# Cartilage-hair hypoplasia: molecular basis and heterogeneity of the immunological phenotype

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**Purpose of review**

To report on the expanding clinical and immunological spectrum associated with ribonuclease mitochondrial RNA-processing mutations and to review the cellular and molecular mechanisms involved in the pathophysiology of cartilage-hair hypoplasia (CHH) and related disorders in humans.

**Recent findings**

Different types of mutations are associated with skeletal or extraskeletal manifestations of CHH, respectively. In particular, severe immunodeficiency is mostly associated with mutations that alter cyclin B2 mRNA cleavage and thus are likely to reflect disturbances in cell cycle control. The first cases of ribonuclease mitochondrial RNA-processing mutations with severe immunodeficiency, but no skeletal abnormalities, have been identified.

**Summary**

Abnormalities of ribosome biogenesis have been shown to cause distinct bone marrow failure syndromes, including CHH. However, the specific role of ribosomal and extraribosomal defects in the pathophysiology of the various phenotypic features of CHH remains undefined. Development of suitable animal models is needed to address this important issue.

**Keywords**

cartilage-hair hypoplasia, cell cycle, immunodeficiency, Omenn syndrome, ribonuclease mitochondrial RNA processing

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## Introduction

Cartilage-hair hypoplasia [CHH; Mendelian Inheritance in Man (MIM) 250250] is an autosomal recessive form of metaphyseal chondrodysplasia, variably associated with extraskeletal features, including immunodeficiency [1,2]. In 2001, it was established that CHH is due to mutations in the ribonuclease mitochondrial RNA-processing (*RMRP*) gene, encoding for the 267-nucleotide-long RNA component of the mitochondrial RNA-processing endonuclease [RNase mitochondrial RNA processing (MRP)], a multiprotein RNA complex involved in ribosomal RNA (rRNA) cleavage, processing of mitochondrial RNA primers, and cleavage of cyclin B2 mRNA [3]. Here, we review recent data that may help explain the basis of the phenotypic heterogeneity of CHH, including variability of immunological impairment.

## The spectrum of clinical manifestations associated with mutations in the *RMRP* gene

Mutations of the *RMRP* gene in humans have been associated with four distinct skeletal disorders: CHH (also known as metaphyseal dysplasia, McKusick type), metaphyseal dysplasia without hypotrichosis (MDWH; Mendelian Inheritance in Man, MIM 250460), kyphomelic dysplasia (MIM 211350) and anauxetic dysplasia (MIM 607095) [4,5••,6]. These disorders differ both in the severity of the associated skeletal abnormalities and in the frequency of other extraskeletal defects.

Originally described in 1965 in the Amish population [1], CHH was later identified in multiple ethnic groups and is particularly frequent among the Amish and the Finns, with a carrier frequency of 1:19 and 1:76, respectively [2]. Short-limbed dwarfism and light-colored hypoplastic hair are the phenotypic hallmarks of CHH; however, additional features, such as a variable degree of impairment of cellular immunity, bone marrow dysplasia, Hirschsprung disease and predisposition to malignancies, have been reported in a sizeable proportion of patients [4,5••,7,8]. Short stature is present also in MDWH, kyphomelic dysplasia and anauxetic dysplasia and is particularly severe in the latter, in which hypodontia and mild mental retardation are also present. In contrast, kyphomelic dysplasia is characterized by flattened vertebrae, short ribs and mild facial dysmorphisms, in addition to short stature. Apart from skeletal abnormalities, there is considerable heterogeneity in the


