U.PORTO

MESTRADO INTEGRADO
MEDICINA

Cartilage-Hair Hypoplasia: A Comprehensive Case Report and Literature Review

Catarina Leal de Vilhena Portela de Carvalho

M

2025

Cartilage-Hair Hypoplasia:
A Comprehensive Case Report and Literature Review

Dissertação de candidatura ao grau de Mestre em Medicina, submetida ao Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

Estudante: Catarina Leal de Vilhena Portela de Carvalho
6º Ano do Mestrado Integrado em Medicina
Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto, 4050-313, Porto, Portugal
Endereço eletrónico: up201907384@up.pt | catarinacarvalho2001@gmail.com

Orientador: Professor Doutor Luís Guedes Martins
Assistente Hospitalar Graduado da Unidade Local de Saúde de Santo António, Centro Materno Infantil do Norte – Departamento da Mulher e da Medicina Reprodutiva, Largo Prof. Abel Salazar, 4099-001 Porto, Portugal
Professor Catedrático Convidado do Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto, 4050-313 Porto, Portugal
Centro de Medicina Fetal, Medicina Fetal Porto—Centro Materno Infantil do Norte, 4099-001 Porto, Portugal
Unidade de Investigação e Formação, Centro Materno Infantil do Norte, 4099-001 Porto, Portugal
Instituto de Investigação e Inovação em Saúde, Universidade do Porto, 4200-319 Porto, Portugal
Endereço eletrónico: luis.guedes.martins@gmail.com

Coorientadora: Professora Doutora Carolina Luísa Cardoso Lemos
Investigadora principal no Instituto de Ciências Biomédicas Abel Salazar (ICBAS), Universidade do Porto, 4050-313, Porto, Portugal
Professora Associada do Instituto de Ciências Biomédicas Abel Salazar (ICBAS), Universidade do Porto, 4050-313, Porto, Portugal
Endereço eletrónico: clclemos@ibmc.up.pt

O artigo intitulado "Prenatal Diagnosis of Cartilage-Hair Hypoplasia: A Narrative Review" foi submetido na revista *Acta Médica Portuguesa* em Junho de 2025 e o artigo "Familial Cartilage-Hair Hypoplasia: Prenatal Ultrasound Features and Clinical Outcomes in Three Siblings with Identical RMRP Variants" foi submetido na revista *BMJ Case Reports* em Maio de 2025, estando formatados de acordo com as normas editoriais das respetivas revistas.

Porto, Junho de 2025

Cartilage-Hair Hypoplasia:
A Comprehensive Case Report and Literature Review

Dissertação de candidatura ao grau de Mestre em Medicina, submetida ao Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

Estudante:

Assinado por: Catarina Leal de Vilhena Portela de Carvalho
Identificação: BI15664931
Data: 2025-06-08 às 22:23:01

(Catarina Leal de Vilhena Portela de Carvalho)

Orientador:

Assinado por: **LUÍS GUEDES MARTINS**
Num. de Identificação: 11429690
Data: 2025.06.08 19:49:45+01'00'

(Luís Guedes Martins)

Coorientadora:

(Carolina Luísa Cardoso Lemos)

Porto, Junho de 2025

DECLARAÇÃO DE INTEGRIDADE CIENTÍFICA

Eu, Catarina Leal de Vilhena Portela de Carvalho, nº 201907384, estudante do 6º ano do Mestrado Integrado em Medicina do Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto, declaro que esta dissertação é da minha autoria e não foi utilizada anteriormente em qualquer outro curso ou unidades curriculares, desta ou de outra instituição. As referências a outros autores (afirmações, ideias, pensamentos) respeitam as regras de atribuição e estão devidamente indicadas no texto e nas referências bibliográficas, de acordo com as regras de referenciação. Tenho conhecimento de que a prática de plágio e auto-plágio constitui uma infração académica.

Porto, Junho de 2025



(Catarina Leal de Vilhena Portela de Carvalho)

A ti, Avó, que já não posso tocar, mas sinto sempre o teu abraço.

AGRADECIMENTOS

Começo por agradecer ao Professor Doutor Luís Guedes Martins, por prontamente acolher o desafio de orientar esta tese na área das displasias ósseas e por, desde início, ter definido uma estrutura clara e organizada. Destaco, em particular, o incentivo e disponibilidade para me introduzir ao processo de submissão dos artigos em revistas científicas, que foi uma experiência enriquecedora e formativa.

Agradeço também à Professora Doutora Carolina Lemos, na qualidade de coorientadora, pela atitude construtiva e serena que sempre demonstrou e que foram essenciais para o bom desenrolar do trabalho.

Um agradecimento especial à Associação Nacional de Displasias Ósseas (ANDO), e em particular à Dra. Inês Alves, por me terem proporcionado a Bolsa ANDO 2023, que me envolveu no tema desta dissertação. Obrigada pelo acompanhamento constante, pautado por ideias e críticas construtivas, que permitiram a realização deste projeto, com vista a contribuir para aumentar o conhecimento científico nesta área.

À Prof. Doutora Lena Lande Wekre, por me ter recebido na Noruega e me ter dado o privilégio de descobrir as displasias ósseas num estágio inesquecível, que marcou profundamente o meu percurso académico.

À minha família e amigos, por reforçarem e motivarem o meu gosto pela Medicina, mas sem nunca descurar as outras vertentes essenciais para o meu desenvolvimento pessoal. Escrevi esta tese alicerçada no vosso apoio e é o reflexo de tudo aquilo que me ensinaram.

RESUMO

A presente dissertação visa abordar a Hipoplasia Cartilagem Cabelo, uma displasia óssea rara, com foco no seu diagnóstico pré-natal. Esta condição é herdada num padrão autossómico recessivo e apresenta manifestações clínicas variáveis, que incluem envolvimento esquelético e extra-esquelético.
Os indivíduos afetados podem evidenciar baixa estatura, hipotricose, disfunção imune, além de terem maior predisposição para doenças hematológicas, oncológicas e gastrointestinais. Algumas das manifestações pré-natais incluem micromelia, encurvamento ósseo e atraso no desenvolvimento torácico. Estes aspetos podem coincidir com os de outros diagnósticos diferenciais, o que constitui um desafio à sua abordagem.
Este trabalho encontra-se estruturado em três capítulos que correspondem a diferentes contributos realizados no âmbito desta temática.

O **primeiro capítulo** inclui um artigo de revisão narrativa intitulado "Prenatal Diagnosis of Cartilage-Hair Hypoplasia: A Narrative Review". Esta revisão procura contextualizar a literatura existente no que concerne o diagnóstico pré-natal desta condição. Para isso, foi realizada pesquisa bibliográfica nas plataformas MEDLINE e PubMed, cuja metodologia se encontra detalhada no artigo.

No **segundo capítulo** encontra-se o caso clínico "Familial Cartilage-Hair Hypoplasia: Prenatal Ultrasound Features and Clinical Outcomes in Three Siblings with Identical RMRP Variants". Este artigo descreve o caso do terceiro filho afetado com Hipoplasia Cartilagem Cabelo numa família em que dois irmãos já tinham sido previamente diagnosticados com a doença. Os achados ecográficos da terceira gravidez levantaram a suspeita de se tratar de uma recorrência e o diagnóstico foi confirmado após o nascimento. Para a utilização dos dados e inclusão das imagens apresentadas foi obtido o devido consentimento informado com a mãe dos pacientes.

O **terceiro capítulo** inclui o poster "Apresentação Pré-natal de Síndrome de Hipoplasia Cartilagem Cabelo: A Propósito de um Caso Clínico", que foi apresentado na Reunião Anual da Associação Portuguesa de Diagnóstico Pré-Natal e que sistematiza os pontos principais do caso clínico.

Esta estrutura permitiu explorar o tema da dissertação de uma forma abrangente e complementar, articulando a revisão teórica com a prática clínica e a divulgação científica. Cada artigo segue a estrutura da revista à qual foi submetido, incluindo cada um resumo, palavras-chave, resultados, discussão e conclusão, além das respetivas figuras e referências bibliográficas.

Palavras-chave: Hipoplasia Cartilagem Cabelo, Osteocondrodisplasias, Diagnóstico Pré-natal.

ABSTRACT

The present dissertation aims to address Cartilage-Hair Hypoplasia, a rare skeletal dysplasia, focusing on its prenatal diagnosis. This condition is inherited in an autosomal recessive pattern and presents variable clinical manifestations, which include skeletal and extra-skeletal involvement. Affected individuals may present with short stature, hypotrichosis and immune dysfunction, as well as having higher predisposition to hematological, oncological and gastrointestinal disorders. Some of the prenatal features include micromelia, bowing of the long bones and delay in thorax growth. These findings may overlap with other differential diagnosis, which presents a challenge to its approach.
This thesis comprises three chapters, each representing a different contribution made within the scope of this subject.

Chapter one presents a narrative review entitled "Prenatal Diagnosis of Cartilage-Hair Hypoplasia: A Narrative Review". This article seeks to review the current knowledge on the prenatal diagnosis of this condition. For this purpose, a bibliographic search was conducted in the MEDLINE and PubMed databases, with the methodology detailed in the article.

Chapter two contains the case report "Familial Cartilage-Hair Hypoplasia: Prenatal Ultrasound Features and Clinical Outcomes in Three Siblings with Identical RMRP Variants". This article describes the case of the third child affected with Cartilage-Hair Hypoplasia in a family with two previous children diagnosed with the condition. The ultrasound findings of the third pregnancy suggested disease recurrence and diagnosis was confirmed postnatally. Informed consent was obtained from the mother of the patients to include the data and images presented.

Chapter three includes the poster "Apresentação Pré-natal de Síndrome de Hipoplasia Cartilagem Cabelo: A Propósito de um Caso Clínico", which was presented in the annual meeting of the Portuguese Association of Prenatal Diagnosis and summarizes the key points of the case report.

This structure enabled a comprehensive and complementary approach to the theme of the dissertation, combining theoretical revision with clinical practice and scientific communication. Each article follows the structure of the journal in which it was submitted, each including an abstract, key words, results, discussion and conclusion, as well as respective figures and bibliographic references.

Keywords: Cartilage-Hair Hypoplasia, Osteochondrodysplasias, Prenatal Diagnosis.

