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ORIGINAL RESEARCH

Identification of CASKIN2 as a Novel Candidate Gene for Müllerian Duct Anomalies in Humans

Jing Wang[1,*], Qiong Xing[2,*], Ying Yang[1], Ruiqi Yin[1], Yunxia Cao[2]

[1]Department of Obstetrics and Gynecology, The Second Affiliated Hospital of Anhui Medical University, Hefei, 230601, People's Republic of China; [2]Reproductive Medicine Center, Department of Obstetrics and Gynecology, The First Affiliated Hospital of Anhui Medical University, Hefei, 230088, People's Republic of China

*These authors contributed equally to this work

Correspondence: Yunxia Cao, Reproductive Medicine Center, Department of Obstetrics and Gynecology, The First Affiliated Hospital of Anhui Medical University, No. 218, Jixi Road, Shushan District, Hefei, Anhui, 230088, People's Republic of China, Tel +86 551 62922071, Fax +86 551 62923241, Email yunxia_cao@163.com

Objective: The aim of this study was to explore potential novel genes associated with Müllerian duct anomalies (MDAs) through next-generation sequencing techniques.

Materials and Methods: Whole-exome sequencing (WES) was conducted for 5 unrelated patients of Chinese Han ethnicity diagnosed with congenital absence of the uterus and vagina (CAUV), alongside 10 unaffected women. Genomic data were sourced from a public database. Diagnosis and classification of the anomalies were based on findings from ultrasound imaging, hysterosalpingography, and hysteroscopy. A previously unreported candidate gene, *CASKIN2*, was identified. Subsequently, 120 unrelated patients with MDAs, who sought infertility treatment at the Center for Reproductive Medicine, The First Affiliated Hospital of Anhui Medical University between January 2008 and December 2011, were included for targeted analysis of candidate genes and variants detected through WES.

Results: Two novel heterozygous missense variants in the *CASKIN2* gene (NM_020753: c.969C>A, p.H323Q; c.1228G>A, p.V410M) were identified in two unrelated patients with CAUV through WES. Further direct sequencing of all coding exons of *CASKIN2* in the cohort of 120 patients with MDA revealed three additional missense variants (c.1128G>A, p.V410M; c.2816C>T, p.T939M; c.3377G>A, p.R1126H). No pathogenic variants were detected among individuals in the control group.

Conclusion: The *CASKIN2* gene, which is evolutionarily conserved across multiple species and known to interact with *CASK*, may represent a novel candidate gene associated with MDAs in people of Chinese Han ethnicity. The CASKIN2–CASK signaling axis appears to play an evolutionarily conserved and indispensable role during human Müllerian-duct development.

Keywords: *CASKIN2*, congenital absence of uterus and vagina, infertility, Müllerian duct anomalies, mutation, whole-exome sequencing

Introduction

Müllerian duct anomalies (MDAs) are the most prevalent congenital abnormalities of the female reproductive tract. These anomalies result from abnormal formation, incomplete fusion, or failure of resorption of the Müllerian ducts during embryologic development of the female genital tract.[1] Among the various congenital abnormalities, uterine anomalies such as didelphic, bicornuate, septate, and unicornuate configurations occur most frequently. Additionally, malformations may affect the vagina, cervix, ovaries, or fallopian tubes, either in isolation or in combination.[2] Congenital absence of the uterus and vagina (CAUV), also referred to as Mayer–Rokitansky–Küster–Hauser (MRKH) syndrome, represents the most severe form of MDAs. These anomalies are often associated with renal abnormalities (25%), musculoskeletal malformations (10–12%), and, less frequently, cardiac or auditory defects.[3] Patients with MDAs are typically asymptomatic until adolescence, when primary amenorrhea becomes apparent. Despite the anatomical anomalies, affected individuals usually present with normal secondary sexual characteristics and a typical 46,XX karyotype.

