Heliyon 10 (2024) e36558

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Prenatal diagnosis of 17q12 copy number variants in fetuses via chromosomal microarray analysis - A retrospective cohort study and literature review

Ruibin Huang [a,1], Chunling Ma [a,b,1], Huanyi Chen [a,1], Fang Fu [a], Jin Han [a], Liyuan Liu [a,b], Lushan Li [a], Shujuan Yan [a], Jianqin Lu [a], Hang Zhou [a], You Wang [a,b], Fei Guo [a], Xiangyi Jing [a], Fucheng Li [a], Li Zhen [a], Dongzhi Li [a], Ru Li [a,**], Can Liao [a,*]

[a] *Prenatal Diagnostic Center, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou, 510620, Guangdong, China*

[b] *The First Clinical Medical College, Southern Medical University, Guangzhou, 510515, Guangdong, China*

ARTICLE INFO

Keywords:
17q12 microdeletion
17q12 microduplication
Chromosomal microarray analysis
Prenatal diagnosis
Copy number variants

ABSTRACT

Purpose: 17q12 copy number variants (CNVs) have variable presentations and incomplete penetrance, challenging prenatal counseling and management. This study aims to investigate the intrauterine phenotype.

Methods: We included 48 fetuses diagnosed with 17q12 microdeletion or microduplication by chromosomal microarray analysis.

Results: For 17q12 deletion, renal anomalies were found in 35 fetuses (35/37, 94.6 %), with hyperechogenic kidneys (HEK, 28/37, 75.7 %) and multicystic dysplastic kidneys (17/37, 45.9 %) being the most common findings. Duodenal obstruction (DO) was most frequently combined in 17q12 duplication fetuses. In addition, cardiac abnormalities were the first reported prenatal phenotype in 17q12 duplication fetuses.

Conclusion: Our study shows that HEK and DO are the most predominant presentations of 17q12 deletion and duplication, respectively, and cardiac structural abnormalities may be associated with the latter. Although 17q12 CNVs have incomplete penetrance and variable expressivity and may be mainly involved in neurodevelopmental disorders, their short-term prognosis appears positive.

1. Introduction

Copy number variants (CNVs) of chromosome 17q12, including microdeletion and microduplication, are associated with a broad range of clinical phenotypes, and the expressivity is highly variable. The 17q12 region, spanning approximately 1.4 Mb at genomic

* Corresponding author. Prenatal Diagnostic Center, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou, Guangdong, China.

** Corresponding author. Prenatal Diagnostic Center, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou, Guangdong, China.

E-mail addresses: linra020@126.com (R. Li), canliao6008@163.com (C. Liao).

[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.heliyon.2024.e36558
Received 14 April 2024; Received in revised form 12 August 2024; Accepted 19 August 2024
Available online 19 August 2024

coordinates 17q12: 34,815,072–36,192,492 (hg19), is considered a hotspot for CNVs due to its flanking by segmental duplications (low copy repeats), making it susceptible to nonallelic homologous recombination (NAHR) [1,2]. Previous studies have shown their prevalence to be approximately 1/14,000 and 1/2675, respectively [3,4]. For 17q12 deletion, *HNF1B* (OMIM *189,907), *LHX1* (OMIM *601,999), and *ACACA* (OMIM *200,350) are considered the primarily affected genes. *HNF1B* variants are the common genetic causes of renal, genitourinary, and endocrine abnormalities, while *HNF1B* heterozygous pathogenic sequence variants may also cause renal cysts and diabetes syndrome (RCAD, OMIM #137920) [5]. *LHX1* is a candidate gene for Mayer-Rokitansky-Kuster-Hauser syndrome (MRKHS, OMIM %277,000), a disorder characterized by abnormalities in the female genital tract [6]. Besides, the protein encoded by *LHX1* is a transcription factor essential for developing the kidney and urogenital systems. The *ACACA* gene encodes the alpha form of acetyl-CoA carboxylase [7]. Although the 17q12 duplication contains the same genes as the 17q12 deletion, it is unclear whether or how mutations of these genes lead to the phenotype associated with the 17q12 duplication.

The postnatal phenotype of 17q12 deletion and duplication have been well documented. The former (17q12 deletion) is characterized by a variable combination of the following three phenotypes: structural or functional abnormalities of the kidneys and urinary tract (e.g., hyperechogenic kidneys (HEK), multicystic dysplastic kidney (MCDK), renal cysts), maturity-onset diabetes of the young type 5 (MODY5), and neurodevelopmental or neuropsychiatric disabilities (e.g., developmental delay (DD), intellectual disability (ID), autism spectrum disorder (ASD), and so on) [2]. In contrast, a broader, more comprehensive range of phenotypic manifestations is present in 17q12 duplication. It is mainly characterized by intelligence ranging from normal to severe disability and other different clinical signs such as speech and motor delays, epilepsy, and other neurodevelopmental and psychiatric disorders. Notably, most individuals with 17q12 deletion and duplication were identified by chromosomal microarray analysis (CMA) during the assessment of DD, ID, and/or ASD [1]. Given the complexity and wide variability of phenotypes, ranging from asymptomatic to fatal, it is essential to adequately understand the prenatal ultrasound features of both CNVs and to identify genotype-phenotype correlations.

In this study, we performed the clinical and molecular cytogenetic analysis of prenatal 17q12 deletion and duplication cases. We also conducted a brief literature review to summarize the intrauterine phenotype and pregnancy outcome of all reported prenatal 17q12 deletion and duplication cases to facilitate accurate prenatal diagnosis and comprehensive genetic counseling.

2. Materials and methods

2.1. Subjects

We conducted a retrospective study of 48 fetuses diagnosed with 17q12 microdeletion or microduplication by CMA at Guangzhou Women and Children Medical Center from September 2013 to December 2022. Using our medical records database, we acquired all clinical data of the patients, including maternal age, gestational age, previous reproductive history, family medical history, ultrasound findings, indications for invasive testing, genetic testing results, pregnancy outcomes, and postpartum treatment (if necessary). All pregnancies were offered genetic counseling and signed informed consent before invasive diagnosis. This study was approved by the Ethics Committee of Guangzhou Women and Children's Medical Center. The report follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies.

2.2. Sample preparation and genetic testing tools

First, genomic DNA was extracted using the Qiagen DNA Blood Midi/Mini kit (Qiagen GmbH, Hilden, Germany) according to the manufacturer's protocol. We analyzed fetal samples by quantitative fluorescence polymerase chain reaction (QF-PCR, Guangzhou Darui Biotechnology Co., Ltd, Guangdong, China) to rapidly detect 13, 18, 21, X, and Y aneuploidies and to exclude the possibility of maternal cell contamination. When QF-PCR results were negative, we used CMA or CMA + karyotype analysis as routine tests to exclude other chromosomal abnormalities and genomic imbalances. Karyotype analysis was conducted using standard G-band technology (>400-band resolution). According to the manufacturer's standard operational procedures, genomic DNA digestion, PCR amplification, product purification, fragmentation, labeling, hybridization, washing, and scanning were performed. The Chromosome Analysis Suite (ChAS) V3.2 software (Affymetrix, California, United States) was used for data analysis, and the CMA results were analyzed using relevant databases to determine the properties of chromosome copy number variants. The built reference genome was aligned on GRCh37/hg19. The CytoScan 750 K or CytoScan HD arrays are used to detect whole genome copy number variants, loss of heterozygosity (LOH), isodisomy of uniparental disomy (iso-UPD), and mosaicism at >30 %. The process has been described in detail elsewhere [8].

