Congenital Bilateral Absence of the Vas Deferens (CBAVD): A Comprehensive Disease Characterization

Disease: Congenital Bilateral Absence of the Vas Deferens (CBAVD) **Identifiers:** OMIM 277180 · ORPHA:48 · MONDO:0009299 · ICD-10 Q55.4 · ICD-11 LB77.0 · MeSH (vas deferens/abnormalities) **Category:** Reproductive System Disorder (congenital male genital malformation)

Summary

Congenital bilateral absence of the vas deferens (CBAVD) is a congenital malformation of the male reproductive ductal system in which both vasa deferentia fail to develop or degenerate before birth, producing **obstructive azoospermia with preserved spermatogenesis**. It accounts for **1–2% of male infertility** and is estimated to affect **~0.1% of all men** (likely an underestimate, since asymptomatic men are rarely evaluated). CBAVD is best understood as the **genital-limited end of the cystic fibrosis (CF) / CFTR-related disorder spectrum**: over 95% of men with classic CF are infertile because of vasal atresia, and isolated CBAVD is most commonly caused by biallelic *CFTR* variants — typically a severe CF-causing allele combined with a mild/variable allele such as the intron-8/9 poly-T (IVS8-5T / TG-T tract) or p.Arg117His.

Genetically, CBAVD is heterogeneous but *CFTR*-dominant. In stringently phenotyped cohorts, *CFTR* variants explain roughly **70–80%** of cases; the X-linked adhesion G-protein-coupled receptor gene **ADGRG2** accounts for **~2%** of cases (a familial X-linked form), and **10–20%** remain genetically unexplained. Importantly, a distinct subset of unexplained CBAVD coexists with **unilateral renal agenesis / solitary kidney**, pointing to an early **mesonephric (Wolffian) duct developmental defect** — mechanistically separate from the progressive fetal duct degeneration seen with *CFTR*/*ADGRG2* variants. Candidate developmental genes (FREM1, WNT2B, TBX6) have recently emerged in this renal-anomaly subgroup.

Clinically, CBAVD is non-life-threatening with a normal life expectancy; its principal consequence is infertility. Because spermatogenesis is intact, **biological paternity is achievable in ~85% of men** via surgical sperm retrieval (MESA/PESA/TESE) combined with intracytoplasmic sperm injection (ICSI). Management is anchored by *CFTR*/*ADGRG2* genetic testing, **partner carrier screening**, and genetic counseling, since ~10% of couples share pathogenic *CFTR* variants and risk a child with CF. A landmark 2025/2026 observation shows that **prenatal CFTR-modulator therapy (elexacaftor/tezacaftor/ivacaftor, ETI) can prevent CBAVD**, defining a fetal critical window; postnatal modulator therapy does **not** reverse established vasal agenesis. CFTR-knockout rats are the animal model that best recapitulates the human bilateral vasal absence phenotype.

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1. Disease Information

CBAVD is a **congenital malformation of the male reproductive tract** characterized by the bilateral absence (aplasia) or atresia of the vasa deferentia — the paired muscular ducts that transport spermatozoa from the epididymis to the ejaculatory ducts. The result is a mechanical (obstructive) block to sperm transport, giving **obstructive azoospermia** despite normal testicular sperm production. It is frequently accompanied by anomalies of adjacent Wolffian-duct derivatives (seminal vesicles, distal epididymis, ejaculatory ducts).

Key identifiers

Resource	Identifier
OMIM	277180 (CBAVD)
Orphanet	ORPHA:48
MONDO	MONDO:0009299
ICD-10	Q55.4 (congenital absence/aplasia/hypoplasia of vas deferens)
ICD-11	LB77.0
MeSH	Vas Deferens / abnormalities

Synonyms / alternative names: CBAVD; congenital bilateral aplasia of the vas deferens; congenital absence of the vas deferens (CAVD, when unspecified laterality); bilateral vasal agenesis; part of the "congenital absence of the vas deferens" (CAVD) family that also includes **congenital unilateral absence of the vas deferens (CUAVD)**.

Data source type: The evidence base is derived from **aggregated disease-level resources** (OMIM, Orphanet, cohort studies, meta-analyses) supplemented by **individual patient reports** (case reports of ADGRG2 pedigrees, MRI series, prenatal ETI case). It is a well-curated Mendelian/complex reproductive disorder rather than an EHR-derived entity.

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2. Etiology

Causal factors — predominantly genetic

CBAVD is overwhelmingly a **genetic** disorder, principally a genital manifestation of *CFTR* dysfunction.

- **CFTR (autosomal recessive, predominant).** The majority of CBAVD men carry at least one CF-causing *CFTR* variant. *"The majority of subjects with CAVD carry at least one cystic fibrosis-causing mutation that warrants CFTR testing"* PMID: 32025909. In a large Chinese isolated-CAVD (iCAVD) cohort (n=199), *"CFTR and ADGRG2 variants were identified in 74.87% of iCAVD patients, with CFTR being the predominant pathogenic gene"* PMID: 42199298.
- **ADGRG2 (X-linked recessive, ~2%).** *"Approximately 2% of the cases of CAVD are hemizygous for a loss-of-function mutation in the ADGRG2 gene that may cause a familial form of X-linked infertility"* PMID: 32025909.
- **Developmental / Wolffian-duct defect (subset with renal agenesis).** *CFTR*-negative cases frequently coexist with a solitary kidney, indicating an early organogenesis disorder (see Section 5 and Section 6).
- **Unexplained (10–20%).** A residual fraction lacks an identified molecular cause.