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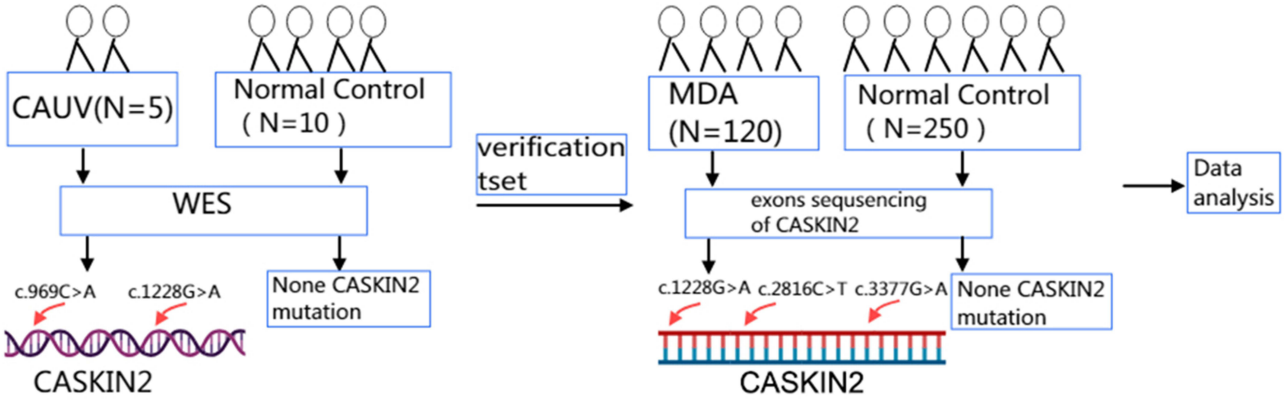
Graphical Abstract



The estimated prevalence of MDAs is approximately 7% in the general female population and may reach 18% among women with recurrent pregnancy loss.[2,4]

MDAs carry significant clinical implications. Patients with these anomalies frequently present with menstrual disorders, infertility, or adverse obstetric outcomes, including miscarriage, preterm labor, and fetal malpresentation.[5,6] The etiology of MDAs is complex and heterogeneous. Contributing factors may include environmental exposures, intrauterine infections, iatrogenic influences, and hormonal imbalances.[7] However, the exact pathogenesis remains unclear, due in part to the condition's complexity and the limited number of comprehensive studies and available patient samples.

Although MDAs are generally sporadic and considered multifactorial in origin, familial clustering observed in some cases indicates a potential genetic basis. Earlier genetic investigations primarily focused on identifying mutations in candidate genes based on phenotypically similar knockout animal models or chromosomal abnormalities. These investigations were followed by validation efforts, typically using Sanger sequencing, in affected and control populations. Identified candidate genes have included members of the homeobox (Hox) gene family, the WNT signaling pathway (*WNT4, WNT5A, WNT7A, WNT9B*), the paired-box gene family (*PAX2, PAX8*), as well as other genes such as *LHX1, EMX2, TP63*, and *TBX6*.[8–12]

Only a few of these candidate genes have yielded positive findings in validation experiments. For instance, mutations in *WNT4* have been implicated in MRKH syndrome, particularly in individuals presenting with elevated androgen levels.[9,13]

WNT9B, which functions upstream of *WNT4*, has been demonstrated to play a role in genitourinary development.[10,14] The Hox gene family comprises conserved embryonic transcription factors responsible for axial patterning during development. Specifically, *HOXA9* is primarily expressed in the fallopian tubes, *HOXA10* in the uterus, *HOXA11* in the lower uterus and endocervix, and *HOXA13* in the ectocervix and upper vagina. Mutations in *HOXA10* have been linked to disrupted female reproductive tract development, and *HOXA13* mutations have been reported in individuals with hand–foot–genital syndrome, which is characterized by urogenital malformations and limb deformities.[15]

Previous approaches have provided only a partial understanding of the genes and pathways involved in female reproductive tract development. Advances in next-generation sequencing (NGS) technologies, including whole-exome sequencing (WES), have enabled more comprehensive and economical identification of rare, potentially causative genetic variants. The present study employed WES to investigate novel candidate genes associated with MDAs.

Materials and Methods

Participants

In the initial phase, data were analyzed from 5 unrelated patients of Chinese Han ethnicity diagnosed with CAUV and from 10 unaffected women. Data were sourced from a public database. Diagnosis and classification of the anomaly were conducted using ultrasound, hysterosalpingography, and hysteroscopy. WES was performed for all five patients and 10 controls.

For extended analysis, a cohort of 120 unrelated patients with MDAs was included. These patients sought infertility treatment at the Center for Reproductive Medicine, The First Affiliated Hospital of Anhui Medical University, between January 2008 and December 2011. The anomalies represented in this cohort included uterine agenesis and hypoplasia, unicornuate uterus, bicornuate uterus, didelphys uterus, and septate uterus. All participants exhibited normal secondary sexual characteristics and had a normal 46,XX karyotype.

