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NLM Citation: Bhavani GSL, Shah H, Shukla A, et al. Progressive Pseudorheumatoid Dysplasia. 2015 Nov 25 [Updated 2020 Dec 23]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Progressive Pseudorheumatoid Dysplasia

Synonyms: Progressive Pseudorheumatoid Arthropathy of Childhood, Spondyloepiphyseal Dysplasia Tarda with Progressive Arthropathy

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Created: November 25, 2015; Updated: December 23, 2020.

Summary

Clinical characteristics

Progressive pseudorheumatoid dysplasia (PPD) is a skeletal dysplasia characterized by predominant involvement of articular cartilage with progressive joint stiffness and enlargement in the absence of inflammation. Onset – typically between ages three and six years – begins with the involvement of the interphalangeal joints. Over time, involvement of large joints and the spine causes significant joint contractures, gait disturbance, and scoliosis and/or kyphosis, resulting in abnormal posture and significant morbidity. Despite the considerable arthropathy, pain is not a major presenting feature of this condition. Initially height is normal; however, short stature (<3rd centile) becomes evident in adolescence as the skeletal changes progress.

Diagnosis/testing

The diagnosis of PPD is established in a proband with characteristic radiographic features and/or identification of biallelic pathogenic variants in *CCN6* (formerly *WISP3*) on molecular genetic testing.

Management

Treatment of manifestations: Treatment is supportive. Pain due to secondary osteoarthritis may respond to nonsteroidal anti-inflammatory drugs. Severe joint pain due to advanced osteoarthritis is treated by joint arthroplasty. Large joint stiffness is managed by physical therapy, activity modification, and walking aids. Small joint arthropathy is managed by an occupational therapist who may advise adaptive devices, modification of activity, and/or vocational training. Scoliosis and mild kyphosis may be treated with bracing. Surgical treatment for angular deformities of the lower limbs as per orthopedic surgeon.

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Surveillance: Monitoring for orthopedic complications including bone deformity, secondary joint disease, spinal deformities, and pain. Annual evaluation by specialist(s) in skeletal dysplasia.

Agents/circumstances to avoid: Immobilization (e.g., casting).

Pregnancy management: Deformities of the pelvis may necessitate delivery by cæsarean section.

Genetic counseling

PPD is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *CCN6* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk relatives and prenatal testing for pregnancies at increased risk are possible if both *CCN6* pathogenic variants have been identified in an affected family member.

Diagnosis

No consensus clinical diagnostic criteria for progressive pseudorheumatoid dysplasia (PPD) have been published.

Suggestive Findings

PPD **should be suspected** in individuals with the following clinical, laboratory, and radiologic features.

Clinical features

- Healthy at birth
- Onset of arthropathy early in childhood, usually between ages three and six years
- Enlargement of interphalangeal joints of hands (Figure 1)
- Progressive restricted mobility of all joints
- Gait abnormalities
- Genu valgum / genu varum
- Progressive hip disease (commonly coxa vara at the late stage)
- Articular pain
- Motor weakness and fatigability
- Spine involvement in late childhood and adolescence with thoracolumbar kyphoscoliosis that leads to short trunk
- Adult height below the third centile
- Absence of signs of inflammation

Laboratory features include normal erythrocyte sedimentation rate and C-reactive protein levels.

Radiologic features include spondyloepiphyseal dysplasia, generalized arthropathy, distinctive joint deformity of the hands (superficially resembling that of juvenile idiopathic arthritis), and diffuse osteoporosis at the late stage.

- **Hands** show enlarged epiphyses, widened metaphyses, and loss of or narrow joint spaces in the metacarpophalangeal and interphalangeal joints, particularly in the proximal interphalangeal joints (Figure 2) [Dalal et al 2012]. Camptodactyly is always present in adulthood.
- **Pelvis.** Hips show enlarged and flattened capital femoral epiphyses and short and wide femoral necks (Figure 3) [Dalal et al 2012, Garcia Segarra et al 2012]. Broadened ilia and irregular acetabular roofs are observed (Figure 3).

- **Spine.** Progressive irregularities in the ossification of vertebral endplates and platyspondyly with loss or narrowing of intervertebral disc spaces are observed in all (Figure 4). Anterior beaking of the vertebral bodies is seen in preadolescents [Garcia Segarra et al 2012].
- **Shoulders and knees.** Osteophytic formations and periarticular calcifications can be seen.

Establishing the Diagnosis

The diagnosis of PPD **can be established** in a proband with characteristic radiographic features (see Suggestive Findings) and/or biallelic pathogenic variants in *CCN6* (formerly *WISP3*) identified on molecular genetic testing (Table 1).

Note: Identification of biallelic *CCN6* variants of uncertain significance (or identification of one known *CCN6* pathogenic variant and one *CCN6* variant of uncertain significance) does not establish or rule out the diagnosis of this disorder.

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

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. 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 PPD has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *CCN6* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by sequence analysis, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

If only one or no pathogenic variant is found, sequence analysis of cDNA from peripheral blood or cultured skin fibroblasts may be performed to detect splicing aberrations resulting from intronic pathogenic variants [Garcia Segarra et al 2012] (see Molecular Genetics).

Targeted analysis for pathogenic variants can include the following:

- c.156C>A (p.Cys52Ter) is the most frequent pathogenic variant in individuals of Turkish ethnicity and accounts for approximately 28% of pathogenic variants worldwide [Author, review of the literature].
- c.1010G>A (p.Cys337Tyr) and c.233G>A (p.Cys78Tyr) are the most common pathogenic variants in the Indian population.

A multigene panel that includes *CCN6* and other genes of interest (see Differential Diagnosis) may also be considered 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.

