African Urology 2024;4:S20-25
https://doi.org/10.36303/AUJ.0152

AFRICAN UROLOGY
ISSN 2710-2750 EISSN 2710-2750

AUJ SPECIAL EDITION

Bladder exstrophy-epispadias-cloacal exstrophy complex: characteristics, aetiologies, and epidemiologic findings

K Fendereski,[1] AJ Schaeffer[1,2]

[1] *Division of Urology, Department of Surgery, University of Utah School of Medicine, United States of America*
[2] *Intermountain Primary Children's Hospital, United States of America*

Corresponding author, email: anthony.schaeffer@hsc.utah.edu

Bladder exstrophy-epispadias-cloacal exstrophy complex (BEEC) is a spectrum of congenital urologic anomalies that involve the bladder, urethra, genitalia, and pelvic musculoskeletal system, and can affect urinary continence, sexual health, and fertility. BEEC includes a wide spectrum of anatomical abnormalities with different levels of severity: epispadias represents the mildest phenotype, classic bladder exstrophy (CBE) is the most common defect, and cloacal exstrophy (CE) – often referred to as omphalocele, exstrophy, imperforate anus, and spinal defects (OEIS) complex – is the most severe form. BEEC disorders cause significant health problems and affect the health-related quality of life (QoL) of affected individuals. There have been significant insights into the aetiology of BEEC in the last decade. Specifically, recent genetic studies have suggested that downstream regulator(s) of *p63, Isl1*, and other genes may play a role in the failure of the lower urinary tract to close.

This narrative review outlines the unique anatomy of bladder exstrophy (BE) and epispadias, with a brief mention of the anatomy found in CE. A literature review using PubMed and Google Scholar databases was used to identify relevant articles on the outlined topics without placing any limitations on publication years or study designs. We included full-text English articles published in peer-reviewed journals related to the terms: "exstrophy" & "epispadias" AND "aetiology", "embryology" and "incidence". We summarise the epidemiology of this rare complex – including what is known about its incidence in Africa – before presenting recent advances in comparative genetics from mouse models and human studies that provide insights into BEEC pathogenesis.

Keywords: exstrophy, epispadias, incidence, prevalence, aetiology

Introduction

Bladder exstrophy-epispadias-cloacal exstrophy complex (BEEC) is a spectrum of congenital urologic anomalies that involve the bladder, urethra, genitalia, and pelvic musculoskeletal system, and can affect urinary continence, sexual health, and fertility.[1,2] Cloacal exstrophy (CE) also affects the gastrointestinal tract and can affect both faecal continence and overall nutrition. Additionally, CE often affects neural tube closure and produces a spina bifida phenotype.[2-4] Besides the technical challenges of the complex surgeries, BEEC also results in physical and psychosocial difficulties, including body image issues, social isolation, and reduced quality of life (QoL).[5,6]

This narrative review outlines the unique anatomy of bladder exstrophy (BE) and epispadias, with a brief mention of the anatomy found in CE. We summarise the epidemiology of this rare complex both in North America and Europe as well as Africa before presenting recent advances in comparative genetics from mouse models and human studies that provide insights into BE and epispadias pathogenesis (Table I).

A literature review using PubMed and Google Scholar databases was used to identify relevant articles on the outlined topics without placing any limitations on publication years or study designs. We included full-text English articles published in peer-reviewed journals related to the terms: "exstrophy" & "epispadias" AND "aetiology", "embryology" and "incidence". Both authors reviewed the articles selected for inclusion and those with findings pertinent to this manuscript's aim were included. Permission was granted for all patient photography contained in this manuscript.

Background and anatomy

The term exstrophy, derived from the Greek word "ekstri-phein" (turn inside out) was first used by Chaussier in 1780.[7] The earliest known historical report is the description found on an Assyrian tablet from approximately 2 000 BC. The first medical description is probably by Aldrovandi in Historia Monstrorum, published in 1646.[7] BEEC includes a wide spectrum of anatomical abnormalities with different levels of severity: epispadias represents the mildest phenotype, BE is the most common defect, and CE – also often referred to as the omphalocele, exstrophy, imperforate anus, and spinal defects (OEIS) complex – is the rarest and most severe form in the spectrum.[8]

Epispadias: the mildest phenotype

Epispadias is characterised by an abnormal opening of the urethra on the dorsal surface of the penis or clitoris and is associated with urinary incontinence, difficulty with voiding, and sexual dysfunction.[2,9] In males, the urethral plate is present (as the urethra failed to tubularize) with this mucosal strip of urethral plate on the penile dorsum that is typically accompanied by dorsal curvature of the penis and/or underdevelopment of the corpora cavernosa.[2,10]