The control group consisted of 250 women without MDAs, as confirmed by ultrasonography or hysterosalpingography. These patients had infertility attributed to fallopian tubal obstruction or male factor infertility. Women diagnosed with an arcuate uterus were excluded. All patients in the case group and the normal control group were excluded from other systemic malformations and had a normal 46, XX karyotype.

This research received ethical approval from the Research Ethics Committee of Anhui Medical University, and all experimental procedures adhered to the approved guidelines.

WES

Genomic DNA was extracted from peripheral blood samples using the QIAamp DNA Blood Mini Kit (Qiagen, Germany) following standard protocols. WES was conducted on samples from five patients with CAUV and 10 unaffected controls. Exon capture was carried out using the SureSelect Human All Exon V5 Enrichment Kit, and high-throughput sequencing was performed using the Illumina HiSeq 4000 platform (Illumina, USA). Sequencing reads were aligned to the human reference genome (UCSC Genome Browser, hg19) using the Burrows–Wheeler Aligner (version 0.5.9). Detection of single nucleotide variants and insertions/deletions was performed in accordance with best practices recommended by the Genome Analysis Toolkit (GATK, USA).[16] Variant annotation was completed using ANNOtate VARiants (ANNOVAR). Variants with a minor allele frequency greater than 0.01 were excluded using public databases, including the 1000 Genomes Project (1000G), the NHLBI Exome Sequencing Project 6500 (NHLBI ESP6500), and the Exome Aggregation Consortium (ExAC). The potential functional effects of the variants were evaluated using four in silico prediction tools: PolyPhen2, SIFT, MutationTaster, and SNP&GO.

Variants Validation

Variants identified through WES were validated by Sanger sequencing of the peripheral blood samples in an expanded cohort of 120 unrelated patients with MDAs and unaffected controls. Polymerase chain reaction (PCR) was used to amplify all coding exons and exon–intron boundaries of the *CASKIN2* gene, followed by direct sequencing using an automated sequencer (ABI 3730XL; Applied Biosystems). Primers specific to *CASKIN2* were designed using Primer Premier version 5.0, based on the human *CASKIN2* reference sequence (GenBank accession number: NM_020753). Primer sequence show in Table 1.

Results

1. Two novel heterozygous missense variants in the *CASKIN2* gene (NM_020753)—c.969C>A and c.1228G>A—were identified in two separate CAUV patients. The c.1228G>A variant exhibited a minor allele frequency of 0.002 in the 1000 Genomes Project database. Both variants were absent from the Exome Sequencing Project (ESP6500), the ExAC, the internal sequencing database (comprising data from 98 patients with MDAs), and from all controls. These variants resulted in amino acid substitutions that were located in evolutionarily conserved regions across multiple species, including *Rattus norvegicus, Mus musculus, Homo sapiens*, and *Bos taurus*

Table 1 The Forward and Reverse Primers Used for Sanger Sequencing of CASKIN2

Gene	Sequence (5′-3′)	Length (bp)
B2-F	CTCTGCACTCCACTTCTGGG	660
B2-R	TGCAGATCACAGTGACCCAC	
B3-F	ATAAACAAGCGGGACTGGGG	563
B3-R	CCCCAAAGGAATCTGACCCC	
B4-F	GTATTTGCTGCGAGCTGTGG	838
B4-R	TAGGAAGAGGTTCGGCTCGA	
B5-6 F	ATGATCCACAGTGGGCACAG	666
B5-6 R	CTCCAGCAGTGCCACACATA	
B7-8 F	GAATTTGGCCGACTCAAGGTG	838
B7-8 R	CACCCGATTCTCTCAGCTACC	
B9-10 F	TCCAGCGTGGTTTTTGCATG	809
B9-10 R	TAACAGCACTGCCTTCCCTG	
B11 F	CATCAGAGGCCAGCTCCTTAG	539
B11 R	CACTGCCCACACTATTCCTGT	
B12-14 F	CAGACAGCCCAGGTACATCC	753
B12-14 R	CTTGCCTCTACCCTGCCCTA	
B15-17 F	AGAGCCTCTGTATGGACTGAA	830
B15-17 R	TCTTCTGATGCCCTGAGATGG	
B18 F	CAAGAGAAGACAGTATGGGGCC	1645
B18 R	GCAGAGACAAAAAGGTTGGCTT	
B19-20 F	CTGTGGGAGAGTCACTGCTG	877
B19-20 R	CAGGTTCTAAGGTGGGCTGC	

(Figure 1). Functional impact predictions were conducted using four in silico algorithms—PolyPhen-2, SIFT, MutationTaster, and SNP&GO—all of which indicated damaging effects (Table 2).

