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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 the CHH-AD spectrum disorders is based on clinical findings, characteristic radiographic findings, and in some cases, evidence of immune dysfunction, macrocytic anemia, and/or gastrointestinal problems. 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:

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- In the newborn. Hypoplastic anemia may require repeated blood transfusions; congenital megacolon or Hirschsprung disease may require surgical resection.
- In childhood. 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 to treat progressive varus deformity associated with ligament laxity in the knees. Pubertal maturation may be delayed and may require hormonal induction.
- For those with immunodeficiency. Treatment of underlying infections based on their type, location, and severity; immediate antiviral treatment with intravenous high-dose acyclovir for varicella; consideration of prophylactic antibiotic therapy and/or immunoglobulin replacement therapy; physiotherapy and acute and long-term medical management for bronchiectasis. Recurrent severe infections and/or the presence of severe combined immunodeficiency (SCID) and/or severely depressed erythropoiesis may warrant bone marrow transplantation.
- Malignancies. Treat in the usual manner.

Prevention of secondary complications: If cervical spinal instability is identified in a person with AD, special care is required during general anesthesia.

Surveillance:

- Skeletal dysplasia. Clinical and (if warranted) radiographic monitoring of growth, joints of the lower extremities, and spine annually in childhood and as required in adulthood. Individuals with AD require annual clinical and radiographic monitoring of the spine.
- Anemia. For those who have not had anemia, observe for clinical signs of anemia; for those in remission after treatment, monitor for evidence of relapse.
- Immunodeficiency/infection. Monitor all children regardless of immune status during the first two years of life for recurrent infections, especially life-threatening varicella. Annual evaluation after age two years. High-resolution CT examination for those with features suggestive of bronchiectasis.
- Malignancies. No specific recommendations exist; regular examination for evidence of lymphomas, basal cell carcinomas, and other associated malignancies is advised.
- Endocrinology. Monitor pubertal maturation.

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 allows for early management of manifestations that can be associated with significant morbidity (e.g., infections, immunization with live vaccines, malignancies).

Genetic counseling

The CHH-AD spectrum is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier of a pathogenic variant, 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 the pathogenic variants in the family have been identified.

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 CHH, as individuals present with highly variable phenotypes.

The cartilage-hair hypoplasia – anauxetic dysplasia (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 (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 using detection of T-cell receptor excision circles is able to identify some of the individuals with CHH prior to recognition of other findings [Kwan et al 2013].

Suggestive Findings

CHH-AD spectrum disorders **should be suspected** in individuals with:

- Mild to severe disproportionate short-limbed short stature (final adult height <85-151 cm)
- Presence of variable metaphyseal dysplasia with epiphyseal and vertebral dysplasia in 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 elbows
- 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 (present in 100% of affected adults; prenatal onset in 76%-93%)
- Short fingers and toes
- Bowed femora and tibiae (present in 77%)
- Laxity of ligaments with hypermobility of joints (87%)
- Limited extension of the elbows (83%)
- Lumbar lordosis, chest deformity (~50%)
- Blonde, sparse, fine silky hair (89%-93%)
- Impaired lymphocyte proliferation and T-lymphocyte function (88%) with increased rate of:
  - Infections in infancy and childhood (35%-65%)
  - Severe varicella infection (11%)
  - Severe combined immunodeficiency
  - Bronchiectasis (29%) [Kostjukovits et al 2017a]
- Macrocytic, hypoplastic anemia in early childhood (79%)
- Lymphomas; leukemia; neoplasms of the skin, eye, and liver (6%-11%)
- Congenital megacolon or Hirschsprung disease (7%-8%)
- Intestinal malabsorption with diarrhea and failure to thrive
- Cutaneous and visceral granulomas [Moshous et al 2011, McCann et al 2014]

Metaphyseal dysplasia without hypotrichosis (MDWH)

- Clinical features similar to CHH, but with normal hair
- Absence of immunodeficiency, anemia, and intestinal manifestations

