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ROR2-Related Robinow Syndrome

Synonym: Fetal Face Syndrome

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Summary

Clinical characteristics

ROR2-related Robinow syndrome is characterized by distinctive craniofacial features, skeletal abnormalities, and other anomalies. Craniofacial features include macrocephaly, broad prominent forehead, low-set ears, ocular hypertelorism, prominent eyes, midface hypoplasia, short upturned nose with depressed nasal bridge and flared nostrils, large and triangular mouth with exposed incisors and upper gums, gum hypertrophy, misaligned teeth, ankyloglossia, and micrognathia. Skeletal abnormalities include short stature, mesomelic or acromesomelic limb shortening, hemivertebrae with fusion of thoracic vertebrae, and brachydactyly. Other common features include micropenis with or without cryptorchidism in males and reduced clitoral size and hypoplasia of the labia majora in females, renal tract abnormalities, and nail hypoplasia or dystrophy. The disorder is recognizable at birth or in early childhood.

Diagnosis/testing

The diagnosis of *ROR2*-related Robinow syndrome is established in a proband with typical suggestive findings and biallelic *ROR2* pathogenic variants identified on molecular genetic testing.

Management

Treatment of manifestations: Corrective surgery for limb and spine defects and for facial abnormalities; orthodontic treatment as needed; surgery for males with scrotal transposition as needed; hormone therapy as needed for the treatment of micropenis.

Genetic counseling

ROR2-related Robinow syndrome is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected with Robinow syndrome, a 50% chance of being a heterozygote (carrier) and usually asymptomatic, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk family members, prenatal diagnosis for pregnancies at increased risk, and

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preimplantation genetic testing are possible when the *ROR2* pathogenic variants have been identified in the family.

Diagnosis

Suggestive Findings

ROR2-related Robinow syndrome **should be suspected** in individuals with the following clinical findings and family history.

Clinical Findings

Craniofacial findings in early childhood [Tufan et al 2005, Brunetti-Pierri et al 2008]:

- Macrocephaly
- Dysmorphic facial features including: broad prominent forehead, marked ocular hypertelorism, prominent eyes with apparent exophthalmos resulting from deficiency of the lower eyelid (giving the eyes a more prominent appearance), midface hypoplasia, short upturned nose with depressed nasal bridge and flared nostrils, large and triangular mouth (usually with tethering of the upper lip in the center so it appears like an inverted V and exposes the incisors and upper gum), micrognathia, and simple, low-set ears (which can be posteriorly rotated)
- Cleft lip and/or cleft palate
- Crowded and misaligned teeth, gum hypertrophy, and ankyloglossia (with bifid tongue in severe cases)

Skeletal

- Short stature. Birth length is reduced; height was consistently ≥2 SD below the mean in one series [Soliman et al 1998].
- Mesomelic or acromesomelic limb shortening, mostly in the forearms
- Brachydactyly with shortening of the distal phalanx, especially the second and fifth digit; clefting of the distal phalanx of the thumb and occasionally other distal phalanges; variable soft-tissue syndactyly involving two or more digits
- Hemivertebrae with fusion of thoracic vertebrae; ribs usually fused or absent [Patton & Afzal 2002, Tufan et al 2005]

Genital

- In males, micropenis with normal scrotum and testes, or cryptorchidism
- In females, reduced clitoral size and hypoplasia of the labia majora

Family History

Family history is consistent with autosomal recessive inheritance. To date *ROR2*-related Robinow syndrome has been reported in consanguineous populations as well as in nonconsanguineous populations showing a founder effect (see Aglan et al [2015] for review).

Establishing the Diagnosis

The diagnosis of *ROR2*-related Robinow syndrome **is established** in a proband with typical suggestive findings in whom biallelic *ROR2* pathogenic variants have been identified by molecular genetic testing (see Table 1).

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, exome array).

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of *ROR2*-related Robinow syndrome is well described, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of *ROR2*-related Robinow syndrome has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic findings and family history suggest the diagnosis of *ROR2*-related Robinow syndrome, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**.