2. Additional variants were detected exclusively in the patient group and not in the control group. These included a missense variant c.1228G>A (p.V410M) in exon 8, four instances of c.2816C>T (p.T939M) in exon 18, and one c.3377G>A (p.R1126H) variant in exon 18. All substitutions occurred in highly conserved regions across species (Figure 2). The predicted pathogenicity of these variants, as determined by in silico analyses, is presented in Table 3.

Discussion

The precise etiology and pathogenesis of MDAs remain largely undefined. Previous investigations have predominantly employed candidate gene mutation screening and linkage analysis, with only a limited number of genes identified as being associated with MDAs.

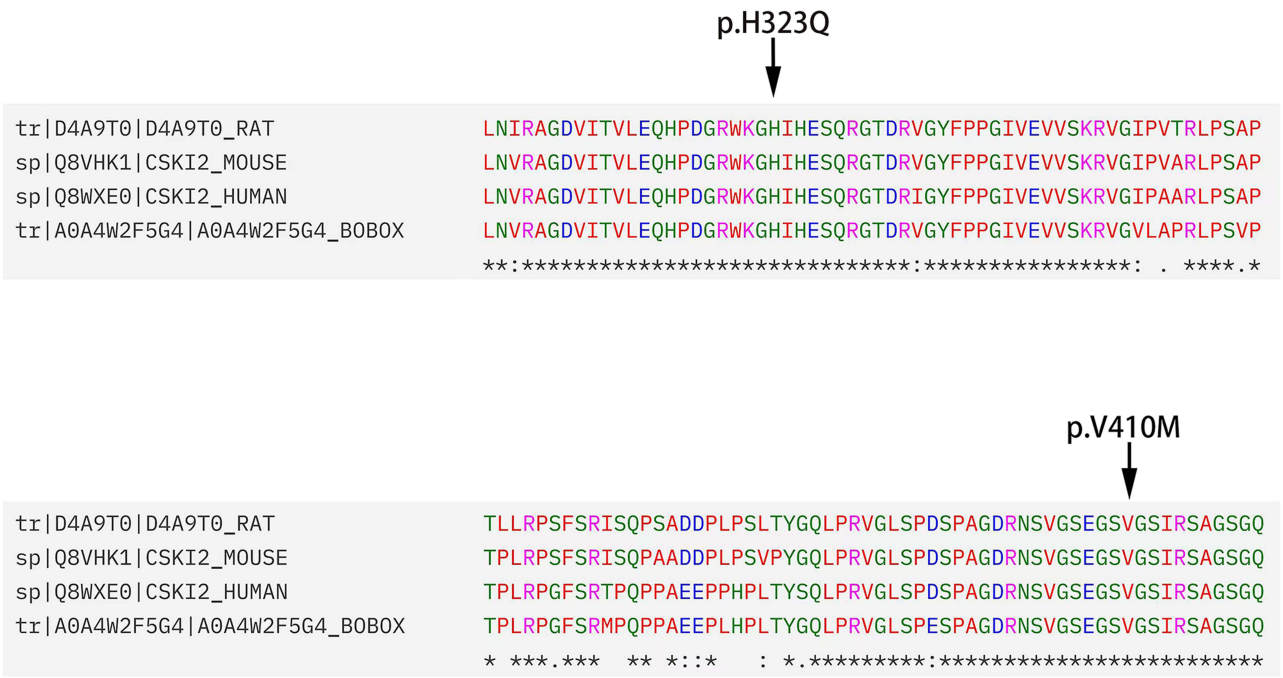


Figure 1 Sequence alignments of CASKIN2 protein among different species. The two novel heterozygous missense variants of CASKIN2 (NM_020753) in two CAUV patients (c.969C>A/p.H323Q, c.1228G>A/p.V410M). The mutations indicated by the arrow are in the conserved region of all the species shown (rat, mouse, human and bobox).

