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A Rare Disease with Unique Findings: *ROR2*-Associated Autosomal Recessive Robinow Syndrome

Benzersiz Bulguları Olan Nadir Bir Hastalık: *ROR2* İlişkili Otozomal Resesif Robinow Sendromu

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ÖZET

Robinow sendromu (RS), ayırt edici kraniyofasiyal özellikler, iskelet anormallikleri ve diğer anomalilerle karakterize, otozomal dominant (DRS) ve resesif (RRS) kalıtılan konjenital bir iskelet displazisidir. Sebep olan genler heterojendir. Robinow sendromunun tüm tipleri genel olarak benzer klinik özelliklere sahip olsa da, bazı genotip-fenotip korelasyonları vardır. Burada amacımız diş tedavisi için başvuran, dismorfik özellikler nedeniyle pediatrik genetik polikliniğine sevk edilen ve *ROR2*'ye bağlı Robinow sendromu tanısı alan 11 yaşındaki kadın hastanın klinik bulgularını tanımlamaktır.

Anahtar Kelimeler: Otozomal resesif, çarpık dişler, mezomeli, robinow sendromu, *ROR2*, skolyoz

ABSTRACT

Robinow syndrome (RS) is a congenital skeletal dysplasia with autosomal dominant (DRS) and recessive (RRS) inheritance, characterized by distinctive craniofacial features, skeletal abnormalities and other anomalies. Causative genes are heterogeneous. Although all types of Robinow syndrome have generally similar clinical features, there is some genotype-phenotype correlation. Here, our aim is to describe the clinical findings of an 11 year-old female patient who applied for dental treatment, was referred to the pediatric genetics outpatient clinic due to dysmorphic features, and was diagnosed with *ROR2*-related Robinow syndrome.

Key words: Autosomal recessive, crooked teeth, mesomelia, robinow syndrome, *ROR2*, scoliosis

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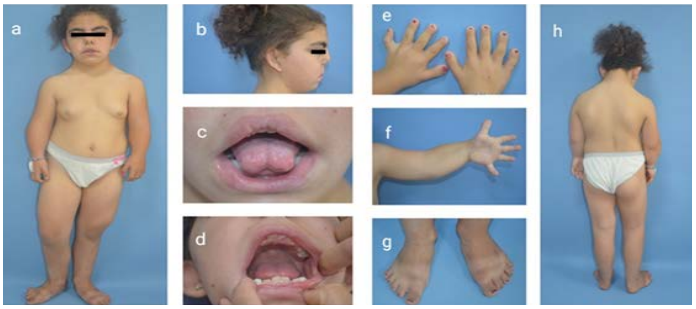
INTRODUCTION

Robinow syndrome (RS) was first described by Meinhard Robinow in 1969. It is genetically heterogeneous and is caused by pathogenic variants of *ROR2, NXN, WNT5A, DVL1* and *DVL3*. While homozygous variants of the *ROR2* gene cause Robinow syndrome, heterozygous variants may be associated with brachydactyly type B1 (BDB1), which is manifested by hypoplasia/aplasia of the distal phalanges and nails of the hands and feet. RS have distinguishable facial features such as relative macrocephaly, flat face, hypertelorism and prominent eyes, short nose and anteverted nasal wings, gingival hyperplasia, crowded teeth, triangular mouth, groove in the middle of the lip, bifid tongue (1). In this paper, we present the clinical findings of an 11 year-old female patient who was referred to the pediatric genetics outpatient clinic for dysmorphic features and was diagnosed with *ROR2*-related Robinow syndrome.