Many classify male epispadias according to the position of the epispadic urethral meatus. This is important as the meatal position helps determine whether the external urethral sphincter is involved in males and thus what the boys' urinary continence outcomes may be. Male epispadias can be classified in order of severity from glanular epispadias (least severe), to penile to penopubic epispadias (most severe). In the latter, the external urethral sphincter

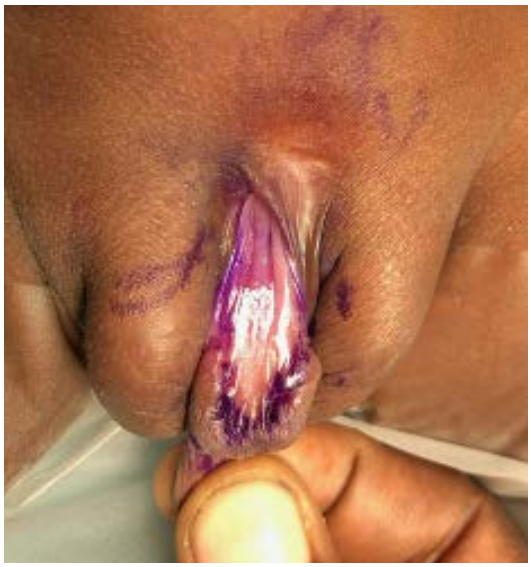

Figure 1: Penopubic male epispadias

is involved and these boys will have no urinary continence without major reconstructive surgery (Figure 1). In females, epispadias is characterised by non-fusion of the anterior labia majora, a bifid clitoris, a large proximal opening into the urinary bladder, and distal to this, an epispadic urethra.[2,10]

Bladder exstrophy: the most common phenotype

BE affects the bony pelvis (and the rectus and other muscles attached to the pelvis), bladder, and external genitalia.[11,12] The bladder and urethra are exposed to the outside environment. Urine is easily seen draining from the ureteral orifices. Close inspection of the proximal (epispadic) urethra reveals the ejaculatory ducts. The pubic bones and rectus abdominis that insert into the pubic bones

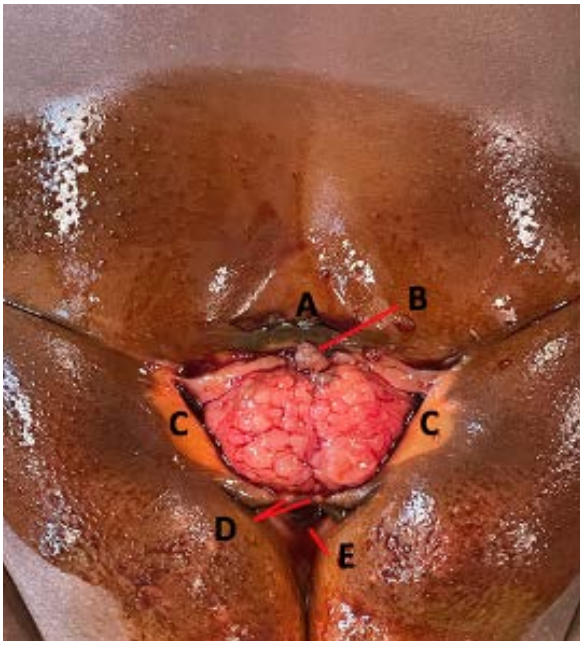

Figure 2: Female patient with bladder exstrophy
A – the scarred area of the umbilicus, B – polyp, C – paraexstrophy skin flaps, D – halves of the clitoris, E – vaginal orifice

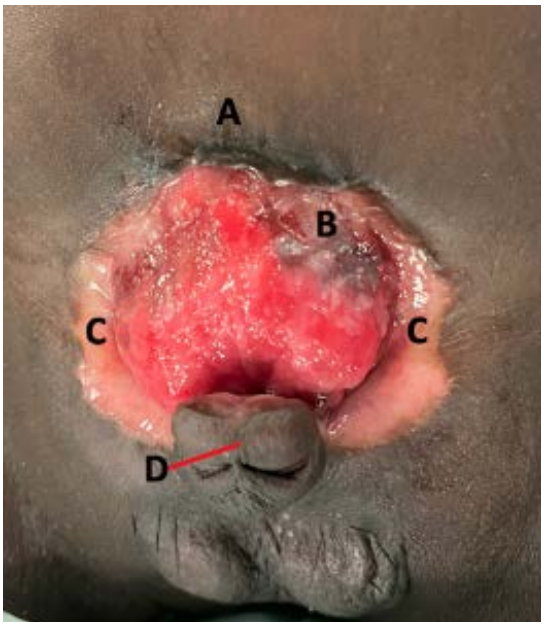

Figure 3: Male patient with bladder exstrophy
A – the scarred area of the umbilicus, B – metaplasia on bladder template, C – paraexstrophy skin flaps, D – epispadiac urethra/penis

are widely separated. The ureters open into the exposed bladder template.[11,12]