A review of the literature revealed minimal research focused on *CASKIN2*. However, several studies have described the biological functions of *CASK*, a multidomain scaffolding protein belonging to the membrane-associated guanylate kinase (MAGUK) family. *CASK* has been implicated in neural development and gene regulation.[17] In murine models, altered *CASK* expression has been associated with cleft palate phenotypes, indicating a broader role in vertebrate developmental processes.[18] Moreover, *CASK* expression in mammalian epithelial cells has been linked to the establishment of cell polarity.[19]

In *Caenorhabditis elegans*, the *CASK* homolog LIN-2 is essential for the membrane localization of the sole epidermal growth factor receptor (EGFR) ortholog, LET-23 receptor tyrosine kinase. LET-23 responds to the LIN-3/EGF-like ligand and activates the FGF/RAS/MAPK signaling pathway. Consistent with prior findings, early Müllerian duct morphogenesis is regulated by various cytokines, including fibroblast growth factor (FGF) and bone morphogenetic protein (BMP). These cytokines function through complex signaling networks that influence gene expression, cellular development, and disease pathogenesis. Specifically, the FGF/RAS/ERK (extracellular signal-regulated kinase, also known as MAP kinase or MAPK) signaling cascade plays a central role in regulating *Lim1* expression, which is critical

Table 2 Silico Analysis of Two CASKIN2 Mutations in the WES of Five CAUV Patients

Variants	MAF[a]	AA Change	PolyPhen[b]	SIFT[c]	MutationTaster[d]	SNP&GO[e]
c.969C>A	0	H323Q	Probably damaging (0.913)	Tolerate (0.358)	Disease causing (0.999)	Neutral (0.182)
c.1228G>A	0.002	V410M	Benign (0.191)	Tolerate (0.063)	Disease causing (0.664)	Neutral (0.033)

Notes: [a]Minor allele frequency in 1000Genomes. [b]Polyphen2 (http://genetics.bwh.harvard.edu/pph2/). Prediction Scores range from 0 to 1 with high scores indicating probably or possibly damaging. When the HumDiv score is greater than 0.908, it is considered harmful. [c]SIFT, ie, Sorting Intolerant From Tolerant (http://sift.jcvi.org/). Scores vary between 0 and 1. Variants with scores close or equal to 0 are predicted to be deleterious. When the score is less than 0.05, it is considered harmful. [d]Mutation Taster (http://www.mutationtaster.org/). The probability value is the probability of the prediction, ie, a value close to 1 indicates a high "security" of the prediction. When the probability of disease onset is greater than 0.5, it is considered harmful. [e]SNPs&GO (http://snps.biofold.org/snps-and-go/). Reliability Index (RI) has a range from 0 to 10. When the predicted result and reliability index are greater than 5, it is considered harmful.
Abbreviations: WES, Whole-exome sequencing; CAUV, congenital absence of the uterus and vagina.

