# Multiple Neonatal Deaths and Alexander's Disease: A Case Report

Renu Makwana[1] Prateek Makwana[1] Simran Thawani[2] Neeraja Reddy Malleda[2]

[1] Department of Obstetrics and Gynecology, Vasundhara Hospital, Nandanvan, Jodhpur, Rajasthan, India
[2] LifeCell International Pvt Ltd, Chennai, Tamil Nadu, India

**Address for correspondence** Simran Thawani, MSc, CGC, LifeCell International Pvt Ltd, Vijayaraghava Road, I Lane, T.Nagar, Chennai - 600017, Tamil Nadu, India (e-mail: simran.m@lifecell.in).

J Fetal Med 2023;10:73–75.

**Abstract**

Factor VII deficiency, also known as Alexander's disease, is a rare bleeding disorder due to homozygous or compound heterozygous mutations in the *F7* gene and is inherited in an autosomal recessive manner. The condition manifests as a wide range of symptoms, based on the severity of the disease, and may appear at any age. While family and personal histories are essential for identification of the disorder, there is usually no history due to the autosomal recessive nature of the condition. Here, we report a case of factor VII deficiency in a family that was identified due to multiple neonatal deaths and the importance of genetic counseling and prenatal diagnosis for such scenarios.

**Keywords**

- Alexander's disease
- prenatal diagnosis
- genetic counseling
- exome sequencing

## Introduction

Factor VII is a vitamin K-dependent serine protease encoded by the *F7* gene located on chromosome 13q34. Factor VII exists as a zymogen at low concentrations in the plasma. While the origin of factor VIIa is still not clear, it binds with tissue factor, a membrane receptor protein that becomes exposed on breakage of the endothelium and activates the extrinsic pathway, leading to formation of the fibrin clot. The deficiency manifests in variable ranges and has been classified as severe, moderate, and mild forms, based on the extent of symptoms.[1]

Alexander's disease can have variable penetrance and manifestation ranging from mild bleeding to hemorrhages, with approximately 33% of individuals remaining asymptomatic throughout their life. Factor VII deficiency is one of the most common among the rare congenital bleeding disorders with a global prevalence of 1:500,000. However, it is more frequent in parts of the world where consanguinity is prevalent. One of the most common causes of death in newborns with factor VII deficiency is intracranial hemorrhage and is seen in almost 4% of the cases.[2]

In this report, we describe identification of factor VII deficiency in a couple after three neonatal deaths and prenatal diagnosis for the current pregnancy.

## Case Report

A 25-year-old female, G4P0D3, Rh-positive, euglycemic and euthyroid, in a non-consanguineous marriage for 10 years, presenting with three neonatal deaths and a current spontaneous pregnancy at 8 weeks gestational age was referred to our hospital. The first pregnancy was full-term, and the child was delivered at home. However, the child passed away on the third day of life, with no apparent reason. The second delivery was in a hospital, where again, the child died on the third day of life with no detected cause. During the third delivery, appropriate antenatal care was undertaken. In the 37th week of gestation, the obstetrician observed fetal distress and performed an emergency lower (uterine) segment caesarean section (LSCS), with steroid cover. Surprisingly, the child also deteriorated and expired on the third day of life due to intracranial hemorrhage and disseminated intravascular coagulation. Each

**article published online**
May 12, 2023

**DOI** https://doi.org/10.1055/s-0043-57020.
**ISSN** 2348-1153.



Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

time, the child passed away before a genetic investigation could be carried out. Other causes of intracranial hemorrhage, including infections, trauma, birth asphyxia, metabolic, cardiac and vascular disease as well insufficiency, were ruled out. Based on the bad obstetric history and an ongoing pregnancy, a clinical exome was suggested for both partners.

Based on the history, the clinical exome sequencing test was performed using Illumina next-generation sequencing systems at a mean coverage of 80 to 100X in the target region. Clinical exome revealed that both partners were heterozygous carriers for a nonsense likely pathogenic variant in the factor VII (NM_000131.4) gene, corresponding to factor VII deficiency in exon 9 (c.882C > A) that results in a stop codon and premature truncation of the protein (p.Tyr294Ter). While nonsense-mediated decay mechanism might come into effect here, as the variant lies in the last exon of the protein, the carboxyl-terminal region has been reported to be crucial for protein secretion. The endoplasmic reticulum (ER) recognizes the factor VII294X protein as a misfolded protein due to the absence of its catalytic domain and is degraded by the proteasome.[3]

The observed variant had a minor allele frequency of 0.0065% in the gnomAD database and was not reported in the 1,000 genome database. The reference base is conserved across the species and in silico predictions by Polyphen, Sorting Intolerant from tolerant (SIFT), and mutation taster were damaging. There are three downstream pathogenic loss of function variants, with the furthest variant being 170 residues downstream of this variant indicating that the region is critical to protein function.

