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Cartilage-Hair Hypoplasia – Anauxetic Dysplasia Spectrum Disorders

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Summary

Clinical characteristics

The cartilage-hair hypoplasia – anauxetic dysplasia (CHH-AD) spectrum disorders are a continuum that includes the following phenotypes:

- Metaphyseal dysplasia without hypotrichosis (MDWH)
- Cartilage-hair hypoplasia (CHH)
- Anauxetic dysplasia (AD)

CHH-AD spectrum disorders are characterized by severe disproportionate (short-limb) short stature that is usually recognized in the newborn, and occasionally prenatally because of the short extremities. Other findings include joint hypermobility, fine, silky hair, immunodeficiency, anemia, increased risk for malignancy, gastrointestinal dysfunction, and impaired spermatogenesis. The most severe phenotype, AD, has the most pronounced skeletal phenotype, may be associated with atlantoaxial subluxation in the newborn, and may include cognitive deficiency. The clinical manifestations of the CHH-AD spectrum disorders are variable, even within the same family.

Diagnosis/testing

Diagnosis of a CHH-AD spectrum disorder is established in a proband with characteristic clinical and radiographic findings. If clinical and radiographic findings are inconclusive, identification of biallelic pathogenic variants in *RMRP* by molecular genetic testing can confirm the diagnosis and allow for family studies.

Management

Treatment of manifestations: If cervical spinal instability is identified in a person with AD, special care is required during general anesthesia; surgery may be needed to fuse unstable cervical vertebrae and/or to treat progressive kyphoscoliosis that compromises lung function in AD; corrective osteotomies may be required for progressive

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varus deformity of the lower extremities; treatment of underlying infections based on their type, location, and severity; immediate high-dose intravenous acyclovir for varicella infection; consideration of prophylactic antibiotic therapy and/or immunoglobulin replacement therapy; recurrent severe infections, severe combined immunodeficiency (SCID), and/or severely depressed erythropoiesis may warrant hematopoietic stem cell transplantation; physiotherapy and other acute and long-term medical management for bronchiectasis per pulmonologist; red blood cell transfusions for severe anemia with iron chelation as needed; standard treatments for malignancies, congenital megacolon, Hirschsprung disease, and intestinal malabsorption; nutritional evaluation in those with short bowel syndrome; hormonal induction as needed for pubertal maturation; developmental and educational support as needed.

Surveillance: Monitor growth using CHH-specific growth curves; clinical and (if warranted) radiographic examination of joints of the lower extremities and spine annually in childhood and as required in adulthood; annual clinical and radiographic examination of the spine in individuals with AD. Monitor all children regardless of immune status during the first two years of life for recurrent infections, especially life-threatening varicella infection, then monitor annually; laboratory assessment for those with suspected infection; laboratory assessment of immune function with frequency based on initial lab results; assess the frequency of respiratory tract infections at each visit; high-resolution CT examination for those with suspected bronchiectasis and lung MRI to monitor bronchiectasis. For those who have not had anemia, observe for clinical signs of anemia; for those in remission after treatment, complete blood count every six months. Clinical and laboratory examination for manifestations of malignancy annually in children and as needed in adults; abdominal ultrasound every one to two years in children and as needed in adults. Assess pubertal development annually throughout adolescence; assess for hypogonadism in those with pubertal delay. Developmental and cognitive assessment as needed in those with AD throughout childhood.

Agents/circumstances to avoid: Administration of live vaccines when signs of abnormal immunologic function or SCID are present.

Evaluation of relatives at risk: Early diagnosis of relatives at risk for the CHH-AD spectrum disorders allows for early management of manifestations that can be associated with significant morbidity (e.g., infections, immunization with live vaccines, malignancies).

Pregnancy management: Fetal growth is generally unaffected; therefore, planned cæsarean section should be considered in term pregnancies in affected women due to cephalopelvic disproportion.

Genetic counseling

CHH-AD spectrum disorders are inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an *RMRP* 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. Once the *RMRP* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives and molecular genetic prenatal and preimplantation genetic testing for CHH-AD spectrum disorders are possible.

GeneReview Scope

Cartilage-Hair Hypoplasia – Anauxetic Dysplasia Spectrum Disorders: Included Phenotypes
• Metaphyseal dysplasia without hypotrichosis (MDWH) • Cartilage-hair hypoplasia (CHH) • Anauxetic dysplasia (AD)

For synonyms and outdated names see Nomenclature.

Diagnosis

There are no formal diagnostic criteria for cartilage-hair hypoplasia – anauxetic dysplasia (CHH-AD) spectrum disorders, as individuals present with highly variable phenotypes.

The CHH-AD spectrum disorders are a continuum ranging from short stature without hypotrichosis with only radiographic evidence of metaphyseal dysplasia (MDWH) [Bonafé et al 2002], to short stature with hypotrichosis and variable metaphyseal dysplasia of the tubular bones (cartilage-hair hypoplasia [CHH]) [McKusick et al 1965, Mäkitie & Kaitila 1993], to severe deforming short stature with metaphyseal, epiphyseal, and vertebral dysplasia (anauxetic dysplasia [AD]) [Horn et al 2001, Thiel et al 2005].

Newborn screening for severe combined immunodeficiency (SCID) using detection of T cell receptor excision circles is able to identify some individuals with CHH prior to recognition of other findings [Kwan et al 2013].

Suggestive Findings

A CHH-AD spectrum disorder **should be suspected** in a proband with:

- Mild-to-severe disproportionate short-limbed short stature
- Presence of variable metaphyseal dysplasia, with epiphyseal and vertebral dysplasia at the severe end of the spectrum

Especially when accompanied by:

- Short tubular bones
- Bowed femora and tibiae
- "Bullet"-shaped middle phalanges, cone-shaped epiphyses, and premature epiphyseal fusion on hand radiographs
- Laxity of ligaments with joint hypermobility, but limited extension of the elbow
- Fine, silky hair
- Increased rate of infections or intestinal dysfunction or anemia

Clinical Findings by Phenotype

Cartilage-hair hypoplasia (CHH)

- Disproportionate (short-limb) short stature
- Short fingers and toes
- Bowed femora and tibiae
- Laxity of ligaments with hypermobility of joints
- Limited extension of the elbows
- Lumbar lordosis
- Chest deformity
- Blond, sparse, fine, silky hair
- Impaired lymphocyte proliferation and T lymphocyte function with increased risk of infections in infancy and childhood, severe varicella infection, SCID, bronchiectasis, and cutaneous and visceral granulomas
- Macrocytic, hypoplastic anemia in early childhood
- Malignancies: lymphoma, leukemia, neoplasms of the skin, eye, and liver
- Intestinal manifestations: congenital megacolon, Hirschsprung disease, intestinal malabsorption

Metaphyseal dysplasia without hypotrichosis (MDWH)

- Clinical features similar to CHH, but with normal hair

- Absence of anemia and intestinal manifestations
- Initial absence of immunodeficiency; late-onset immunodeficiency is possible [Vakkilainen et al 2020b].

Anauxetic dysplasia (AD)

- Prenatal onset of extreme short-limb short stature (100% of affected individuals)
- Barrel chest
- Hyperlordosis and kyphoscoliosis
- Dislocated hips
- Atlantoaxial subluxation leading to cervical spine compression
- Craniofacial features: midfacial hypoplasia, macroglossia, dental abnormalities
- Mild intellectual disability

Radiographic Findings by Phenotype

Note: Radiographic findings tend to be highly variable.

