset condition and their babies had no other anomalies.

DISCUSSION

Our two-layer strategy karyotyping plus CNV-seq as the first pass, then trio-WES for those who cleared it identified a genetic cause in 34.7% (51/147) of our FPDK cases in Yunnan Province. To our knowledge, this is the largest FPDK cohort reported from this province, providing data that have been lacking. However, 96 cases (65.3%) remained unresolved a clear indication that further work is needed.

Chromosomal abnormalities and the 17q12 deletion

Trisomy 21 was the single most common chromosome problem we saw (10/147, 6.8%). That's consistent with what others have reported bright fetal kidneys often go hand in hand with common aneuploidies [12]. This is a good reminder that karyotyping still has a place as a first-line test in FPDK, especially when there are other ultrasound markers.

The 17q12 deletion deserves a closer look. It accounted for 10 of the 14 CNVs we found (71.4%) and 6.8% of all FPDK cases in our series. This deletion knocks out one copy of *HNF1B* and produces a syndrome with a wide range of features: kidney cysts, renal dysplasia, and MODY5 [6]. The high rate we observed makes a strong case for routine CNV-seq as part of first-tier testing in fetuses with echogenic kidneys, even when nothing else looks off on ultrasound. Interestingly, this frequency seems to line up with what other Asian groups have reported, suggesting that 17q12 deletion is a major cause of FPDK regardless of ethnicity.

Monogenic causes: more than just ADPKD and ARPKD

PKHD1 (ARPKD) and *PKD1* (ADPKD) together accounted for just over half (10/19, 52.6%) of our trio-WES diagnosed cases. But we also ran into a surprising variety of other genes, many of them involved in primary cilia function. Bardet-Biedl genes (*BBS2*, *BBS7*) and Meckel/Joubert genes (*TMEM67*, *TMEM237*) showed up in four cases all with extrarenal anomalies that fit a ciliopathy pattern [13,14]. This is a useful reminder that FPDK can be the first sign of a syndromic ciliopathy, and when these genes come up, you really need to look hard for findings outside the kidneys.

One case stands out: a *FRAS1* compound heterozygote with classic Fraser syndrome features horseshoe kidneys, absent bladder, situs inversus. Both variants were formally classified as VUS, but the phenotype was so unmistakable that we felt comfortable making a clinical diagnosis. The family chose termination. This case illustrates that in prenatal settings with strong ultrasound findings, even VUS can inform decision-making when there's no better explanation [15].

Why so many negatives?

Despite a fairly comprehensive approach, most of our cases (65.3%) stayed unsolved. We think a few things are going on.

First, non-coding variants slip past standard WES. Deep intronic changes, promoter mutations, or regulatory disruptions can affect gene expression without touching coding sequences [16]. There's growing evidence that non-coding variants in *PKHD1* and *PKD1* might account for some unsolved cystic kidney cases [17].

Second, structural variants balanced translocations, inversions, complex rearrangements don't get reliably picked up by CNV-seq or standard WES. Long-read sequencing or optical genome mapping could help down the road [18].

Third, mosaic variants with low allele fractions can be missed, especially when fetal DNA comes from cultured amniocytes. Deep sequencing (> 500×) or targeted ultra-deep sequencing might improve the odds [19].

Fourth, there may be novel disease genes not yet linked to FPDK. The 13 VUS cases in our cohort (40.6% of WES-tested) might well include pathogenic variants in genes that aren't currently on the FPDK radar. Functional studies patient-derived organoids or animal models will be needed to figure this out [20].

Fifth, some cases may just be isolated, non-genetic developmental anomalies transient findings with no underlying genetic defect. Mild echogenicity without cysts, for instance, can sometimes resolve after birth.

Finally, incomplete phenotyping is a real challenge. Fetal ultrasound can't catch everything retinal issues in Bardet-Biedl, cognitive problems in ADPKD, and so on. Postnatal follow-up may eventually reclassify some of our unsolved cases as syndromic.