- **Single-gene testing.** Sequence analysis of *ROR2* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If only one or no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.
- **A multigene panel** that includes *ROR2* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the diagnosis of *ROR2*-related Robinow syndrome has not been considered, affected individuals are most likely to be diagnosed using **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved). **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

Exome array (when clinically available) may be considered if exome sequencing is not diagnostic.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in *ROR2*-Related Robinow Syndrome

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
ROR2	Sequence analysis [3]	>95%
	Gene-targeted deletion/duplication analysis [4]	Unknown [5]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
5. The frequency of exon or whole-gene deletions and duplications in this disorder is not known; however, exon deletions have been reported [Brunetti-Pierri et al 2008].

Clinical Characteristics

Clinical Description

ROR2-related Robinow syndrome is characterized by distinctive craniofacial features, skeletal abnormalities, and other anomalies.

Craniofacial. Facies are characteristic at birth and in early childhood (see Suggestive Findings). The face in early childhood resembles a fetal face at eight weeks' gestation; this becomes less noticeable with age. Accelerated growth of the nose in adolescence gives the face a more normal appearance, but the broad forehead, broad nasal root, and ocular hypertelorism persist into adulthood.

Midline cleft lip and palate has been reported but is not a common finding. A rather unusual form of clefting involving the lower lip has been described in some individuals.

Dental problems, including wide retromolar ridge, alveolar ridge deformation, malocclusion, dental crowding, and hypodontia, are also common in Robinow syndrome.

Hyperplastic gingival tissues may also interfere with dental eruption and orthodontic treatments [Grothe et al 2008, Beiraghi et al 2011].

Skeletal. Short stature is almost always present in childhood and persists into adulthood; however, the final degree of short stature may be mild [Tufan et al 2005].

The forearms are more noticeably affected by mesomelic or acromesomelic shortening than the lower limbs, often with radioulnar dislocation.

The phalanges and carpal bones may be fused. Partial cutaneous syndactyly or ectrodactyly (i.e., split hand) may be seen. Hand function is not severely affected.

Kyphoscoliosis is often severe. The chest may be deformed and ribs are often fused, as in spondylocostal dysostosis; some ribs may even be absent. Primary lung function is normal, but changes in the chest wall and thoracic vertebrae may reduce cough effort and predispose to respiratory infections [Sleesman & Tobias 2003].

Urogenital. At birth, the genitalia are abnormal, sometimes leading (primarily in males) to issues related to sex assignment. In males, the penis is small; scrotum and testes are normal. Cryptorchidism has been reported. In females, clitoral size is reduced; labia majora may be hypoplastic.

Wilcox et al [1997] determined that in Robinow syndrome the penis is buried inferiorly and posteriorly within the scrotum because the penile crura insert inferiorly and posteriorly onto the medial aspect of the ischial tuberosity (rather than onto the anteromedial aspect of the pubic bone). Thus, a normal-sized penis appears shorter and inferiorly placed in the scrotum.

Endocrine investigations are usually normal; however, Soliman et al [1998] reported low basal serum testosterone concentration and low testosterone response to human chorionic gonadotropin stimulation in boys. Puberty is usually normal.

Renal abnormalities may be associated with the genital abnormalities. Hydronephrosis is common and cystic dysplasia of the kidney has been reported.

Other

- Congenital heart defects are seen in 15%. In addition to pulmonary valve stenosis or atresia, cardiac defects include atrial septal defect, ventricular septal defect, coarctation of the aorta, tetralogy of Fallot, and tricuspid atresia [Al-Ata et al 1998]. Congenital heart defects are the major cause of early death.
- Nail hypoplasia or dystrophy may be present.
- Intellect is usually within the normal range; however, developmental delay has been reported.

Genotype-Phenotype Correlations

No genotype-phenotype correlations are known.

Nomenclature

Other names by which Robinow syndrome has been known in the past:

- Costovertebral segmentation defect with mesomelia (COVESDEM): this name is no longer used because it causes confusion with similar vertebral defect syndromes, and in *ROR2*-related Robinow syndrome, acromesomelia as well as mesomelia is present.
- Robinow-Silverman syndrome

Prevalence

ROR2-related Robinow syndrome is rare. More than 100 cases have been reported in the literature. It commonly occurs in consanguineous families; for example, those of Turkish and Omani origin.