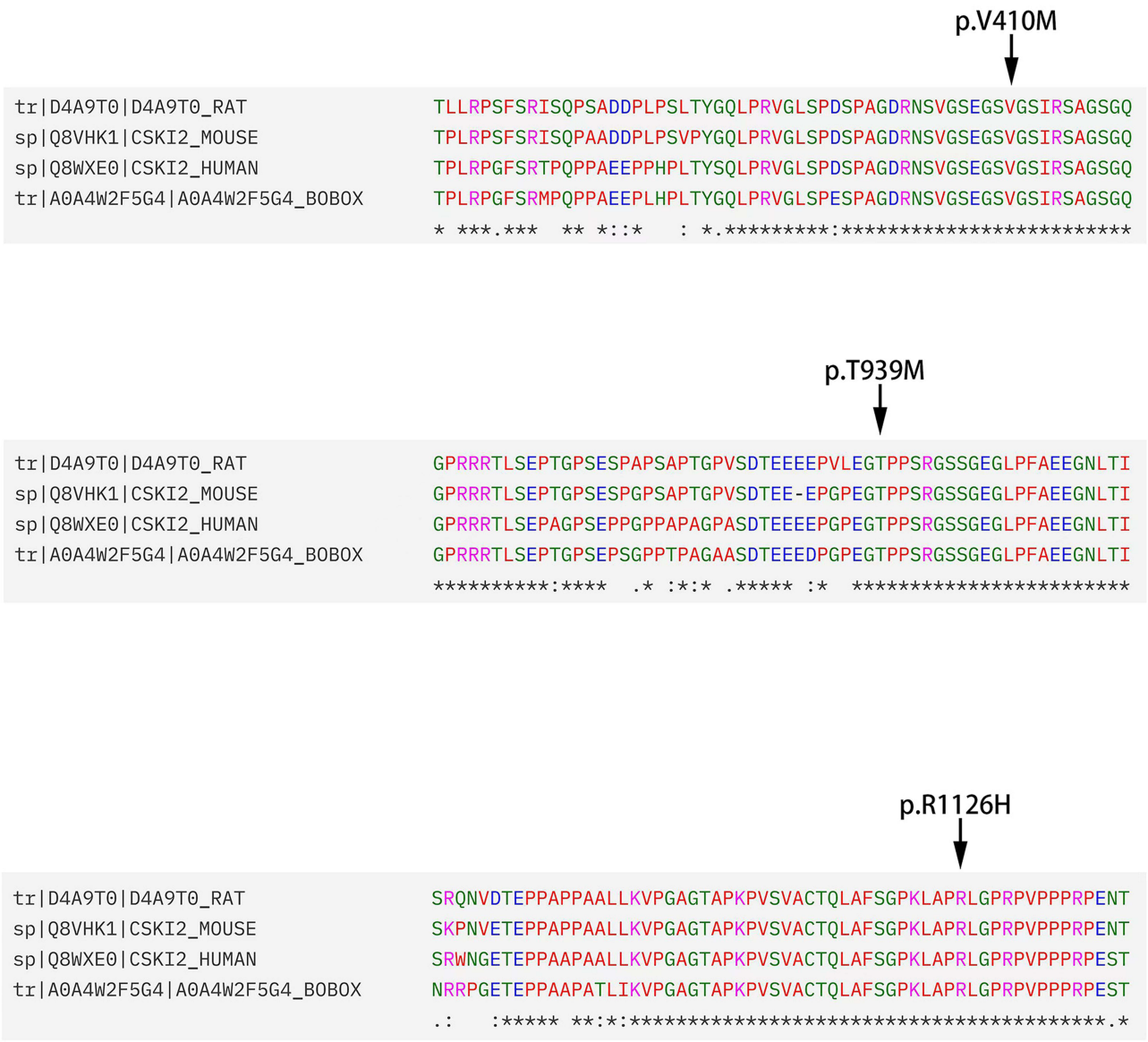


Figure 2 Sequence alignments of CASKIN2 protein among different species. The three novel heterozygous missense variants of CASKIN2 (NM_020753) in 120 unrelated patients with MDAs (c.1228G>A/p.V410M, c.2816C>T/p.T939M, c.3377G>A/p.R1126H). The mutations indicated by the arrow are in the conserved region of all the species shown (rat, mouse, human and bobox).

for Müllerian duct invagination and apical constriction, processes required for epithelial cell induction and vulval development.[20]

During vulval development in *C. elegans*, LIN-2 functions in close coordination with LIN-7 and LIN-10. Mutations in any of these genes produce a comparable vulvaless (Vul) phenotype.[21] The LIN-2/LIN-7/LIN-10 protein complex has been demonstrated to mediate EGFR localization to the basolateral membrane of vulval precursor cells. LIN-2 recruits EGFR substrate protein 8 (EPS-8) into this receptor localization complex, which serves as a novel component regulating LET-23 trafficking and the specification of anchor cell fate. EPS-8 expression has been observed to contribute to a positive feedback loop that sustains activation of the EGFR/RAS/MAPK signaling pathway.[22]

Additional evidence indicates that LIN-7 may also function independently of the complex by directly interacting with EGFR at the plasma membrane. Overexpression of LIN-7 has been demonstrated to partially rescue the vulval phenotype in LIN-2 and LIN-10 mutants.[23] LIN-7 interacts directly with LET-23 EGFR and colocalizes with LET-23 EGFR on

Table 3 Silico Analysis of Three CASKIN2 Mutations in the Validation MDAs Patients

Variants	MAF[a]	AA Change	PolyPhen[b]	SIFT[c]	MutationTaster[d]	SNP&GO[e]
c.1228G>A	0.002	V410M	Benign (0.191)	Tolerate (0.063)	Disease causing (0.664)	Neutral (0.033)
c.2816C>T	0	T939M	Benign (0.266)	Tolerate (0.596)	Polymorphism (0.990)	Neutral (0.049)
c.3377G>A	0	R1126H	Benign (0.008)	Tolerate (0.271)	Disease causing (0.532)	Neutral (0.030)

Notes: [a]Minor allele frequency in 1000Genomes. [b]Polyphen2 (http://genetics.bwh.harvard.edu/pph2/). Prediction Scores range from 0 to 1 with high scores indicating probably or possibly damaging. When the HumDiv score is greater than 0.908, it is considered harmful. [c]SIFT, ie, Sorting Intolerant From Tolerant (http://sift.jcvi.org/). Scores vary between 0 and 1. Variants with scores close or equal to 0 are predicted to be deleterious. When the score is less than 0.05, it is considered harmful. [d]Mutation Taster (http://www.mutationtaster.org/). The probability value is the probability of the prediction, ie, a value close to 1 indicates a high "security" of the prediction. When the probability of disease onset is greater than 0.5, it is considered harmful. [e]SNPs&GO (http://snps.biofold.org/snps-and-go/). Reliability Index (RI) has a range from 0 to 10. When the predicted result and reliability index are greater than 5, it is considered harmful.
Abbreviation: MDA, Müllerian duct anomaly.

