Autosomal Recessive Robinow Syndrome: A Case Report

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ABSTRACT

Recessive Robinow syndrome (RRS) is an extremely rare short stature genetic condition with significant and characteristic oral, dental, and facial attributes that generally requires coordinated multidisciplinary dental and medical interventions. This paper describes the clinical findings and dental management over the course of 4 years of a US-born Caucasian female with recessive Robinow syndrome who presented to our dental clinic at age 11 years, 0 months and who is now age 15 years, 3 months. Of special interest was the extent to which the patient's hyperplastic gingival tissues impeded both normal tooth eruption and orthodontic tooth movement. (J Dent Child 2008;75:48-54)
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In 1969, Robinow, Silverman, and Smith described "a newly recognized dwarfing syndrome," later named "Robinow syndrome" that they observed in 4 members of a single family.[1] These first cases were representative of the autosomal dominant form of the syndrome (**DRS**). Shortly thereafter, in 1973 and 1978, the first cases of an autosomal recessive form of Robinow syndrome (**RRS**) were described.[2,3] Today, Robinow syndrome (**RS**) is the broad term used to depict both the autosomal dominant (OMIM entry no. 180700) and the autosomal recessive (OMIM entry no. 268310) forms of this hereditary short stature syndrome having significant craniofacial and orodental abnormalities.[4,5] The overall incidence of RS is approximately 1:500,000, with a 1:1 male/female ratio.[6] Both the autosomal dominant and recessive forms of this inherited multi-system syndrome are characterized by skeletal and nonskeletal growth disturbances, including:

1. short stature;
2. characteristic dysmorphic facial features, such as:
   a. frontal forehead bossing;
   b. orbital hypertelorism;
   c. widened palpebral fissures;
   d. midface hypoplasia;
   e. broad and depressed nasal bridge; and
   f. short nose with upturned tip and prominent nostrils;
3. orodental abnormalities, such as:
   a. hypoplastic retrusive mandible;
   b. gingival hyperplasia; and
   c. dental malocclusions;
4. mesomelic limb shortening; and
5. hypoplastic genitalia, represented by either a:
   a. micropenis; or
   b. hypoplastic clitoris and labia minorae.[7-10]

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RECESSIVE ROBINOW SYNDROME

RRS is extremely rare in the United States, representing only 5 of the approximately 120 documented cases of RS in this country.[11] RRS is relatively more common in consanguineous families in Turkey, Pakistan, Czechoslovakia, and certain Arabic countries.[12-19] RRS is due to homozygous mutations in the ROR2 gene located on chromosome 9q22 (the long arm of chromosome 9).[20,21] The ROR2 gene codes for a receptor tyrosine kinase, which is required for normal cartilage and growth plate development. Similar phenotypic expressions of RRS occur with homozygous mutations in the ROR2 gene regardless of which domains in the ROR2

gene are affected. Experimentally induced homozygous loss-of-function mutations in ROR2 in various laboratory species result in clinical manifestations similar to RRS in humans. Heterozygous mutations of the ROR2 gene cause autosomal dominant brachydactyly type B (RRS is allelic to dominantly inherited brachydactyly type B).[16]

Genetic testing is available for RRS that detects the ROR2 mutation in patients' DNA.[16,20,21] The gene responsible for DRS has only very recently been identified, therefore, it is anticipated that genetic tests will soon be available.[22] Compared to DRS, persons affected with RRS will exhibit an increase in the number and severity of skeletal developmental disturbances.[23,24] They will generally be of shorter stature than those affected with the autosomal dominant form and, additionally, will have hemivertebrae, brachydactyly, clinodactyly (usually the fifth finger), radial head dislocations, and other vertebral and rib anomalies. Fused ribs are considered pathognomonic for RRS. The clinical features associated with RRS vs DRS are summarized and contrasted in Table.

