Received: 14 April 2020 | Revised: 30 August 2020 | Accepted: 2 September 2020

DOI: 10.1002/ajmg.a.61884

AMERICAN JOURNAL OF medical genetics PART A WILEY

ORIGINAL ARTICLE

Extremity anomalies associated with Robinow syndrome

Amjed Abu-Ghname[1,2] | Jeffrey Trost[1] | Matthew J. Davis[1,2] | V. Reid Sutton[3,4] | Chaofan Zhang[3] | Diana E. Guillen[2] | Claudia M. B. Carvalho[3] | Renata S. Maricevich[1,2]

[1]Division of Plastic Surgery, Michael E. DeBakey Department of Surgery, Baylor College of Medicine, Houston, Texas

[2]Division of Plastic Surgery, Texas Children's Hospital, Houston, Texas

[3]Department of Molecular & Human Genetics, Baylor College of Medicine, Houston, Texas

[4]Department of Molecular & Human Genetics, Texas Children's Hospital, Houston, Texas

Correspondence
Renata S. Maricevich, Texas Children's Hospital, Baylor College of Medicine, 6701 Fannin St. Suite 610.00, Houston, TX 77030.
Email: renata.maricevich@bcm.edu

Funding information
Eunice Kennedy Shriver National Institute of Child Health & Human Development (NICHD), Grant/Award Number: 1R03HD092569; US National Human Genome Research Institute (NHGRI)/ National Heart Lung and Blood Institute (NHLBI), Grant/Award Number: UM1HG006542

Abstract

Robinow syndrome, a rare genetic disorder, is characterized by skeletal dysplasia with, among other anomalies, extremity and hand anomalies. There is locus heterogeneity and both dominant and recessive inheritance. A detailed description of associated extremity and hand anomalies does not currently exist due to the rarity of this syndrome. This study seeks to document the hand anomalies present in Robinow syndrome to allow for improved rates of timely and accurate diagnosis. A focused assessment of the extremities and stature was performed using clinical examination and standard photographic images. A total of 13 patients with clinical and molecular diagnosis consistent with dominant Robinow syndrome or recessive Robinow syndrome were evaluated. All patients had limb shortening, the most common of which was mesomelia; however, rhizomelia and micromelia were also seen. These findings are relevant to clinical characterization, particularly as Robinow syndrome has classically been defined as a "mesomelic disorder." A total of eight distinct hand anomalies were identified in 12 patients with both autosomal recessive and dominant forms of Robinow syndrome. One patient did not present with any hand differences. The most common hand findings included brachydactyly, broad thumbs, and clinodactyly. A thorough understanding of the breadth of Robinow syndrome-associated extremity and hand anomalies can aid in early patient identification, improving rates of timely diagnosis and allowing for proactive management of sequelae.

KEYWORDS

DVL1, mesomelia, *NXN*, Robinow syndrome, *ROR*, *WNT5A*

1 | INTRODUCTION

In 1969, Robinow et al. described a new, rare form of dwarfism with mesomelic limb shortening, hemivertebrae, and genital hypoplasia in several individuals in a single family (Robinow, Silverman, & Smith, 1969). Over the years, this syndrome has also been known as Robinow dwarfism, fetal face, fetal face syndrome, fetal facies syndrome, acral dysostosis with facial and genital abnormalities, and mesomelic dwarfism-small genitalia syndrome. Describing the features of Robinow syndrome has proven challenging due to the considerable phenotypic heterogeneity and the very low prevalence of this syndrome. While a total of at least six associated genes have been identified, there has been limited detailed analysis of genotype–phenotype correlations (Bain, Winter, & Burn, 1986; Bunn et al., 2014; Mazzeu et al., 2007; Patton & Afzal, 2002). Phenotypic characteristics of Robinow syndrome include craniofacial, genital, and extremity abnormalities (Mazzeu et al., 2007). Extremity anomalies have been loosely described in the context of broad documentation of phenotypic variants; however, a detailed description of the extremity and hand manifestations by a single expert evaluator along with genotype–phenotype correlation has not been done (Bain et al., 1986; Bunn et al., 2014; Mazzeu et al., 2007; Patton & Afzal, 2002).

The types of Robinow syndrome can be distinguished by the severity of signs and symptoms and by the pattern of inheritance.

Autosomal recessive and autosomal dominant forms of Robinow syndrome have been previously described (Afzal et al., 2000; Balci et al., 1993; Birgmeier et al., 2018; Bunn et al., 2015; Bunn et al., 2014; Danyel, Kortum, Dathe, Kutsche, & Horn, 2018; Nagasaki et al., 2018; Ohkawara, Yamamoto, Tada, & Ueno, 2003; Person et al., 2010; Roifman et al., 2015; Seemanova, Jirasek, Sevcikova, Jodl, & Kreisinger, 1974; Soliman, Rajab, Alsalmi, & Bedair, 1998; White et al., 2015; White et al., 2018; White et al., 2016). Biallelic variants in the Receptor Tyrosine Kinase Like Orphan Receptor 2 (*ROR2*) gene [Mendelian Inheritance in Man (MIM):268310] and Nucleoredoxin (*NXN*) [MIM: 618529] gene have all been implicated as causative genes in recessive forms of the disease, though patients with *NXN* variants have more mild skeletal defects compared to those with *ROR2*-related Robinow syndrome (Afzal et al., 2000; Birgmeier et al., 2018; White et al., 2018).

The autosomal dominant form is similarly rare, and the craniofacial and limb anomalies have been described as milder than those seen in *ROR2*-related Robinow syndrome (Bunn et al., 2014; Bunn et al., 2015; Danyel et al., 2018; Nagasaki et al., 2018; Person et al., 2010; Roifman et al., 2015). The musculoskeletal system is often minimally affected, and there may be relatively normal stature with little or no limb shortening, making diagnosis particularly challenging (Furukawa, Hall, & Smith, 1972; Golabi & Rosen, 1984; Maroteaux, Sauvegrain, Chrispin, & Farriaux, 1989; Nagasaki et al., 2018; Neri, Gurrieri, Zanni, & Lin, 1998; Opitz, Guttenberger, & Pellet, 1969; Orrico et al., 2010; So et al., 2005; Vora & Bianchi, 2009). Multiple genes have been identified to cause the autosomal dominant form, including missense variants and deletions of *WNT5A* [MIM:180700], −1 frameshift variants in the penultimate exon of the disheveled segment polarity protein 1 (*DVL1*) [MIM: 616331], −1 frameshift variants in the penultimate or ultimate exon of the disheveled segment polarity protein 3 (*DVL3*) [MIM: 616894], and missense and nonsense variants of Frizzled Class Receptor 2 (*FZD2*) (Bunn et al., 2014; Bunn et al., 2015; Danyel et al., 2018; Nagasaki et al., 2018; Person et al., 2010; Roifman et al., 2015; White et al., 2015; White et al., 2016; White et al., 2018).

