Genetic Counseling for Bladder Exstrophy-Epispadias Complex

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Abstract

Bladder exstrophy-epispadias complex (BEEC) represents the severe end of the urorectal malformation spectrum and has profound impact on continence, sexual, and renal function. Treatment of BEEC is primarily surgical, and the main goals are safe closure of the abdominal wall, urinary continence while preserving renal function, and adequate cosmetic and functional genital reconstruction. Psychosocial and psychosexual outcomes and adequate health-related quality of life depend on long-term multidisciplinary care. The overall outcome is now considered very positive and affected individuals usually lead self-determined and independent lives with the desire to start their own families later in life. Certainty about the risk of recurrence and the provision of information about the current state of knowledge about the identified genetic causes with high penetrance will have an impact on family planning for healthy parents with an affected child and for affected individuals themselves. This review addresses this information and presents the current state of knowledge.

Keywords
- bladder exstrophy-epispadias complex
- genetic counseling
- recurrence risk
- genetic testing

Introduction

The bladder exstrophy-epispadias complex (BEEC; OMIM % 600057) represents the severe end of human congenital anomalies of the kidney and urinary tract, and involves the abdominal wall, pelvis, all of the urinary tract, the genitalia, and occasionally the spine and gastrointestinal tract. The severity spectrum of the BEEC comprises: the mildest form, isolated epispadias (E) with the incidence of 2.4:100,000 births; the intermediate and most common form (incidence 1–2:50,000 births), classic bladder exstrophy (CBE); and the most severe and unusual form (incidence 0.5–1:200,000 births), the cloacal exstrophy (CE), which is often referred to as the OEIS complex—omphalocele, exstrophy, imperforate anus, and spinal defects.[1,2] About one-third of all cases present additional anomalies of the urinary system (e.g., ectopic kidney, renal agenesis). Prenatal diagnosis could be obtained in up to 40% of the cases, with the findings of absence of bladder filling, low-set umbilicus, and diminutive genitalia.[3,4] In case of CE, there is a combination of an omphalocele. Management of the BEEC is primarily surgical, and the main aims are the achievement of abdominal wall closure, urinary or, in case of CE, urinary and fecal continence with preservation of renal function, and adequate functional genital reconstruction.[2] Even with modern surgical techniques, incontinence is a major problem with approximately 40% of the adults being dry in optimal conditions.[5] Many patients will end up with a continent or incontinent urinary diversion. Only 25% of the patients with CBE are expected to void normally per urethra without reliance on catheterization or incontinent diversion.[6] The sexual function is reported to be impaired in both sexes. Of great concerns in

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men are a short penile length with a dorsal curvature and ejaculation abnormalities and in women vaginal stenosis and uterine prolapse. Fertility is decreased in men, partly due to a low sperm quality and low ejaculate volumes.[7,8] In females, BEEC has been shown to have a negative impact not only on fertility, but also on fetal and neonatal outcome. Maternal complications are common even if successful pregnancies and deliveries are possible.[9] Furthermore, associated long-term complications comprise bladder cancers.[10,11] In newly published reviews it is reported that the overall health-related quality of life may be impaired in patients with BEEC, and incontinence and sexual dysfunction seem to have a negative impact.[12,13]

Recently, the CBE live prevalence for Germany has been estimated to be approximately 1:30,700.[14] Given the overall European population of approximately 450,000,000 (https://ec.europa.eu/) citizens, it has to be assumed that there are 15,000 people living with CBE in Europe. Hence, besides classical operative care of this constantly increasing patient population, health care must encounter other medical disciplines including human genetics, which has often been underestimated in many areas of the classical medical disciplines. Genetic counseling is of importance and is in demand by parents expecting a child with suspected BEEC, having an affected child, or being affected and planning for reproduction.

Inheritance of the BEEC and Early Genetic Studies

Although the BEEC can occur as part of a complex malformation syndrome, the majority of cases (~98.5%) are classified as nonsyndromic isolated.[15] About 30 multiply affected families have been reported in the literature. Some appear to follow a Mendelian mode of inheritance.[16] Hitherto, the general consensus in the field is that in the majority of individuals the genetic basis appears to be multifactorial.[17] In accordance with this the reported recurrence risk for CBE among siblings ranges between 0.3 and 2.3% whereas the reported CBE recurrence risk for offspring of affected individuals is 1.4%, representing an approximately 400-fold increase compared with the general population.[18]

Earlier case reports describe chromosomal anomalies in approximately 20 individuals with BEEC comprising structural and numeric aberrations.[19] Besides the description of chromosomal anomalies, candidate gene analysis in individuals with nonsyndromic BEEC were reported. Selection of these candidate genes was based on their embryonic expression, their function, or their position in the genome (e.g., regions of chromosomal imbalances). However, none of these candidate gene studies comprising *CNTNAP3*, *CYR61*, *HLXB9*, *FGF10*, *PARM1*, *SET*, and *SRY* identified any disease-causing variant.[20–25]

Putative Syndromic Disease Genes *MYH9*, *PORCN*, or *UPB1*

For a few individuals with syndromic BEEC probably disease-causing variants have been detected in three different syndrome-related genes: *MYH9*, *PORCN*, and *UPB1*. Yet, follow-up studies of these genes did not support them as direct disease-causing genes for isolated BEEC.[26–28] Furthermore, to the best of our knowledge, there are no further reports on the association of BEEC and disease variants in *MYH9*, *PORCN*, or *UPB1*.

