DOI: 10.21088/ijgmr.2319.4782.14125.3

Indian Journal of Genetics and Molecular Research
Volume 14 Number 1, January–June 2025

Case Report

Sudden Unexplained Death in Childhood (SUDC) in 3 Sibs

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How to cite this article:

Dhanashree J. Warang, Prochi F. Madon, Arundhati S. Athalye et. al, Sudden unexplained death in childhood (SUDC) in 3 sibs. Ind J Genet Mol Res. 2025; 14(1): 21-25.

ABSTRACT

This case report is directed at genomic testing and genetic counselling in unexplained rare genetic disorders of sudden unexplained death in childhood (SUDC) in a consanguineous couple where all three children, two boys and a girl, died between the ages of 1-4 years. No genetic test had been done previously. Whole exome sequencing (WES) of the parents later, showed that both carried a variant in the Desmoplakin (DSP) gene which has an autosomal recessive pattern of inheritance resulting in cardiomyopathy, and in the Sodium voltage-gated channel, beta subunit 3 (SCN3B) gene which has an autosomal dominant inheritance pattern with variable penetrance, late or early onset and is associated with Brugada syndrome. From the case histories, it was possible to determine that the daughter was homozygous for the DSP variant, while the sons inherited the SCN3B variant. During post-test genetic counselling, the reproductive option given was preimplantation genetic testing for monogenic disorders and aneuploidies (PGT-M + PGT-A). This study reasserts the application of genomic testing such as WES in routine medical assisted reproductive practices.

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➢ **Received:** 01-04-2025 ➢ **Accepted:** 10-06-2025

KEYWORDS

• Sudden unexplained death in children • SUDC • Brugada syndrome • Preimplantation genetic testing • PGT • Genetic counselling.

INTRODUCTION

The term 'sudden unexplained death in childhood' (SUDC) or 'sudden infant death syndrome' (SIDS) (OMIM 272120) is used to describe a clinical condition of sudden death of children. SUDC is the unexpected death of a child over the age of 12 months that remains unexplained.[1] Since the decedent is an infant or child, this intensifies the anguish of family, friends and the community at large. SUDC, with a rate of 1.0-1.4 deaths per 100,000 of the population, affects mainly toddlers aged greater than 1 year with the highest incidence in 1-4-year-olds.[2] Mechanisms underlying SUDC remain largely speculative. Epidemiological, clinical, biochemical, immunological and pathological evidence indicates that three factors must coincide for SIDS to occur: a vulnerable developmental stage of the immune system and central nervous system in the infant, predisposing factors, and external trigger events.[3] Pathological evidence implicates abnormalities in brainstem autonomic and serotonergic nuclei, critical for arousal, cardiorespiratory control, and reflex responses to life-threatening hypoxia or hypercarbia in sleep.[4] Specific genetic contributions to sudden unexplained death in paediatric cases were reported in 11% of the cohort of a genomic study including 73 whole exome sequencing trios by Koh et al., highlighting the role of genetics and indicating diverse mechanisms for the diagnosis.[5] Among the 37 variants seen in these cases, 13 were in genes related to neurologic disease, 18 in cardiac-related disease genes, and 6 in systemic or syndromic disease genes. In another large genomic study, *de novo* variants were mainly seen in genes associated with cardiac and seizure disorders relative to controls, and contributed to 9% of deaths.[6] The present case report of genetic testing and counselling is from a consanguineous family of Thane, Maharashtra, with a history of sudden death in three children. Details of clinical report and genetic investigation include performance of whole exome sequencing of the couple to unearth likely pathogenic variations in genes and offer genetic counselling before considering assisted reproduction.

CASE REPORT

A consanguineous couple, first cousins, approached us for genetic counselling with a history of sudden death in three children. The wife was 32 years old and the husband was 39. They were married for 11 years. They wanted to investigate the options of having a normal living child using their own gametes.

Setting: A multi-speciality private hospital.

Consent for genetic study: The genetic study of the couple was done elsewhere and they approached us with the reports for reproductive genetic counselling.

Ethics clearance: Ethics clearance was not required as no invasive testing was done, and the identity of the couple has not been revealed.

Clinical history:

Their eldest son was born by normal delivery. Antenatal sonography was normal. His birth weight was 2.75kg. Till 14 months all the developmental milestones were normal. One night after 14 months, he had three episodes of vomiting. 12 hours later he was active and playful. Suddenly he had convulsions and sudden cyanosis and was brought dead to the hospital. Autopsy revealed interstitial pneumonitis with cerebral oedema.

Their 2nd child, a daughter, was born full term by Caesarean section. At the age of four years, she had normal motor milestones but delayed speech. At this stage, she was diagnosed with dilated and restrictive cardiomyopathy and died after seven months.

The 3rd child, a son, was born full term by Caesarean section. At the age of two years, all his developmental milestones were normal. He had a single episode of vomiting while playing followed by sudden convulsions and was brought dead to the hospital.