As a result of this syndrome's documented phenotypic and locus heterogeneity, the differential diagnosis can be extensive (White et al., 2018). In the 2019 revised Nosology and Classification of Genetic Skeletal Disorders, Robinow syndrome was expanded and classified in the mesomelic and rhizomelic category, confirming such phenotypic variability (Mortier et al., 2019). While genetic testing is best able to differentiate disorders with overlapping phenotypes, a thorough evaluation of a patient's extremity abnormalities could be a helpful clinical tool to narrow the differential and arrive at the correct clinical diagnosis (Al-Namnam, Hariri, Thong, & Rahman, 2019; Castori et al., 2013; Vogels & Fryns, 2006). In this study, we set out to more precisely delineate and systematically describe the extremity and hand manifestations of Robinow syndrome.

2 | METHODS

Patients with clinically identified Robinow syndrome were invited to Texas Children's Hospital for a multidisciplinary evaluation and an educational symposium for the patients' families. A multidisciplinary team comprised representatives from Plastic Surgery, Urology, Neuropsychology, and Genetics evaluated a total of 13 patients with a clinical and molecular diagnosis of Robinow syndrome. A review of known phenotypic characteristics was used to evaluate patients (Table 1; Mazzeu et al., 2007). A focused assessment of the extremity and hand manifestations by authors A.A. and J.T. using clinical examination was performed as previously described (Aase, 1990). All findings were later corroborated by the senior author. Following patient consent, standardized photographs were obtained using a digital camera and 100 mm macro lens. Full body and four bilateral hand full color photographs were obtained on each participant. Genetic testing was also performed to correlate phenotypes and genotypes; methodology included exome sequencing, genomic sequencing, and Sanger sequencing of target genes associated with Robinow syndrome (Zhang et al. submitted). This study was approved by the Institutional review board at Baylor College of Medicine (protocol no. H-43246).

3 | RESULTS

A total of 13 individuals with clinical and molecular diagnosis consistent with Robinow syndrome were included in this study. The patients ranged from 5 to 51 years of age. Ten (77%) were males and three (23%) were females.

TABLE 1 Spectrum of limb and stature abnormalities in patients with Robinow syndrome previously reported in the literature (Mazzeu et al., 2007)

1. Stature anomalies	a. Limb shortening skeletal dysplasia
2. Forearm anomalies	a. Forearm brachymelia (shortened radius and ulna) b. Bowing of radius c. Madelung deformity d. Dislocation of radial head
3. Hand anomalies	a. Brachydactyly b. Nail hypoplasia or dystrophy c. Distal phalanx duplication d. Dermatoglyphic anomalies (hypothenar whorl, absent interphalangeal and transverse creases) e. Ectrodactyly f. Syndactyly g. Broad thumbs h. Clinodactyly i. Camptodactyly j. Hypoplastic phalanges k. Polydactyly l. Fusion of phalanges or carpal bones
4. Functional limitations	a. Decreased forearm rotation b. Restricted forearm extension
5. Others	a. Genu valgum b. Lower limb brachymelia c. Pes cavus d. Club foot e. Broad great toe

TABLE 2 Summary of patients' genotypes

BAB8295	BAB9236	BAB9138	BAB14232	BAB10151	Patient 1	Mother of patient 1	BAB9136	BAB8841	BAB5264	BAB10973	BAB9128	BAB9126	BAB number
M	M	M	M	F	M	F	M	F	M	M	M	M	Sex
11	14	8	5	14	8	—	22	7	10	34	21	51	Age (years)
115.1 (0.01)	160 (21)	104 (0.01)	92.7 (0.02)	154.4 (18)	—	—	142 (0.02)	116.8 (13)	129.7 (5)	165.1 (7)	161.5 (2)	166.8 (11)	Height (cm) (centile)
Het	Het	Het	Compound Het	Het	Het	Het	Compound Het	Hom	Het	Compound Het	Het	Het	Zygosity
Proband	Proband	Proband (adopted)	Proband	Proband	Proband	Mother of patient 1	Proband	Proband	Proband	Proband, (adopted)	Proband	Proband	Relationship
GPC4	*DVL1*	*WNT5A*	*ROR2*	*DVL1*	*WNT5A*	*WNT5A*	*ROR2*	*NXN*	*DVL1*	*NXN*	*DVL1*	*DVL1*	Affected gene

Abbreviations: Hom, homozygous; Het, heterozygous.

3.1 | Genotype

Five (38%) patients presented with heterozygous variants affecting *DVL1* and three (23%) presented with heterozygous variants affecting *WNT5A*, comprising a total of eight (61%) patients with autosomal dominant disease. Two of the individuals with *WNT5A* variants were related; mother and son. Four (31%) had autosomal recessive Robinow syndrome, with two (15%) presenting with biallelic variants affecting *ROR2* and two (15%) presenting with biallelic variants affecting *NXN*. One patient (8%) had an X-linked variant of *GPC4*. Table 2 summarizes the genotypes of our population.

3.2 | Phenotype—Skeletal dysplasia

All patients (100%) demonstrated signs of short-limbed skeletal dysplasia (Figure 1). The most commonly observed form of dysplasia was mesomelia, seen in six (46%) individuals and encompassing all genetic variants except *NXN*. This was followed by micromelia which was found in four individuals (31%) with *DVL1*, *NXN*, and *WNT5A* variants. Rhizomelia was found in three (23%) patients with *DVL1* and *NXN* variants. Individuals with *ROR2* and *GPC4* variants exclusively demonstrated mesomelic skeletal dysplasia.