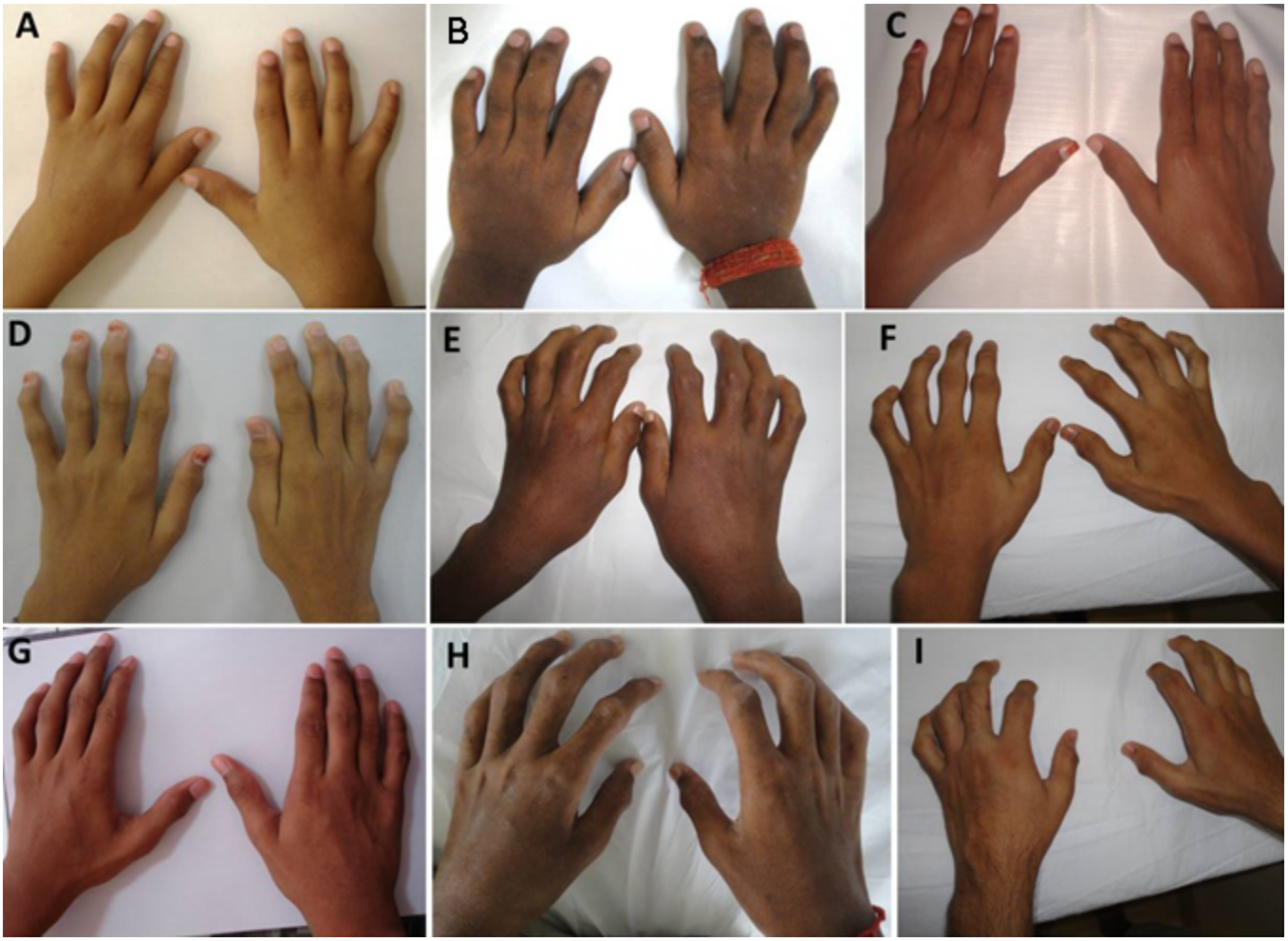

Figure 1. Hands of individuals showing progressive swelling and limited range of movement of the interphalangeal joints

A. Age 5 years

B. Age 7 years

C. Age 11 years

D. Age 12 years

E. Age 13 years

F. Age 15 years

G. Age 16 years

H. Age 17 years

I. Age 23 years

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 PPD has not been considered because an individual has atypical phenotypic features, **comprehensive genomic testing**, which does not require the clinician to determine which gene is likely involved, is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