Anauxetic dysplasia (AD)

- Prenatal onset of extreme short-limb short stature (100%)
- Barrel chest with hyperlordosis and kyphoscoliosis
- Dislocated hips
- Atlantoaxial subluxation leading to cervical spine compression
- Facial features. Midfacial hypoplasia and 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
- Short and bullet-shaped metacarpals and phalanges with cone-shaped epiphyses
- Metaphyseal dysplasia of all tubular bones, most prominent changes at the knees
- Distal metaphyses. Wide, flared, occasionally scalloped with cystic areas; poor ossification with trabeculation
- Epiphyseal changes. Absent or mild in the femoral head
- Vertebral bodies. Normal or mild biconvexity with increased height, lumbar lordosis, reduced widening of interpediculate distance in the lumbar spine

Metaphyseal dysplasia without hypotrichosis (MDWH). Similar to those in CHH

Anauxetic dysplasia (AD)

- Vertebral bodies. Late-maturing ovoid with concave dorsal surfaces in the lumbar region; dislocation in the cervical spine
- Femora. Small capital femoral epiphyses with hypoplastic femoral necks
- Iliac bodies. Hypoplastic
- Acetabulae. Shallow
- Metacarpals. Short with widened shafts (I and V)
- Phalanges. Very short and broad with small, late ossifying epiphyses and bullet-shaped middle phalanges

Establishing the Diagnosis

The diagnosis of CHH-AD **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 variants in *RMRP* by molecular genetic testing (see Table 1) can confirm the diagnosis and allow for family studies.

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 phenotype of CHH-AD is 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 CHH-AD molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *RMRP* detects nucleotide variants and small intragenic deletions/insertions/duplications; typically, heterozygous whole-gene deletions/duplications are not detected. Perform sequence analysis first. Sequence analysis should cover both the transcribed region and the promoter region. If only one or no pathogenic variant is found perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.

  Targeted analysis for the common g.70A>G pathogenic variant can be performed first in individuals of Finnish or Amish ancestry.

  Note: This noncoding RNA spans only 268 bp; therefore, targeted testing by sequence analysis is likely to result in analysis of the entire gene.

- **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 at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For 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) is the best option. **Exome sequencing** is most commonly used, but **genome sequencing** is also possible; however, regardless of the method, *RMRP* pathogenic variants may not be detected because *RMRP* is a small (268-bp) untranslated gene without introns and exons. Note that although exome sequencing is defined traditionally as the sequence encompassing all exons of protein-coding genes in the genome it also may be extended to target 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 CHH-AD 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 allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include 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 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 CHH-AD 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; and
- At the severe end, the rare anauxetic dysplasia (AD), with the most pronounced skeletal phenotype.

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

Disproportionate short-limb short stature is the hallmark finding and is usually recognized in the newborn 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. 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 IgG and undetectable IgA 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 the more recent 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]. Chronic viral infections with bocavirus and norovirus have been reported [Kainulainen et al 2014]. Impaired cellular immunity persists into adulthood. Individuals with CHH and combined immunodeficiency are at particular risk for chronic bronchiectasis [Toiviainen-Salo et al 2008], which may, however, develop even in individuals with mild immunodeficiency [Kostjukovits et al 2017a]. Fatal enteroviral meningoencephalitis has been reported in a child with CHH [Vatanavicharn et al 2010].

Autoimmune complications. In rare instances autoimmune complications and a form of severe allergic reaction have been observed in 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 cases [Mäkitie et al 1992b]. Severe and persistent anemia resembling that of Diamond-Blackfan syndrome is seen in about 6% [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].

Malignancies. Extended follow up of persons with CHH revealed that about 11% of the cohort (14/123) followed for 39 years had developed malignancies [Taskinen et al 2008]. 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 initial diagnosis of the malignancy. Underlying pathogenic variants in *RMRP* and severity of preceding immunodeficiency varied and did not correlate with 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.