2.3. Literature review

The terms "17q12 microdeletion", "17q12 microduplication", "prenatal diagnosis", "chromosomal microarray analysis" and their synonyms were used to search the Medical Literature Analysis and Retrieval System Online (MEDLINE), PreMEDLINE, PubMed Central, and Record supplied by Publisher, with 227 articles retrieved. To reduce the chance of missing publications, two authors independently reviewed these documents' titles, abstracts, and full texts, and 20 were finally included. The prenatal ultrasound manifestations, clinical phenotypes, and pregnancy outcomes of the cases described in the literature were summarized and categorized.

3. Results

3.1. Research subjects

From September 2013 to December 2022, we collected 37 fetuses with 17q12 microdeletion and 11 fetuses with 17q12 microduplication diagnosed by CMA. The mean maternal age was 27.5 years (range: 21.0–40.0 years), and the median gestational age was 25.4 weeks (range: 13.7–33.0 weeks). Chorionic villus, amniotic fluid, or cord blood was extracted based on gestational age. Of these, 64.6 % (31/48) underwent amniocentesis, while percutaneous umbilical cord blood sampling and chorionic villus sampling were performed in 33.3 % and 2.1 % of pregnancies, respectively.

3.2. CMA and ultrasound results

3.2.1. 17q12 microdeletion

As shown in Table 1, the size of the 17q12 microdeletion ranged from 1.42 Mb to 1.94 Mb in these cases, all of which contained the *HNF1B*, *LHX1*, and *ACACA* genes. A total of 27 fetal parents underwent CMA validation, with 22 (81.5 %) confirmed as de novo variants, and another five were inherited from their parents. Considering the financial factor, other parents refused the offer of parental CMA verification because its price was close to 1000 dollars. Apart from an isolated abdominal cyst or ependymal cyst detected by prenatal ultrasound in Del 36 and Del 37, renal anomalies were found in other 35 fetuses (94.6 %), with HEK (28/37, 75.7 %) and MCDK (17/37, 45.9 %) being the most common findings. In addition, our study has reported 3 MCDK fetuses combined with other first-reported ultrasound findings (e.g., congenital cystic adenomatoid malformation, short limbs, and enlarged cisterna magna), expanding the phenotypic spectrum of this CNV.

3.2.2. 17q12 microduplication

The common duplication in 11 cases of 17q12 microduplication fetuses encompasses a genomic region of about 1.41 Mb (chr17: 34,822,466–36,236,609, GRCh37/hg19), and all of the duplicated regions include the *HNF1B*, *LHX1*, and *ACACA* genes. We obtained seven cases with parental CMA validation results, of which four (4/7, 57.1 %) were parentally inherited, lower than previously reported in the literature [1]. Clinical information of all cases is summarized in Table 2. The "double bubble sign" was observed in 4 cases (Dup 1-4), including Dup 3 and Dup 4 combined with polyhydramnios, strongly indicating the occurrence of duodenal obstruction (DO). In addition, cardiac structural abnormalities (ventricular septal defect (VSD), pentalogy of Cantrell, and echogenic intracardiac focus) were identified as new prenatal phenotypes of 17q12 duplication.

3.3. Pregnancy outcomes

For 37 pregnancies with 17q12 deletion, pregnancy outcomes were obtained in 36 cases (97.3 %). Twenty-eight families (75.7 %) chose to terminate the pregnancy, and seven cases (18.9 %) were live births, including four isolated HEK fetuses and the other three HEK fetuses combined with MCDK or polyhydramnios. All children underwent postnatal ultrasound, except for Del7, in which biliary dilation and hydronephrosis were found; the remaining six cases showed no abnormalities or were consistent with prenatal ultrasound findings. Moreover, Del 24 was intra-uterine fetal death, and Del 6 was lost to follow-up. While 11 cases of 17q12 duplication were chosen to terminate the pregnancy, none agreed to a further autopsy.

3.4. Literature review

The flowchart of literature retrieval and review progression is illustrated in Fig. 1. The search strategy identified 227 studies, of which 194 were excluded, and another 33 were reviewed in full text, with 20 articles eventually enrolled, containing 56 fetuses with 17q12 deletion and 17 fetuses with 17q12 duplication [9–28]. We summarized and categorized the prenatal and postnatal ultrasound phenotypes, CMA findings, and pregnancy outcomes of the cases reported in the included articles (Tables 3 and 4). In addition, we counted the ultrasound abnormalities found in the available literature (including our study, Figs. 2 and 3), and we identified HEK and DO as the most common prenatal ultrasound phenotypes for 17q12 microdeletion and microduplication, respectively.

4. Discussion

With the development and widespread use of CMA technology in the last decade, 17q12 microdeletion is considered the second most common CNV in fetuses with abnormal ultrasound findings and normal karyotype after 22q11.2 deletion syndrome (OMIM #188400) [29]. Whereas 17q12 microduplication was first described by Sharp et al. [30] in 2006, at least 50 individuals have been reported, and these individuals were often further tested for CMA because of ID and/or DD. Increased numbers of postpartum cases are being reported, accompanied by a better description of their postpartum phenotype. However, there are few large prenatal cohort studies to elucidate further the genetic and clinical value of CMA in fetuses with 17q12 CNVs. Therefore, this study aims to investigate the intrauterine phenotype of fetuses with 17q12 CNVs, thus providing a useful reference for prenatal diagnosis and genetic counseling.

The 17q12 microdeletion is closely associated with renal abnormalities, especially HEK. In our study, the rate of kidney abnormalities in 17q12 deletion fetuses was as high as 94.6 %, higher than the rate of 80%–85 % reported in the previous literature [13].

Table 1
Clinically relevant characteristics of 17q12 deletion fetuses and pathogenic CMA findings.