basolateral membranes of vulva precursor cells. Furthermore, LIN-7 basolateral localization was not dependent on the LET-23 EGFR PDZ interaction motif. LIN-7 can promote signaling independently without the interaction of LET-23 EGFR. When lacking LIN-2 or LIN-10, LIN-7 can promote the recycling and reuse of a small amount of LET-23 EGFR.

The mammalian homologs of *LIN-7* and *LIN-10* are referred to as Velis/Mals/LIN-7 and Mint1/APBA1, respectively. The CASK/LIN-7/APBA1 complex has been demonstrated to regulate the synaptic localization of the NMDA receptor subunit NR2B and maintain synaptic adhesion in mammalian neurons.[24,25] Mammalian *LIN-7* encodes an adaptor protein that interacts with both β-catenin and cadherin, forming a complex that plays a role in the structural organization of epithelial and neuronal junctions. The presence of β-catenin enhances the localization of LIN-7 at cadherin-mediated junctions. Additionally, in the cytoplasm, LIN-7 binds to β-catenin and contributes to the regulation of cytoplasmic β-catenin, which functions as a coactivator of gene transcription.[26]

The β-catenin is a multifunctional protein and a key signaling molecule in the canonical WNT signaling pathway, which is essential for regulating gene expression. The WNT/β-catenin pathway, in particular, has been demonstrated to be critical for the development of the female reproductive tract.[27] In the absence of WNT signaling, cytoplasmic β-catenin undergoes phosphorylation by a degradation complex composed of axin, adenomatous polyposis coli, casein kinase I, and glycogen synthase kinase 3β (GSK3β). This process leads to β-catenin ubiquitylation and subsequent degradation via the proteasome. Upon activation of WNT signaling, the degradation complex is disrupted, enabling β-catenin to translocate into the nucleus, where it regulates the transcription of target genes.[28] Based on these molecular interactions, a potential link between the CASK (LIN-2)/LIN-7 (LIN-7)/APBA1 (LIN-10) complex and the WNT/β-catenin signaling pathway is hypothesized to contribute to reproductive tract development. However, the precise mechanisms underlying this association are yet to be elucidated.

CASKIN1 and CASKIN2 are known ligands of CASK. CASKIN1 expression has been reported to be restricted to the brain in vertebrates, whereas CASKIN2 is broadly expressed across various adult tissues.[29] Previous investigations primarily examined the role of CASKIN2 in neuronal cells, with limited evidence regarding its localization, interaction partners, and biological functions in non-neuronal contexts. Recent findings indicated that CASKIN2 functions as a scaffold protein that promotes cell migration by interacting with talin- and Abi1-binding proteins.[30] In endothelial cells, CASKIN2 has been identified as a novel regulatory factor, and its downregulation has been linked to endothelial cell activation.[31] Given its function as a CASK ligand, CASKIN2 may be involved in the CASK/Velis/Mint1 complex, potentially contributing to Müllerian duct development. However, functional experiments were not performed in the present study to elucidate the specific mechanism of action of CASKIN2. Further research is necessary to investigate its molecular interactions and clarify its role in reproductive tract development, for this purpose, we have created a schematic diagram to show the relevant signaling pathways and possible mechanisms of action (Figure 3). In the present study, whole-exome sequencing revealed two rare functional missense mutations in the *CASKIN2* gene among patients diagnosed with CAUV. Subsequent mutation screening in a broader cohort of patients with sporadic MDAs identified additional rare missense mutations in the same gene. This represents the first investigation of *CASKIN2* mutations in the context of human MDAs. These findings support the possibility that *CASKIN2* may regulate epithelial