Cartilage-hair hypoplasia (CHH)

- Short and thick tubular bones with metaphyseal dysplasia most prominent at the knees. Distal metaphyses are wide, flared, and occasionally scalloped with cystic areas and poor ossification with trabeculation. Epiphyses are normal or show only mild dysplasia of the femoral head.
- Metacarpals and phalanges are short and bullet-shaped with cone-shaped epiphyses.
- Vertebral bodies are normal or have mild biconvexity with increased height, lumbar lordosis, and reduced widening of interpediculate distance in the lumbar spine.

Metaphyseal dysplasia without hypotrichosis (MDWH). Radiographic findings are similar to those in CHH.

Anauxetic dysplasia (AD)

- Vertebral bodies are late-maturing ovoid with concave dorsal surfaces in the lumbar region; dislocation is seen in the cervical spine.
- Femora have small capital femoral epiphyses with hypoplastic femoral necks.
- Iliac bodies are hypoplastic.
- Acetabulae are shallow.
- Metacarpals are short with widened shafts (I and V).
- Phalanges are very short and broad with small, late ossifying epiphyses and bullet-shaped middle phalanges.

Establishing the Diagnosis

The diagnosis of a CHH-AD spectrum disorder **is established** in a proband with the above suggestive findings including clinical and characteristic radiographic findings. If clinical and radiographic findings are inconclusive, identification of biallelic pathogenic (or likely pathogenic) variants in *RMRP* by molecular genetic testing (see Table 1) can confirm the diagnosis and allow for family studies.

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic, and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of biallelic *RMRP* variants of uncertain significance (or of one known *RMRP* pathogenic variant and one *RMRP* variant of uncertain significance) does not establish or rule out the diagnosis.

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. Because the phenotypes of CHH-AD spectrum disorders are broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with short stature and/or immune deficiency are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of a CHH-AD spectrum disorder, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *RMRP* is performed first to detect nucleotide variants and small intragenic deletions/insertions/duplications; Sequence analysis should include both the transcribed region and the promoter region. 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 the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

  Note: Targeted analysis for the common *RMRP* pathogenic variant g.71A>G can be performed first in individuals of Finnish or Amish ancestry (see Table 6).

- **A multigene panel** that includes *RMRP* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition 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 an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by short stature, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) may be considered. **Exome sequencing** is most commonly used, but **genome sequencing** is also possible. Note: *RMRP* pathogenic variants may not be detected on exome sequencing because *RMRP* is a small (268 bp) untranslated gene without introns and exons. Exome analysis may be designed to include sequencing of functional non-protein-coding elements such as *RMRP*.

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 Cartilage-Hair Hypoplasia – Anauxetic Dysplasia Spectrum Disorders

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
RMRP	Sequence analysis [3]	~100% [4]
	Gene-targeted deletion/duplication analysis [5]	None reported [6]

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 nucleotide substitution and small intragenic deletions. Typically, whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Martin & Li [2007]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. To date, no large deletions or duplications involving *RMRP* have been reported to cause cartilage-hair hypoplasia – anauxetic dysplasia spectrum disorders [Ridanpää et al 2001, Thiel & Rauch 2011].

Clinical Characteristics

Clinical Description

Cartilage-hair hypoplasia – anauxetic dysplasia (CHH-AD) spectrum disorders are a continuum that includes three phenotypes:

- Metaphyseal dysplasia without hypotrichosis (MDWH)
- Cartilage-hair hypoplasia (CHH), with metaphyseal dysplasia and hypotrichosis
- At the severe end, the rare anauxetic dysplasia (AD), the most pronounced skeletal phenotype

The mechanisms for phenotypic variability are incompletely understood (see Genotype-Phenotype Correlations).

Disproportionate short-limb short stature is usually evident in the newborn period and occasionally prenatally. Proportionate short stature has been observed in some individuals [van der Burgt et al 1991, Mäkitie & Kaitila 1993]. Normal growth in childhood has also been reported [Klemetti et al 2017]. Growth failure is progressive and associated with the degree of disproportion. Final adult height range is <85 cm to 151 cm. Lumbar lordosis and scoliosis may contribute to the short stature.

Marked inter- and intrafamilial variability of short stature has been observed. Growth curves for Finnish individuals with CHH have been published. Final adult height ranges from 104 to 151 cm in CHH (median: 131 cm in males; 122 cm in females) and less than 85 cm in AD [Mäkitie et al 1992a, Mäkitie & Kaitila 1993, Horn et al 2001].

Laxity of ligaments with joint hypermobility is marked, especially in the hands and feet. The laxity of lateral ligaments of the knees contributes to the varus deformity of the lower extremities.

Fine, silky hair. Sparse hair, reduction of the diameter of the hair shaft, and loss of the central pigmented core of the hair shaft contribute to the distinctive appearance of the hair. About 15% of affected persons have complete primary alopecia including scalp hair and eyelashes, eyebrows, and body hair.

Immunodeficiency may manifest as lymphopenia and defects in T lymphocyte function and/or proliferation [Kavadas et al 2008]. Sometimes defects in B lymphocyte proliferation with low immunoglobulin G and undetectable immunoglobulin A are observed. Although deficient cellular immunity is present in most affected

individuals (88%), an increased rate of infection is noted in only 35%-65%, usually during infancy and childhood. Early reports on fatal varicella infection conflict with later publications on larger cohorts of individuals with CHH with mostly uncomplicated varicella disease [Mäkitie et al 1998]. Severe respiratory disease (e.g., lymphoplasmacytic bronchiolitis) has been reported in children [Bailly-Botuha et al 2008]. Bronchiectasis is reported in 29%-52% of individuals with CHH; however, clinical relevance and progression of bronchiectasis can be insignificant [Vakkilainen et al 2021]. Individuals with CHH and combined immunodeficiency are at risk for chronic bronchiectasis [Toiviainen-Salo et al 2008], which may also develop in individuals with mild immunodeficiency [Kostjukovits et al 2017a]. Chronic viral infections with bocavirus and norovirus have been reported [Kainulainen et al 2014]. Impaired cellular immunity persists into adulthood. Fatal enteroviral meningoencephalitis has been reported in a child with CHH [Vatanavicharn et al 2010]. Cutaneous granulomas can be caused by vaccine-strain rubella virus in individuals with CHH [Buchbinder et al 2019]. Anti-TNF-α therapy has been used successfully in the treatment of cutaneous and visceral granulomas. However, fatal progressive multifocal leukoencephalopathy caused by JC (John Cunningham) virus has been described during treatment with anti-TNF-α antibodies. Hematopoietic stem cell transplantation resulted in disappearance of granulomas in two of three transplanted individuals [Moshous et al 2011].

Autoimmune complications. Clinical autoimmunity is common, and its spectrum is broad in individuals with CHH [Vakkilainen et al 2018]. Autoimmune complications and a form of severe allergic reaction have been rarely observed in individuals with CHH; however, the pathophysiology is still unknown [Bacchetta et al 2009, Narra & Shearer 2009]. Cutaneous and visceral granulomatous inflammatory lesions have been described in five individuals with CHH [Moshous et al 2011, McCann et al 2014]. Individuals with CHH demonstrate broad autoantibody reactivity compared to healthy controls [Biggs et al 2017].