Cases	GA (weeks)	MA (years)	Prenatal ultrasound findings	CMA findings	Size (Mb)	Inheritance	Outcomes
1	27.3	26	Isolated HEK	arr17q12 (34,822,493–36,243,365) × 1	1.42	ND	TOP
2	29.6	29	Isolated HEK	arr17q12 (34,822,466–36,418,529) × 1	1.60	De novo	TOP
3	26.2	26	Isolated HEK	arr17q12 (34,822,466–36,243,365) × 1	1.42	ND	TOP
4	24.9	29	Isolated HEK	arr17q12 (34,822,466–36,404,136) × 1	1.58	De novo	TOP
5	26.3	38	Isolated HEK	arr17q12 (34,822,465–36,418,529) × 1	1.60	ND	Live birth (Normal)
6	29.4	23	Isolated HEK	arr17q12 (34,822,465–36,307,773) × 1	1.49	Inherited	Lost to follow-up
7	33.1	27	Isolated HEK	arr17q12 (34,822,465–36,307,773) × 1	1.49	Inherited	Live birth (CBD, Hydronephrosis)
8	26.4	29	Isolated HEK	arr17q12 (34,822,465–36,404,555) × 1	1.58	Inherited	Live birth (Normal)
9	23.1	30	Isolated HEK	arr17q12 (34,822,465–36,418,529) × 1	1.60	ND	Live birth (HEK)
10	23.3	26	Isolated HEK	arr17q12 (34,822,465–36,307,773) × 1	1.49	De novo	TOP
11	25.3	23	Isolated HEK	arr17q12 (34,822,465–36,243,365) × 1	1.42	De novo	TOP
12	21.4	34	HEK, MCDK	arr17q12 (34,835,984–36,307,773) × 1	1.47	ND	TOP
13	24.7	30	HEK, MCDK	arr17q12 (34,822,466–36,418,529) × 1	1.60	Inherited	Live birth (MCDK)
14	22.3	24	HEK, MCDK	arr17q12 (34,822,466–36,243,365) × 1	1.42	ND	TOP
15	26.3	27	HEK, MCDK	arr17q12 (34,822,465–36,243,365) × 1	1.42	ND	TOP
16	24.7	28	HEK, MCDK	arr17q12 (34,822,465–36,311,009) × 1	1.49	De novo	TOP
17	23.4	31	HEK, MCDK	arr17q12 (34,822,465–36,404,136) × 1	1.58	De novo	TOP
18	25.7	28	HEK, MCDK	arr17q12 (34,822,465–36,244,332) × 1	1.42	Inherited	TOP
19	25.6	28	HEK, MCDK	arr17q12 (34,822,465–36,307,773) × 1	1.49	De novo	TOP
20	23.6	24	HEK, MCDK	arr17q12 (34,475,679–36,410,720) × 1	1.94	De novo	Live birth (MCDK)
21	27.9	26	HEK, MCDK	arr17q12 (34,822,465–36,404,555) × 1	1.58	De novo	TOP
22	32.1	25	HEK, MCDK, enlarged kidney, polyhydramnios	arr17q12 (34,477,479–36,404,104) × 1	1.93	De novo	TOP
23	24.7	23	HEK, polyhydramnios	arr17q12 (34,822,465–36,243,365) × 1	1.42	De novo	Live birth (HEK)
24	23.9	34	HEK, renal cysts, polyhydramnios	arr17q12 (34,822,466–36,370,997) × 1	1.55	De novo	IUFD
25	23.9	24	HEK, renal dysplasia	arr17q12 (34,822,465–36,418,529) × 1	1.60	De novo	TOP
26	25.4	33	HEK, enlarged kidney	arr17q12 (34,822,465–36,404,555) × 1	1.58	De novo	TOP
27	25.7	31	HEK, duplex kidney	arr17q12 (34,822,466–36,404,555) × 1	1.58	De novo	TOP
28	30.6	28	HEK, pyelectasis	arr17q12 (34,822,492–36,404,104) × 1	1.58	De novo	TOP
29	24.3	40	Isolated MCDK	arr17q12 (34,822,466–36,404,104) × 1	1.58	De novo	TOP
30	28.1	28	MCDK, hydronephrosis	arr17q12 (34,822,465–36,307,773) × 1	1.49	ND	TOP
31	25.4	22	MCDK, polyhydramnios	arr17q12 (34,822,465–36,316,144) × 1	1.49	De novo	TOP
32	25.6	31	MCDK, CCAM, polyhydramnios	arr17q12 (34,822,465–36,418,529) × 1	1.60	De novo	TOP
33	26.3	37	MCDK, enlarged cisterna magna	arr17q12 (34,822,465–36,418,529) × 1	1.60	De novo	TOP

(*continued on next page*)

Table 1 (*continued*)

Cases	GA (weeks)	MA (years)	Prenatal ultrasound findings	CMA findings	Size (Mb)	Inheritance	Outcomes
34	25.9	24	MCDK, short limbs	arr17q12 (34,822,465–36,404,104) × 1	1.58	ND	TOP
35	26.1	35	Hydronephrosis	arr17q12 (34,822,465–36,283,612) × 1	1.46	De novo	TOP
36	26.1	30	Abdominal cyst	arr17q12 (34,822,465–36,410,559) × 1	1.59	ND	TOP
37	31.6	27	Ependymal cyst	arr17q12 (34,822,465–36,316,144) × 1	1.49	De novo	TOP

CMA: chromosome microarray analysis; GA: gestational age; MA: maternal age; HEK: hyperechogenic kidneys; ND: not documented; TOP: termination of pregnancy; CBD: congenital biliary dilation; MCDK: multicystic dysplastic kidney; IUFD: intra-uterine fetal death; CCAM: congenital cystic adenomatoid malformation.

Table 2
Clinically relevant characteristics of 17q12 duplication fetuses and pathogenic CMA findings.

Cases	GA (weeks)	MA (years)	Prenatal ultrasound findings	CMA findings (hg19)	Size (Mb)	Inheritance	Outcomes
1	24.3	28	Duodenal obstruction	arr17q12(34,822,466–36,378,678) × 3	1.56	Inherited	TOP
2	22.7	24	Duodenal obstruction	arr17q12(34,440,082–36,283,612) × 3	1.84	ND	TOP
3	30.1	25	Duodenal obstruction, polyhydramnios	arr17q12(34,822,465–36,410,559) × 3	1.59	Inherited	TOP
4	25.9	34	Duodenal obstruction, polyhydramnios	arr17q12(34,822,466–36,397,279) × 3	1.57	ND	TOP
5	26.1	33	VSD	arr17q12(34,822,466–36,283,612) × 3	1.46	ND	TOP
6	13.7	19	Pentalogy of Cantrell	arr17q12(34,449,165–36,243,365) × 3	1.79	De novo	TOP
7	26.1	21	Echogenic intracardiac focus	arr17q12(34,822,466–36,307,773) × 3	1.49	ND	TOP
8	18.7	26	Cystic hygroma	arr17q12(34,440,082–36,375,201) × 3	1.94	Inherited	TOP
9	28.3	26	Microcephaly, agenesis of the corpus callosum	arr17q12(34,822,465–36,378,678) × 3	1.56	De novo	TOP
10	18.8	40	Normal (Age = 40 years)	arr17q12(34,440,089–36,236,609) × 3	1.80	Inherited	TOP
11	17.9	38	Normal (Autism in the last pregnancy)	arr17q12(34,822,465–36,350,028) × 3	1.53	De novo	TOP

CMA: chromosome microarray analysis; GA: gestational age; MA: maternal age; TOP: termination of pregnancy; ND: not documented; VSD: ventricular septal defect.

Although the association of 17q12 deletion with renal abnormalities has been initially described, the mechanism leading to developmental anomalies is still under investigation. Mutations in *HNF1B*, the gene encoding hepatocyte nuclear factor 1β, are the most common genetic cause of kidney malformations [31,32]. Furthermore, the most common mutation in about 50 % of cases is a deletion of the entire gene occurring in the context of 17q12 microdeletion [32,33]. Compared to intragenic *HNF1B* pathogenic variants, 17q12 deletion fetuses were born with better renal function and a lower risk of progression to end-stage renal disease [34,35]. Clissold et al. [34] revealed that significant DNA methylation changes were observed in cases with a 17q12 heterozygous deletion. They speculated that this might be a regulatory mechanism in response to haploinsufficiency across the entire deleted region. In a large retrospective study illustrating the correlation between fetal kidney abnormalities and CNVs, Su et al. [36] indicated that HEK had a CMA diagnostic yield of up to 39.58 %. In comparison, approximately 31.3 % of HEK cases were associated with 17q12 deletion. As shown in Fig. 2, HEK is the most common prenatal phenotype among the cases reported in the available literature (64/93, 68.8 %), while it may result from various renal abnormalities. Of these, 34.4 % (32/93) of 17q12 deletion fetuses were found with isolated HEK, which signals that without CMA testing, these cases may be ignored without predicting their prognosis, providing sufficient evidence for the necessity of CMA testing for HEK fetuses.

17q12 duplication fetuses exhibit a broad phenotypic spectrum, and DO appears to be closely associated with this CNV. Besides neurological and psychiatric symptoms, congenital heart disease, duodenal atresia, and microcephaly have been reported in some 17q12 duplication adults [37,38]. In contrast, the ultrasound phenotype of 17q12 duplication fetuses has rarely been reported, with several studies indicating that DO may be closely associated with this CNV [9,26,28]. Our study identified four (4/11, 36.4 %) fetuses suspected of DO, two combined with polyhydramnios. Although the correlation between *HNF1B* and the phenotype related to 17q12 duplication has not been clearly elucidated, the *HNF1B* gene is widely and early expressed in several organs, such as the gut, genitourinary tract, bile duct, and thymus [39]. For the gut, several studies showed that *HNF1B* might function in intestinal differentiation.