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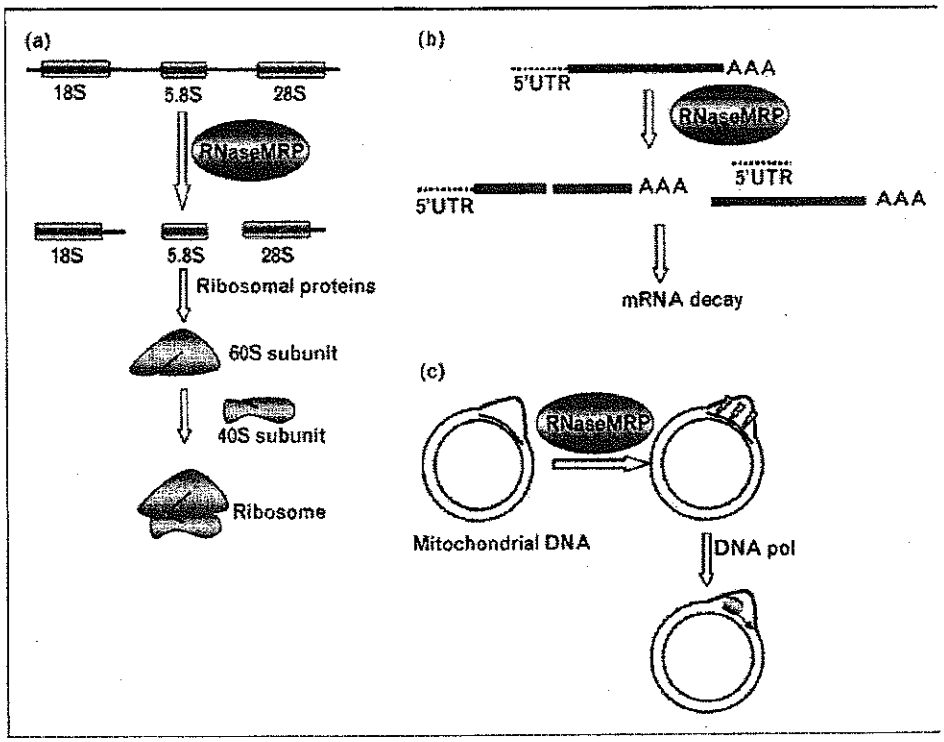
prevalence of other clinical features among CHH, MDWH, kyphomelic dysplasia and anauxetic dysplasia. In particular, neither immunodeficiency nor hair abnormalities have ever been reported in MDWH, whereas combined immunodeficiency and aplastic anemia are common in kyphomelic dysplasia [9••]. Although the mechanisms underlying such phenotypic heterogeneity have remained obscure for many years, recent evidence indicates that distinct mutations in the *RMRP* gene may affect differently the function of the RNase MRP multiprotein complex, thus providing the basis for a genotype–phenotype correlation [5••,9••].

## Structure and function of RNase mitochondrial RNA processing

The RNase MRP ribonucleoprotein complex is composed of the RNA component and at least 10 associated proteins (hPOP1, RPP29, hPOP5, RPP14, RPP20, RPP21, RPP25, RPP30, RPP38, RPP40). RNase MRP is evolutionarily highly related to RNase P, but these complexes have functionally diverged: RNase P has a role in transcription, as well as in 5′-end maturation of tRNA and RNA processing [10,11], whereas RNase MRP is mainly located in the nucleolus in which it participates in ribosomes' biogenesis by performing the endonucleolytic cleavage of the rRNA that ultimately leads to generation of mature 5.8S rRNA (Fig. 1a). In addition, RNase MRP processes mitochondrial RNA primers (an essential step to activate mitochondrial DNA replication) and participates in cell cycle control by cleaving cyclin mRNA [11,12] (Fig. 1b, c). At least eight out of the 10 proteins that compose the RNase MRP complex are also part of the RNase P complex in eukaryotes [13•,14•].