Risk factors

- **Genetic risk factors:** biallelic *CFTR* variants (a severe allele such as p.Phe508del combined with a mild/variable allele — e.g., IVS8-5T poly-T with long TG tract, or p.Arg117His-T7); hemizygous truncating *ADGRG2* variants; candidate developmental variants (FREM1,

WNT2B, TBX6) in the renal-anomaly subtype. The **IVS9-5T (poly-T 5T)** allele is a major low-penetrance risk allele, especially in East Asian populations.

- **Environmental risk factors:** No established toxic, occupational, infectious, or lifestyle exposure causes CBAVD. It is a developmental/genetic disorder; **sex is male-only** (defining), and **family history** of CF or CBAVD is relevant.

Protective factors

- **Genetic:** By definition, the wild-type / functional *CFTR* and *ADGRG2* alleles are "protective"; the poly-T **7T/9T** tracts confer normal splicing/function versus the risk-associated 5T.
- **Environmental / therapeutic: Prenatal CFTR-modulator therapy (ETI) prevents CBAVD** in genetically susceptible fetuses (Section 6, Finding F006) — an intervention that restores CFTR channel function during the fetal critical window.

Gene–environment interactions

The clearest gene–environment interaction is **pharmacologic restoration of CFTR function in utero**. The poly-T/TG polymorphic tract is itself a *cis*-genetic modifier of splicing that determines residual CFTR activity and hence penetrance of the genital phenotype (the TG12-T5 combination reduces CFTR function; PMID: 42572672). No classical toxin-by-gene interaction has been documented.

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3. Phenotypes

CBAVD presents in otherwise healthy, normally virilized men, typically discovered during **infertility evaluation** (adult-onset presentation of a congenital anatomic defect).

Phenotype	Type	Onset / severity / frequency	Suggested HPO
Non-palpable / absent bilateral vas deferens	Physical/ clinical sign	Congenital; bilateral; ~100% (defining)	HP:0000798 (Abnormality of the vas deferens); "Aplasia of the vas deferens"
Obstructive azoospermia	Laboratory abnormality	Congenital anatomic cause, detected in adulthood; severe; ~100%	HP:0000027 (Azoospermia)
Low ejaculate volume	Laboratory/ clinical	Congenital; frequent	HP:0012869 (Decreased ejaculate volume)
Low semen pH (acidic)	Laboratory	Frequent	Abnormal seminal pH
Low/absent seminal fructose	Laboratory	Frequent (reflects seminal-vesicle involvement)	—
Seminal vesicle agenesis/ hypoplasia	Physical/ imaging	Variable — bilateral agenesis, unilateral agenesis, or present	HP:0011878 (Abnormality of the seminal vesicle)
Epididymal partial absence	Physical/ imaging	Variable; genotype-correlated	HP:0000029 (Abnormality of the epididymis)
Male infertility	Clinical outcome	Adult; severe; ~100%	HP:0003251 (Male infertility)
Unilateral renal agenesis (subset)	Physical/ imaging	Congenital; in developmental subtype	HP:0000122 (Unilateral renal agenesis)

Supporting evidence. *"The incidence of congenital bilateral absence of the vas deferens (CBAVD) in infertile men is 1-2%"* PMID: 35109852. Seminal-vesicle involvement is variable: among 47 CBAVD patients, *"29 had bilateral agenesis of the seminal vesicles, 9 had unilateral agenesis, and 9 had bilateral presence"* PMID: 40533736. Epididymal involvement tracks with *CFTR* genotype: *"patients carrying at least one non-5 T variant were associated with an 8.17-fold increased risk of epididymal partial absence compared to those having the homozygous 5 T mutation"* PMID: 39592508.

Quality-of-life impact. The dominant impact is **infertility** and its psychosocial burden; there is no pain, disability, or systemic morbidity in isolated CBAVD. Because sperm retrieval + ICSI achieves paternity in most couples, the long-term QoL impact is limited relative to systemic diseases. Men should also be counseled about the possibility of an underlying **CFTR-related disorder** (e.g., pancreatitis, sinopulmonary disease) that may manifest later.

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4. Genetic / Molecular Information

Causal genes

- **CFTR** (HGNC:1884; OMIM 602421; chr7q31.2) — cystic fibrosis transmembrane conductance regulator; a cAMP-activated Cl^-/HCO_3^- channel. **Predominant cause of CBAVD.**
- **ADGRG2** (HGNC:18023; OMIM 300572; chrXp22.13) — adhesion GPCR G2 (GPR64), epididymal- and efferent-duct-specific. **X-linked cause (~2%).**
- **Candidate developmental genes:** FREM1, WNT2B, TBX6 in *CFTR*-negative CBAVD with renal anomalies PMID: 40921938.

