Peertechz

Journal of Gynecological Research and Obstetrics OPEN ACCESS JOURNAL

ISSN: 2581-5288 DOI: https://dx.doi.org/10.17352/jgro

Case Report

PBX1 Gene Disorder in the United Kingdom: Case Report and Review of Available Literature

Anthony Emeka Madu*

Specialist Registrar (Clinical Attachment), PGCE, FHEA, Department of Obstetrics and Gynaecology, Gynaecological Services, Chelsea and Westminster University Hospital NHS Foundation Trust, 369 Fulham Rd., London SW10 9NH, UK

Received: 13 September, 2025
Accepted: 25 September, 2025
Published: 26 September, 2025

***Corresponding author**: Dr Anthony Emeka Madu, Specialist Registrar (Clinical Attachment), PGCE, FHEA, Department of Obstetrics and Gynaecology, Gynaecological Services, Chelsea and Westminster University Hospital NHS Foundation Trust, 369 Fulham Rd., London SW10 9NH, UK, E-mail: emymadu@yahoo.co.uk

Keywords: PBX1 genetic disorder; Renal and renal tract syndrome; Diaphragmatic eventration; Respiratory disorders

Copyright License: © 2025 Madu AE. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

https://www.clinsurggroup.us

Check for updates

Abstract

It has been well-established that as science advances, genetic and inherited conditions that could not have been detected centuries ago will become detectable, and affected individuals will have at least a diagnosis in hopeless situations. Such was very apparent in this case. For decades, the three main chromosomal trisomies, Turner's syndrome, Fragile X syndrome, and Triple-X syndrome, have been dominant in the medical literature, in relation to prenatal diagnosis. However, with recent advances in prenatal diagnosis, the scientific community is now able to detect and analyze new rare conditions that could not have been detected 50 or more years ago.

Rare diseases are often known to be life-threatening and chronic, and on average, it takes four years or more to receive an accurate diagnosis of a rare disease. Most rare diseases currently have no effective treatment.

Autosomal dominant (de novo) mutations in the PBX1 gene, which are rare, are known to cause congenital abnormalities of the kidney and urinary tract (CAKUT), with or without extra-renal abnormalities.

We present a rare case of PBX1 disorder, in which an extensive literature search with the search term "PBX1-related disorders in the UK" did not reveal significant local or national publications.

Introduction

Genetic disorders usually occur when mutations of genes take place, and this is also known as a pathogenic variant. These disorders can occur when an individual has the wrong amount of genetic material. We know genes make up the chromosomes and are, in turn, made of deoxyribonucleic acid (DNA), which contains instructions for cell functioning and the characteristics that make an individual unique.

An individual receives half his or her genes from each biological parent. This individual may, in turn, inherit a gene mutation from a parent or both parents. There are occasions when genetic mutations take place due to issues within the DNA. This subsequently raises an individual's risk of having a genetic disorder, and most of these cases occur *de novo*, indicating the change in the DNA sequencing of an individual's gene occurred for the first time and has not appeared in previous generations (parents, grandparents, great grandparents, etc) of the individual, as in this case.

The rare disorders can be non-genetic, chromosomal, monogenic (single gene), or multifactorial (complex). The latter occurs due to a combination of gene mutations and other factors, which include diet, alcohol, tobacco, chemical exposure, and some medications.

Oxford Health NHS [1] stated that the European Union (EU)

Citation: Madu AE. PBX1 Gene Disorder in the United Kingdom: Case Report and Review of Available Literature. J Gynecol Res Obstet. 2025;11(2):019-023. Available from: https://dx.doi.org/10.17352/jgro.000134

defined a disease or condition as rare if it affects fewer than 1 in 2,000 people within the general population, and that, at present, there are over 6,000 known rare diseases, and that new conditions are being added to the medical literature regularly. The authors stated further that 8 out of 10 rare diseases have a genetic cause, and 99% of genetic conditions are classed as rare.

According to the UK Policy White Paper [2], which essentially mirrors that of the EU, a rare disease is defined as a condition that affects less than 1 in 2,000 people. At present, there are estimated to be over 7,000 rare diseases, with new conditions continually being identified as research and testing advances. While 80% of rare diseases have an identified genetic origin, they can also be caused by disordered immunity, infections, allergies, or disruption to *in utero* development.