At birth, BE typically presents as a red, wet, glistening mass on the lower abdominal wall. When the neonate cries, their increased abdominal pressure frequently pushes the bladder plate further out above the surface of the abdomen, like a large hernia.[9,13] In males, the penis is short and flattened, and the testes can be undescended.[12] BE is less common in females with a male-to-female ratio as high as 2 : 1 or 3 : 1. In females, the external genitalia demonstrate clitoral separation, widely separated labia majora, and anterior displacement of the vaginal opening.[13,14] BE can also affect the development of the rectum and anus, and an anteriorly positioned anus may be present (Figures 2 and 3).

Cloacal exstrophy: the most severe phenotype

CE is a rare malformation that affects the development of the urogenital and anorectal regions, and results in lateral separation of the bladder, rectum, and genitalia.[15] Like BE, the pubic bones and all the muscles that attach to them are widely separated. The pubic diastasis is typically greater in CE than in BE. The bladder is exposed and divided into two halves where the ipsilateral ureteral orifice opens. Medial to these bladder halves are bowel structures – the ileocecal plate and prolapsed distal ileum.

In CE, the colon ends blindly in the lower part of the pelvis and the anus is imperforate. The genital tubercle is split into two halves, resulting in the formation of two widely diastatic hemipenes, or hemiclitori and hemivaginas. The grossly atypical appearance of the external genitalia leads many to erroneously consider the genital phenotype as ambiguous genitalia.[16] Unlike epispadias and BE, which generally do not involve any organ systems other than the genitourinary (GU) and abdominopelvic musculoskeletal systems, CE always involves the gastrointestinal system and can

also include a malformed abdominal wall (i.e. an omphalocele above the exstrophy defect) or an open neural tube.[2]

Omphalocele, gastrointestinal malrotation and duplication, short bowel syndrome, and various spinal bony anomalies have been reported in association with CE.[2,4] CE and the OEIS complex share common features, primarily the presence of an exposed bladder outside the abdominal wall and an imperforated anus. These overlapping characteristics can sometimes lead to overlapping terminology.

Epidemiology

There are no studies specifically focusing on the incidence and prevalence of epispadias in Africa. However, North American studies estimate an incidence of 1 in 120 000 male and 1 in 500 000 female live births.[17] The incidence of epispadias varies by geographic region and is more common in some populations, such as North American Natives and Hispanics. Epispadias occurs more frequently in males than females, with a male-to-female ratio of approximately 2 : 1. The incidence of epispadias may be increasing, possibly due to better detection and reporting of the condition.[17]

Interestingly, the incidence of epispadias is less than that of BE, making epispadias one disease spectrum where the less severe phenotype occurs much less frequently than the more severe phenotype.[13] In the United States, the incidence of BE is approximately 1 in 20 000 to 1 in 50 000 live births.[18,19] In Europe, the incidence ranges from 1 in 10 000 to 1 in 40 000 live births, with the highest incidence reported in northern European countries.[20] In Asia, the incidence of BE is approximately 1 in 50 000 to 1 in 100 000 live births.[21]

The exact incidence of CE is difficult to determine as it is a rare condition and often under- or misdiagnosed. Nonetheless, it is estimated to occur in approximately 1 in 200 000–400 000 live births.[15,22,23] CE has a higher incidence in females.[15] There are also differences in the incidence and prevalence of CE between different races and geographic regions. For example, the incidence is higher in Hispanics and lower in Asians.[15]

Unfortunately, epidemiology estimates for epispadias, BE, or CE on the African continent are limited to a few articles. There are no studies specifically estimating the incidence and prevalence of these conditions. Studies from Ethiopia support the concept of a significant backlog of untreated or delayed cases; it is plausible that the incidence could be greater than that of North America.[24,25]

Though not strictly an epidemiology study, this article demonstrates that many patients in one East African country are present, awaiting management, and that access to and treatment for this rare condition may be limited and sparse.[24] The problem is that the number of patients at risk (the birth rate) is unknown, and there are no established country-specific birth defect registries that we are aware of. This problem is compounded by limited exstrophy care, the rarity of and limited exposure to the condition, and the social stigma parents of children with BEEC face after their children are born, which may limit their reporting of the child's condition. The severe paucity of data presents a major opportunity for researchers and epidemiologists in Africa to better delineate this rare condition's incidence and prevalence.