Because of considerable conservation between RNase P and RNase MRP, the structure and function of the much more studied RNase P domains have been derived to RNase MRP, in particular to model the catalytic domain and several protein-binding regions. Of particular interest are the regions that surround the supposed catalytic core (junctions between P1 and P2 and between P4 and P1 regions) and the eight nucleotides that are invariably conserved in all different species in which the gene has been sequenced. Among these nucleotides, four nucleotides (nucleotides 70, 71, 74, 75) are crucial for intramolecular nucleotide pairing. The P3 region is involved in nucleolar localization of the complex and in binding to hPOP1, Rpp20 and Rpp25 [15•,16•], whereas the P12 region (nucleotides 120–176) is involved

**Figure 1 Functions of the RNase mitochondrial RNA-processing complex**




(a) Endonucleolytic cleavage of the rRNA that ultimately leads to generation of mature 5.8S rRNA and to ribosome biogenesis; (b) cleavage in the 5′UTR or mRNA, leading to mRNA decay; and (c) cleavage of mitochondrial RNA in order to produce primers for DNA replication.

in RPP38 binding and is evolutionarily conserved among vertebrates [17•].

Despite strong evidence for structural evolutionary conservation, *RMRP* is a highly polymorphic gene, and more than 20 different nucleotide changes or insertions have been reported (almost 10% of the entire length of the transcript). It has been hypothesized that these polymorphisms may play a role as disease modifiers, though no studies have been conducted to analyze their effect on the structure and function of the RNase MRP complex [5••,18,19].

In contrast, more than 60 different disease-causing *RMRP* mutations have been described [5••,6,9••,19–25,26•]. The mutations are located both within the promoter and in the transcribed sequence, and, in most cases, they affect highly conserved residues [6]. The most common mutation is a g.70 A>G nucleotide substitution. The overrepresentation of the mutation is partly due to its recurrence in genetic isolates such as the Amish and the Finnish populations, and a founder effect, that took place between 3800 and 4900 years ago, has been established. In the general CHH population, the g.70 A>G mutation is observed in 30–48% of the cases [2,19].

Recent studies have shed some light on the mechanisms by which *RMRP* mutation affects the structure and the function of this complex. In many cases, mutations cause instability and rapid decay of the mRNA [26•]. The g.70A>G mutation affects one of the invariant nucleotides located in the hypothetical catalytic domain, with obvious effects on the function; in addition, the mutated *RMRP* mRNA is extremely unstable [26•]. Mutations in the P3 region (that interacts with Rpp25 and Rpp20) alter folding of the P3 hairpin and drastically impair protein binding [27•].

Mutations in the promoter region of *RMRP* are relatively common. In most cases, they are represented by insertions or duplications of variable length in the region between the TATA box and the transcription initiation site. These mutations reduce the efficiency of the interaction between RNA polymerase III and the *RMRP* gene and thus drastically decrease the transcription efficiency [18]. Interestingly, homozygosity or compound heterozygosity for mutations in the promoter region of RMRP has not been reported in the literature, leading to hypothesize that complete loss or drastic reduction of *RMRP* transcription could be lethal. In keeping with this, homozygous deletion of the homologous gene in yeast is lethal. However, we have recently identified the first patient in which compound heterozygosity for deleterious mutations in the promoter region of RMRP was compatible with life, and resulted in combined immunodeficiency [28].

The observation that most disease-causing mutations (either located in the transcribed region or in the promoter region of the gene) alter *RMRP* RNA levels has led to postulate that reduced amounts of *RMRP* RNA, albeit of normal structure (as in promoter region mutations), are more deleterious than having normal amounts of structurally abnormal *RMRP* RNA [6].

As previously mentioned, *RMRP* defects account for different etiological entities, some of which are more severe, such as anauxetic dysplasia. Mutations leading to this disease have been shown to be different from the ones associated with other phenotypes and are clustered in a region that is presumably involved in rRNA cleavage, as this function is absolutely impaired, whereas it is less affected in patients with CHH, in which severe impairment in cyclin mRNA cleavage has been reported [5••,20]. In the attempt to analyze the molecular basis of CHH phenotypic spectrum, Bonafé *et al.* [6] have divided their cohort of 36 patients into three groups: those with short stature and skeletal manifestations only; those with short stature and severe immunodeficiency or anemia or both; and those with both skeletal and extra-skeletal manifestations, but in which immunodeficiency or hematological abnormalities or both were mild or subclinical. They found that the severity of skeletal manifestations did not correlate with the severity of extra-skeletal abnormalities. More recently, Thiel *et al.* [5••] have shown that decreased levels of rRNA cleavage are associated with severe bone dysplasia, whereas deficiency in mRNA cleavage and thus in cell cycle progression is more correlated with immunodeficiency and cancer proneness.