Pathogenic variants — CFTR

Isolated CBAVD is typically caused by a **trans-heterozygous combination** of one severe CF-causing allele plus one mild/variable allele:

- **p.Phe508del (F508del)** — the classic severe deletion; predominant in Europeans.
- **Poly-T / TG tract (IVS8-5T; c.1210-34TG(n)T(m))** — the **T5** allele with a long TG repeat reduces exon-9 inclusion and lowers functional CFTR. *"the combination of T5 with longer TG repeats is associated with reduced CFTR function"* — as in a compound heterozygote p.Phe508del + TG12T5 PMID: 42572672.
- **p.Arg117His** — associated with CBAVD and other CFTR-related disorders; a French cohort (n=179) found *"83 isolated CBAVD, 67 other CFTR-related phenotypes"* with an overall mild phenotype PMID: 23378603.
- **IVS9-5T** — the most common allele in Chinese CBAVD (~54.5%), with regional variants such as p.Gln1352His (c.4056G>C).

Variant classification follows ACMG/AMP tiers (pathogenic / likely pathogenic / VUS). **Variant types** include missense (p.Arg117His), in-frame deletion (p.Phe508del), splice-modulating poly-T/TG tracts, nonsense, frameshift, and deep-intronic/large rearrangements — hence the

recommendation for **whole-exon + flanking + rearrangement** *CFTR* screening in CAVD PMID: 40065563. **Origin is germline. Functional consequence** is **loss of function** (reduced Cl^-/HCO_3^- conductance).

Pathogenic variants — ADGRG2

Hemizygous **protein-truncating** variants: *"c.1545dupT (p.Glu516Ter), c.2845delT (p.Cys949AlafsTer81), and c.2002_2006delinsAGA (p.Leu668ArgfsTer21)"* PMID: 27476656; additional c.G118T (p.Glu40*) and the nonsense c.908C>G (p.Ser303*) PMID: 37273165. These are **loss-of-function**, X-linked, maternally inherited, and typically **absent from population databases**. Western blot confirms a **truncated ADGRG2 protein** [PMID: 37273165].

Modifier genes / epigenetics / chromosomal abnormalities

- **Modifiers:** the **poly-T/TG tract** functions as the principal *cis*-modifier of CFTR splicing and penetrance. **SLC9A3** interacts functionally with CFTR (Sections 6/7).
- **Epigenetics:** No disease-specific DNA-methylation or histone signature has been established for CBAVD.
- **Chromosomal abnormalities:** Not a primary cause. A single case report describes a 47,XYY mosaic karyotype coexisting with CBAVD PMID: 35109852; this appears coincidental rather than causal.

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5. Environmental Information

- **Environmental factors / toxins / radiation / occupational exposure:** None established as causal. CBAVD is a developmental-genetic disorder.
- **Lifestyle factors (smoking, diet, alcohol, exercise):** No demonstrated role in causation.
- **Infectious agents:** Not applicable — CBAVD is congenital and non-infectious. (Acquired vasal obstruction from infection or vasectomy is a *separate* differential diagnosis, not CBAVD.)

The only "environmental" (i.e., non-germline) modifier with proven effect is **pharmacologic** — prenatal CFTR modulator exposure (protective; Section 6).

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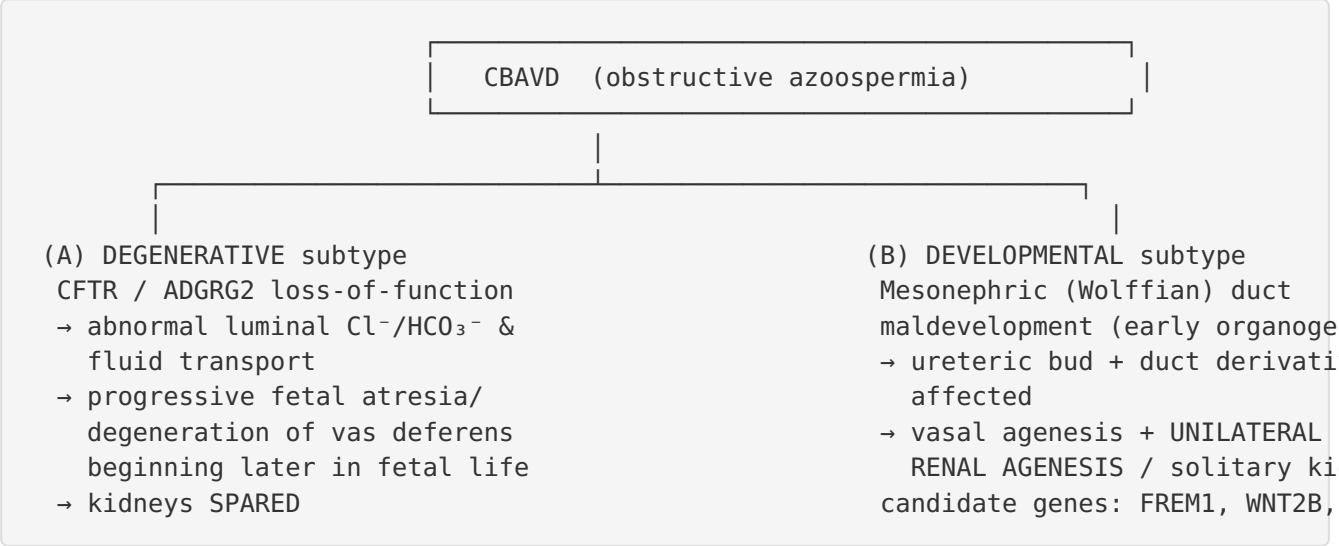
6. Mechanism / Pathophysiology

