Case Report

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Robinow Syndrome: Rare Case Report With Novel Variant Frameshift Mutation Of The ROR2 Gene And Orofacial Manifestations

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Authors' contributions
AK, MM, ID, LA, RA, HD, RA, NM, and AI interpreted the patient data regarding the disease, designed the case report, and contributed to the manuscript. All authors read and approved the final manuscript.

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1. Abstract

Robinow syndrome is a rare genetic disorder caused by mutations in the ROR1, WANT5A, DVL1, and DVL3 genes, which can be inherited in an autosomal recessive or autosomal dominant manner. This syndrome is characterized mainly by limb anomalies, orofacial defects, micropenis, and hemivertebrae. We report a newborn with autosomal recessive Robinow syndrome and autosomal dominant brachydactyly, a rare variant associated with ROR2 gene mutations, characterized by bilateral cleft lips, hypertelorism, mesomelic limbs, a buried small penis, and hemivertebrae, in addition to cleft palate and scoliosis, which are unusual anomalies in this syndrome. Robinow syndrome is a rare genetic disorder with diagnostic and treatment challenges, and there are few cases reported worldwide. This case is reported from a developing country with limited facilities for genetic studies.

2. Keywords: Robinow syndrome, Facial dysmorphism, autosomal recessive, ROR2 gene, Sudan

3. Background

Robinow syndrome is a rare genetic heterogeneous condition caused by variation in a series of genes such as receptor tyrosine kinase-like orphan receptor2 (ROR), nucleoredoxin (NXN), WNT family member 5A (WNT5A), Frizzled class receptor 2(FZD2) DVL1, DVL3 as they are considered to be part of the non canonical beta-catenin-independent signaling cascade, The syndrome is characterized by mesomelic limb shortening associated with facial and genital anomalies that can be inherited in an autosomal dominant or recessive mode [1]. So far, approximately 200 cases have been reported worldwide [2].

ROR2-associated Robinow syndrome is inherited as an autosomal recessive disorder, whereas DVL1 and DVL3 variants are autosomal dominant [3]. Other features include a fetus-like face, increased orbital distance, a wide mouth, and a short nose. Infrequent anomalies include visible gingival hyperplasia and mesomelic limb shortening. Males usually have a micropenis. Other associated anomalies include brachydactyly with small hands for age [4].

Here, we report a case of Robinow syndrome confirmed by genetic testing, with a likely pathogenic variant in the ROR2 gene (c.1067del (p.Pro356Leufs*89). To our knowledge, this variant has not been reported in individuals with ROR2-related conditions.

4. Case Presentation

A male baby was admitted to our neonatal unit from birth due to multiple congenital anomalies. An antenatal scan had detected abnormal bone development and craniofacial abnormalities. The patient's parents were consanguineous with no family history of Robinow syndrome. He was delivered at term by spontaneous vaginal delivery. On physical examination, birth weight was 2.6 kg, and his length was 42 cm(below the 3rd percentile); his head circumference was 36 cm (on the 50th percentile). There were obvious dysmorphic features, including a broad forehead, an excessive amount of hair on the forehead, cheeks, and external ears. Ears were low-set and posteriorly rotated. Eyes showed hypertelorism; normal eyelashes and eyebrows with an epicanthic fold; pupils were reactive. Broad flat nasal bridge with a deformed nose attached to bilateral cleft lip and bilateral full cleft palate, gingival hypertrophy, and segmented with the shape of teeth. (Figure 1), The lower lip, chin, and tongue were normal. Chest examination: bulging right side, widely spaced nipples with well-developed breast tissue 1.5cm both lateral to the mid-clavicular line, bifid xiphoid process (Figure 2).

Musculoskeletal examination: short stature with short limbs;

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Length 42cm (below 3rd percentile), arm span 34cm, both right and left upper limbs 13 cm, from shoulder to elbow joint 8 cm, and from elbow to wrist 5 cm. Upper segment 25cm, lower segment 17cm (upper segment/Lower segment 1.4). Hands and feet examination revealed brachydactyly, clinodactyly, and amputation-like phenotype (Figure 3,4).

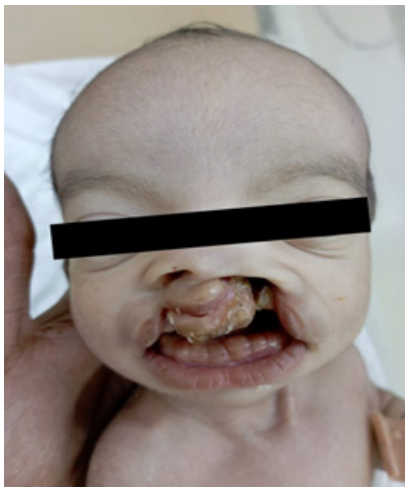

Figure 1. Characteristic facial features.