Genetically Related (Allelic) Disorders

Brachydactyly type B1 (BDB1) is caused by heterozygous truncating pathogenic variants in *ROR2* that result in expression of abnormal but stable ROR2 on the cell membrane consistent with gain of function; see Molecular Genetics, **Abnormal gene product**) [Oldridge et al 2000, Schwabe et al 2000].

BDB1 affects the fourth and fifth digits with shortening of the middle phalanges and absence of the terminal phalanges. Affected individuals may show mildly abnormal facial features including wide-spaced eyes, downslanting palpebral fissures, short philtrum, and prominent nose. Inheritance is autosomal dominant.

Differential Diagnosis

***NXN*-related Robinow syndrome** (OMIM 618529), an autosomal recessive form of Robinow syndrome, was described in three individuals with biallelic *NXN* pathogenic variants from two unrelated families. All three had classic clinical findings of Robinow syndrome including typical craniofacial features, mesomelic shortening, and brachydactyly [White et al 2018]. One individual, born to consanguineous parents, was homozygous for a

nonsense *NXN* variant; the two affected sibs in the other family had compound heterozygous *NXN* pathogenic variants.

Note: The NXN protein is a relevant partner in the WNT5A signaling pathway that is intimately involved in Robinow syndrome causation. ROR2 binds to WNT5A and interacts with FZD2. The effect of this interaction is routed to disheveled proteins (DVL1, DVL3) that are further stabilized by NXN. This complex activates JNK signaling responsible for cytoskeletal reorganization and cell polarity.

Biallelic *WNT5A* pathogenic variants were identified in one individual with findings similar to those of *ROR2*-related Robinow syndrome [Author, unpublished observation].

Autosomal dominant Robinow syndrome, described by Robinow et al [1969], is similar to *ROR2*-related Robinow syndrome, but has more severe dental anomalies and less severe skeletal defects:

- Vertebral anomalies and radial head dislocation are rare [Bain et al 1986].
- Vertebral anomalies and scoliosis are seen in far fewer of those with AD Robinow syndrome (<25%) compared to those with AR Robinow syndrome (>75%) [Mazzeu et al 2007].
- Height is usually nearer the normal range in AD Robinow syndrome.

Autosomal dominant Robinow syndrome is rarer than autosomal recessive Robinow syndrome.

The diagnosis of autosomal dominant Robinow syndrome is established in a proband with typical suggestive findings and/or by the identification of a heterozygous pathogenic variant in *DVL1*, *DVL3*, or *WNT5A* through molecular genetic testing. *WNT5A* is a known coreceptor of the tyrosine kinase receptor, *ROR2*, which would explain the overlap in clinical phenotype of *WNT5A*- and *ROR2*-associated Robinow syndrome.

Jarcho-Levin syndrome and **spondylocostal dysostosis** (see Spondylocostal Dysostosis, Autosomal Recessive) are diagnosed radiologically and show vertebral and rib abnormalities similar to those found in *ROR2*-related Robinow syndrome; short trunk and respiratory insufficiency are present.

I-cell disease (mucolipidosis type II) is a lysosomal storage disorder showing growth failure, coarse facial features, hypertrophic gums, skeletal abnormalities, developmental delay, and hypotonia.

Aarskog syndrome (OMIM 100050). Facial features are similar to those in *ROR2*-related Robinow syndrome: wide-spaced eyes, anteverted nostrils, and broad upper lip. Vertebral abnormalities are not observed. The shawl scrotum and lax ligaments of Aarskog syndrome are not found in *ROR2*-related Robinow syndrome.