Putative Nonsyndromic Disease Gene *SLC20A1*

Recently, Rieke et al described *SLC20A1*, encoding a sodium-phosphate symporter, as the first putative monogenic dominant disease gene for nonsyndromic BEEC.[29] They identified monoallelic dominant de novo variants in affected individuals in three independent families and were able to support their human genetic data by immunohistochemistry staining of *SLC20A1* in non-BEEC human embryos in the urogenital sinus and morpholino knockdown and rescue experiments in the zebrafish ortholog *slc20a1a*.[29] While the evidence provided by Rieke et al to support *SLC20A1* as the first monogenic disease gene for the BEEC is strong, these findings warrant replication in further cohorts and should currently be taken with caution in the setting of routine genetic prenatal testing.

Copy-Number Variation (CNV) Analysis

In the context of scientific studies on the genetic causes of the BEEC, the systematic employment of array-based molecular karyotyping and multiplex ligation-dependent probe amplification (MLPA) analysis by Lundin et al and Draaken et al, respectively, in 36 and 66 individuals with CBE detected in 3 independent families 3 de novo and 1 inherited 22q11.2 duplication in 4 unrelated individuals with CBE (4% in 102 individuals).[30,31] In a follow-up study, Draaken et al performing MLPA in 217 individuals with CBE identified 4 additional 22q11.21 duplication carriers (2%).[32] Physical alignment of these duplications revealed a 414 kb phenocritical region harboring 12 RefSeq genes.[32] Additional follow-up studies on 110 BEEC individuals in 2012 and on 170 BEEC individuals in 2013, respectively by Draaken et al and von Lowtzow et al, detected a de novo duplication (0.9 Mb) involving chromosomal region 19p13.12 in an individual with CBE and 8 very rare inherited CNVs not present in 1.307 in-house controls (frequency < 0.0008) suggesting that some of these CNVs might contribute to the BEEC in a multifactorial disease-model.[33,34] In 2019, Beaman et al identified 3 additional CBE individuals in a cohort of 92 who carried a microduplication 22q11.2.[35] In summary, MLPA screening and array-based CNV analysis of 411 BEEC individuals detected 11 carriers of microduplication 22q11.2 (3%). Independent of this, A further case report describes a single individual with CBE and 22q11.2 duplication who also presented with delayed psychomotor development and short stature.[36] In this context, two individuals with CBE and 22q11.2 duplication described by Lundin et al also displayed hearing impairment, and one of these individuals also presented with a mild neuropsychiatric disorder not further specified by the authors.[31] All other

individuals with CBE and 22q11.2 duplication did not show any additional phenotypic features, besides their BEEC phenotype.

Counseling and Routine Genetic Testing

Counseling of Healthy Parents with an Affected Child and Affected Individuals

From a medical genetic point of view, the following aspects should be noteworthy:

- The majority of affected individuals (~98.5%) are classified as nonsyndromic isolated. In a broader sense, this implies that almost all affected individuals have an inconspicuous neurocognitive development.
- For healthy parents of an affected individual with CBE or CE, the recurrence risk has been estimated to range between 0.3 and 2.3%.
- The reported CE or CBE recurrence risk for offspring of an affected individual has been estimated with 1.4%, representing an approximately 400-fold increase compared with the general population.
- While there has not been a comparable study, the findings by Shapiro et al[18] suggest that in the majority of cases, the underlying mode of inheritance is multifactorial with an overall low recurrence risk.

General Recommendations for Genetic Testing

- Hitherto, de novo or inherited microduplications 22q11.2 have been the only genetic alteration that have been repeatedly associated with the formation of the BEEC.
- In the case of co-occurring CBE with hearing impairment and/or additional neuropsychiatric disorder and/or delayed psychomotor development, genetic testing for the presence of microduplication 22q11.2 should be advised.
- The general detection rate of 22q11.2 among isolated nonsyndromic CE or CBE individuals resides within the range of 1–3%. Therefore, testing for the presence of 22q11.2 in the presence of isolated nonsyndromic CE or CBE appears optional.

Conclusions

The BEEC represents a major birth defect with high impact on the affected individuals and their families. Assurance about the low recurrence risk and provision of information on the current knowledge of the identified genetic causes with high penetrance will have an impact on family planning for healthy parents with an affected child and affected individuals themselves. According to the current knowledge, healthy parents should be encouraged to have a child without worry, if there is a desire to have further children, as the risk of recurrence for further affected children is extremely low. Accordingly, affected adults should also be encouraged to have children of their own, as the risk of recurrence is also very low for this group of people. Nowadays, the outcome of affected persons is considered to be positive on the whole, and this data is important to communicate to parents expecting a child with suspected bladder exstrophy.

Conflict of Interest
None declared.

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