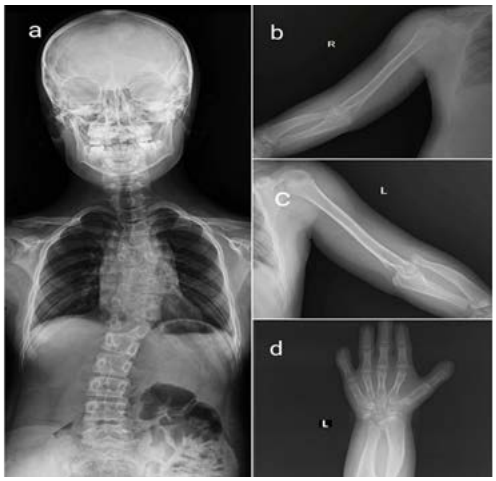
CASE

The patient, who was evaluated by the dentist for crooked teeth, was referred to the pediatric genetics department due to dysmorphic facial appearance. Our patient was the second living child of healthy Turkish parents from the same village. It was learned that she was followed up in the antenatal period due to shortness in the stature and arms. Invasive prenatal testing was recommended to the family. Cytogenetic analysis was performed with cordocentesis and normal karyotype was determined. She was born at term by Caesarean section. Her birth weight was 3050 g (-0,65 SDS) and her height was 45 cm (-2,1 SDS). The patient, whose limb was found to be short, was discharged after being observed in the neonatal unit for a few days for follow-up. When the developmental stages of the patient are evaluated, it has been learned that she has gained the ability to hold her head up, sitting, walking and speaking on time. Her mother, father, and sister's heights and hand-foot sizes were normal. There was no dysmorphic finding similar to the case. In our examination; weight 42 kg (1.4 SDS), height 123 cm (-2 SDS), head circumference 54 cm (0.86 SDS), stroke length 105 cm, mesomelic shortness especially in the upper extremity. The head was relatively macrocephalic, flattened face, midface hypoplasia, widely spaced and prominent eyes, lateral lower palpebral fissure was everted. She had a broad nasal root, tubular and short nose, narrow and anteverted nostrils. Wide and triangular mouth with downward-turned corners of the mouth, bifid tongue, ankyloglossia, gingival hypertrophy and crooked teeth, retromicrognathia were noted. Ears prominent and antihelical folds reduced. Brachydactyly was detected in the finger examination. There were no distal interphalangeal lines of the 2-5 fingers. There were cutaneous syndactyly and hypoplastic nails. Thumbs were broad and prominent. Bilateral 5th fingers were clinodactylic. Supination at the wrist was limited. The feet were large, with brachydactyly in the toes. Scoliosis was detected in the thoracic region. Puberty Tanner stage 3 and labia majors were observed as hypoplasic (Figure 1). Despite the fact that our patient completed the neurodevelopmental stages on time, she struggled in school. Her bashful demeanor drew our attention.



a) Relative macrocephaly, midface hypoplasia, low-set ears, hypertelorism, wide palpebral fissures, downslanting palpebral fissures, prominent eyes, long eyelashes, short, upturned nose, broad nasal bridge, anteverted nares.
b) Flat facial profile, long philtrum, micrognathia, retrognathia.
c) Downturned mouth corners, triangular mouth, groove in the middle of the lip, macroglossia, bifid tongue.
d) Gingival hyperplasia, crowded teeth.
e) Small hands, brachydactyly, clinodactyly, broad thumbs, cutaneous syndactyly, nail dysplasia.
f) Mesomelic shortening.
g) Broad toes, brachydactyly.
h) Scoliosis.

Figure 1. Clinical features of Robinow syndrome in our patient



a) Scoliosis, vertebral segmentation defects (hemivertebrae, butterfly vertebra) and fused ribs.
b-c) Radioulnar dislocation and mesomelia.
d) Brachymesophalangism and clinodactyly of the 5th finger.

Figure 2. Radiological features of Robinow syndrome seen in this patient

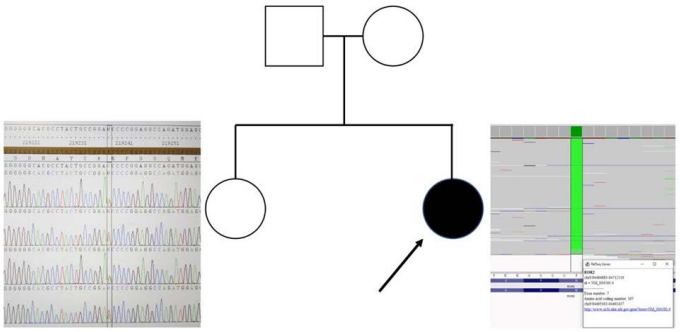


Figure 3. Chromatogram of identified disease-causing variant in patient; *ROR2*: c.1100A>T (p.Asn367Ile). IGV view of variant detected in patient and pedigree of patient.

X-ray examination; scoliosis, block vertebra and hemivertebra appearance in the thoracic region, acromesomelia and radioulnar dislocation, fusion in the ribs, and hypoplasia of the middle phalanges of the bilateral 5th fingers were observed (Figure 2).