What this means for practice in Yunnan and beyond

Based on what we found, we suggest a two-layer testing protocol for FPDK:

First layer (parallel): Karyotyping plus CNV-seq for everyone. Karyotyping catches aneuploidies; CNV-seq picks up 17q12 deletions and other CNVs.

Second layer: Trio-WES for families who clear the first round, especially when there are extrarenal anomalies or when recurrence risk matters.

The fact that trio-WES diagnosed 59.4% of the cases we tested backs up its role as a powerful second-tier tool. Getting an early genetic diagnosis improves prognostic counseling: ARPKD generally means a poor perinatal outlook, while ADPKD often allows pregnancy continuation with postnatal follow-up. For ciliopathies like Bardet-Biedl, multidisciplinary postnatal care is a must [14].

Our findings also have implications specifically for genetic counseling in Yunnan. The province is home to 25 officially recognized ethnic minority groups, and that diversity may add genetic heterogeneity that our single center cohort didn't fully capture. Larger, population based studies will be needed to see whether certain FPDK associated variants are more common in specific ethnic subgroups.

Limitations

We should be upfront about a few limitations. First, not all eligible families agreed to WES because of cost (only 32 of those with negative first-tier results went ahead), so we may be underestimating the true diagnostic yield. Second, the VUS rate (40.6%) is high this reflects the limited functional data available for prenatal variants and the lack of fetal specific reference databases. Third, we didn't have complete postnatal follow-up for some of the pregnancies that continued. Fourth, non-coding and structural variants not captured by WES may account for some of our unsolved cases. Fifth, as a single center study, our findings may not apply to other regions or populations in China.

Conclusions

Fetal polycystic kidney disease is genetically diverse. In our Yunnan cohort, trisomy 21, 17q12 deletion, and *PKHD1*/*PKD1* mutations topped the list. A two-layer strategy parallel first-tier karyotyping and CNV-seq, then trio-WES for negatives substantially boosts detection and gives families the information they need for counseling and management. That said, two -thirds of our cases stayed unsolved, underscoring the need for better tools and longer follow up. This study adds region specific data from Yunnan Province to the growing global picture of FPDK genetics.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Yunnan Provincial First People's Hospital (approval No. KHLL2022-KY017). The work followed the 1964 Helsinki declaration and its later updates. All parents or guardians gave written informed consent.

Consent for publication

Not applicable. No individual person's data images, videos, or personal details appear in this manuscript.

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Author Contribution

Dongmei Li: study concept, data collection, analysis, drafting, funding, revision. Jianhong Ye: WES analysis, software, validation, data curation. Lei Wang: CNV-seq analysis, software, validation, formal analysis. Tongpan Pu: karyotyping, resources, data curation. Chaobei Yang:fetal ultrasound. investigation, visualization, follow-up.Jinman Zhang: study concept, project oversight, supervision, revision, funding. All authors read and approved the final version.

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Data Availability

The datasets generated and/or analyzed during the current study are not publicly available due to patient privacy protection and ethical restrictions imposed by the institutional review board (Yunnan Provincial First People's Hospital Ethics Committee, approval No. KHLL2022-KY017). Reasonable requests for access should be directed to the corresponding authors, who will coordinate with the ethics committee to review requests and determine appropriate data sharing arrangements.