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

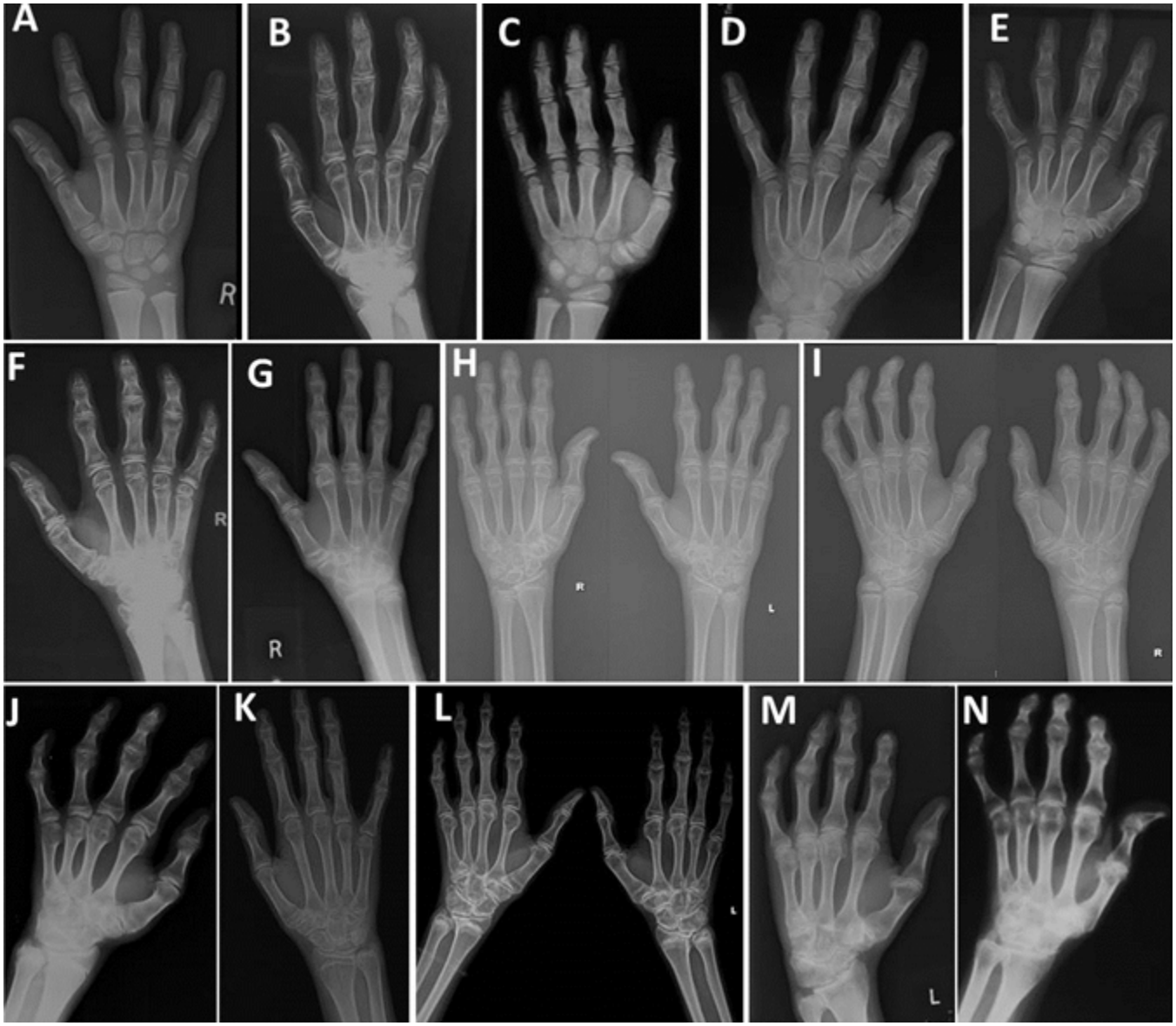

Figure 2. Radiographs of hands showing large epiphyses and widened metaphyses of metacarpals and phalanges. Joint space is also reduced.