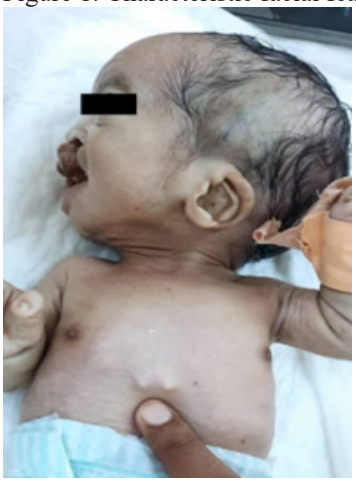

Figure 2. Bifid xiphoid process

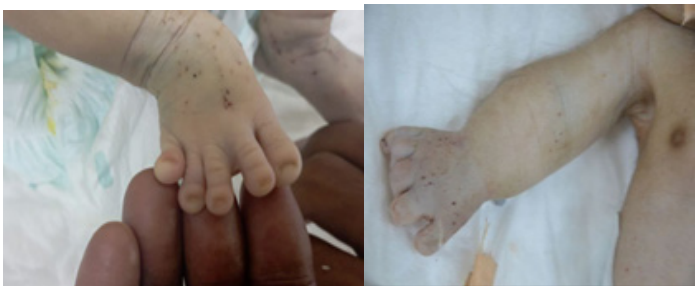

Figure 3. Clinodactyly of the toes. Figure 4. Brachydactyly, clinodactyly, and amputated-shaped fingers.

Genital examination showed a buried penis with a descended testis (Figure 5).

The cardiovascular system, the central nervous system, and the abdominal and back examination didn't show any abnormality, and his anus was patent.

Chest and limbs X-ray showed severe micromelic shortness, right clavicular dislocation, hemi-vertebra, scoliosis, and fused ribs. (Figure 6, 7). Echocardiography and abdominal ultrasound were normal.

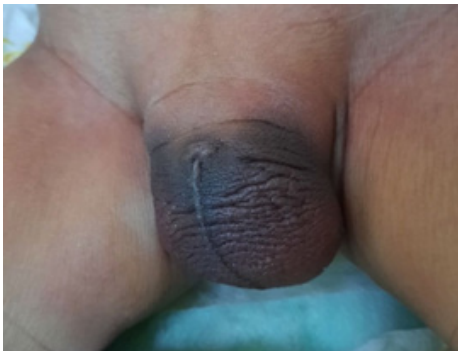

Figure 5. Micropenis.

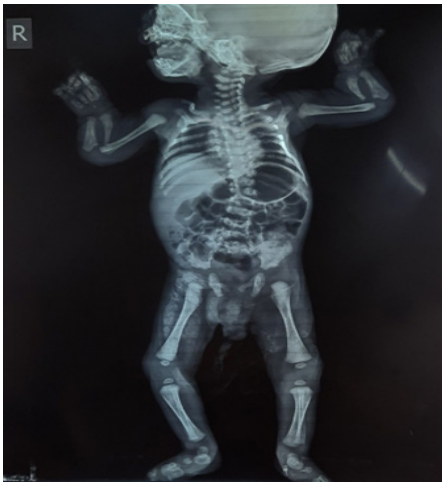

Figure 6. Chest and four limbs X-ray showed severe micromelic shortness, right clavicular dislocation, hemi-vertebra, and scoliosis.

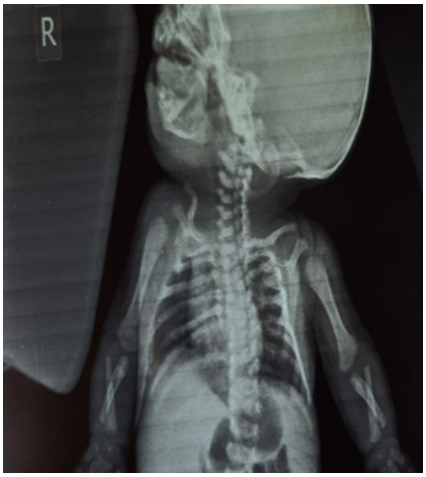

Figure 7. Chest X-ray showing hemi-vertebra, scoliosis, and abnormal rib development.

Because of the rarity of such findings, plastic surgery, orthopedics, urology, nephrology, pediatrics, and surgery were involved.

