

Pregnancy Outcomes and Genetic Etiology in Fetuses with Congenital Renal Agenesis: A Follow-up Study

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Abstract

Background

Renal agenesis (RA) is a rare congenital fetal malformation associated with an increased risk of perinatal death, childhood renal dysfunction, and end-stage renal disease. In total, 25,000 pregnant women who received a prenatal diagnosis between January 2016 and February 2026 were enrolled in this retrospective analysis. Prenatal ultrasound identified 87 fetuses with RA. Amniotic fluid and umbilical cord blood samples were collected at different gestational ages for chromosomal karyotyping and chromosomal microarray analysis (CMA). Whole-exome sequencing (WES) was performed in selected cases. Chromosome karyotype analysis was performed on 85 fetal samples.

Result

Except for one case of amniotic fluid cell culture failure in a pregnant woman with advanced gestational age, only two cases of fetal chromosomal aneuploidy were found. Along with 2 cases consistent with karyotype results, 11 additional cases of Copy Number Variations (CNVs) were detected. Among these, 9 cases were pathogenic CNVs and 2 had unknown clinical significance. Further, 9 RA fetuses with negative karyotype and CMA underwent further WES, and two single gene mutations were detected in *BCOR* and *ANOS1*, respectively. In total, 84 fetuses with RA were successfully followed up, of which 20 underwent termination of pregnancy (8 with pathogenic CNVs and 2 with single gene mutations), 3 pregnant women were still pregnant, and 61 were live births. Postnatal follow-up of the 61 live births revealed associated anomalies in 7 infants (including one postnatal death due to cardiac disease), whereas the majority (n = 54) had a favorable outcome.

Conclusion

RA is correlated with copy number variations and single gene mutations, and the detection rate of genetic abnormalities is significantly increased when combined with ultrasound soft markers and other structural malformations. Follow-up showed that the pregnancy outcome of RA fetuses mainly depended on the presence of pathogenic genetic abnormalities and severe structural abnormalities. Fetuses with bilateral renal agenesis underwent termination of pregnancy, whereas most fetuses with unilateral renal agenesis were born alive and grew well. These findings may provide evidence for prenatal genetic counseling, precise diagnosis, and perinatal management of affected fetuses

Background

Renal agenesis (RA) is a common and severe form of Congenital Anomalies of the Kidney and Urinary Tract (CAKUT), with absence of one or both kidneys being the main pathological feature. Based on the number of missing kidneys, RA can be classified as unilateral RA (URA) and bilateral RA (BRA)^[1]. The pathogenesis of RA is attributed to the failure of ureteral bud formation on one or both sides, or obstruction of the mechanism by which ureteral buds reach and induce the posterior renal mesenchyme, resulting in the inability of ureteral buds to normally induce the differentiation of posterior renal primordia into the posterior kidney, and ultimately, inability to form a normal renal structure^[2]. Fetuses with BRA and URA show significant differences in clinical manifestation. BRA is a serious birth defect with an extremely high mortality rate. Most fetuses die in utero or during the neonatal period because of underdeveloped lungs or pulmonary hypertension. Therefore, family members often choose to terminate the pregnancy^[3]. Most fetuses with URA show compensatory hypertrophy of the healthy kidney^[4], and most have no obvious clinical symptoms and may remain undetected throughout their lives. However, vigilance regarding the risks of elevated diastolic blood pressure, latent hypertension, and urinary tract infections remains necessary^[5, 6].

The etiology of RA currently remains unclear. Although several studies have explored its pathogenic factors^[7, 8], they have been limited by the low incidence and mostly new sporadic cases RA in the population; existing studies have mostly been carried out on the disease spectrum of CAKUT, and systematic studies with large sample sizes for simple RA remain difficult. Precise etiological diagnosis and prognosis assessment for fetuses with RA detected through prenatal ultrasound is of great significance for reducing the incidence of birth defects and promoting healthy reproduction. Simultaneously, for fetuses with URA, perinatal management and early postnatal intervention can reduce the occurrence of long-term complications and improve the outcome of children. With rapidly developing molecular genetics technologies, chromosomal microarray analysis (CMA) has been widely used in prenatal diagnosis. Compared with conventional karyotyping, CMA, especially single nucleotide polymorphism (SNP) arrays, can detect microdeletions and microduplications at the genome-wide level, which cannot be achieved by conventional karyotyping. This has significantly improved the genetic detection rate of fetal structural malformations including RA^[9]. In recent years, application of whole-exome sequencing (WES) technology for prenatal diagnosis has increased, providing a powerful tool for exploring the monogenic etiology of RA. The discovery of *PAX2*, *EYA1*, *SIX1*, *HNF1B*, and other genes related to renal agenesis^[10] is expected to further improve the etiological diagnosis rate of RA based on karyotype and CMA analysis.

This study aimed to systematically analyze the genetic etiology of fetuses with RA and explore the association between genetic diagnosis results and fetal pregnancy outcomes as well as neonatal prognosis. Overall, these findings will provide local data and a theoretical basis for prenatal

genetic counseling, precise diagnostic pathway selection, and perinatal management of fetuses with RA and help reduce the incidence of birth defects as well as improve the long-term prognosis of children.