A. Age 5 years

B. Age 6 years

C. Age 7 years

D. Age 8 years

E. Age 9 years

F. Age 10 years

G. Age 11 years

H. Age 12 years

I. Age 13 years

J. Age 15 years

K. Age 16 years

L. Age 17 years

M. Age 30 years

N. Age 50 years

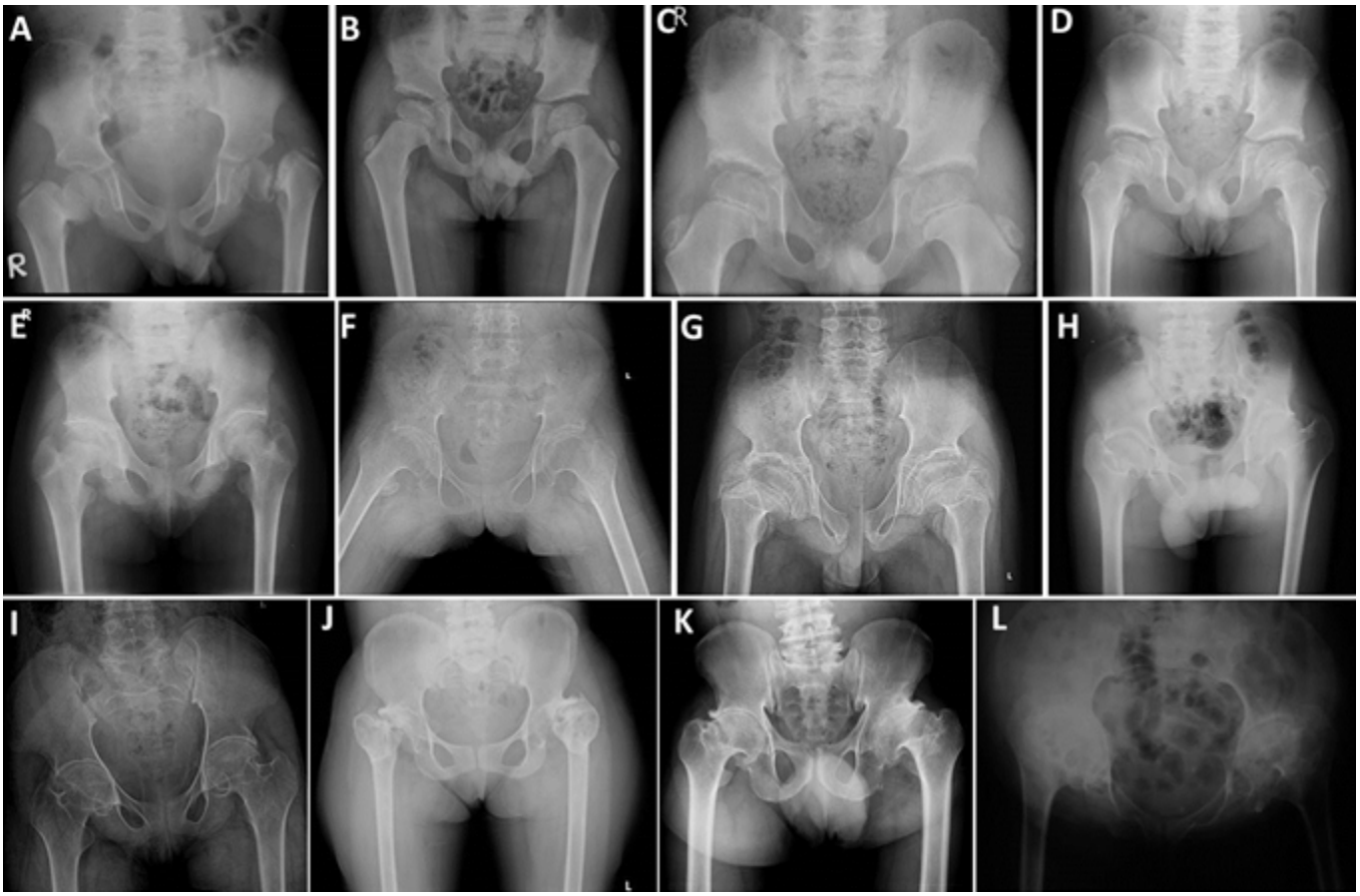

Figure 3. Pelvic radiographs demonstrating reduced hip joint spaces, large capital femoral epiphyses, short and broad femoral necks, and irregular acetabular roofs. Iliac crests are also irregular in adolescence.

A. Age 5 years

B. Age 7 years

C. Age 8 years

D. Age 9 years

E. Age 11 years

F. Age 12 years

G. Age 13 years

H. Age 15 years

I. Age 16 years

J. Age 19 years

K. Age 30 years

L. Age 50 years

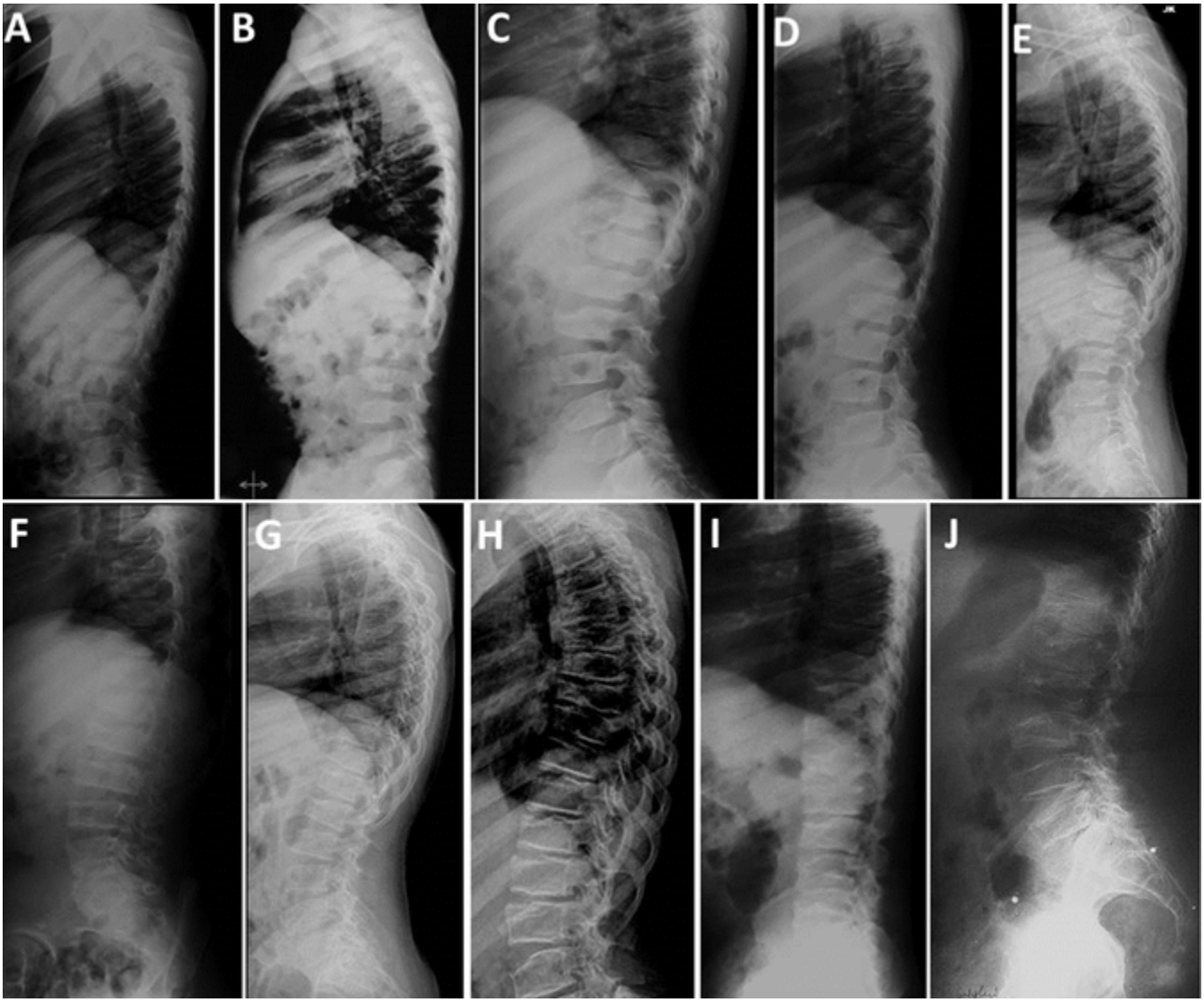

Figure 4. Progressive platyspondyly due to erosion of the superior and inferior articular cartilages