Intestinal problems

- **Newborn period.** Hirschsprung disease with short-segment or total colon aganglionosis is observed in 7%-8% of those with CHH, especially infants with the severe forms of CHH [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 failure to thrive. Although most intestinal manifestations occur in the first two years of life, they can occur later in childhood. Intestinal problems have not been described in 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 function of the RNase MRP (complex formed of the RMRP transcript and other proteins)
- 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 biallelic pathogenic variants that severely alter function OR
- Compound heterozygosity for:
  - One pathogenic variant within the transcript that severely alters the RNase MRP function AND
  - A hypomorphic (reduced function) 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 by McKusick and his colleagues [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 1:1,000-2:1,000 (carrier frequency 1:10) and in Finland with an incidence of 1:23,000 (carrier frequency 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. Disorders to Consider in the Differential Diagnosis of Cartilage-Hair Hypoplasia – Anauxetic Dysplasia (CHH-AD) Spectrum Disorders

Differential Diagnosis Disorder	Gene(s)	MOI	Clinical Features	
			Overlapping	Distinguishing
Anauxetic dysplasia 2 (OMIM 617396)	*POP1*	AR	• Short stature & metaphyseal dysplasia • ↓ peripheral blood mononuclear cell proliferation ability [1]	In anauxetic dysplasia 2: no clinical symptoms of immunodeficiency
Anauxetic dysplasia 3 (OMIM 618853)	*NEPRO*	AR	• Short stature& metaphyseal dysplasia • Hair hypoplasia [2]	In anauxetic dysplasia 3: no clinical symptoms or laboratory signs of immunodeficiency
Schmid dysplasia	*COL10A1*	AD	Short stature & radiographic metaphyseal abnormalities (metaphyseal dysplasia especially in proximal femur) resembling CHH	In Schmid dysplasia: no extraskeletal manifestations
Jansen dysplasia (OMIM 156400)	*PTH1R*	AD	Short stature & radiographic metaphyseal abnormalities resembling CHH	In Jansen dysplasia: hypercalcemia & hypercalciuria [3]
Shwachman-Diamond syndrome (SDS)	*SBDS*	AR	• Short stature & radiographic metaphyseal abnormalities resembling CHH • ↑ infections • Anemia	In SDS: • Milder skeletal features (usually) • Principal manifestations: exocrine pancreatic insufficiency, neutropenia, & failure to thrive [4]
Schimke immunoosseous dysplasia (SIOD)	*SMARCAL1*	AR	• Short stature • Cellular immune deficiency [5]	In SIOD: • Short stature caused by short trunk (vs short-limbed short stature in CHH-AD) • Characteristic facies • Vascular problems
Combined immunodeficiency syndromes	See footnote 6.	AD AR XL	Immunodeficiency	In most immunodeficiency syndromes: no skeletal abnormalities
Omenn syndrome (OMIM 603554)	*RAG1* *RAG2* *DCLRE1C*	AR	• Short stature • Hematologic changes • Immunologic changes	Omenn syndrome is more severe & incls: • Ichthyosiform skin changes • Septicemia

Table 2. continued from previous page.

Differential Diagnosis Disorder	Gene(s)	MOI	Clinical Features	
			Overlapping	Distinguishing
Isolated congenital neutropenia (See *ELANE*-Related Neutropenia.)	See footnote 8.	AD AR XL	Congenital neutropenia	Skeletal phenotype in CHH
Syndromic congenital neutropenia [7] (See *WAS*-Related Disorders, G6PC3 Deficiency.)				