3.3 | Phenotype—Arm and forearm

Other limb anomalies identified included radial bowing (7%; *ROR2*) and dislocation of the radial head (7%; *DVL1*). Five (38%) patients demonstrated decreased forearm rotation; this functional abnormality was associated with all genetic variants except the *GPC4* variant.

3.4 | Phenotype—Hand

The phenotypic hand manifestations, broken down by genetic variant, are demonstrated in Figure 2. In this cohort of patients, no single hand anomaly was observed in all patients. A total of eight distinct hand anomalies were identified across 12 individuals. One patient did not present with any hand anomalies. The two most common hand abnormalities were brachydactyly (92%) and clinodactyly (85%); both were identified in all genetic variants. Remaining anomalies were more restricted in their genetic distribution. Broad thumbs (69%) were detected in four of the genetic variants. Distal phalanx spatulations (38%), nail hypoplasia (23%), hypoplastic phalanges (15%), camptodactyly (15%), and distal phalanx duplications (8%) were less common and had more strict genetic associations. Ectrodactyly and polydactyly were not found in any of our patients.

All individuals with *DVL1*, *ROR2*, and *GPC4* variants showed signs of brachydactyly, clinodactyly, and broad thumbs. Distal phalanx duplications were only observed in one (8%) patient who carried the *WNT5A* variant. One patient with an *NXN* variant did not show any signs of hand anomalies.

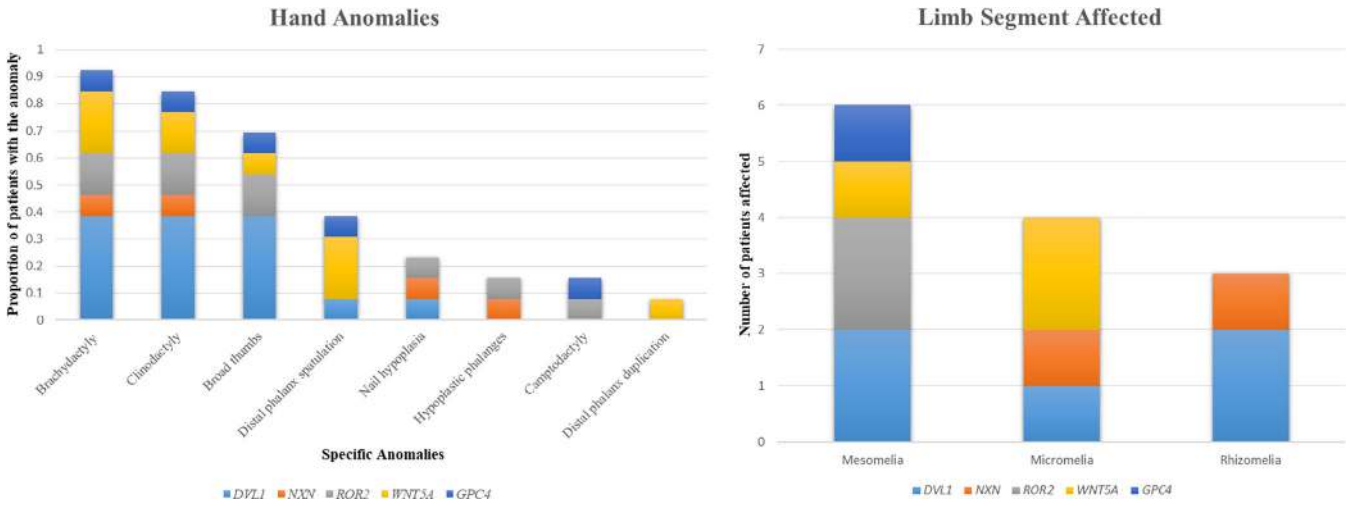

FIGURE 1 Skeletal dysplasias and hand phenotypes stratified by genetic variants. *DVL1*, disheveled segment polarity protein 1; *NXN*, Nucleoredoxin; *ROR2*, Receptor Tyrosine Kinase Like Orphan Receptor 2; *WNT5A*, Wnt Family Member 5A; *GPC4*, Glypican 4 [Color figure can be viewed at wileyonlinelibrary.com]

3.5 | Phenotype—Lower extremity

Three patients demonstrated lower extremity anomalies. The first individual (*DVL1* genetic variant) had genu valgus and broad great toes. The second individual, also with a *DVL1* variant, solely demonstrated genu valgus. The third patient, with a *WNT5A* variant, had brachydactyly of the foot and a duplicated great toe. Foot sizes and measurements were not taken.

4 | DISCUSSION

Robinow syndrome is a rare, genetically heterogeneous disorder that was originally described as a form of mesomelic dwarfism with genital hypoplasia, normal intellect, and distinctive facial features (Mazzeu et al., 2007; Robinow et al., 1969). While Robinow syndrome has typically been described to have mesomelia, our study demonstrates that rhizomelia and acromesomelia are also seen. The shortening of the forearm tends to be more severe than the shortening of the lower extremity segments. In the hands, brachydactyly and nail hypoplasia or dystrophy have been all been described as common Robinow syndrome features. Broad and occasionally bifid thumbs have also been reported. Partial cutaneous syndactyly can also occur in the hands and feet, but no consistent pattern has emerged in the literature (Patton & Afzal, 2002), nor was it seen in our cohort.

The constellation of Robinow syndrome-associated limb skeletal abnormalities is extensive and requires a systematic approach to ensure adequate assessment. Furthermore, in more subtle presentations, recognition of nuanced features associated with Robinow syndrome is vital to making the diagnosis and guiding genetic testing. To our knowledge, this series of Robinow syndrome patients represents the largest cohort to be genotypically and phenotypically characterized to date. The following is a comprehensive account of the identified extremity findings in our patient cohort. We first describe our clinical assessment for dysplasias, and then for a more detailed discussion of limb abnormalities, we divide the limb into functionally significant regions: the proximal and distal extremity. The proximal extremity includes arm, forearm, thigh, and leg, and the distal extremity includes the wrist, hand, fingers, ankle, foot, and toes.