Subjects and Methods

Participants

From January 2016 to February 2026, a total of 25000 pregnant women were admitted to the Medical Genetic Diagnosis and Treatment Center of Fujian Provincial Maternity and Children's Hospital. Among them, 87 cases with fetal congenital absence of the kidney detected by ultrasound screening in the second and third trimester and providing informed consent for invasive prenatal diagnosis were finally included in the study. The gestational age of the pregnant women ranged from 17 to 33 weeks, and their age ranged from 16 to 40 years. The fetuses were divided into three groups based on ultrasound manifestations: Group A with isolated RA (n = 41), Group B with RA combined with abnormal ultrasound soft markers (n = 24), and Group C with RA combined with other structural abnormalities (n = 22). Considering the decline in amniotic fluid cell viability of the fetus, two pregnant women with advanced gestational age did not undergo karyotype analysis. The remaining 85 pregnant women underwent karyotype analysis and 87 pregnant women underwent CMA. Among the cases with negative CMA results, only nine parents agreed to undergo WES after being informed of its necessity (Fig. 1). This study was approved by the Ethics Committee of the Fujian Maternity and Child Health Hospital (approval number: 2021KRD09001).

Prenatal ultrasound

Examinations were performed by physicians with specialized training and qualifications in prenatal ultrasound diagnosis using high-resolution color Doppler ultrasound diagnostic instruments, such as GE Voluson E8, GE Voluson E10, SAMSUNG WS80A, PHILIPS EPIQ/ELITE W, and PHILIPS EPIQ7, with the frequencies of the protrusion array probes ranging from 1–6 MHz and 3–9 MHz. The frequency of the high-frequency linear array probe ranged from 4–18 MHz. Various physiological parameters of the fetus were measured, including biparietal diameter, head circumference, abdominal circumference, femur length, and humerus length. The structure of each system of the fetus was detected, and the blood flow spectrum of the placenta, umbilical cord, amniotic fluid and umbilical artery was observed. The kidneys of a normal fetus are located on both sides of the spine and below the level of the stomach. Bilateral renal agenesis was diagnosed if repeated multi-section and multi-angle exploration in and around the renal fossa on both sides of the fetal spine failed to show an echo of the fetal kidney and normal renal structure, the adrenal glands relatively enlarged in the bilateral renal bed area, a "lying flat" sign was observed, the color Doppler flow imaging could not detect the blood flow signal of the renal artery on both sides, and the fetus showed phenomena such as anuria and oligohydramnios. Unilateral renal agenesis was diagnosed if there was no normal renal echo, no renal artery blood flow signal in the renal bed area of the affected side, and the ipsilateral adrenal "lying flat" sign was present, whereas the contralateral kidney showed a normal structure and compensatory enlargement. The renal artery blood flow signal could be detected, the fetal bladder was full, and the amniotic fluid volume was normal in such cases^[11, 12].

Chromosome karyotype analysis

For cell culture and karyotype analysis, 40ml of amniotic fluid (17–24 weeks of gestation) or 3 ml of umbilical cord blood (25–33 weeks of gestation) were obtained by amniocentesis. The extracted amniotic fluid was placed into a sterile centrifuge tube and centrifuged at 2000 rpm for 10 min; the supernatant was discarded, the pellet was added to the medium, mixed, and inoculated in a culture bottle, and cultured at 37°C with 5% CO₂ for 7 ~ 8 days in adherent cell culture. When the amniotic fluid cells produced more cell clones, the culture medium was changed, and the culture was continued for 1 to 2 days. When the adherent cells grew vigorously, they were harvested. For the umbilical cord blood sample, the extracted blood was placed into a sterile centrifuge tube, centrifuged at 2000 rpm for 10 min, the supernatant was discarded, the pellet was resuspended in a complete medium containing phytohemagglutinin (PHA), inoculated in a culture bottle, placed at 37°C with 5% CO₂ and cultured in suspension for 3 days. Colchicine was added to block the cells in metaphase. G-banding was performed after trypsin digestion, hypotonic processing, fixation, and preparation of chromosomal specimens. Twenty cells were counted, and five karyotypes were analyzed using a GSL-120 automatic chromosome scanner. In cases of suspected mosaicism, an increased number of metaphase cells were counted and analyzed. Chromosome nomenclature was based on the International System for Human Cytogenetics Nomenclature 2024 (ISCN 2024^[13]).

Chromosomal microarray analysis

Genomic DNA was extracted from amniotic fluid cells, peripheral blood, and umbilical cord blood samples according to the instructions of the BioChain Kit and QIAamp DNA Blood Mini Kit, and its concentration and purity were measured using a micro UV spectrophotometer. Affymetrix Genome CytoScan 750 K gene chip (United States) was used to carry out DNA digestion, amplification, purification, fragmentation, signal labeling, hybridization, washing, staining and scanning procedures in accordance with the manufacturer's instructions. The duplication or deletion detected was compared with genomic data (<http://www.genome.ucsc.edu>) (GRCh37/hg19) to systematically evaluate and judge its clinical significance. According to the 2013 American College of Obstetricians and Gynecologists guidelines^[14, 15], CNVs were classified into five types: pathogenic,

possibly pathogenic, copy number variation of unclear clinical significance (VOUS), possibly benign, and benign. For copy number variations classified as pathogenic or variants of uncertain clinical significance in the initial analysis, further CMA tests were conducted on the peripheral blood samples of the parents. The final pathogenicity of these CNVs was comprehensively determined via pedigree analysis, and selected validation was conducted for CMA-positive results. Cell suspensions obtained from cultured amniotic fluid and cord blood cells were used for slide preparation, followed by fluorescence in situ hybridization.