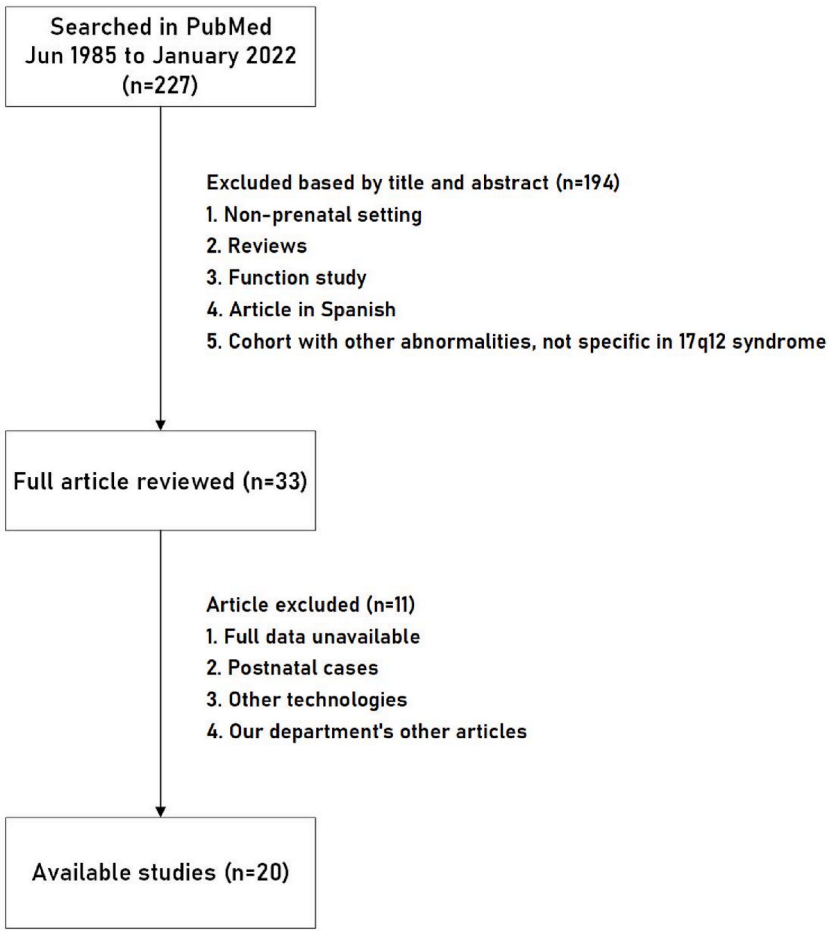

Fig. 1. Flowchart of literature retrieval and review progression.

It has been shown, for example, in animal models, that *HNF1B* is required for regional gut specification [40,41]. In mice, the expression of *Hnf1b* is essential for endoderm differentiation of the viscera and morphogenesis of the intestine, liver, and biliary tract [42,43]. In zebrafish, it is expressed in the foregut and hindgut endoderm [44]. Moreover, 17q12 duplication does not seem to be significantly relevant to renal anomalies but may be a genetic cause of cardiovascular abnormalities. Zhou et al. [28] first reported two fetuses with combined cardiac structural abnormalities (tetralogy of Fallot, tricuspid regurgitation) in 2021. In this study, we have reported three cases of 17q12 duplication fetuses combined with isolated cardiac structural abnormalities such as VSD, pentalogy of Cantrell, and echogenic intracardiac focus, further complicating the associated cardiac phenotype of this CNV.

Neurodevelopmental disorder or neuropsychiatric impairment is one of the most concerning extrarenal features of 17q12 deletion or duplication. For 17q12 deletion, several studies have indicated an increased risk of neurodevelopmental/neuropsychiatric disorders [32,37,45,46]. In a case-control study, Moreno-De-Luca et al. [45] indicated that 17q12 deletion patients are exposed to an increased risk of ASD and schizophrenia. They speculated that one or more of these 15 genes within the deletion interval are dose-sensitive and critical for normal brain development and function. Moreover, compared to the general population, Lalième et al. [47] found that *HNF1B* gene deletion increased the risk of developing neuropsychiatric disorders. However, when considering 17q12 deletion patients secondary to renal abnormalities, the neurological outcome was not as severe as in patients diagnosed for neurological reasons. Therefore, there is a need for more studies to ascertain the role of *HNF1B* in the human brain. Besides, *LHX1* is another candidate gene for neurodevelopmental anomalies. *Lhx1* was demonstrated to function in the transcriptional control of axonal guidance and the differentiation of neuronal cells and was shown to regulate head formation in early mouse embryos [48–50]. Therefore, we speculate that *LHX1* may also help explain the neurodevelopmental manifestations resulting from this deletion. As for 17q12 duplication patients, the main clinical presentations are intelligence ranging from normal to severe disability, cerebral dysplasia, epilepsy, behavioral abnormalities, and DD [1]. However, due to its incomplete penetrance and extreme phenotypic variability, it is difficult to establish its gene-phenotype correlation, and overexpression of genes in this region does not explain the different phenotypic expressions of 17q12 duplication patients. Therefore, it poses a challenge for prenatal counseling; we need to inform the pregnancies and families about the penetrance and possible phenotypes of this CNV. If the parents intend to continue the pregnancy, then further detailed ultrasound and genetic testing must be performed during the pregnancy to determine if the fetus is normal. Furthermore, prompt neuropsychiatric

Table 3
Clinically relevant features and pathogenic CMA findings in fetuses with 17q12 deletion syndrome in published cases.