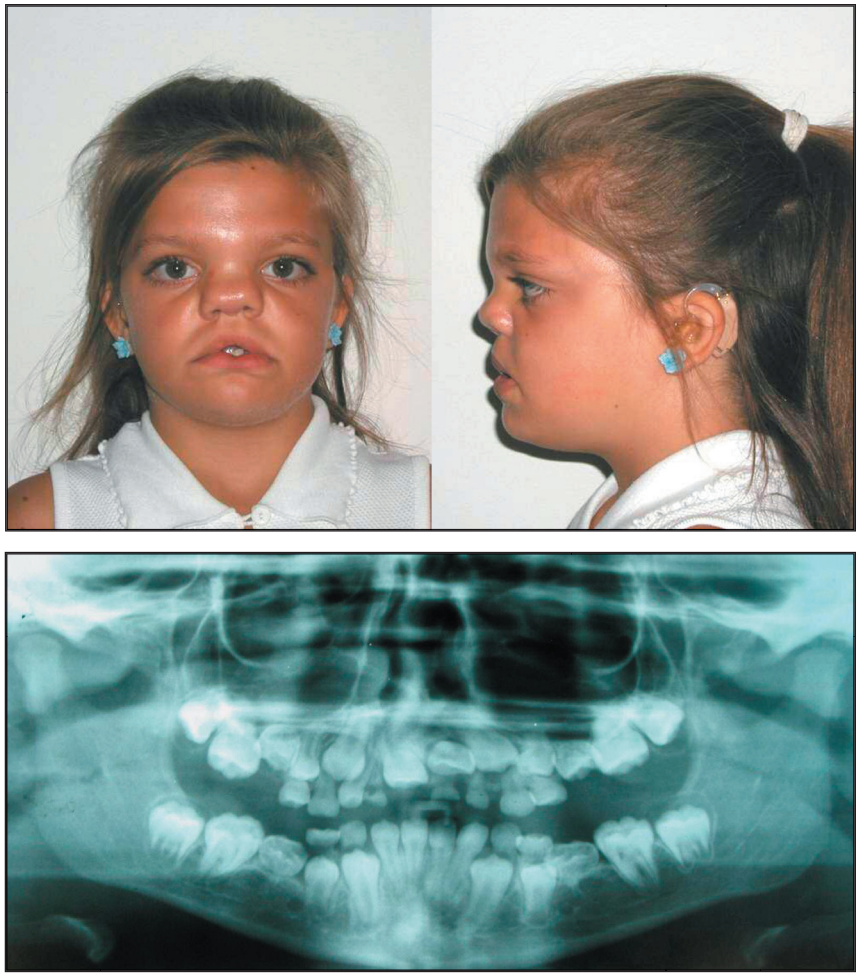


Figure 1. Panoramic radiograph and craniofacial clinical photographs at 11 years, 0 months (initial presentation). Note dolichocephalic skull flattened anteriorly with frontal bossing, hypertelorism, bilateral epicanthal folds, overfolded ear helices, midfacial hypoplasia, short broad-based nose with an upturned bifid tip, short philtrum, tented upper lip, and triangular (inverted "v") mouth. Radiographically, note congenitally missing second premolars, missing permanent maxillary left lateral incisor, delayed eruption/unerupted teeth, and ankylosed/submerged primary maxillary and mandibular second molars.