5 | MESOMELIA

In our population of patients with Robinow syndrome, all individuals demonstrated signs of a short-limbed dysplasia (Figure 3). While Robinow syndrome was initially characterized by mesomeic shortening, it was later expanded by Mortier to include rhizomelic dysplasia and micromelia, which were also detected in our population (Mortier et al., 2019; Robinow et al., 1969). The most common form of dysplasia in our population was mesomelic limb shortening, followed by micromelia and rhizomelia.

If the diagnosis of skeletal dysplasia is determined in the prenatal period or based on family history, then genetic testing or radiographs should be obtained to confirm the diagnosis. If skeletal dysplasia is otherwise suspected, then a systematic assessment should be conducted. Once the newborn is stable, a thorough physical exam should be performed—key measurements include head circumference, birth weight and length, and palm and middle finger lengths. Any dysmorphic features should be carefully delineated. Additional attention should be paid to the proportion of the upper arm and forearm. In most newborns they appear subjectively in a one to one ratio. In contrast, those with skeletal disorders display disproportioned ratios. Significant shortening of the forearm or lower leg relative to the arm or thigh, respectively, suggests a mesomelic dysplasia, as is most often seen in Robinow syndrome.

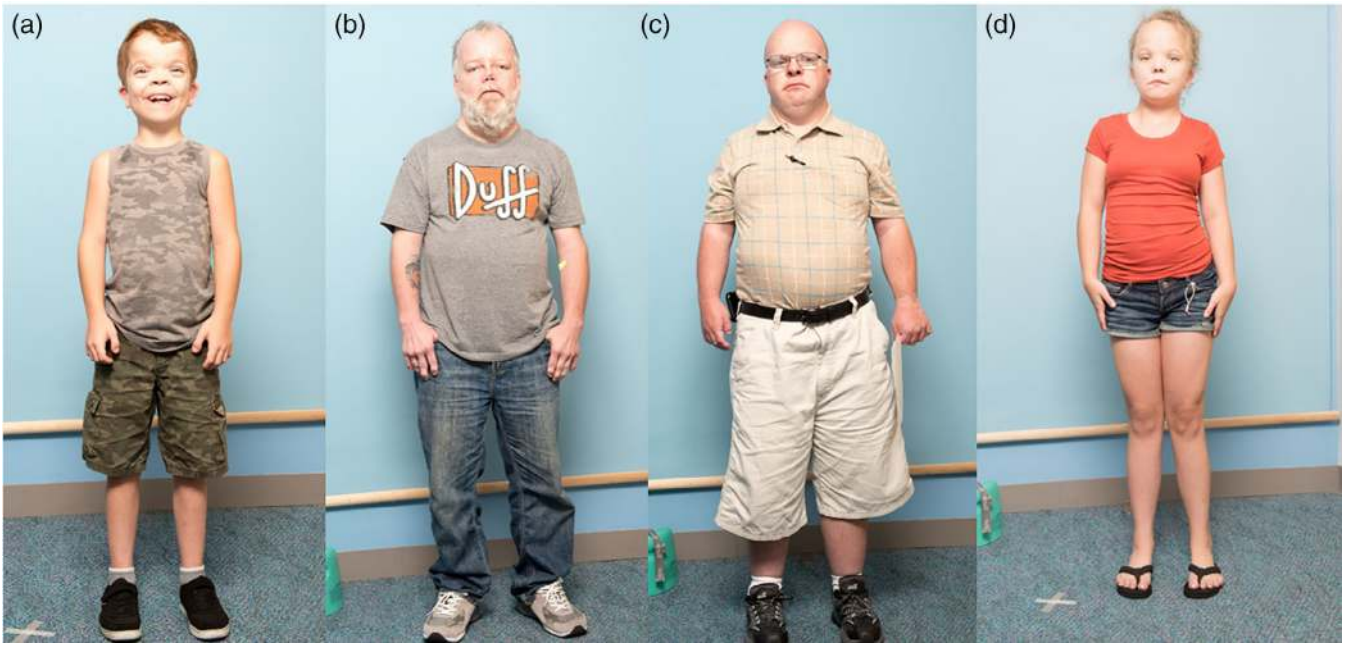

FIGURE 2 Spectrum of skeletal dysplasias and genu valgus in patients with Robinow syndrome. (a) Mesomelia. (b) Rhizomelia. (c) Micromelia. (d) Genu valgus [Color figure can be viewed at wileyonlinelibrary.com]

After clinical evaluation, it is critical to obtain complete anterior/posterior and lateral radiographs. This includes images of the skull, proximal and distal extremities, and the spine. Organ system abnormalities beyond the skeleton should also be assessed and can provide relevant clues to the clinical diagnosis. For example, genital anomalies should increase suspicion for Robinow syndrome.

6 | PROXIMAL EXTREMITY—ARM, FOREARM, THIGH, AND LEG

Proximal upper extremity abnormalities observed in our population included radial bowing, dislocation of the radial head, and functionally decreased forearm rotation. While previously reported in the Robinow syndrome literature, there were no cases of Madelung deformity or restricted elbow extension in our cohort (Balci et al., 1993; Patton & Afzal, 2002). Findings centered around the proximal lower extremity included genu valgum.

Following adequate exposure, proximal extremity examination begins with gross inspection for deformities, disproportions, swelling, and malalignments. All findings must be compared with the contralateral side. Joint and neurovascular examination follows, with particular focus on range of motion and functional limitations. Radial head dislocation occurs when the radial head is displaced from its normal articulation with the ulna and the humerus at the annular ligament. The radial head can be traumatically or congenitally dislocated in isolation or in association with other congenital anomalies (Gupta, Kundu, Sangwan, & Lamba, 2013). Dislocations can be easily missed on radiographs and therefore require a high index of suspicion (Lincoln & Mubarak, 1994). Undiagnosed radial dislocations can result in chronic pain, limited supination and pronation of the forearm, and restricted terminal elbow flexion. Therefore, timely identification and treatment by hand surgeons are paramount.