In spite of the advances in the biochemical and structural characterization of the RNase MRP complex, the molecular pathophysiology of human disorders associated with *RMRP* mutations remains poorly defined. One of the major limitations in understanding the basis of these disorders is a product of the lack of animal models. Attempts to generate *RMRP*-deficient mice have failed. Recently, the murine ortholog of the human g.70A>G mutation has been successfully introduced into embryonic stem cells, generating heterozygous embryonic stem cells. In these cells, the mutant transcript was underrepresented (20–30%) as compared with wild-type transcript [26•], in keeping with the knowledge that this mutation reduced *RMRP* mRNA stability.

## The immunological spectrum associated with ribonuclease mitochondrial RNA-processing mutations

Patients with CHH may present a variable degree of immunodeficiency, which predominantly affects T-cell-mediated immunity [7,29,30]. Reduced number of

T lymphocytes, impaired in-vitro proliferative responses to mitogens and decreased in-vivo delayed hypersensitivity have been documented in more than 80% of the patients [29–31]. Although humoral immunity has been often considered to be normal in CHH, deficiency of IgA and of IgG subclasses has been described by Mäkitie *et al.* [30] in seven out of 35 prospectively followed patients. Altogether, impairment of cell-mediated immunity may account for the reported increased risk of severe varicella and of malignancies (especially non-Hodgkin's lymphoma) [1,32], whereas antibody deficiencies may contribute to recurrent upper and lower respiratory tract infections among patients with CHH [7].

Toivianen-Salo *et al.* [33] have recently shown that patients with CHH are also at higher risk for bronchiectasis. In particular, they demonstrated bronchiectasis in eight out of 15 CHH patients (79 and 71% of which had impairments of cell-mediated and of humoral immunity, respectively). As compared to the general CHH population, patients with bronchiectasis tended to have more severe growth abnormalities and more significant defects of humoral immunity.

However, when considering the nature and the significance of immunological abnormalities in CHH, two important considerations have to be taken into account. Firstly, studies of immune function in relatively large cohorts of patients with CHH have been performed only in the Finnish population and thus mostly pertain to patients with the common g.70A>G mutation. Furthermore, there is growing evidence that the spectrum of immunological phenotypes associated with *RMRP* mutations is much broader than originally thought. In particular, some affected individuals have been shown to present with severe combined immune deficiency (SCID) [3,34,35]. In addition, we have previously reported two patients in whom *RMRP* mutations were associated with Omenn syndrome, a combined immunodeficiency characterized by generalized erythroderma, lymphadenopathy, failure to thrive and eosinophilia, associated with the presence of autologous, oligoclonal, activated and poorly functioning T lymphocytes that infiltrate target organs and cause autoimmune-like severe manifestations [24,35]. It is of interest that autoimmunity (hemolytic anemia, neutropenia, hyperthyroidism) has been recently reported in other patients with CHH [6], raising the possibility that the effects of *RMRP* mutations on the immune system may also include immune dysregulation.

More recently, we have identified a series of patients that expand further the spectrum of immunological phenotypes associated with *RMRP* mutations to include selective CD8 lymphopenia and even combined immune deficiency without skeletal abnormalities [28]. The latter observation is in keeping with previous data that indicated lack of correlation between the severity of skeletal and extraskeletal manifestations associated with *RMRP* mutations [6]. Hematopoietic cell transplantation (HCT) has resulted in successful immune reconstitution in CHH patients who present with SCID or with Omenn syndrome [34–36].