Anemia. Deficient erythropoiesis may lead to mild-to-severe macrocytic anemia. Mild anemia is seen in about 80% of those with CHH and resolves spontaneously in childhood in most individuals [Mäkitie et al 1992b]. Severe and persistent anemia resembling that of Diamond-Blackfan syndrome is seen in about 6% of affected individuals [Williams et al 2005]. About 50%-75% of those with severe anemia require lifelong transfusions or bone marrow transplantation (see Management); on occasion spontaneous resolution is observed [Williams et al 2005]. In individuals requiring repeated transfusions iron chelation is successful and well tolerated when needed [Taskinen et al 2013]. A single case report demonstrated the efficacy of an mTOR inhibitor in the treatment of anemia in an individual with CHH [Del Borrello et al 2022].

Malignancies. Extended follow up of persons with CHH revealed that about 11% of the cohort (14/123) followed for 39 years developed malignancies [Taskinen et al 2008]. A Kaplan-Meier estimate gave a probability of a cancer event (excluding basal cell carcinoma) of 41% by age 65 years. Nine of the 14 malignancies were diagnosed in persons age 15-44 years. Of the 14 who developed malignancies, nine have died; median time to death was three months after malignancy diagnosis. Underlying pathogenic variants in *RMRP* and severity of preceding immunodeficiency varied and did not correlate with the risk of malignancy.

The most frequently observed cancers are non-Hodgkin lymphoma, followed by squamous cell carcinoma, leukemia, and Hodgkin lymphoma; non-aggressive basal cell carcinoma was also common. There are isolated reports of uterine carcinoma and vocal cord carcinoma [Kostjukovits et al 2017b]. Rarely, two or more malignancies are observed in one individual.

A case series of 16 individuals with CHH and lymphoma revealed that the most common lymphoma type was diffuse large B cell lymphoma [Kukkola et al 2022]. Mortality due to lymphoma is high in individuals with CHH (11/16, 69%), probably due to the advanced stage of lymphoma at the time of diagnosis. In almost all surviving individuals with CHH and lymphoma, the diagnosis was made either during routine follow up or after evaluation for nonspecific mild symptoms. Other CHH-related manifestations were poor predictors of lymphoma development, implying that all individuals with CHH should be regularly screened for malignancy.

Intestinal issues

- **Newborn period.** Hirschsprung disease with short-segment or total colonic aganglionosis is observed in 7%-8% of those with CHH, especially infants with a more severe CHH phenotype [Mäkitie et al 2001a].
- **Infancy.** When Hirschsprung disease has been excluded, malabsorption secondary to gastrointestinal infections can occur in the first two years of life [Mäkitie et al 1995]. The main findings are "celiac syndrome" with diarrhea and poor weight gain. Although most intestinal manifestations occur in the first two years of life, they can occur later in childhood. Intestinal issues have not been described in individuals with AD or MDWH.

Impaired spermatogenesis. Because of a defect in cell proliferation, males with CHH have defects in sperm concentration, motility, morphology, and immunology [Mäkitie et al 2001b]. Testicles are smaller than normal for age and pubertal status; however, serum concentrations of testosterone, inhibin B, and gonadotropins are within the normal range in most individuals.

Delayed puberty. Girls with CHH may have hypogonadotropic or normogonadotropic hypogonadism with no spontaneous pubertal development [Holopainen et al 2018].

Additional findings observed in some persons with AD [Horn et al 2001]:

- Atlantoaxial subluxation with fatal cervical compression
- Mild intellectual disability

Genotype-Phenotype Correlations

The CHH-AD spectrum includes a range of phenotypes. *RMRP* is not translated into a protein; thus, genotype-phenotype correlation depends on the position of the pathogenic variant in the transcript and the proposed effect on transcript folding and RNA-protein interaction (see Molecular Genetics).

The milder phenotypes are usually caused by either of the following:

- Compound heterozygous or homozygous pathogenic variants within the transcript resulting in little to intermediate effect on the function of RNase MRP (see Molecular Pathogenesis)
- Compound heterozygosity for one pathogenic variant within the transcript and one pathogenic variant in the promoter region

AD is caused by either of the following:

- Compound heterozygous or homozygous pathogenic variants that severely alter function
- Compound heterozygosity for one pathogenic variant within the transcript that severely alters the RNase MRP function and a hypomorphic allele (e.g., pathogenic variant leading to an unstable transcript)

Nomenclature

Cartilage-hair hypoplasia (CHH) or metaphyseal chondrodysplasia, McKusick type was first described in the Old Order Amish population [McKusick et al 1965].

Individuals with normal hair and metaphyseal dysplasia, called metaphyseal dysplasia without hypotrichosis (MDWH), were reported by Bonafé et al [2002].

Anauxetic dysplasia was named after the Greek "not to permit growth" [Horn et al 2001].

Prevalence

About 700 individuals are currently known to have a CHH-AD spectrum disorder [Kaitila, personal communication]. The most severe form, AD, is extremely rare: fewer than ten affected individuals have been reported.

Affected individuals have been reported in most populations; however, a high incidence of CHH was noted in the Old Order Amish population, with a prevalence of 1-2:1,000 (carrier frequency of 1:10), and in Finland, with an incidence of 1:23,000 (carrier frequency of 1:76) [Mäkitie 1992, Mäkitie & Kaitila 1993].

Genetically Related (Allelic) Disorders

Single individuals with biallelic *RMRP* pathogenic variants and immunodeficiency without skeletal features [Ip et al 2015] and with Omenn syndrome [Roifman et al 2006] and normal childhood growth [Klemetti et al 2017] have been described.

Differential Diagnosis

Table 2. Genes of Interest in the Differential Diagnosis of Cartilage-Hair Hypoplasia – Anauxetic Dysplasia Spectrum Disorders

Gene(s)	Disorder	MOI	Features of Disorder	
			Overlapping w/CHH-AD	Distinguishing from CHH-AD
ACP5	*ACP5*-related spondyloenchondrodysplasia w/ immune dysregulation (OMIM 607944)	AR	• Skeletal dysplasia • Immunodeficiency	• Spondylometaphyseal dysplasia • DD, spasticity, intracranial calcifications
Multiple genes incl: *ADA* *ADA2* *IL2RG*	Combined immunodeficiency syndromes (See Adenosine Deaminase Deficiency, Adenosine Deaminase 2 Deficiency, XL Severe Combined Immunodeficiency, & OMIM PS300755.)	AR XL	Immunodeficiency	In most immunodeficiency syndromes: no skeletal abnormalities
COL10A1	*COL10A1*-related metaphyseal dysplasia Schmid (See Schmid Metaphyseal Chondrodysplasia.)	AD	Short stature & radiographic metaphyseal abnormalities (metaphyseal dysplasia esp in proximal femur) resembling CHH	No extraskeletal manifestations
DCLRE1C *RAG1* *RAG2*	Omenn syndrome (OMIM 603554)	AR	• Short stature • Hematologic changes • Immunologic changes	Omenn syndrome is more severe & incl ichthyosiform skin changes & septicemia.
DNAJC21 *EFL1* *SBDS* *SRP54*	Shwachman-Diamond syndrome (SDS)	AR AD	• Short stature & radiographic metaphyseal abnormalities resembling CHH • ↑ infections • Anemia	• Milder skeletal features (usually) • Principal manifestations: exocrine pancreatic insufficiency, neutropenia, poor weight gain, & growth deficiency

Table 2. continued from previous page.