Whole-exome sequencing

Using fetal genomic DNA as the detection material, DNA quality control was performed using the Qubit fluorescence method, NanoDrop and agarose gel electrophoresis were used to verify the concentration, purity, and integrity of the samples. The qualified genomic DNA was ultrasonically fragmented into 150–300bp fragments and a DNA library was constructed. The DNA in the exon region of the target gene was hybridized, captured, and enriched using the NimbleGen 2.1M Ti probe system. After washing, PCR amplification, and quality assessment, qualified exon enrichment libraries were obtained. The purified libraries were loaded onto the Illumina NextSeq CN500 platform for paired-end 100 bp sequencing, and raw sequencing data in the FASTQ format were generated. Sequencing data were analyzed and compared with the human reference genome using bioinformatics. Candidate variants associated with clinical phenotypes were screened using multiple databases, including OMIM, dbSNP, and ClinVar, as well as *in silico* protein functional prediction tools. Common polymorphisms and non-pathogenic variants were filtered based on the population allele frequency data, and variants were classified according to the ACMG genetic variation classification criteria and guidelines. The detected pathogenic and possibly pathogenic mutations were verified by Sanger sequencing, and pedigree segregation verification was performed on positive fetuses and parental samples.

Follow-up

Enrolled subjects were systematically followed up by combining a review of electronic medical records and standardized telephone interviews. The pregnancy outcome follow-up mainly included data on pregnancy outcomes, gestational age at delivery, birth weight, Apgar score, congenital birth defects, and adverse pregnancy outcomes (including spontaneous abortion, stillbirth, fetal growth restriction, birth defects, postpartum hemorrhage, hysterectomy, and maternal death). Neonatal and infant follow-ups included congenital anomalies, except for RA, NICU admission status, hospitalization days, major complications, infections, respiratory distress, feeding difficulties, and corresponding treatment. During infancy and early childhood, growth and development (height and weight), neuropsychological development (gross motor skills, fine motor skills, adaptability, language, and personal-social behavior), urology-related diseases (urinary tract infections, hypertension, and abnormal renal function), surgical history, hospitalization history, and social adaptability (feeding, sleep, emotional behavior, and parent-child interaction) were assessed.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 31.0, and graphs were generated using GraphPad Prism 10 software. For comparing categorical variables between groups, such as the detection rate of genetic abnormalities, the χ^2 test (chi-square test) was used. A continuity-corrected chi-square test was adopted when the theoretical frequencies ranged from 1 to 5, and Fisher's exact test was applied for cases with theoretical frequencies less than 1. All statistical tests were two-sided with a significance level of $\alpha = 0.05$. $P < 0.05$ was considered statistically significant, and $P < 0.01$ was considered to indicate a highly significant difference.

Results

Prenatal ultrasonic findings of fetuses

In total, 87 fetal samples were enrolled in this study. Of these, 41 cases (47.13%, 41/87) presented isolated RA, 24 had RA with abnormal ultrasound soft markers (27.59%, 24/87), and 22 had RA accompanied by other structural abnormalities (25.29%, 22/87). Among fetuses with RA combined with abnormal ultrasonic soft markers, mild cardiac valvular regurgitation was the most prevalent, occurring in 12 cases, followed by echogenic bowel in 6 cases (Fig. 2). Among RA cases complicated by additional structural anomalies, ventricular septal defect was the most common abnormality, occurring in nine fetuses, followed by abnormal masses or structural anomalies in seven cases (Fig. 3). Meanwhile, 84 fetuses presented with URA and 3 presented with BRA in this cohort. All fetuses with BRA were complicated with oligohydramnios or anhydramnios.

Genetic testing results

Chromosome karyotype analysis was performed on 85 fetal samples. Except for one case of amniotic fluid cell culture failure in a pregnant woman with advanced gestational age, two pathogenic abnormalities were detected in the remaining 84 cases, both corresponding to chromosomal aneuploidies: 47,XXX (triple X syndrome) and 47,XXY (Klinefelter syndrome). The detection rate of karyotype analysis in fetuses with RA was 2.38% (2/84). All 87 fetal samples were analyzed using an SNP array. Clinically significant CNVs were detected in 13 fetuses, with a

detection rate of 14.94% (13/87), comprising 11 cases (12.64%, 11/87) of pathogenic CNVs and 2 cases of VOUS (2.30%, 2/87). Pedigree analysis was further performed in three fetuses with pathogenic CNVs, revealing two de novo aberrations and one maternal deletion. Among 11 pathogenic CNVs, there were 2 aneuploidies (consistent with the karyotype) and 9 microdeletions/microduplications (Table 1). Among the 74 RA cases with negative CMA results, only nine parents agreed to undergo WES after providing informed consent. Pathogenic monogenic variants were identified in two cases: one variant of unknown origin in *BCOR* and one maternally inherited variant in *ANOS1*. The remaining seven samples showed no pathogenic mutations related to the clinical manifestations, with a detection rate of 22.22% (2/9) (Table 2).