The *ROR2* gene sequence analysis was performed considering the autosomal recessive Robinow syndrome with acromesomelic shortening when the distinctive face abnormalities, limb malformations, radiographic results, and being from the same village were reviewed. Our differential diagnoses included Jarcho-Levin syndrome, Spondylocostal dysostosis, and Omodysplasia, which are other autosomal recessive diseases. In sequence analysis, the *ROR2* gene (NM_004560.4): c.1100 A>T (p.Asn367Ile) (N367I) homozygous missense variant was detected (Figure 3). This variant, detected according to The American College of Medical Genetics and Genomics criteria, was considered pathogenic with a high probability. Since the mother and father did not want another pregnancy, they did not accept the genetic examination. The healthy sister carried this variant heterozygous. Genetic counseling was given to the family about this rare syndrome and the possibilities of preimplantation genetic diagnosis were explained if pregnancy is considered. Informed consent was obtained from all guardians for these procedures and for the publication of data and photographs.

DISCUSSION

Robinow syndrome (RS), a genetically heterogeneous skeletal dysplasia. Genes responsible for RS (*WNT5A, ROR2, FZ2, DVL1, DVL3, NXN*) are part of the noncanonical Wnt signaling pathway (2). Wnt signaling pathway regulates cell motility, survival, proliferation and differentiation, limb development and bone morphogenesis, which play an important role in embryonic development and tissue formation (3). Autosomal recessive RRS causes the more severe phenotype and is typically caused by biallelic loss-of-function mutations in *ROR2, WNT5A* and *NXN* (4,5). In relation to *ROR2*; fewer than 100 cases have been reported in the literature to date. The *ROR2* (receptor tyrosine kinase-like orphan receptor 2) gene is located at 9q22.31 belongs to the receptor tyrosine kinase (RTK) family, and its homozygous mutation causes Robinow syndrome, while its heterozygous mutation can lead to brachydactyly type B1 (BDB1) (6). RTKs are involved in the control of most essential cellular processes, including cell proliferation, differentiation, migration and metabolism. *ROR2* contains nine exons. The *ROR2* protein consists of 943 amino acids. Generally, extracellular (containing immunoglobulinlike (Ig) domain, Frizzled-like cysteine-rich domain (FRZ or CRD) and kringle domain (KD)), transmembrane and intracellular (tyrosine kinase (TK), serine/threonine-rich and proline-rich structures) consists of regions (7). According to Afzal et al. the CRD and KD regions have been shown to have an important role for *ROR2* (8). Variants that cause RRS are usually of the nonsense, missense and frameshift type. BDB1-related variants are usually of the nonsense or frameshift type and are located near the N-terminal region of the protein. Truncating variants are cause gain of function (9). *ROR2* (NM_004560.4); c.1100A>T (p.Asn367Ile) homozygous missense variant was detected in our patient. Although this variant is reported as likely pathogenic by Lupski Lab, Baylor-Hopkins CMG, Baylor College of Medicine in 2020, there is no functional evidence in ClinVar for this variant yet (10). The parent and sister were both of average height and lacked brachydactyly. The same variant heterozygous was detected at her sister. This mutation in Exon 7 did not cause brachydactyly type B1 clinic in the sibling. Mutations reported in *ROR2*-associated RS have so far been in exons 5, 7, 8, and 9 of the gene. These mutations correspond to the cysteine-rich domain (CRD), the kringle domain (KD), the region between the KD and TK domains, and the tyrosine kinase domain (TK) of the protein, respectively. People with heterozygous *ROR2* loss-of-function mutations are unaffected carriers (6). We think that this is the reason why our patient's parents and sister with a proven mutation did not show any BDB1 clinic. The phenotype of DRS is reported to be more uncertain. RRS has rib and vertebral anomalies and distinctive limb and unique craniofacial abnormalities that increase the accuracy of clinical diagnosis (11). Beiraghi et al. (12) studied 37 patients with *ROR2*-related RS. The most common craniofacial anomalies were short nose, anteverted nostril, wide nasal bridge, upturned nose, hypertelorism, and midface hypoplasia present in up to 90% of the patients. Musculoskeletal findings such as acromesomelia/mesomelia, short stature, brachydactyly, and hemivertebrae were also reported in up to 90% of patients,

but scoliosis was less common (~77%). These were the most striking features in our patient as well.

While micropenis is seen in all male patients, hypoplastic labia minor/clitoris was detected in approximately 80% of women. It was reported that only 10% of the patients had renal and cardiac anomalies. In addition, developmental delay can be observed in 10-15% of individuals with RS (1). Heart defects and kidney anomalies were not observed in our case.

As a conclusion, RRS is a clinically and radiologically recognizable syndrome. In countries where consanguineous marriage is common, the autosomal recessive inheritance pattern should be considered, and we emphasize the importance of planning genetic testing to provide carrier detection, prenatal diagnosis, and appropriate genetic counseling to families with this disorder.

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