According to ICMR [3], WHO defined a rare disease as an often debilitating lifelong disease or disorder with a prevalence of 1 or less per 1000 population. The average prevalence thresholds used to define rare diseases vary between jurisdictions and range from 1 to 6 cases/10,000 people, with the WHO recommending that a prevalence of less than 10/10,000 population for defining rare diseases. However, according to ICMR [3], different countries have their own definitions to suit their specific needs or requirements and in the context of their own population, health care system, and resources.

According to Fitzgerald KK, et al. [4], the PBX1 gene encodes the PBX1 protein, a transcription factor vital to embryonic development, particularly in regulating the development of organs like the kidneys and urinary tract. Mutations (variants) in the PBX1 gene are capable of disrupting its normal function, leading to defects in development. These mutations are associated with congenital anomalies of the kidney and urinary tract (CAKUT), potentially including hearing loss, abnormal ears, and developmental delays. The symptoms and phenotypes of PBX1 disorder include;

Congenital anomalies of the kidney and urinary tract (CAKUT).

Renal hypoplasia; hearing loss and or abnormal ears

Developmental delay/intellectual disability:

Other reported anomalies are: external ear anomalies, abnormal branchial arch derivatives, heart malformations, diaphragmatic hernia, and ambiguous genitalia.

Examples of PBX1-related disorders are:

CAKUTHED syndrome: Congenital anomalies of the kidney and urinary tract syndrome with or without hearing loss, abnormal ears, or developmental delay.

Congenital heart disease: mutations in PBX1 have been linked to specific types of CHD, such as tetralogy of Fallot.

We present a case of a rare genetic disorder arising *de novo* in an otherwise normal couple without the defective genes.

Case history

A 35-year-old lady, gravida 2 para 0 plus 1, booked for antenatal care with no medical or social problems. She and her partner had no known medical problems and did not smoke or drink alcohol. She had a medical termination of pregnancy at 8weeks of gestation without any complications. Family history in both partners revealed no significant information. Her pregnancy was classed as a low-risk pregnancy. She had a dating scan at 13weeks and no fetal or pregnancy-related problems were noted. Routine combined screening gave a low risk for trisomy 21, 18, and 13. She had an anomaly scan at 19 weeks of gestation, and the following were the findings:

Fetal growth and amniotic fluid were normal.

Flexed breech, fetal movements were visualised.

Placenta, anterior, high. 3 vessel cord. Hyperechoic bowel. Enlarged heart.

The significant findings were discussed with her, and she was told these findings could be normal, related to PV bleeding, fetal infection, cyst fibrosis, or a rare chromosomal and genetic anomaly. Amniocentesis was discussed, and the couple later accepted it. She was later tested for CMV, toxoplasmosis, and cystic fibrosis (CF), all of which returned negative findings.

She was booked for a fetal echo and a rescan in the Fetal Medicine Unit (FMU). The findings were: *a ventricular septal defect (VSD), depressed sternum, and generalised skin oedema.* There was a hypoplastic right lung, and an eventration of the diaphragm was suspected. The latter was further confirmed on subsequent fetal MRI. There was a small stomach and a low-lying and mal-rotated left kidney. Amniocentesis revealed the following:

A normal QF-PCR analysis for chromosomes 21, 18, and 13 and X, and a normal arrayCGH.

In view of the abnormalities, exome sequencing was offered and accepted.

Exome sequencing was consistent with a molecular diagnosis of PBX1-related disorder:

The male fetus is heterozygous for the PBX1 c.863G>A p.(Arg288Gin) pathogenic variant.

Pathogenic variants in the PBX1 gene (MIM176310) are associated with congenital anomalies of the kidney and urinary tract with or without hearing loss, abnormal ears, or developmental delay (MIM617641).

After an MDT, it was decided that the PBX1 disorder contributed to the fetal presentation and that diaphragmatic eventration and respiratory issues after birth had been reported in neonates with this condition. However, the apparent absence of kidney/or urinary tract anomalies in the index fetus seemed to be unusual for the rate of PBX1-related disorder. Testing the couple showed no evidence of this variant in their lymphocyte DNA. These results were consistent with PBX1 c.863G>A

Citation: Madu AE. PBX1 Gene Disorder in the United Kingdom: Case Report and Review of Available Literature. J Gynecol Res Obstet. 2025;11(2):019-023. Available from: https://dx.doi.org/10.17352/jgro.000134

p.(Arg288Gin), a pathogenic variant having arisen *de novo* in the index fetus, and supported the evidence that this is a pathogenic variant of this disorder.