Gene(s)	Disorder	MOI	Features of Disorder	
			Overlapping w/CHH-AD	Distinguishing from CHH-AD
Multiple genes incl: *ELANE* *G6PC3* *GFI1* *HAX1* *WAS*	Isolated & syndromic [1] congenital neutropenia (See *ELANE*-Related Neutropenia, G6PC3 Deficiency; *WAS*-Related Disorders, & OMIM PS202700.)	AD AR XL	Congenital neutropenia	Absence of CHH skeletal phenotype
EXTL3	*EXTL3*-related spondyloepimetaphyseal dysplasia w/immune deficiency & intellectual disability (immunoskeletal dysplasia w/neurodevelopmental abnormalities) (OMIM 617425)	AR	• Skeletal dysplasia • Immunodeficiency	• Spondyloepimetaphyseal dysplasia • DD, dysmorphic features, liver cysts
NEPRO	*NEPRO*-related metaphyseal dysplasia w/short stature (CHH-like) (anauxetic dysplasia 3) (OMIM 618853)	AR	• Short stature & metaphyseal dysplasia • Sparse scalp hair	No clinical symptoms or laboratory signs of immunodeficiency
PGM3	*PGM3*-related spondyloepimetaphyseal dysplasia w/immune deficiency (immunodeficiency 23 [IMD23]) (OMIM 615816)	AR	• Skeletal dysplasia • Immunodeficiency	• Spondylometaphyseal dysplasia • Cardiovascular abnormalities, DD, dysmorphic features
POP1	*POP1*-related metaphyseal dysplasia w/short stature (CHH-like) (anauxetic dysplasia 2) (OMIM 617396)	AR	• Short stature & metaphyseal dysplasia • ↓ peripheral blood mononuclear cell proliferation ability [2]	No clinical symptoms of immunodeficiency
PTH1R	*PTH1R*-related metaphyseal dysplasia, Jansen type (OMIM 156400)	AD	Short stature & radiographic metaphyseal abnormalities resembling CHH	Hypercalcemia & hypercalciuria
RNU4ATAC	*RNU4ATAC*-related Roifman syndrome (See RNU4atac-opathy.)	AR	• Skeletal dysplasia • Immunodeficiency	• Spondyloepiphyseal dysplasia • Humoral immunodeficiency • Retinal dystrophy, DD, characteristic facial features
SMARCAL1	*SMARCAL1*-related immuno-osseous dysplasia (Schimke type) (See Schimke Immunoosseous Dysplasia.)	AR	• Short stature • Cellular immune deficiency [3]	• Short stature caused by short trunk (vs short-limb short stature in CHH-AD spectrum disorders) • Characteristic facies • Vascular issues • Glomerulopathy, abnormal skin pigmentation

AD = autosomal dominant; AR = autosomal recessive; CHH = cartilage-hair hypoplasia; CHH-AD; cartilage-hair hypoplasia – anauxetic dysplasia; DD = developmental delay; MOI = mode of inheritance; XL = X-linked

1. Congenital neutropenia that occurs as part of a syndrome can be caused by pathogenic variants affecting glucose metabolism or lysosomal function.

2. Glazov et al [2011]

3. If recurrent infections are present, milder forms of Schimke immunoosseous dysplasia may be confused with cartilage-hair hypoplasia [Baradaran-Heravi et al 2008].

Management

No clinical practice guidelines for cartilage-hair hypoplasia – anauxetic dysplasia (CHH-AD) spectrum disorders have been published. Guidelines for the management of immunodeficiency in CHH have been published [Vakkilainen et al 2020b].

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with a CHH-AD spectrum disorder, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Cartilage-Hair Hypoplasia – Anauxetic Dysplasia Spectrum Disorders: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Musculoskeletal	Full skeletal survey	To incl (in AD) views of cervical spine to identify cervical vertebral abnormalities & assess risk of atlantoaxial subluxation
	Orthopedic consult	Eval for complications of joint laxity, lumbar lordosis, chest deformity, scoliosis, & varus deformity of lower extremities
Allergy/Immunology	Assess for immunodeficiency: [1] • Serum concentration of IgG, IgA, IgM, & IgG subclasses • CD3, 4, 8, 19, 16/56 • Post-vaccine titers • Other immunologic parameters: allogeneic lymphocyte cytotoxicity; T cell subsets, TREC analysis; T cell repertoire; proliferation response to PHA; proliferation response to anti-CD3	Immunology consultation in those w/abnormal immunologic testing or recurrent infections for assessment & treatment & to determine vaccination program & approach to varicella prophylaxis
Respiratory	Pulmonary consult	Eval for evidence of respiratory disease
Hematologic/Lymphatic	CBC w/differential cell count	Eval for macrocytic anemia & immunodeficiency [1]
	Hematologic consult	If blood count is abnormal, for further assessment & treatment
Gastrointestinal/Feeding	Gastroenterology consult	Eval for congenital megacolon in those w/suggestive manifestations
Development/Cognition	Developmental assessment	For those w/AD as needed
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of CHH-AD spectrum disorders to facilitate medical & personal decision making

AD = anauxetic dysplasia; CBC = complete blood count; CHH = cartilage-hair hypoplasia; Ig = immunoglobulin; PHA = phytohemagglutinin; TREC = T cell receptor excision circles
1. Rider et al [2009]

Treatment of Manifestations

There is no cure for CHH-AD spectrum disorders.

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 4).

Table 4. Cartilage-Hair Hypoplasia – Anauxetic Dysplasia Spectrum Disorders: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Musculoskeletal manifestations	• If cervical spine abnormality &/or instability is identified, special care when general anesthesia is administered • In persons w/AD, surgery as needed to fuse malformed cervical vertebrae in infancy & to correct/prevent progression of kyphoscoliosis that can compromise lung function • Corrective osteotomies as needed in late childhood or adolescence for excessive varus deformity of lower extremities [1]	• Orthopedic surgery may be complicated by low bone density. • Treatment w/recombinant growth hormone has not shown any sustained benefit in persons w/CHH & cannot be recommended. [2]
Immunodeficiency	• Treatment of underlying infections based on type, location, & severity • Immediate high-dose IV acyclovir w/onset of varicella infection to prevent complications • Consider prophylactic antibiotics for those w/ recurrent infections, neutropenia, or severe lymphopenia. • Consider IVIG if immunoglobulin or IgG subclass levels are low, or if vaccine responses are inadequate. • Treatments for granulomas have included anti-TNF-α therapy & HSCT. [3]	• Consider HSCT in persons w/CHH w/ recurrent infections & autoimmune manifestations or bone marrow dysplasia for whom a well-matched donor is available. [4] • HSCT has resulted in normalization of T lymphocyte numbers & function, resolution of autoimmune manifestations, & catch-up growth, probably due to ↓ infections. • Overall survival rates have been reported at 63% for unrelated donor transplants & as high as 80% for matched sibs.
Bronchiectasis	Physiotherapy & other acute & long-term treatment for bronchiectasis per pulmonologist	
Anemia	• Red blood cell transfusions for severe anemia secondary to depressed erythropoiesis • HSCT is rarely needed. [5] • Iron chelation for those requiring recurrent red blood cell transfusions	Although steroids have been effective in treating anemia in some persons w/CHH, data are not sufficient to recommend this therapy in general, esp considering potential side effects of immune suppression & growth deficiency.
Malignancy	No specific recommendations for treatment of observed malignancies are available.	Non-Hodgkin lymphoma often has poor prognosis w/conventional cytotoxic protocols. [6]
Gastrointestinal	• Standard treatments for congenital megacolon, Hirschsprung disease, intestinal malabsorption • Nutrition eval in those w/short bowel syndrome	
Endocrine	Hormonal induction as needed for delayed pubertal maturation	
Development/Cognition	Developmental & educational support as needed	