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; XL = X-linked

1. Glazov et al [2011]
2. Narayanan et al [2019]
3. Savoldi et al [2013]
4. Levin et al [2015]
5. If recurrent infections are present, milder forms of SIOD may be confused with CHH [Baradaran-Heravi et al 2008].
6. See OMIM Phenotypic series: Immunodeficiency (Select Examples) - PS300755 for genes associated with this phenotype in OMIM.
7. Congenital neutropenia that occurs as part of a syndrome can be caused by pathogenic variants affecting glucose metabolism or lysosomal function.
8. See OMIM Phenotypic series: Neutropenia, severe congenital - PS202700 for genes associated with this phenotype in OMIM.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with a cartilage-hair hypoplasia – anauxetic dysplasia (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. Recommended Evaluations Following Initial Diagnosis in Individuals with CHH-AD Spectrum Disorder

System/Concern	Evaluation	Comment
Respiratory	Pulmonary consultation	Eval for evidence of respiratory disease
Gastrointestinal/ Feeding	Gastroenterologic consultation	Eval for congenital megacolon if clinical observation is suggestive
Musculoskeletal	Full skeletal survey	To incl (in AD) views of cervical spine to identify cervical vertebral abnormalities & assess risk for atlantoaxial subluxation
	Orthopedic consultation	Eval for complications of joint laxity, lumbar lordosis, chest deformity, scoliosis, & varus deformity of lower extremities
Hematologic/ Lymphatic	Complete blood count w/differential cell count	Eval for macrocytic anemia & immunodeficiency [1]
	Hematologic consultation	If blood count is abnormal, for further assessment & treatment

Table 3. continued from previous page.

System/Concern	Evaluation	Comment

Allergic/ Immunologic	Laboratory evals for immunodeficiency [1]	To incl:
		• Serum concentration IgG, IgA, IgM, & IgG subclasses
		• CD3, 4, 8, 19, 16/56
		• Post-vaccine titers
		• Other immunologic parameters:
		  ◦ Allogeneic lymphocyte cytotoxicity
		  ◦ TREC analysis
		  ◦ T-cell repertoire
		  ◦ Proliferation response to PHA
		  ◦ Proliferation response to anti-CD3

	Immunologic consultation	If immunologic testing is abnormal or if child has infections, for assessment & treatment & to determine vaccination program & approach to varicella prophylaxis
Miscellaneous/ Other	Consultation w/clinical geneticist &/or genetic counselor	

AD = anauxetic dysplasia; TREC = T-cell receptor excision circles
1. Rider et al [2009]

Treatment of Manifestations

Skeletal dysplasia

- Corrective osteotomies may be warranted in late childhood or adolescence for excessive varus deformity of the lower extremities [Riley et al 2015].
- In persons with AD, surgery may be needed to fuse malformed cervical vertebrae in infancy and to correct or prevent the progression of kyphoscoliosis.
- Orthopedic surgery may be complicated by low bone density.

Short stature. Treatment with recombinant growth hormone has not shown any sustained benefit in individuals with CHH and cannot be recommended [Obara-Moszynska et al 2013].

Immunodeficiency and infection. The treatment of infections in individuals with immunodeficiency is based on their type, location, and severity.

- Immediate antiviral treatment with intravenous high-dose acyclovir must be considered at the first symptoms of varicella infection to prevent complications.
- Consider prophylactic antibiotic therapy if the individual has recurrent infections or if neutropenia/severe lymphopenia is present. Consider also immunoglobulin replacement therapy if immunoglobulin or IgG subclass levels are low, or if vaccine responses are inadequate.
- Individuals with bronchiectasis need proper management of infectious exacerbations and physiotherapy. Consider also long-term treatment with inhaled antibiotics or oral macrolide [Altenburg et al 2015].
- Recurrent severe infections and/or the presence of severe combined immunodeficiency (SCID) may warrant bone marrow transplantation / hematopoietic stem cell transplantation (HSCT) [Guggenheim et al 2006]. HSCT has resulted in normalization of T-lymphocyte numbers and function, resolution of autoimmune manifestations, and catch-up growth, probably due to reduced infections. Overall survival rates have been reported at 63% for unrelated donor transplants and as high as 80% for matched sibs. HSCT should be considered in selected individuals with CHH with recurrent infections and autoimmune manifestations or bone marrow dysplasia for whom a well-matched donor is available [Bordon et al 2010].