ABBREVIATIONS

AC – Abdominal circumference
AD – Anauxetic dysplasia
CHH – Cartilage hair hypoplasia
CMA – Chromosome microarray analysis
CT – Computed tomography
FL – Femur length
MDWH - Metaphyseal dysplasia without hypotrichosis
NGS – Next generation sequencing
RMRP – Ribonuclease mitochondrial ribonucleic acid processing
SD – Skeletal dysplasias
TD – Thanatophoric dysplasia
WES – Whole exome sequencing
WGS – Whole genome sequencing

TABLE OF CONTENTS

AGRADECIMENTOS ..... **i**
RESUMO ..... **ii**
ABSTRACT ..... **iii**
ABBREVIATIONS ..... **iv**
LIST OF FIGURES ..... **vi**
CHAPTER ONE **1**
ABSTRACT 2
RESUMO 2
INTRODUCTION 3
METHODS 3
RESULTS 3
DISCUSSION 6
CONCLUSION 7
AUTHORS CONTRIBUTION 7
REFERENCES 8
FIGURE LEGENDS 9
CHAPTER TWO **12**
TITLE OF CASE 13
SUMMARY 13
BACKGROUND 13
CASE PRESENTATION 14
OUTCOME AND FOLLOW-UP 15
DISCUSSION 16
LEARNING POINTS/TAKE HOME MESSAGES 18
REFERENCES 18
FIGURE/VIDEO CAPTIONS 19
CHAPTER THREE **25**
CONCLUSION **26**

LIST OF FIGURES

CHAPTER ONE

Figure 1 - Simplified article selection flowchart.

Figure 2 - Diagnostic approach for prenatal CHH evaluation.

CHAPTER TWO

Figure 1 – Third child. Ultrasound assessment at 22 weeks. Short femur (<P5).

Figure 2 – Third child. Ultrasound assessment at 27 weeks. Small thorax dimensions.

Figure 3 – First child in early childhood. Short-limbed short stature. Genu varum.

Figure 4 – Second child as a toddler. Short-limbed short stature. Genu varum.

Figure 5 – Third child. Newborn in the delivery room. Asymmetric small for gestational age.

CHAPTER ONE

"Prenatal Diagnosis of Cartilage-Hair Hypoplasia: A Narrative Review"

Title: Prenatal Diagnosis of Cartilage-Hair Hypoplasia: A Narrative Review

Título: Diagnóstico Pré-natal da Hipoplasia Cartilagem Cabelo: Uma Revisão Narrativa

Short title: Prenatal diagnosis of CHH

Authors: Catarina Portela Carvalho[1], Inês Alves[2,3], Carolina Lemos[2,4,5], Luís Guedes-Martins[1,6,7]

[1] Instituto de Ciências Biomédicas Abel Salazar, University of Porto, 4050-313 Porto, Portugal
[2] ANDO Portugal - National Association for Skeletal Dysplasias, 7005-144 Évora, Portugal
[3] School of Health and Human Development - CHRC, University of Évora, 7000-516 Évora, Portugal
[4] Unidade Multidisciplinar de Investigação Biomédica (UMIB), Instituto de Ciências Biomédicas Abel Salazar (ICBAS), Universidade do Porto, Portugal
[5] ITR—Laboratory for Integrative and Translational Research in Population Health, Porto, Portugal
[6] Centro de Medicina Fetal, Medicina Fetal Porto - Centro Materno Infantil do Norte, 4099-001 Porto, Portugal
[7] Departamento da Mulher e da Medicina Reprodutiva, Serviço de Obstetrícia, Unidade Local de Saúde de Santo António EPE, Centro Materno Infantil do Norte, Largo Prof. Abel Salazar, 4099-001 Porto, Portugal

Corresponding author: Catarina Portela Carvalho, Instituto de Ciências Biomédicas Abel Salazar, University of Porto, R. de Jorge de Viterbo Ferreira 228, 4050-313 Porto, Portugal
Email: up201907384@up.pt
Orcid ID: https://orcid.org/0009-0005-4530-757X

Funding: The authors received no specific funding for this work.

Ethical Considerations: The authors declare no conflicts of interest.

ABSTRACT

Cartilage-hair hypoplasia is a rare autosomal recessive skeletal dysplasia. It is particularly prevalent in the finnish and Amish populations but increasing reports have been documented worldwide. It is caused by mutations in the RMRP gene. The clinical presentation is highly variable and may include short-limbed short stature, metaphyseal abnormalities, hypotrichosis and immune deficiency, among other features. Some of the manifestations may present early in the prenatal period and ultrasound assessment is often the tool that raises suspicion for this condition. The aim of this review is to summarize the current knowledge regarding the prenatal diagnosis of cartilage-hair hypoplasia, focusing on its molecular basis and the role of imaging and genetic testing. A comprehensive literature search was conducted in the MEDLINE and PubMed databases using the terms 'Prenatal diagnosis', 'Cartilage-hair hypoplasia', 'Skeletal dysplasias', 'Osteochondrodysplasias' and 'RMRP mutation'. Prenatal diagnosis of this condition remains challenging, as ultrasound findings may overlap with other osteochondrodysplasias, including lethal forms. Lethality predictors and the potential of molecular testing are also explored. A structured prenatal approach, combined with timely genetic counselling, may allow for an earlier diagnosis and support informed reproductive decisions. Given the recent advances in reproductive technologies and the potential impact of cartilage-hair hypoplasia on affected individuals, this condition should be actively considered in futures studies addressing the prenatal diagnosis of skeletal dysplasias.

Keywords: Cartilage-hair Hypoplasia, Osteochondrodysplasias, Prenatal Diagnosis

RESUMO

A hipoplasia cartilagem cabelo é uma displasia óssea rara, herdada de forma autossómica recessiva. Embora seja particularmente prevalente nas populações finlandesa e Amish, verificam-se cada vez mais casos documentados noutras populações. A doença é causada por mutações no gene RMRP. A apresentação clínica é muito variável e pode incluir baixa estatura com membros curtos, alterações metafisárias, hipotricose e imunodeficiência, entre outras manifestações. Alguns achados podem apresentar-se precocemente no período pré-natal e a avaliação ecográfica é, muitas vezes, a ferramenta que levanta suspeição para esta condição. O propósito desta revisão é sintetizar a literatura existente sobre o diagnóstico pré-natal da hipoplasia cartilagem cabelo, focando-se na sua base molecular e no papel da imagem e dos testes genéticos. Foi realizada pesquisa nas plataformas MEDLINE e PubMed usando os termos 'Prenatal diagnosis', 'Cartilage-hair hypoplasia', 'Skeletal dysplasias', 'Osteochondrodysplasias' e 'RMRP mutation'. O diagnóstico pré-natal desta doença permanece um desafio, visto que os achados ecográficos podem coincidir com os de outras osteocondrodisplasias, nomeadamente formas letais. A discussão incluiu também preditores de letalidade e o potencial dos testes moleculares. Uma abordagem estruturada na avaliação pré-natal desta patologia, combinada com aconselhamento genético atempado, podem permitir um diagnóstico mais precoce e auxiliar as famílias nas decisões reprodutivas. Dado os avanços recentes nas tecnologias reprodutivas e o potencial impacto que a hipoplasia cartilagem cabelo pode ter nos indivíduos afetados, esta patologia deve ser ativamente considerada em estudos futuros que explorem o diagnóstico pré-natal das displasias esqueléticas.

Palavras-chave: Hipoplasia Cartilagem Cabelo, Osteocondrodisplasias, Diagnóstico Pré-natal

INTRODUCTION

Cartilage-hair hypoplasia (CHH) is a rare autosomal recessive disorder first described in 1965 by McKusick *et al*[1] among the Amish community. The global prevalence is difficult to establish given its rarity and underdiagnosis, but in specific populations, such as the Finnish and the Old Order Amish, it has been reported as 1 in 23000 births and 1-2 in 1000 births, respectively.[2-4] It is caused by mutations in the ribonuclease mitochondrial ribonucleic acid processing (RMRP) gene, which is involved in cell proliferation and differentiation.[2] The disease is characterized by short-limbed short stature and extra-skeletal manifestations such as hypotrichosis and variable degrees of immune dysfunction. There is also an increased risk for anemia, recurrent infections, Hirschsprung disease and malignancy.[2,4,5] Fetal diagnosis is difficult, considering that the ultrasound findings resemble other skeletal dysplasias (SD). Some of the first prenatal manifestations include micromelia, bowing of the long bones and delay in the thorax growth.[6-8]
The purpose of this study is to review the current knowledge on the prenatal diagnosis of this condition, focusing on the techniques available, their limitations and clinical implications. Early diagnosis is crucial to allow parents to make informed decisions regarding possible medical interventions and to guide the management of future pregnancies. Further characterizing the genotype-phenotype correlations may improve prediction of disease severity and support a multidisciplinary approach to address potential complications.

METHODS

To develop this narrative review, we performed a bibliographic search in the MEDLINE and PubMed databases. Articles in English published within the last 30 years, between 1995 and March 2025, were considered. Combining the terms 'Cartilage-hair hypoplasia' and 'Prenatal diagnosis' in these platforms yields nine results, mainly case reports, which emphasizes the lack of literature on this topic. Additional search terms used were 'Skeletal dysplasias', 'Osteochondrodysplasias' and 'RMRP mutation' combined, using Boolean operators. To further corroborate the findings, some articles referenced in the selected articles were also included in the final review, among which was the original CHH report in 1965. No restrictions were placed on study design. In total, 35 articles were included (Fig. 1).