In terms of gender, BE affects males more commonly than females, with a male-to-female ratio of approximately 2 : 1. The prevalence of BE also appears to be higher in certain ethnic groups than in other groups, such as Caucasians and Ashkenazi Jews.[2] Recent advances in surgical techniques and neonatal care have improved the outcomes for infants born with BE. However, the condition still requires lifelong management and can have significant psychosocial and functional consequences for affected individuals.

Heritability and risk factors

The BEEC spectrum is a heritable condition that presents with chromosomal aberrations and a high concordance rate in monozygotic twins.[2,17,26,27] The incidence of monozygotic twins with BEEC is 62%, compared to 11% for dizygotic twins, and a 4 500-fold incidence compared to the normal population. Affected individuals have a higher risk of passing on BEEC to their children.[2,28] Although the existing epidemiologic studies have not identified major teratogenic factors, twin studies and epidemiological data suggest environmental factors play a role.[29] Environmental factors that have been suggested to contribute to the development of BE and CE include maternal age, smoking, and maternal exposure to certain medications (such as valproic acid).[17,30] Studies have suggested that advanced parental age is also a risk factor for BEEC spectrum disorders.[31]

Additionally, several studies have reported a higher incidence of BEEC spectrum disorders in certain racial and ethnic groups such as Caucasians.[7,18] Assisted reproductive technologies (ART), including in vitro fertilisation (IVF), have been associated with an increased risk of certain birth defects, including those within the BEEC spectrum. However, the extent of this risk and the underlying mechanisms are not fully understood.[7] While there is some evidence to suggest an increased risk of BEEC among children conceived through ART, the evidence is not conclusive and the mechanisms underlying this association are not fully understood. Future studies with larger sample sizes and more comprehensive data on potential confounders are needed to firmly establish the epidemiological, teratogenic, and ART influences on BEEC.

Aetiology: recent advances in genetics and animal models

It should be noted that there is no single unifying hypothesis regarding epispadias, BE, or CE maldevelopment. A common theme is either maldevelopment of the genital tubercle and urethral plate in epispadias, the cloacal membrane in BE, or the urorectal septum in CE.[2,7,11,17,27]. However, great progress was made in the last decade towards understanding the genetic basis of BE – in part due to highly specific animal models and human genome-wide association studies (GWAS), which may help to elucidate the abnormal embryogenesis of BEEC more fully in the near future.

Historically, a fetal sheep model of BE was the only animal model available for researchers to study exstrophy development.[32] However, this large animal model was quite limited because

the defect was created by in utero trauma to the urinary bladder rather than by a genetic and molecular basis. More recent animal models, such as the mouse and chick, have been used to study the embryonic development of the genital tubercle and to identify potential genetic and environmental factors that may contribute to the development of epispadias.[33,34] As stated above, there is no single mechanism that explains the pathogenesis of BEEC. Nonetheless, it is generally believed that either the overgrowth of the cloacal membrane prevents adequate mesodermal migration, or the premature rupture of the cloacal membrane leaves the exstrophy defect.[17,29,31]

Epispadias

Several genes have been implicated in the pathogenesis of epispadias, including *HOXA13*, *FGFR2*, and *BMP4*.[35] Mutations in these genes can disrupt normal embryonic development of the genital tubercle, leading to the abnormal opening of the urethra on the dorsal surface of the penis or clitoris [27]

Bladder exstrophy

In the last decade, there have been several studies identifying putative pathogenic gene abnormalities for BE, with the most promising of these being *p63* and *Sonic Hedgehog* (*Shh*).[36,37] The *p63* gene, located on chromosome 3q28, is known as the "master regulator" of stratified epithelium. It plays an important role in the development of the skin, limbs, and urogenital tract, and is involved in the regulation of epithelial-mesenchymal interactions during development.[37] In particular, *p63* regulates the formation of the urorectal septum and the development of the bladder and urinary tract. Studies have shown that mutations in *p63* and its downstream targets are associated with the development of BEEC spectrum disorders.[36,38]