- Anti-TNFa therapy has been used successfully in the treatment of cutaneous and visceral granulomas. However, fatal progressive multifocal leukoencephalopathy caused by JC virus has been described during treatment with anti-TNFa antibodies. HSCT resulted in disappearance of granulomas in two of three transplanted individuals [Moshous et al 2011].

Anemia

- Treatment of severe anemia secondary to depressed erythropoiesis may require repeated red cell transfusions in infancy and childhood; lifelong transfusions or bone marrow transplantation are rarely needed [Williams et al 2005]. In individuals requiring repeated transfusions iron chelation is successful and well tolerated when needed [Taskinen et al 2013].
- Although steroid treatment has been effective in treating anemia in some persons with CHH, the available data are not sufficient to recommend this therapy in general, especially considering the potential side effects of immune suppression and growth retardation.

Malignancy. No specific recommendations for the treatment of the observed malignancies are available. Non-Hodgkin lymphoma often has a poor prognosis with conventional cytotoxic protocols [Taskinen et al 2008].

Endocrine. Pubertal maturation may be delayed and may require hormonal induction.

Prevention of Secondary Complications

If a cervical spine abnormality and/or instability is identified, special care should be exercised when general anesthesia is administered.

Surveillance

Skeletal dysplasia

- Children with CHH require annual measurement of linear growth and body proportions; comparison with published disease-specific growth curves [Mäkitie et al 1992a] is helpful.
- Pubertal development should be monitored during annual follow-up visits and hypogonadism excluded if puberty is significantly delayed.
- Clinical assessment for deformities of the lower extremities and joints is appropriate. Radiographic evaluation and orthopedic consultation is necessary if symptomatic misalignment, restricted knee or hip mobility, or symptomatic joint laxity is present.
- Individuals with AD require annual clinical and radiographic monitoring of the spine.

Immunodeficiency and infection

- As no clinical parameters predict susceptibility to infection in children, ongoing follow up by physicians with experience in this condition is recommended, including routine physical examination and laboratory testing for early detection of infection.
- Particularly in the first two years of life, children with normal initial immunologic assessment should be monitored for recurrent infections, especially life-threatening varicella infections [Notarangelo et al 2008, Rider et al 2009].
- Laboratory markers for immunodeficiency may fluctuate in children with CHH, thus emphasizing the need for regular yearly follow up [Kainulainen et al 2014].
- Bronchiectasis should be suspected especially in subjects with frequent respiratory tract infections and combined immunodeficiency; high-resolution computed tomography should be used for diagnosis [Toiviainen-Salo et al 2008]; lung MR examination is recommended for follow up [Kostjukovits et al 2017a].

Anemia

- Observe for clinical signs of anemia starting from the time of the initial diagnosis until early adolescence.
- Follow RBC, hematocrit, and hemoglobin levels in those in remission after treatment for anemia at least every six months or when clinical signs of anemia reappear.

  Note: (1) No data are available on the likely timing of recurrence of anemia after successful treatment; (2) 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.

Malignancy

- **Children.** Although no specific recommendations exist, it is advised that children be evaluated annually by their pediatrician or primary health care provider for lymphomas and other associated malignancies by careful clinical examination and routine blood tests.

  Skin should be inspected for abnormal changes, lymph nodes for enlargement, and abdomen for hepatomegaly, splenomegaly, or other abnormalities. Abdominal ultrasound is recommended at a regular one- to two-year interval, as well as yearly laboratory tests including blood counts with differential, LDH, and uric acid.
- **Adults.** As no clinical parameters predict susceptibility to malignancy in adults, ongoing regular follow up beyond adolescence is recommended, including routine physical examination and laboratory testing for early detection of malignancy, as described above. The frequency of follow-up visits needs to be determined on an individual basis.

Endocrinology. Monitor pubertal maturation.

Agents/Circumstances to Avoid

Routine immunizations with inactivated vaccines are considered safe in persons with CHH. However, 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 SCID [Rider et al 2009].