Table 1
Additional 11 CNVs identified using SNP array

Case	Prenatal ultrasound findings	SNP array result	Size	CNV type	Pedigree validation	Clinical classification	Outcome
1	Ectopic right kidney in pelvic cavity with polycystic changes, unilateral renal agenesis	arr[hg19]4q31.3q32.2(155,463,038–162,158,990)×1 dn	6.7 Mb	Deletion	De novo	Pathogenic	TP
2	Tetralogy of Fallot, anhydramnios, fetal bladder not shown, bilateral renal agenesis	arr[hg19]22q11.21(18,648,855 – 21,800,471)×1	3.15Mb	Deletion	—	Pathogenic	TP
3	Left renal agenesis, left cardiac axis deviation, mild tricuspid regurgitation, and focal fetal echogenic bowel	arr[hg19]16p11.2(29,580,020–30,190,029)×1	0.61 Mb	Deletion	—	Pathogenic	Cesarean delivery, liveborn male infant
4	Fused kidney, right renal agenesis, left duplex kidney, polyhydramnios	arr[hg19]16p11.2(28,786,704 – 29,032,280)×3	0.245 Mb	Duplication	—	Pathogenic	TP
5	Left renal agenesis or renal hypoplasia, aberrant right subclavian artery	arr[hg19]16p11.2(29,567,297 – 30,350,748)×1	0.78 Mb	Deletion	—	Pathogenic	TP
6	Cystic lesion in the right pelvic cavity, right renal agenesis	arr[hg19]14q21.1q21.2(43,452,954 – 45,173,883)×3	1.72 Mb	Duplication	—	VOUS	Cesarean delivery, liveborn male infant
7	Bilateral renal agenesis, oligohydramnios, right clubfoot	arr[hg19]16p11.2(29,591,326 – 30,176,508)×1	0.585 Mb	Deletion	—	Pathogenic	TP
8	Left renal agenesis or renal hypoplasia	arr[hg19]17p12(14,083,054 – 15,482,833)×1 mat	1.4 Mb	Deletion	Maternal	Pathogenic	Lost to follow-up
9	Right renal agenesis	arr[hg19]3q28(188,788,120–191,331,505)×1,15q11.2(23,620,191 – 24,978,547)×3	2.54 Mb 1.36 Mb	Deletion with Duplication	—	VOUS	Lost to follow-up
10	Ventricular septal defect, left renal agenesis or hypoplasia	arr[hg19]7q11.23(72,701,098 – 74,069,645)×3 dn	1.37 Mb	Duplication	De novo	Pathogenic	TP
11	Fetal growth restriction, ventricular septal defect, aortic stenosis, left renal hypoplasia or agenesis, echogenic bowel	arr[hg19]16q23.2q24.3(79,800,878 – 90,146,366)hmz,16p13.3p12.3(94,807 – 19,302,326) hmz	10.35 Mb 19.20Mb	Homozygous deletion	—	Pathogenic	TP
TP, termination of pregnancy							

Table 2
Two additional single gene mutations detected using WES

Case	Prenatal ultrasound findings	Gene(OMIM)	Variant	Associated disease (OMIM No.)	Variant origin	ACMG variant classification	Pregnancy outcome
1	Suspected ventricular septal defect (width $\approx$ 0.15 cm), left ventricular echogenic focus, tachycardia, left kidney not visualized	BCOR	c.251dupT p.N87Kfs*6	Microphthalmia, syndromic 2(300166)	Unknown	Likely pathogenic	TP
2	Left renal agenesis	ANOS1	c.1187C > A p.S396*	Hypogonadotropic hypogonadism 1 with or Without anosmia (Kallmann syndrome 1), (308700)	Maternal	Pathogenic	TP
TP, termination of pregnancy							

Detection rates of genetic abnormalities were compared across different detection methods, ultrasound phenotypes, and unilateral/bilateral RA. In this cohort, the detection rate was the highest for WES at 22.22% (2/9), followed by that for CMA at 14.94% (13/87) and that of conventional karyotyping was the lowest at 2.38% (2/84). The differences between the three methods were statistically significant ($P < 0.005$). Among the three groups of ultrasound phenotypes, fetuses with RA combined with other structural abnormalities had the highest rate of chromosomal abnormalities (22.73%), followed by those showing RA with ultrasound soft marker abnormalities (20.83%), while the lowest rate was 7.32% in isolated RA. No significant differences were observed among the three groups. Similarly, no statistically significant difference in the detection rate of genetic abnormalities was found between fetuses with URA and those with BRA.

Pregnancy outcome

In the follow-up of 87 pregnant women, 3 cases (3.45%, 3/87) were lost to follow-up or declined cooperation, whereas successful follow-up was accomplished in the remaining 84 cases (94.55%, 84/87) (Table 3). RA combined with additional structural abnormalities significantly increased the incidence of adverse pregnancy outcomes. Most fetuses with RA could be born successfully in terms of the live birth rate. Only one patient (1.15%) experienced neonatal death after delivery, and no spontaneous abortion was observed, indicating an overall favorable prognosis.