Genu valgum, commonly called "knock-knee," is a common condition affecting the lower limbs in which the knees angle in and touch each other when the legs are straightened. Individuals with severe valgus deformities are typically unable to touch their feet together while simultaneously straightening the legs, subsequently affecting the patient's gate and balance (Espandar, Mortazavi, & Baghdadi, 2010; Greene, 1994). This altered gate may cause additional problems such as limping, joint stiffness, flat footedness, and pain (Espandar et al., 2010). The extent of angular malalignment is evaluated by measuring the tibiofemoral angle. In the vast majority of children with genu valgum, the tibiofemoral angle is within two standard deviations of an age-appropriate physiologic mean. These patients can be treated with observation and parental reassurance as the deformity resolves over time with no functional deficits (White & Mencio, 1995). Pathologic genu valgum, in which individuals have tibiofemoral angles that are outside two standard deviations of the mean, is much less common. Physical examination should include an accurate assessment of the patient's stature and the location of the valgus deformity. The severity of the angulation should be documented by either goniometric measurement of the tibiofemoral angle or, more simply, by linear measurement of the distance between the medial malleoli with the patient supine and the knees together, as advocated for by Howorth et al (Howorth, 1971). Early identification and management is crucial, as untreated pathologic genu valgum can lead to significant functional deficits, meniscal tears, and osteoarthritis (Espandar et al., 2010). Children with clinical features suggestive of pathologic genu valgum should be referred to a specialized orthopedic surgeon.

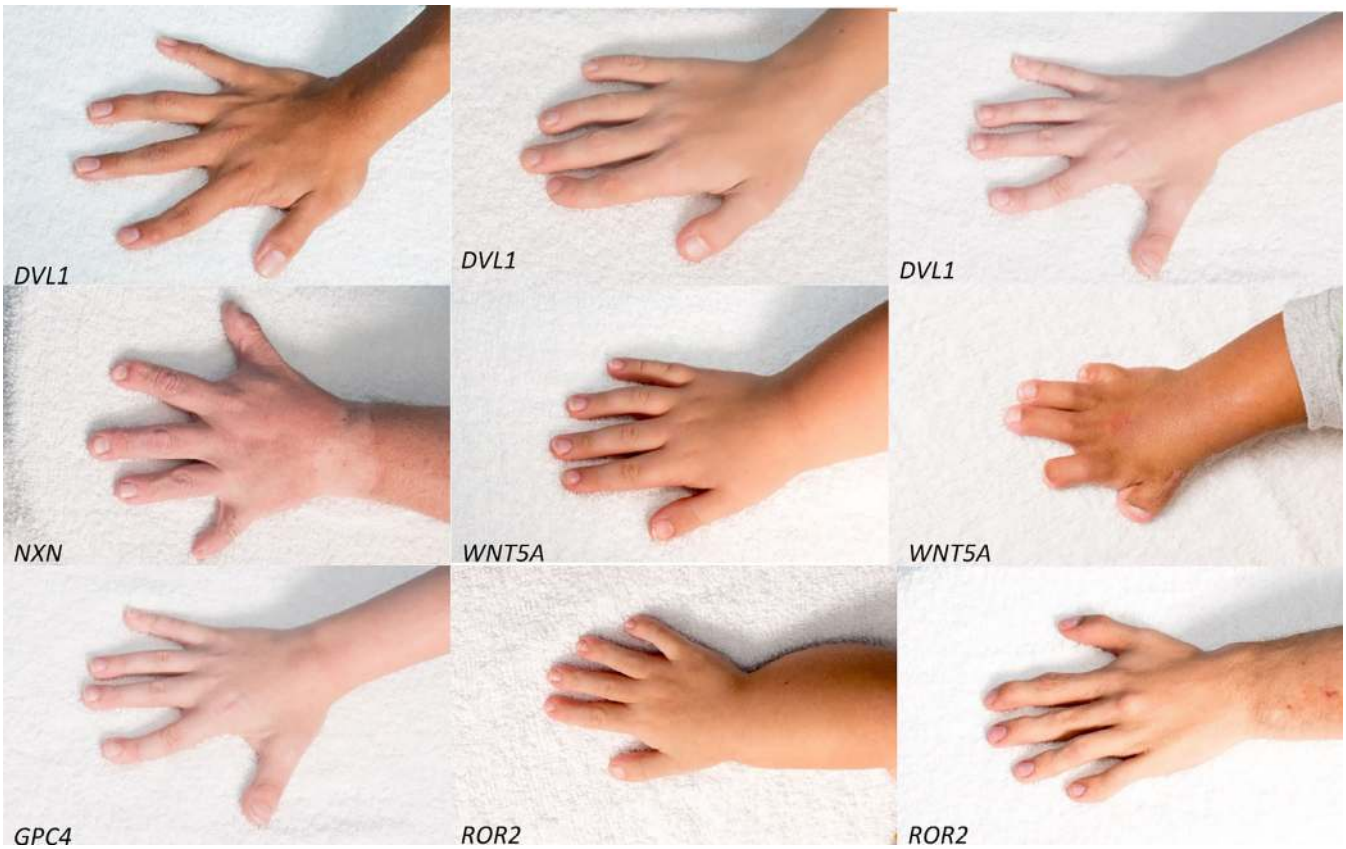

FIGURE 3 Spectrum of hand anomalies stratified by genetic variants in patients with Robinow syndrome. *DVL1*, disheveled segment polarity protein 1; *NXN*, Nucleoredoxin; *ROR2*, Receptor Tyrosine Kinase Like Orphan Receptor 2; *WNT5A*, Wnt Family Member 5A; *GPC4*, Glypican 4 [Color figure can be viewed at wileyonlinelibrary.com]

7 | DISTAL EXTREMITY—WRIST, ANKLE, HAND, FEET, FINGERS, AND TOES

In agreement with the literature, the majority of patients in our cohort presented with hand anomalies. The two most consistent hand features were brachydactyly and broad thumbs, and both were identified in all genetic variants. This is consistent with some of the earliest as well as more recent phenotypic reports of Robinow Syndrome (Kargi et al., 2004; Kelly, Benson, Temtamy, Plotnick, & Levin, 1975; Saraiva, Cordeiro, & Santos, 1999). Brachydactyly is an abnormal shortening of the fingers and toes. In most cases, it does not impair function or cause any pain; however, severe thumb shortening can impair grip strength (Temtamy & Aglan, 2008). Evidence of brachydactyly is usually present at birth but may become more apparent with growth. Diagnosis is typically made clinically, and plain films can confirm and further characterize the diagnosis (Temtamy & Aglan, 2008). The consistent finding of brachydactyly in our study conforms with the short size hand profile previously described in the literature and quantified by Butler et al. (Butler, Gale, Meaney, Wadlington, & Robinow, 1987). The authors analyzed the metacarpophalangeal pattern profile on 15 individuals with Robinow syndrome and quantifiably confirmed clinical homogeneity of such a hand profile in Robinow syndrome.

