Coexistence of urogenital malformations in a female fetus with de novo 15q24 microdeletion and a literature review

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Abstract

Background: 15q24 microdeletion is a relatively new syndrome caused by nonallelic homologous recombination (NAHR) between low-copy repeats (LCRs) in the 15q24 chromosome region. This syndrome is characterized by a spectrum of clinical symptoms including global developmental delay, intellectual disability, facial dysmorphisms, and congenital malformations of the extremities, eye, gastrointestinal tract, genitourinary system, and genitalia.

Method: Molecular cytogenetic analysis was performed using whole genome single-nucleotide polymorphism (SNP) microarray analysis. Autopsy examination including gross and microscopic examination were performed. In addition, a thorough review of the literature on 15q24 microdeletion was completed and summarized in table format.

Result: Molecular cytogenetic analysis revealed a 3.88 MB interstitial deletion within 15q24.1 to 15q24.3 (74,353,735–78,228,485 bp) in our case. Autopsy examination showed congenital malformations within the genitourinary system and genitalia, including left kidney agenesis and uterus didelphys. After thorough literature review, we found a series of midline defects associated with 15q24 microdeletion syndrome.

Conclusion: We report the first case of coexistence of urogenital abnormalities, including left kidney agenesis and uterus didelphys, with 15q24 microdeletion syndrome, which is also associated with midline defects secondary to abnormal development. Since 15q24 microdeletion syndrome is a relatively new entity, fully characterizing its variation and severity requires additional examination of the genetics, molecular profile and structural and functional abnormalities in affected patients. Due to the limited data in the literature, statistical analysis of abnormalities in each organ system is not possible. However, we can predict that novel genetic pathways involving cell migration, adhesion, apoptosis, and embryo development might be discovered with the advanced study of 15q24 microdeletion syndrome.

KEYWORDS
15q24 microdeletion, intrauterine growth restriction (IUGR), kidney agenesis, uterus didelphys
1 | INTRODUCTION

15q24 microdeletion syndrome [OMIM# 613406] is a recently described genetic disorder caused by nonallelic homologous recombination (NAHR) between low-copy repeats (LCRs) in the 15q24 chromosome region, which affects males and females equally. The syndrome manifests with a variable clinical spectrum including global developmental delay, failure to thrive, intellectual disability, malformations of the face, eye, extremities, gastrointestinal tract, genitourinary system, genitalia, etc (Magoulas & El-Hattab, 2012).

The majority of the genitourinary abnormalities reported in 15q24 microdeletion cases affected males with only one case report showing female genital malformation with labial adhesion (IS, Chin, Ec, & Tan, 2011). Here, we report a female fetus with de novo 15q24 microdeletion, who presented with combined urogenital abnormalities including uterus didelphys, left kidney nodular fibrotic agenesis, and absent left adrenal gland. In addition, a small placenta and a single umbilical artery were also present. To the best of our knowledge, this is the first case report of uterus didelphys combined with urogenital abnormalities in a female with 15q24 microdeletion syndrome.

2 | CLINICAL HISTORY

The mother is a 28-year-old female with obstetric history significant for two prior spontaneous abortions (G3P0020). The mother presented at 37 weeks of pregnancy with decreased fetal movement and an intrauterine fetal demise was diagnosed. Other abnormalities in the current gestation include polyhydramnios, intrauterine growth restriction (IUGR), and undetectable left kidney on the fetal anatomy ultrasound performed at 20 weeks of pregnancy. Further imaging examination at 25 weeks showed a small round hypoechoic structure measuring 1.2 cm within the left pelvis, which was thought to be the left kidney. Fetal echocardiogram revealed a small

![Figure 1](image-url)
possible ventricular septal defect which was closed at 35th weeks of gestation.

Given her history of repeated spontaneous abortions, a fertility workup was performed including genetic counseling and all of her results were normal. The father is phenotypically normal as well. A recent follow-up showed the mother delivered a healthy baby girl in April, 2019.

3 | EDITORIAL POLICIES AND ETHICAL COMPLIANCE

Written informed consent was obtained from the mother. Ethical approval for this study was obtained from Institution Review Board of University of Pennsylvania.

