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Prenatal Diagnosis of Cartilage-Hair Hypoplasia: A Narrative Review

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

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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 pathogenic variants 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. This review aims 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 PubMed/MEDLINE database 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 skeletal dysplasias, 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 future studies addressing the prenatal diagnosis of skeletal dysplasias.
Keywords: Hair; Osteochondrodysplasias; Prenatal Diagnosis

RESUMO

A hipoplasia cartilagem-cabelo é uma displasia óssea rara, com hereditariedade 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 variantes patogénicas 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 doença. 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 na base de dados PubMed/MEDLINE 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 displasias ósseas, 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, pode 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: Cabelo; Diagnóstico Pré-natal; Osteocondrodisplasias

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 challenging to determine due to the condition's rarity and frequent underdiagnosis; however, in certain populations – such as the Finnish and the Old Order Amish – it has been reported at approximately 1 in 23 000 births and 1 - 2 in 1000 births, respectively.[2-4] It is caused by pathogenic variants in the *RMRP* gene, which encodes the RNA component of the mitochondrial RNA-processing endoribonuclease, involved in cell proliferation and differentiation.[2] Within the nosology of genetic skeletal disorders, CHH is classified among the metaphyseal dysplasias.[5] 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.[2,4,6] Fetal diagnosis is difficult, considering that the ultrasound findings resemble other skeletal dysplasias (SD). Some of the first prenatal manifestations include micromelia (shortening of all segments of the limbs), bowing of the long bones and delay in the thorax growth.[7-9] These abnormalities are most often detected during

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the second trimester; however, the timing of presentation varies in the literature.[2,4-7]

The purpose of this article is to review the current knowledge on the prenatal diagnosis of this condition, focusing on the available techniques, 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 the prediction of disease severity and support a multidisciplinary approach to address potential complications.

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. Imaging modalities such as magnetic resonance imaging (MRI) and computed tomography (CT) can also provide relevant information in selected cases. 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.[10] 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. The NGS technology also enables tests such as whole exome sequencing (WES) and whole genome sequencing (WGS).[10]

Some of these techniques could potentially be applied to CHH, which will be further discussed.

METHODS

To develop this narrative review, we performed a literature search in the PubMed/MEDLINE database. 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 yielded 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, 36 articles were included as shown in Fig. 1.

RESULTS

Molecular basis and clinical significance

To better understand the prenatal diagnostic approach of CHH, it is important to clarify its molecular basis and pathophysiology. Variants in the *RMRP* gene have been well established as the cause for this condition. So far, over 100 pathogenic variants have been identified, the most common of which being n.71A>G, which is especially prevalent in the Finnish population.[2,11] 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.[2,12,13] 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.[12,13]

Cartilage-hair hypoplasia integrates a spectrum that ranges from a milder phenotype, metaphyseal dysplasia without hypotrichosis (MDWH), to a more severe condition, anauxetic dysplasia (AD).[12] Short stature with varying degrees of metaphyseal dysplasia is the defining characteristic of this group of conditions. Metaphyseal dysplasia without hypotrichosis 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 spondylometaepiphyseal dysplasia without extra-skeletal manifestations.[7,12,14,15]

Variants in 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 promoter and the transcription start site, potentially reducing *RMRP* transcription.[2,12,13] Although some reported cases describe severe phenotypes, including homozygous promoter variants associated with chondrodysplasia and severe immunodeficiency, variability has also been observed and promoter variants alone do not account for the full spectrum of disease manifestations.[2,12,16,17]

The second group, which mostly consists of variants 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.[2,12,13]

Interestingly, variants 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 severity of skeletal manifestations.[4,12] Conversely, variants 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.[2,12,15,17]

The pathophysiological mechanisms of CHH are still not entirely understood but relevant advances have been made in recent years. In 2019, a study conducted by Vakkilainen *et al*[18] 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 PI3K-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* pathogenic variants have a significant impact on the cell cycle network, which may be the basis for the clinical manifestations observed in CHH.[18]

Another study from 2019 developed a zebrafish model to study the mechanisms underlying CHH, since there are currently no viable animal models and zebrafish 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.[11]