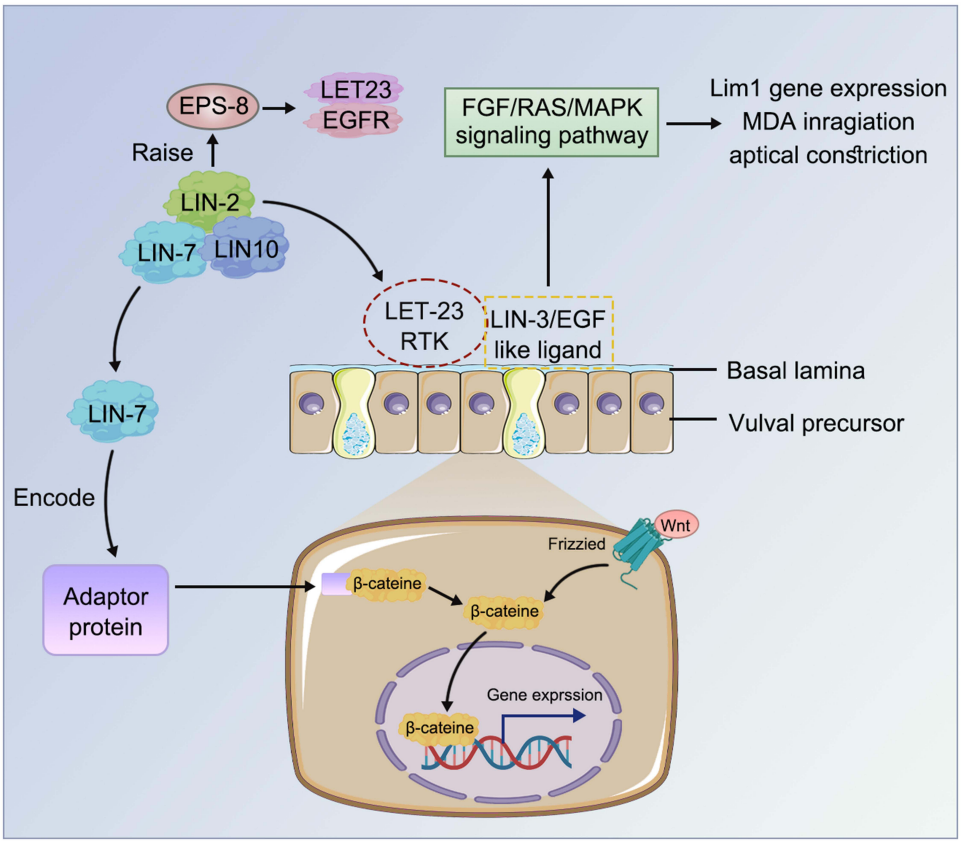


Figure 3 In Caenorhabditis elegans, LIN-2, LIN-7 and LIN-10 interact to regulate the membrane localization of LET-23 receptor tyrosine kinase on the basement membrane, thereby inducing the FGF/RAS/MAPK signaling pathway and regulating the expression of downstream genes.
Abbreviation: MDA, Müllerian duct anomaly.

cell function and gene expression through interaction with other proteins involved in key developmental signaling cascades, such as the WNT/β-catenin pathway. However, one limitation of the present study is that all enrolled cases were sporadic. Müllerian-duct anomalies—especially the severe CAUV/MRKH phenotype—almost invariably present as isolated cases in the general population, most likely owing to de-novo mutation or incomplete penetrance. Although our case–control design revealed a significant association, validation of CASKIN2 in multiplex families or direct demonstration of pathogenicity through functional assays will be required to consolidate our conclusions.

Conclusions

CASKIN2 is evolutionarily conserved across species. Whole-exome sequencing of five patients with congenital absence of the uterus and vagina identified CASKIN2 as a differentially expressed candidate; subsequent large-scale targeted sequencing detected CASKIN2 variants exclusively in affected individuals, implicating the gene as a potential causative factor. Cross-species interrogation further revealed that the CASK ligand—its Caenorhabditis elegans ortholog LIN-2—governs reproductive-tract development in worms, prompting the hypothesis that the CASKIN2–CASK axis performs an ancient and central role in reproductive-tract morphogenesis from lower to higher organisms. This study provides the first investigation of CASKIN2 in human Müllerian-duct anomalies and, through comparative biology, offers mechanistic insight that will guide future in vitro and in vivo functional analyses and downstream pathway discovery.

Abbreviations

CAUV, Congenital absence of uterus and vagina; MDAs, Müllerian duct anomalies; MRKH, Mayer–Rokitansky–Küster–Hauser; WES, Whole-exome sequencing; NGS, next-generation sequencing.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

The investigation was sanctioned by the the Research Ethics Committee of Anhui Medical University (Approval No. PJ 2015-04-08). This study was conducted in accordance with the declaration of Helsinki. Written informed consent was obtained from all patients.

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Disclosure

The authors declare that they have no competing interests.

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