A. Age 5 years

B. Age 7 years

C. Age 9 years

D. Age 11 years

E. Age 13 years

F. Age 15 years

G. Age 16 years

H. Age 17 years

I. Age 30 years

J. Age 50 years

Table 1. Molecular Genetic Testing Used in Progressive Pseudorheumatoid Dysplasia

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
CCN6	Sequence analysis [3]	Nearly 100% [4, 5]
	Gene-targeted deletion/duplication analysis [6]	~1% [7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or 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. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2017]
5. Among the pathogenic variants were three intronic variant alleles identified by fibroblast cDNA sequence analysis; two of the three are deep intronic pathogenic variants [Garcia Segarra et al 2012]. Targeted analysis for these intronic variants or genomic sequencing may also be used.
6. 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.
7. A 9-kb deletion encompassing the 5′ untranslated region and exon 1 was reported in one family [Neerinckx et al 2015].

Clinical Characteristics

Clinical Description

Progressive pseudorheumatoid dysplasia (PPD) is a skeletal dysplasia characterized by predominant involvement of articular cartilage with progressive joint stiffness and enlargement, and the absence of signs of inflammation [Dalal et al 2012]. Progression of the disease severely affects gait and posture and causes significant morbidity.

PPD does not have any extraskeletal manifestations, such as craniofacial features or cognitive involvement.

To date, approximately 215 families with members affected with PPD have been identified with biallelic pathogenic variants in *CCN6* [Dalal et al 2012, Garcia Segarra et al 2012, Bhavani et al 2015]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Progressive Pseudorheumatoid Dysplasia: Frequency of Select Features

Feature	% of Persons with Feature	Comment
Interphalangeal joint involvement	100%	Giving appearance of swollen joints that are painless
Large joint involvement	100%	Typically knees, hips, wrists, & elbows
Spine involvement	93%	Typically platyspondyly
Short stature	50%	Not all have short stature.

Onset. Children with PPD are normal at birth and during infancy. Onset is typically between ages three and six years [Wynne-Davies et al 1982, Garcia Segarra et al 2012]; the range of onset age is from one year to 16 years [Delague et al 2005, Dalal et al 2012].

Initial presenting features in the majority are interphalangeal joint swelling, pain, and gait abnormalities. Joint deformities become manifest over time. Joint pain is rarely the presenting symptom and is disproportionately mild compared to the severity of arthropathy.

Joints. Enlargement, stiffness, and restricted range of movement in the hands start in the proximal interphalangeal joints and progress to the distal interphalangeal joints (Figure 1) [Garcia Segarra et al 2012]. These joints develop progressive contractures.

The joint enlargement, stiffness, and restricted range of movement gradually involve all large joints (e.g., knees, hips, wrists, and elbows) [Dalal et al 2012, Garcia Segarra et al 2012]. Hip involvement commonly manifests as coxa vara later in the disease course. The knees show either genu varum or genu valgum. Typically, the shoulder joints are not severely affected [Dalal et al 2012].

Spine. Scoliosis and/or kyphosis are noted in a majority of affected individuals during adolescence. Lordosis may also be seen. The neck is only occasionally involved [Dalal et al 2012].

Height. Height is initially normal; however, short stature becomes evident in some individuals as the skeletal changes progress. Adult height is typically below the third centile [Garcia Segarra et al 2012]. Flexion deformities at the hips and knees as well as spinal changes contribute in part to the short stature.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been observed.

Mild variation in age of onset, severity, and progression noted in different families is not explained by the type of pathogenic variants or their locations.

Intrafamilial variation has been observed [Bhavani et al 2015].

Nomenclature

The name "progressive **pseudorheumatoid** dysplasia" reflects its resemblance to juvenile rheumatoid arthritis.

PPD was previously referred to as "spondyloepiphyseal dysplasia with progressive arthropathy" or "progressive pseudorheumatoid chondrodysplasia."

Prevalence

The prevalence of PPD has been estimated at one per million in the United Kingdom (prevalence category of <1-9:1,000,000) [Wynne-Davies et al 1982]. However, the disease may be underdiagnosed due to the overlap of clinical features with juvenile idiopathic arthritis. To date more than 215 families with molecularly confirmed PPD have been reported.

PPD is more frequent in communities with a high rate of consanguinity [Delague et al 2005, Dalal et al 2012]. The largest series has been published from India [Dalal et al 2012, Bhavani et al 2015].

PPD has also been observed among populations with a high rate of consanguinity in Kuwait, Lebanon, Iran, Jordan, Saudi Arabia, Syria, Palestine, and Morocco.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *CCN6* (formerly *WISP3*).

Differential Diagnosis

Juvenile idiopathic arthritis and all skeletal dysplasias with epiphyseal and spondylar involvement are to be considered in the differential diagnosis of progressive pseudorheumatoid dysplasia (PPD).

Juvenile idiopathic arthritis (JIA) is the disorder most commonly confused with PPD. The main differentiating features are:

- Joint inflammation (tenderness and warmth) in JIA
- Elevation of erythrocyte sedimentation rate and C-reactive protein levels in JIA and not in PPD. However, in some instances elevation of these acute reactants in JIA can be minimal.
- In JIA, joint destruction is seen on radiographs. In PPD, radiographs show dysplasia along with epiphyseal enlargement and platyspondyly.

Skeletal dysplasias with epiphyseal and spondylar involvement. See Table 3.