Two etiologic subtypes (bimodal pathogenesis)

CBAVD arises through **two mechanistically distinct routes**, a key organizing insight of this investigation (Finding F005):



Evidence for the split: *"An important proportion of these unexplained CAVDs coexist with a solitary kidney suggesting an early organogenesis disorder (Wolffian duct), unlike CAVDs related to CFTR or ADGRG2 mutations, which might be the result of progressive degeneration that begins later in fetal life"* PMID: 32025909. The shared embryology of the developmental subtype: *"The embryonic insult that results in unilateral renal agenesis may involve not only the ureteral bud but also other mesonephric duct derivatives, including the seminal vesicles, vas deferens, and epididymis"* PMID: 16985610. MRI data support **acquired/progressive** vasal agenesis in the CFTR-type: *"Preliminary findings in this study are consistent with the theory of acquired vasal agenesis in CBAVD"* PMID: 41255074.

Molecular pathways and protein dysfunction

- **CFTR pathway (degenerative subtype).** CFTR is a **cAMP-activated Cl^- and HCO_3^- channel** governing the luminal microenvironment of the male tract. Loss of function disturbs anion/fluid secretion and the **HCO_3^-/soluble adenylyl cyclase/cAMP/CREB** and **NF-κB/COX-2/PGE_2** signaling axes relevant to tract development and sperm function: *"CFTR is emerging as a versatile player with roles in mediating different signaling pathways... in addition to its long-recognized role in electrolyte and fluid transport that regulates the luminal*

microenvironment of the male reproductive tract" PMID: 22709980. Abnormal luminal fluid handling is thought to drive the **progressive atresia** of the vas: *"cystic fibrosis (CF) leads to infertility in over 95% of cases, due to early and progressive atresia of the vas deferens, resulting in obstructive azoospermia"* PMID: 42380629.

- **ADGRG2 pathway (X-linked subtype).** ADGRG2 is an **adhesion GPCR** expressed apically in **non-ciliated efferent-duct epithelium**: *"ADGRG2 expression was restricted to the apical membranes of non-ciliated epithelia in human efferent ducts"* PMID: 32314195. Loss of function causes **obstructive infertility** by disrupting efferent-duct fluid reabsorption (recapitulated in Adgrg2-knockout mice: *"Adgrg2-knockout male mice develop obstructive infertility"* PMID: 27476656).
- **SLC9A3 (NHE3) interaction.** SLC9A3 loss reduces CFTR protein and causes obstruction: *"depleted Slc9a3 in male mice causes infertility due to the abnormal dilated lumen of the rete testis and efferent ductules"* PMID: 28384194 — implicating a shared ion-transport/CFTR-stability module.

Cellular processes, cell types, and compartments

- **Cell types (CL):** ductal epithelial cells of the vas deferens/epididymis; **non-ciliated efferent-duct epithelial cells** (ADGRG2^{+}); seminal-vesicle epithelium.
- **Cellular process:** disrupted transepithelial anion/fluid transport → luminal microenvironment failure → epithelial/duct **degeneration and atresia** (degenerative subtype) or failed duct **morphogenesis** (developmental subtype).
- **Subcellular compartments (GO CC): apical plasma membrane** (GO:0016324) — site of CFTR and ADGRG2 function; anion channel activity.
- **Suggested GO BP:** GO:0006821 (chloride transport), GO:0055085 (transmembrane transport), GO:0048754 (branching morphogenesis of an epithelial tube), GO:0035239 (tube morphogenesis), GO:0007283 (spermatogenesis — preserved).

Critical window — a therapeutic mechanism

The degenerative subtype is **preventable in utero**. In a male CF infant (homozygous F508del) whose carrier mother began ETI at 27+4 weeks: *"ultrasound at 8 weeks demonstrated bilateral vas deferens, a structure typically absent in nearly all male patients with CF at birth"* and *"These findings suggest that prenatal CFTR modulation - even when initiated late"* can preserve the duct PMID: 41654435. Conversely, *"At present male patients taking CFTR modulators have not shown improvement in infertility"* PMID: 39288989 — establishing that restoration must occur **before** the duct is lost.

7. Anatomical Structures Affected

- **Organ level (primary):** vas deferens (UBERON:0001000) — bilateral. **Secondary/ associated:** epididymis (UBERON:0001301), seminal vesicle (UBERON:0000998), ejaculatory duct, efferent ducts (UBERON:0003074). **Kidney (UBERON:0002113)** in the developmental subtype (unilateral renal agenesis).
- **Body system:** male reproductive/genital system (UBERON:0000079); urinary system involvement in the renal-anomaly subtype.
- **Tissue / cell level:** ductal **epithelium** (transporting epithelium) and surrounding smooth muscle of the vas; **non-ciliated efferent-duct epithelial cells** (ADGRG2^{+}). Testicular seminiferous tissue is **preserved** (spermatogenesis intact).
- **Subcellular:** apical plasma membrane (GO:0016324); anion channel machinery.
- **Localization / lateralization: bilateral** by definition (CBAVD); the CAVD family also includes **unilateral (CUAVD)** and asymmetric presentations. Seminal-vesicle and epididymal involvement is frequently **asymmetric** PMID: 40533736.