AD = anauxetic dysplasia; CHH = cartilage-hair hypoplasia; HSCT = hematopoietic stem cell transplantation; Ig = immunoglobulin; IVIG = intravenous immunoglobulin

1. Riley et al [2015]
2. Obara-Moszynska et al [2013]
3. Moshous et al [2011]
4. Bordon et al [2010]
5. Williams et al [2005]
6. Taskinen et al [2008]

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 5 are recommended.

Table 5. Cartilage-Hair Hypoplasia – Anauxetic Dysplasia Spectrum Disorders: Recommended Surveillance

System/Concern	Evaluation	Frequency
Musculoskeletal	Measurement of linear growth & body proportions & comparison w/CHH-specific growth curves [1]	Annually throughout childhood
	Clinical assessment for deformities of lower extremities & joints	At each visit
	X-ray eval & orthopedic consultation	In those w/symptomatic misalignment, restricted knee or hip mobility, &/or symptomatic joint laxity
	Clinical assessment of spine	Annually in those w/AD
	Spine x-rays	
Immunology	Assess for recurrent infections, esp manifestations of life-threatening varicella infection.	At each visit, particularly in the first 2 yrs of life, then annually after age 2 yrs
	Physical exam	
	Laboratory assessment for suspected infection	As needed for early detection in those w/suspected infection
	• Serum concentration of IgG, IgA, IgM • CD3, 4, 8, 19, 16/56 • Post-vaccine titers • Other immunologic parameters: T cell subsets, TREC analysis; T cell repertoire; proliferation response to PHA; proliferation response to anti-CD3	• At diagnosis in all persons • Frequency of follow-up labs is based on initial results.
Respiratory	Assess frequency of respiratory tract infections.	At each visit
	High-resolution CT	For diagnosis in those w/suspected bronchiectasis [2]
	Lung MRI	As needed to monitor those w/bronchiectasis [3]
Anemia	Assess for clinical signs of anemia.	At each visit from diagnosis until early adolescence
	CBC	At least every 6 mos in those in remission after treatment for anemia or when clinical signs of anemia reappear [4]
Malignancy	• Assess for skin changes, enlarged lymph nodes, hepatomegaly, splenomegaly, & other signs of malignancy. • CBC w/differential [5] • LDH & uric acid	• Annually in children • In adults, frequency of follow up is determined on individual basis.
	Abdominal ultrasound	• Every 1-2 yrs in children • In adults, frequency of follow up is determined on individual basis.
Endocrine	Assess pubertal development.	Annually throughout adolescence
	Assess for hypogonadism.	As needed in those w/significant pubertal delay

Table 5. continued from previous page.

System/Concern	Evaluation	Frequency
Development/Cognition	Developmental & cognitive assessment	As needed throughout childhood in those w/AD

AD = anauxetic dysplasia; CBC = complete blood count; CHH = cartilage-hair hypoplasia; Ig = immunoglobulin; LDH = lactate dehydrogenase; PHA = phytohemagglutinin; TREC = T cell receptor excision circles
1. Mäkitie et al [1992a]
2. Toiviainen-Salo et al [2008]
3. Kostjukovits et al [2017a]
4. No data are available on the likely timing of recurrence of anemia after successful treatment.
5. Severe anemia in adolescents and adults with CHH can be the presenting symptom of malignancy and may require extensive investigations with bone marrow evaluation and imaging studies.

Agents/Circumstances to Avoid

Immunization with live vaccines should be carefully considered in those with CHH and evidence of abnormal immunologic function and should be avoided in those with CHH and severe combined immunodeficiency [Rider et al 2009].

Note: (1) Routine immunizations with inactivated vaccines are safe in persons with CHH. (2) No serious adverse events have been recorded after immunization with live viral vaccines in individuals of Finnish ancestry with CHH. (3) Individuals with CHH generate humoral and cellular immune response to live viral vaccines. Immunization with live vaccines may be considered in selected individuals with CHH without immunodeficiency or with clinically mild immunodeficiency [Vakkilainen et al 2020a].

Evaluation of Relatives at Risk

Early diagnosis of relatives (i.e., sibs) at risk for CHH-AD spectrum disorders is important for early recognition and management of manifestations that can be associated with significant morbidity (e.g., infections, immunization with live vaccines, malignancies). Relatives at risk should be tested if clinical features, especially short stature, are present; completely asymptomatic individuals need not be tested. Evaluations can include:

- Molecular genetic testing if the pathogenic variants in the family are known;
- Radiographic evaluation and *RMRP* molecular genetic testing if the pathogenic variants in the family are not known.

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

Pregnancy Management

Despite significant short stature in women with CHH and other potential CHH-related effects on pregnancy outcome, most pregnancies lead to a term cæsarean section delivery. Fetal growth is generally unaffected; therefore, planned cæsarean section should be considered in term pregnancies due to cephalopelvic disproportion [Holopainen et al 2020].

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.

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

The cartilage-hair hypoplasia – anauxetic dysplasia (CHH-AD) spectrum disorders are inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are presumed to be heterozygous for an *RMRP* pathogenic variant.
- If a molecular diagnosis has been established in the proband, molecular genetic testing is recommended for the parents of the proband to confirm that both parents are heterozygous for an *RMRP* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- According to previous evaluations, heterozygotes (carriers) are not at increased risk for cancer and are asymptomatic [Mäkitie et al 1999].

Sibs of a proband

- If both parents are known to be heterozygous for an *RMRP* 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.
- The clinical manifestations of the CHH-AD spectrum disorders are variable, even within the same family.
- According to previous evaluations, heterozygotes (carriers) are not at increased risk for cancer and are asymptomatic [Mäkitie et al 1999].

Offspring of a proband. Unless an affected individual's reproductive partner also has a CHH-AD spectrum disorder or is a carrier, offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *RMRP* (see **Family planning**).

Other family members. Each sib of the proband's parents has a 50% chance of being a carrier of an *RMRP* pathogenic variant.

Carrier Detection

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

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

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.
- Carrier testing for the reproductive partners of known carriers and for the reproductive partners of individuals affected with a CHH-AD spectrum disorder should be considered, particularly if both partners are of the same ethnic background. A high incidence of CHH has been reported in the Old Order Amish population, with a prevalence of 1-2:1,000 (carrier frequency of 1:10), and in Finland, with an incidence of 1:23,000 (carrier frequency of 1:76) [Mäkitie 1992, Mäkitie & Kaitila 1993].

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the *RMRP* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing for a CHH-AD spectrum disorder are possible.