Other hand anomalies seen in our series and/or reported in the literature includ clinodactyly, camptodactyly, dystrophic nails, hypoplastic phalanges, spatulation or duplication of the distal phalanges, bifid distal phalanges, and fusion of the phalanges or carpal bones. Clinodactyly describes a usually asymptomatic but abnormal curvature of a digit (a finger or toe) in the plane of the palm, most commonly seen in the little finger. Some of these distinct phalangeal and nail anomalies are similar to what was described by Kelly et al. in a Robinow syndrome case report (Kelly et al., 1975). The authors reported on a 13-year-old patient with broad, short hands, broad thumb with bifid nails, and hypoplastic terminal phalanges. While not present in our study, bifid distal phalanges have been proposed by Murali et al. to be the hallmark feature of all types of Robinow Syndrome, further demonstrating the versatility of this syndrome (Murali, Keena, & Zackai, 2018).

A trained hand surgeon should be able to identify each of the above findings and appropriately trigger subsequent workup when Robinow syndrome is suspected. The greatest barrier to more accurately diagnosing and treating these individuals is awareness. The congenital anomalies associated with this syndrome, including mesomelic dysplasia, brachydactyly, and distal phalanx abnormalities are routinely evaluated for in the immediate postpartum period. Therefore, we recommend a strict adherence to the published well baby examination practice guidelines in order to recognize and treat these malformations (Turner, 2018). A referral to Plastic or Orthopedic Surgery when these anomalies are detected can aid in the early diagnosis and

management of the sequelae of the syndrome. Radiologic skeletal survey and a confirmatory genetic panel consisting of *DVL1*, *DVL3*, *FZD2*, *NXN*, *ROR2*, *WNT5A*, and *GPC4* should be obtained if craniofacial evaluation substantiates a high suspicion for Robinow syndrome.

This report is not without limitations. The patients reported on in this study are not a representative sample of all individuals with Robinow syndrome, as many of the reported cases are in Eastern Europe and Western hemispheric patients, making these populations underrepresented in this sample. Additionally, patients self-selected for inclusion in this study. Radiographic imaging was not obtained, so reported results were largely based on clinical examination alone. As the number of recognized cases of Robinow syndrome increases, clearer phenotype–genotype associations can be elucidated. This is a potential focus of future research in this field. Our discussion thoroughly characterizes how Robinow syndrome presents in the extremities, which to date has been missing in the literature. However, we do not describe any interventions conducted by our institution. As Robinow syndrome is rare and widely disrupts the human body's physiology, we highlight the importance of educating all providers, including hand surgeons, regarding its spectrum of possible presentations.

Based on our experience, we recommend that individuals with a combination of shortening appendicular skeletal dysplasia and brachydactyly receive thorough evaluation with Robinow syndrome included on the differential diagnosis. These individuals should also be referred for subspecialist evaluation by a hand surgeon. Patients with a phenotype consistent with Robinow syndrome should also undergo genetic testing to definitively diagnose the condition and ensure proper management.

8 | CONCLUSION

We present a comprehensive analysis of the extremity findings in 13 individuals with a confirmed diagnosis of Robinow syndrome, describing the characteristic morphological features in a manner relevant to early recognition and focused evaluation. Our systematic evaluation has identified that Robinow syndrome is not purely associated with mesomelia, but that rhizomelia and micromelia also occur. Recognizing the extremity features of patients with Robinow syndrome and comprehending its multisystemic nature and its propensity for rare concurrent anomalies are imperative for proper management of these patients. Particularly when surgical options are being considered, radiographic evaluation is paramount for complete phenotypic characterization of the extremities. Individuals with suspected Robinow syndrome should be treated in a multidisciplinary setting and referred to a hand surgeon for thorough evaluation and management.

ACKNOWLEDGMENT

The authors would like to thank the individuals and their families who contributed to this study, and the Robinow Syndrome Foundation for facilitating this collaboration.

CONFLICT OF INTEREST

None.

AUTHORS' CONTRIBUTIONS

All the authors contribute equally to the manuscript. Amjed Abu-Ghname and Jeffrey Trost: primary patient examination, photographic evaluation, data interpretation, and manuscript writing. Matther Davis: data interpretation, graphic design, and manuscript writing. V. Reid Sutton, Chaofan Zhang, and Claudia M. B. Carvalho: project design, genetic data analysis, manuscript editing. Diana E. Guillen: secondary patient examination, data documentation, and manuscript editing. Renata S. Maricevich: secondary patient examination, data interpretation, manuscript editing and final recommendations, designing and implementing the project.

DATA AVAILABILITY STATEMENT

The submission numbers for identified variants were deposited into ClinVar with the preliminary identifiers: SUB7033670. The dbGAP accession number for all exome sequences reported in this paper and for which informed consent for data sharing in controlled-access databases has been provided is dbGAP:phs000711.v5.p1.

ORCID

Amjed Abu-Ghname https://orcid.org/0000-0002-9660-0697
Claudia M. B. Carvalho https://orcid.org/0000-0002-2090-298X

REFERENCES

Aase, J. M. (1990). *Diagnostic dysmorphology*. New York, NY: Plenum Medical Book Co.

Afzal, A. R., Rajab, A., Fenske, C. D., Oldridge, M., Elanko, N., Ternes-Pereira, E., … Jeffery, S. (2000). Recessive Robinow syndrome, allelic to dominant brachydactyly type B, is caused by mutation of ROR2. *Nature Genetics*, *25*(4), 419–422. https://doi.org/10.1038/78107

Al-Namnam, N. M., Hariri, F., Thong, M. K., & Rahman, Z. A. (2019). Crouzon syndrome: Genetic and intervention review. *Journal of Oral Biology and Craniofacial Research*, *9*(1), 37–39. https://doi.org/10.1016/j.jobcr.2018.08.007

Bain, M. D., Winter, R. M., & Burn, J. (1986). Robinow syndrome without mesomelic "brachymelia": A report of five cases. *Journal of Medical Genetics*, *23*, 350–354.