CASE REPORT

HISTORY

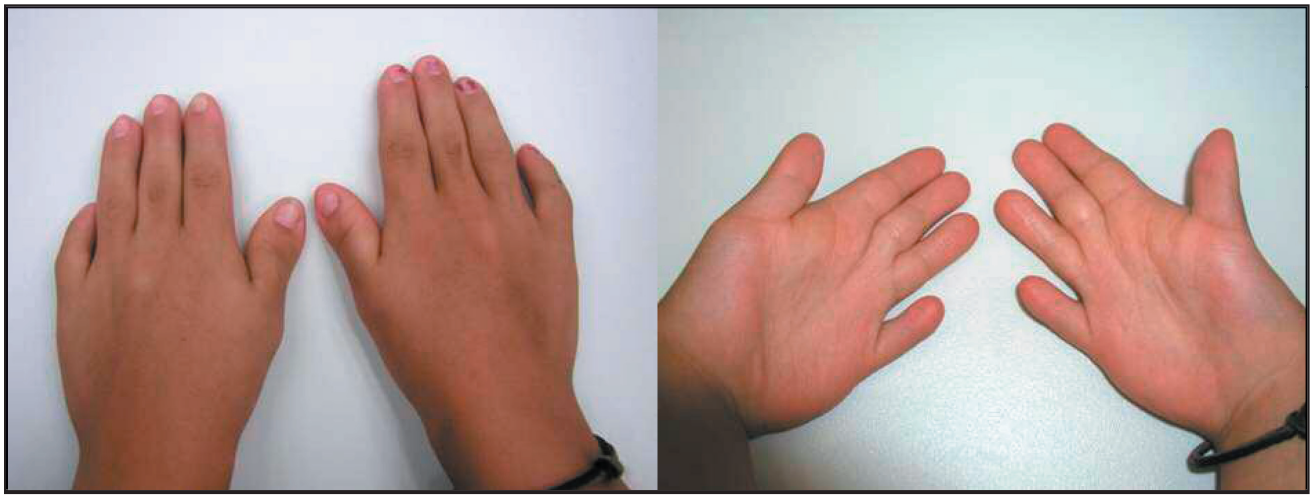
We report on a 15-year, 3-month-old Caucasian female with RRS, first seen in our clinic for consultation at age 11 years, 0 months. She was delivered by Caesarian-section at 41 weeks of gestation to nonconsanguineous parents. Her prenatal history, otherwise unremarkable, includes the discovery of shortened limbs during routine fetal ultrasound screenings at 6 months of prenatal age. Apgar scores of 7 and 8 were recorded at 1 and 5 minutes, respectively. The clinical diagnosis of RS was made shortly after birth. She was discharged with no complications following a 3-day hospitalization for evaluation of her respiratory system. Subsequently, her neonatal history was unremarkable and her developmental milestones have been normal.

At 11 years, 0 months of age, the patient presented to the dental school's pediatric dentistry clinic subsequent to a referral to evaluate "dental/surgery concerns" related to her medical diagnosis of RRS. These concerns included difficulty chewing, missing teeth, delayed tooth eruption, impacted teeth, and submerged/ankylosed primary second molars associated with hyperplastic gingival tissue. The patient was referred to the school's multidisciplinary craniofacial clinic for further evaluation and treatment recommendations.

NONDENTAL FINDINGS

The patient's clinical presentation and radiographic findings are classic for RRS. Some of the nondental findings had been reported in her medical records and were not observed directly by the authors. The patient had a large head circumference and a dolichocephalic skull flattened anteriorly with frontal bossing. Her eyes exhibited hypertelorism and bilateral epicanthal folds. Both ears had overfolded helices and she had been diagnosed with both conductive and sensorineural hearing loss. She had midfacial hypoplasia and a short, broad-based nose with an upturned bifid tip. Her lower face exhibited a short philtrum with tented upper lip, triangular (inverted "v") mouth, and mild micrognathia (Figure 1).

Skeletal features included short-stature (significantly below the fifth percentile in height), multiple thoracic hemivertebrae, rib anomalies (13 ribs on the right and 11 on the left), and mild pectus excavatum. Her upper extremities exhibited marked mesomelic brachymelia with



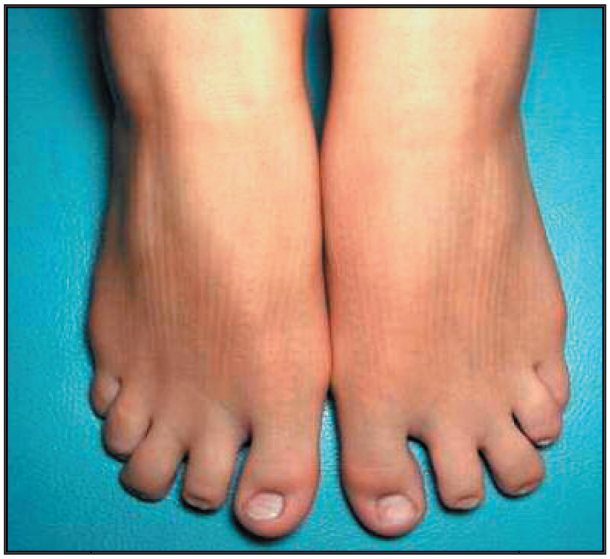


Figure 2. Clinical photographs of hands and feet at initial presentation (11 years, 0 months). Note mild webbing of thumbs and fingers, short distal phalanges and metacarpals, bilateral fifth finger clinodactyly, flat broad feet, short toes, and hypoplastic nails.