Further testing:

Following MDT discussion, further imaging of the fetal kidney and urinary tract was recommended. Prenatal testing could be offered to the couple in any future pregnancy to rule out the low risk of recurrence due to germline mosaicism.

Since this pathogenic germline was detected, the remaining filtered variants were not fully analysed. If the variant is not sufficient to fully explain the clinical phenotype in the fetus, scientists advised staff to contact the laboratory to initiate the analysis of the remaining data.

The last growth scan was at 30 weeks and 6 days. The findings were as follows:

Amniotic fluid, mildly increased, largest pool 10.5 cm

Fetal growth and dopplers maintained with AC on the 2nd centile

Small chest but proportional to a small abdomen.

Indentation on the chest (sternum).

Collapsed stomach.

Increased amniotic fluid volume suggestive of upper gastrointestinal obstruction

Fetal echo indicated cardiomegaly and a small muscular apical VSD.

Fetal movements were seen on the scan.

The couple was attended to by the FMU Specialist and the Clinical and Paediatric Genetic Specialist. The latter counseled the couple, and the options for management were: continuation of the pregnancy or termination of the pregnancy. The couple opted for the termination of the pregnancy.

Three days later, the woman was given oral mifepristone and advised to attend the labour ward two days later or earlier if she had signs of labour. She attended the labour ward 2 days later, as advised, for the induction of labour. She was given a bereavement package and placed under the local bereavement protocol.

Following vaginal examination, her cervix was closed and she was given vaginal misoprostol 100 mcg and then 6 hours later commenced on oral misoprostol 100 mcg 6 hourly. She was placed on 4-hourly observation.

At 21:00 the following day, her temperature was 38.9 degrees centigrade. She was given antipyretics, had venous access and a sepsis screen, and commenced on intravenous broad-spectrum antibiotics. She was placed under close observation.

The next day at 10:00 hours, her cervix was 2-3 cm dilated and significantly effaced. And oral misoprostol was continued.

At 14:00 hours, her cervix was 4 cm dilated and then 8 cm dilated at 15.30, and she delivered at 15:41.

Findings at delivery were:

Slightly macerated male fetus, with no signs of life.

The head circumference of the baby was 31 cm.

The length of the baby was 40 cm. The weight of the baby was 1,870 g.

Estimated blood loss was 200 mls.

24 hours later, her temperature remained normal; the intravenous antibiotics were stopped, and she went back on 4-hourly observations. Her temperature remained normal following delivery, and sepsis screen results did not reveal any significant findings. The couple declined post-mortem examination and also declined contraception, three days post-delivery. Two weeks later, placental histology stated:

Macroscopic description

A singleton placenta measuring 227X182x21 mm with a trimmed weight of 299 g. The umbilical cord is inserted marginally and measures 249 mm in length and 11 mm in diameter. The cord is oedematous in appearance; on slicing, three vessels are identified. Foetal membranes are present and appear slightly fibrotic. The maternal surface appeared complete and is lobulated. On slicing of the placental disc, a beefy red cut surface is identified and is unremarkable.

Microscopic description

The membranes show no inflammation. There is no funisitis of chorionic vasculitis. The chorionic villi show normal maturation. There are no avascular villi or thrombosed foetal vessels. There is no villitis or intervillositis. There is no infarction or increased perivillous fibrin deposit. There is no decidual vasculopathy.

Final diagnosis: normal weight and histology of the placenta. The ratio of the baby's weight at birth and the placental weight; that is, 1,870 g: 299 g, and the result was 6.25, which was normal.

Discussion

Pre-B-cell (PB) leukemia transcription factor 1 is a protein that in humans is encoded by the PBX1 gene. PBX1 is a member of the Three Amino Acid Loop Extension (TALE) class of homeodomain transcription factors, which are components of heteromeric protein complexes that regulate developmental gene expression and maintain differentiated cell states [5].