All three children had no dysmorphic features and no developmental delay. Their height and weight were normal. No genetic testing was carried out for any of the children before or after their death.

Family history:

The couple had consanguinity in their extended family too, including the wife's parents. The husband's brother died in infancy. No reason for death was reported. The wife's sister died suddenly at the age of 3 years. Again, no cause of death was available. The family tree is shown in Figure 1.

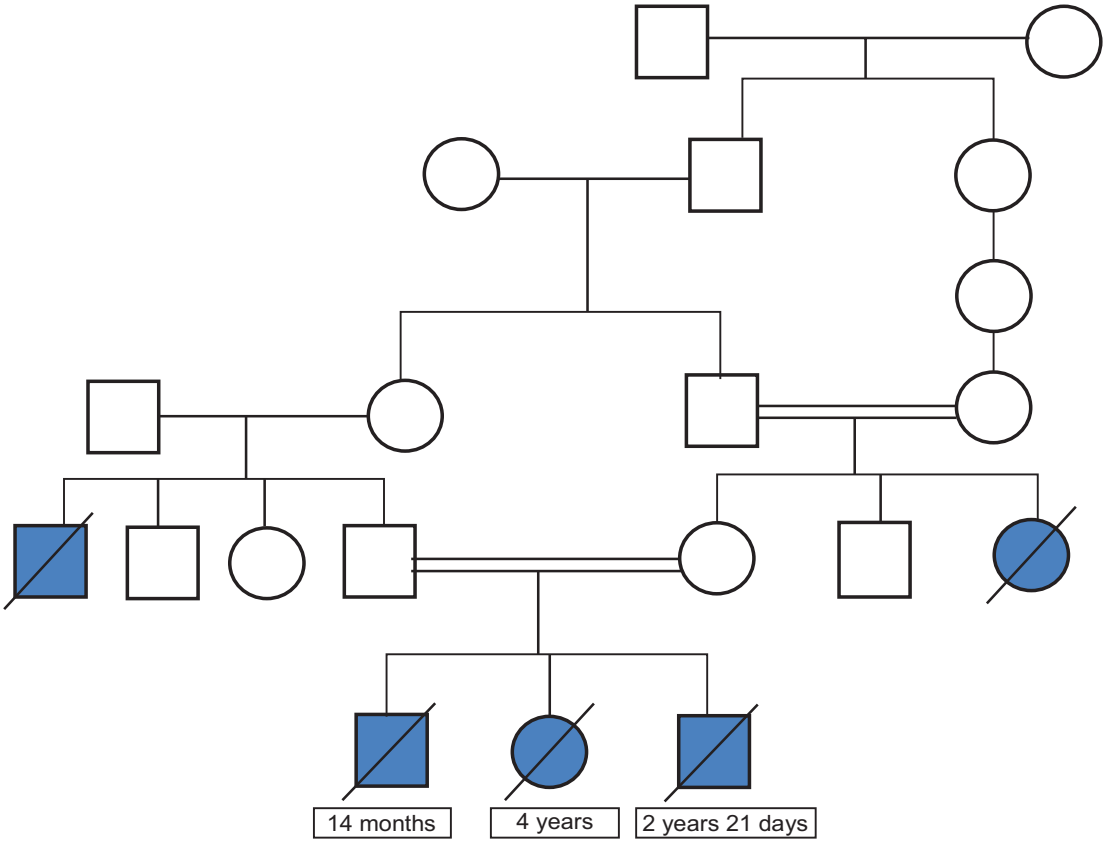

Figure 1: Pedigree analysis of the family

INVESTIGATIONS

Karyotyping of the couple was carried out elsewhere using standard methods to check for the presence of any structural rearrangements. Both their karyotypes were normal.

Since the couple had a cousin marriage, they were earlier also advised whole exome sequencing (WES) elsewhere to identify likely pathogenic variant/s which could have caused the sudden death of their two sons and cardiomyopathy in their daughter. WES revealed that both partners were heterozygous for likely-pathogenic variants in the following 2 genes:

Variant c.3384_3388delGGAAG of Desmoplakin (DSP) gene in Exon 23 on chromosome 6 at the p24 region. This variant causes the deletion (p.glu1129Glnfs*3) in the DSP protein sequence. The gene encodes a protein that anchors intermediate filaments to desmosomal plaques and forms an obligate component of functional desmosomes. Variations in this gene are the cause of several cardiomyopathies and keratodermas, including skin fragility-woolly hair syndrome (NCBI-Gene 1832). The transmission of this disorder is in an autosomal recessive manner. It is associated with dilated cardiomyopathy, woolly hair and keratoderma.[7] Individuals with this disorder suffer heart failure in their early years resulting in early morbidity.[8] This suggested that their daughter may have been homozygous for this variation resulting in cardiomyopathy.

Variant c.160G>A in the sodium voltage gated channel, beta subunit 3 (SCN3B) gene Exon 2 on chromosome 11 at 11q24.1.