bilateral radial head dislocations, resulting in abnormal forearm supination and pronation. All of her upper extremity digits (fingers and thumbs) exhibited mild webbing, short distal phalanges, and short metacarpals. She had bilateral fifth finger clinodactyly. In the lower extremities, she had dislocated hips, genu varum, flat broad feet, short toes, and hypoplastic nails (Figure 2).

Genitourinary features, as reported in her medical records, included a hypoplastic clitoris and hypoplastic labia minorae. The Table contrasts, compares, and summarizes the clinical features of DRS, RRS, and this case.

DENTAL FINDINGS

The patient's oral and dental features, consistent with RRS, included:

1. a flat palate with a palatal twin stripe and bifid uvula;
2. shallow vestibules;
3. hyperplastic gingiva (even present at birth, when she was examined by a geneticist and oral pathologist, and also noted during subsequent medical examinations at 3 months and 7 months of age);
4. high frenum attachments; and
5. ankyloglossia.

Also contributing to her chief complaint of "difficulty chewing" were anterior and posterior crossbites and lack of interocclusal dental contacts (Figure 3). Additionally, she was congenitally missing all permanent second premolars and her permanent maxillary left lateral incisor. She also exhibited significantly delayed eruption of the primary and permanent dentitions. This was apparent at 11 years of age, when her 4 primary maxillary incisors were still present and her 3 permanent maxillary incisors were unerupted. Her primary maxillary and mandibular second molars were ankylosed within hyperplastic gingival tissue (Figure 1). The speech pathologist noted that the arrangement of her dentition was possibly preventing precise articulation of "s" and "sh" sounds, although her speech was deemed to be acceptable overall. Dental findings are also summarized in the Table.

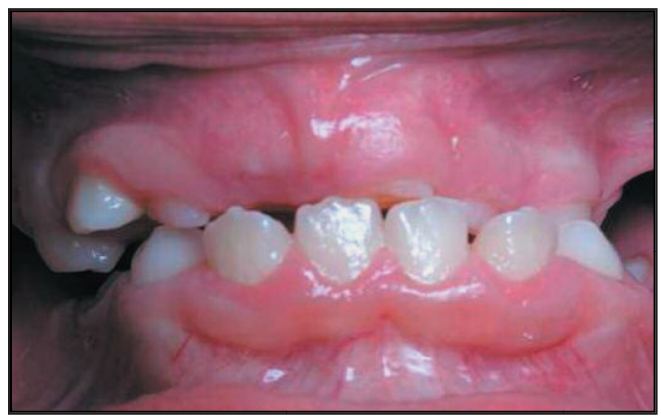


Figure 3. Intraoral clinical photograph at initial presentation (11 years, 0 months). Note flat palate with a palatal twin stripe, shallow vestibules, hyperplastic gingiva, high frenum attachments, ankyloglossia, anterior and posterior crossbites, and lack of interocclusal dental contacts.