RESULTS

Molecular basis and clinical significance

To better understand the prenatal diagnostic approach of CHH, it is important to try to clarify its molecular basis and pathophysiology. Mutations in the *RMRP* gene have been well established as the cause for this condition. So far, over 100 known pathogenic mutations have been identified, the most common of which being n.71A>G, especially prevalent in the Finnish population.[2,9] The *RMRP* gene encodes a long non-coding RNA, which, in association with ten proteins, constitutes the ribonuclease for mitochondrial RNA processing complex (RNase MRP complex). This ribonucleoprotein complex is implicated in several cellular functions that contribute to the CHH presentation. The most extensively studied functions include ribosome synthesis, mitochondrial DNA replication and cell cycle regulation.[2,10,11] The RMRP non-coding RNA also seems to create a complex with telomerase-associated reverse transcriptase that produces double-stranded RNA, which in turn downregulates *RMRP* expression.[10,11]
CHH integrates a spectrum that ranges from a milder phenotype, metaphyseal dysplasia without hypotrichosis (MDWH), to a more severe condition, anauxetic dysplasia (AD).[10] Short stature with varying degrees of metaphyseal dysplasia is the defining characteristic of this group of conditions. MDWH presents with mild metaphyseal dysplasia with no hair abnormalities, CHH exhibits moderate metaphyseal dysplasia with hair hypoplasia, immunodeficiency, hematological abnormalities, among other features and AD involves severe spondylo-meta-epiphyseal dysplasia without extra-skeletal manifestations.[6,10,12,13]
Mutations of the *RMRP* gene can be subdivided into two main groups: duplications/insertions in the promoter region and mutations within the RMRP transcript. The first group influences the distance between the promotor and the transcription starting point, which can decrease the transcription level of *RMRP*, but does not seem to explain the phenotypical diversity observed in the patients.[2,10,11] There are very few cases described of homozygous variants in the promoter region, which reinforces

RMRP role in cell life.[14,15] The second group, which mostly consists of mutations in the conserved region of the *RMRP* sequence, can lead to RNA instability or impact the RNase MRP complex function, reducing its enzymatic activity. This group seems to better explain the clinical variability.[2,10,11]

Interestingly, mutations associated with AD, the severe end of the spectrum, appear to cause marked skeletal dysplasia but are not associated with non-skeletal features. This seems to be linked with a particularly reduced rRNA cleavage activity. Therefore, the degree of disruption of rRNA cleavage seems to correlate with the degree of bone dysplasia.[4,10] Conversely, mutations that lead to reduced mRNA cleavage activity, which impacts cell-cycle regulation, are particularly observed in patients with MDWH and CHH. This suggests that lower mRNA cleavage activity is associated with milder skeletal presentation, but more pronounced extra-skeletal manifestations, such as malignancy susceptibility, proliferative bone marrow dysfunction and hair hypoplasia.[2,10,13,15]

The pathophysiological mechanisms of CHH are still not entirely understood but relevant advances have been made in the recent years. In 2019, a study conducted by Vakkilainen *et al*[16] compared fibroblast cultures from five patients with CHH and five controls. RNA sequencing found 35 upregulated genes and 130 downregulated genes in CHH fibroblasts. The upregulated genes were involved in the Pl3K-Akt signaling pathway, which is associated with cartilage and bone differentiation, as well as malignancies, whereas the downregulated genes affected cell cycle pathways. These findings support that *RMRP* mutations have a significant impact on the cell cycle network which may be the basis for the clinical manifestations observed in CHH.[16]

Another research from 2019 developed a zebra fish model to study the mechanisms underlying CHH, since there are currently no viable animal models and zebra fish share approximately 60% of the *RMRP* transcribed region with humans. Using a *rmrp* knockout model, the researchers performed bone and cartilage staining to assess skeletal development. The results were in accordance with the CHH phenotype, with disrupted chondrogenesis and bone ossification. Wnt-β-catenin signaling appears to be upregulated in *rmrp* mutants, suggesting a role in disease pathogenesis and identifying it as a potential therapeutic target. Additionally, intestinal staining revealed impairment in the gastrointestinal tract development, which may correlate with digestive manifestations observed in some CHH patients.[9]

The general process of prenatal assessment of a condition involves various techniques applied to screening and diagnosis. Screening encompasses serum analysis, ultrasonography, cell-free DNA testing and carrier studies. For diagnostic purposes, the procedures available during the prenatal period include chorionic villus sampling, amniocentesis and fetal blood sampling, the latter being rarely used due to a higher risk of fetal loss. Through these techniques, it is possible to conduct diagnostic tests such as karyotyping, chromosome microarray analysis (CMA), targeted mutation testing and next-generation sequencing (NGS) panels. NGS technology also enables tests such as whole exome sequencing (WES) and whole genome sequencing (WGS).[17]

Some of these techniques may be applicable in the particular case of CHH, which will be further discussed.

Role of prenatal imaging

Ultrasonography constitutes the primary screening method for SD with prenatal presentation. The sensitivity rate of ultrasound for SD varies among the literature but is estimated to be between 40 and 60%.[18-20] The main hallmark of most SD on ultrasound, including CHH, is the presence of short long bones, especially if they are disproportionate in relation to the head circumference.[19] Ossification of the appendicular skeleton occurs around 12 weeks of gestation so it may be possible to suspect a SD even in the first trimester. Earlier presentation usually correlates with a more severe phenotype.[18,20] The presence of femur length below the 5th percentile during routine screening in the second trimester requires further investigation.[18,19]

The usefulness of ultrasound is particularly relevant in assessing lethality risk. Several predictors have been described in the literature, with different sensitivity rates.[18-20] Among the most significant are a chest-to-abdominal circumference ratio of less than 0.6 and a femur length-to-abdominal circumference ratio of less than 0.16.[19] Additional factors that can be considered include the femur length-to-biparietal diameter ratio, micromelia more than 3 standard deviations below the mean, amniotic fluid volume, bone mineralization and the presence of marked bowing or fractures.[18,20] Of note, linear femur measurements may be affected by bowing which could lead to an inaccurate estimation of true femur length.[20]

SD lethality seems to correlate more with pulmonary hypoplasia resultant from small chest circumference, rather than with limb shortening.[19,20] Therefore, fetal lung volumes and chest-to-abdominal circumference ratio are important to assess the risk of lethal pulmonary hypoplasia.[18]

However, there are SD that show ultrasonographic evidence of a small thorax and are not lethal. Despite this, patients with non-lethal SD may still have respiratory compromise in the neonatal period and thus require close monitoring.[19]

Ultrasound also allows identification of additional findings, such as facial abnormalities, malformed digits or vertebral anomalies, that may help in differential diagnosis between SD with overlapping features. As an example, campomelic dysplasia commonly presents with hypoplastic or absent scapula, which can help distinguish it from other conditions associated with long bone bowing, such as CHH.[18,20]

Phenotypical variability is a characteristic of CHH and it can be noted even in the prenatal period. There are reports describing ultrasound abnormalities as early as 12 and 15 weeks of gestation[6,21], others only toward the end of the third trimester[5,15] and some are only detected after birth[13,22,23].

Hall *et al*[6] reported a case series in 2021 that is highly relevant in the context of prenatal diagnosis of CHH. They describe three sibling fetuses that presented at 12 weeks of gestation with abnormal ultrasound findings. The parents were healthy, non-consanguineous, and had a healthy daughter. The thoracic and abdominal circumferences were found to be at the 5th percentile and the long bones were below the 5th percentile and bowed. Increased nuchal translucency was also noted. The pregnancy was terminated, and postmortem radiographs and autopsies confirmed bowed, shortened long bones, as well as a small thorax with mild rib shortening. Additional findings included acetabula with a trident-shaped appearance, narrow sacrosciatic notches and flattening of the vertebral bodies. This led the team to suspect the presence of Thanatophoric dysplasia, one of the most common lethal SD. However, genetic testing did not corroborate this; instead, RMRP mutations were detected, consistent with CHH diagnosis.[6]

Crahes *et al*[12] describe another case of a couple with two healthy children, in whom routine ultrasound during the current pregnancy showed findings consistent with a SD. Marked limb shortening was detected at 23 weeks of gestation and at 26 weeks mild macrocrania was noted. Screening for FGFR3 mutations associated with achondroplasia was negative. At 31 weeks, the ultrasound confirmed bowed femora with absence of bone growth. A medical termination of pregnancy was carried out due to suspected severity of the condition and an autopsy was performed. In addition to confirming bilateral rhizomelic limb shortening, post-mortem findings revealed thymic hypoplasia with immune dysfunction, which pointed towards CHH. RMRP mutations were identified through genetic analysis, confirming the diagnosis.[12]

In families with a previous child affected by CHH, ultrasound still has a crucial role and may even allow for an earlier recognition in subsequent pregnancies. The case described by Dungan *et al*[7] emphasizes this. A healthy couple had a first child affected with CHH whose rhizomelic limb shortening was only noted at birth. During the second pregnancy, serial ultrasonography allowed for detection of bowed, shortened femurs and a small rib cage at 17 weeks gestation, which raised suspicion for CHH recurrence. Given the older sibling´s history of immune dysfunction and recurrent infections, a bone marrow transplantation was performed in the second child shortly after birth. This intervention appeared to be beneficial, as this child experienced fewer infections.[7]

Apart from the role of two-dimensional ultrasonography, other imaging modalities have been described in the context of SD. Three-dimensional ultrasound allows for enhanced visualization of facial abnormalities and may be helpful in the differential diagnosis of SD with distinctive craniofacial features.[18,19] Fetal MRI may sometimes be more accurate in fetal morphological assessment than ultrasound and does not cause any harm to the fetus or mother.[24] It may be useful in fetal spine evaluation in cases suggestive of vertebral malformations. It may also have a complementary role in assessing fetal lung volumes, particularly in cases when ultrasound findings are inconclusive or in the late stages of pregnancy.[19,20] Gilligan *et al*[25] corroborate this and propose that fetal MRI also provides relevant findings regarding the brain, calvarium and cartilage, possibly allowing for earlier genetic counselling and testing.[25]

In contrast, in utero radiographs do not offer any advantage to the SD prenatal diagnosis and require unnecessary exposure to ionizing radiation.[18] However, despite also involving ionizing radiation, low-dose computed tomography (CT) has recently been reported in the literature in the context of SD, as a potential tool to improve diagnostic accuracy, due to higher skeletal resolution.[18,26] A prospective study using low-dose CT prenatally diagnosed SD in 17 out of 19 fetuses suspected through ultrasound, with postnatal confirmation differing in only one infant. This technique showed a higher specificity and positive predictive value than ultrasound alone.[26] The potential role of low-dose CT has also been reported as a complement to ultrasound in the specific cases of achondroplasia and hypochondroplasia.[27]

To the best of our knowledge, there are no published reports on the use of these alternative imaging modalities in the prenatal diagnosis of CHH.

Genetic testing

As stated before, ultrasound is unable to reach a diagnosis in almost half of the SD cases.[18-20] Accuracy in the specific case of CHH has not yet been established. Genetic testing enables definitive CHH confirmation, through identification of pathogenic RMRP mutations. The approach differs depending on whether the mutation has already been detected in the family or not.

