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Mayer-Rokitansky-Küster-Hauser syndrome associated with 7q11.23 microduplication: A case report

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ABSTRACT

Introduction: Mayer-Rokitansky-Küster-Hauser syndrome (MRKHS) is characterized by the congenital absence of the uterus and vagina in females with 46, XX karyotype. The genetic etiology remains poorly understood.
Case presentation: We described a 29-year-old female patient with a main complaint of primary amenorrhea. The MRKHS diagnosis was confirmed, and molecular analysis revealed a 7q11.23 microduplication in the proband that was shown to be inherited from her mother. In the literature, müllerian malformations have been reported in only a few cases of 7q11.23 microduplication. However, the abnormalities observed in our patient have not been described previously. To the best of our knowledge, this is the first documented case of a patient with the coexistence of 7q11.23 microduplication syndrome and MRKHS.
Discussion/conclusion: Identification of the 7q11.23 duplication could suggest a new candidate region for MRKHS and add to the already described signs of 7q11.23 microduplication syndrome.

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Introduction

Mayer-Rokitansky-Küster-Hauser syndrome (MRKHS) is a congenital disorder affecting 1 in 4500–5000 females newborns. This condition is characterized by agenesis/aplasia of the uterus and the upper two-thirds of the vagina. Affected women typically exhibit normal secondary sexual characters and a normal female karyotype (46, XX) [1,2]. Generally, primary amenorrhea is usually the first clinical sign. Thelarche and pubarche occur spontaneously due to normal ovarian function. Although the endocrine profile is usually normal, gonadal dysgenesis and ovarian agenesis have also been reported in the literature [3,4]. Other complaints include abdominal pain, which presents cyclically, dyspareunia and infertility [5].

Although the etiology of MRKHS is not totally clear, the hypothesis that it has a genetic contribution is supported by the presence of familial aggregation, showing possible autosomal dominant inheritance with incomplete penetrance [6]. Multiple copy number variations (CNVs) have been identified in this patient group, including alterations in 1q21.1, 16p11.2, 17q12, 22q11.21 and Xp22 regions [4,7]. Additionally, monogenic causes have been reported, including variants in genes such as *LHX1*, *HNF1B* and *WNT4* [3,8]. Studies have also identified variants in *TBX6, RBM8A, GREB1L* and *WNT9B*, and, among others, these genes have been proposed as candidates [9,10]. To our knowledge, this case report is the first to describe a female patient diagnosed with MRKHS who harbors a single CNV known to cause the 7q11.23 microduplication syndrome.

Methods

The patient described in this study was referred to our Clinical Genetics Unit at the Brasília University Hospital with a complaint of primary amenorrhea, peripheral blood samples were collected from the patient, and genetic testing was subsequently performed as described below.

Study approval was granted by the Ethics Committee of the University of Brasília (nº 60695716.1.0000.5558). The informed consent was signed by the patient.

Karyotype

The G-banding technique was performed according to standard procedures.

Polymerase chain reaction (PCR) for SRY amplification

PCR for the *SRY* gene was performed to exclude translocation of this gene, which is considered an initiator of the male developmental pathway. Primer sequences and conditions were executed in accordance with the previously described methodology [11].

Chromosomal microarray analysis (CMA)

CMA was performed in the proband using the CytoScanTM 750k platform (ThermoFisher®, Carlsbad, USA). DNA hybridization was performed according to the manufacturer´s protocol. Data was analyzed using the Chromosome Analysis Suite (ChAS) Software (ThermoFisher®, Carlsbad, USA).

Whole exome sequencing (WES)

WES was performed using the Illumina HiScan™ SQ and data were analyzed using the Franklin Genoox platform.

Multiplex ligation-dependent probe amplification (MLPA)

MLPA was performed using a commercial kit (SALSA MLPA Probemix P064-C1, MRC-Holland®) to investigate the proband's parents. MLPA reactions were performed according to the manufacturer's instructions and the data were analyzed using the Coffalyser.net (MRC-Holland®) software.