8. Temporal Development

- **Onset: Congenital** — the anatomic defect is present at (or develops before) birth. In the degenerative CFTR subtype, atresia is *"early and progressive"* during fetal life [PMID: 42380629]; the developmental subtype originates at early organogenesis. Clinically, however, the disorder is usually **detected in adulthood** during infertility work-up (insidious, asymptomatic until then).
- **Progression:** The **structural defect is fixed/non-progressive after birth** (the vas is already absent). There are no post-natal "stages." Disease course is **stable and lifelong**; the associated infertility is chronic unless overcome by ART.
- **Patterns / critical periods:** The single actionable **critical period is fetal** — CFTR function must be preserved during gestation to prevent vasal loss (prenatal ETI, [PMID: 41654435]). No spontaneous remission occurs.

9. Inheritance and Population

Epidemiology

- **Prevalence:** *"The prevalence of CAVDs in men is reported to be approximately 0.1%"* PMID: 32025909 (likely underestimated).
- **Frequency in male infertility:** CBAVD accounts for **1–2%** of infertile men PMID: 35109852.
- **Incidence:** Not precisely established (congenital, detected at reproductive age).

Inheritance (genetic etiology)

Feature	CFTR-related CBAVD	ADGRG2-related CBAVD
Pattern	Autosomal recessive (biallelic)	X-linked recessive (hemizygous)
Share of cases	~70–80%	~2%
Penetrance	**Incomplete/variable**, modulated by poly-T/TG tract	High but variable
Expressivity	Variable (isolated CBAVD ↔ broader CFTR-RD)	Variable (one carrier had normal fertility)
Reproductive risk	Offspring CF risk if partner carries severe allele	X-linked transmission via carrier mothers

- **Penetrance / expressivity:** Variable and incomplete for the genital phenotype; sweat chloride does **not** correlate with severity in p.Arg117His carriers PMID: 23378603. For ADGRG2, an obligate-carrier male with the p.Ser303 *variant had normal fertility**, illustrating variable expressivity PMID: 37273165.
- **Genetic anticipation / mitochondrial inheritance:** Not applicable.
- **Founder effects / geographic allele spectra: Population-specific**. **p.Phe508del** predominates in Europeans; **IVS9-5T is the most common allele in Chinese CBAVD (~54.5%)** with regional p.Gln1352His. *"There are no obvious hotspot CFTR mutations in Chinese CBAVD patients besides the IVS9-5 T allele"* PMID: 35119551.
- **Consanguinity / carrier frequency:** *CFTR* carrier frequency is high in populations with elevated CF prevalence (up to ~1/25 in Europeans), underpinning the reproductive-risk concern. **~10% of iCAVD couples share pathogenic *CFTR* variants:** *"10.14% of couples carried shared pathogenic or likely pathogenic CFTR variants"* PMID: 42199298.

Population demographics

- **Sex:** male only (defining).
- **Geographic variation of variants:** European vs East Asian allele spectra differ markedly (above).
- **Age distribution:** presents at reproductive age (typically 20s–40s at infertility work-up).

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10. Diagnostics

Clinical tests

- **Physical exam:** bilateral **non-palpable vasa deferentia** — the cornerstone finding.
- **Semen analysis (laboratory): azoospermia**, **low ejaculate volume**, **low (acidic) pH**, **low/absent fructose** (reflecting seminal-vesicle contribution). Normal serum FSH/testosterone and normal testicular volume support an obstructive (not spermatogenic) cause.
- **Imaging:** scrotal ultrasound (confirms absent/atretic vas, evaluates epididymis), **transrectal ultrasound** (seminal vesicles, ejaculatory ducts), and **MRI** for the intra-abdominal vas and seminal-vesicle pathology — *"detailed findings are obtained by MRI even in the evaluation of the intra-abdominal part of the VD"* PMID: 41255074. **Renal ultrasound is mandatory** to detect solitary kidney (developmental subtype).
- **Biopsy/histopathology:** testicular biopsy shows **preserved spermatogenesis** (not routinely needed).

Genetic testing

- **Recommended approach:** Comprehensive **CFTR** analysis first — including **full exon + flanking-region sequencing, the poly-T/TG tract, and large-rearrangement detection** — because standard panels miss deep-intronic and rearrangement alleles: *"the urgent need for extensive CFTR screening, including sequencing of whole exons and flanking regions and detection of large rearrangements and deep intronic CF-causing variants"* PMID: 40065563. If *CFTR* is negative **and renal ultrasound is normal**, test **ADGRG2**: *"Pathogenic variants in ADGRG2 are important to look for when CFTR analysis is negative and renal ultrasonography is normal"* PMID: 41886210.

- **Modalities:** targeted *CFTR* single-gene/panel testing; WES/WGS for unexplained cases and developmental candidate genes (FREM1, WNT2B, TBX6); karyotype only if a broader syndrome is suspected.