In the cases described by Hall *et al*[6] the diagnosis was confirmed post-mortem through WES of fetal tissue from the second affected fetus, followed by targeted Sanger sequencing of the *RMRP* gene in the other siblings and parents. Crahes *et al*[12] also confirmed the diagnosis post-mortem through *RMRP* gene sequencing.

When a familial *RMRP* mutation is known, invasive prenatal diagnosis can be offered in subsequent pregnancies to assess recurrence risk.[8] Vatanavicharn *et al*[15] identified *RMRP* mutations after birth in a child with CHH, who died at 23 months of age due to infection. In a subsequent pregnancy, chorionic villus sampling at 14 weeks of gestation allowed for DNA sequencing, which suggested that the fetus was unlikely to be affected. Ultrasound at 18 weeks of gestation confirmed normal morphology. The parents decided to continue the pregnancy, and a healthy child was born.[15] In other cases, a mutation is detected postnatally, and in a subsequent pregnancy the parents decline invasive prenatal testing, opting to carry out the pregnancy and have the confirmation after birth.[21]

The literature regarding prenatal genetic testing in SD cases arising *de novo* with suggestive ultrasound manifestations does not appear to include CHH. A recent article from 2025 studied 26 fetuses with suspected SD using a sequential analysis with karyotyping, CMA and WES. This approach warranted a 61,5% detection rate. *FGFR3* gene mutations were the most frequently detected.[28] A cohort study conducted by Jian *et al*[29] analyzed 147 fetuses with suspected SD and performed CMA, followed by WES in the CMA negative cases. WES detected pathogenic variants in 21 out of 58 cases, with a 36.2% detection rate. Thanatophoric dysplasia, achondroplasia and osteogenesis imperfecta were the most common diagnoses.[29] In another study where medical trio exome sequencing was performed, these were also the conditions most frequently identified. This technique was able to provide definite molecular diagnosis in 24 out of the 27 fetuses evaluated.[30]

Non-invasive prenatal screening is a promising area in the field of genetic evaluation. It has been more extensively studied regarding chromosomal abnormalities, but there is a growing interest in its application to single-gene disorders through cell-free fetal DNA.[17,31]

In the context of SD, this technique has been shown to provide definitive prenatal diagnosis of thanatophoric dysplasia and achondroplasia[18,32,33]. However, its use has not yet been explored in the context of CHH.

DISCUSSION

CHH is a rare osteochondrodysplasia caused by mutations in the *RMRP* gene. The pathophysiology is not entirely understood but there have been interesting advances in the recent years, trying to correlate the genotype with the diverse phenotype presented.[9-11,13,15,16] Mutations may impact the promotor region or the RMRP transcript itself, and depending on the RNA function impaired, the disease can present with varying degrees of skeletal and extra-skeletal manifestations.[2,10,11,13,15]

CHH does not have a cure, but characterizing its molecular basis might open potential therapeutic targets, as suggested by Sun *et al*[9].

Regarding CHH prenatal diagnosis, ultrasound is often the tool that raises suspicion for this condition. Suggestive findings may include marked shortening of the long bones, with relative macrocephaly, as well as a narrow thorax.[5-7,12,15,21] As reported by Hall *et al*[6], these features might overlap with those of lethal SD, such as thanatophoric dysplasia. It is suggested that the earlier a SD is detected, the more severe the prognosis.[18,20] However, CHH can present early in prenatal life and still result in a viable fetus with a mild phenotype, reported especially when there is a positive family history.[7,21]

Among the lethality predictors described, femur length is a key component in several diagnostic ratios. However, accurate measurement can be affected by femoral bowing and angulation.[18-20] This is particularly relevant in CHH, since patients often present with bowed femurs and should therefore be carefully assessed to avoid misdiagnosing disease severity.[3,20] A small thorax and subsequent pulmonary hypoplasia are also commonly referenced in the literature as major lethality predictors.[18-20] However, it is important to note that CHH is among the non-lethal SD that can also present with a small rib cage[7].

Additional imaging methods, such as fetal MRI and low-dose CT, might play a complementary role to ultrasound, but literature evaluating them in the context of CHH is needed to assess their sensitivity and utility.[18-20,24-27]

Therefore, genetic testing and counselling are essential to guide parents in the decision-making, particularly when sonographic features are ambiguous.

CHH prenatal genetic testing is scarcely explored in the literature. When a familial mutation is known, targeted testing can be performed through invasive methods in subsequent pregnancies to assess potential recurrence.[8,15] When ultrasound suggests features compatible with SD, the priority is to rule out lethal conditions, such as thanatophoric dysplasia and osteogenesis imperfecta type II.[18,34] NGS panels that include the *RMRP* gene or WES may be able to identify *RMRP* pathogenic variants, but the role of molecular testing in the prenatal period is controversial.[18] Savarirayan *et al*[18] argue that these comprehensive tests may have long turnaround times, and results may not be available before delivery. It might be reasonable to defer testing to the postnatal period in non-lethal conditions such as CHH. With the advancement in technology, these tests may warrant results faster and thus be recommended in the prenatal period.[18,30]

It is important to note that exome sequencing does not include the whole genome, it only assesses exon regions, which are involved in protein coding. Therefore, the information provided can be incomplete, and data from promoter and enhancer regions may also be missed.[35] Given that the *RMRP* gene encodes a non-coding RNA and that mutations can arise in the promoter region, this may explain why CHH was not identified in the recent SD studies evaluating the role of NGS panels and WES.[28-30] Genome sequencing is also a possible approach, although it remains more costly and less readily available.[4]

Considering the growing interest in non-invasive techniques for prenatal diagnosis and the fact that CHH is a monogenic disorder, it seems plausible to hypothesize that testing through cell-free fetal DNA might be possible in the future.[18,31]

The proposed diagnostic algorithm (Fig. 2) outlines a prenatal approach to CHH suspicion, depending on whether RMRP mutations are known. If there is positive family history and ultrasound findings suggest recurrence, invasive testing may confirm the diagnosis. When there is no known history, the priority is to assess lethality, focusing on specific ratios and signs of pulmonary hypoplasia. Clinicians should be aware that CHH can present early with a small thorax and bowed femurs, and yet not be lethal. If findings do not suggest a lethal dysplasia, molecular testing may be possible prenatally or deferred. This algorithm encompasses a general framework, but decisions should be individualized.

CONCLUSION

In conclusion, CHH is a complex skeletal dysplasia that continues to pose diagnostic challenges, particularly in the prenatal period. Despite its low prevalence, CHH significantly impacts affected individuals, as well as their families. This review attempts to address a gap in the literature regarding this condition, by compiling current knowledge on its molecular basis, imaging features and available genetic testing. Given its highly variable presentation and increasing identification in multiple countries, there is a clear need for additional case reports and cohort studies to better characterize genotype-phenotype correlation and long-term outcomes.

Combining sonographic findings with molecular diagnosis through an integrated and standardized approach may facilitate early and accurate diagnosis. Timely genetic counselling, supported by early identification, will allow parents to make informed reproductive decisions while mitigating uncertainty in the prenatal setting.

The recent advances in technology regarding imaging and genetic testing are promising and we propose that CHH should be actively considered in future studies exploring prenatal diagnosis of skeletal dysplasias.

AUTHORS CONTRIBUTION

All authors made substantial contributions to the submitted work. CPC drafted the paper, designed the figures and conducted the literature review. IA and CL provided critical revision of the work. LGM provided the concept of the work and did critical review of the manuscript. Final approval for publication was agreed upon by all authors.

REFERENCES

1. McKusick VA, Eldridge R, Hostetler JA, Ruangwit U, Egeland JA. DWARFISM IN THE AMISH. II. CARTILAGE-HAIR HYPOPLASIA. Bull Johns Hopkins Hosp. 1965 May;116:285–326.
2. Vakkilainen S, Taskinen M, Mäkitie O. Immunodeficiency in cartilage-hair hypoplasia: Pathogenesis, clinical course and management. Scand J Immunol 2020;92:e12913.
3. Riley P, Weiner DS, Leighley B, Jonah D, Morton DH, Strauss KA, et al. Cartilage hair hypoplasia: Characteristics and orthopaedic manifestations. Journal of Children's Orthopaedics 2015;9:145–52.
4. Mäkitie O, Vakkilainen S. Cartilage-Hair Hypoplasia – Anauxetic Dysplasia Spectrum Disorders [Internet]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews. Seattle (WA): University of Washington, Seattle; 1993– [updated 2023 May 11; cited 2025 May 2]. Available from: https://www.ncbi.nlm.nih.gov/books/
5. Kwan A, Manning MA, Zollars LK, Hoyme HE. Marked variability in the radiographic features of cartilage-hair hypoplasia: Case report and review of the literature. American J of Med Genetics Pt A 2012;158A:2911–6.
6. Hall CM, Liu B, Haworth A, Reed L, Pryce J, Mansour S. Early prenatal presentation of the cartilage-hair hypoplasia / anauxetic dysplasia spectrum of disorders mimicking recurrent thanatophoric dysplasia. European Journal of Medical Genetics 2021;64:104162.
7. Dungan JS, Emerson DS, Phillips OP, Shulman LP. Cartilage-Hair Hypoplasia Syndrome: Implications for Prenatal Diagnosis. Fetal Diagn Ther 1996;11:398–401.
8. Sulisalo T, Sillence D, Wilson M, Ryynänen M, Kaitila I. Early prenatal diagnosis of cartilage-hair hypoplasia (CHH) with polymorphic DNA markers. Prenatal Diagnosis 1995;15:135–40.
9. Sun X, Zhang R, Liu M, Chen H, Chen L, Luo F, et al. Rmrp Mutation Disrupts Chondrogenesis and Bone Ossification in Zebrafish Model of Cartilage-Hair Hypoplasia via Enhanced Wnt/β-Catenin Signaling. Journal of Bone and Mineral Research 2019;34:2101-16.
10. Thiel CT, Rauch A. The molecular basis of the cartilage-hair hypoplasia–anauxetic dysplasia spectrum. Best Practice & Research Clinical Endocrinology & Metabolism 2011;25:131–42.
11. Venturi G, Montanaro L. How Altered Ribosome Production Can Cause or Contribute to Human Disease: The Spectrum of Ribosomopathies. Cells 2020;9:2300.
12. Crahes M, Saugier-Veber P, Patrier S, Aziz M, Pirot N, Brasseur-Daudruy M, et al. Foetal presentation of cartilage hair hypoplasia with extensive granulomatous inflammation. European Journal of Medical Genetics 2013;56:365–70.
13. Park JH, Im M, Kim Y-J, Jang J-H, Lee S-M, Kim M-S, et al. Cartilage-hair hypoplasia–anauxetic dysplasia spectrum disorders harboring RMRP mutations in two Korean children: A case report. Medicine 2024;103:e37247.
14. Kavadas FD, Giliani S, Gu Y, Mazzolari E, Bates A, Pegoiani E, et al. Variability of clinical and laboratory features among patients with ribonuclease mitochondrial RNA processing endoribonuclease gene mutations. Journal of Allergy and Clinical Immunology 2008;122:1178–84.
15. Vatanavicharn N, Visitsunthorn N, Pho-iam T, Jirapongsananuruk O, Pacharn P, Chokephaibulkit K, et al. 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.
16. Vakkilainen S, Skoog T, Einarsdottir E, Middleton A, Pekkinen M, Öhman T, et al. The human long non-coding RNA gene RMRP has pleiotropic effects and regulates cell-cycle progression at G2. Sci Rep 2019;9:13758.
17. Krstić N, Običan SG. Current landscape of prenatal genetic screening and testing. Birth Defects Research 2020;112:321–31.
18. Savarirayan R, Rossiter JP, Hoover-Fong JE, Irving M, Bompadre V, Goldberg MJ, et al. Best practice guidelines regarding prenatal evaluation and delivery of patients with skeletal dysplasia. American Journal of Obstetrics and Gynecology 2018;219:545–62.
19. Krakow D, Lachman RS, Rimoin DL. Guidelines for the prenatal diagnosis of fetal skeletal dysplasias. Genetics in Medicine 2009;11:127–33.
20. Milks KS, Hill LM, Hosseinzadeh K. Evaluating skeletal dysplasias on prenatal ultrasound: an emphasis on predicting lethality. Pediatr Radiol 2017;47:134–45.
21. Lugli L, Ciancia S, Bertucci E, Lucaccioni L, Calabrese O, Madeo S, et al. Homozygous n.64C>T mutation in mitochondrial RNA-processing endoribonuclease gene causes cartilage hair hypoplasia syndrome in two siblings. European Journal of Medical Genetics 2021;64:104136.
22. Gamliel A, Lee Y, Lev A, AbuZaitun O, Rechavi E, Levy S, et al. Immunologic Heterogeneity in 2 Cartilage-Hair Hypoplasia Patients With a Distinct Clinical Course. J Investig Allergol Clin 2023;33:263–70.