Role of prenatal imaging

Ultrasonography constitutes the primary screening method for SD with prenatal presentation. Its sensitivity varies in the literature but is estimated to be between 40% and 60%.[19-21] The main hallmark of most SD on ultrasound, including CHH, is short long bones, especially if disproportionate to head circumference.[20] Ossification of the appendicular skeleton occurs around 12 weeks of gestation, which could allow suspicion of SD in the first trimester, although in most entities, abnormalities are only detected later in pregnancy. An earlier presentation usually correlates with a more severe phenotype.[19,21] The presence of long bone length below the 5th percentile in the second trimester warrants further investigation, and additional features such as bowing or suspected fractures may also suggest a SD, even with normal bone length.[19,20]

Ultrasound is particularly relevant for assessing lethality risk. Several predictors have been described in the literature, with different sensitivity rates.[19-21] 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.[20] Additional factors include femur length-to-biparietal diameter ratio, micromelia more than three standard deviations below the mean, the presence of polyhydramnios or hydrops, abnormal bone mineralization, and marked bowing or fractures.[19,21] Of note, linear femur measurements may be affected by bowing which could lead to inaccurate estimates of true femur length.[21]

SD lethality seems to correlate more with pulmonary hypoplasia resultant from small chest circumference than with limb shortening.[20,21] Therefore, fetal lung volumes and chest-to-abdominal circumference ratio are important to assess the risk of lethal pulmonary hypoplasia.[19] However, some SD, such as osteogenesis imperfecta type IV or achondroplasia, may present with a small thorax but are not invariably lethal. In such cases, neonatal respiratory compromise may still occur, requiring close monitoring.[19,20]

Ultrasound may also reveal additional findings, such as facial abnormalities, malformed digits or vertebral anomalies, that help distinguish 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.[19,21]

Phenotypical variability is a characteristic of CHH and it can be noted even in the prenatal period. Abnormalities have been reported as early as 12 and 15 weeks of gestation[7,22], others only toward the end of the third trimester[6,17] and some are only detected after birth.[15,23,24]

Hall *et al*[7] reported a case series in 2021 of three sibling fetuses presenting at 12 weeks with abnormal ultrasound findings. The parents were healthy, non-consanguineous, and had a healthy daughter. Thoracic and abdominal circumferences were in the 5th percentile, and long bones were below the 5th percentile and bowed. Increased nuchal translucency was also noted. The pregnancy was terminated due to suspicion of severe skeletal dysplasia and poor prognosis, despite normal chromosomal testing. Postmortem radiographs and autopsies confirmed bowed, shortened long bones, as well as

a small thorax with mild rib shortening. Additional findings included trident-shaped acetabula, narrow sacrosciatic notches and flattened vertebral bodies. Thanatophoric dysplasia (a severe and typically lethal skeletal dysplasia) was suspected, but genetic testing revealed pathogenic *RMRP* variants instead, consistent with CHH diagnosis.[7]

Crahes *et al*[14] describe another case of a couple with two healthy children, in whom routine ultrasound during their third pregnancy showed findings consistent with a SD. Marked limb shortening was detected at 23 weeks of gestation and mild macrocrania at 26 weeks. *FGFR3* testing for achondroplasia was negative. At 31 weeks, ultrasound confirmed bowed femora with absent bone growth. Termination of pregnancy was carried out due to suspected severity of the condition and an autopsy was performed. In addition to confirming bilateral rhizomelic (proximal) limb shortening, post-mortem findings revealed thymic hypoplasia with immune dysfunction, which pointed towards CHH. Pathogenic *RMRP* variants were identified through genetic analysis, confirming the diagnosis.[14]

The case described by Dungan *et al*[8] illustrates that in families with a previous child affected by CHH, ultrasound may allow recognition of recurrence in subsequent pregnancies. While this case was reported before the widespread use of molecular diagnostics, ultrasound still represents the first tool to raise suspicion, with genetic testing subsequently enabling confirmation when a familial variant has been identified.[8]