Balci, S., Erçal, M. D., Say, B., & Atasü, M. (1993). Robinow syndrome: with special emphasis on dermatoglyphics and hand malformations (split hand). *Clinical dysmorphology*, *2*(3), 199–207.

Birgmeier, J., Esplin, E. D., Jagadeesh, K. A., Guturu, H., Wenger, A. M., Chaib, H., … Bernstein, J. A. (2018). Biallelic loss-of-function WNT5A mutations in an infant with severe and atypical manifestations of Robinow syndrome. *American Journal of Medical Genetincs*, *176*(4), 1030–1036. https://doi.org/10.1002/ajmg.a.38636

Bunn, K. J., Daniel, P., Rosken, H. S., O'Neill, A. C., Cameron-Christie, S. R., Morgan, T., … Robertson, S. P. (2015). Mutations in DVL1 cause an osteosclerotic form of Robinow syndrome. *American Journal of Human Genetics*, *96*(4), 623–630. https://doi.org/10.1016/j.ajhg.2015.02.010

Bunn, K. J., Lai, A., Al-Ani, A., Farella, M., Craw, S., & Robertson, S. P. (2014). An osteosclerotic form of Robinow syndrome. *American Journal of Medical Genetincs*, *164A*(10), 2638–2642. https://doi.org/10.1002/ajmg.a.36677

Butler, M. G., Gale, D. D., Meaney, F. J., Wadlington, W. B., & Robinow, M. (1987). Metacarpophalangeal pattern profile analysis in Robinow syndrome. *American Journal of Medical Genetics*, *27*(1), 219–223. https://doi.org/10.1002/ajmg.1320270125

Castori, M., Valiante, M., Pascolini, G., Leuzzi, V., Pizzuti, A., & Grammatico, P. (2013). Clinical and genetic study of two patients with Zimmermann-Laband syndrome and literature review. *European Journal of Medical Genetics*, *56*(10), 570–576. https://doi.org/10.1016/j.ejmg.2013.08.004

Danyel, M., Kortum, F., Dathe, K., Kutsche, K., & Horn, D. (2018). Autosomal dominant Robinow syndrome associated with a novel DVL3 splice mutation. *American Journal of Medical Genetincs*, *176*(4), 992–996. https://doi.org/10.1002/ajmg.a.38635

Espandar, R., Mortazavi, S. M., & Baghdadi, T. (2010). Angular deformities of the lower limb in children. *Asian Journal of Sports Medicine*, *1*(1), 46–53. https://doi.org/10.5812/asjsm.34871

Furukawa, C. T., Hall, B. D., & Smith, D. W. (1972). The Aarskog syndrome. *Journal of Pediatrics*, *81*(6), 1117–1122. https://doi.org/10.1016/s0022-3476(72)80242-7

Golabi, M., & Rosen, L. (1984). A new X-linked mental retardation-overgrowth syndrome. *Journal of Medical Genetics*, *17*(1), 345–358. https://doi.org/10.1002/ajmg.1320170128

Greene, W. B. (1994). Genu varum and genu valgum in children. *Instructional Course Lectures*, *43*, 151–159.

Gupta, V., Kundu, Z., Sangwan, S., & Lamba, D. (2013). Isolated post-traumatic radial head dislocation, a rare and easily missed injury-a case report. *Malaysian Orthopaedic Journal*, *7*(1), 74–78. https://doi.org/10.5704/MOJ.1303.003

Howorth, B. (1971). Knock knees. With special reference to the stapling operation. *Clinical Orthopaedics and Related Research*, *77*, 233–246.

Kargi, E., Acun, C., Tomaç, N., Savranlar, A., Dursun, A., & Babuccu, O. (2004). Midline cleft of the lower lip associated with Robinow syndrome. *Scandinavian Journal of Plastic and Reconstructive Surgery and Hand Surgery*, *38*(6), 361–364. https://doi.org/10.1080/02844310410032792

Kelly, T. E., Benson, R., Temtamy, S., Plotnick, L., & Levin, S. (1975). The Robinow syndrome: An isolated case with a detailed study of the phenotype. *American Journal of Diseases of Children*, *129*(3), 383–386. https://doi.org/10.1001/archpedi.1975.02120400081022

Lincoln, T. L., & Mubarak, S. J. (1994). "isolated" traumatic radial-head dislocation. *Journal of Pediatric Orthopedics*, *14*(4), 454–457. https://doi.org/10.1097/01241398-199407000-00006

Maroteaux, P., Sauvegrain, J., Chrispin, A., & Farriaux, J. P. (1989). Omodysplasia. *American Journal of Medical Genetincs*, *32*(3), 371–375. https://doi.org/10.1002/ajmg.1320320321

Mazzeu, J. F., Pardono, E., Vianna-Morgante, A. M., Richieri-Costa, A., Ae Kim, C., Brunoni, D., … Otto, P. A. (2007). Clinical characterization of autosomal dominant and recessive variants of Robinow syndrome. *American Journal of Medical Genetincs*, *143*(4), 320–325. https://doi.org/10.1002/ajmg.a.31592

Mortier, G. R., Cohn, D. H., Cormier-Daire, V., Hall, C., Krakow, D., Mundlos, S., … Warman, M. L. (2019). Nosology and classification of genetic skeletal disorders: 2019 revision. *American Journal of Medical Genetics*. Part A, *179*(12), 2393–2419. https://doi.org/10.1002/ajmg.a.61366

Murali, C. N., Keena, B., & Zackai, E. H. (2018). Robinow syndrome: A diagnosis at the fingertips. *Clinical Dysmorphology*, *27*(4), 135–137. https://doi.org/10.1097/MCD.0000000000000230