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Postnatally, he passed through a stormy course of respiratory distress and sepsis, where the blood culture was positive for pseudomonas aerugiosa.

A blood sample was taken from the patient and sent to the USA for genetic study, a skeletal disorders panel was performed at INVITAE corporation, and the result came back positive for Robinow syndrome, which showed two pathogenic variants identified in ROR2, which is associated with autosomal dominant brachydactyly (MedGen UID:349432) and autosomal recessive Robinow syndrome(MedGen UID:341431).

This result is consistent with a predisposition to, or a diagnosis of, AR ROR2-related conditions. Additional Variants of Uncertain Significance were identified.

Variant details:
ROR2, Exon 7, c.1067del (p.Pro356Leufs*89) homozygous, pathogenic.

This sequence change creates a premature translation stop signal (p.Pro356Leufs*89) in the ROR2 gene. It is expected to result in an absent or disrupted protein product. Loss-of-function variants in ROR2 are known to be pathogenic (PMID: 10932186)

This variant is not present in population databases (GenoAD, no frequency)

This variant has not been reported in the literature in individuals affected with ROR2-related conditions

For these reasons, this variant has been classified as pathogenic.

On the 15th day, the patient developed seizures, decreased level of consciousness, bulging anterior fontanelle, pallor, and acidotic breathing. He received anticonvulsants, and investigations showed acute kidney injury and anaemia. Unfortunately, the patient passed away due to severe sepsis.

5. Discussion

In 1969, Robinow and colleagues described a syndrome of mesomelic shortening, hemivertebrae, genital abnormalities, and facial dysmorphism. [5]

Robinow syndrome is an extremely rare genetic disorder that exhibits variable clinical features and genetic mutations [1]. Our case identified two pathogenic variants in ROR2, which is associated with autosomal dominant brachydactyly and autosomal recessive Robinow syndrome. This result is consistent with a predisposition to, or diagnosis of, AR ROR2-related conditions with the following variant details: ROR2, Exon 7, c.1067del (p.Pro356Leufs*89), homozygous, pathogenic. This sequence change creates a premature translational stop signal (p.Pro356Leufs*89) in the ROR2 gene. It is expected to result in an absent or disrupted protein product. Loss-of-function variants in ROR2 are known to be pathogenic (PMID: 10932186).

This variant is not present in the population database (gnomAD no frequency). This variant has not been reported in the literature in individuals affected with ROR2-related conditions. For these reasons, this variant has been classified as Pathogenic.

In only two previous case reports, mutations were reported in Exon 7: the first in 2000, in which band shifts suggestive of homozygous changes were observed on single-stranded conformational polymorphism (SSCP) analysis in exon 7 (6). The second case report in 2008 reported the clinical and molecular findings of two sibling pairs from the same extended family with Robinow syndrome due to a novel intragenic ROR2 deletion involving exons 6 and 7 that could not be detected by sequencing [7]. In another case reported in 2002, they mentioned that the Autosomal recessive Robinow syndrome is caused by distinct homozygous missense, nonsense, and frameshift mutations; while the heterozygous terminating mutations in the ROR2 gene were shown to cause the autosomal dominant condition of brachydactyly type B, which is characterized by terminal deficiency of fingers and toes [8].

Regarding our patient the gene point mutation was frameshift mutation c .1067del (p.Pro356Leufs*89); few case reports were found to be associated with ROR2 frameshift mutations; one case report in the year 2000 where they reported four novel mutations in ROR2 two of them were frameshift, one splice mutation and one nonsense mutation in five families with brachydactyly type B. [6]. Another case report in 2015 where they identified de novo frameshift mutation in DVL1, a mediator of both canonical and non-canonical Wnt signaling [9]. A recent 2022 case report described a novel frameshift heterozygous mutation in DVL1, inducing Robinow syndrome (c.1620delC(p S542Vfs*107)[1]. It is noted that most frameshift mutations are associated with autosomal-dominant Robinow syndrome, whereas in our patient, the genetic study results are consistent with an autosomal recessive ROR2-related condition.

In our case, the pregnancy and delivery were uneventful with a normal birth weight, which is consistent with the literature, as 100% had a normal pregnancy, 89% normal birth weight; however, there was no family history of Robinow syndrome, as 41% usually have a positive family history [10].

Most of the dysmorphic features in our case were reported in the literature. Hypertelorism, short upturned nose, and mesomelic brachymelia, which are present in our case, have been described to be present in 100% of cases. Our case had gingival hyperplasia, which is present in 65%, and cleft lip and palate, which is present in only 9% of cases.