3.1 | Pathologic finding

The fetus weighed 2,135 g (<10th percentile) and measured 35.5 cm (crown to rump) and 49.5 cm (crown to heel), both > 50th percentile for 37-week gestation. Head circumference was 30.5 cm (<10th percentile). All fetal organ systems were normal in anatomic position and structure, except for the urogenital system.

The two-vessel umbilical cord contained only one umbilical artery (Figure 1a) with myxoid change (Figure 1b) and calcifications (Figure 1c). Sections from the abnormally small placenta (<10th percentile) showed terminal villous hypoplasia (Figure 1d) and increased syncytial knots (Figure 1e) suggestive of a low flow state and uteroplacental vascular insufficiency. The uterus showed two cervical

**FIGURE 2** Urogenital abnormalities. (a) The uterus clearly shows two cornua; (b) Bisection of uterus demonstrates two cervical and endometrial canals, consistent with uterus didelphys; (c) histological section of uterus shows vascular proliferation; (d) Histological section from normally developed right kidney shows normal glomerular and tubular development; (e) The agenesis renal nodule within the left pelvis (arrow); (f) Histological sections from the left pelvic agenesis renal nodule show nonidentifiable renal tissue, but only dense fibrous tissue; (g) High power view of portion of left pelvic nodule
and endometrial canals, consistent with uterus didelphys (Figure 2a,b). Sections of the uterus also showed vascular proliferation (Figure 2c).

The right kidney weighed 14.7 grams (Normal range: 16.1–28.9 g) and was located in the usual position with normal glomerular and tubular development (Figure 2d). The right ureter was probe patent into the bladder. Dissection within the left pelvis revealed a fibrotic nodule measuring 1.3 × 0.8 × 0.3 cm (Figure 2e, arrow) within the expected anatomic location for the left kidney. This nodule was attached to the left ureter, and was not continuous with the bladder. Histologic sections from this nodule showed dense fibrous tissue with no identifiable renal tissue (Figure 2f,g). The right adrenal gland was normal in position and development. The left adrenal gland was not identified despite thorough dissection.

3.2 Molecular cytogenetic finding

Molecular cytogenetic analysis was performed using whole genome SNP microarray analysis by Integrated Genetics LabCorp - Specialty Testing Group (Santa FE Reproductive lab) which reported a 3.88 MB interstitial deletion at 15q24.1 to 15q24.3 (74,353,735–78,228,485 bp). Since both parents are phenotypically normal and the results of the mother's genetic counseling were normal, we presume this 15q24 microdeletion is a de novo deletion.

4 DISCUSSION

The 15q24 region (NCBI Build 36) on chromosome 15 spans from 72.4 to 78.0 Mb, which contains three sub-bands: 15q24.1 (72,400,001–74,900,000 bp), 15q24.2 (74,900,001–76,300,000 bp), and 15q24.3 (76,300,001–78,000,000 bp) (UCSC Genome Browser on Human, 2013). Deletions in the 15q24 region were noted as early as 1984 with a female newborn suffering cystic renal dysplasia (Clark, 1984). Due to technical limitations, detailed genetic information was unavailable at that time. The concept of 15q24 microdeletion syndrome was first proposed by Sharp et al in 2007 and was characterized by growth retardation, microcephaly, digital abnormalities, hypospadias, loose connective tissue, and dysmorphic facial features (Sharp et al., 2007). Thereafter, additional cases with 15q24 microdeletion were reported with variable clinical manifestations and genetic deletions, which are review by Magoulas and El-Hattab (2012).

The majority of 15q24 deletions are mediated by the nonallelic homologous recombination (NAHR) with breakpoints in the five identified low-copy repeats (LCR15q24A to LCR15q24E). The reported 15q24 deletions range from 1.7 to 6.1 Mb with the smallest region of overlap of 1.2 Mb between LCR15q24B and LCR15q24C (Andrieux et al., 2009; El-Hattab et al., 2009, 2010; Magoulas & El-Hattab, 2012).