There are *p63* -/- mouse models that have been developed that reproduce the entire spectrum of BEEC, including bony, muscle, and GU defects.[38,39] Interestingly, human GWAS have found that the *p63* gene itself is normal in BEEC, but downstream targets of *p63*, such as the *PERP* gene, are affected.[38,40] This suggests that *p63* is involved in the regulation of other genes that contribute to the development of BEEC. In addition, there is evidence to suggest that the *p63* gene may play a role in the regulation of promoters that are involved in the development of BEEC.[37,41] In summary, *p63* is a "master regulator" of stratified epithelium and is involved in the regulation of epithelial-mesenchymal interactions during development. Though *p63* -/- mouse models have reproduced the entire spectrum of BEEC, human GWAS have shown that *p63* is not affected but that its downstream targets, such as *PERP*, are abnormal and may contribute to the development of BE.[27,42]

The *Isl1* gene, located on chromosome 5q11.1-2, was discovered from a GWAS as a potential BEEC gene.[43] This gene is known to play an important role in the development of the heart, limbs, kidneys, and neurons.[43,44] More recent studies have shown that *Isl1* is involved in the development of the bladder and genital tubercle, and mutations in the *Isl1* gene are associated with the development of BEEC and other congenital urological anomalies (CUAs).[43,44] These findings suggest that *Isl1* is a key gene involved in the development of the bladder and GU system. In summary, *Isl1*, a transcription factor associated with the development of the heart, limbs, kidneys, neurons, and the GU tract, may contribute to the development of BE.

Shh is a gene that encodes a signalling protein also critical to epithelial-mesenchymal interactions that occur during development, including the interaction between the urothelium (bladder lining) and detrusor (muscle layer) of the bladder.[45] In BEEC, there are defects in the formation of the urorectal septum and abnormal development of the bladder and urinary tract. Studies have shown that *Shh* signalling has a vital role in the formation and closure of the cloacal membrane, and disruption of this signalling may contribute to the development of classic bladder exstrophy (CBE).[46,47] In addition to regulating cloacal membrane growth via epithelial-mesenchymal interactions, *Shh* signalling plays a role in the development of the urethral plate, and its disruption may contribute to the development of epispadias.[17,27] Overall, *Shh* signalling plays an important role in the development of the bladder and urinary tract, and its disruption may contribute to the development of BEEC spectrum disorders. Further research is needed to fully understand the role of *Shh* in these disorders.

BEEC is typically thought to be caused by sporadic mutations, but recent studies have shown that BEEC can also be associated with heritable chromosomal aberrations. One such aberration that was identified is a deletion of a segment of chromosome 22q11.[48] This deletion is associated with a higher incidence of BEEC.[37,48] Additionally, it has been suggested that this chromosomal aberration may also be associated with other developmental anomalies and syndromes, such as DiGeorge syndrome and velocardiofacial syndrome, which are characterised by a wide range of congenital anomalies affecting multiple organ systems.[49,50] The discovery of multiple chromosomal aberrations associated with BEEC highlights the complex genetic aetiology of this disorder. Further research is needed to fully elucidate the role of chromosomal aberrations and other genetic factors in the development of BEEC.[27]

Table I: Key points regarding the epidemiology and pathogenesis of BEEC

1. The incidence of BE in North American studies is approximately 1 in 20 000–50 000 live births.
2. The incidence of epispadias in North American studies is 1 in 120 000 male and 1 in 500 000 female live births.
3. The incidence of epispadias, BE, and CE is unknown in African countries. This represents an area for additional research.
4. There is no single unifying hypothesis that explains the BE phenotype. However, many believe it is due to the premature rupture of the cloacal membrane or failed migration of the urogenital membrane.
5. Knockout gene studies in animals and human GWAS show that *p63* (or downstream targets like *PERP*), *Insl1*, and *Shh* reproduce the phenotype of BE or are found to be deficient.

Conclusion

BE and epispadias are rare congenital anomalies that cause significant health problems and affect the health-related QoL of affected individuals. This is a rare combination of diseases with a known incidence between 1 in 20 000 (BE) and 1 in 120 000 (epispadias) live births in North American and European studies. Unfortunately, the incidence and prevalence of BEEC in Africa is not understood. There have been significant insights into the aetiology of BEEC in the last decade. Specifically, recent genetic studies have suggested that downstream regulator(s) of *p63*, *Isl1*, and other genes may play a role in the failure of the lower urinary tract to close.

Conflict of interest

The authors declare no conflict of interest.

Funding source

Dr. Schaeffer is supported by the career development award NIH K08DK119535; however, this work was not specifically funded.

Ethical approval

The authors declare that this submission is in accordance with the principles laid down by the Responsible Research Publication Position Statements as developed at the Second World Conference on Research Integrity in Singapore, in 2010. This narrative review/study is exempt from Institutional Review Board approval because it did not involve human subjects. Permission was granted for patient photography and all photography is without personally identifying information.

