

# Enchondromatosis

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[Abstract](#)

[Keywords](#)

[Disease name/Synonyms](#)

[Definition/Diagnostic methods](#)

[Clinical description](#)

[Radiography](#)

[Diagnosis](#)

[Differential diagnosis and "formes cliniques"](#)

[Prognosis](#)

[Histopathology](#)

[Genetics](#)

[Etiology, Molecular defect and Pathogenesis](#)

[Cytogenetics and molecular genetics](#)

[Molecular mechanisms involved in malignant transformation](#)

[Genetic counseling/antenatal diagnosis](#)

[Unresolved questions](#)

[Treatment](#)

[References](#)

## Abstract

*Enchondromas are common intraosseous benign cartilage tumors which develop in close proximity to growth plate cartilage. Enchondromatosis or Ollier's disease is defined by the presence of at least three enchondromas. It is characterized by an asymmetric distribution of the lesions and an extreme clinical variability. Clinical problems caused by enchondromas include skeletal deformities, limb-length discrepancy, and the potential risk for malignant change to chondrosarcoma. The condition in which multiple enchondromatosis is associated to soft tissue hemangiomas is known as Maffucci syndrome. Neither Ollier's disease nor Maffucci syndrome are genetically determined in a simple Mendelian manner. The estimated birth incidence of Ollier's disease is 1/100,000. There is no medical treatment for enchondromatosis. Surgical treatment is indicated in case of complications (pathological fractures, growth defect, malignant transformation).*

## Keywords

cartilaginous tumor, clinical variability, malignancy, *PTHR1* gene

## Disease name/Synonyms

Ollier's disease, Multiple enchondromatosis, Dyschondroplasia

## Definition/Diagnostic methods

Enchondromas are common benign usually asymptomatic cartilage tumors which develop in the metaphysis and may become incorporated into the diaphyses of long tubular bones, in close proximity to growth plate cartilage (1-3).

Enchondromatosis or Ollier's disease is defined by the presence of at least three enchondromas. It is characterized by an extreme clinical variability (size, number, location, evolution of enchondromas, age of onset and of diagnosis, requirement for surgery). The diagnosis is based on clinical and conventional radiological evaluations. Additional investigations (scintigraphy, echography, MRI) are not useful for the diagnosis. There are indicated for the evaluation and surveillance of lesions becoming symptomatic (pain, increase in size).

### Clinical description

Clinical manifestations in Ollier's disease often appears in the first decade of life and consist of the appearance of palpable bony masses on a finger or a toe, an asymmetric shortening of an extremity with limping, osseous deformities associated or not with pathologic fractures (1-3). Upon physical examination, enchondromas present on the extremities are usually visible as masses embedded within phalanges, metacarpal and metatarsal bones. Enchondromas frequently affect the long tubular bones, particularly the tibia, the femur, and the fibula; flat bones, especially the pelvis, are also affected. The lesions are multiple and asymmetrically distributed, exclusively or predominantly affecting one side of the body. Affected bones are often shortened and deformed. Indeed bone shortening may be the only clinical sign. These bone shortenings are often associated with bone bending and curvature, and articular movement limitation. Forearm deformity is frequently encountered and is similar to that observed in HME. The trunc is usually not affected, except for rib enchondromas and scoliosis resulting from pelvis imbalance. In childhood, the lesions are subjected to pathologic fractures.

### Radiography

Enchondromas are rarely observed at birth, although the lesions may be present. Roentgenograms typically show multiple, radiolucent, homogenous lesions with an oval or elongated shape and well defined slightly thickened bony margin (1-3). The lesions and long bone axis run parallel. The lesions usually calcify with time and become diffusely punctated or stippled, a light trabeculation may be visible. Enchondromas are frequently assembled as clusters, thus resulting in the metaphyseal widening. When localized at the bone border, the enchondromas produce a typical notch-like image. A minor delay in bone age, on average 0.6-year, has been reported in children with affected with Ollier's disease (4).

Enchondromas are almost exclusively localized in the metaphysis of long bones and in the little bones of the hands and feet. They are originally localized close to the growth plate cartilage, and progressively migrate towards the diaphysis. The epiphyseal region next to an affected metaphysis may present irregularities (2, 5).

Again, it is important to insist on the irregular distribution of the lesions, which can be localized to one limb, or to one half of the body; however, one or two enchondromas are frequently present on the other side, in particular on bones of the hand. If the entire body presents lesions, one half is more affected. In the hands, the lesions almost never affect all the metacarpal bones and phalanges.