Due to the gene-rich property of the 15q24 region, the clinical manifestations of 15q24 microdeletion are highly variable (El-Hattab et al., 2010; Magoulas & El-Hattab, 2012). The most commonly deleted region in 15q24 microdeletion syndrome contains many enzyme coding genes involving glycoprotein metabolism (mannose phosphate isomerase (MPI, OMIM 154,550), alpha-mannosidase 2C1 (MAN2C1, OMIM 154,580), Electron transfer flavoprotein alpha subunits (ETFA, OMIM 608,053) and Lectin Mannose-binding 1-like protein (LMAN1L, OMIM 609,548), steroidogenesis by cytochrome P450 side chain-cleavage enzyme (CYP11A1, OMIM 118,485); vitamin A metabolism (Stimulated by retinoic acid 6 (STRA6, OMIM 610,745)), and secretory carrier membrane proteins (Secretory carrier membrane protein 2 (SCAMP2, OMIM 606,912)) and Secretory carrier membrane protein 5 (SCAMP5, OMIM 613,766) (Masurel-Paulet et al., 2009).

4.1 Urological abnormality in 15q24 microdeletion

The urogenital system is derived from the urogenital ridge, which develops into three tubular nephric structures: the pronephros, the mesonephros, and the metanephros. The mesonephric duct (Wolffian duct) from the mesonephros forms the male genital ducts, the ureter and collecting duct system, the major and minor calyces and the renal pelvis. The metanephrogenic blastemal differentiates into the renal tubules, including the proximal convoluted tubules, loops of Henle, and distal convoluted tubules. Any perturbation in these inductive events can cause inhibition of the ureteric bud growth resulting in renal hypoplasia or agenesis.

Renal development involves a retinoic acid-dependent induction process. As a morphogen derived from vitamin A, retinoic acid plays important roles in cell growth, differentiation, and organogenesis (Duester, 2008). The STRA6 gene (74.47–74.50 Mb) is vital in retinoic acid metabolism, whose defects can cause hydronephrosis, horse-shoe kidney formation and dysplastic kidney formation (Pasutto et al., 2007). Our case had a large deletion from 74.35 to 78.23 Mb resulting in loss of the STRA6 gene, which likely contributed to the left renal agenesis.