Table 3
Pregnancy Outcomes of RA Fetuses

Item	Indication distribution of TP			
	Pathogenic CNVs carriers	Single-gene mutation carriers	BRA fetuses	Other ultrasound abnormalities
Cases	8	2	3	10
Total	20			
Proportion	22.99%			
Item	Incidence of adverse pregnancy outcomes and statistical results			
Group	A	B	C	
Cases	6	4	11	
Proportion	14.63%	16.67%	50.00%	
Statistical parameters	Overall $\chi^2=10.790$, $P = 0.005$; A vs B: adjusted $\chi^2=0.000$, $P = 1.000$; A vs C: $\chi^2=9.089$, $P = 0.003$; B vs C: $\chi^2=5.804$, $P = 0.016$			
Item	Pregnancy prognosis outcomes			
	Continuing pregnancy	Live birth	Neonatal death	Spontaneous abortion
Cases	3	61	1	0
Proportion	Live birth rate = 70.11%			
BRA, bilateral renal agenesis; TP, termination of pregnancy				

Postnatal follow-up

Among 61 live births, 7 newborns had abnormalities other than RA after birth (Table 4). The remaining 54 infants (88.52%, 54/61) had favorable postnatal prognoses. Among the 13 fetuses with chromosomal abnormalities, 3 chose to continue with the pregnancy and live birth. Their parents reported no abnormal clinical complaints to date, and physical assessment results, including height, body weight, and intellectual development, were normal.

Table 4
Detailed conditions other than neonatal renal agenesis

Other Abnormalities and Clinical Outcomes	Cases
Horseshoe kidney / Ectopic kidney	2
Cardiac anomalies; post-surgery with favorable prognosis	2
Anal atresia; post-surgery with favorable prognosis	1
Urinary tract infection diagnosed as vesicoureteral reflux	1
Neonatal death due to congenital heart disease	1

Discussion

RA is likely closely related to ultrasonic cardiac abnormalities. In this cohort, mild cardiac valvular regurgitation was the most common ultrasound soft marker associated with RA, whereas ventricular septal defect was the most prevalent structural abnormality. Previous literature has reported that cardiovascular malformations occur in 11.2–34% of patients with CAKUT^[16]. San Agustin et al.^[17] demonstrated that the regulation of cardiovascular developmental signaling pathways is associated with kidney morphogenesis. Therefore, a thorough examination of cardiovascular-related soft markers or structural abnormalities is recommended when congenital renal agenesis is detected on fetal ultrasonography.

In this study, 2 cases of chromosome aneuploidy and 11 cases of chromosome microdeletion/microduplication were detected by chromosome karyotype analysis and SNP array, with a detection rate of 14.94% (13/87), which was comparable to the pathogenic CNV detection rate reported by Su et al.^[18] and Cai et al. (12.64%, 10.5%). However, other studies have shown a weak association between RA and chromosomal abnormalities, indicating that chromosomal abnormalities and CNVs are not predominant pathogenic contributors to RA. Discrepancies in detection rates across published studies^[19] may stem from the phenotypic heterogeneity of enrolled cohorts and differences in diagnostic methodologies.

The hotspot regions of some CNVs can also be used as important biomarkers for the prenatal diagnosis of RA. Four cases of microdeletions and microduplications associated with 16p11.2 were found using the SNP array in our study, and this genomic interval is the most common recurrent deletion zone. Among these, the deletion spanning the BP4-BP5 breakpoint contains the *TBX6* gene, which is critically related to renal development, and its haploinsufficiency directly leads to defective nephrogenesis.^[20] Further, the adaptor protein encoded by the *SH2B1* gene, located in the minimal overlapping deletion region of 16p11.2, can bind to and enhance the activity of multiple receptor tyrosine kinases such as RET. Deletion of this region leads to *SH2B1* haploinsufficiency and attenuates RET tyrosine kinase activity, which may impair normal transmission of the RET-GDNF signaling pathway, disturb the normal developmental program of the kidney, and eventually lead to the CAKUT phenotype including RA^[21]. The 22q11.2 microdeletion syndrome presents a wide spectrum of clinical phenotypes with significant interindividual variability. The incidence of congenital heart disease is as high as 60–80% in affected patients, among which tetralogy of Fallot is the most common^[22]. Members of the same family carrying the same 22q11.21 microdeletion have been reported to present different phenotypes: the fetus showed typical cardiac malformation, while the mother carried a deletion fragment excluding the *TBX1* gene and manifested right renal agenesis, suggesting that the 22q11.21 microdeletion without *TBX1* may be more likely to cause renal agenesis rather than cardiac malformation^[23]. In this study, one fetus showed 22q11.21 microdeletion with bilateral renal agenesis and oligohydramnios detected by prenatal ultrasound, accompanied by features of Fallot heart disease, which was highly consistent with previous case reports, suggesting that the renal agenesis phenotype cannot be ignored in 22q11.21 microdeletion syndrome.