Table. Clinical Features Associated With Recessive and Dominant Robinow Syndrome

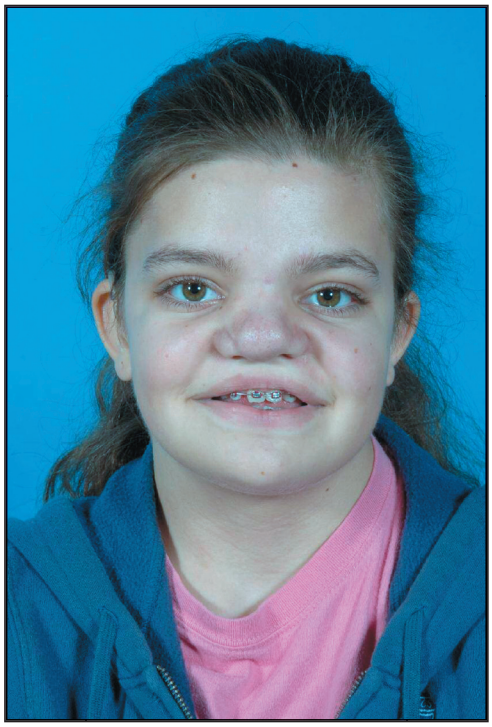
Characteristics/findings (generally more severe in recessive cases)*	Dominant Robinow Syndrome (%)	Recessive Robinow Syndrome (%)	This Case
Frontal bossing	79	78	✓**
Orbital hypertelorism	100	100	✓
Midface hypoplasia	81	94	✓
Depressed nasal bridge	78	49	✓
Short nose	81	93	✓
Upturned nose	87	97	✓
Anteverted nares	96	96	✓
Triangular mouth	65	86	✓
Down-slanted mouth corners	63	95	✓
Micrognathia	57	68	✓
Retrognathia	44	37	– †
Bifid tongue	39	59	–
Gingival hyperplasia	36	71	✓
Dental malocclusion	49	94	✓
Infranumary teeth	16	18	✓
Short stature (post-gestational)/(dwarfism)	81	97	✓
Hemivertebrae	23	98	✓
Rib anomalies and/or rib fusion (pathognomonic for RRS[9])	NR ‡	100	✓
Scoliosis	18	77	–
Mesomelic brachymelia (short forearms and legs)	80	100	✓
Limited elbow supination/radial head dislocations	0	37	✓
Short hands	62	84	✓
Clinodactyly (usually fifth finger)	70	89	✓
Hypoplastic genitalia in males (micropenis)	84	100	NA §
Hypoplastic genitalia in females (hypoplastic labia minora/clitoris)	50/46	81/79	✓
Displasia of fingernails and/or toenails	22	35	✓
Spacing between large and second toes	15	NA	✓

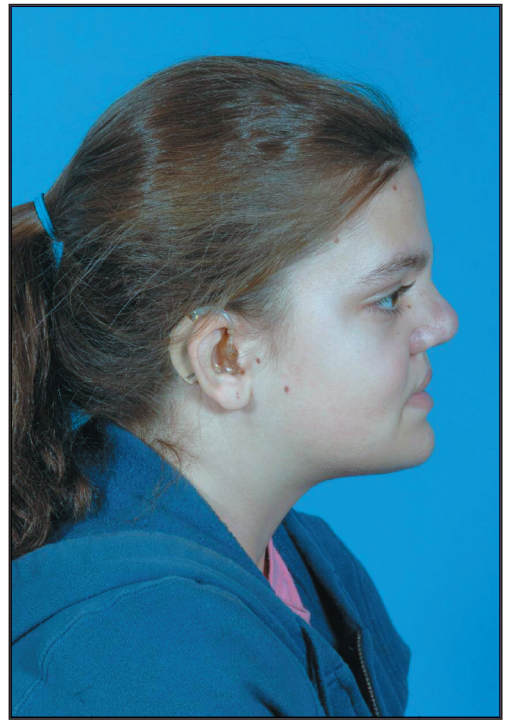
*Adapted from Mazzeu, et al [25] * Shaded cells=frequency>50%. Data rounded to nearest whole number.*
*** Present. † Not present. ‡ Not reported. § Not available.*

MEDICAL AND DENTAL TREATMENT

Nonsurgical interventions included the use of hearing aids, eyeglasses, and, beginning at age 11 years, 9 months, growth hormone therapy (Nutropin 2.0 mg daily). Surgical interventions included ear tubes in infancy and early childhood, surgical removal of 2 dermatomyofibroma neck lesions, and rhinoplastic surgery (using bone harvested from her hip) at age 11 years, 11 months. At the time of her rhinoplasty, an oral surgeon performed a full-mouth gingivectomy to remove hyperplastic gingival tissue, extracted her 11 remaining primary teeth—including the 4 ankylosed molars—and uncovered her horizontally positioned and impacted maxillary incisors to allow placement of orthodontic traction.