Ultrasound examination. If the *RMRP* pathogenic variants have not been identified in an affected family member, prenatal diagnosis for a pregnancy at increased risk may also be possible through fetal ultrasound studies at 16-18 weeks' gestation.

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.

- **Little People of America**
  Phone: 888-LPA-2001; 714-368-3689
  Fax: 707-721-1896
  Email: info@lpaonline.org
  lpaonline.org
- **Lyhytkasvuiset – Kortväxta Ry**
  Finland
  Email: toimisto@lyhytkasvuiset.fi
  www.lyhytkasvuiset.fi
- **European Society for Immunodeficiencies (ESID) Registry**

Email: esid-registry@uniklinik-freiburg.de
ESID Registry

- **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. Cartilage-Hair Hypoplasia - Anauxetic Dysplasia Spectrum Disorders : Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
RMRP	9p13.3	Not applicable	RMRP	RMRP

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 Cartilage-Hair Hypoplasia - Anauxetic Dysplasia Spectrum Disorders (View All in OMIM)

157660	MITOCHONDRIAL RNA-PROCESSING ENDORIBONUCLEASE, RNA COMPONENT OF; RMRP
250250	CARTILAGE-HAIR HYPOPLASIA; CHH
250460	METAPHYSEAL DYSPLASIA WITHOUT HYPOTRICHOSIS; MDWH
607095	ANAUXETIC DYSPLASIA 1; ANXD1

Molecular Pathogenesis

RMRP encodes the untranslated RNA subunit of the ribonucleoprotein endoribonuclease complex RNase MRP [Ridanpää et al 2001]. The *RMRP* transcript consists of 267 bp with a type 3 promoter, a PSE element, a TATA box, and transcription factor binding sites upstream of the transcription initiation site. The mRNA transcript folds into a highly complex secondary structure and combines with at least ten proteins to form the mitochondrial RNA processing ribonuclease, RNase MRP, which is localized in the nucleolus and in mitochondria [Welting et al 2004, Hermanns et al 2005, Thiel et al 2005, Thiel et al 2007, Welting et al 2008]. This complex is involved in (1) 5.8S rRNA cleavage leading to mature 5.8S rRNA (a necessary step to complete ribosome assembly) and (2) cleavage of cyclin B1 mRNA (encoded by *CCNB1*) needed in cell cycle regulation progression. RNase MRP also forms a complex with telomerase reverse transcriptase catalytic subunit (encoded by *TERT*), which may play a role in cellular senescence [Maida et al 2009].

Most pathogenic variants are in conserved regions of the *RMRP* RNA transcript. Pathogenic variants within the transcribed region affect either (1) evolutionary highly conserved nucleotides that are likely to alter the secondary structure through mispairing in stem regions or (2) RNA-protein interaction forming the RNase MRP complex.

Occasionally small insertions, duplications, or triplications in the promoter region increase the distance between regulatory elements (e.g., the TATA box and the transcription start site). An increase of 24-26 bps between the regulatory elements leads to promoter inefficiency and reduced *RMRP* transcript levels [Ridanpää et al 2001, Nakashima et al 2007]. Such variants have been observed in compound heterozygosity with pathogenic variants within the transcript.

RMRP pathogenic variants may affect both mRNA and rRNA cleavage and thus cell cycle regulation and protein synthesis (see Thiel et al [2007] and references therein). The decrease in rRNA cleavage caused by some pathogenic variants strongly correlates with the degree of bone dysplasia [Thiel et al 2007], whereas the

disruption of the rRNA cleavage function correlates with the degree to which additional features including hair hypoplasia, immunodeficiency, anemia, and susceptibility to cancer are present. However, the actual phenotype in persons with compound heterozygous *RMRP* transcript variants can be quite variable, depending on the functional impairment resulting from the specific combination of pathogenic variants.

Mechanism of disease causation. Loss of function

***RMRP*-specific laboratory technical considerations.** *RMRP* is an intronless gene encoded by nuclear DNA. The *RMRP* RNA transcript is not translated into a protein.

Table 6. Notable *RMRP* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment
NG_017041.1	g.71A>G	--	Founder pathogenic variant present in 100% of Old Order Amish, 92% of Finnish, & 48% of non-Finnish persons w/CHH

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.

Chapter Notes

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References

Literature Cited

Bacchetta J, Ranchin B, Brunet AS, Bouvier R, Duquesne A, Edery P, Fabien N, Peretti N. Autoimmune hypoparathyroidism in a 12-year-old girl with McKusick cartilage hair hypoplasia. Pediatr Nephrol. 2009;24:2449–53. PubMed PMID: 19626344.

Bailly-Botuha C, Jaubert F, Taam RA, Galmiche L, Picard C, Bellon G, de Blic J. Diffuse lymphoplasmacytic bronchiolitis in cartilage-hair hypoplasia. J Pediatr. 2008;152:429–33. PubMed PMID: 18280854.

Baradaran-Heravi A, Thiel C, Rauch A, Zenker M, Boerkoel CF, Kaitila I. Clinical and genetic distinction of Schimke immuno-osseous dysplasia and cartilage-hair hypoplasia. Am J Med Genet A. 2008;146A:2013–7. PubMed PMID: 18627050.

Biggs CM, Kostjukovits S, Dobbs K, Laakso S, Klemetti P, Valta H, Taskinen M, Mäkitie O, Notarangelo LD. Diverse autoantibody reactivity in cartilage-hair hypoplasia. J Clin Immunol. 2017;37:508–10. PubMed PMID: 28631025.

Bonafé L, Schmitt K, Eich G, Giedion A, Superti-Furga A. RMRP gene sequence analysis confirms a cartilage-hair hypoplasia variant with only skeletal manifestations and reveals a high density of single-nucleotide polymorphisms. Clin Genet. 2002;61:146–51. PubMed PMID: 11940090.

Bordon V, Gennery AR, Slatter MA, Vandecruys E, Laureys G, Veys P, Qasim W, Friedrich W, Wulfraat NM, Scherer F, Cant AJ, Fischer A, Cavazzana-Calvo M, Bredius RG, Notarangelo LD, Mazzolari E, Neven B, Güngör T, et al. Clinical and immunologic outcome of patients with cartilage hair hypoplasia after hematopoietic stem cell transplantation. Blood. 2010;116:27–35. PubMed PMID: 20375313.

Buchbinder D, Hauck F, Albert MH, Rack A, Bakhtiar S, Shcherbina A, Deripapa E, Sullivan KE, Perelygina L, Eloit M, Neven B, Pérot P, Moshous D, Suarez F, Bodemer C, Bonilla FA, Vaz LE, Krol AL, Klein C, Seppanen M, Nugent DJ, Singh J, Ochs HD. Rubella virus-associated cutaneous granulomatous disease: a unique complication in immune-deficient patients, not limited to DNA repair disorders. J Clin Immunol. 2019;39:81–9. PubMed PMID: 30607663.

Del Borrello G, Miano M, Micalizzi C, Lupia M, Ceccherini I, Grossi A, Cavalli A, Gustincich S, Rusmini M, Faraci M, Dell'Orso G, Ramenghi U, Mesini A, Ricci E, Schiavone M, Di Iorgi N, Dufour C. Sirolimus restores erythropoiesis and controls immune dysregulation in a child with cartilage-hair hypoplasia: a case report. Front Immunol. 2022;13:893000. PubMed PMID: 35663969.