23. Uchida N, Ishii T, Nishimura G, Sato T, Kuratsuji G, Nagasaki K, et al. RMRP -related short stature: A report of six additional Japanese individuals with cartilage hair hypoplasia and literature review. American J of Med Genetics Pt A 2024;194:e63562.
24. Berceanu C, Gheonea IA, Vlădăreanu S, Cîrstoiu MM, Vlădăreanu R, Mehedinţu C, et al. Ultrasound and MRI comprehensive approach in prenatal diagnosis of fetal osteochondrodysplasias. Cases series. Med Ultrason 2017;19:66.
25. Gilligan LA, Calvo-Garcia MA, Weaver KN, Kline-Fath BM. Fetal magnetic resonance imaging of skeletal dysplasias. Pediatr Radiol 2020;50:224–33.
26. Waratani M, Ito F, Tanaka Y, Mabuchi A, Mori T, Kitawaki J. Prenatal diagnosis of fetal skeletal dysplasia using 3-dimensional computed tomography: a prospective study. BMC Musculoskelet Disord 2020;21:662.
27. Waratani M, Hasegawa T, Shimura K, Tanaka Y, Ito F, Takahata A, et al. Prenatal diagnosis of achondroplasia and hypochondroplasia using three-dimensional computed tomography: a case series at a single institution. Quant Imaging Med Surg 2024;14:9543–51.
28. Cui L, Hu H, Zhai X, Qi M, Liu Y, Han C, et al. Analysis of a Series of 26 Cases With Prenatal Skeletal Dysplasia via Multiplatform Genetic Detection. Molec Gen & Gen Med 2025;13:e70062.
29. Jiang M, Zhang B, Wang J, Qiao W, Mao X, Yu B. Sequential prenatal diagnosis of fetal skeletal dysplasia: A cohort study. Acta Obstet Gynecol Scand 2025;104:860–74.
30. Han J, Yang Y, He Y, Liu W, Zhen L, Pan M, et al. Rapid prenatal diagnosis of skeletal dysplasia using medical trio exome sequencing: Benefit for prenatal counseling and pregnancy management. Prenatal Diagnosis 2020;40:577–84.
31. Sirica R, Ottaiano A, D'Amore L, Ianniello M, Petrillo N, Ruggiero R, et al. Advancing Non-Invasive Prenatal Screening: A Targeted 1069-Gene Panel for Comprehensive Detection of Monogenic Disorders and Copy Number Variations. Genes 2025;16:427.
32. Chitty LS, Khalil A, Barrett AN, Pajkrt E, Griffin DR, Cole TJ. Safe, accurate, prenatal diagnosis of thanatophoric dysplasia using ultrasound and free fetal DNA. Prenatal Diagnosis 2013;33:416–23.
33. Vivanti AJ, Costa J -M., Rosefort A, Kleinfinger P, Lohmann L, Cordier A -G., et al. Optimal non-invasive diagnosis of fetal achondroplasia combining ultrasonography with circulating cell-free fetal DNA analysis. Ultrasound in Obstet & Gyne 2019;53:87–94.
34. Stembalska A, Dudarewicz L, Śmigiel R. Lethal and life-limiting skeletal dysplasias: Selected prenatal issues. Adv Clin Exp Med 2021;30:641–7.
35. Liu Y, Wang L, Yang Y-K, Liang Y, Zhang T-J, Liang N, et al. Prenatal diagnosis of fetal skeletal dysplasia using targeted next-generation sequencing: an analysis of 30 cases. Diagn Pathol 2019;14:76.

FIGURE LEGENDS

Figure 1. Simplified article selection flowchart.

Figure 2. Diagnostic approach for prenatal CHH evaluation. FL: femur length; AC: abdominal circumference. Icon from NIAID Visual & Medical Arts. (07/10/2024). Pregnant Human and Fetus. NIAID NIH BIOART Source. bioart.niaid.nih.gov/bioart/421 (accessed on 4 June 2025)

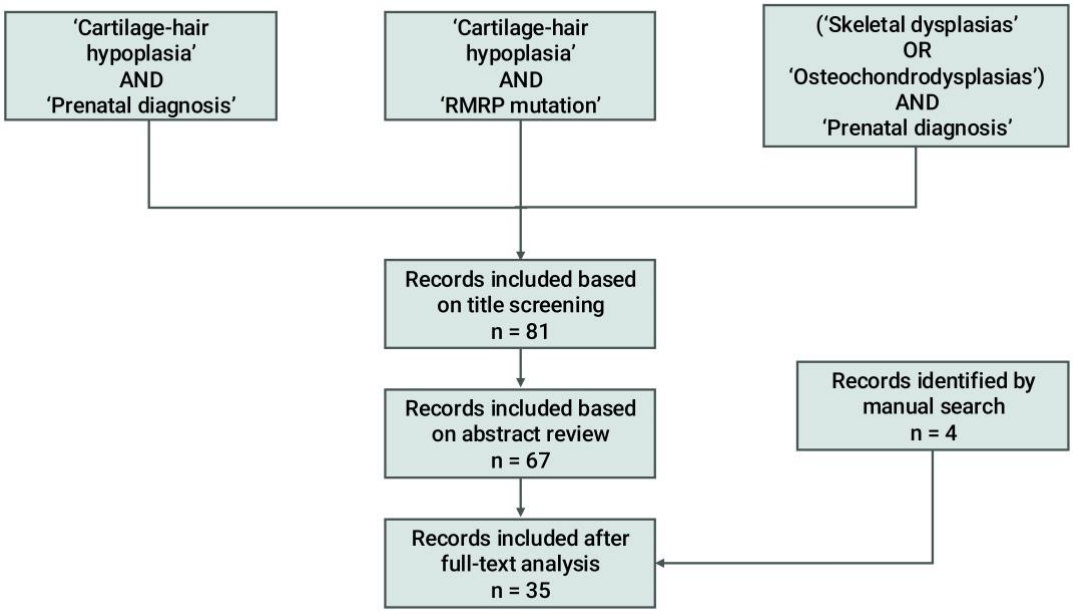


Figure 1. Simplified article selection flowchart.

