No family history of recurrent abortion.
O/E wife unremarkable.
Husband tall others unremarkable.
Diagnostic Workup: Chromosomal study from peripheral blood sample of the women (wife) showed one metaphase with three copies of chromosome 21. All other 19 metaphases were normal female karyotype.
Interphase FISH (fluorescent in situ hybridization) was performed using Locus Specific Probe for 21q22.13-q22.2 to look for gain/loss of chromosome 21. Of a total of 200 interphase nuclei examined, 6.5% of the cells showed 3 signals for chromosome 21. This is a very low level of mosaic trisomy 21. Again this results have been confirmed with another fresh blood sample.
Chromosomal study from peripheral blood sample of the husband showed presence of one metaphase with extra X chromosome while other 19 metaphases were normal male karyotype.
FSH studies using probe for DXZ1 (X centromere) and SRY (Yp11.3) showed presence of 3 types of clones:
- 5.5% 2 signals for DXZ1 and 1 signal for SRY (47,XXY).
-4.5% 2 signals for DXZ1 and 2 signal for SRY (48,XXYY).
-90% 1 signal for DXZ1 and 1 signal for SRY (46,XY).

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Genetic characterization of *PYCR1*-associated De Barsy syndrome in a Pakistani family through whole exome trio sequencing

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Treatment and Management: The neonate was admitted to the neonatal intensive care unit immediately post-birth due to respiratory distress, receiving low-flow oxygen (2L/min), which was increased to 4L/min via bCPAP due to increased respiratory effort. Broad-spectrum antibiotics and antifungals were started preemptively to control potential sepsis, and caffeine citrate was administered for apnea of prematurity. Nutritional needs were supported via total parenteral nutrition. A multidisciplinary team, including a neonatologist, pediatric surgeon, orthopedic specialist, and ophthalmologist, was engaged to manage and monitor complications. Early interventions for bilateral talipes equinovarus, such as taping and strapping, were initiated. The family received counseling on the prognosis and home care requirements.
Outcome and Follow-Up: The proband experienced progressive failure to thrive with persistent respiratory and feeding difficulties. Despite supportive care, he passed away on 15th day of life after suffering a massive pulmonary hemorrhage. Genetic counseling was provided to the family to explain recurrence risks and prenatal screening for future pregnancies.
Discussion: This case represents the first genetically confirmed report of DBS in Pakistan. Although a case of DBS was reported in a family of Pakistani origin in 2008, no confirmatory genetic testing was performed. Previous studies have shown that Arg251 is directly involved in stabilization of the inter-homodimer interactions and thus loss of multimerization leads to severe phenotype. Moreover, Arg215His variant is also reported to correlate with reduced expression of *PYCR1* in skin fibroblasts.
Conclusion: In conclusion, this report highlights the clinical and diagnostic complexity of DBS and underscores the value of comprehensive genetic testing, as an essential diagnostic and management tool for rare genetic disorders with phenotypic overlap.
Introduction: De Barsy Syndrome (DBS), or cutis laxa type IIIB, is a rare autosomal recessive connective tissue disorder predominantly caused by variants in the *PYCR1* gene. It is clinically characterized by progeroid features, cutis laxa, skeletal abnormalities, and multi-system involvement, that mimics other progeroid syndromes, making diagnosis challenging. Here, we present a genetically confirmed case of DBS expanding the phenotypic spectrum and underscoring the utility of whole exome trio sequencing (ES-Trio) in differentiating rare yet overlapping disorders.
Case Presentation: We report a one-day-old male infant born at 34 weeks gestation to a multigenerationally consanguineous family (gravida 6, para 6) via lower segment cesarean section, following a two-week history of oligohydramnios and intrauterine growth restriction. At birth, Apgar scores were 7 and 8 at 1 and 5 minutes, respectively, with anthropometric measurements: weight of 1290g, length of 38cm, and occipital-frontal circumference of 27.5cm. Key clinical features included a progeroid appearance, extensive skin wrinkling, triangular face, large fontanelles, wide cranial sutures, corneal clouding, hyperextensible joints with finger contractures, prominent chest and abdominal veins, bilateral cryptorchidism, and bilateral talipes equinovarus.
Diagnostic Workup: Standard G-banding karyotyping was unremarkable, revealing 46,XY genotype. Initially suspected to have Wiedemann-Rautenstrauch syndrome, the infant underwent genetic testing for *POLR3A*, which did not reveal pathogenic or likely pathogenic variants. The case was then referred to a geneticist for further assessment and underwent ES-Trio. Whole blood samples from the proband and parents were collected for DNA extraction and sequencing. Variants were interpreted according to ACMG/AMP guidelines, and structural modeling tools were used to assess the functional impact of variant under investigation.
The proband harbored a likely pathogenic variant in a homozygous state within exon 6 of *PYCR1* (c.752G>A; p.Arg251His). The variant had high pathogenicity scores (REVEL, SIFT, PolyPhen-2), and structural analysis indicated disruption of a salt bridge between Arg251 and Glu246. The genotype-phenotype correlation and the heterozygous carrier status of the parents for this variant confirmed the diagnosis of DBS.

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