Nagasaki, K., Nishimura, G., Kikuchi, T., Nyuzuki, H., Sasaki, S., Ogawa, Y., & Saitoh, A. (2018). Nonsense mutations in FZD2 cause autosomal-dominant omodysplasia: Robinow syndrome-like phenotypes. *American Journal of Medical Genetincs*, *176*(3), 739–742. https://doi.org/10.1002/ajmg.a.38623

Neri, G., Gurrieri, F., Zanni, G., & Lin, A. (1998). Clinical and molecular aspects of the Simpson–Golabi–Behmel syndrome. *American Journal of Medical Genetincs*, *79*(4), 279–283. https://doi.org/10.1002/(sici)1096-8628(19981002)79:4<279::aid-ajmg9>3.0.co;2-h

Ohkawara, B., Yamamoto, T. S., Tada, M., & Ueno, N. (2003). Role of glypican 4 in the regulation of convergent extension movements during gastrulation in *Xenopus laevis*. *Development*, *130*(10), 2129–2138. https://doi.org/10.1242/dev.00435

Opitz, J. M., Guttenberger, J. E., & Pellet, J. R. (1969). The G syndrome of multiple congenital anomalies. *Birth Defects*, *2*, 95–102.

Orrico, A., Galli, L., Faivre, L., Clayton-Smith, J., Azzarello-Burri, S. M., Hertz, J. M., … Sorrentino, V. (2010). Aarskog-Scott syndrome: Clinical update and report of nine novel mutations of the FGD1 gene. *American Journal of Medical Genetincs*, *152A*(2), 313–318. https://doi.org/10.1002/ajmg.a.33199

Patton, M. A., & Afzal, A. R. (2002). Robinow syndrome. *Journal of Medical Genetics*, *39*(5), 305–310. https://doi.org/10.1136/jmg.39.5.305

Person, A. D., Beiraghi, S., Sieben, C. M., Hermanson, S., Neumann, A. N., Robu, M. E., … Lohr, J. L. (2010). WNT5A mutations in patients with autosomal dominant Robinow syndrome. *Developmental Dynamics*, *239*(1), 327–337. https://doi.org/10.1002/dvdy.22156

Robinow, M., Silverman, F. N., & Smith, H. D. (1969). A newly recognized dwarfing syndrome. *The American Journal of Diseases of Children*, *117*(6), 645–651. https://doi.org/10.1001/archpedi.1969.02100030647005

Roifman, M., Marcelis, C. L., Paton, T., Marshall, C., Silver, R., Lohr, J. L., … Chitayat, D. (2015). De novo WNT5A-associated autosomal dominant Robinow syndrome suggests specificity of genotype and phenotype. *Clinical Genetics*, *87*(1), 34–41. https://doi.org/10.1111/cge.12401

Saraiva, J. M., Cordeiro, I., & Santos, H. G. (1999). Robinow syndrome in monozygotic twins with normal stature. *Clinical Dysmorphology*, *8*(2), 147–150.

Seemanova, E., Jirasek, J. E., Sevcikova, M., Jodl, J., & Kreisinger, J. (1974). Fetal face syndrome with mental retardation. *Humangenetik*, *23*(1), 79–81. https://doi.org/10.1007/bf00295686

So, J., Suckow, V., Kijas, Z., Kalscheuer, V., Moser, B., Winter, J., … Schweiger, S. (2005). Mild phenotypes in a series of patients with Opitz GBBB syndrome with MID1 mutations. *American Journal of Medical Genetincs*, *132A*(1), 1–7. https://doi.org/10.1002/ajmg.a.30407

Soliman, A. T., Rajab, A., Alsalmi, I., & Bedair, S. M. (1998). Recessive Robinow syndrome: With emphasis on endocrine functions. *Metabolism*, *47*(11), 1337–1343. https://doi.org/10.1016/s0026-0495(98)90301-8

Temtamy, S. A., & Aglan, M. S. (2008). Brachydactyly. *Orphanet Journal of Rare Diseases*, *3*, 15. https://doi.org/10.1186/1750-1172-3-15

Turner, K. (2018). Well-child visits for infants and young children. *American Family Physician*, *98*(6), 347–353.

Vogels, A., & Fryns, J. P. (2006). Pfeiffer syndrome. *Orphanet Journal of Rare Diseases*, *1*, 19. https://doi.org/10.1186/1750-1172-1-19

Vora, N., & Bianchi, D. W. (2009). Genetic considerations in the prenatal diagnosis of overgrowth syndromes. *Prenatal Diagnosis*, *29*(10), 923–929. https://doi.org/10.1002/pd.2319

White, J., Mazzeu, J. F., Hoischen, A., Jhangiani, S. N., Gambin, T., Alcino, M. C., … Carvalho, C. M. (2015). DVL1 frameshift mutations clustering in the penultimate exon cause autosomal-dominant Robinow syndrome. *American Journal of Human Genetics*, *96*(4), 612–622. https://doi.org/10.1016/j.ajhg.2015.02.015

White, J. J., Mazzeu, J. F., Coban-Akdemir, Z., Bayram, Y., Bahrambeigi, V., Hoischen, A., … Carvalho, C. M. B. (2018). WNT signaling perturbations underlie the genetic heterogeneity of Robinow syndrome. *American Journal of Medical Genetincs*, *102*(1), 27–43. https://doi.org/10.1016/j.ajhg.2017.10.002

White, J. J., Mazzeu, J. F., Hoischen, A., Bayram, Y., Withers, M., Gezdirici, A., … Carvalho, C. M. B. (2016). DVL3 alleles resulting in a −1

frameshift of the last exon mediate autosomal-dominant Robinow syndrome. *American Journal of Human Genetics*, *98*(3), 553–561. https://doi.org/10.1016/j.ajhg.2016.01.005

White, R. G., & Mencio, A. G. (1995). Genu Valgum in children: Diagnostic and therapeutic alternatives. *Journal of the American Academy of Orthopaedic Surgeons*, *3*(5), 275–283. https://doi.org/10.5435/00124635-199509000-00003

How to cite this article: Abu-Ghname A, Trost J, Davis MJ, et al. Extremity anomalies associated with Robinow syndrome. *Am J Med Genet Part A*. 2020;1–9. https://doi.org/10.1002/ajmg.a.61884