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 aid in the differential diagnosis of SD with distinctive craniofacial features.[19,20] Fetal MRI may provide greater accuracy than ultrasound in fetal morphological assessment and is considered safe for both fetus and mother.[25] It may be useful for fetal spine evaluation in suspected vertebral malformations and for assessing lung volumes, particularly when findings are inconclusive or in late pregnancy.[20,21] Gilligan *et al*[26] 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.[26]

In contrast, *in utero* radiographs do not offer any advantage in prenatal SD diagnosis and require unnecessary exposure to radiation.[19] Nevertheless, in the postnatal setting, X-rays remain, along with genetic testing, the gold standard for CHH diagnosis.[4]

Despite also involving ionizing radiation, low-dose CT has been reported in the literature in the context of SD, as a potential tool to improve diagnostic accuracy, due to higher skeletal resolution.[19,27] In one prospective study, it correctly 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.[27] Low-dose CT has also been reported as a complement to ultrasound in cases of achondroplasia and hypochondroplasia, among other skeletal dysplasias.[28]

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 fails to reach a diagnosis in almost half of the SD cases.[19-21] Its accuracy in the context of CHH has not yet been established. Genetic testing enables definitive CHH confirmation, through identification of pathogenic *RMRP* variants. The approach differs depending on whether the variant has already been detected in the family.

In some settings, particularly among consanguineous couples, expanded carrier screening for recessive disorders may be considered. In CHH, once the familial *RMRP* variant is identified, carrier testing of at-risk relatives and reproductive partners is also possible.[4]

In the cases described by Hall *et al*[7] the diagnosis was confirmed post-mortem through WES of fetal tissue from the second affected fetus, followed by targeted Sanger sequencing of the previously identified *RMRP* variant in the other siblings and parents. Crahes *et al*[14] also confirmed the diagnosis post-mortem through *RMRP* sequencing.

When a familial variant is known, invasive prenatal diagnosis can be offered in subsequent pregnancies.[9] Vatanavicharn *et al*[17] identified *RMRP* pathogenic variants after birth in a child with CHH, who died at 23 months. In a subsequent pregnancy, chorionic villus sampling at 14 weeks enabled targeted DNA sequencing for the previously identified variant, which confirmed that the fetus was unaffected. Ultrasound at 18 weeks showed normal morphology, and the pregnancy progressed uneventfully, resulting in the birth of a healthy child.[17] In other cases, parents may decline invasive testing in the prenatal period, opting to await postnatal confirmation.[22]

The literature regarding prenatal genetic testing in SD cases arising in the absence of family history, but 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.[29] Jian *et al*[30] analyzed 147 fetuses with suspected SD, using CMA, followed by WES in CMA-negative cases. Whole exome sequencing achieved a 36.2% detection rate, with thanatophoric dysplasia, achondroplasia and osteogenesis imperfecta being the most common diagnoses.[30] In another study where medical trio exome sequencing was performed, these were also the conditions most frequently identified, and a definite molecular diagnosis was accomplished in 24 out of the 27 fetuses evaluated.[31]

Non-invasive prenatal screening, widely studied for chromosomal abnormalities, is increasingly applied to single-gene disorders through cell-free fetal DNA.[10,32] In the context of SD, it has been shown to provide definitive prenatal diagnosis of thanatophoric dysplasia and achondroplasia, as both are associated with recurrent *FGFR3* mutations that can be specifically targeted in cell-free DNA analysis.[19,33,34] However, this approach has not yet been explored for CHH.

DISCUSSION

Cartilage-hair hypoplasia is a rare skeletal dysplasia caused by pathogenic variants 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 phenotypes presented.[11-13,15,17,18] Variants may impact the promoter 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.[2,12,13,15,17]

Although CHH has no cure, establishing a definitive diagnosis is essential to ensure adequate multidisciplinary follow-up and surveillance, and characterizing its molecular basis might open potential therapeutic targets, as suggested by Sun *et al.*[11]

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.[6-8,14,17,22] As reported by Hall *et al*,[7] 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.[19,21] However, unlike lethal SD, CHH may also be identified early in pregnancy and remain compatible with postnatal survival.[8,22]