Table 3. Genes of Interest in the Differential Diagnosis of Progressive Pseudorheumatoid Dysplasia

Gene(s)	DiffDx Disorder	MOI	Features of DiffDx Disorder	
			Overlapping w/PPD	Distinguishing from PPD
COL2A1	Spondyloepimetaphyseal dysplasia, Strudwick type (See Type II Collagen Disorders Overview.)	AD	Severe disproportionate short stature, platyspondyly, scoliosis, genu valgum	Presents in infancy, characteristic flat facial profile, ocular abnormalities, delayed ossification & metaphyseal flaring, absence of large epiphyses
COL2A1	Mild spondyloepiphyseal dysplasia with premature-onset arthrosis (See Type II Collagen Disorders Overview.)	AD	Progressive joint pain & limitation of motion at hips & knees, epiphyseal dysplasia & early-onset osteoarthrosis	Flattened, small epiphyses
COL2A1 *FN1*	Spondylometaphyseal dysplasia, corner fracture type	AD	Short stature, scoliosis, coxa vara, genu varum or valgum, joint pain	Vision impairment, normal epiphyses
COL2A1 [1]	Spondyloepiphyseal dysplasia w/ metatarsal shortening (formerly Czech dysplasia) (See Type II Collagen Disorders Overview.)	AD	Early-onset osteoarthritis; radiologic features as in PPD: platyspondyly w/ irregular endplates & usually anterior-posteriorly elongated vertebral bodies, coxa vara, short femoral neck, & narrow joint spaces)	Severe joint pain in lower limbs before adolescence, normal stature, & hypoplastic 3rd, 4th, & 5th toes
GALNS *GLB1* *GNS* *HGSNAT* *IDS* *IDUA* *NAGLU* *SGSH*	Mucopolysaccharidoses (e.g. MPS I, MPS II, MPS III, MPS IVA, & MPS IVB) [2]	AR XL	Vertebral deformities (hook-shaped vertebral bodies w/inferior beaking or platyspondyly w/central beaking) & progressive joint limitation similar to those in PPD.	Extraskeletal manifestations observed in the MPSs (e.g., coarse facies, corneal clouding, hepatomegaly, ID) are not present in PPD.
LACC1	*LACC1*-related juvenile arthritis (OMIM 618795)	AR	Onset in childhood, joint deformities, joint contractures, joint pain, joint swelling	Erosive arthritis, ↑ markers of inflammation. Fever, erythematous rash, generalized lymphadenopathy, & hepatosplenomegaly seen in some persons

Table 3. continued from previous page.

Gene(s)	DiffDx Disorder	MOI	Features of DiffDx Disorder	
			Overlapping w/PPD	Distinguishing from PPD
TRAPPC2	X-linked spondyloepiphyseal dysplasia tarda (XL-SEDT)	XL	Develops in adolescence or adulthood & is assoc w/disproportionate short stature w/short trunk & arm span significantly greater than height. Affected males exhibit linear growth deficiency from age ~6-8 yrs. Progressive joint & back pain w/ osteoarthritis; hip, knee, & shoulder joints are commonly involved	Interphalangeal joints are typically spared.

AD = autosomal dominant; AR = autosomal recessive; DiffDx = differential diagnosis; ID = intellectual disability; MOI = mode of inheritance; MPSs = mucopolysaccharidoses; PPD = progressive pseudorheumatoid dysplasia; XL = X-linked
1. Czech dysplasia is typically associated with the *COL2A1* p.Arg275Cys pathogenic variant.
2. See Mucopolysaccharidoses: OMIM Phenotypic Series to view genes associated with this phenotype in OMIM.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with progressive pseudorheumatoid dysplasia (PPD), the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Progressive Pseudorheumatoid Dysplasia

System/Concern	Evaluation	Comment
Skeletal	• Complete skeletal survey • Referral to pediatric orthopedic surgeon or specialist in treating bone dysplasias	
Genetic counseling	By genetics professionals [1]	To inform affected persons & families re nature, MOI, & implications of PPD to facilitate medical & personal decision making

MOI = mode of inheritance; PPD = progressive pseudorheumatoid dysplasia
1. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

Treatment of Manifestations

Treatment is supportive. No specific therapy for PPD is available.

Table 5. Treatment of Manifestations in Individuals with Progressive Pseudorheumatoid Dysplasia

Manifestation/Concern	Treatment	Considerations/Other
Pain due to secondary osteoarthritis	NSAIDs may be helpful.	Other anti-inflammatory medications incl steroids & immunosuppressive drugs (cyclosporine & methotrexate) have a limited role in treatment & are best avoided in view of their significant side effects.
	Severe joint pain due to advanced osteoarthritis is treated by joint arthroplasty (e.g., hip & knee replacement).	Early hip replacement (2nd decade of life) can be successful in relieving pain & restoring ambulation.
Progressive joint stiffness	• Large-joint stiffness is managed by PT, activity modification, & walking aids. • Small joint arthropathy is managed by OT, who may advise adaptive devices, modification of activity, &/or vocational training.	Immobilization (e.g., casting) should be avoided.
Scoliosis & mild kyphosis	Bracing per pediatric orthopedic surgeon w/expertise in treating bone dysplasias	
Spinal canal stenosis	Decompression, fusion, & instrumentation per pediatric orthopedic surgeon w/expertise in treating bone dysplasias	
Angular deformities of lower limbs	Treatment per pediatric orthopedic surgeon w/expertise in treating bone dysplasias	Indications for surgical correction: to restore normal alignment of lower limbs & alleviate gait disturbance, instability, &/or pain

NSAIDs = nonsteroidal anti-inflammatory drugs; OT = occupational therapist; PT = physical therapist

Surveillance

No specific guidelines for surveillance have been published.