4.2 Genital abnormality in 15q24 microdeletion

The embryo is sexually indifferent in the first 6 weeks of gestation, regardless of the genetic determination at the time of fertilization. Both male and female embryos have mesonephric ducts (Wolffian ducts) and paramesonephric
| Author (Publish year) | Pt # | Deletion Start site (Chrom. band or Mb) | Stop site (Mb) | Sex | Male Genital malformation | Female genital malformation | Midline defect | Notes |
|----------------------|------|---------------------------------------|----------------|-----|----------------------------|----------------------------|---------------|-------|
|                       |      |                                       |                |     | Hypospadiasis | Microphallus | Cryptorchidism | Labial Adhesion | Uterus abnormal | Kidney malformation | Bifid uvula | Clef lip | Cleft palate | Diaphragm hernia | Heart septal defect | Notes |
| Clark (1984)          | 1    | 15q22                                 | 15q24          | F   | X            | X            | X            | —               | —               | —               | N/A         | N/A     | N/A         | N/A         | N/A               | N/A   |
| Kristoffersson et al. (1987) | 2    | 15q24                                 | 15qter         | M   | —            | —            | +            | X               | X               | N/A             | N/A         | N/A     | N/A         | N/A         | N/A               | Maternal translocation, 46, XX; t(6;15)(p25;q24) |
|                       | 3    | 15q24                                 | 15qter         | M   | N/A          | N/A          | N/A          | X               | X               | Cystic kidney    | N/A         | N/A     | N/A         | N/A         | N/A               | Maternal balanced translocation, 46, XX; t(6;15)(p25;q24); Single umbilical artery |
| Formiga et al. (1988) | 4    | 15q22                                 | 15q25          | F   | X            | X            | —            | —               | —               | N/A             | N/A         | N/A     | N/A         | N/A         | N/A               | N/A   |
|                       | 5    | 15q21                                 | 15q24          | F   | X            | X            | X            | —               | —               | —               | N/A         | N/A     | N/A         | N/A         | N/A               | N/A   |
|                       | 6    | 15q24                                 | N/A            | M   | —            | +            | —            | X               | X               | N/A             | N/A         | N/A     | N/A         | N/A         | N/A               | N/A   |
| Cushman et al. (2005) | 7    | 15q24                                 | N/A            | M   | X            | X            | X            | N/A             | N/A             | N/A             | N/A         | N/A     | N/A         | N/A         | N/A               | N/A   |
|                       | 8    | 15q22.3                               | 15q24          | M   | +            | —            | —            | X               | X               | —               | N/A         | N/A     | N/A         | N/A         | N/A               | N/A   |
|                       | 9    | 72.15                                 | 76.01          | M   | —            | —            | —            | X               | X               | N/A             | N/A         | N/A     | N/A         | N/A         | N/A               | N/A   |
|                       | 10   | 72.15                                 | 76.01          | M   | +            | +            | —            | X               | X               | N/A             | N/A         | N/A     | N/A         | N/A         | N/A               | N/A   |
| Sharp et al. (2007)   | 11   | 72.15                                 | 73.85          | M   | +            | —            | —            | X               | X               | N/A             | N/A         | N/A     | N/A         | N/A         | N/A               | N/A   |
|                       | 12   | 70.4                                  | 74.21          | M   | +            | —            | —            | X               | X               | N/A             | N/A         | N/A     | N/A         | N/A         | N/A               | Maternal balanced translocation, 46, XX; t(6;15)(p25;q24) |
| Klopopcki et al. (2008) | 13  | 72.2                                  | 75.9           | M   | —            | +            | —            | X               | X               | —               | N/A         | N/A     | N/A         | N/A         | N/A               | N/A   |
| Abe et al. (2008)     | 14   | 15q24                                 | 15qter         | M   | N/A          | N/A          | N/A          | X               | X               | —               | N/A         | N/A     | N/A         | N/A         | N/A               | N/A   |
| van Esch et al. (2009) | 15  | N/A                                   | N/A            | M   | —            | +            | +            | X               | X               | N/A             | +           | —       | —           | +           | —               | N/A   |
| Masurel-Paulet et al. (2009) | 16  | 70.75                                 | 73.86          | M   | —            | +            | —            | X               | X               | N/A             | N/A         | N/A     | N/A         | N/A         | N/A               | N/A   |
|                       | 17   | 72.25                                 | 75.94          | M   | —            | —            | —            | X               | X               | N/A             | N/A         | N/A     | N/A         | N/A         | N/A               | N/A   |
|                       | 18   | 72.13                                 | 76.08          | F   | X            | X            | X            | —               | —               | —               | N/A         | N/A     | N/A         | N/A         | N/A               | N/A   |
| El-Hattab et al. (2009) | 19  | 70.75                                 | 73.86          | M   | +            | —            | —            | X               | X               | N/A             | N/A         | N/A     | N/A         | N/A         | N/A               | N/A   |
|                       | 20   | 70.71                                 | 73.86          | M   | —            | +            | —            | X               | X               | N/A             | N/A         | N/A     | N/A         | N/A         | N/A               | N/A   |