With the widespread application of whole-exome sequencing in large cohorts of patients with RA, more than ten RA-associated core genes have been identified. We identified two cases of single-gene mutations in *BCOR* and *ANOS1* via WES. Variants in the *BCOR* gene are closely associated with X-linked dominant syndromic microphthalmia type 2 and oculofaciocardiodental syndrome (OFCD)^[24]. A case report^[25] described a male patient diagnosed with bilateral anophthalmia, narrow palpebral fissures, and moderate chronic renal insufficiency secondary to bilateral renal dysplasia at birth. WES confirmed that the patient carried the maternally inherited *BCOR* c.254C > T variant. The authors also stated that 40% of male individuals carrying the *BCOR* hemizygous variant have abnormalities in their genitourinary systems. This case is highly similar to Case 1 in our study, which expands the phenotypic spectrum of *BCOR* mutations. Loss-of-function mutations in *ANOS1* are associated with X-linked Kallmann syndrome (KS). The incidence of renal agenesis in patients with KS is 35–40%. A systematic evaluation of renal imaging in 17 patients from 6 families with X-linked Kalman syndrome showed that 6 males had unilateral renal agenesis. Two other patients died during the neonatal

period because of bilateral renal agenesis^[26]. The *ANOS1* mutation in the offspring of this study mainly presented the heterozygous mutation of c.1187C>A in exon 8 of *ANOS1* from the mother. The male offspring carried hemizygous mutations, whereas the females were carriers.

In this study, 87 fetuses with RA were grouped according to their prenatal ultrasound phenotypes. The detection rate of CNVs showed an increasing trend in the isolated RA, RA with abnormal ultrasound soft markers, and RA with other structural abnormalities groups. Further, among 13 cases of pathogenic CNVs, 10 were combined with abnormal ultrasound soft markers or with other system abnormalities, consistent with the findings of Yang et al.^[7] and Qin et al.^[19]: the detection rate of RA genetic abnormalities increased the risk of other abnormalities and specific ultrasound phenotypes. Although the differences in abnormal detection rates among the three groups did not reach statistical significance, the incidence of adverse pregnancy outcomes in the group with other structural abnormalities was significantly higher than that in the other two groups ($P < 0.01$, $P < 0.05$). Moreover, among 13 fetuses with chromosomal abnormalities, 8 were terminated (1 case of 47, XXY and 7 cases of pathogenic CNVs), 2 fetuses with a single-gene mutation were induced to labor, and 3 fetuses with bilateral renal agenesis were induced to labor, suggesting that the presence of pathogenic genetic abnormalities or severe structural abnormalities is an important factor for family members in deciding to terminate the pregnancy. Interestingly, the pregnancy outcomes of four cases with 16p11.2-related mutations (three microdeletions and one microduplication) were variable: two cases with microdeletions and one case with microduplication resulted in induced abortion, while one fetus with microdeletion was live-born with a favorable prognosis, indicating that the 16p11.2 region has a high degree of clinical heterogeneity in the prenatal phenotype and prognosis. The analysis revealed that the deletion fragment in the live birth was smaller (0.61Mb), whereas the larger deletion may contain more dosage sensitive genes, or increase the risk of combining other developmental abnormalities, resulting in worse perinatal outcomes^[27]. In terms of the prognosis of live births, most children with isolated URA are compensated by the hypertrophy of the contralateral kidney, showing a high survival rate after birth and good prognosis, but lifelong monitoring of blood pressure and renal function is required^[6, 28]. In contrast, the prognosis of children with severe structural abnormalities or BRA is extremely poor^[29].

Based on karyotyping, we adopted an SNP array and additionally identified 11 CNVs (9 pathogenic and 2 VOUS), increasing the positive detection rate to 12.94% (11/85), and the difference was extremely statistically significant. The results suggest that SNP array has a significantly higher detection rate of genetic abnormalities in our cohort than that of conventional karyotype analysis. Karyotype analysis combined with CMA has become a routine technique for the prenatal diagnosis of fetuses with RA^[30]. CMA can detect an additional 2.47–6.5% of pathogenic CNVs in isolated renal agenesis^[31]. WES can further improve the diagnostic rate of complex cases with a negative karyotype and CMAs. Among the nine fetuses that underwent WES in this study, two additional likely pathogenic variants were detected, with a detection rate of 22.22% (2/9), consistent with the 13.9–50% rate reported in the literature^[32]. However, WES cannot detect variations in noncoding regions, complex structural rearrangements, or epigenetic changes^[33]. Given the high genetic heterogeneity of RA, the detection rate of known pathogenic gene mutations is only approximately 16%^[34]. In future, whole-genome sequencing is expected to overcome these limitations, especially regarding the study of pathogenic mechanisms in non-coding regions^[35].

This study had some limitations. As a single-center retrospective analysis, the sample size of fetuses with RA was limited and the number of cases in some subgroups was small, which may reduce the statistical power of the test. Meanwhile, the application rate of WES within this cohort was limited. Supplementary sequencing was conducted only for cases with negative karyotypes and SNP arrays, making it difficult to fully reveal the single-gene variation spectrum. Functional verification of candidate gene expression was not conducted; thus, the molecular regulatory mechanisms could not be clarified. Further, the follow-up duration of some live-born neonates was short, the data were incomplete, and only short-term development could be evaluated, lacking long-term prognostic data. Therefore, in the future, we will expand the scale of samples for RA, broaden WES detection coverage, and verify the research conclusions. Further, we will establish long-term follow-up files for children with RA, improve long-term prognosis assessment, and explore the pathogenic mechanisms of genes such as *BCOR* and *ANOS1* in renal development using cell and animal models.