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.[19-21] This is particularly relevant in CHH, since patients often present with bowed femora and should therefore be carefully assessed to avoid misdiagnosing disease severity.[3,21] A small thorax and subsequent pulmonary hypoplasia are also commonly referenced in the literature as major lethality predictors.[19-21] Nevertheless, it is important to note that CHH is among the non-lethal SD that can also present with a small rib cage.[8]

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.[19-21,25-28]

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

Cartilage-hair hypoplasia prenatal genetic testing is scarcely explored in the literature. When a familial causal variant is known, targeted testing can be performed through invasive methods in subsequent pregnancies to assess potential recurrence.[9,17] When ultrasound suggests features compatible with SD, the priority is to rule out lethal conditions, such as thanatophoric dysplasia and osteogenesis imperfecta type II.[19,35] Next-generation sequencing panels that include the *RMRP* gene, WES or WGS may be able to identify *RMRP* pathogenic variants, but the role of molecular testing in the prenatal period is still debated.[19] Savarirayan *et al*[19] argued that these comprehensive tests could have long turnaround times and that results might not be available before delivery. However, with recent technological advances, results can now be obtained much faster, reducing this limitation. In non-lethal conditions such as CHH, it may still be reasonable to defer testing to the postnatal period, when sampling can be performed with lower risk compared to invasive prenatal procedures.[19,31]

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.[36] Given that the *RMRP* gene encodes a non-coding RNA and that variants 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. Moreover, coverage of the *RMRP* locus can be suboptimal in WES, NGS panels, and carrier screening tests, which may explain reported diagnostic failures.[29-31] 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.[19,32]

The proposed diagnostic algorithm (Fig. 2) outlines a prenatal approach to CHH suspicion, depending on whether *RMRP* pathogenic variants are known. If there is a 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 femora, 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.

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AUTHOR CONTRIBUTIONS

CPC: Drafting of the manuscript, conducted the literature review.
IA, CL: Critical review of the manuscript.
LGM: Study design, critical review of the manuscript.
All authors approved the final version to be published.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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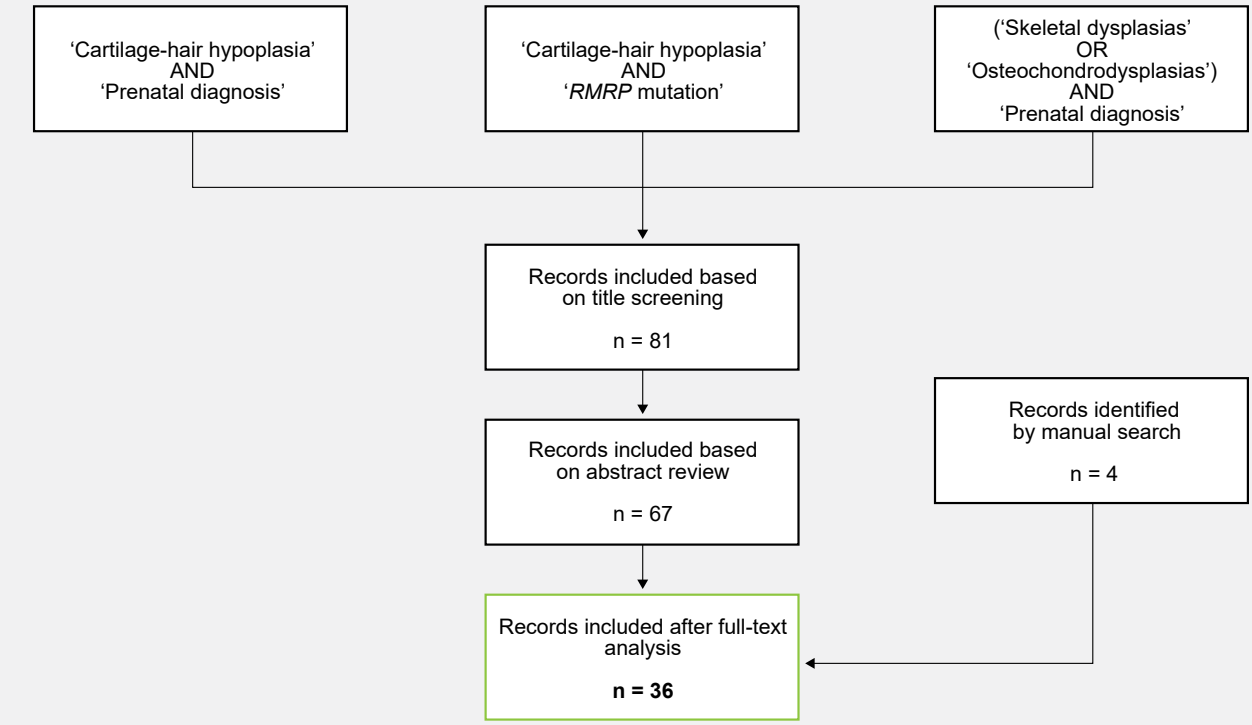