References

1. Avni FE, Garel C, Cassart M, et al. Imaging and classification of congenital cystic renal diseases. AJR Am J Roentgenol. 2012;198(5):1004–13.
2. Bergmann C. Genetics of autosomal recessive polycystic kidney disease and its differential diagnoses. Front Pediatr. 2018;5:306.
3. Harris PC, Torres VE. Polycystic kidney disease. N Engl J Med. 2014;371(6):544–55.
4. Forsythe E, Beales PL. Bardet–Biedl syndrome. Eur J Hum Genet. 2013;21(1):8–13.
5. Hartill V, Szymanska K, Sharif SM, et al. Meckel–Gruber syndrome: a review. Clin Genet. 2017;91(6):801–11.
6. Clissold RL, Hamilton AJ, Hattersley AT, et al. HNF1B–associated renal disease: a review of the clinical and molecular spectrum. Nat Rev Nephrol. 2015;11(3):161–72.
7. Chen CP, Chen CY, Chern SR, et al. Prenatal diagnosis and molecular cytogenetic characterization of chromosome 17q12 microdeletion syndrome. Taiwan J Obstet Gynecol. 2020;59(5):745–50.
8. Riedhammer KM, Stock J, Meitinger T, et al. Exome sequencing in fetuses with structural malformations. Ultrasound Obstet Gynecol. 2021;58(4):566–74.
9. ISUOG Clinical Standards Committee. Performance of first-trimester fetal ultrasound scan. Ultrasound Obstet Gynecol. 2013;41(1):102–13.
10. Riggs ER, Andersen EF, Cherry AM, et al. Technical standards for the interpretation and reporting of constitutional copy number variants. Genet Med. 2020;22(2):245–57.
11. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the ACMG and AMP. Genet Med. 2015;17(5):405–24.
12. Benacerraf BR. Sonographic findings in fetuses with trisomy 21. Ultrasound Obstet Gynecol. 2018;51(2):171–8.
13. De Tomasi L, David P, Humbert C, et al. Mutations in GREB1L cause congenital kidney and urinary tract anomalies. Hum Mutat. 2017;38(8):948–55.
14. Mone F, Quinn R, Robson SC, et al. Prenatal diagnosis of cystic kidney disease: a systematic review. Prenat Diagn. 2022;42(3):350–63.
15. Vora NL, Gilmore K, Branham K, et al. Genetic testing in fetuses with structural anomalies. Am J Obstet Gynecol. 2022;226(3):339–45.
16. Venter JC, Adams MD, Myers EW, et al. The sequence of the human genome. Science. 2001;291(5507):1304–51.
17. Bergmann C. ARPKD and early manifestations of ADPKD: the original polycystic kidney disease and phenocopies. Pediatr Nephrol. 2015;30(1):15–30.
18. Logsdon GA, Vollger MR, Eichler EE. Long–read human genome sequencing and its applications. Nat Rev Genet. 2020;21(10):597–614.
19. Wright CF, Prigmore E, Rajan D, et al. Clinically–relevant postzygotic mosaicism in parents and children with developmental disorders. Nat Genet. 2019;51(10):1480–5.
20. Schutgens F, Clevers H. Human organoids: tools for understanding biology and treating diseases. Annu Rev Pathol. 2020;15:211–34.

Figures

Figure 1

Figure 1. Stepwise diagnostic algorithm and genetic yield in 147 fetuses with fetal polycystic kidney disease (FPDK).