Table 6. Recommended Surveillance for Individuals with Progressive Pseudorheumatoid Dysplasia

System/Concern	Evaluation	Frequency
Skeletal	Monitor for orthopedic complications incl bone deformity, secondary joint disease, spinal deformities, & pain.	At each visit
	Eval by specialist in skeletal dysplasia or multidisciplinary skeletal dysplasia clinic	Annually

Agents/Circumstances to Avoid

Avoid immobilization (e.g., casting).

Evaluation of Relatives at Risk

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

Pregnancy Management

Deformities of pelvis may necessitate delivery by cæsarean section in pregnant women who have PPD.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to 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, mode(s) of 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; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Progressive pseudorheumatoid dysplasia (PPD) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., presumed to be carriers of one *CCN6* [*WISP3*] pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *CCN6* pathogenic variant and to allow reliable recurrence risk assessment. (In rare families, only one parent of a proband with an autosomal recessive disorder is heterozygous and the proband is affected as the result of either (1) one pathogenic variant inherited from the heterozygous parent and a second pathogenic variant that occurred *de novo* in the proband or (2) uniparental isodisomy and consequent homozygosity for the pathogenic variant transmitted by a heterozygous parent [Jónsson et al 2017].)
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a *CCN6* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Mild-to-moderate intrafamilial clinical variability may be observed in sibs who inherit biallelic *CCN6* pathogenic variants.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with PPD are obligate heterozygotes for a pathogenic variant in *CCN6*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *CCN6* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *CCN6* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic 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

Once the *CCN6* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing for PPD are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

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.

- **Arthritis Foundation**
  1330 W. Peachtree Street
  Suite 100
  Atlanta GA 30309
  Phone: 800-283-7800 (toll-free); 404-872-7100
  www.arthritis.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

- **UCLA International Skeletal Dysplasia Registry (ISDR)**
  Phone: 310-825-8998
  International Skeletal Dysplasia Registry

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. Progressive Pseudorheumatoid Dysplasia: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
CCN6	6q21	Cellular communication network factor 6	WISP3 database	CCN6	CCN6

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 Progressive Pseudorheumatoid Dysplasia (View All in OMIM)

208230	PROGRESSIVE PSEUDORHEUMATOID DYSPLASIA; PPRD
603400	CELLULAR COMMUNICATION NETWORK FACTOR 6; CCN6

Molecular Pathogenesis

CCN6 encodes Wnt1 inducible signaling pathway protein 3 (WISP-3) (also called cellular communication network factor 6). WISP-3 comprises five functional domains: peptide signal sequence, insulin-like growth factor binding proteins (IGF-BP) like domain, von Willebrand factor type C (VWC) repeat domain, thrombospondin type I domain, and cysteine knot domain [Hurvitz et al 1999]. WISP-3 is a member of the CCN (connective tissue growth factor/cysteine-rich61/nephroblastoma overexpressed) family of growth factors [Pennica et al 1998]. WISP-3 regulates type II collagen and aggrecan expression by the activation of SOX9 transcription factors [Sen et al 2004] and plays a major role in cartilage homeostasis by inhibiting cell proliferation and promoting precursor cell differentiation of chondrocytes [Wang et al 2013].

Mechanism of disease causation. The pathophysiology of *CCN6* variants resulting in PPD is not completely understood. However, studies show that WISP-3 expression is significantly reduced in the chondrocytes of individuals with PPD [Zhou et al 2007]. Mutated articular chondrocytes with very low levels of WISP-3 expression show an increased rate of proliferation, increased cell viability, and decreased apoptosis, suggesting that they are in an immature and hyper-proliferative state, which may explain the enlarged metaphyses observed in individuals with PPD. Mutated WISP-3 shows abnormal aggregation in the cytoplasm and cell membrane of chondrocytes [Wang et al 2013]. As mutated WISP-3 delays intracellular collagen synthesis and inhibits extracellular collagen secretion, the cartilage flexibility in individuals with PPD diminishes.

***CCN6*-specific laboratory technical considerations.** Two deep intronic missense variants that caused alternative splicing were identified in fibroblast cDNA [Garcia Segarra et al 2012]. A 9-kb deletion encompassing the 5′ untranslated region and first exon was identified by quantitative real-time PCR [Neerinckx et al 2015].

Table 7. Notable *CCN6* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_003880.3 NP_003871.1	c.156C>A	p.Cys52Ter	Most common pathogenic variant in persons of Turkish ancestry; most common variant observed across all ethnicities (~28%)
	c.233G>A	p.Cys78Tyr	Two most common pathogenic variants in Indian population
	c.1010G>A	p.Cys337Tyr	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Cancer and Benign Tumors

Loss or downregulation of WISP-3 is associated with breast cancers, colorectal cancers, and hepatocellular carcinoma as reduction of WISP-3 stimulates tumorigenesis. The COSMIC (Catalogue of Somatic Mutations in Cancer) database shows 1,290 unique *CCN6* variants in tissues associated with cancers.

Chapter Notes

Acknowledgments

Indian Council of Medical Research – Clinical and molecular evaluation of inherited arthropathies and multiple vertebral segmentation defects (BMS 54/2/2013)

Department of Science and Technology – Application of autozygosity mapping and exome sequencing to identify genetic basis of disorders of skeletal development (SB/SO/HS/005/2014)

Revision History

- 23 December 2020 (sw) Comprehensive update posted live
- 25 November 2015 (me) Review posted live
- 30 June 2015 (kmg) Original submission

References

Literature Cited

Bhavani GS, Shah H, Dalal AB, Shukla A, Danda S, Aggarwal S, Phadke SR, Gupta N, Kabra M, Gowrishankar K, Gupta A, Bhat M, Puri RD, Bijarnia-Mahay S, Nampoothiri S, Mohanasundaram KM, Rajeswari S, Kulkarni AM, Kulkarni ML, Ranganath P, Ramadevi AR, Hariharan SV, Girisha KM. Novel and recurrent mutations in WISP3 and an atypical phenotype. Am J Med Genet A. 2015;167A:2481–4. PubMed PMID: 25988854.

