

Bladder Exstrophy Epispadias Complex

Subjects: Genetics & Heredity

Submitted by:  William Newman

Definition

The bladder exstrophy–epispadias complex (BEEC) is an abdominal midline malformation comprising a spectrum of congenital genitourinary abnormalities of the abdominal wall, pelvis, urinary tract, genitalia, anus, and spine. The vast majority of BEEC cases are classified as non-syndromic and the etiology of this malformation is still unknown.

1. Introduction

Congenital anomalies of the lower urinary tract (CALUT) are a group of birth defects of the ureter, bladder, and urethra, which includes bladder exstrophy–epispadias complex (BEEC, MIM #600057). BEEC is an abdominal midline malformation comprising a spectrum of congenital genitourinary abnormalities of the abdominal wall, pelvis, urinary tract, genitalia, anus, and spine [1]. The severity of BEEC ranges from epispadias (E), representing the mildest form to include classic bladder exstrophy (CBE), and extending to cloacal exstrophy (CE), the latter complex—previously referred to as OEIS (omphalocele, exstrophy, imperforate anus, and spinal defects)—being the most severe [1][2]. BEEC is further subdivided into “classic/typical” forms (E, CBE, and CE) and “atypical” forms (duplicated exstrophy, covered exstrophy, and pseudo-exstrophy) [1][3]. In the majority of cases, BEEC is non-syndromic (that is, it is not associated with other congenital birth malformations). The etiology of this malformation is still unknown. Theories have proposed an abnormal overdevelopment of the cloacal membrane preventing medial migration of mesenchyme between the ectodermal and endodermal layers of the lower abdominal wall, resulting in abnormal development of the lower abdominal wall [4] or the involvement of cloacal membrane and mesenchymal tissues during their defective embryogenesis [5][6].

2. Evidence of a Genetic Basis to BEEC

The vast majority of BEEC cases are non-syndromic, however, a number of cases have been reported whereby BEEC has also been associated with various other syndromes, malformations, and congenital diseases (Table 1). There are a number of reported cases of OEIS (CE) with multiple cardiac malformations [7][8][9]. A population study undertaken by Kallen et al., 2000 [10] of 5260 infants with multiple malformations identified 194 infants with OEIS, however, no association with cardiac defects was detected.

Table 1. BEEC and associated birth defects adapted from Ludwig et al., 2009 [11].

Type	Type of BEEC	OMIM
BEEC-associated syndromes		
Al Awadi/Raas-Rothschild syndrome	CBE	276820
Acrorenal syndrome	CBE	102520
Duane’s syndrome	CBE	126800
Elis-van Creveld Syndrome	E	225500
Epidermolysis bullosa junctionalis	CBE	226650
Epstein syndrome	CE	153650
Fraser syndrome	Pseudoexstrophy	219000
Goldenhar syndrome	CE	164210

Type	Type of BEEC	OMIM
Goltz-Gorlin syndrome	CE	228250
Gollop-Wolfgang complex	CE	305600
Microcephalic osteodysplastic primordial dwarfism type III	CBE	210730
Oculoectodermal syndrome	CBE	600268
Opitz G/BBB syndrome	CBE	145410
BEEC associations		
Axial mesodermal dysplasia	CE	608160
Caudal dysplasia	CBE	600145
VATER association	CBE	192350
BEEC-associated Malformations		
Head and neck		
Chiari I malformation	CE	118420
Frontonasal dysplasia	CE	136760
Otocephaly-holoprosencephaly	CE	202650
Posterior cleft palate	CE	119540
Severe early-onset hearing loss	CE	561000
Skeletal		
Bilateral club feet	CE	119800
Severe lower limb defects	CE	-
Right thumb hypoplasia	CE	-
Cardiovascular		
Duplication of vena cava	CE	-
DORV, PV-atresia, right-sided aortic arch with PDA	Covered CBE	217095
Abdomen		
Gastroschisis	CBE	230750
Gastroschisis	Pseudoexstrophy	230750

BEEC, bladder-exstrophy-epispadias complex; CBE, classic bladder exstrophy; E; epispadias; CE, exstrophy of the cloaca; DORV, double outlet right ventricle; PV, pulmonic valve; PDA, patent ductus arteriosus. The majority of individuals affected by BEEC have no positive family history of BEEC. However, even though familial occurrence is rare, 30 multiplex families have been described [11][12][13][14]. A number of these appear to follow a Mendelian mode of inheritance. However, in the majority of affected individuals, the genetic basis of BEEC is consistent with a multifactorial etiology [15]. In the majority of multiplex families, only two members are affected. Two families have been reported with three affected members, including males and females with differing degrees of BEEC severity [11]. Reutter et al., 2003 [12] described a unique Moroccan family of three males (two cousins and a maternal uncle) being affected with CBE. In these rare multiplex families, the inheritance of BEEC would be consistent with autosomal dominant with reduced penetrance, autosomal recessive, or X-linked patterns [12]. The lack of recurrence

may in part be due to reduced reproductive fitness. This may change due to surgical advances and improvements in reproductive medicine facilitating the birth of children to affected individuals. Studies have shown that individuals with CBE with non-consanguineous and non-affected parents have a recurrence risk among siblings from 0.3 to 2.3% [16][17]. The recurrence risk for offspring from affected parents is 1.4%. The risk of having a second affected child from non-consanguineous and non-affected parents shows an approximate 400-fold increase compared to the general population [16].

Reutter et al., 2007 [14] reported higher concordance rates in monozygotic twins (62%) compared to dizygotic twins (11%) with BEEC, supporting a genetic etiology. A number of reports have shown recurrence of CE within families [18]; an increased occurrence in conjoined and monozygotic twins [19][20][21][22][23][24][25]; concordant conjoined twins [26], and discordant dizygotic twins [6]. Xu et al., 2020 [27] reported CE in twins (n = 28) and triplets (n = 2), including monozygotic (n = 20), dizygotic (n = 3), trizygotic (n = 2), and unknown zygosity (n = 5). Of the CE anomalies within the 20 monozygotic twins, 9 were concordant and 11 were discordant. The higher incidence of CE in monozygotic twins compared to dizygotic twins could suggest a possible genetic contribution to the occurrence of these anomalies. Fullerton et al., 2017 [28] reported that approximately 14% of CE cases occurred in same-sex twins, which supported their hypothesis that the embryogenesis of CE could be related to errors in monozygotic splitting.

3. Conclusions

The application of array-based, GWAS, and next generation sequencing techniques in large BEEC cohorts has helped to identify putative disease-causing genes and chromosomal regions in the human genome for both Mendelian and multifactorial BEEC. Functional analysis of embryonic pathways provides a better understanding of the molecular biological mechanisms underlying normal, urorectal, and genitourinary malformations within the embryology of the human urogenital system.

It is reasonable to propose that both inherited and *de novo* highly penetrant variants could be relevant to the etiology of BEEC as they have been shown for many genetically heterogeneous congenital birth defects such as congenital heart disease.

New approaches such as gene and pathway enrichment analyses of high-impact *de novo* variants from whole exome or whole genome data in parent-offspring trios will likely aid in the identification of novel genes and/or pathways to better understand the underlying genetic mechanisms of BEEC, and the potential to use these data to develop therapeutic approaches to help children affected by this devastating congenital disorder.

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Keywords

BEEC;bladder exstrophy;epispadias;cloacal exstrophy