It made sense to open this discussion with Perry, et al. 2024 [6], which was one of the two citations of the Rare and Inherited Disease Genomic Laboratory. These authors stated that the Pre-B cell leukemia homeobox 1 (PBX1) gene on chromosome 1 encodes a transcription factor belonging to a family of proteins that interact with Hox proteins to regulate cellular proliferation and differentiation. The authors stated further that PBX1 was constitutively expressed in many tissues

Citation: Madu AE. PBX1 Gene Disorder in the United Kingdom: Case Report and Review of Available Literature. J Gynecol Res Obstet. 2025;11(2):019-023. Available from: https://dx.doi.org/10.17352/jgro.000134

throughout the body, including the bladder, kidneys, heart, and brain. During embryonic development, it was crucial in various pathophysiological processes in osteogenesis, renal morphogenesis, and morphologic mapping, these authors concluded.

Also, Perry, et al. [6] went on to state that several PBX1 variants have been recently reported to be associated with congenital anomalies of the kidney and urinary tract (CAKUT) syndrome, characterized by kidney and urinary tract syndrome with or without hearing loss, abnormal ears, or developmental delay (CAKUTHED). Additional case reports demonstrated *de novo* missense PBX1 variants in patients with congenital cardiac defects, such as outflow tract anomalies, septal defects, and great arteries.

Chen H, et al. [7], in a similar way, stated that PBX1 enhanced the recruitment of homeobox genes and the expression of target genes that regulate cellular proliferation and differentiation, and was a key transcriptional regulator of the development of multiple tissues and organs. The authors stated that it's tight binding to homeobox genes facilitated their transcriptional regulation, and that in the nervous system, PBX1 and its family members were important transcriptional regulators of neurons.

Peltenburge and Murre [8] stated that the PBX1 is a three-amino acid loop extension (TALE)-class homeodomain transcription factor that forms heterodimeric complexes with a subset of Hox homeodomain proteins essential for regulating segmental identities during development. However, in 1997, Peltenburg and Murre [9] stated that two classes of homeodomain proteins, Hox and Engrailed, have been shown to act in concert with the atypical homeodomain proteins PBX and extradenticle.

According to Arts P, et al. [10], autosomal dominant (*de novo*) mutations in *PBX1* are known to cause congenital abnormalities of the kidney and urinary tract (CAKUT), with or without extra-renal abnormalities. The authors stated that using trio exome sequencing, they were able to identify a *PBX1* p.(Arg107Trp) mutation in a deceased one-day-old neonate presenting with CAKUT, asplenia, and severe bilateral diaphragmatic thinning and eventration.

Writing from China, Nie L, et al. [11] stated in relation to a Chinese patient that congenital anomalies of the kidney and urinary tract syndrome(CAKUT) with or without hearing loss, abnormal ears, or developmental delay(CAKUTHED) was a rare autosomal dominant disorder, and variants in PBX1 were involved in the etiology of this syndrome. Precise diagnosis was difficult without genetic tests, the authors concluded.

Other Chinese researchers, Lou M, et al. 2022 [12], stated the PBX1 gene was located on chromosome 1q23.3. And encoded a transcription factor that promoted protein interaction and played a crucial role in several developmental processes. These researchers went further to state that PBX1 haploinsufficiency had been reported to lead to syndromic congenital anomalies of the kidney and urinary tract, and that patients with deletions involving the long arm of chromosome 1 were rare.

Researchers from Australia [13] noted that translocation (t1:19) q23:p13) occurs in about 5% of children with acute lymphoblastic leukemia and is often identified in African children, but the exact incidence in caucasian children remained unknown.

The case history chronicled the evolving scene from 19 weeks of gestation when the hyperechoic bowel and enlarged heart were identified on a routine anomaly scan, and investigations were therefore escalated, to the final genetic confirmation.

According to further evidence for classification from the Rare & Inherited Disease Genomic Laboratory, this variant was absent from the genomAD population database (PM2_ moderate), hence the author felt the need to report it. The apparent absence of kidney/or urinary tract anomalies in the index fetus seemed to be unusual to rare in PBX1-related disorder, which also made this case unique. This disorder had been reported to be *de novo* in individuals with PBX 1 1-related disorder [6], and our case also arose *de novo* with prenatal relationship as confirmed in this fetus (PS4_moderate, PS2_ strong), by scientists at the Rare & Inherited Disease Genomic Laboratory.