Omodysplasia (OMIM 258315 and 164745) is similar to *ROR2*-related Robinow syndrome, with short limbs and radial dislocation; however, no genital abnormalities are present [Venditti et al 2002].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *ROR2*-related Robinow syndrome, the evaluations summarized in this section (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Clinical assessment for presence of cleft lip/palate and the need for surgical repair
- Orthodontics consultation as needed for misaligned, crowded teeth
- Clinical and radiographic evaluation of the spine and rib cage to assess the severity of kyphoscoliosis and vertebral and rib anomalies, as these can lead to postural and respiratory complications [Wilcox et al 1997]
- Radiographic documentation of radioulnar synostosis, forearm shortening, and brachydactyly

- Urology consultation in males with cryptorchidism and abnormal penile insertion / penoscrotal transposition for consideration of reconstructive surgery
- Endocrine consultation to assess the possibility of hormone therapy for males with micropenis
- Renal ultrasound examination
- Echocardiogram to evaluate for structural heart defects
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Corrective surgeries may be required for the following:

- Syndactyly
- Severe scoliosis secondary to hemivertebrae and rib abnormalities
- Cleft lip/palate
- Abnormal penile insertion / penoscrotal transposition. Although it was not possible to detach the abnormal insertion of the penile crura, which can cause a normal-sized penis to be buried in the scrotum and thus appear small, Wilcox et al [1997] improved the cosmetic appearance by transposing the scrotum downward.

Injection of human chorionic gonadotropin and testosterone therapy improved penile length and testicular volume in three boys with severe micropenis [Soliman et al 1998]. Hormone therapy should be monitored by a pediatric endocrinologist.

Orthodontic treatment is usually required.

Perioperative management of individuals with Robinow syndrome should include the following [Macdonald & Dearlove 1995, Lirk et al 2003, Sleesman & Tobias 2003]:

- Preoperative radiologic assessment of the vertebrae and ribs because of the risk for respiratory complications
- Preoperative cardiac evaluation for the presence of congenital heart defects
- Awareness that endotracheal intubation may be difficult as a result of midface hypoplasia

Surveillance

The following are appropriate:

- Surveillance for evidence of scoliosis until growth is completed
- Dental evaluation every six months to one year or as recommended by the dental professional on initial assessment
- Regular cardiac and renal assessment by respective specialists as needed if abnormalities are identified

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

ROR2-related Robinow syndrome is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one *ROR2* pathogenic variant).
- Heterozygotes may display findings consistent with brachydactyly type B1 [Oldridge et al 2000, Schwabe et al 2000].
- Molecular genetic testing of parents could be considered for confirmation studies and for future prenatal testing purposes.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being a heterozygote and usually asymptomatic, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes may display findings consistent with brachydactyly type B1.

Offspring of a proband

- The offspring of an individual with Robinow syndrome are obligate heterozygotes for an *ROR2* pathogenic variant.
- The risk that the offspring of a proband will be affected is small unless the reproductive partner is related to the proband or has a family history of *ROR2*-related Robinow syndrome (see Prevalence).

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *ROR2* pathogenic variant.

Carrier (Heterozygote) Detection

Carrier testing for at-risk family members is possible if the pathogenic variants have been identified in the family. Note: Carriers are heterozygotes for this autosomal recessive disorder and may display findings consistent with brachydactyly type B1.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the *ROR2* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While most centers would consider decisions regarding prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

Ultrasonagraphy. High-resolution ultrasound examination may detect skeletal and cardiac abnormalities in high-risk pregnancies [Percin et al 2001]. Real-time ultrasound may also detect the following in an affected fetus: increased nuchal translucency, reduced humerus and femur length, shortening of the forearms, frontal bossing, mild hypertelorism, reduced thoracic perimeter, and hemivertebrae at the thoracic level [Percin et al 2001, Guven et al 2006].