|                       | 21   | N/A                                   | N/A            | M   | +            | +            | —            | X               | X               | —               | N/A         | N/A     | N/A         | N/A         | N/A               | N/A   |
| Andreux et al. (2009) | 22   | N/A                                   | N/A            | M   | +            | —            | —            | —               | —               | —               | N/A         | N/A     | N/A         | N/A         | N/A               | N/A   |
|                       | 23   | N/A                                   | N/A            | M   | —            | —            | —            | X               | X               | —               | N/A         | N/A     | N/A         | N/A         | N/A               | N/A   |
|                       | 24   | N/A                                   | N/A            | F   | X            | X            | X            | —               | —               | —               | N/A         | N/A     | N/A         | N/A         | N/A               | N/A   |
| Author (Publish year) | Pt # | Deletion Start site (Chrom. band or Mb) | Stop site (Mb) | Sex | Male Genital malformation | Female genital malformation | Midline defect | Notes |
|-----------------------|------|----------------------------------------|---------------|-----|---------------------------|---------------------------|----------------|-------|
| McInnes (2010)        | 25   | 69.84 (15q23)                          | 72.9          | M   | —                         | —                         | X             | X     |
| El-Hattab et al.      | 26   | 71.81                                  | 74.42         | M   | —                         | —                         | X             | X     |
| Sing et al. (2011)    | 27   | 76.08                                  | 80.34 (15q25) | M   | N/A                       | N/A                       | X             | X     |
| Is et al. (2011)      | 28   | 70.69                                  | 73.86         | F   | X                         | X                         | +             | —     |
| Mefford et al. (2012) | 29   | 70.06                                  | 72.43         | F   | N/A                       | N/A                       | —             | —     |
|                        | 30   | 70.73                                  | 73.33         | M   | —                         | —                         | —             | —     |
|                        | 31   | 70.73                                  | 73.33         | M   | —                         | —                         | —             | —     |
|                        | 32   | 70.73                                  | 73.33         | M   | N/A                       | N/A                       | X             | X     |
|                        | 33   | 70.73                                  | 73.33         | M   | N/A                       | N/A                       | X             | X     |
|                        | 34   | 70.73                                  | 73.89         | F   | X                         | X                         | —             | —     |
|                        | 35   | 70.73                                  | 73.89         | F   | X                         | X                         | —             | —     |
|                        | 36   | 70.73                                  | 73.89         | M   | —                         | —                         | —             | —     |
|                        | 37   | 70.73                                  | 73.74         | M   | +                         | —                         | —             | —     |
|                        | 38   | 72.22                                  | 73.81         | M   | N/A                       | N/A                       | X             | X     |
|                        | 39   | 72.2                                   | 74.04         | M   | N/A                       | N/A                       | X             | X     |
|                        | 40   | 72.2                                   | 75.95         | F   | X                         | X                         | N/A           | N/A   |
|                        | 41   | 73.32                                  | 73.59         | M   | N/A                       | N/A                       | X             | X     |
|                        | 42   | 73.38                                  | 73.88         | F   | X                         | X                         | N/A           | N/A   |
|                        | 43   | 75.12                                  | 75.6          | M   | +                         | —                         | +             | —     |
| Narumi et al. (2012)  | 44   | 72.49                                  | 75.92         | M   | +                         | —                         | —             | —     |
| Haemmerling et al. (2012) | 45   | 70.75                                  | 73.33         | M   | +                         | —                         | —             | —     |
| Brun et al. (2012)    | 46   | 74.42                                  | 75.95         | M   | N/A                       | N/A                       | X             | X     |
| Samuelson et al. (2015)| 47   | 74.79                                  | 76.31         | M   | —                         | —                         | X             | X     |
|                        | 48   | 74.79                                  | 76.31         | M   | —                         | —                         | X             | X     |
|                        | 49   | 74.79                                  | 76.31         | F   | X                         | X                         | —             | —     |
ducts (Müllerian ducts). The SRY gene on the Y chromosome determines the development of the testis, sertoli cells and leydig cells. Müllerian inhibitory factor from sertoli cells triggers degradation of the paramesonephric ducts. Testosterone from leydig cells stimulates development of mesonephric ducts to form the male internal sexual organs (sperm ducts, epididymis, ejaculatory duct, and the ductus deferens). The female embryo lacks the Y chromosome and hence undergoes default phenotypic differentiation, resulting in the degeneration of the mesonephric ducts, fusion and canalization of the paramesonephric ducts to form the fallopian tubes, uterus, and upper 1/3 of the vagina.