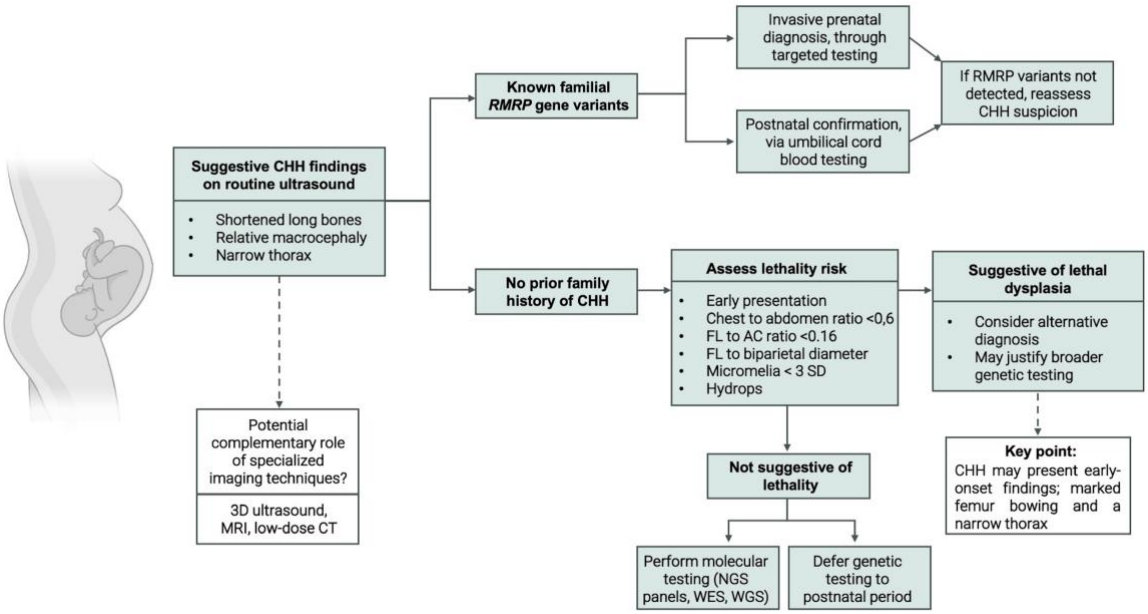


Figure 2. Diagnostic approach for prenatal CHH evaluation. FL: femur length; AC: abdominal circumference. Icon from NIAID Visual & Medical Arts. (07/10/2024). Pregnant Human and Fetus. NIAID NIH BIOART Source. bioart.niaid.nih.gov/bioart/421 (accessed on 4 June 2025)

CHAPTER TWO

"Familial Cartilage-Hair Hypoplasia: Prenatal Ultrasound Features and Clinical Outcomes in Three Siblings with Identical RMRP Variants"

Journal: *BMJ Case Reports*

Article Type: Case report

Date Submitted by the Author: 28-May-2025

Complete List of Authors:

Portela Carvalho, Catarina; Unidade Local de Saúde de Santo António EPE, Medicine; University of Porto Institute of Biomedical Sciences Abel Salazar

Martins, Andreia; University of Porto Institute of Biomedical Sciences Abel Salazar; Unidade Local de Saúde de Santo António, Department of Women and Reproductive Medicine

Alves, Inês; ANDO Portugal - National Association for Skeletal Dysplasias; University of Évora School of Health and Human Development

Guedes-Martins, Luís; University of Porto Institute of Biomedical Sciences Abel Salazar, Department of Obstetrics; Unidade Local de Saúde de Santo António, Department of Women and Reproductive Medicine

Specialty: Obstetrics and gynaecology

Keywords: Prenatal Diagnosis, Ultrasonography, Genetic screening / counselling < Genetics

TITLE OF CASE

Familial Cartilage-Hair Hypoplasia: Prenatal Ultrasound Features and Clinical Outcomes in Three Siblings with Identical RMRP Variants

SUMMARY

Cartilage-hair hypoplasia (CHH) is a rare autosomal recessive skeletal dysplasia. It is often associated with short stature, metaphyseal abnormalities, hair hypoplasia and immune dysfunction.

This case describes a pregnant woman in her mid-30s with two previous children diagnosed with CHH with molecular confirmation of two pathogenic variants of the ribonuclease mitochondrial ribonucleic acid processing gene. The couple is healthy and non-consanguineous.

Routine ultrasound examination of the current pregnancy suggested this fetus was also likely to be affected. The couple opted not to perform invasive prenatal diagnosis. Umbilical cord blood was collected at birth for genetic testing, confirming the diagnosis.

CHH has a significant impact on the quality of life of those affected. Genetic counseling may help parents understand the disease and its prognosis. Obstetric ultrasound plays an important role in the diagnosis by allowing early detection of suspected cases as well as assessing fetal growth.

BACKGROUND

Cartilage-hair hypoplasia (CHH) is a rare skeletal dysplasia inherited in an autosomal recessive pattern, first described in 1965 by McKusick *et al*. It is also known as McKusick type metaphyseal chondrodysplasia. The disease has a higher prevalence among the Finnish (1 in 23000 births) and the Old Order Amish populations (1-2 in 1000 births)[1]. The prevalence in other parts of the world is unknown but estimated to be significantly lower. It is caused by mutations in the ribonuclease mitochondrial ribonucleic acid processing gene (RMRP gene). The clinical presentation is variable but some of the common traits include short-limb short stature, hair abnormalities, such as fine, sparse hair, and immune dysfunction. Additional traits include increased incidence of anemia, Hirschsprung disease and malignancy[1,2,3].

Fetal diagnosis is difficult, considering that the ultrasound findings suggest several differential diagnoses. Some of the first prenatal manifestations include micromelia, bowing of the long bones and delay in the thorax growth[4,5].

The aim of this study is to present a clinical case of the third child affected by CHH in a Portuguese family, where two siblings were previously diagnosed with identical *RMRP* variants. This enables the understanding of genotype-phenotype correlations in this rare condition and includes a review of the relevant literature.

CASE PRESENTATION

We report the case of a pregnant woman in her mid-30s. Gravida 3, para 2, two previous children diagnosed with CHH with molecular confirmation of compound heterozygosity with two pathogenic variants of the *RMRP* gene (deleterious variants n.197C>T and n.-25_-4dup). Other than having nontoxic nodular goiter, the patient is healthy. Both her and her partner are not affected by CHH and are non-consanguineous.

To provide context, we summarized the relevant data regarding the first two pregnancies.

First Pregnancy

Prenatal Findings: The ultrasound performed at 21 weeks gestation identified shortening of the long bones, with progressive worsening of the growth discrepancy between the long bones and the head and abdominal circumference as gestational age advanced. Due to the fetal growth restriction and the suspicion of a skeletal dysplasia, prenatal genetic testing was performed, including exome sequencing and CGH array. Two genetic variants of the *RMRP* gene were identified and the parental study allowed to conclude that they were located on different alleles.

Perinatal Data: The child was born via cesarean section at 39 weeks, due to pelvic presentation. He weighed 2910 g (15th percentile), measured 41 cm (<1st percentile) and had a head circumference of 35 cm (69th percentile). He had rhizomelic shortening and bowing of the long bones and relative macrocephaly. He had genu varum and a slight elbow flexion. The thorax had normal dimensions. His hair was thin, sparse and light-colored.

Postnatal Developments: During infancy, it was noted that the child had CD8 lymphopenia and hypogammaglobulinemia. He was followed in a primary immunodeficiency consultation. A lymphocyte transformation test was performed, which showed low response to mitogens.

Current Status: At the time of writing, the couple´s first child remains clinically stable, with no history of significant infectious complications or other major medical issues. He is not receiving any specific treatments or therapies.

Second Pregnancy

Prenatal Findings: The second child also had a normal first trimester ultrasound, but during the second trimester it was noted significant shortening and bowing of the limbs and he was growing below the 5th percentile since 25 weeks of gestation. The parents decided not to have invasive prenatal testing performed, choosing to do umbilical cord blood sampling after birth.

Perinatal Data: A cesarean section was scheduled at 40 weeks gestation, due to pelvic presentation. At birth, the baby weighed 3025 g (25th percentile), measured 42 cm (<1st percentile) and had a head circumference of 33.50 cm (19th percentile). On physical examination, marked limb shortening was noted with bowing of some segments, mainly of the legs, bilaterally and symmetrically. He had limited elbow extension and joint stiffness.

Postnatal Developments: The molecular study of the umbilical cord blood confirmed the diagnosis of CHH. The complete blood cell count indicated lymphopenia with CD19 levels of 344 cells/cm^3. His hair was initially described as brown, without thinning. However, as a toddler it was noted to be fine, sparse and light. A consultation around that time revealed decreased levels of CD8, CD19 and IgG.

Current Status: The child is currently in early childhood and is not undergoing any specific therapies. He has had no major medical issues. His height and weight remain below the 1st percentile for age.

Third Pregnancy

Despite the 25% risk of recurrence, the couple planned a spontaneous third pregnancy, opting not to resort to assistive reproductive technology such as preimplantation genetic testing. Routine ultrasound examination of the current pregnancy performed at 13 weeks showed no abnormalities. At 20 weeks of gestation, the ultrasound revealed significant shortening of the long bones, below the fifth percentile (<P5), with no other apparent morphological abnormalities (Figure 1). At 27 weeks, the thorax dimensions were found to be below average for the gestational age (Figure 2). These findings, combined with the previous history, were suggestive of CHH recurrence. The couple was informed of the available techniques for prenatal diagnosis and decided against them, opting to have the etiological study performed after birth, as was done in the second pregnancy, since they would want to carry out the pregnancy either way.
The pregnancy was otherwise uneventful, and an elective cesarean section was performed at 39 weeks. The fetus was in breech presentation. The birth weight was 2465 g (3rd percentile), the length 39.20 cm (<1st percentile) and the head circumference 35 cm (69th percentile). The newborn boy presented with an APGAR score of 7 in the 1st minute and 9 in the 5th and 10th minutes. On physical examination, he presented with short limbs, being considered asymmetrical small for gestational age. Umbilical cord blood was collected for genetic testing. He initially showed signs of respiratory distress, which resolved after receiving nasal CPAP for the first 24 hours and intermittent high flow nasal cannula oxygen therapy until day 8th of life. Bowel movements were present since the first 24 hours of life. Enteral feeding was initiated on day 1 with good tolerance, achieving full oral intake by day 9. He had glycemic stability, no fluid and electrolyte imbalances and preserved urine output. The complete blood count showed no evidence of blood dyscrasia, with a hemoglobin level of 18.6 g/dl, leucocyte count 16,810/µL and platelet count 287,000/µL.

OUTCOME AND FOLLOW-UP

The newborn was discharged from the hospital on the 11th day in good general condition and with adequate weight gain but showing signs of stiffness in the extension of the elbows, worse on the left side, and difficulty in mobilizing the left hand, as well as a slight limitation in hip abduction. The abdomen was distended, but soft, without palpable masses or organomegalies, nor tenderness on palpation. The remaining physical examination was unremarkable. Given the stiffness of the limbs, he was referred to rehabilitation medicine. The umbilical cord blood analysis also detected the familial variants n.197C>T and n.-25_-4dup, confirming the diagnosis of CHH. During infancy, there have been no major medical issues, other than a single episode of acute bronchiolitis, which was

managed with supportive care in an outpatient setting, without the need for bronchodilators or antibiotic therapy. No episodes of cyanosis or respiratory arrests reported during the follow-up.