Sanger sequencing via invasive prenatal testing for the variant was performed on the current fetus and the variant was not detected (►**Fig. 1**). A quantitative fluorescent-polymerase chain reaction was also performed to rule out any additional aneuploidy. A male child was delivered at the hospital with no complications, is currently 4 years old, and is alive and well. Extensive coagulation studies performed on the child and parents were reported to be normal (►**Fig. 2**).

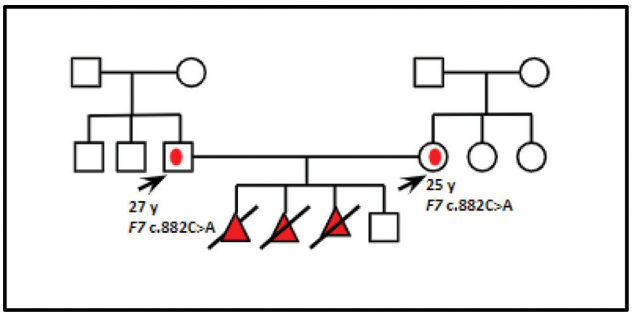


**Fig. 2** Three generational pedigree showing no family history of the disorder and three neonatal deaths at day 3 of life.

## Discussion

The identified variant has been reported as compound heterozygous with a pathogenic missense variant in the *F7* gene in an individual affected with asymptomatic factor VII deficiency.[3] An in vitro study based on pulse–chase experiments revealed that the identified variant led to extensive intracellular degradation of the protein, as compared to wild-type F7. In addition, the p.Tyr294Ter mutant protein was only observed in the ER, suggesting that it is not released extracellularly, leading to factor VII deficiency.[3]

Factor VII deficiency can be diagnosed using biochemical assays including factor VII:C and factor VIIa assays. It can also be identified based on the association between normal activated partial thromboplastin time and prolonged prothrombin time.[4] Prenatal diagnosis of the deficiency can be achieved by molecular genetic methods and has been reported in several cases with fetal hydrocephalus and intracranial bleeding being prenatal indicators.[4–7]

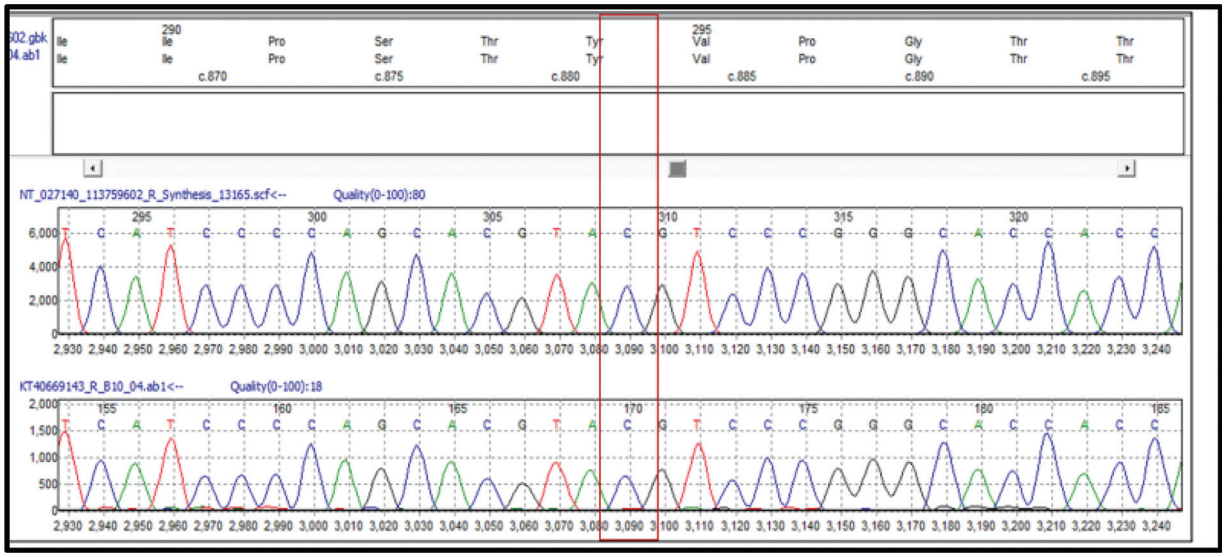


**Fig. 1** Sanger sequencing data (electropherogram) showing no nucleotide change at chr13, c.882C > A,(p.Tyr294Ter) in the *F7* gene in the prenatal sample for fourth child.