The heterogeneity of immunological abnormalities associated with *RMRP* mutation has been confirmed by several authors [5••,6,19]. As reported above, it appears that immunodeficiency and bone marrow dysfunction are more common and more severe among patients who carry *RMRP* mutations that lead to diminished cyclin B2 mRNA cleavage [5••]. Importantly, these mutations are also associated with milder skeletal phenotypes.

Little is known on the cellular and molecular mechanisms involved in immune dysfunction in CHH. Castigli *et al.* [37] showed that the impaired in-vitro lymphocyte proliferation is associated with reduced secretion of IL-2 and IFN-γ and with defective expression of IL-2 receptor α. The proliferative defect could not be rescued by either addition of exogenous IL-2 or by stimulation with phorbol myristate acetate and ionomycin, agents that bypass receptor-mediated signaling. Similar results were also reported by Kooijman *et al.* [38] who found that CHH patients have a reduced number of naive ($CD45RA^+$) T lymphocytes. Yel *et al.* [39] studied one patient with CHH and showed that increased apoptosis of circulating T lymphocytes was associated with increased expression of Fas and Fas ligand (FasL) and of the proapoptotic molecule Bax, whereas expressions of the antiapoptotic molecules bcl-2 and inhibitory of apoptosis (IAP) were reduced. As mentioned above, *RMRP* immunodeficiency-causing mutations compromise cyclin B2 mRNA cleavage and may therefore result in increased levels of cyclin B2. Overexpression of this molecule leads to accumulation of cells in late mitosis and contributes to chromosomal instability [40,41]. However, a detailed analysis of cell cycle in lymphocytes from patients with CHH is still lacking.

To what extent the cell-mediated immunodeficiency of CHH reflects defects in thymic development or in peripheral lymphocyte function or in both remains to be determined. The patients reported to suffer from CHH associated with Omenn syndrome had oligoclonal T cells and their thymus was dysplastic, with complete loss of corticomedullary demarcation and lack of Hassall's corpuscles [24]. More recently, we have used levels of T-cell receptor excision circles (TRECs) as a measure of thymic output in patients with *RMRP* mutations and combined

immunodeficiency: out of five patients studied, four had very low levels of TRECs already at diagnosis, whereas another patient started with normal TREC levels, that however became undetectable within few years, paralleling deterioration of immune function [28]. In any case, the observation that HCT can normalize TREC levels [35] indicates that the SCID phenotype potentially associated with *RMRP* mutations reflects lymphoid-intrinsic (or hematopoietic or both)-intrinsic defects rather than abnormalities of thymic epithelium.

The observation that CHH may associate with immune deficiency and hematological abnormalities has led to search for *RMRP* mutations in patients with bone marrow failure syndromes. However, analysis of 108 consecutive patients with aplastic anemia has failed to disclose association with *RMRP* mutations [25].

## Conclusion

In the last years, mutation analysis has shown that the spectrum of clinical and laboratory phenotype associated with *RMRP* gene defects is broader than originally thought. Although the severity of skeletal manifestations does not correlate with that of extraskeletal features, the first cases of severe immunodeficiency due to *RMRP* mutations without short stature or skeletal involvement have been observed. Immunodeficiency of CHH is more common and severe in patients carrying mutations that affect cyclin B2 mRNA cleavage, yet the precise molecular and cellular mechanisms of immune impairment remain poorly defined. Importantly, three bone marrow failure syndromes (CHH, Diamond–Blackfan anemia and Shwachman–Diamond syndrome) have been recently shown to result from defects in ribosome biogenesis [42•], yet the mechanisms underlying the different aspects of these diseases remain unknown. Development of suitable animal models is needed to better characterize the pathophysiology of CHH, including its variable immunodeficiency.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 590–591).


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