ORCID

K Fendereski https://orcid.org/0000-0002-9622-1427
AJ Schaeffer https://orcid.org/0000-0002-5546-5118

References

1. Harris KT, Villela NA, Alam R, et al. The exstrophy experience: a national survey assessing urinary continence, bladder management, and oncologic outcomes in adults. J Pediatr Urol. 2023;19(2):178.e1-7. https://doi.org/10.1016/j.jpurol.2022.11.014.
2. Ebert A-K, Reutter H, Ludwig M, Rösch WH. The exstrophy-epispadias complex. Orphanet J Rare Dis. 2009;4:23. https://doi.org/10.1186/1750-1172-4-23.
3. Singh S, Kayastha A, Thapa A, Thapa B, Dahal S. Omphalocele, exstrophy of cloaca, imperforate anus, and spinal defects complex: a case report. JNMA J Nepal Med Assoc. 2023;61(260):375-8. https://doi.org/10.31729/jnma.8048.
4. Kumar N, Chatur C, Balani A, et al. Patterns of spinal cord malformation in cloacal exstrophy. J Neurosurg Pediatr. 2021:1-8. Epub 2021 Jun 4. https://doi.org/10.3171/2021.1.PEDS20648.
5. Bujons A, Lopategui DM, Rodríguez N, et al. Quality of life in female patients with bladder exstrophy-epispadias complex: long-term follow-up. J Pediatr Urol. 2016;12(4):210.e1-6. https://doi.org/10.1016/j.jpurol.2016.05.005.
6. Spinoit A-F, Waterschoot M, Sinatti C, et al. Fertility and sexuality issues in congenital lifelong urology patients: male aspects. World J Urol. 2021;39(4):1013-9. https://doi.org/10.1007/s00345-020-03121-2.
7. Ludwig M, Ching B, Reutter H, Boyadjiev SA. Bladder exstrophy-epispadias complex. Birth Defects Res A Clin Mol Teratol. 2009;85(6):509-22. https://doi.org/10.1002/bdra.20557.
8. Lee T, Weiss D, Roth E, et al. Prenatal diagnosis of bladder exstrophy and OEIS over 20 years. Urology. 2023;172:174-7. https://doi.org/10.1016/j.urology.2022.11.020.
9. Maruf M, Benz K, Jayman J, et al. Variant presentations of the exstrophy-epispadias complex: a 40-year experience. Urology. 2019;125:184-90. https://doi.org/10.1016/j.urology.2018.10.049.
10. Cendron M, Cho PS, Pennison M, et al. Anatomic findings associated with epispadias in boys: implications for surgical management and urinary continence. J Pediatr Urol. 2018;14(1):42-6. https://doi.org/10.1016/j.jpurol.2017.09.022.
11. Gearhart JP, Mathews R. The exstrophy—epispadias complex: research concepts and clinical applications. New York: Springer Science & Business Media; 2013. https://doi.org/10.1007/978-1-4757-3056-2.
12. Peng Z, Huang Y, Tang W, et al. Pelvic floor anatomical variations in children with exstrophy-epispadias complex using magnetic resonance imaging. Urology. 2022;165:305-11. https://doi.org/10.1016/j.urology.2022.01.008.
13. Tourchi A, Inouye BM, Di Carlo HN, et al. New advances in the pathophysiologic and radiologic basis of the exstrophy spectrum. J Pediatr Urol. 2014;10(2):212-8. https://doi.org/10.1016/j.jpurol.2013.11.017.
14. Anusionwu I, Tekes A, Stec AA, Gearhart JP, Wright EJ. Comparison of musculoskeletal anatomic relationships, determined by magnetic resonance imaging, in postpubertal female patients with and without classic bladder exstrophy. BJU Int. 2013;112(2):E195-200. https://doi.org/10.1111/j.1464-410X.2012.11753.x.
15. Feldkamp ML, Botto LD, Amar E, et al. Cloacal exstrophy: an epidemiologic study from the International Clearinghouse for Birth Defects Surveillance and Research. Am J Med Genet C Semin Med Genet. 2011;157C(4):333-43. https://doi.org/10.1002/ajmg.c.30317.
16. Meyer-Bahlburg HFL. Gender identity outcome in female-raised 46,XY persons with penile agenesis, cloacal exstrophy of the bladder, or penile ablation. Arch Sex Behav. 2005;34(4):423-38. https://doi.org/10.1007/s10508-005-4342-9.
17. Hall SA, Manyevitch R, Mistry PK, Wu W, Gearhart JP. New insights on the basic science of bladder exstrophy-epispadias complex. Urology. 2021;147:256-63. https://doi.org/10.1016/j.urology.2020.10.004.