Clinical criteria & differential diagnosis

- **Diagnosis** rests on the triad of **non-palpable vasa** + **obstructive azoospermia** + **low-volume acidic fructose-negative semen**, confirmed by imaging and genetics.
- **Differential diagnosis:** other causes of obstructive azoospermia (ejaculatory-duct obstruction, post-infectious or post-vasectomy obstruction, Young syndrome) and non-obstructive azoospermia (distinguished by normal FSH/testicular volume and preserved spermatogenesis in CBAVD).

Screening

- **Partner CFTR carrier screening** is essential before ART (couple co-carrier risk ~10%).
- **Cascade testing** of family members for ADGRG2 pedigrees.

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11. Outcome / Prognosis

- **Survival / mortality: Isolated CBAVD carries no excess mortality; life expectancy is normal.** Prognosis for survival is excellent. (Men should nonetheless be evaluated for a broader CFTR-related disorder that could have its own morbidity.)
- **Morbidity / function:** The sole functional impact is **infertility**; no disability or organ failure in isolated disease.
- **Fertility outcome (the key prognostic domain):** Excellent with ART. Because spermatogenesis is preserved, surgical sperm retrieval + ICSI is highly successful: in a Chinese cohort, *"Spermatozoa were successfully retrieved in 46 patients, and 39 of the patients had their own offspring through ICSI"* (≈85% paternity) PMID: 35119551.
- **Prognostic factors:**
- **Residual CFTR activity** predicts retrieval success — MESA extraction failure was higher in CF than CFTR-RD: *"Extraction failure rates were 18.6% for cystic fibrosis and 3.9% for CFTR-RD (P = 0.01)"*, and worse with no residual activity (27.9% vs 3.7% failure, P<0.001) PMID: 40850271.

- **Sperm motility** predicts ICSI outcome: *"the clinical pregnancy rates, embryo implantation rates, and live birth rates in the high motility group were significantly increased"* PMID: 34313208.
- **Complications:** principally reproductive/ART-related (e.g., risk of transmitting CF to offspring; rare ART complications such as monochorionic/conjoined twinning after embryo transfer, PMID: 42215739).

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12. Treatment

CBAVD has **no medical cure for the anatomic defect**; management is **fertility-focused** plus genetic counseling.

Assisted reproduction (mainstay)

- **Surgical sperm retrieval: MESA** (microsurgical epididymal sperm aspiration), **PESA** (percutaneous epididymal sperm aspiration), **TESE** (testicular sperm extraction). *(NCIT: Sperm Retrieval; Testicular Sperm Extraction.)*
- **ICSI** (intracytoplasmic sperm injection): the definitive route to biological paternity; ~85% success in achieving offspring [PMID: 35119551]. *(NCIT: Intracytoplasmic Sperm Injection.)*
- **Optimization:** select high-motility sperm to maximize live-birth rate [PMID: 34313208].

CFTR modulator therapy — a disease-modifying frontier

- **Prenatal ETI (elexacaftor/tezacaftor/ivacaftor)** can **prevent CBAVD** when administered to the fetus via a carrier mother during gestation PMID: 41654435. This is investigational and raises ethical/consent questions for heterozygous fetuses PMID: 39543810.
- **Postnatal modulators do NOT reverse** established CBAVD/infertility PMID: 39288989.

Pharmacogenomics / personalized medicine

- **Genotype-guided counseling:** *CFTR* genotype informs residual function, retrieval prognosis, CFTR-RD surveillance, and modulator eligibility.
- **Couple-level genotyping** guides **preimplantation genetic testing (PGT)** to avoid transmitting CF.

Not applicable

Gene therapy, cell therapy, RNA therapeutics, immunotherapy, and chemotherapy have **no established role** in CBAVD.

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13. Prevention

- **Primary prevention: Prenatal CFTR-modulator therapy** is the only demonstrated means of preventing the vasal defect itself (investigational) [PMID: 41654435]. Broadly, primary prevention is limited because CBAVD is congenital/genetic.
- **Secondary prevention / early detection:** Genetic diagnosis at infertility work-up enables timely ART and CFTR-RD surveillance.
- **Tertiary prevention:** Optimizing sperm-retrieval/ICSI protocols and PGT to prevent CF offspring.
- **Genetic screening & counseling (central): CFTR carrier screening of both partners** before ART is essential; ~10% of couples are co-carriers [PMID: 42199298]. Options include **preimplantation genetic diagnosis** and prenatal testing. Comprehensive *CFTR* screening (exons + flanking + rearrangements) is recommended before ART [PMID: 40065563].
- **Immunization / public-health / environmental measures:** Not applicable (non-infectious, non-environmental).

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14. Other Species / Natural Disease

- **Taxonomy affected (models):** *Rattus norvegicus* (rat, NCBI:txid10116), *Mus musculus* (mouse, NCBI:txid10090), plus large-animal CF models — ferret, pig, sheep, rabbit.
- **Orthologous genes:** *Cftr* (rat/mouse), *Adgrg2*, *Slc9a3* orthologs.
- **Natural / comparative disease:** CF animal models frequently show **absent vas deferens/ epididymis with normal testicular histology**, mirroring human CBAVD: *"CFTR-knockout rats more closely reproduce the human phenotype, showing bilateral absence of the vas deferens and epididymal hypoplasia, although they exhibit more pronounced hypospermatogenesis than observed in men"* PMID: 42380629. Evolutionary conservation of CFTR-dependent duct development underlies the cross-species recapitulation.