Reference	Number of cases	GA (weeks)	Prenatal ultrasound findings	CMA findings (hg19)	Size (Mb)	Inheritance	Outcomes
Tutulan et al., 2022	2	24	Unilateral MCDK	arr17q12 (34,817,422–36,168,104) × 1	1.35	ND	TOP
		17	Megabladder, SUA, CPCs	arr17q12 (34,851,537–36,168,104) × 1	1.31	ND	TOP
Deng et al., 2022	6	26.1	Isolated HEK	arr17q12 (34,475,679–36,423,183) × 1	1.95	ND	Live birth (Normal)
		24.1	Isolated HEK	arr17q12 (34,823,295–36,404,104) × 1	1.58	ND	TOP
		ND	HEK, SUA	arr17q12 (34,822,465–36,316,144) × 1	1.49	ND	TOP
		21.9	HEK, unilateral MCDK	arr17q12 (34,822,466–36,418,529) × 1	1.60	ND	TOP
		30.7	HEK, polyhydramnios	arr17q12 (34,822,465–36,307,773) × 1	1.49	ND	Live birth (HEK)
		26.4	HEK, polyhydramnios	arr17q12 (34,822,465–36,418,529) × 1	1.60	ND	TOP
Wang et al., 2022	2	23	HEK, polyhydramnios	arr17q12 (36,486,626–37,930,498) × 1	1.44	De novo	TOP
		20	HEK, bilateral MCDK	arr17q12 (34,822,466–36,300,630) × 1	1.48	De novo	TOP
Qiao et al., 2022	1	22.6	Isolated HEK	arr17q12 (34,460,443–36,316,144) × 1	1.90	ND	TOP
Zhang et al., 2021	2	23.4	Hydronephrosis, polyhydramnios	arr17q12 (34,822,465–36,243,365) × 1	1.40	Inherited	TOP
		26.2	HEK, polyhydramnios	arr17q12 (34,822,465–36,243,365) × 1	1.40	Inherited	TOP
Zhou et al., 2021	10	23	HEK, polyhydramnios	arr17q12 (34,477,479–36,243,365) × 1	1.76	Inherited	TOP
		32	Isolated HEK	arr17q12 (34,822,465–36,378,678) × 1	1.55	ND	ND
		26	HEK, enlarged kidney	arr17q12 (34,822,492–36,216,603) × 1	1.39	De novo	TOP
		20	Unilateral MCDK	arr17q12 (34,822,465–36,300,466) × 1	1.47	De novo	TOP
		18	17q12 deletion in the last pregnancy	arr17q12 (34,822,465–36,311,009) × 1	1.48	Inherited	TOP
		23	Isolated HEK	arr17q12 (34,822,465–36,243,365) × 1	1.42	De novo	Live birth (Bilateral polycystic kidneys)
		25	Isolated HEK	arr17q12 (34,822,465–36,404,555) × 1	1.58	Inherited	TOP
		25	Isolated HEK	arr17q12 (34,822,465–36,387,880) × 1	1.56	De novo	TOP
		29	Hydronephrosis, polyhydramnios	arr17q12 (34,476,877–36,425,336) × 1	1.94	De novo	TOP
		26	Isolated HEK	arr17q12 (34,822,492–36,397,279) × 1	1.57	De novo	ND
Cleper et al., 2021	1	32	Cystic kidneys	arr17q12 (34,822,465–36,410,720) × 1	1.50	Inherited	TOP
Wu et al., 2020	2	18	Enlarged kidney, oligohydramnios	arr17q12 (34,820,000–36,220,000) × 1	1.40	De novo	TOP
		22	HEK, smaller kidneys	arr17q12 (34,822,465–36,307,773) × 1	1.48	De novo	TOP
Shang et al., 2020	5	29	Isolated HEK	arr17q12 (34,822,465–36,351,919) × 1	1.53	ND	TOP
		31	Isolated HEK	arr17q12 (34,817,422–36,168,104) × 1	1.35	De novo	TOP
		30	HEK, polyhydramnios	arr17q12 (34,822,465–36,307,773) × 1	1.49	De novo	TOP
		26	HEK, smaller kidneys	arr17q12 (34,817,422–36,168,104) × 1	1.35	De novo	TOP
		28	HEK, polyhydramnios	arr17q12 (34,880,000–36,060,000) × 1	1.18	ND	Lost to follow-up
Wan et al., 2019	5	ND	MCDK	arr17q12 (34,822,465–36,404,555) × 1	1.58	De novo	Live birth (Developmental Delay, MCDK)
		ND	Pyelectasis	arr17q12 (34,822,465–36,307,773) × 1	1.48	De novo	Live birth (Normal)

(*continued on next page*)

Table 3 (*continued*)

Reference	Number of cases	GA (weeks)	Prenatal ultrasound findings	CMA findings (hg19)	Size (Mb)	Inheritance	Outcomes
		ND	Isolated HEK	arr17q12 (34,822,465–36,404,555) × 1	1.58	De novo	Neonatal death (Abdominal distension)
		ND	Hydronephrosis	arr17q12 (34,822,465–36,243,365) × 1	1.42	De novo	TOP
		ND	Bilateral dysplastic kidneys	arr17q12 (34,822,465–36,404,104) × 1	1.58	De novo	TOP
Hu et al., 2019	8	ND	Hydronephrosis	arr17q12 (34,476,877–36,243,365) × 1	1.77	ND	TOP
		ND	Isolated HEK	arr17q12 (34,822,465–36,418,529) × 1	1.60	De novo	TOP
		ND	Isolated HEK	arr17q12 (34,476,877–36,243,365) × 1	1.77	De novo	TOP
		ND	Isolated HEK	arr17q12 (34,822,465–36,404,555) × 1	1.58	De novo	TOP
		ND	Isolated HEK	arr17q12 (34,822,465–36,418,529) × 1	1.60	De novo	TOP
		ND	Isolated HEK	arr17q12 (34,835,983–36,378,678) × 1	1.54	De novo	TOP
		ND	Isolated HEK	arr17q12 (34,822,465–36,307,773) × 1	1.49	De novo	TOP
		ND	Isolated HEK	arr17q12 (34,822,465–36,243,365) × 1	1.42	De novo	TOP
Pan et al., 2019	2	26	Unilateral MCDK	arr17q12 (34,817,422–36,168,104) × 1	1.35	De novo	TOP
		26	Isolated HEK	arr17q12 (34,817,422–36,168,104) × 1	1.35	De novo	TOP
Jiang et al., 2017	3	25.2	Bilateral MCDK	arr17q12 (34,822,465–36,404,555) × 1	1.50	De novo	TOP
		32.9	Isolated HEK	arr17q12 (34,822,465–36,425,336) × 1	1.60	De novo	TOP
		18	Isolated HEK	arr17q12 (34,822,465–36,243,365) × 1	1.40	Inherited	TOP
Xi et al., 2016	2	ND	Unilateral MCDK	arr17q12 (34,823,294–36,316,144) × 1	1.49	Inherited	ND
		ND	Unilateral MCDK	arr17q12 (34,822,465–36,404,104) × 1	1.58	Inherited	ND
Yap et al., 2015	3	27	HEK, CDH, pyelectasis, polyhydramnios	arr17q12 (34,822,465–36,418,529) × 1	1.60	Inherited	Live birth (CDH, HEK, cystic kidneys, abnormal kidney function)
		27	HEK, pyelectasis	arr17q12 (34,822,465–36,418,529) × 1	1.60	Inherited	Live birth (HEK, cystic kidneys)
		21	HEK, CDH	arr17q12 (34,822,465–36,311,009) × 1	1.49	De novo	Live birth (CDH, Normal kidneys)
Chen et al., 2013	1	20	Hydronephrosis	arr17q12 (34,653,178–36,402,867) × 1	1.75	Inherited	TOP
Hendrix et al., 2012	1	20	Isolated CDH	arr17q12 (31,890,483–33,281,801) × 1	1.40	ND	Neonatal death

CMA: chromosomal microarray analysis; GA: gestational age; MCDK: multicystic dysplastic kidney; ND: not documented; TOP: termination of pregnancy; SUA: single umbilical artery; CPCs: choroid plexus cyst; HEK: hyperechogenic kidneys; CDH: congenital diaphragmatic hernia.

evaluation and monitoring should be conducted after birth to allow for early intervention.

Either 17q12 deletion or duplication, the short-term prognosis seems to be positive. The follow-up period was approximately three months to three years and seven months after birth. There were seven cases of 17q12 deletion in our study who chose to continue the pregnancy. Del7 suggested an isolated HEK on prenatal ultrasound, but on postnatal ultrasound, the infant showed biliary dilation and hydronephrosis, and the remaining six cases had no additional findings. Furthermore, Del 5, Del 8, and Del 23 underwent renal function and urinalysis in infancy without any abnormality, and the remaining four cases have not been tested. As shown in Table 3, for eight live birth cases, six (75 %) had no additional findings on postpartum follow-up ultrasound or normal renal function tests. Wan et al. [21] described a fetus with MCDK detected by prenatal ultrasound, and the diagnosis was confirmed by postnatal ultrasound. The child had DD and poor physical characteristics one year after birth. At two years old, the child still had poor language expression, could not walk, and was admitted to regular rehabilitation training. Yap et al. [25] reported a case of identical twins in which prenatal ultrasound showed bilateral HEK and mild renal pelvic dilatation in both twins. In addition, in twin 1, a left-sided diaphragmatic hernia that was surgically repaired after delivery. Postnatal ultrasound showed bilateral HEK and cortical cysts in both twins, but renal function scan (MAG-3) demonstrated left-sided renal absence and normal right-sided renal function in twin 1. For 17q12 duplication, 11 cases in our study chose to terminate the pregnancy due to ultrasound and CMA findings. As shown in Table 4, a total of eight of the

Table 4
Clinically relevant features and pathogenic CMA findings in fetuses with 17q12 duplication syndrome in published cases.