18. Nelson CP, Dunn RL, Wei JT. Contemporary epidemiology of bladder exstrophy in the United States. J Urol. 2005;173(5):1728-31. https://doi.org/10.1097/01.ju.0000154821.21521.9b.
19. Jayachandran D, Bythell M, Platt MW, Rankin J. Register based study of bladder exstrophy-epispadias complex: prevalence, associated anomalies, prenatal diagnosis and survival. J Urol. 2011;186(5):2056-60. https://doi.org/10.1016/j.juro.2011.07.022.
20. Ebert A-K, Zwink N, Reutter HM, Jenetzky E. A prevalence estimation of exstrophy and epispadias in Germany from public health insurance data. Front Pediatr. 2021;9:648414. https://doi.org/10.3389/fped.2021.648414.
21. Yang X, Zeng J, Gu Y, et al. Birth defects data from hospital-based birth defect surveillance in Guilin, China, 2018–2020. Front Public Health. 2022;10:961613. https://doi.org/10.3389/fpubh.2022.961613.
22. Woo LL, Thomas JC, Brock JW. Cloacal exstrophy: a comprehensive review of an uncommon problem. J Pediatr Urol. 2010;6(2):102-11. https://doi.org/10.1016/j.jpurol.2009.09.011.
23. Cervellione RM, Mantovani A, Gearhart J, et al. Prospective study on the incidence of bladder/cloacal exstrophy and epispadias in Europe. J Pediatr Urol. 2015;11(6):337.e1-6. https://doi.org/10.1016/j.jpurol.2015.03.023.
24. Yousef Y, Lee A, Ayele F, Poenaru D. Delayed access to care and unmet burden of pediatric surgical disease in resource-constrained African countries. J Pediatr Surg. 2019;54(4):845-53. https://doi.org/10.1016/j.jpedsurg.2018.06.018.
25. Wiersma R. Overview of bladder exstrophy: a third world perspective. J Pediatr Surg. 2008;43(8):1520-3. https://doi.org/10.1016/j.jpedsurg.2007.11.005.
26. Zaki MS, Gillessen-Kaesbach G, Vater I, et al. Bladder exstrophy and extreme genital anomaly in a patient with pure terminal 1q deletion: expansion of phenotypic spectrum. Eur J Med Genet. 2012;55(1):43-8. https://doi.org/10.1016/j.ejmg.2011.09.003.
27. Mahfuz I, Darling T, Wilkins S, White S, Cheng W. New insights into the pathogenesis of bladder exstrophy-epispadias complex. J Pediatr Urol. 2013;9(6 Pt B):996-1005. https://doi.org/10.1016/j.jpurol.2013.05.001.
28. Kajbafzadeh A-M, Tajik P, Payabvash S, Farzan S, Solhpour AR. Bladder exstrophy and epispadias complex in sibling: case report and review of literature. Pediatr Surg Int. 2006;22(9):767-70. https://doi.org/10.1007/s00383-006-1741-5.
29. Reutter H, Boyadjiev SA, Gambhir L, et al. Phenotype severity in the bladder exstrophy-epispadias complex: analysis of genetic and nongenetic contributing factors in 441 families from North America and Europe. J Pediatr. 2011;159(5):825-31.e1. https://doi.org/10.1016/j.jpeds.2011.04.042.
30. Margiana R, Juwita W, Ima K, Faizah Z, Supardi S. Analyzing the factors that contribute to the development of embryological classical type of bladder exstrophy. Anat Cell Biol. 2023;56(4):421-7. https://doi.org/10.5115/acb.23.056.
31. Boyadjiev SA, Dodson JL, Radford CL, et al. Clinical and molecular characterization of the bladder exstrophy-epispadias complex: analysis of 232 families. BJU Int. 2004;94(9):1337-43. https://doi.org/10.1111/j.1464-410X.2004.05170.x.
32. Slaughenhoupt BL, Chen CJ, Gearhart JP. Creation of a model of bladder exstrophy in the fetal lamb. J Urol. 1996;156(2 Pt 2):816-8.
33. Männer J, Kluth D. A chicken model to study the embryology of cloacal exstrophy. J Pediatr Surg. 2003;38(5):678-81. https://doi.org/10.1016/jpsu.2003.50181.
34. Ridderbusch I, Bergholz R, Fattouh M, et al. A chicken embryo model for the study of umbilical and supraumbilical body wall malformations. Eur J Pediatr Surg. 2015;25(3):257-61. https://doi.org/10.1055/s-0034-1371718.
35. Ching ST, Infante CR, Du W, et al. *Isl1* mediates mesenchymal expansion in the developing external genitalia via regulation of *Bmp4*, *Fgf10* and *Wnt5a*. Hum Mol Genet. 2018;27(1):107-19. https://doi.org/10.1093/hmg/ddx388.