Results

Clinical presentation

A 29-year-old woman, daughter of non-consanguineous parents, presented to our institution with a main complaint of primary amenorrhea. The patient is 1.68 m high (75–90th centile), 98.6 kg (> 97th centile) and cephalic perimeter 60 cm (> 98th centile). The clinical examination found normal secondary sexual characteristics, a low hairline implantation on the forehead, small ears with adherent lobes, prominent supraorbital ridge, downward slating palpebral fissures, a mid-to-high nasal bridge, mild asymmetry of the nasal alae (left smaller than right), a medium-length philtrum, high-arched palate, prominent chin and cervical acanthosis nigricans. Hands appear unremarkable, with fetal pads present on the 3rd to 5th fingers, hyperconvex nails, pronounced folliculitis on the thighs, flat feet, and mild micrognathia.

Ultrasound examination revealed absence of uterus, normal ovaries bilaterally and vagina of approximately 0.5 cm in length. The patient initiated non-surgical treatment for neovagina creation using dilators, achieving an increase in the vaginal canal length to approximately 3.3 cm. No renal changes were observed.

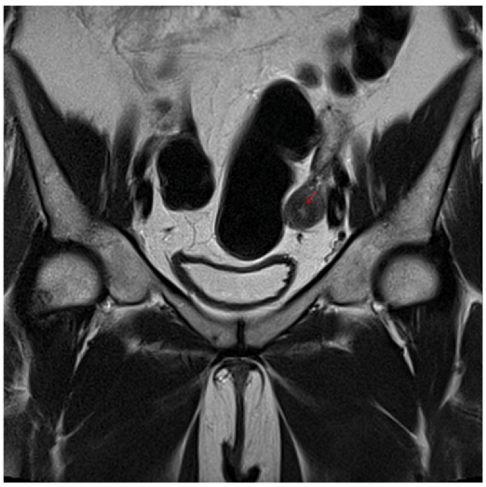

Fig. 1. MRI image in coronal plane. The red arrow indicates uterine horn with 0.3 cm of functional endometrial tissue.

Magnetic resonance imaging (MRI) demonstrated an expansive lesion in the left adnexal region of probable neoplastic nature, with a possible fibrous component. Complete x-ray of the spine revealed left-convex thoracic scoliosis and anterolateral marginal osteophytes. The patient refers to normal echocardiography and audiometry.

A new MRI was requested, and it was observed that the uterus was not characterized in its usual form and topography. A rudimentary uterine horn in the left adnexal region, with zonal anatomy, sign and enhancement similar to uterus, measuring 3.5 cm and with 0.3 cm of functional endometrial tissue (Fig. 1). In the right adnexal region, there is minor rudimentary uterine formation, but no zonal or endometrial tissue differentiation. Ovaries with some cysts measuring up to 1.7 cm, all of them present functional aspect.

Hormonal tests were also performed: LH: 4.21mIU/mL; FSH: 4.85mIU/mL; estradiol: 74 pg/mL; total testosterone: 36.2 ng/dL; prolactin: 13.40 ng/mL; progesterone: 1.28 ng/mL, all within normal limits.

Genetic findings

The karyotype determined for the patient was 46, XX. PCR amplification of the *SRY* gene was negative. CMA analyses and WES identified a 1.4 Mb duplication on chromosome 7q11.23 arr[hg19]7q11.23(72,732,834 – 74,136,633)x3 which includes 23 OMIM genes: *TRIM50, FKBP6, FZD9, BAZ1B, BCL7B, TBL2, MLXIPL, VPS37D, STX1A, LINC00035, CLDN3, CLDN4, WBSCR27, WBSCR28, ELN, LIMK1, EIF4H, MIR590, LAT2, RFC2, CLIP2, GTF2IRD1* and *GTF2I* (Fig. 2). DNA from both parents was obtained to verify the origin of the detected variant by MLPA. The duplication identified in the proband was inherited from her mother.