In conclusion, RA is a relatively rare congenital disease. Fetuses with RA need to undergo enhanced screening for cardiac-related abnormalities using ultrasound during the second trimester of pregnancy. They also show other genetic abnormalities. The detection rate of genetic aberrations was significantly higher when accompanied by ultrasonic soft markers or structural anomalies. Follow-up results showed that the outcome and prognosis of RA pregnancy depended on the presence of pathogenic genetic abnormalities and severe structural abnormalities: BRA fetuses were induced, URA fetuses were mostly born live, and the incidence of adverse outcomes was the highest in fetuses with other structural abnormalities. In terms of diagnostic strategy, chromosome karyotype analysis combined with SNP array can markedly improve the detection rate of abnormalities. Further, WES can supplement the detection of single-gene mutations missed by conventional methods, and is recommended as a follow-up test for stratified detection protocols.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of Fujian Maternal and Child Health Hospital (Approval No. 2021KRD09001). All procedures were applied following the Declaration of Helsinki, as well as international and

national laws, guidelines and regulations. Signed informed consent was obtained from all the pregnant women enrolled in this study.

Consent for publication

Not applicable.

Availability of data and materials

Data is provided within the manuscript.

Competing interests

The authors declare no competing interests.

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Authors' contributions

L.X. designed the study. Y.L. wrote the manuscript. W.C. managed the study. N.L. interpreted the data. M.C. obtained the funding and supervised the project. All co-authors approved the final version.