• **Transmission / zoonosis:** Not applicable (genetic malformation).

15. Model Organisms

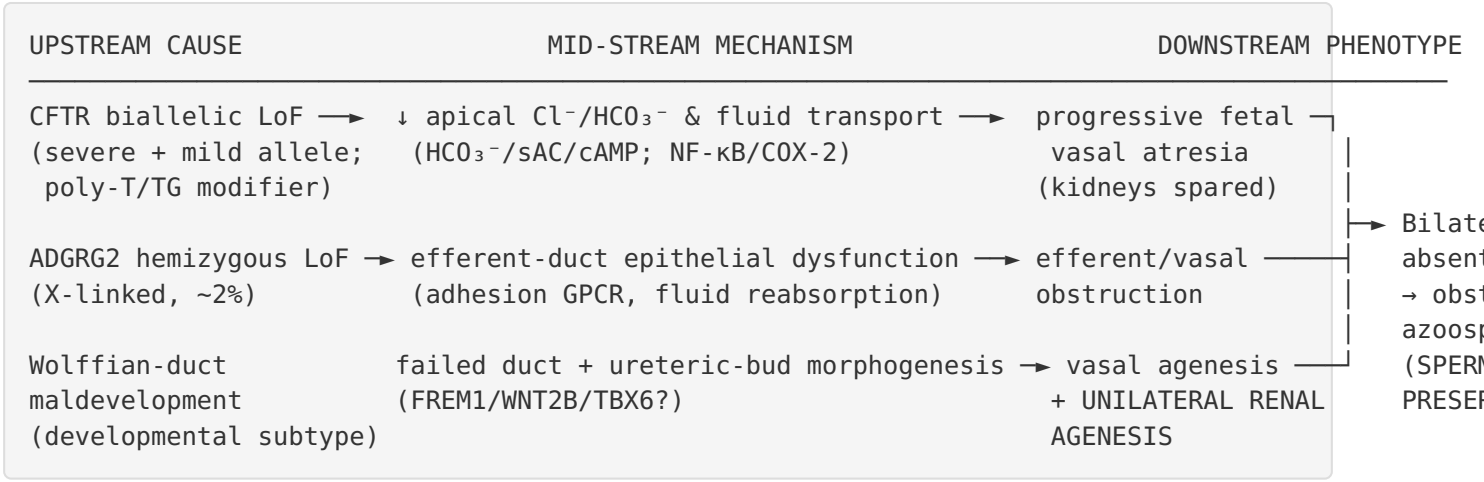
Model	Genetic manipulation	Phenotype recapitulation	Key limitation
CFTR-knockout rat	Complete Cftr KO	**Best model** — bilateral vas absence + epididymal hypoplasia	More severe hypospermatogenesis than men
Mouse — knock-in / partial KO	Hypomorphic	Usually **remain fertile**	Fails to model vasal absence
Mouse — complete Cftr KO	Full KO	May develop **vas atresia with aging**	Age-dependent, heterogeneous
Large animals (ferret, pig, sheep, rabbit)	CF models	Frequently **absent vas/ epididymis, normal testis**	Cost, husbandry
Adgrg2-knockout mouse	Adgrg2 KO	**Obstructive infertility** (efferent-duct model)	Models ADGRG2 subtype only
Slc9a3-knockout mouse	Slc9a3 KO	Obstructive azoospermia; **reduced CFTR** in epididymis/vas	Models NHE3/CFTR interaction

Supporting quotes. *"knock-in or partial knockout models usually remain fertile, whereas complete knockouts may develop vas deferens atresia with aging"* PMID: 42380629. *"Adgrg2-knockout male mice develop obstructive infertility"* PMID: 27476656. *"depleted Slc9a3 in male mice causes infertility due to the abnormal dilated lumen of the rete testis and efferent ductules"* PMID: 28384194.

Applications: these models allow study of CFTR-dependent duct morphogenesis, the fetal critical window for modulator rescue, efferent-duct fluid handling (ADGRG2/SLC9A3), and CFTR-modulator pharmacology. **Databases:** MGI, RGD, IMPC/KOMP, IMSR.

Mechanistic Model / Interpretation

CBAVD is best conceptualized as a **convergent obstructive-azoospermia phenotype reached by two upstream routes**:



Upstream vs downstream: the genetic lesion (CFTR/ADGRG2 LoF or a developmental-gene defect) is upstream; disrupted epithelial ion/fluid transport (or failed morphogenesis) is the mid-stream mechanism; duct atresia/agenesis and consequent obstructive azoospermia are downstream. The **testis is not in the causal chain** — spermatogenesis is preserved, which is precisely why sperm retrieval + ICSI works. The **presence/absence of a solitary kidney** is the single most useful clinical discriminator between the developmental and degenerative subtypes and should redirect genetic testing (renal-anomaly → developmental genes; normal kidneys + CFTR-negative → ADGRG2).