Dalal A, Bhavani G SL, Togarrati PP, Bierhals T, Nandineni MR, Danda S, Danda D, Shah H, Vijayan S, Gowrishankar K, Phadke SR, Bidchol AM, Rao AP, Nampoothiri S, Kutsche K, Girisha KM. Analysis of the WISP3 gene in Indian families with progressive pseudorheumatoid dysplasia. Am J Med Genet A. 2012;158A:2820–8. PubMed PMID: 22987568.

Delague V, Chouery E, Corbani S, Ghanem I, Aamar S, Fischer J, Levy-Lahad E, Urtizberea JA, Mégarbané A. Molecular study of WISP3 in nine families originating from the Middle-East and presenting with progressive pseudorheumatoid dysplasia: identification of two novel mutations, and description of a founder effect. Am J Med Genet A. 2005;138A:118–26. PubMed PMID: 16152649.

Garcia Segarra N, Mittaz L, Campos-Xavier AB, Bartels CF, Tuysuz B, Alanay Y, Cimaz R, Cormier-Daire V, Di Rocco M, Duba HC, Elcioglu NH, Forzano F, Hospach T, Kilic E, Kuemmerle-Deschner JB, Mortier G, Mrusek S, Nampoothiri S, Obersztyn E, Pauli RM, Selicorni A, Tenconi R, Unger S, Utine GE, Wright M, Zabel B, Warman ML, Superti-Furga A, Bonafé L. The diagnostic challenge of progressive pseudorheumatoid dysplasia (PPRD): a review of clinical features, radiographic features, and WISP3 mutations in 63 affected individuals. Am J Med Genet C Semin Med Genet. 2012;160C:217–29. PubMed PMID: 22791401.

Hurvitz JR, Suwairi WM, Van Hul W, El-Shanti H, Superti-Furga A, Roudier J, Holderbaum D, Pauli RM, Herd JK, Van Hul EV, Rezai-Delui H, Legius E, Le Merrer M, Al-Alami J, Bahabri SA, Warman ML. Mutations in the CCN gene family member WISP3 cause progressive pseudorheumatoid dysplasia. Nat Genet. 1999;23:94–8. PubMed PMID: 10471507.

Jónsson H, Sulem P, Kehr B, Kristmundsdottir S, Zink F, Hjartarson E, Hardarson MT, Hjorleifsson KE, Eggertsson HP, Gudjonsson SA, Ward LD, Arnadottir GA, Helgason EA, Helgason H, Gylfason A, Jonasdottir A, Jonasdottir A, Rafnar T, Frigge M, Stacey SN, Th Magnusson O, Thorsteinsdottir U, Masson G, Kong A, Halldorsson BV, Helgason A, Gudbjartsson DF, Stefansson K. Parental influence on human germline de novo mutations in 1,548 trios from Iceland. Nature. 2017;549:519–22. PubMed PMID: 28959963.

Neerinckx B, Thues C, Wouters C, Lechner S, Westhovens R, Van Esch H. A homozygous deletion of exon 1 in WISP3 causes progressive pseudorheumatoid dysplasia in two siblings. Hum Genome Var. 2015;2:15049. PubMed PMID: 27081554.

Pennica D, Swanson TA, Welsh JW, Roy MA, Lawrence DA, Lee J, Brush J, Taneyhill LA, Deuel B, Lew M, Watanabe C, Cohen RL, Melhem MF, Finley GG, Quirke P, Goddard AD, Hillan KJ, Gurney AL, Botstein D, Levine AJ. WISP genes are members of the connective tissue growth factor family that are up-regulated in wnt-1-transformed cells and aberrantly expressed in human colon tumors. Proc Natl Acad Sci U S A. 1998;95:14717–22. PubMed PMID: 9843955.

Sen M, Cheng YH, Goldring MB, Lotz MK, Carson DA. WISP3-dependent regulation of type II collagen and aggrecan production in chondrocytes. Arthritis Rheum. 2004;50:488–97. PubMed PMID: 14872491.

Stenson PD, Mort M, Ball EV, Evans K, Hayden M, Heywood S, Hussain M, Phillips AD, Cooper DN. The Human Gene Mutation Database: towards a comprehensive repository of inherited mutation data for medical research, genetic diagnosis and next-generation sequencing studies. Hum Genet. 2017;136:665–77. PubMed PMID: 28349240.

Wang M, Man XF, Liu YQ, Liao EY, Shen ZF, Luo XH, Guo LJ, Wu XP, Zhou HD. Dysfunction of collagen synthesis and secretion in chondrocytes induced by wisp3 mutation. Int J Endocrinol. 2013;2013:679763. PubMed PMID: 23573089.

Wynne-Davies R, Hall C, Ansell BM. Spondylo-epiphysial dysplasia tarda with progressive arthropathy. A "new" disorder of autosomal recessive inheritance. J Bone Joint Surg Br. 1982;64:442–5. PubMed PMID: 6807993.

Zhou HD, Bu YH, Peng YQ, Xie H, Wang M, Yuan LQ, Jiang Y, Li D, Wei QY, He YL, Xiao T, Ni JD, Liao EY. Cellular and molecular responses in progressive pseudorheumatoid dysplasia articular cartilage associated with compound heterozygous WISP3 gene mutation. J Mol Med (Berl). 2007;85:985–96. PubMed PMID: 17483925.

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