Glazov EA, Zankl A, Donskoi M, Kenna TJ, Thomas GP, Clark GR, Duncan EL, Brown MA. Whole-exome re-sequencing in a family quartet identifies POP1 mutations as the cause of a novel skeletal dysplasia. PLoS Genet. 2011;7:e1002027. PubMed PMID: 21455487.

Hermanns P, Bertuch AA, Bertin TK, Dawson B, Schmitt ME, Shaw C, Zabel B, Lee B. Consequences of mutations in the non-coding RMRP RNA in cartilage-hair hypoplasia. Hum Mol Genet. 2005;14:3723–40. PubMed PMID: 16254002.

Holopainen E, Vakkilainen S, Mäkitie O. Diversity of pubertal development in cartilage-hair hypoplasia; two illustrative cases. J Pediatr Adolesc Gynecol. 2018;31:422–5. PubMed PMID: 29462708.

Holopainen E, Vakkilainen S, Mäkitie O. Outcomes of 42 pregnancies in 14 women with cartilage-hair hypoplasia: a retrospective cohort study. Orphanet J Rare Dis. 2020;15:326. PubMed PMID: 33213509.

Horn D, Rupprecht E, Kunze J, Spranger J. Anauxetic dysplasia, a spondylometaepiphyseal dysplasia with extreme dwarfism. J Med Genet. 2001;38:262–5. PubMed PMID: 11370632.

Huang SJ, Amendola LM, Sternen DL. Variation among DNA banking consent forms: points for clinicians to bank on. J Community Genet. 2022;13:389–97. PubMed PMID: 35834113.

Ip W, Gaspar HB, Kleta R, Chanudet E, Bacchelli C, Pitts A, Nademi Z, Davies EG, Slatter MA, Amrolia P, Rao K, Veys P, Gennery AR, Qasim W. Variable phenotype of severe immunodeficiencies associated with RMRP gene mutations. J Clin Immunol. 2015;35:147–57. PubMed PMID: 25663137.

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.

Kainulainen L, Lassila O, Ruuskanen O. Cartilage-hair hypoplasia: follow-up of immunodeficiency in two patients. J Clin Immunol. 2014;34:256–9. PubMed PMID: 24402619.

Kavadas FD, Giliani S, Gu Y, Mazzolari E, Bates A, Pegoiani E, Roifman CM, Notarangelo LD. Variability of clinical and laboratory features among patients with ribonuclease mitochondrial RNA processing endoribonuclease gene mutations. J Allergy Clin Immunol. 2008;122:1178–84. PubMed PMID: 18804272.

Klemetti P, Valta H, Kostjukovits S, Taskinen M, Toiviainen-Salo S, Mäkitie O. Cartilage-hair hypoplasia with normal height in childhood-4 patients with a unique genotype. Clin Genet. 2017;92:204–7. PubMed PMID: 28094436.

Kostjukovits S, Klemetti P, Föhr A, Kajosaari M, Valta H, Taskinen M, Toiviainen-Salo S, Mäkitie O. High prevalence of bronchiectasis in patients with cartilage-hair hypoplasia. J Allergy Clin Immunol. 2017a;139:375–8. PubMed PMID: 27568079.

Kostjukovits S, Klemetti P, Valta H, Martelius T, Notarangelo LD, Seppänen M, Taskinen M, Mäkitie O. Analysis of clinical and immunologic phenotype in a large cohort of children and adults with cartilage-hair hypoplasia. J Allergy Clin Immunol. 2017b;140:612–4.e5. PubMed PMID: 28284971.

Kukkola HL, Utriainen P, Huttunen P, Taskinen M, Mäkitie O, Vakkilainen S. Lymphomas in cartilage-hair hypoplasia - A case series of 16 patients reveals advanced stage DLBCL as the most common form. Front Immunol. 2022;13:1004694. PubMed PMID: 36211439.

Kwan A, Church JA, Cowan MJ, Agarwal R, Kapoor N, Kohn DB, Lewis DB, McGhee SA, Moore TB, Stiehm ER, Porteus M, Aznar CP, Currier R, Lorey F, Puck JM. Newborn screening for severe combined immunodeficiency and T-cell lymphopenia in California: results of the first 2 years. J Allergy Clin Immunol. 2013;132:140–50. PubMed PMID: 23810098.

Maida Y, Yasukawa M, Furuuchi M, Lassmann T, Possemato R, Okamoto N, Kasim V, Hayashizaki Y, Hahn WC, Masutomi K. An RNA-dependent RNA polymerase formed by TERT and the RMRP RNA. Nature. 2009;461:230–5. PubMed PMID: 19701182.

Mäkitie O. Cartilage-hair hypoplasia in Finland: epidemiological and genetic aspects of 107 patients. J Med Genet. 1992;29:652–5. PubMed PMID: 1404295.

Mäkitie O, Kaitila I. Cartilage-hair hypoplasia--clinical manifestations in 108 Finnish patients. Eur J Pediatr. 1993;152:211–7. PubMed PMID: 8444246.

Mäkitie O, Kaitila I, Rintala R. Hirschsprung disease associated with severe cartilage-hair hypoplasia. J Pediatr. 2001a;138:929–31. PubMed PMID: 11391344.

Mäkitie O, Kaitila I, Savilahti E. Susceptibility to infections and in vitro immune functions in cartilage-hair hypoplasia. Eur J Pediatr. 1998;157:816–20. PubMed PMID: 9809821.

Mäkitie O, Perheentupa J, Kaitila I. Growth in cartilage-hair hypoplasia. Pediatr Res. 1992a;31:176–80. PubMed PMID: 1542548.

Mäkitie O, Pukkala E, Teppo L, Kaitila I. Increased incidence of cancer in patients with cartilage-hair hypoplasia. J Pediatr. 1999;134:315–8. PubMed PMID: 10064668.

Mäkitie O, Rajantie J, Kaitila I. Anaemia and macrocytosis--unrecognized features in cartilage-hair hypoplasia. Acta Paediatr. 1992b;81:1026–9. PubMed PMID: 1290847.

Mäkitie O, Sulisalo T, de la Chapelle A, Kaitila I. Cartilage-hair hypoplasia. J Med Genet. 1995;32:39–43. PubMed PMID: 7897625.

Mäkitie OM, Tapanainen PJ, Dunkel L, Siimes MA. Impaired spermatogenesis: an unrecognized feature of cartilage-hair hypoplasia. Ann Med. 2001b;33:201–5. PubMed PMID: 11370774.

Martin AN, Li Y. RNase MRP RNA and human genetic diseases. Cell Res. 2007;17:219–26. PubMed PMID: 17189938.

McCann LJ, McPartland J, Barge D, Strain L, Bourn D, Calonje E, Verbov J, Riordan A, Kokai G, Bacon CM, Wright M, Abinun M. Phenotypic variations of cartilage hair hypoplasia: granulomatous skin inflammation

and severe T cell immunodeficiency as initial clinical presentation in otherwise well child with short stature. J Clin Immunol. 2014;34:42–8. PubMed PMID: 24217815.

McKusick VA, Eldridge R, Hostetler JA, Ruangwit U, Egeland JA. Dwarfism in the Amish. II. Cartilage-hair hypoplasia. Bull Johns Hopkins Hosp. 1965;116:285–326. PubMed PMID: 14284412.