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Human Growth Foundation (HGF)**
  997 Glen Cove Avenue
  Suite 5
  Glen Head NY 11545
  Phone: 800-451-6434 (toll-free)
  Fax: 516-671-4055
  Email: hgf1@hgfound.org
  www.hgfound.org
- **Little People of America, Inc. (LPA)**
  250 El Camino Real
  Suite 201
  Tustin CA 92780
  Phone: 888-572-2001 (toll-free); 714-368-3689
  Fax: 714-368-3367
  Email: info@lpaonline.org
  www.lpaonline.org
- **MAGIC Foundation**
  4200 Cantera Drive #106
  Warrenville IL 60555
  Phone: 800-362-4423 (Toll-free Parent Help Line); 630-836-8200
  Fax: 630-836-8181
  Email: contactus@magicfoundation.org
  www.magicfoundation.org

- **National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)**
  1 AMS Circle
  Bethesda MD 20892-3675
  Phone: 877-226-4267 (toll-free); 301-565-2966 (TTY)
  Fax: 301-718-6366
  Email: niamsinfo@mail.nih.gov
  www.niams.nih.gov
- **Restricted Growth Association (RGA)**
  PO Box 15755
  Solihull B93 3FY
  United Kingdom
  Phone: +44 0300 111 1970
  Fax: +44 0300 111 2454
  Email: office@restrictedgrowth.co.uk
  www.restrictedgrowth.co.uk

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. ROR2-Related Robinow Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ROR2	9q22.31	Tyrosine-protein kinase transmembrane receptor ROR2	ROR2 @ LOVD	ROR2	ROR2

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for ROR2-Related Robinow Syndrome (View All in OMIM)

268310	ROBINOW SYNDROME, AUTOSOMAL RECESSIVE 1; RRS1
602337	RECEPTOR TYROSINE KINASE-LIKE ORPHAN RECEPTOR 2; ROR2

Molecular Pathogenesis

ROR2 encodes a member of the ROR-family receptor tyrosine kinases, which functions in diverse intracellular signaling cascades and cell and tissue functions including multiple processes that regulate embryonic development (reviewed by Stricker et al [2017]).

Gene structure. *ROR2* comprises nine exons encoding a 4,099-bp transcript (NM_004560.3). See Table A, **Gene** for a detailed summary of gene and protein information.

Pathogenic variants. *ROR2*-related Robinow syndrome is caused by biallelic pathogenic missense, nonsense, or frameshift variants that are distributed throughout the gene, affecting the regions encoding both the extracellular and the intracellular domains of the ROR2 protein [Afzal et al 2000, van Bokhoven et al 2000, Afzal & Jeffery 2003]; reviewed by Stricker et al [2017].

Homozygous deletions involving exons 6 and 7 have also been reported in Robinow syndrome [Brunetti-Pierri et al 2008].

Normal gene product. The 943-amino-acid ROR2 protein is a tyrosine-protein kinase transmembrane receptor (NP_004551.2) [Masiakowski & Carroll 1992]. It has an extracellular portion with domains responsible for protein-protein interactions and an intracellular portion responsible for catalytic kinase activity that regulates relevant signaling pathways. The known interacting proteins and binding regions in the ROR2 receptor were reviewed by Stricker et al [2017].

ROR2 is essential for normal bone growth. Murine *Ror2* is expressed early in embryo development in the developing face, proliferative chondrocytes, genital tubercle, heart, lungs, kidney, and thymus [Matsuda et al 2001].

Abnormal gene product. Biallelic pathogenic variants that cause *ROR2*-related Robinow syndrome result in loss of function of ROR2. Changes in cysteine content are predicted to affect protein folding. Pathogenic missense variants in the catalytic domain are predicted to abolish enzyme function. Nonsense-mediated mRNA decay and abnormal protein trafficking or degradation are suspected molecular consequences of some pathogenic variants [Afzal & Jeffery 2003]. Pathogenic variants that truncate the protein in the tyrosine kinase domain are predicted to affect phosphorylation and abolish kinase activity [Afzal et al 2000].

Studies by Schwarzer et al [2009] of affected individuals and murine models provide strong evidence that the phenotypic differences between *ROR2*-related Robinow syndrome and BDB1 are determined by the relative degree of ROR2 retention/degradation and the amount of mutated protein reaching the plasma membrane (see Genetically Related Disorders, **Brachydactyly type B1**.

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Chapter Notes

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Revision History

- 12 September 2019 (aa) Revision: *NXN*-related Robinow syndrome added to Differential Diagnosis
- 26 July 2018 (bp) Comprehensive update posted live
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