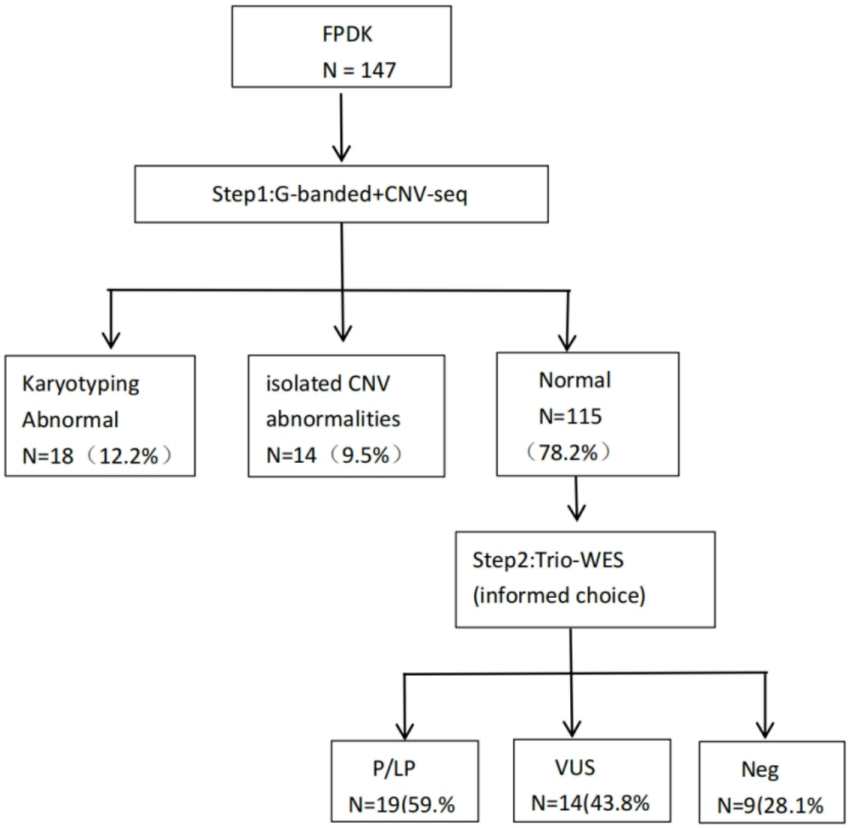


Figure 1. Diagnostic algorithm and genetic yield in 147 fetuses with fetal polycystic kidney disease (FPDK).

First-tier parallel testing with G-banded karyotyping and CNV-seq was performed in all 147 cases, identifying 18 chromosomal abnormalities (12.2%) and 14 isolated CNV abnormalities (9.5%), respectively, with no overlap between the two methods. Second-tier trio whole-exome sequencing (trio-WES) was offered to 32 families with negative results from both first-tier tests (normal karyotype and no isolated CNV abnormalities), identifying 19 pathogenic or likely pathogenic single-gene variants (59.4% of WES-tested, 12.9% of total). Overall diagnostic yield: 34.7% (51/147).

Figure 1

See image above for figure legend.

Figure 2. Distribution of genetic etiologies in 51 confirmed cases of fetal polycystic kidney disease (FPDK).

Pie chart showing the proportion of each genetic etiology among the 51 fetuses who received a definite or likely genetic diagnosis. Trisomy 21 and isolated 17q12 microdeletion were the two most common etiologies, each accounting for 19.6% (n=10) of diagnosed cases. Other chromosomal abnormalities contributed 15.7% (n=8). Among monogenic causes, *PKD1* mutations were the most frequent (11.8%, n=6), followed by *PKHD1* (7.8%, n=4) and other monogenic disorders (17.6%, n=9). Other isolated CNV abnormalities accounted for 7.8% (n=4).

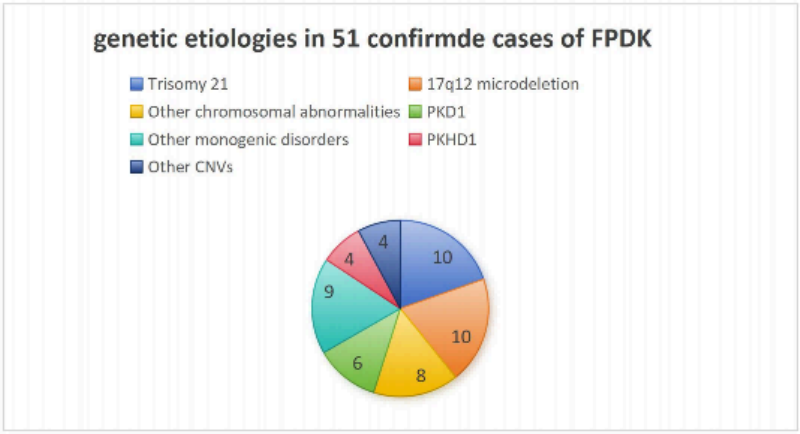


Figure 2

See image above for figure legend.

Supplementary Files

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

- SupplementaryTableS1.xlsx