From the USA, Fitzgerald KK, et al. [4] reported three individuals with inherited pathogenic intragenic PBX1 deletion with variable clinical features typical of this syndrome, and all have *de novo* variants, as in our case. The authors stated that heterozygous *de novo* pathogenic variants in PBX1 disorder resulting in haloinsufficiency were associated with congenital malformations of the kidney and urinary tract, most commonly renal hypoplasia, as well as malformations involving the external ear, branchial arch, heart, and genitalia. The authors noted that the deletion also caused intellectual disability and developmental delay.

Petzold F, et al. [14], from Germany, reported a case of novel somatic PBX1 mosaicism likely masking syndromic CAKUT in an adult with bilateral kidney hypoplasia, which was found on a University of Manchester Library search.

An extensive literature search with the search term "PBX1-related disorders in the UK" did not reveal significant local or national publications. However, AI Overview stated that in the UK, PBX1-related disorders, especially those affecting kidney and urinary tract development, were rare but could be associated with congenital anomalies, hearing loss, and other developmental issues, with some cases linked to B-lymphoblastic leukemia (AI Overview, 2024).

McNeill A (undated) [15] from the University of Sheffield, England, United Kingdom stated the following: "*After the initial report in 2017 of a neurodevelopmental disorder associated with PBX1 single nucleotide variants, only single case reports have been published. We have collected 25 novel patients with PBX1 variants via DDD/100K/Genematcher. We wish to examine any genotype-phenotype correlation of missense and loss-of-function variants. We have pilot data of an episignature. We would like additional cases to help refine our genotype-phenotype correlation and episignature work*".

Citation: Madu AE. PBX1 Gene Disorder in the United Kingdom: Case Report and Review of Available Literature. J Gynecol Res Obstet. 2025;11(2):019-023. Available from: https://dx.doi.org/10.17352/jgro.000134

Also in Genomics England, there have been three inputs by Genomic England Curators; one had low evidence and was on the red list, two had some evidence and were on the amber list, unconfirmed by a curator, and seven were on the green list, confirmed by a curator [16]. We note there are indeed similarities between the presentation of this case and some of the other cases reported in Australia, Germany, China, and the US.

The author strongly believes an autopsy would have revealed more information about the various similar anatomical anomalies reported on serial ultrasound scans and MRI in this case, especially in relation to CAKUT and CAKUTHED syndromes. However, the author recognised the importance of respecting the wishes of a severely traumatised couple, who made an informed decision to decline an autopsy.

Conclusion

This case provided staff with new knowledge about the evolving and dynamic nature of advancing science. It emphasised the need for clinical vigilance, a high index of suspicion, and to look beyond what we already know, in relation to congenital and inherited anomalies, as new ones can present without warning. Our case was unique, as stated, and worthy of being reported and added to the medical literature.