Moshous D, Meyts I, Fraitag S, Janssen CE, Debré M, Suarez F, Toelen J, De Boeck K, Roskams T, Deschildre A, Picard C, Bodemer C, Wouters C, Fischer A. Granulomatous inflammation in cartilage-hair hypoplasia: risks and benefits of anti-TNF-α mAbs. J Allergy Clin Immunol. 2011;128:847–53. PubMed PMID: 21714993.

Nakashima E, Tran JR, Welting TJ, Pruijn GJ, Hirose Y, Nishimura G, Ohashi H, Schurman SH, Cheng J, Candotti F, Nagaraja R, Ikegawa S, Schlessinger D. Cartilage hair hypoplasia mutations that lead to RMRP promoter inefficiency or RNA transcript instability. Am J Med Genet A. 2007;143A:2675–81. PubMed PMID: 17937437.

Narra MB, Shearer WT. Cartilage-hair hypoplasia and severe allergy. J Allergy Clin Immunol. 2009;123:1418–9. PubMed PMID: 19394685.

Obara-Moszynska M, Wielanowska W, Rojek A, Wolnik-Brzozowska D, Niedziela M. Treatment of cartilage-hair hypoplasia with recombinant human growth hormone. Pediatr Int. 2013;55:e162–4. PubMed PMID: 24330304.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. PubMed PMID: 25741868.

Ridanpää M, van Eenennaam H, Pelin K, Chadwick R, Johnson C, Yuan B, vanVenrooij W, Pruijn G, Salmela R, Rockas S, Mäkitie O, Kaitila I, de la Chapelle A. Mutations in the RNA component of RNase MRP cause a pleiotropic human disease, cartilage-hair hypoplasia. Cell. 2001;104:195–203. PubMed PMID: 11207361.

Rider NL, Morton DH, Puffenberger E, Hendrickson CL, Robinson DL, Strauss KA. Immunologic and clinical features of 25 Amish patients with RMRP 70 A-->G cartilage hair hypoplasia. Clin Immunol. 2009;131:119–28. PubMed PMID: 19150606.

Riley P Jr, Weiner DS, Leighley B, Jonah D, Morton DH, Strauss KA, Bober MB, Dicintio MS. Cartilage hair hypoplasia: characteristics and orthopaedic manifestations. J Child Orthop. 2015;9:145–52. PubMed PMID: 25764362.

Roifman CM, Gu Y, Cohen A. Mutations in the RNA component of RNase mitochondrial RNA processing might cause Omenn syndrome. J Allergy Clin Immunol. 2006;117:897–903. PubMed PMID: 16630949.

Taskinen M, Ranki A, Pukkala E, Jeskanen L, Kaitila I, Mäkitie O. Extended follow-up of the Finnish cartilage-hair hypoplasia cohort confirms high incidence of non-Hodgkin lymphoma and basal cell carcinoma. Am J Med Genet A. 2008;146A:2370–5. PubMed PMID: 18698627.

Taskinen M, Toiviainen-Salo S, Lohi J, Vuolukka P, Gräsbeck M, Mäkitie O. Hypoplastic anemia in cartilage-hair hypoplasia-balancing between iron overload and chelation. J Pediatr. 2013;162:844–9. PubMed PMID: 23140882.

Thiel CT, Horn D, Zabel B, Ekici AB, Salinas K, Gebhart E, Rüschendorf F, Sticht H, Spranger J, Müller D, Zweier C, Schmitt ME, Reis A, Rauch A. Severely incapacitating mutations in patients with extreme short stature identify RNA-processing endoribonuclease RMRP as an essential cell growth regulator. Am J Hum Genet. 2005;77:795–806. PubMed PMID: 16252239.

Thiel CT, Mortier G, Kaitila I, Reis A, Rauch A. Type and level of RMRP functional impairment predicts phenotype in the cartilage hair hypoplasia-anauxetic dysplasia spectrum. Am J Hum Genet. 2007;81:519–29. PubMed PMID: 17701897.

Thiel CT, Rauch A. The molecular basis of the cartilage-hair hypoplasia-anauxetic dysplasia spectrum. Best Pract Res Clin Endocrinol Metab. 2011;25:131–42. PubMed PMID: 21396580.

Toiviainen-Salo S, Kajosaari M, Piilonen A, Mäkitie O. Patients with cartilage-hair hypoplasia have an increased risk for bronchiectasis. J Pediatr. 2008;152:422–8. PubMed PMID: 18280853.

Vakkilainen S, Kleino I, Honkanen J, Salo H, Kainulainen L, Gräsbeck M, Kekäläinen E, Mäkitie O, Klemetti P. The safety and efficacy of live viral vaccines in patients with cartilage-hair hypoplasia. Front Immunol. 2020a;11:2020.

Vakkilainen S, Klemetti P, Martelius T, Seppänen MJ, Mäkitie O, Toiviainen-Salo S. Pulmonary follow-up imaging in cartilage-hair hypoplasia: a prospective cohort study. J Clin Immunol. 2021;41:1064–71. PubMed PMID: 33675005.

Vakkilainen S, Mäkitie R, Klemetti P, Valta H, Taskinen M, Husebye ES, Mäkitie O. A wide spectrum of autoimmune manifestations and other symptoms suggesting immune dysregulation in patients with cartilage-hair hypoplasia. Front Immunol. 2018;9:2468. PubMed PMID: 30410491.

Vakkilainen S, Taskinen M, Mäkitie O. Immunodeficiency in cartilage-hair hypoplasia: pathogenesis, clinical course and management. Scand J Immunol. 2020b;92:e12913. PubMed PMID: 32506568.

van der Burgt I, Haraldsson A, Oosterwijk JC, van Essen AJ, Weemaes C, Hamel B. Cartilage hair hypoplasia, metaphyseal chondrodysplasia type McKusick: description of seven patients and review of the literature. Am J Med Genet. 1991;41:371–80. PubMed PMID: 1789294.

Vatanavicharn N, Visitsunthorn N, Pho-iam T, Jirapongsananuruk O, Pacharn P, Chokephaibulkit K, Limwongse C, Wasant P. An infant with cartilage-hair hypoplasia due to a novel homozygous mutation in the promoter region of the RMRP gene associated with chondrodysplasia and severe immunodeficiency. J Appl Genet. 2010;51:523–8. PubMed PMID: 21063072.

Welting TJ, Mattijssen S, Peters FM, van Doorn NL, Dekkers L, van Venrooij WJ, Heus HA, Bonafé L, Pruijn GJ. Cartilage-hair hypoplasia-associated mutations in the RNase MRP P3 domain affect RNA folding and ribonucleoprotein assembly. Biochim Biophys Acta. 2008;1783:455–66. PubMed PMID: 18164267.

Welting TJ, van Venrooij WJ, Pruijn GJ. Mutual interactions between subunits of the human RNase MRP ribonucleoprotein complex. Nucleic Acids Res. 2004;32:2138–46. PubMed PMID: 15096576.

Williams MS, Ettinger RS, Hermanns P, Lee B, Carlsson G, Taskinen M, Mäkitie O. The natural history of severe anemia in cartilage-hair hypoplasia. Am J Med Genet A. 2005;138:35–40. PubMed PMID: 16097009.

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