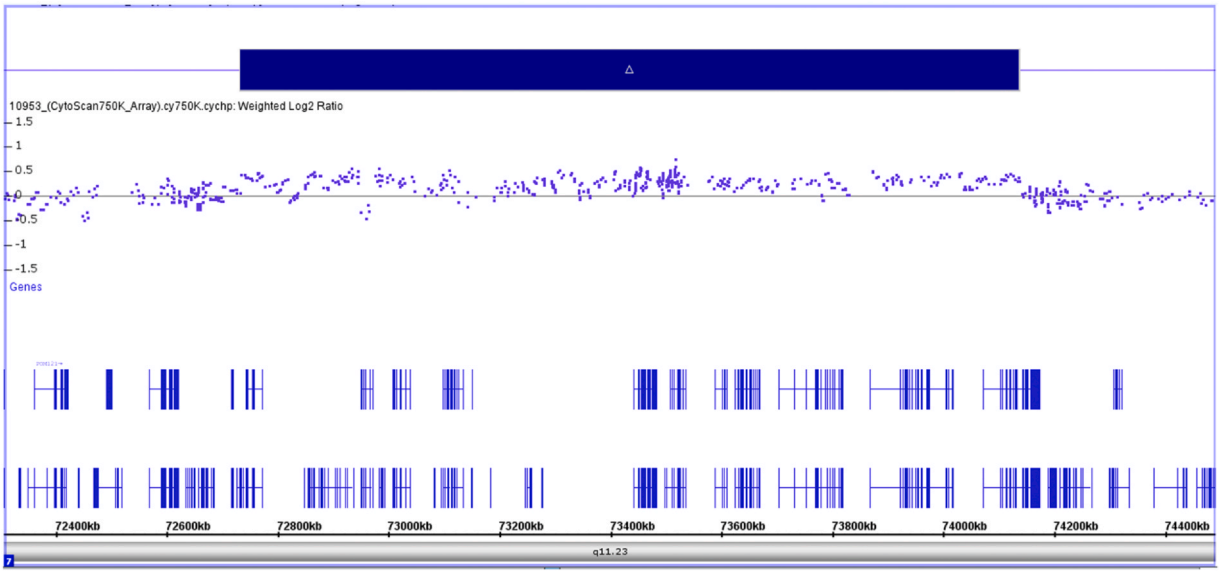

Fig. 2. Chromosome microarray profile showing a gain of 1.4 Mb in chromosome 7 of the proband. CMA shows duplication of 7q11.23 arr[hg19] 7q11.23(72,732,834 – 74,136,633)x3 indicated by the blue rectangle. The image was generated using the ChAS (Chromosome Analysis Suite).

Discussion

MRKHS is considered one of the most frequent causes of primary amenorrhea. The patient described here began her medical evaluation for MRKHS due to primary amenorrhea and developed secondary sexual characteristics. Cytogenetics analysis and imaging exams played a role in confirming the MRKHS diagnosis in our patient. Karyotype, which is considered important for differential diagnosis, confirmed normal female karyotype (46, XX) helping to distinguish MRKHS from other conditions such as Complete Androgen Insensivity Syndrome (46, XY).

Deletions and duplications have been reported in cases of MRKHS [7,12]. Although the identification of these chromosomal imbalances has contributed to the selection of candidate genes in this field, they are found only in a small proportion of women with MRKHS [13,14].

We identified in our patient a 1.4 Mb duplication at 7q11.23, a recurrent chromosome segment involved in a microduplication syndrome described by Somerville in 2005 [15]. The reciprocal deletion of this region is known to cause Williams syndrome (WS), a contiguous gene syndrome that encompasses between 26 and 28 genes, with a 1.5 Mb deletion size [16].

