Cancer Prone Disease Section
Review

Cartilage-hair hypoplasia (CHH)
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Identity
Other names: Metaphyseal chondrodysplasia, McKusick type
Inheritance: Autosomal recessive.

Clinics
Note: CHH was first described in the Amish, an isolated religious group in the USA by Victor McKusick in 1965. It is a multi-systemic disorder characterized by short stature, blond fine sparse hair, but this may be quite variable, and defective cellular immunity predominantly affecting T-cell mediated responses. Patients may have severe combined immunodeficiency, requiring bone marrow transplantation or they may be asymptomatic. Gastrointestinal dysfunctions are frequently observed such as mal-absorption or Hirschsprung¹s disease.

The incidence of CHH in the Amish is 1.5 in 1,000 births, whereas in Finland it is 1 in 18,000 to 23,000 live births.

Phenotype and clinics
The metaphyses of tubular bones are widened, scalloped and irregularly sclerotic. Delayed ossification and trabeculation of the long bones are also characteristic findings on X-rays. All long bones are affected. The relative length of the humerus, ulna, radius, tibia and fibula decreases rapidly in early childhood and again at puberty. Relatively short and broad phalanges of the hands are observed.

Neoplastic risk
A predisposition to certain cancers primarily lymphomas has been reported.

Treatment
- Disproportionate short stature: Treatment with growth hormone is likely not beneficial in children with CHH. Surgical bone lengthening is occasionally considered.
- Orthopedic problems: The lumbar lordosis and ligamentous laxity can cause joint pains of the lower spine, the knees and ankles.
- Immunodeficiency: The cellular immunity may be defective whereas the humoral immunity is usually intact. However, there are a few cases that have combined immune deficiency.
- Vaccination: immunization with live vaccines is contraindicated in patients with impaired cellular immunity.
- Anemia: Patients with severe anemia (5% of CHH patients) require repeated transfusions. A few cases might need lifelong transfusions and/or bone marrow transplantation.
- Gastrointestinal dysfunction: This can present with signs of malabsorption, diarrhea, celiac disease, and failure to thrive. This requires symptomatic treatment. It also may present as Hirschsprung¹s disease that can be surgically corrected.
- Malignancies: Patients should be monitored closely, since they have a higher risk of developing lymphomas and leukemias.

Prognosis
Adult height ranges between 111 and 151 cm in males and between 104 and 137 cm in females. No more than 20% of CHH patients exhibit recurrent and severe infections. These patients show evidence of immune deficiency in vivo and in vitro.
**Genes involved and Proteins**

**Note:** CHH is mainly caused by mutations in the RMRP gene, but a Uniparental Disomy of 9p13 has been reported as well in one CHH patient.

**RMRP (RNA component of Mitochondrial RNA-Processing endoribonuclease)**

**Location:** 9p13

**DNA/RNA**

RMRP is the RNA component of the RNase MRP protein complex. It functions as an RNA and is not translated into a protein.

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- The RMRP gene is an intronless gene, that is 267 bp long (blue). The promoter region contains a SP1 binding site (violet), an octamer (olive green), a proximal sequence element (PSE) (turquoise) and a TATA box (red).
- Transcription: In vitro analysis of the RMRP promoter revealed that the four described promoter elements are sufficient for RMRP transcription. It is transcribed by the DNA dependent RNA polymerase III and is encoded in the nucleolus. The complex is localized primarily in the nucleolus and to a lesser extend in the mitochondria. Studies in yeast revealed multiple functions of this protein complex. RNase MRP is involved in mitochondrial DNA replication by cleaving the RNA primer starting mitochondrial replication and is also involved in the RNA primer formation itself. In addition it plays a role in cell cycle progression at the end of mitosis. RNase MRP cleaves the 5’ UTR of the CLB2 gene thus causing a rapid CLB2 degradation, which leads to a cell cycle progression. If CLB2 is not cleaved cell cycle will be arrested. The best understood function is its processing of pre-ribosomal RNAs. It cleaves the pre-ribosomal RNA at the A3 site thus helping in the maturation of the short and active form of the 5.8S rRNA.
Protein
Expression: Strong ubiquitous expression in mouse embryos (E9.5 to E18.5 have been tested) and in adult animals. In bone Rmrp is more strongly expressed in hypertrophic chondrocytes and perichondrium than in the zone of proliferating chondrocytes. There is also very strong expression in the epiphysis.

Function: The RNase MRP complex is highly conserved among a variety of different species (human, mouse, rat, cow, frog, yeast and plants).

Homology
The functional analysis of the RNase MRP endoribonuclease is complicated by the fact, that eight proteins are shared by a related ribonucleoprotein complex, called RNase P. RNase P is also a ribonucleoprotein endoribonuclease and is mainly involved in rRNA precursor maturation.

Mutations
The most frequently found mutation among CHH patients is a 70 A to G transition mutation with an ancient founder origin established in Finland, a country where the disorder is uncommonly frequent. In fact it is the only mutation found in Amish CHH patients. Over 93 different mutations have been described in CHH patients. These include promoter duplications, triplications and insertions exclusively between the TATA box and the transcription start site. These mutations decrease the RMRP transcription efficiency. Single base pair substitutions are spread out over the entire RMRP transcript. Also small deletions of and insertions in the transcribed region of the gene have been observed as well. These mutations might influence the secondary structure of the RNA, the binding of the proteins to the RNA or the RNA stability.

In addition many polymorphisms and rare sequence variants have been observed. This is remarkable considering the very small size of the RMRP gene.
To be noted

So far no complete deletion of the entire RMRP gene has been observed. This suggests that complete loss of RMRP function might be incompatible with life. This is also supported by the fact that the knock out in yeast is lethal.

References


This article should be referenced as such: Hermanns P, Lee B. Cartilage-hair hypoplasia (CHH). Atlas Genet Cytofgenet Oncol Haematol.2008;12(6):481-484.