Reference	Number of cases	GA (weeks)	Prenatal ultrasound findings	CMA findings (hg19)	Size (Mb)	Inheritance	Outcomes
Zhang et al., 2022	6	33.3	Duodenal obstruction, polyhydramnios	arr17q12 (34,449,165–36,236,086) × 3	1.78	Inherited	Live birth (Duodenal obstruction)
		25.1	Duplex kidney	arr17q12 (34,822,465–36,351,919) × 3	1.50	Inherited	TOP
		19	IUGR, increased NT	arr17q12 (34,440,088–36,243,365) × 3	1.80	ND	Lost to follow-up
		24	Duodenal obstruction, polyhydramnios	arr17q12 (34,424,710–36,307,773) × 3	1.88	De novo	TOP
		30.7	Duodenal obstruction, polyhydramnios	arr17q12 (34,822,466–36,243,365) × 3	1.42	Inherited	Live birth (Duodenal obstruction)
		34.6	Duodenal obstruction	arr17q12 (34,822,465–36,404,104) × 3	1.58	Inherited	Live birth (Duodenal obstruction)
Cai et al., 2022	5	18.3	Strong echo in left ventricle	arr17q12 (34,440,088–36,351,919) × 3	1.90	Inherited	Live birth (Normal)
		26.3	ACC, ventriculomegaly, dysplasia of the septum pellucidum	arr17q12 (34,822,465–36,378,678) × 3	1.50	Inherited	Live birth (Normal)
		19	Normal (High-risk for Down's screening)	arr17q12 (34,440,088–36,243,365) × 3	1.80	ND	TOP
		23.9	Duodenal obstruction	arr17q12 (34,440,088–36,243,365) × 3	1.80	ND	TOP
		28.6	Duodenal obstruction	arr17q12 (34,426,244–36,300,630) × 3	1.80	ND	Live birth (Duodenal obstruction)
Zhou et al., 2021	4	29	TOF, FL, and HL < 5 centile	arr17q12 (34,822,465–36,307,773) × 3	1.48	Inherited	TOP
		30	BPD and HC < 5 centile	arr17q12 (34,822,465–36,300,630) × 3	1.47	Inherited	ND
		25	Duodenal obstruction, polyhydramnios	arr17q12 (34,822,465–36,243,365) × 3	1.42	Inherited	TOP
		22	Pulmonary artery stenosis, tricuspid regurgitation	arr17q12 (34,822,465–36,300,630) × 3	1.47	De novo	TOP
Wan et al., 2019	1	ND	Polyhydramnios	arr17q12 (34,822,465–36,404,104) × 3	1.58	De novo	Live birth (Normal)
Chen et al., 2016	1	17	Normal (Age = 36 years)	arr17q12 (34,611,377–36,248,889) × 3	1.64	Inherited	Live birth (Normal)

CMA: chromosome microarray analysis; GA: gestational age; TOP: termination of pregnancy; IUGR: intrauterine growth retardation; NT: nuchal translucency; ND: not documented; ACC: agenesis of the corpus callosum; TOF: tetralogy of Fallot; FL: femur length; HL: humerus length; BPD: biparietal diameter; HC: head circumference.

17 included cases chose to continue the pregnancy, and four underwent surgery after birth due to DO; the remaining four cases had no significant abnormalities on postnatal follow-up, which undoubtedly increases the confidence of other families to opt to continue the pregnancy. Although some children are currently normal in terms of growth and psychomotor development, detailed renal function monitoring and neuropsychiatric evaluation should be assured in the future for timely intervention, which is one of the significances of our prenatal diagnosis in the prenatal setting.

We acknowledge important limitations when reviewing these findings. First, this is a retrospective study and may have recall bias. Second, some families do not choose to do the parent CMA verification because it costs close to $1000, and we could consider using the MLPA testing for 17q11.2 CNV later as a cheaper option for family member testing. Finally, neurodevelopmental disorders may not manifest until a later age, so further long-term follow-up of these cases must be established to discuss prenatal-postnatal phenotypic correlations for better prenatal genetic counseling and management.

5. Conclusion

To our knowledge, this is the most extensive prenatal study using CMA for genetic analysis of fetuses with 17q12 CNVs. Our study shows that HEK and DO are the most predominant prenatal ultrasound presentations of 17q12 deletion and duplication, respectively, and cardiac structural abnormalities may be associated with the latter. Although 17q12 CNVs have incomplete penetrance and variable expressivity and may be mainly involved in neurodevelopmental disorders, their short-term prognosis appears positive.

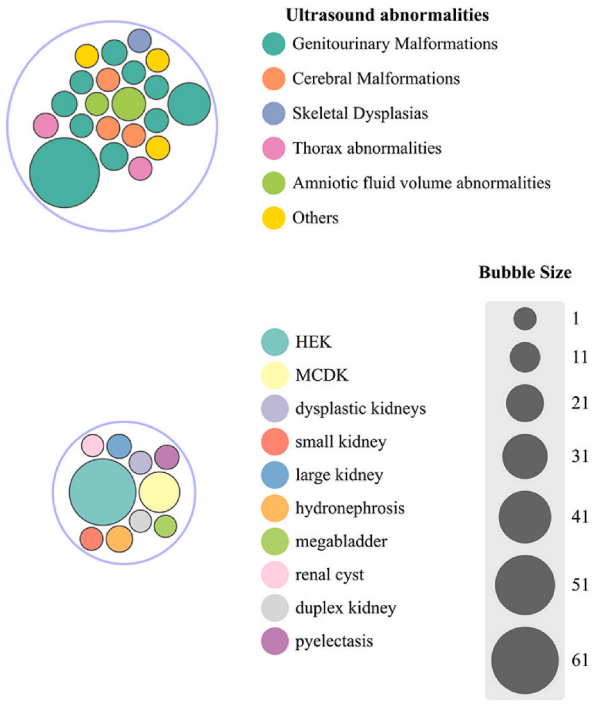

Fig. 2. Associated malformations identified by ultrasound in fetuses with 17q12 microdeletion syndrome in the available literature (including our study) (Image produced at https://www.chiplot.online/).