The 7q11.23 microduplication syndrome is characterized by developmental delay, intellectual disability, kidney and cardiovascular anomalies, neurological abnormalities, and macrocephaly. Those affected may also exhibit autistic behavior, aggression, anxiety, and a predisposition to developing schizophrenia [17,18].

The facial phenotype includes straight eyebrows, a broad forehead, a short philtrum, a thin upper lip, a wide nose and high implantation, and ear anomalies [19]. Our patient has a typical duplication size and facial dysmorphisms including macrocephaly, a wide nose, and ear anomalies. However, she does not present cardiovascular, renal, or intellectual impairment. In addition, the duplication was inherited from her mother who, despite not having uterovaginal alterations that were observed in our patient, shares similar physical characteristics with her.

In addition to dysmorphic features, the patient has uterine horns, a short vaginal canal, functional ovaries, scoliosis, and osteophytosis, receiving the diagnosis of MRKHS. Morris et al., described two patients with classic 1.5 Mb microduplication of 7q11.23 with phenotypic features including müllerian malformations [20]. The first patient was a female fetus at 40 weeks of gestation that also had a 10 kb deletion of Xq28 and presented malformations including unilateral renal agenesis, müllerian agenesis, and the presence of 11 ribs. The second case was a female fetus at 39 weeks of gestation with ventriculomegaly, left renal agenesis, and uterus didelphys.

Moreover, the joint analysis of other cases with 7q11.23 microduplication showed that renal alterations were found in 18 % of the evaluated patients. The authors suggest that women with renal malformation, or agenesis, should have the müllerian structures evaluated [20].

In 2014, Zarate et al., reported their study patients with 7q11.23 duplication of varying sizes [21]. One of these cases was a 5-year-old male patient with a 1.8 Mb duplication who presented, among other malformations, genitourinary alterations such as ipsilateral cryptorchidism with absent left gonad and unilateral renal agenesis. The mother of this patient has a 212 kb duplication and presented alterations such as unilateral left renal agenesis, left ovarian agenesis, and left fallopian tube agenesis. The authors suggests that the male patient inherited a 212 kb duplication from his mother in addition to having a de novo 1.8 Mb duplication.

The most interesting aspect of our case is the identification of a woman with MRKHS and 7q duplication, which, to our knowledge, has not been previously reported in literature. This finding will broaden the phenotypic spectrum for 7q11.23 syndrome and contribute to new insights into the genetic variability of MRKHS. In addition, it highlights the importance of genetic testing to identify alterations that standard karyotyping may overlook. Certain limitations of our study should be acknowledged, such as the difficulty in accessing family members. The lack of a detailed family history and pedigree limits our understanding of the segregation patterns associated with this alteration.

However, the microduplication was maternally transmitted, supporting the hypothesis of incomplete penetrance. Additionally, this could represent a case of variable expressivity, as it is possible that the patient's mother has milder müllerian malformations, but these could not be confirmed because she was unavailable for imaging assessments in this study. Our results suggest that uterovaginal aplasia could be associated with loci responsible for 7q microduplication syndrome and should be considered a candidate region for MRKHS. Uterovaginal aplasia can be an additional feature of the broad spectrum of dup7q phenotype and patients diagnosed with this condition should be assessed for genital malformations. Moreover, the genes potentially associated with müllerian alterations in this region are still to be determined.

Conclusion

In conclusion, our study highlights the importance of genetic investigation in cases of MRKHS. The identification of a woman with MRKHS and a 7q11.23 duplication, suggests a potential association between uterovaginal agenesis and 7q11.23 microduplication syndrome. The possible presence of gynecological malformations in female patients with 7q11.23 microduplication should be investigated.

Ethical approval

Study approval was granted by the Ethics Committee of the University of Brasília (nº 60695716.1.0000.5558). All patients provided informed written consent for the molecular investigation.

Declaration of Competing Interest

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

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