Due to the patient's inability to fully cooperate in the clinical dental setting, initial orthodontic appliances were placed at this time under general anesthesia by one of the authors. Orthodontic traction was used in the maxillary anterior region, utilizing the posterior teeth for anchorage. The degree of gingival hyperplasia has both impeded the normal eruption of the molars into occlusal contact and has drastically slowed orthodontic tooth movement. The patient is currently receiving her primary dental care from private practitioners and comprehensive orthodontic treatment at Gillette Children's Specialty Healthcare by one of the authors (C A-C). Due to the hyperplastic gingival tissues, significant orthodontic tooth movement was delayed,





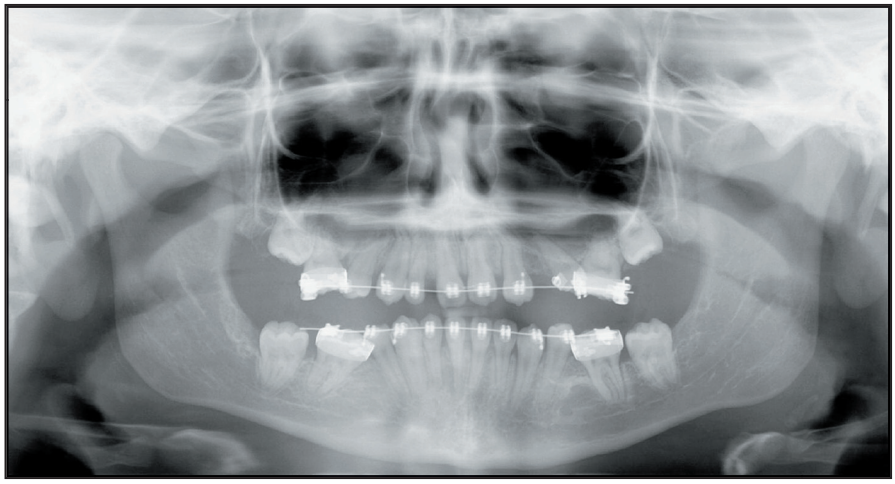


Figure 4. Craniofacial clinical photographs and panoramic radiograph at 15 years, 3 months. Note slow orthodontic progress attributed to hyperplastic gingival tissue.

extending the orthodontic treatment time (Figures 4 and 5). To date, the patient has had 2 gingivectomies, but is plagued by persistent regrowth of the hyperplastic gingival tissue, characteristic of the syndrome.[10] The clinical diagnosis of RRS was confirmed genetically at age 12 years.