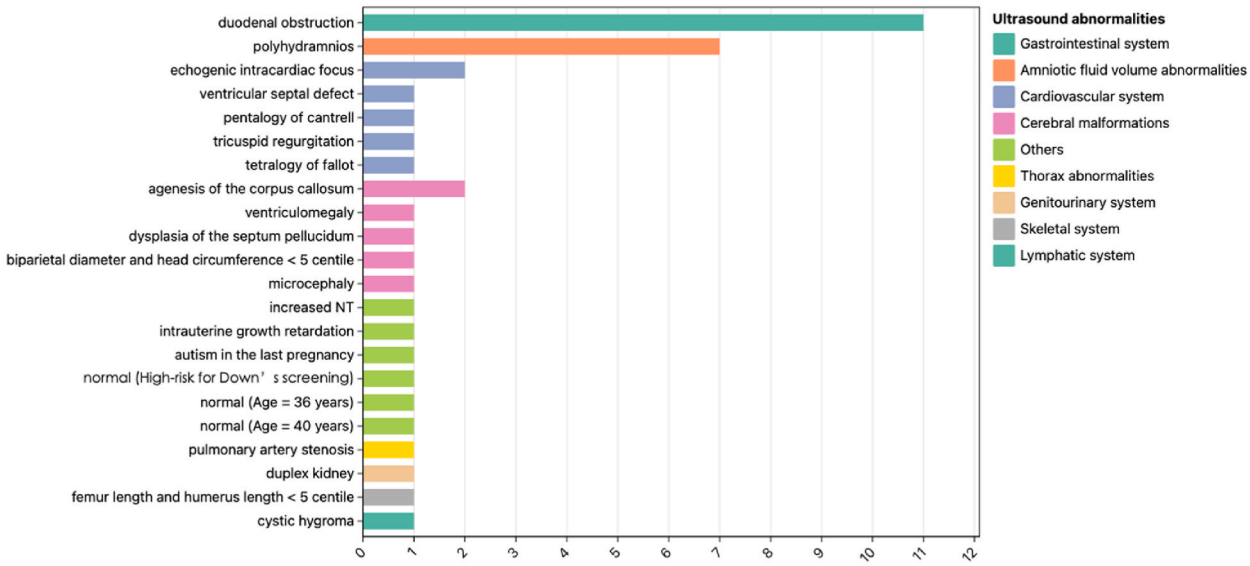

Fig. 3. Associated malformations identified by ultrasound in fetuses with 17q12 microduplication syndrome in the available literature (including our study) (Image produced at https://www.chiplot.online/).

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Guangzhou Women and Children's Medical Center (Approval number: 2021-356B01). This study was performed in line with the principles of the Declaration of Helsinki and its later amendments. Informed consent was obtained from all individual participants included in the study.

Funding

This research was funded by the sub-project of the National Key R&D Program (2021YFC2701002), the National Natural Science Foundation of China (82101796, 82201884), the Guangdong Basic and Applied Basic Research Foundation (2023A1515010115), Guangzhou Science and Technology Project (202201020643, 202201010879, 20221A011029, 202201020604, 202102020061).

Data availability statement

The data that support the findings of this study are not publicly available as the information contained could compromise the privacy of research participants. Further inquiries can be directed to the corresponding author.

CRediT authorship contribution statement

Ruibin Huang: Writing – original draft, Conceptualization. **Chunling Ma:** Visualization, Resources, Investigation, Data curation. **Huanyi Chen:** Writing – original draft, Conceptualization. **Fang Fu:** Validation, Supervision, Funding acquisition. **Jin Han:** Methodology, Investigation, Data curation. **Liyuan Liu:** Writing – original draft, Conceptualization. **Lushan Li:** Validation, Investigation, Data curation. **Shujuan Yan:** Visualization, Methodology, Investigation. **Jianqin Lu:** Visualization, Investigation, Formal analysis, Data curation. **Hang Zhou:** Visualization, Investigation, Formal analysis, Data curation. **You Wang:** Investigation, Data curation. **Fei Guo:** Visualization, Investigation, Data curation. **Xiangyi Jing:** Software, Project administration, Methodology, Data curation. **Fucheng Li:** Software, Methodology, Investigation, Data curation. **Li Zhen:** Visualization, Resources, Data curation. **Dongzhi Li:** Validation, Supervision, Project administration, Data curation. **Ru Li:** Writing – review & editing, Validation, Supervision. **Can Liao:** Writing – review & editing, Validation, Supervision, Funding acquisition.

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.

List of abbreviations

CNVs	Copy number variants
Mb	Megabase
NAHR	nonallelic homologous recombination
OMIM	Online Mendelian Inheritance in Man
RCAD	renal cysts and diabetes syndrome
MRKHS	Mayer-Rokitansky-Kuster-Hauser syndrome
HEK	hyperechogenic kidneys
MCDK	multicystic dysplastic kidney
MODY5	maturity-onset diabetes of the young type 5
DD	developmental delay
ID	intellectual disability
ASD	autism spectrum disorder
CMA	chromosomal microarray analysis
QF-PCR	quantitative fluorescence polymerase chain reaction
ChAS	Chromosome Analysis Suite;
LOH	loss of heterozygosity
iso-UPD	isodisomy of uniparental disomy
MEDLINE	Medical Literature Analysis and Retrieval System Online;
Del	deletion
Dup	duplication
DO	duodenal obstruction
VSD	ventricular septal defect
MAG-3	mercaptoacetyltriglycine.

References

[1] H. Mefford, 17q12 recurrent duplication, in: M.P. Adam, et al. (Eds.), *GeneReviews*(®), University of Washington, Seattle, 1993. Copyright © 1993-2023, University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved.: Seattle (WA).