Figure 1 – Simplified article selection flowchart

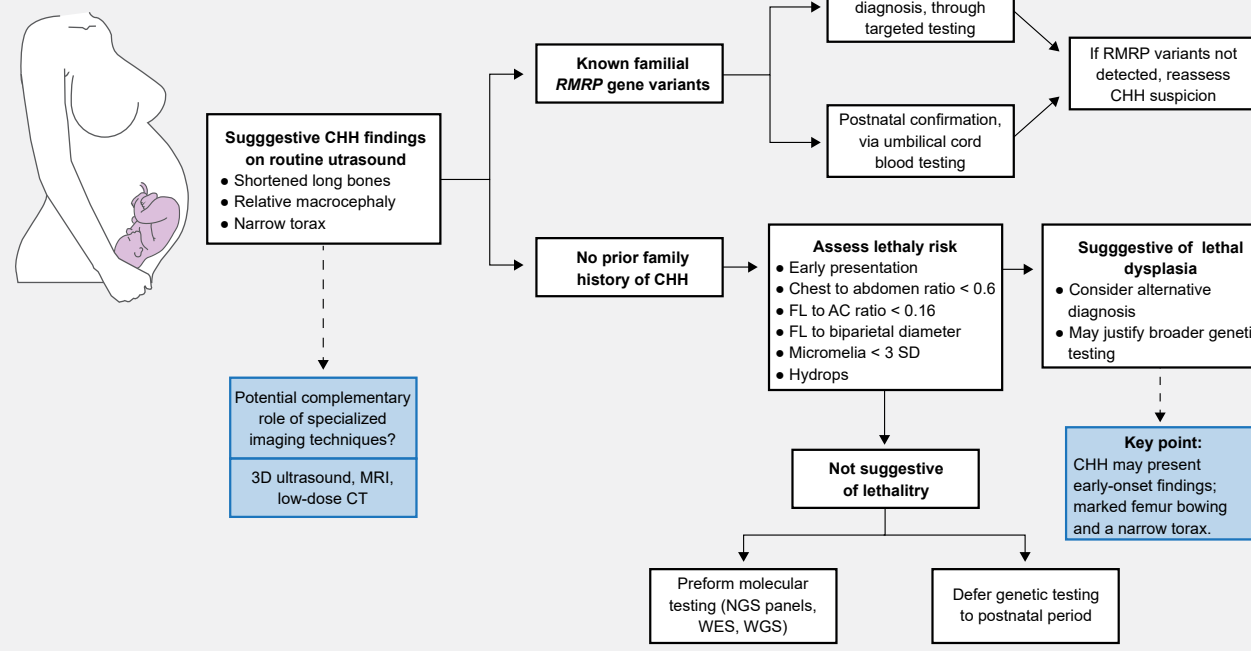

Figure 2 – Diagnostic approach for prenatal CHH evaluation

AC: abdominal circumference; CHH: cartilage-hair hypoplasia; CT: computed tomography; FL: femur length; MRI: magnetic resonance imaging; NGS: next-generation sequencing; SD: standard deviation; WES: whole exome sequencing; WGS: whole genome sequencing; 3D: three-dimensional.