Uterine development in females requires fusion of the paramesonephric ducts. Similarly, development of male external genitalia involves fusion of the urethral folds. Defects in this fusion process can lead to bicornuate uterus or uterus didelphys in females and hypospadias in males, respectively. Our case had uterus didelphys, which is the first case reported in a female with 15q24 microdeletion. Interestingly, the association of renal agenesis and Mullerian duct anomalies is commonly reported in various conditions (Fedele, Motta, Frontino, Restelli, & Bianchi, 2013; Tanaka et al., 1998). Development of the external genitalia in females does not involve fusion of the urethral folds, rather nonfusion of the folds results in formation of the labia minora. Thus, males with 15q24 microdeletion, frequently demonstrate hypospadias, but females do not commonly demonstrate abnormalities in the external genitalia.

### 4.3 Midline defects in 15q24 microdeletion

The embryonic development stage (3rd to 8th week after conception) is a critical period for organogenesis and axes formation. The determination of the left–right axis is crucial for proper organogenesis, which requires coordinated processes involving cell proliferation, differentiation, migration, adhesion, and apoptosis. After reviewing the literature summarized in Table 1, we found that defects within the midline of the body are common in 15q24 microdeletion syndrome, including cleft lip and/or cleft palate (Abe et al., 2008; Brun et al., 2012; Cushman et al., 2005; Samuelsson, Zagoras, & Hafstrom, 2015; Sing et al., 2011), bifid uvula (Van Esch, Backx, Pijkels, & Fryns, 2009), gluteal cleft (Cushman et al., 2005), diaphragmatic hernia (Van Esch et al., 2009; Sharp et al., 2007), imperforate anus (Andrieux et al., 2009; Mefford et al., 2012), hypospadias (Andrieux et al., 2009; Cushman et al., 2005; El-Hattab et al., 2009; Haemmerling et al., 2012; Mefford et al., 2012; Narumi et al., 2012; Sharp et al., 2007), and uterus didelphys in our case.
Cilia and microtubules play an important role in cellular migration and adhesion. Silencing of the Bardet–Biedl syndrome-4 gene (72.68–72.74 Mb, BBS4, OMIM 600,374) induces deanchoring of centrosomal microtubules (Kim et al., 2004). Cellular migration and adhesion during development requires the Neogenin gene (73.05–73.31 Mb, NEO1, OMIM 601,907) (Wilson & Key, 2006). In Table 1, all of the hypospadias patients with 15q24 microdeletion syndrome, except one, had complete or partial deletion of these two genes. The only reported 15q24 microdeletion with female external genital abnormality also included these two genes (Is et al., 2011). Given the limitation of the current study, the roles of these two genes in hypospadias and female external genital abnormalities should be further studied. It is possible that the genes affect genital development via haploinsufficiency or a mutated recessive allele on the intact chromosome. Because these genes were not sequenced, we cannot rule out either possibility.

Although the microdeletion in our case does not include the above two genes, it does contain two other gene deletions including the Cytoplasmic tyrosine kinase gene (74.78–74.80 Mb, CSK, OMIM 124,095) and the UNC51-like kinase 3 gene (74.83–74.84 Mb, ULK3, OMIM 613,472). Loss of the CSK gene can cause disorganization of tissue architecture (Baumeister et al., 2005) and the ULK3 gene is essentially for cellular autophagy (Braden & Neufeld, 2016). We can infer that loss of the ULK3 gene may interfere with the removal of the uterine septum resulting in didelphys.

5 | CONCLUSION

Since 15q24 microdeletion syndrome is a relatively new entity, fully comprehending the variability and severity of 15q24 microdeletion syndrome requires further characterization of the genotype, molecular profile, and structural and functional abnormalities identified in affected patients. Based on the available literature and the present case, we can reasonably conclude that coordination of genes in the 15q24 region is critical for embryonic development and organogenesis. Due to the limited data in the literature, statistical analysis of abnormalities in each organ system is not possible. We can predict that novel genetic pathways involving cell migration, adhesion, apoptosis, and embryonic development might be discovered with further investigation of 15q24 microdeletion syndrome. This could help develop novel screening guidelines to reduce the morbidity of 15q24 microdeletion syndrome.

ACKNOWLEDGMENTS
The publication is supported by Pennsylvania Hospital, Department of Pathology for the funding.

CONFLICT OF INTEREST
The authors declared that they have no conflict of interest.

AUTHOR CONTRIBUTIONS
Both authors contribute equally to the acquisition of the clinical data, gross and histological autopsy diagnosis, and analysis and interpretation of the data. Dr. Yaobin Liu contributes to manuscript drafting, patient follow-up and request for written consent form. Dr. Beth Mapow contributes to the revising the manuscript and finalization.

DATA AVAILABILITY STATEMENT
The patient’s information data are not publicly available due to their containing information that could compromise the privacy of research participants.

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How to cite this article: Liu Y, Mapow B. Coexistence of urogenital malformations in a female fetus with de novo 15q24 microdeletion and a literature review. *Mol Genet Genomic Med.* 2020;8:e1265. https://doi.org/10.1002/mgg3.1265