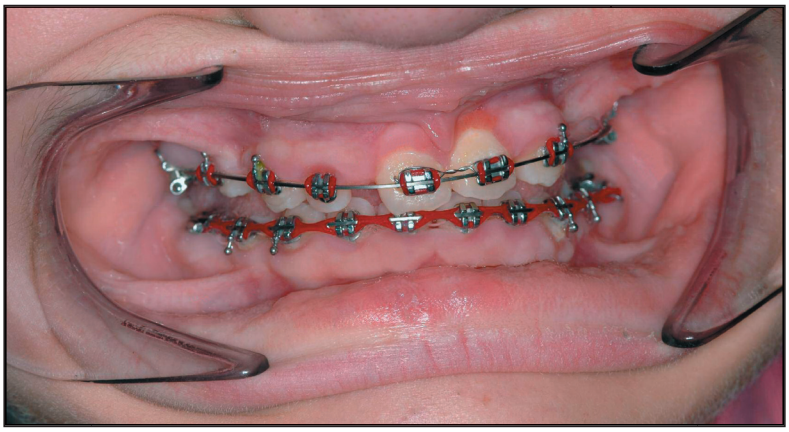
DISCUSSION

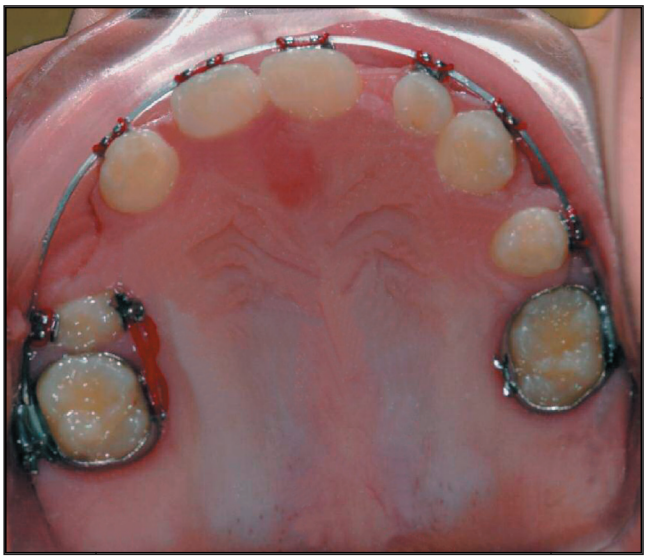
Due to the unique clinical and radiographic features, an accurate diagnosis of RS is generally possible at birth and prenatal diagnosis is possible at 19 weeks using fetal ultrasound. Genetic testing is available for RRS but not for DRS.

RS patients will often require numerous medical and dental interventions, including:

1. orthopedic braces and/or surgery for vertebral anomalies and scoliosis;
2. facial reconstructive surgeries to modify facial anomalies;
3. oral surgical procedures;
4. orthodontic treatment for malocclusions, retained primary teeth, and unerupted teeth;
5. gingivectomies to remove excessive fibrotic hyperplastic gingival tissue;
6. hearing aids and speech therapy;
7. human growth hormone for short stature; and
8. human chorionic gonadotropin (hCG) and/or testosterone during infancy for hypoplastic genitalia.[7,25,26]

While no anesthesia complications associated with RS have been reported to date, the following recommendations have been published:





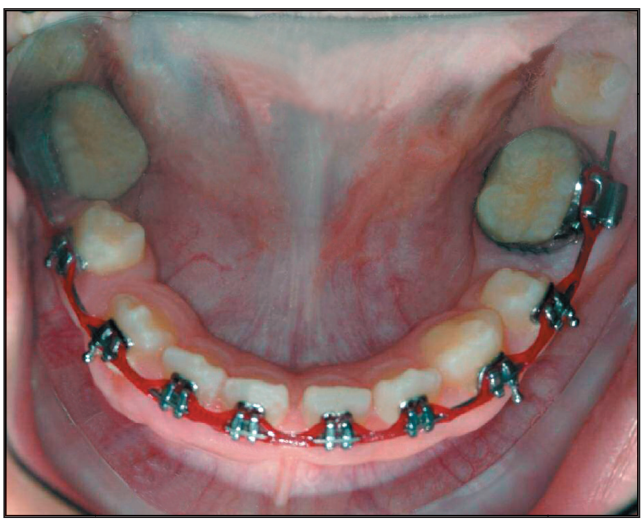


Figure 5. Intraoral clinical photographs at 15 years, 3 months. Note lack of posterior occlusion and hyperplastic gingival tissue.

1. transthoracic ultrasound of the heart and great vessels to evaluate cardiac defects and vessel stenosis;
2. laboratory tests, including blood urea nitrogen, creatinine, liver function, full blood count, coagulation, and urinalysis;
3. evaluation of current medications, especially steroid hormones;
4. preoperative evaluation of vertebral structures if contemplating regional anesthesia; and
5. consideration of fiber optic intubation technique and availability of difficult airway trolley.[27,28]

SUMMARY

This case report highlights the clinical findings, multidisciplinary dental management considerations, and genetic information necessary to knowledgably care for dental patients with Robinow syndrome. Of special interest in this case was the extent to which the intractable hyperplastic gingival tissues impeded both normal tooth eruption and orthodontic tooth movement. As discussed, this persistent hyperplastic gingival tissue was present at birth and recurred following 2 gingivectomies.

ACKNOWLEDGMENTS

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