36. Ching BJ, Wittler L, Proske J, et al. p63 (TP73L) a key player in embryonic urogenital development with significant dysregulation in human bladder exstrophy tissue. Int J Mol Med. 2010;26(6):861-7. https://doi.org/10.3892/ijmm_00000535.
37. Beaman GM, Cervellione RM, Keene D, Reutter H, Newman WG. The genomic architecture of bladder exstrophy epispadias complex. Genes (Basel). 2021;12(8):1149. https://doi.org/10.3390/genes12081149.
38. Qi L, Chen K, Hur DJ, et al. Genome-wide expression profiling of urinary bladder implicates desmosomal and cytoskeletal dysregulation in the bladder exstrophy-epispadias complex. Int J Mol Med. 2011;27(6):755-65. https://doi.org/10.3892/ijmm.2011.654.
39. Wilkins S, Zhang KW, Mahfuz I, et al. Insertion/deletion polymorphisms in the ΔNp63 promoter are a risk factor for bladder exstrophy epispadias complex. PLoS Genet. 2012;8(12):e1003070. https://doi.org/10.1371/journal.pgen.1003070.
40. Reutter H, Keppler-Noreuil K, Keegan CE, et al. Genetics of bladder-exstrophy-epispadias complex (BEEC): systematic elucidation of Mendelian and multifactorial phenotypes. Curr Genomics. 2016;17(1):4-13. https://doi.org/10.2174/1389202916666151014221806.
41. Reutter H, Draaken M, Pennimpede T, et al. Genome-wide association study and mouse expression data identify a highly conserved 32 kb intergenic region between *WNT3* and *WNT9b* as possible susceptibility locus for isolated classic exstrophy of the bladder. Hum Mol Genet. 2014;23(20):5536-44. https://doi.org/10.1093/hmg/ddu259.
42. Ihrie RA, Marques MR, Nguyen BT, et al. *Perp* is a p63-regulated gene essential for epithelial integrity. Cell. 2005;120(6):843-56. https://doi.org/10.1016/j.cell.2005.01.008.
43. Draaken M, Knapp M, Pennimpede T, et al. Genome-wide association study and meta-analysis identify *ISL1* as genome-wide significant susceptibility gene for bladder exstrophy. PLoS Genet. 2015;11(3):e1005024. https://doi.org/10.1371/journal.pgen.1005024.
44. Zhang R, Knapp M, Suzuki K, et al. *ISL1* is a major susceptibility gene for classic bladder exstrophy and a regulator of urinary tract development. Sci Rep. 2017;7:42170. https://doi.org/10.1038/srep42170.
45. Shiroyanagi Y, Liu B, Cao M, et al. Urothelial sonic hedgehog signaling plays an important role in bladder smooth muscle formation. Differentiation. 2007;75(10):968-77. https://doi.org/10.1111/j.1432-0436.2007.00187.x.
46. Haraguchi R, Matsumaru D, Nakagata N, et al. The hedgehog signal induced modulation of bone morphogenetic protein signaling: an essential signaling relay for urinary tract morphogenesis. PLoS One. 2012;7(7):e42245. https://doi.org/10.1371/journal.pone.0042245.
47. Haraguchi R, Mo R, Hui C, et al. Unique functions of Sonic hedgehog signaling during external genitalia development. Development. 2001;128(21):4241-50. https://doi.org/10.1242/dev.128.21.4241.
48. Draaken M, Baudisch F, Timmermann B, et al. Classic bladder exstrophy: frequent 22q11.21 duplications and definition of a 414 kb phenocritical region. Birth Defects Res A Clin Mol Teratol. 2014;100(6):512-7. https://doi.org/10.1002/bdra.23249.
49. Lundin J, Söderhäll C, Lundén L, et al. 22q11.2 microduplication in two patients with bladder exstrophy and hearing impairment. Eur J Med Genet. 2010;53(2):61-5. https://doi.org/10.1016/j.ejmg.2009.11.004.
50. Draaken M, Reutter H, Schramm C, et al. Microduplications at 22q11.21 are associated with non-syndromic classic bladder exstrophy. Eur J Med Genet. 2010;53(2):55-60. https://doi.org/10.1016/j.ejmg.2009.12.005.