Currently, the child is growing below the 1st percentile for weight and length, with 5105 g and 50 cm, respectively, whereas the head circumference is between the 5th and 15th percentile (41.4 cm). The marked limb shortening is more evident at the rhizomelic level in the lower limbs. On physical examination, he has a pectus carinatum and wrist asymmetry, with hyperextension of the left wrist. It is also noted some difficulty in leg extension. Hip mobility is apparently preserved. Normal lung and cardiac sounds. No hair abnormalities apparent. A radiograph performed suggested alteration of the distal metaphysis of the radius and ulna, as well as the metacarpals. All phalanges are present, with normal anatomy. In terms of psychomotor development, he is still unable to sit, roll over or bring objects to his mouth. He babbles a lot, showing excellent social interaction. He is undergoing physiotherapy once a week and occupational therapy twice a week.

DISCUSSION

Many skeletal dysplasias such as Thanatophoric dysplasia (TD) and Ellis van Creveld syndrome have shown to present sonographic finds by 14 weeks gestation. The early prenatal diagnosis is facilitated by a known family history. Although many of the responsible genes for osteochondrodysplasias are known, the existence of multiple mutations and genetic variants make it difficult for an accurate prenatal molecular diagnosis. Therefore, postnatal exams are usually necessary[6].

Ultrasonography is highly operator-dependent but defining uniform criteria may bring many advantages to the prenatal diagnosis of skeletal dysplasias, in particular CHH. Developing charts of fetal size has been shown to help distinguish TD from other conditions[7]. This is especially important since TD is usually a lethal condition and can be confused with CHH[4]. Using parameters such as head and abdominal circumference, thoracic dimensions and long bone length that are adjusted to the typical growth pattern of CHH during gestation may facilitate diagnosis and support parental decision-making regarding the need for invasive testing or pregnancy termination.

A similar case to ours was described in 1996, in which a prenatal diagnosis of a fetus was made based on ultrasound findings and family history of CHH. The couple was also healthy and non-consanguineous and had a previous child affected by the condition, diagnosed after birth. The fetus had a normal appearance at 14 weeks of gestation and at 17 weeks marked limb shortening was noted. In our case, all three siblings also had normal first trimester ultrasounds and only after 20 weeks of gestation did they start to exhibit abnormal growth. The report questions a direct relationship between the severity of growth abnormalities and the immune system involvement. Although both siblings had marked limb shortening, the younger one seemed to have a lesser degree of immunodeficiency, which could have been related to an earlier bone marrow transplantation[8]. A more recent article, from 2023, studied thirty-two children with CHH and concluded that shorter birth length correlated with lower lymphocyte counts and the occurrence of infections[9].

In our case, none of the children have had recurrent infections. The birth length of the first child was 41 cm and he appears to have the most significant immune dysfunction with CD8 lymphopenia

and hypogammaglobulinemia. The second child measured 42 cm at birth and has shown CD19 lymphopenia, as well as progressively decreasing levels of CD8 and IgG. The third child, born with the shortest length, 39.2 cm, has not demonstrated any immunological or hematological abnormalities to date. All the siblings are growing below the 1st percentile in terms of length and weight. Long-term follow-up may help further characterize their clinical manifestations. However, up to this point, no clear correlation has been observed between the degree of limb shortening and the severity of immune dysfunction. A case report from Japan also corroborates this, as they did not find differences in birth length between affected individuals with and without extraskeletal symptoms[10]. It is important to note that this could have been due to the small sample size in our cases.

A report from 2013 describes another case suspected antenatally at 23 weeks gestation through shortened limbs (<3rd percentile) and bowing femora. A medical termination was performed and the CHH diagnosis confirmed *postmortem*. They also discuss the association between birth length, levels of IgG, IgA and Nk cells after birth and the subsequent infection risk. CHH patients appear to exhibit marked heterogeneity. Given that phenotypic variability has been described among siblings, factors beyond *RMRP* mutations might contribute to the phenotype[5]. The siblings described in our report appear to have a similar phenotype with marked rhizomelic limb shortening and bowing of the femurs, as illustrated in the photographs provided (Figures 3-5). The two oldest siblings show evidence of hypotrichosis. The youngest has not exhibited any hair abnormalities to date. However, since such features were also not noted at birth in the older siblings, it is possible that he may develop over time.

Studying the genotype-phenotype correlation may also help determine which *RMRP* mutations are linked to more severe forms of the disease. The *RMRP* gene is located on chromosome 9p13.3 and has been shown to be involved in cell cycle regulation, mitochondrial RNA processing and ribosome synthesis. Compound variants in the *RMRP* gene have been shown to lead to functional impairment, which could affect various organs, such as bone marrow, hair and cartilage. However, the mechanisms underlying the link between this gene and CHH remain unclear[11].

The variants identified in our case were n.197C>T and n.-25_-4dup. The variant n.197C>T is reported in the gnomAD database with an estimated frequency of 0.00003464 (24/692778 alleles) and is classified as pathogenic. Twelve of the alleles are from Latin Americans, two from African/African-Americans, nine from non-Finnish Europeans and one from another ethnic group. This variant was first described in the literature in 2002 in a patient with metaphyseal dysplasia without hypotrichosis[12]. Two recent studies conducted by *Gomes et al* analyzed Brazilian patients with CHH and identified a particularly high prevalence of the variant in their population, suggesting a possible founder effect. They advance the hypothesis that this variant originated from a single mutational event and was transmitted from a common ancestor with a possible European origin[13,14]. Given the historical ties and migratory flows between Portugal and Brazil, it is interesting to observe the presence of this mutation in a Portuguese case, such as the one we present in this report. Haplotype analysis in additional cases could help trace the origin of this variant, determining whether it arose from a single occurrence and subsequently spread globally. Regarding the other variant identified in our case, n.-25_-4dup, it is not listed in the gnomAD database. Although its clinical significance remains uncertain, the fact that it was found in trans with the n.197C>T variant supports its pathogenicity. Of the 23 patients studied by Gomes *et al* in 2019, five harbored the n.-

25_-4dup variant, four of whom shared the same genotype as the siblings in our case. To our knowledge, these are the only reports in the literature identifying this variant.

LEARNING POINTS/TAKE HOME MESSAGES

- CHH is a rare disease with important skeletal and extra-skeletal manifestations that require close and ongoing multidisciplinary monitoring starting in the prenatal period.
- Prenatal ultrasound can be a valuable diagnostic tool, allowing for an early recognition of skeletal abnormalities and for serial assessment of fetal growth, particularly of the limbs and thorax.
- Defining standardized ultrasonographic criteria adjusted to the CHH growth patterns may improve diagnostic accuracy and support parental decision-making regarding the need for invasive testing or pregnancy termination.
- Characterizing the genotype-phenotype correlation may contribute to expanding current knowledge and guiding prognosis and management strategies.
- Genetic testing confirming pathogenic variants in the *RMRP* gene is crucial to establish the diagnosis and provide family counselling, especially in recurrent cases, such as this one.

REFERENCES

1. Mäkitie O, Vakkilainen S. Cartilage-Hair Hypoplasia – Anauxetic Dysplasia Spectrum Disorders. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2024 [updated 2022 Jun 16; cited 2025 May 16]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK84550/
2. Vakkilainen S, Taskinen M, Mäkitie O. Immunodeficiency in cartilage-hair hypoplasia: Pathogenesis, clinical course and management. Scand J Immunol 2020;92:e12913. https://doi.org/10.1111/sji.12913.
3. Riley P, Weiner DS, Leighley B, Jonah D, Morton DH, Strauss KA, et al. Cartilage hair hypoplasia: Characteristics and orthopaedic manifestations. Journal of Children's Orthopaedics 2015;9:145–52. https://doi.org/10.1007/s11832-015-0646-z.
4. Hall CM, Liu B, Haworth A, Reed L, Pryce J, Mansour S. Early prenatal presentation of the cartilage-hair hypoplasia / anauxetic dysplasia spectrum of disorders mimicking recurrent thanatophoric dysplasia. European Journal of Medical Genetics 2021;64:104162. https://doi.org/10.1016/j.ejmg.2021.104162.
5. Crahes M, Saugier-Veber P, Patrier S, Aziz M, Pirot N, Brasseur-Daudruy M, et al. Foetal presentation of cartilage hair hypoplasia with extensive granulomatous inflammation. European Journal of Medical Genetics 2013;56:365–70. https://doi.org/10.1016/j.ejmg.2013.04.004.
6. Khalil A, Pajkrt E, Chitty LS. Early prenatal diagnosis of skeletal anomalies. Prenatal Diagnosis 2011;31:115–24. https://doi.org/10.1002/pd.2676.
7. Chitty LS, Khalil A, Barrett AN, Pajkrt E, Griffin DR, Cole TJ. Safe, accurate, prenatal diagnosis of thanatophoric dysplasia using ultrasound and free fetal DNA. Prenatal Diagnosis 2013;33:416–23. https://doi.org/10.1002/pd.4066.

8. Dungan JS, Emerson DS, Phillips OP, Shulman LP. Cartilage-Hair Hypoplasia Syndrome: Implications for Prenatal Diagnosis. Fetal Diagn Ther 1996;11:398–401. https://doi.org/10.1159/000264353.
9. Pello E, Kainulainen L, Vakkilainen M, Klemetti P, Taskinen M, Mäkitie O, et al. Shorter birth length and decreased T-cell production and function predict severe infections in children with non–severe combined immunodeficiency cartilage–hair hypoplasia. Journal of Allergy and Clinical Immunology: Global 2024;3:100190. https://doi.org/10.1016/j.jacig.2023.100190.
10. Uchida N, Ishii T, Nishimura G, Sato T, Kuratsuji G, Nagasaki K, et al. *RMRP* -related short stature: A report of six additional Japanese individuals with cartilage hair hypoplasia and literature review. American J of Med Genetics Pt A 2024;194:e63562. https://doi.org/10.1002/ajmg.a.63562.
11. Gao J, Zheng J, Chen S, Lin S, Duan S. RMRP variants inhibit the cell cycle checkpoints pathway in cartilage-hair hypoplasia. Mol Med Rep 2025;31:81. https://doi.org/10.3892/mmr.2025.13446.
12. 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. Clinical Genetics 2002;61:146–51. https://doi.org/10.1034/j.1399-0004.2002.610210.x.
13. Gomes ME, Calatrava Paternostro L, Moura VR, Antunes D, Caffarena ER, Horovitz D, et al. Identification of Novel and Recurrent RMRP Variants in a Series of Brazilian Patients with Cartilage-Hair Hypoplasia: McKusick Syndrome. Mol Syndromol 2019;10:255–63. https://doi.org/10.1159/000501892.
14. Gomes ME, Kehdy F, De Neves-Manta FS, Horovitz DDG, Sanseverino MT, Leal GF, et al. Identification of a founder effect involving n.197C>T variant in RMRP gene associated to cartilage-hair hypoplasia syndrome in Brazilian patients. Sci Rep 2024;14:13436. https://doi.org/10.1038/s41598-024-64407-8.