[2] M.W. Mitchel, et al., 17q12 recurrent deletion syndrome, in: M.P. Adam, et al. (Eds.), *GeneReviews*(®), University of Washington, Seattle, 1993. Copyright © 1993-2023, University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved.: Seattle (WA).
[3] H. Stefansson, et al., CNVs conferring risk of autism or schizophrenia affect cognition in controls, Nature 505 (7483) (2014) 361–366.
[4] C.L. Martin, et al., Identification of neuropsychiatric copy number variants in a health care system population, JAMA Psychiatr. 77 (12) (2020) 1276–1285.
[5] C. Bingham, et al., The generalized aminoaciduria seen in patients with hepatocyte nuclear factor-1 alpha mutations is a feature of all patients with diabetes and is associated with glucosuria, Diabetes 50 (9) (2001) 2047–2052.
[6] S. Ledig, P. Wieacker, Clinical and genetic aspects of Mayer-Rokitansky-Küster-Hauser syndrome, Med. Genet. 30 (1) (2018) 3–11.
[7] F. López-Casillas, et al., Structure of the coding sequence and primary amino acid sequence of acetyl-coenzyme A carboxylase, Proc. Natl. Acad. Sci. U. S. A. 85 (16) (1988) 5784–5788.
[8] R. Huang, et al., Prenatal diagnosis of talipes equinovarus by ultrasound and chromosomal microarray analysis: a Chinese single-center retrospective study, Genes 13 (9) (2022).
[9] M. Cai, et al., Prenatal ultrasound phenotypic and genetic etiology of the 17q12 microduplication syndrome, Front Pediatr 10 (2022) 910497.
[10] C.P. Chen, et al., Detection of recurrent transmission of 17q12 microdeletion by array comparative genomic hybridization in a fetus with prenatally diagnosed hydronephrosis, hydroureter, and multicystic kidney, and variable clinical spectrum in the family, Taiwan. J. Obstet. Gynecol. 52 (4) (2013) 551–557.
[11] C.P. Chen, et al., Prenatal diagnosis of familial transmission of 17q12 microduplication associated with no apparent phenotypic abnormality, Taiwan. J. Obstet. Gynecol. 55 (6) (2016) 871–873.
[12] R. Cleper, et al., Improving renal phenotype and evolving extra-renal features of 17q12 deletion encompassing the HNF1B gene, Transl. Pediatr. 10 (12) (2021) 3130–3139.
[13] L. Deng, et al., Prenatal diagnosis and outcome of fetal hyperechogenic kidneys in the era of antenatal next-generationsequencing, Clin. Chim. Acta 528 (2022) 16–28.
[14] N.W. Hendrix, et al., Prenatally diagnosed 17q12 microdeletion syndrome with a novel association with congenital diaphragmatic hernia, Fetal Diagn. Ther. 31 (2) (2012) 129–133.
[15] T. Hu, et al., Prenatal diagnosis of chromosomal aberrations by chromosomal microarray analysis in fetuses with ultrasound anomalies in the urinary system, Prenat. Diagn. 39 (12) (2019) 1096–1106.
[16] Y.L. Jiang, et al., [Prenatal diagnosis of 17q12 microdeletion syndrome in fetal renal abnormalities], Zhonghua Fu Chan Ke Za Zhi 52 (10) (2017) 662–668.
[17] H. Pan, et al., [Prenatal diagnosis of two fetuses with renal structural anomalies caused by 17q12 deletion syndrome], Chin. J. Prev. Med. 22 (9) (2019) 673–677.
[18] F. Qiao, et al., [Prenatal diagnosis of fetuses with renal anomalies by whole genome sequencing], Zhonghua Yi Xue Yi Chuan Xue Za Zhi 39 (8) (2022) 819–823.
[19] T. Shang, et al., [Prenatal diagnosis and clinical analysis of 17q12 chromosome microdeletion syndrome, Prog. Obstet. Gynecol. 9 (3) (2020) 181–184.
[20] A. Ţuţulan-Cuniţă, et al., Phenotypic variability of 17q12 microdeletion syndrome - three cases and review of literature, Balkan J. Med. Genet. 24 (2) (2021) 71–82.
[21] S. Wan, et al., Prenatal diagnosis of 17q12 microdeletion and microduplication syndrome in fetuses with congenital renal abnormalities, Mol. Cytogenet. 12 (2019) 19.
[22] X. Wang, X. Xu, [Prenatal diagnosis of two fetuses with 17q12 microdeletion syndrome, Zhonghua Yi Xue Yi Chuan Xue Za Zhi 39 (10) (2022) 1153–1157.
[23] Q. Wu, et al., [Clinical phenotype and genetic analysis of three pedigrees with 17q12 microdeletion syndrome], Zhonghua Yi Xue Yi Chuan Xue Za Zhi 37 (4) (2020) 397–400.
[24] Q. Xi, et al., Copy number variations in multicystic dysplastic kidney: update for prenatal diagnosis and genetic counseling, Prenat. Diagn. 36 (5) (2016) 463–468.
[25] P. Yap, et al., Fetal phenotype of 17q12 microdeletion syndrome: renal echogenicity and congenital diaphragmatic hernia in 2 cases, Prenat. Diagn. 35 (12) (2015) 1265–1267.
[26] H. Zhang, et al., [Prenatal ultrasonography findings and genetic analysis of 17q12 microduplication syndrome], J. Zhengzhou Univ. (Eng. Sci.) 57 (5) (2022) 654–657.
[27] Y. Zhang, et al., [Prenatal diagnosis and genetic analysis of two fetuses with paternally derived 17q12 microdeletions], Zhonghua Yi Xue Yi Chuan Xue Za Zhi 38 (3) (2021) 224–227.
[28] C.X. Zhou, et al., Prenatal features of 17q12 microdeletion and microduplication syndromes: a retrospective case series, Taiwan. J. Obstet. Gynecol. 60 (2) (2021) 232–237.
[29] J.C. Donnelly, et al., Association of copy number variants with specific ultrasonographically detected fetal anomalies, Obstet. Gynecol. 124 (1) (2014) 83–90.
[30] A.J. Sharp, et al., Discovery of previously unidentified genomic disorders from the duplication architecture of the human genome, Nat. Genet. 38 (9) (2006) 1038–1042.
[31] D.Y. Hwang, et al., Mutations in 12 known dominant disease-causing genes clarify many congenital anomalies of the kidney and urinary tract, Kidney Int. 85 (6) (2014) 1429–1433.
[32] F. Laffargue, et al., Towards a new point of view on the phenotype of patients with a 17q12 microdeletion syndrome, Arch. Dis. Child. 100 (3) (2015) 259–264.
[33] H.C. Mefford, et al., Recurrent reciprocal genomic rearrangements of 17q12 are associated with renal disease, diabetes, and epilepsy, Am. J. Hum. Genet. 81 (5) (2007) 1057–1069.
[34] R.L. Clissold, et al., Genome-wide methylomic analysis in individuals with HNF1B intragenic mutation and 17q12 microdeletion, Clin. Epigenet. 10 (1) (2018) 97.
[35] D. Dubois-Laforgue, et al., Diabetes, associated clinical spectrum, long-term prognosis, and genotype/phenotype correlations in 201 adult patients with hepatocyte nuclear factor 1B (HNF1B) molecular defects, Diabetes Care 40 (11) (2017) 1436–1443.
[36] J. Su, et al., Association of prenatal renal ultrasound abnormalities with pathogenic copy number variants in a large Chinese cohort, Ultrasound Obstet. Gynecol. 59 (2) (2022) 226–233.
[37] M. Rasmussen, et al., 17q12 deletion and duplication syndrome in Denmark-A clinical cohort of 38 patients and review of the literature, Am. J. Med. Genet. 170 (11) (2016) 2934–2942.
[38] T. Bierhals, et al., Expanding the phenotype associated with 17q12 duplication: case report and review of the literature, Am. J. Med. Genet. 161a (2) (2013) 352–359.
[39] C. Bingham, A.T. Hattersley, Renal cysts and diabetes syndrome resulting from mutations in hepatocyte nuclear factor-1beta, Nephrol. Dial. Transplant. 19 (11) (2004) 2703–2708.
[40] C. Haumaitre, et al., Lack of TCF2/vHNF1 in mice leads to pancreas agenesis, Proc. Natl. Acad. Sci. U. S. A. 102 (5) (2005) 1490–1495.
[41] F. Quintero-Rivera, et al., Duodenal atresia in 17q12 microdeletion including HNF1B: a new associated malformation in this syndrome, Am. J. Med. Genet. 164a (12) (2014) 3076–3082.
[42] C. Coffinier, et al., Bile system morphogenesis defects and liver dysfunction upon targeted deletion of HNF1beta, Development 129 (8) (2002) 1829–1838.
[43] C. Coffinier, et al., Essential role for the homeoprotein vHNF1/HNF1beta in visceral endoderm differentiation, Development 126 (21) (1999) 4785–4794.
[44] Z. Sun, N. Hopkins, vhnf1, the MODY5 and familial GCKD-associated gene, regulates regional specification of the zebrafish gut, pronephros, and hindbrain, Genes Dev. 15 (23) (2001) 3217–3229.
[45] D. Moreno-De-Luca, et al., Deletion 17q12 is a recurrent copy number variant that confers high risk of autism and schizophrenia, Am. J. Hum. Genet. 87 (5) (2010) 618–630.
[46] K. Raile, et al., Expanded clinical spectrum in hepatocyte nuclear factor 1b-maturity-onset diabetes of the young, J. Clin. Endocrinol. Metab. 94 (7) (2009) 2658–2664.
[47] F. Lalière, et al., School level of children carrying a HNF1B variant or a deletion, Eur. J. Hum. Genet. 28 (1) (2020) 56–63.

[48] I. Costello, et al., Lhx1 functions together with Otx2, Foxa2, and Ldb1 to govern anterior mesendoderm, node, and midline development, Genes Dev. 29 (20) (2015) 2108–2122.
[49] W. Shawlot, R.R. Behringer, Requirement for Lim 1 in head-organizer function, Nature 374 (6521) (1995) 425–430.
[50] O. Avraham, et al., Transcriptional control of axonal guidance and sorting in dorsal interneurons by the Lim-HD proteins Lhx9 and Lhx1, Neural Dev. 4 (2009) 21.