 

Management of factor VII deficiency includes fresh frozen plasma, factor VII concentrates, and recombinant factor VIIa.[5]

Farah et al reported prenatal diagnosis of two individuals affected by factor VII deficiency, one of whom had a near normal life after being treated with recombinant factor VII since birth, while the other has recurrent central nervous system bleedings leading to neurological manifestations.[4]

Absence of an established cause or uncertain reason for death often leaves the parents in distress. Neonatal death is a traumatic event for a family and can have devastating effects on the mother. It is often associated with guilt and depression and multiple neonatal deaths can magnify the emotional issues. During such instances, or cases where a definitive diagnosis or cause of death cannot be established, medical personnel often turn to genetic testing to look for answers and can be offered during the prenatal or early postnatal period.

Genetic counseling can prove to be helpful for couples and families to navigate the medical and psychological aspects of their diagnostic odyssey. It can help them understand inheritance patterns and risk of recurrence. Absence of any significant family history, with respect to the disorder, is often seen in India, even in nonconsanguineous marriages, due to a high prevalence of endogamy. Prenatal genetic testing helps in taking an informed decision about the pregnancy. In cases where the parents decide to continue the pregnancy with an affected fetus, it helps in preparing for life-saving early intervention along with giving the parents and families a chance to prepare themselves psychologically. Genetic counseling can also help couples understand and explore other assisted reproductive methods, such as in vitro fertilization with preimplantation genetic diagnosis or gamete donation.[8,9]

**Conflict of Interest**
None declared.

## References

1 Bernardi F, Mariani G. Biochemical, molecular and clinical aspects of coagulation factor VII and its role in hemostasis and thrombosis. Haematologica 2021;106(02):351–362
2 İnce Z, Bulut Ö, Tuğrul-Aksakal M, Ünüvar A, Devecioğlu Ö, Çoban A. Asymptomatic intracranial hemorrhage in a newborn with congenital factor VII deficiency and successful treatment with recombinant activated factor VII. Turk J Pediatr 2018;60(05): 562–565
3 Suzuki K, Sugawara T, Ishida Y, Suwabe A. Compound heterozygous mutations (p.Leu13Pro and p.Tyr294*) associated with factor VII deficiency cause impaired secretion through ineffective translocation and extensive intracellular degradation of factor VII. Thromb Res 2013;131(02):166–172
4 Farah R, Al Danaf J, Braiteh N, et al. Life-threatening bleeding in factor VII deficiency: the role of prenatal diagnosis and primary prophylaxis. Br J Haematol 2015;168(03):452–455
5 Landau D, Rosenberg N, Zivelin A, Staretz-Chacham O, Kapelushnik J. Familial factor VII deficiency with foetal and neonatal fatal cerebral haemorrhage associated with homozygosis to Gly180Arg mutation. Haemophilia 2009;15(03):774–778
6 Giansily-Blaizot M, Aguilar-Martinez P, Mazurier C, et al. Prenatal diagnosis of severe factor VII deficiency using mutation detection and linkage analysis. Br J Haematol 2001;112(01):251–252
7 Ariffin H, Millar DS, Cooper DN, Chow T, Lin HP. Prenatal exclusion of severe factor VII deficiency. J Pediatr Hematol Oncol 2003;25 (05):418–420
8 Komlosi K, Diederich S, Fend-Guella DL, et al. Targeted next-generation sequencing analysis in couples at increased risk for autosomal recessive disorders. Orphanet J Rare Dis 2018;13(01): 23. Doi: 10.1186/s13023-018-0763-0
9 Berisha SZ, Shetty S, Prior TW, Mitchell AL. Cytogenetic and molecular diagnostic testing associated with prenatal and postnatal birth defects. Birth Defects Res 2020;112(04):293–306

 