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Figures

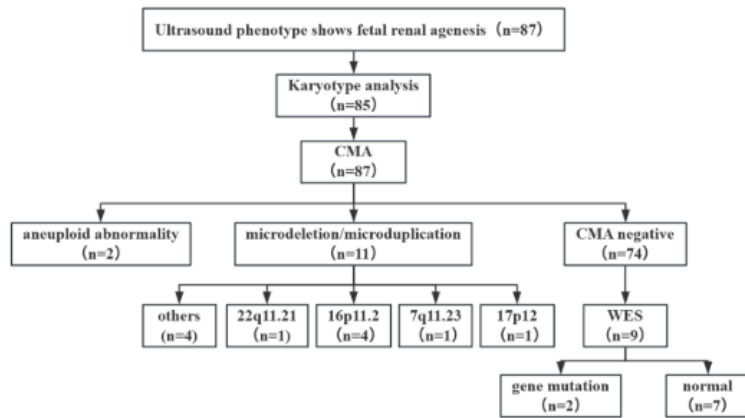


Figure 1

Procedure for the prenatal diagnosis of fetuses with renal agenesis

Distribution of Abnormal Ultrasonic Soft Markers

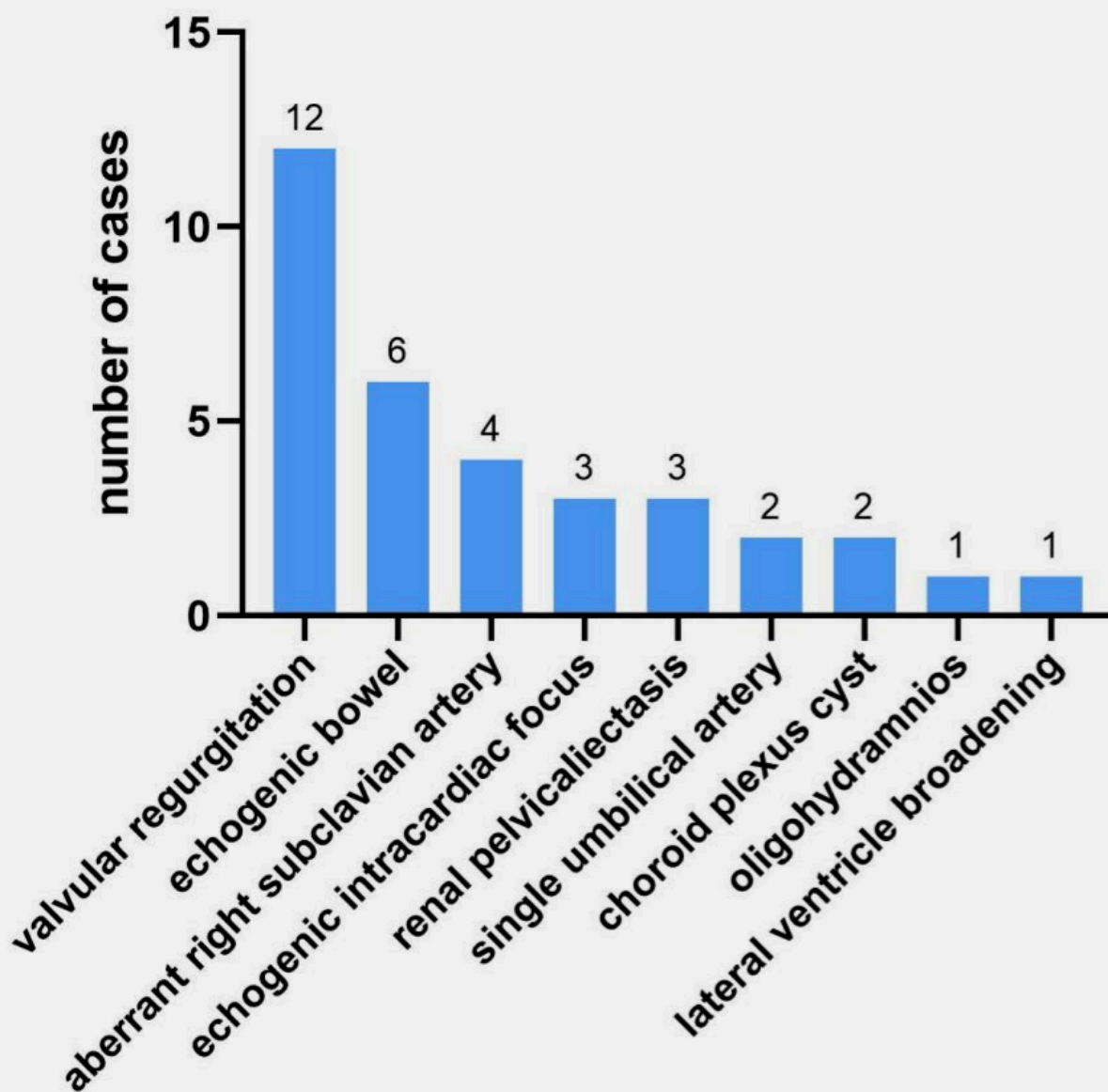


Figure 2

Distribution of abnormal ultrasonic soft markers

Distribution of Other Fetal Structural Abnormalities

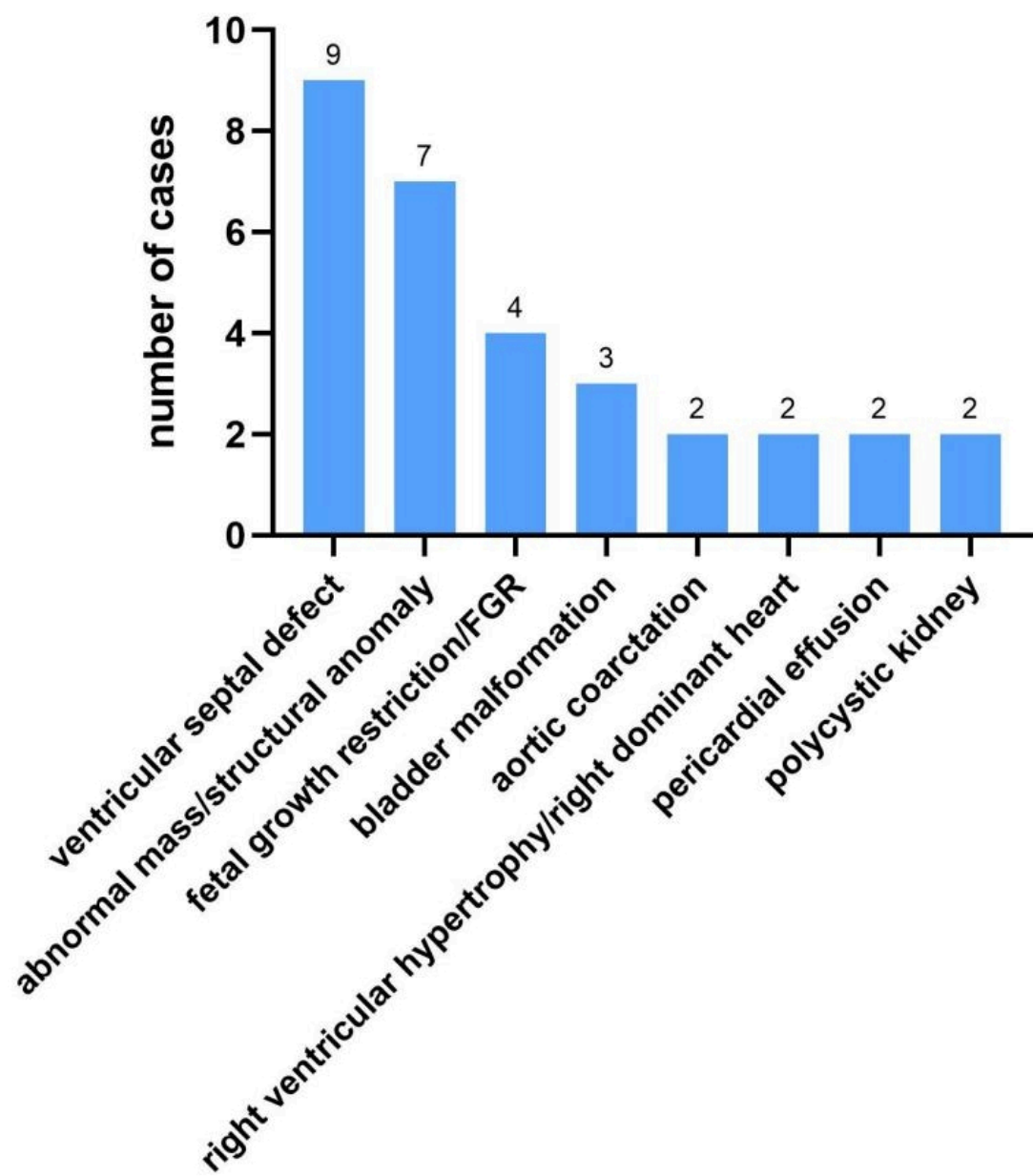


Figure 3
Distribution of various structural anomalies