References

1. Oxford Health NHS Foundation Trust. Genetic and Rare Disorders. 2021. Available from: https://www.oxfordhealth.nhs.uk/cit/resources/genetic-rare-disorders/
2. UK Gov. The UK Rare Diseases Framework. 2021. Available from: https://www.gov.uk/government/publications/uk-rare-diseases-framework
3. Indian Council of Medical Research (ICMR). National Consortium for Research and Development on Therapeutics for Rare Diseases: Rare diseases. 2020. Available from: https://rdrdb.icmr.org.in/#:~:text=Rare%20Diseases%3A,health%20care%20system%20and%20resources. Accessed on 9 February 2025
4. Fitzgerald KK, Powell-Hamilton N, Shillingford AJ, Robinson B, Gripp KW. Inherited Intragenic PBX1 Deletion: Expanding Phenotype. Am J Med Genet A. 2021;185(1):234–237. Available from: https://onlinelibrary.wiley.com/doi/10.1002/ajmg.a.61932
5. Mazilu JK, McCabe ERB. Moving toward personalized cell-based interventions for adrenal cortical disorders: Part 1—Adrenal development and function, and roles of transcription factors and signaling proteins. Mol Genet Metab. 2011;104:72–79. Available from: https://www.sciencedirect.com/science/article/pii/S1096719211001820
6. Perry E, Miller M, Heuerman A, Ahn H. P797: A likely pathogenic variant of PBX1: Abnormal renal morphology and multiple cardiac anomalies identified by fetal ultrasound. Conference Presentation Abstracts. 2024. Available from: https://scholarlyworks.beaumont.org/obgyn_confabstract/67/ Accessed on 9 February 2025
7. Chen H, Yu Z, Niu Y, Want L, Xu K, Liu J. Research progress of PBX1 in developmental and regenerative medicine. Int J Med Sci. 2023;20(2):225–231. Available from: https://www.medsci.org/v20p0225.htm
8. Peltenburg LT, Murre C. Engrailed and Hox homeodomain proteins contain a related Pbx interaction motif that recognizes a common structure present in Pbx. EMBO J. 1996;15(13):3385–3393. Available from: https://pubmed.ncbi.nlm.nih.gov/8698039/
9. Peltenburg LT, Murre C. Specific residues in the Pbx homeodomain differentially modulate the DNA-binding activity of Hox and Engrailed proteins. Development. 1997;124(5):1089–1098. Available from: https://journals.biologists.com/dev/article/124/5/1089/39786
10. Arts P, Garland J, Byrne AB, Hardy TSE, Schreiber AW, Crawford A, et al. Paternal mosaicism for a novel PBX1 mutation associated with recurrent perinatal death: Phenotypic expansion of the PBX1-related syndrome. Am J Med Genet A. 2020;182:1273–1277. Available from: https://onlinelibrary.wiley.com/doi/10.1002/ajmg.a.61541
11. Nie L, Li Y, Xiao T, Zhang B, Zhao J, Hou W. A Pathogenic Variant of PBX1 Identified by Whole Exome Sequencing in a Chinese CAKUTHED Case. Nephron. 2023;147(5):311–316. Available from: https://www.karger.com/Article/FullText/526847
12. Lou M, Gu X, Zhou T, Chen C. Prenatal diagnosis and molecular cytogenetic analysis of a prenatal inherited deletion of 1q23.3 encompassing the PBX1 gene. Mol Cytogenet. 2022;15:53. Available from: https://molecularcytogenetics.biomedcentral.com/articles/10.1186/s13039-022-00632-y
13. Kager L, Lion T, Attarbaschi A, Koenig M, Strehl S, Haas OA, et al. Incidence and outcome of TCF3-PBX1-positive acute lymphoblastic leukemia in Austrian children. Haematologica. 2007;92(11):1561–1564. Available from: https://haematologica.org/article/view/4616
14. Petzold F, Jin W, Hantmann E, Korbach K, Schönauer R, Halbritter J. Novel somatic PBX1 mosaicism likely masking syndromic CAKUT in an adult with bilateral kidney hypoplasia. Clin Kidney J. 2022;15(7):1333–1339. Available from: https://academic.oup.com/ckj/article/15/7/1333/6602147
15. McNeill A. Expanding the Phenotype of PBX syndrome. Undated. Accessed 9 April 2025. Available from: https://ern-ithaca.eu/our-research-activities/calls-for-collaboration/expanding-the-phenotype-of-pbx1-syndrome.
16. Genomics England. Gene: PBX1. Undated. Available from: https://panelapp.genomicsengland.co.uk/panels/entities/PBX1

Discover a bigger Impact and Visibility of your article publication with Peertechz Publications

Highlights

- Signatory publisher of ORCID
- Signatory Publisher of DORA (San Francisco Declaration on Research Assessment)
- Articles archived in worlds' renowned service providers such as Portico, CNKI, AGRIS, TDNet, Base (Bielefeld University Library), CrossRef, Scilit, J-Gate etc.
- Journals indexed in ICMJE, SHERPA/ROMEO, Google Scholar etc.
- OAI-PMH (Open Archives Initiative Protocol for Metadata Harvesting)
- Dedicated Editorial Board for every journal
- Accurate and rapid peer-review process
- Increased citations of published articles through promotions
- Reduced timeline for article publication

Submit your articles and experience a new surge in publication services
https://www.peertechzpublications.org/submission

Peertechz journals wishes everlasting success in your every endeavours.

Citation: Madu AE. PBX1 Gene Disorder in the United Kingdom: Case Report and Review of Available Literature. J Gynecol Res Obstet. 2025;11(2):019-023. Available from: https://dx.doi.org/10.17352/jgro.000134