Evidence Base

PMID	Contribution	Supports finding
32025909	Genetics review — CFTR predominance, ADGRG2 ~2%, prevalence 0.1%, developmental/degenerative split	F001, F005, F009
42199298	Large Chinese iCAVD cohort — 74.87% CFTR/ADGRG2; 10.14% couple co-carriers	F001, F009
27476656	Original ADGRG2 truncating variants; Adgrg2-KO mouse	F002, F007
32314195	ADGRG2 efferent-duct localization; novel LoF variant	F002
35109852	CBAVD incidence 1–2%; 47,XYY mosaic case	F003
40533736	Seminal-vesicle status distribution (47 patients)	F003
39592508	Non-5T → 8.17× epididymal partial-absence risk	F003
42380629	CF male reproductive phenotype; CFTR-KO rat best model	F004, F007
23378603	p.Arg117His CBAVD/CFTR-RD spectrum; couples at CF risk	F004
16985610	Mesonephric-duct embryology of renal + vasal agenesis	F005
40921938	FREM1/WNT2B/TBX6 in CFTR-negative CBAVD with renal anomalies	F005
41255074	MRI evidence for acquired/progressive vasal agenesis	F005
41654435	Prenatal ETI prevents CBAVD (case)	F006
39288989	Postnatal modulators do not reverse infertility	F006
28384194	SLC9A3 KO → obstructive azoospermia, ↓CFTR	F007
35119551	ICSI outcomes; Chinese allele spectrum (IVS9-5T)	F008, F009
40850271	Residual CFTR activity predicts MESA success	F008
34313208	Sperm motility predicts ICSI outcome	F008
40065563	Meta-analysis; comprehensive CFTR screening needed	Diagnostics
42572672	TG12T5 splicing variant in CFTR-RD	Section 4
37273165	ADGRG2 p.Ser303*; carrier with normal fertility	Sections 4, 9
41886210	ADGRG2 testing when CFTR-negative + normal kidneys	Diagnostics

PMID	Contribution	Supports finding
22709980	CFTR signaling pathways in male fertility	Section 6
39543810	CFTR modulators & reproductive health; fetal exposure	Sections 12, 13

Consistency: Findings are mutually reinforcing across independent European and East Asian cohorts, case reports, MRI series, and multiple animal models. No major contradictions were identified; the chief tension is the **"progressive degeneration" vs "developmental agenesis"** debate, which the two-subtype model reconciles (degenerative = CFTR/ADGRG2, kidneys spared; developmental = Wolffian-duct defect, renal agenesis).

Limitations and Knowledge Gaps

1. **Unexplained fraction (10–20%).** A substantial minority of CBAVD lacks a molecular diagnosis; developmental genes (FREM1, WNT2B, TBX6) are candidates but not yet validated at scale.
2. **Single-case evidence for prenatal prevention.** The ETI-prevents-CBAVD observation rests on **one infant** [PMID: 41654435]; timing, dosing, the true critical window, and long-term/heterozygote safety are unknown, with unresolved ethical questions.
3. **Penetrance/expressivity poorly quantified.** The poly-T/TG modifier and the normal-fertility ADGRG2 carrier show incomplete penetrance that is not yet predictable at the individual level.
4. **Model limitations.** No model perfectly reproduces isolated human CBAVD; rats over-express hypospermatogenesis, and most mouse models remain fertile.
5. **Epidemiology.** Prevalence (~0.1%) is likely underestimated; incidence and non-European/non-East-Asian allele spectra are under-characterized.
6. **Epigenetics.** No disease-specific epigenetic signature has been defined.
7. **Long-term offspring outcomes** after prenatal modulator exposure are unstudied.

Proposed Follow-up Experiments / Actions

1. **Systematic renal imaging + developmental-gene panel** (FREM1, WNT2B, TBX6, and broader WES/WGS) in all *CFTR*/*ADGRG2*-negative CBAVD to validate the developmental subtype and expand the gene set.
2. **Registry/prospective study of prenatal CFTR-modulator exposure** with structured male genital-tract follow-up (vas patency by ultrasound, later fertility) to define the fetal critical window, efficacy, and safety.
3. **Functional dissection of the ADGRG2–CFTR–SLC9A3 module** in efferent-duct organoids/animal models to map shared fluid-transport mechanisms.
4. **Genotype-stratified sperm-retrieval outcome studies** to formalize residual-CFTR-activity and motility as pre-procedure prognostic tools (building on [PMID: 40850271], [PMID: 34313208]).
5. **Universal comprehensive CFTR screening protocol** (exons + flanking + poly-T/TG + rearrangements + deep-intronic) with mandatory partner carrier screening and PGT counseling before ART.
6. **Population-specific allele catalogues** beyond European/Chinese cohorts to improve carrier-screening panels globally.
7. **Longitudinal CFTR-RD surveillance** of isolated-CBAVD men to quantify later pancreatic/sinopulmonary risk.

Report compiled from a 5-iteration autonomous investigation: 9 confirmed findings, 27 papers reviewed. Evidence types span human clinical cohorts, case reports, imaging series, in vitro studies, and model-organism data.