This variant causes a missense mutation (p.Val54Met) in the SCN3B protein sequence. The voltage-gated sodium channels are transmembrane glycoprotein complexes composed of a large alpha subunit and one or more regulatory beta subunits. They are responsible for generation and propagation of action potentials in neurons and muscle. This gene encodes one member of the sodium channel beta subunit gene family and influences the inactivation kinetics of the sodium channel (NCBI-gene 55800). The transmission of this disorder is autosomal dominant. It is associated with Brugada syndrome 7.[9] A male predominance has also been reported, characterized by cardiac conduction abnormalities such as ST-segment abnormalities on ECG and a high risk for ventricular arrhythmias, which could result in sudden death.[10] It presents primarily in adulthood, but it may be diagnosed from infancy to late adulthood. Though the mean age of sudden death is seen as 40 years, the sudden unexplained infantile death syndrome (SUDS) in childhood is also known to occur. It could be due to homozygosity of the autosomal dominant disorder in a consanguineous marriage, as in the present case. Hence the diagnosis of Brugada Syndrome 7 in both the sons, who had sudden unexplained infantile death in the present case, is very likely.

Both the partners also had death of a sib in childhood hence it is likely that those sibs could have been homozygous for the DSP gene variant, or may have had Brugada Syndrome 7, which is autosomal dominant with incomplete penetrance, variable expressivity and can have a late onset.

In addition, both partners were also heterozygous for different autosomal recessive variants, LMNA (Exon 6 c.1027c>T) related to Emery-Dreifuss muscular dystrophy in the husband and SCN5A (Exon 2 c.123G>C) related to Sick sinus syndrome 1 in the wife, though this is not significant.

DISCUSSION

Two likely pathogenic variants were identified in this study in an Indian family. One was autosomal recessive in the DSP gene, while the other was autosomal dominant in the SCN3B gene, seen in Brugada Syndrome 7 (OMIM 613120), with incomplete penetrance, variable expressivity and late onset. It is characterized by a type 1 electrocardiogram (ECG) with ST-segment elevations in the right precordial leads (V1-V3), and can lead to a high risk of sudden cardiac death in patients with structurally normal hearts. Though the inheritance is autosomal dominant, the onset of symptom visibility can be around the age of 40. Since the husband was 39 years old and the wife was 32 years, the couple were informed of the possible risk of having symptoms for Brugada Syndrome 7 later in life, and hence were advised to consult a cardiologist and consequences of the occurrence of sudden cardiac complications were explained. They were also counselled to test their sibs for the Brugada Syndrome 7 variation.

Reproductive Genetic counselling

The option of preimplantation genetic testing for monogenic disorders (PGT-M) for the DSP and SCN3B variants after pre-PGT Sanger sequencing, together with 24-chromosome aneuploidy testing (PGT-A) as extra steps during assisted reproduction with intracytoplasmic sperm injection (ICSI), if not cost prohibitive, would help to select an unaffected embryo for transfer to the uterus.[11-12] This would help to avoid the trauma of losing another child. After getting pregnant with PGT, prenatal diagnosis from CVS at 11-12 weeks, or amniotic fluid around 17 weeks is recommended for reconfirmation. Alternatively, the most cost-effective option would be intrauterine insemination (IUI) with donor sperm after checking the WES report of the donor.

Brugada syndrome could also pose arrhythmic risk during pregnancy due to hormonal and hemodynamic changes, hence the option of surrogacy was also discussed. This illustrates how genetic counsellors can play a crucial role in guiding patients to be aware of specific late onset disorders and actionable variants, if genomic testing suggests that they may be prone to develop some symptoms later on.

CONCLUSION

This case report highlights the importance of genomic testing and genetic counselling in unexplained genetic disorders. Even though the couple's three children had sudden unexplained death (SUDC) and no genetic testing or DNA storage was done

earlier, whole exome sequencing carried out subsequently on the consanguineous couple picked up variants in two genes, DSP and SCN3B, which could have been the likely cause of demise. To avoid this in a future pregnancy, preimplantation genetic testing (PGT) of the embryos from trophectoderm biopsies after intracytoplasmic sperm injection would help to select the best embryo for single embryo transfer. An economical option would be the use of a donor gamete. Such information is explained to couples by genetic counsellors. This couple is also at increased risk of premature cardiac problems since SCN3B has an autosomal dominant pattern of inheritance and a later age of onset. Genetic counsellors recognize such actionable variants and inform patients to be aware and consult a specialist such as a cardiologist in this case, for early detection and monitoring. DNA extraction from blood collected in EDTA, or a tissue such as a toe, or products of conception in case of a miscarriage is very useful for future studies in the families. In an emergency, samples could be refrigerated till arrangements are made for pick up by any of the large genomic laboratories even from small towns in our country for DNA extraction and storage at a minimal cost for future use. This should become a part of routine clinical practice now.

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