FIGURE/VIDEO CAPTIONS

Figure 1 – Third child. Ultrasound assessment at 22 weeks. Short femur (<P5).

Figure 2 – Third child. Ultrasound assessment at 27 weeks. Small thorax dimensions.

Figure 3 – First child in early childhood. Short-limbed short stature. Genu varum.

Figure 4 – Second child as a toddler. Short-limbed short stature. Genu varum.

Figure 5 – Third child. Newborn in the delivery room. Asymmetric small for gestational age.

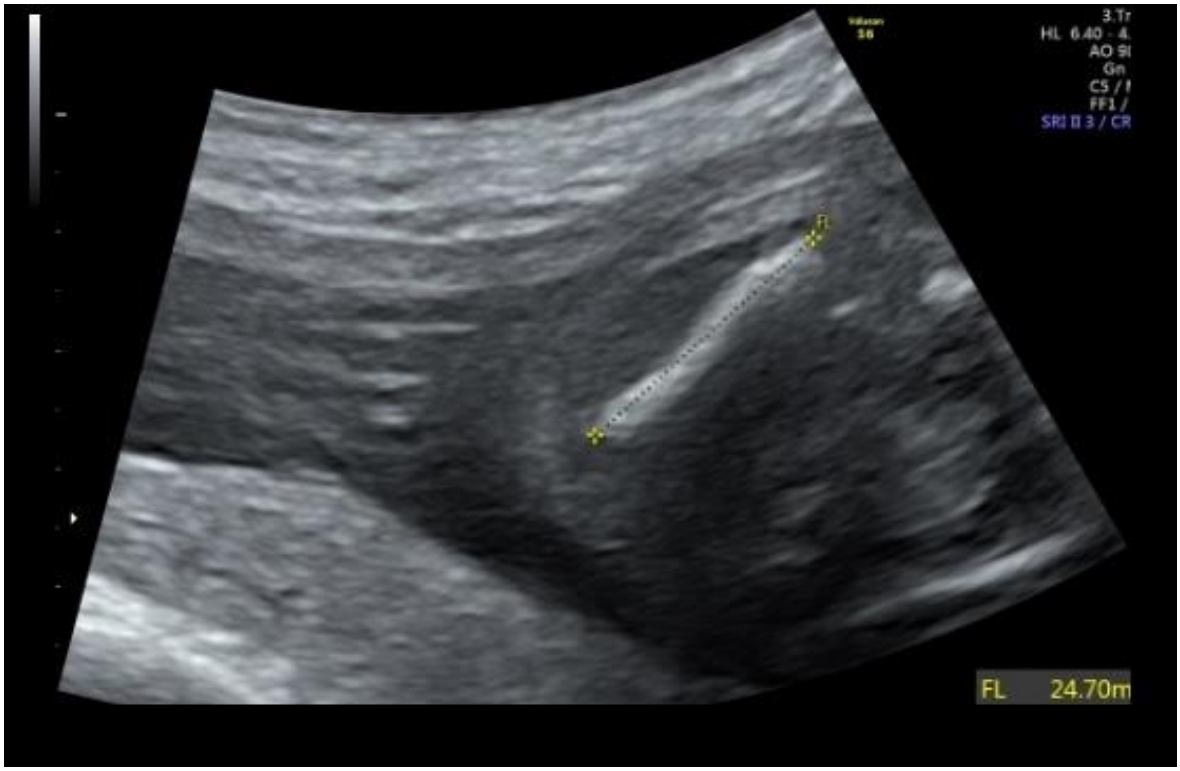


Figure 1 – Third child. Ultrasound assessment at 22 weeks. Short femur (<P5).



Figure 2 – Third child. Ultrasound assessment at 27 weeks. Small thorax dimensions.



Figure 3 – First child in early childhood. Short-limbed short stature. Genu varum.



Figure 4 – Second child as a toddler. Short-limbed short stature. Genu varum.



Figure 5 – Third child. Newborn in the delivery room. Asymmetric small for gestational age.

CHAPTER THREE

“Apresentação Pré-natal de Síndrome de Hipoplasia Cartilagem Cabelo: A Propósito de um Caso Clínico”

APRESENTAÇÃO PRÉ-NATAL DE SÍNDROME DE HIPOPLASIA CARTILAGEM CABELO

A PROPÓSITO DE UM CASO CLÍNICO

Andreia Lima Martins1, Catarina Carvalho2, Luísa Ferreira1,2, Luís Guedes Martins1,2
1-Centro Materno Infantil do Norte, Centro Hospitalar Universitário de Santo António; 2-Instituto de Ciências Biomédicas Abel Salazar

SÍNDROME DE HIPOPLASIA CARTILAGEM - CABELO

A **Hipoplasia Cartilagem Cabelo (HCC)** é uma doença genética rara, de hereditariedade autossómica recessiva, causada por mutações no gene RMRP. Trata-se de uma **displasia óssea** caracterizada por baixa estatura, hipotricose, variados graus de imunodeficiência, anemia e problemas gastrointestinais. A apresentação fenotípica e o prognóstico são bastante variáveis.

As primeiras manifestações ocorrem no **período pré-natal** com micromelia, encurvamento dos ossos longos e atraso de crescimento do tórax fetal. No entanto, o diagnóstico fetal é difícil, apresentando os achados ecográficos uma grande variedade de diagnósticos diferenciais.

CASO CLÍNICO

Grávida, 37 anos. 3G2P, 2 filhos com diagnóstico de HCC com confirmação molecular de heterozigotia composta para duas variantes patogênicas do gene RMRP (variantes deletérias n.196C>T. e n.-25dup).

Apesar do risco de recorrência de 25%, o casal planeou nova **gravidez espontânea.**
Em **ecografia** realizada às 20 semanas é detectado um **encurtamento significativo dos ossos longos (<P5),** sem outras alterações morfológicas aparentes.
Posteriormente, às 27 semanas, constata-se **tórax de dimensões reduzidas** para a idade gestacional. Embora possível e disponível, o diagnóstico pré-natal laboratorial não foi opção do casal.



Fig 1. Avaliação ecográfica às 22 semanas. Ossos longos curtos <P5 (fémur na imagem)



Fig 2. Avaliação ecográfica às 27 semanas. Tórax de reduzidas dimensões



Fig 3. Recém-nascido no bloco de partos. LIG assimétrico

A gravidez decorreu sem outras intercorrências. Foi realizada **cesariana eletiva** às 39 sem, que resultou num recém-nascido do sexo masculino, com 2465g, APGAR 7/9/9. Ao exame objetivo destacam-se **membros curtos, que condicionam um LIG assimétrico.** Foi realizada colheita de sangue do cordão umbilical para **teste genético,** para confirmação diagnóstica.

Teve alta hospitalar ao 11º dia de vida, com **bom estado geral e adequado aumento ponderal,** encaminhado para consulta externa de Neonatologia e Medicina Física e de Reabilitação por sinais de rigidez na extensão dos cotovelos e dificuldade na mobilização ativa e preensão da mão esquerda.

CONCLUSÕES

A **HCC** é uma **condição genética rara** na população portuguesa (1 em 200 000).

Está associada a **importantes comorbilidades**, exigindo uma **gestão em contexto multidisciplinar.** O **aconselhamento genético** revela-se particularmente importante, ajudando as famílias a compreender a **patologia e o seu prognóstico.**

A **ecografia obstétrica** representa um papel preponderante no seu diagnóstico, ao permitir uma **identificação precoce** de casos suspeitos e, de uma forma seriada, **avaliar o crescimento fetal**, com particular atenção ao desenvolvimento dos membros e tórax.

Referências:
1. OUTI MAKITIE; VAKKILAINEN, S. Cartilage-Hair Hypoplasia – Anauxetic Dysplasia Spectrum Disorders. Disponível em: <https://www.ncbi.nlm.nih.gov/books/NBK84550/>. Acesso em: 14 out. 2024 2. MAKITIE, O. Cartilage-hair hypoplasia in Finland: epidemiological and genetic aspects of 107 patients. Journal of Medical Genetics, v. 29, n. 9, p. 652–655, 1 set. 1992
3. RILEY, P. et al. Cartilage hair hypoplasia: characteristics and orthopaedic manifestations. Journal of Children's Orthopaedics, v. 9, n. 2, p. 145–152, 1 abr. 2015. 4. HALL, C. M. et al. Early prenatal presentation of the cartilage-hair hypoplasia / anauxetic dysplasia spectrum of disorders mimicking recurrent thanatophoric dysplasia. European Journal of Medical Genetics, v. 64, n. 3, p. 104162–104162, 7 fev. 2021. 5. DUNGAN, J. S. et al. Cartilage-Hair Hypoplasia Syndrome: Implications for Prenatal Diagnosis. Fetal Diagnosis and Therapy, v. 11, n. 6, p. 398–401, 1996.

CONCLUSION

The primary purpose of this dissertation was to address the topic of skeletal dysplasias and to raise awareness about the specific case of CHH. Despite being rare, this condition has an undeniable impact on those affected, requiring the need for a multidisciplinary support.
CHH can present early in the prenatal period and developing a standardized approach combining imaging and genetic testing may allow for early recognition and timely management.
The structure of this work is organized in three complementary chapters that aim to contribute to a scarcely explored area in the literature.
Reviewing the available information on the prenatal diagnosis of CHH as well as presenting the case of a Portuguese family with three children affected by it allowed for a better understanding of the condition, particularly regarding its presentation, diagnosis and clinical significance.
However, further research is needed, including studies with larger sample sizes, to more accurately characterize genotype-phenotype correlations and the underlying pathophysiological mechanisms.
In conclusion, it is hoped that this thesis encourages discussion around rare skeletal dysplasias, with the ultimate goal of improving healthcare responses to the specific needs of these patients and their families.

INSTITUTO DE **CIÊNCIAS BIOMÉDICAS ABEL SALAZAR**