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* sequence analysis 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

No issues are known; however, experience is limited.

Therapies Under Investigation

Varicella vaccine is being investigated for children with CHH who have not had varicella.

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

Mode of Inheritance

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 obligate heterozygotes (i.e., carriers of one *RMRP* pathogenic variant).
- According to previous evaluations, heterozygotes (carriers) are not at increased risk for cancer and are asymptomatic [Mäkitie et al 1999].

Sibs of a proband

- At conception, each sib of an affected individual has 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; intrafamilial variability in disease severity has been observed.
- 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 individual with CHH-AD spectrum disorder has children with an affected individual or a carrier, his/her offspring will be obligate heterozygotes (carriers of an *RMRP* pathogenic variant).

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, clarification of carrier status, 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

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

Ultrasound examination. Prenatal diagnosis may also be possible through fetal ultrasound studies at 16 to 18 weeks' gestation.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While most centers would consider 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, Inc. (LPA)**
  250 El Camino Real
  Suite 201
  Tustin CA 92780
  Phone: 888-572-2001 (toll-free); 714-368-3689
  Fax: 714-368-3367
  Email: info@lpaonline.org
  www.lpaonline.org

- **Lyhytkasvuiset – Kortväxta Ry**
  PL 14, 02601 Espoo
  Finland
  Email: toimisto@lyhytkasvuiset.fi
  www.lyhytkasvuiset.fi

- **European Society for Immunodeficiencies (ESID) Registry**
  Dr. Gerhard Kindle
  University Medical Center Freiburg Centre of Chronic Immunodeficiency
  Engesserstr. 4
  79106 Freiburg

Germany
Phone: 49-761-270-34450
Email: esid-registry@uniklinik-freiburg.de
ESID Registry

- **International Skeletal Dysplasia Registry**
  UCLA
  615 Charles E. Young Drive
  South Room 410
  Los Angeles CA 90095-7358
  Phone: 310-825-8998
  Fax: 310-206-5266
  Email: Salon@mednet.ucla.edu
  International Skeletal Dysplasia Registry

- **Skeletal Dysplasia Network, European (ESDN)**
  Institute of Genetic Medicine
  Newcastle University, International Centre for Life
  Central Parkway
  Newcastle upon Tyne NE1 3BZ
  United Kingdom
  Email: info@esdn.org
  www.esdn.org

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

Gene structure. *RMRP* is an intronless gene encoded by nuclear DNA. The *RMRP* transcript consists of only 267 bp with a type 3 promoter, a PSE element, and a TATA box, and transcription factor binding sites upstream of the transcription initiation site. The *RMRP* RNA transcript is not translated into a protein. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. More than 90 different pathogenic variants have been described [Ridanpää et al 2001, Bonafé et al 2005, Hermanns et al 2006, Martin & Li 2007, Thiel et al 2007, Thiel & Rauch 2011, Cherkaoui Jaouad et al 2015].

A founder pathogenic variant (g.70A>G) is present in 100% of Old Order Amish, 92% of Finnish, and 48% of non-Finnish individuals with CHH.

Occasionally small insertions, duplications, or triplications in the promoter region increase the distance between regulatory elements (i.e., the TATA box and the transcription start site). An increase of 24 to 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.

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.

The position of the pathogenic variant in the *RMRP* transcript and the proposed effect on transcript folding and RNA/protein interaction results in variable phenotypes in the CHH-AD spectrum (see Genotype-Phenotype Correlations).

Interestingly, *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.

Table 4. *RMRP* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequence
g.70A>G	Not applicable	NG_017041.1

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.

Normal gene product. *RMRP* encodes the untranslated RNA subunit of the ribonucleoprotein endoribonuclease complex RNase MRP [Ridanpää et al 2001]. 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 (*CCNB1*) needed in cell-cycle regulation progression. RMRP 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].

Abnormal gene product. None.

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Chapter Notes

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