Our case had hypoplastic genitalia, which is present in 94% of the patients, but both testes were descended, as cryptorchidism is present in 65% of cases [10]. Around 15% of published cases have had congenital heart defects [11], but they were not identified in our patient, the same as renal anomalies, as they were reported in 29% of patients [10].

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Additionally, in nearly all previously reported cases, the most commonly observed skeletal dysplasia was mesomelia [10], whereas our patient exhibited micromelia. Previously, micromelia had been reported in only four patients with Robinow syndrome, and it was concluded that while Robinow syndrome has typically been described as a mesomelic syndrome, rhizomelia and mesomelia are also observed. Forearm shortening tends to be more severe than shortening of the lower-extremity segments [12], as in our patient's skeletal presentation. Moreover, our patient had a right dislocation of the acromioclavicular joint, and only a few case reports have described bilateral hip joint dislocation [1] and radioulnar dislocation in two sisters with Autosomal recessive Robinow syndrome [13].

Robinow syndrome generally has a favorable prognosis, attributable to the limited involvement of the nervous system and other vital organs. Our index case passed through a stormy course of neonatal sepsis and died on day 15 of birth. This is not unusual, as patients with Robinow syndrome are usually prone to infections [14].

6. Conclusion

In conclusion, we have described a neonate with Robinow syndrome who is considered to be the youngest patient diagnosed and reported, and the first to be reported in Sudan. Also, we have identified a novel pathogenic variant associated with ROR2 mutations. This case underscores the importance of predicting Robinow syndrome in similar conditions and highlights the need to perform genetic analysis in families with such clinical features.

References

1. Ruolan Hu , Yu Qiu , Yifewi Li JL. A novel frameshift mutation of DVL1-induced Robinow syndrome: A case report and literature review. Mol Genet Genomic Med . 2022 ;10(3):e1886.
2. Saraswat S, Mohanty S. Robinow syndrome: A rare case report from a tertiary care hospital in Eastern India. Int J Pediatr. 2016;4(10):3643–9.
3. Kirat E, Mutlu Albayrak H, Sahinoglu B, Gurler AI, Karaer K. Autosomal recessive Robinow syndrome with novel ROR2 variants: Distinct cases exhibiting the clinical variability. Clin Dysmorphol. 2020;29(3):137–40.
4. Al Kaissi A, Bieganski T, Baranska D, Chehida FB, Gharbi H, Ghachem MB, et al. Robinow syndrome: Report of two cases and review of the literature. Australas Radiol. 2007;51(1):83–6.
5. Robinow M, Silverman FN, Smith HD. A newly recognized dwarfing syndrome. Am J Dis Child 1969;117:645-51.
6. Afzal AR, Rajab A, Fenske CD, Oldridge M, Elanko N, Ternes-Pereira E, et al. Recessive Robinow syndrome, allelic to dominant brachydactyly type B, is caused by mutation of ROR2. Nat Genet. 2000;25(4):419–22.
7. Brunetti-Pierri N, Del Gaudio D, Peters H, Justino H, Ott CE, Mundlos S, et al. Robinow syndrome: Phenotypic variability in a family with a novel intragenic ROR2 mutation. Am J Med Genet Part A. 2008;146(21):2804–9.
8. Patton M , Afzal A. Robinow Syndrome. J Med Genet. 2002 ; 39(5): 305–310.
9. Bunn KJ, Daniel P, Rösken HS, O'Neill AC, Cameron-Christie SR, Morgan T, et al. Mutations in DVL1 cause an osteosclerotic form of robinow syndrome. Am J Hum Genet. 2015;96(4):623–30.
10. Butler MG, Wadlington WB. Robinow syndrome: report of two patients and review of literature. Clin Genet. 1987;31(2):77–85.
11. Webber SA, Wargowski DS, Chitayat D, Sandor GGS. Congenital heart disease and Robinow syndrome: Coincidence or an additional component of the syndrome? Am J Med Genet. 1990;37(4):519–21.
12. Abu-Ghname A, Trost J, Davis MJ, Sutton VR, Zhang C, Guillen DE, et al. Extremity anomalies associated with Robinow syndrome. Am J Med Genet Part A. 2021;185(12):3584–92.
13. Mehawej C, Chouery E, Maalouf D, Baujat G, Le M, Cormier-daire V, et al.Identification of a novel causative mutation in the ROR2 gene in a Lebanese family with a mild form of recessive Robinow syndrome. Eur J Med Genet . 2012;55(2):103–8.
14. Bain MD. Robinow syndrome without mesomelic 'brachymelia': A report of five cases. J Med Genet 1986;23:350-4.