Enchondromas result in severe growth defects (more severe than that observed in multiple exostosis). Affected diaphysis are short and massive, and may present bending next to the metaphysis. Cubital shortening is usually more important than that of the radius, fingers are of irregular sizes.

Signs of pathological fractures may be present. Signs of malignant transformation should be looked for (cortical erosion, extension of the tumor into soft tissues).

### Diagnosis

The diagnosis is based on the clinical and radiological evaluations. Additional investigations such as scintigraphy, echography and MRI are indicated for the evaluation of symptomatic enchondromas (pain, increase in size).

### Differential diagnosis and "formes cliniques"

Ollier's disease must be differentiated from [hereditary multiple exostosis](#) (HME) (1-3). HME is an autosomal dominant disorder characterized by multiple bone tumors capped by cartilage, occurring mostly in the metaphyses of long bones. The differential diagnosis is clinical and radiological.

Other rare forms of chondromatosis, which include [metachondromatosis](#), [spondyloenchondrodysplasia](#) and genochondromatosis type I and II, are described and have been well defined (2).

### Prognosis

The prognosis of Ollier's disease is difficult to assess (2). Wildly spread forms may have a better evolution than localized ones which may induce major shortening of a lower extremity and limb asymmetry, especially if already present in a very young child. Similarly, precocious development of enchondromas in phalanges may lead to major finger deformities. As is generally the case, forms with an early onset

appear more severe. Neural compressions are less frequently observed than in HME. Enchondromas in Ollier's disease present a risk of malignant transformation to chondrosarcomas. Malignant transformation to chondrosarcomas in the setting of enchondromatosis occurs in young adults, thus usually at an earlier age than that in patients having chondrosarcoma alone. The reported incidence of malignant transformation is variable and estimated to be between 5-50% (3, 6-8). It is higher in Maffucci's syndrome, the prognosis of which is more severe than that of Ollier's disease (1, 2), and lower in HME. Association of Ollier's disease with other tumors have been reported (2, 9-11).

### Histopathology

Macroscopic examination of enchondromas shows usually multiple oval-shaped or round cartilaginous nodules in osseous portions of bone (1, 2). The individual nodules are limited at their periphery by woven or lamellar bone, and are separated from each other by intertrabecular marrow spaces. The cartilaginous tumor matrix is usually solid, with myxoid changes, which manifest as frayings of the matrix. Enchondromas are characterized by the presence of a striking heterogeneity and diversity in the degree of cellularity and chondrocyte phenotype. This heterogeneity depends in part on factors such as localization and patients's age. In part due to this important cellular heterogeneity, the distinction between benign enchondromas and malignant chondrosarcomas by histochemical criteria is difficult.

### Genetics

Ollier's disease -and Maffucci syndrome- are usually non-familial disorders (1-3). Neither are genetically determined in a simple Mendelian manner. The systematization and irregular distribution of the lesions in Ollier's disease and their nature strongly suggest that it is a constitutive, not acquired, disorder of endochondral bone. It is consistent with a post-zygotic mutation, expressed in a somatic mosaic state. In two instances, enchondromatosis has been observed in sons whose fathers presented with mild skeletal dysplasia but no evidence of enchondromas (12, 13). In one of these cases, a mutation in the *PTHR1* gene (R150C) was carried in the germline and was inherited from the father (see below) (13).

### Etiology, Molecular defect and Pathogenesis

Endochondral bone ossification is a highly regulated process, which requires the linear

phenotypic progression of undifferentiated mesenchymal cells into hypertrophic chondrocytes and the subsequent replacement of mineralized cartilage matrix by bone (14, 15). Enchondromas develop in the metaphysis of long tubular bones in close proximity to the growth plate. Consequently, it is proposed that they result from abnormalities in signaling pathways controlling the proliferation and differentiation of chondrocytes that lead to the development of the intraosseous cartilaginous foci.

Parathyroid hormone-related protein (PTHrP) and Indian Hedgehog (IHH) acting on their respective receptors PTHR1 and PTCH1 exert a tight coupled signaling relay, which is critical for the regulation of endochondral ossification. A mutant *PTHR1* (R150C) has been identified in enchondromas from two from six unrelated patients affected with enchondromatosis (13). The mutation was also present in genomic DNA from one patient and his father who presented with atypical mild skeletal dysplasia but no enchondromatosis. However, neither the R150C mutation (35 patients) nor any other (11 patients) mutations in the *PTHR1* gene could be identified in another study, suggesting a molecular heterogeneity (16).

The mutant *PTHR1* (R150C) seems to constitutively activate the PTHrP pathway, which may lead to a decrease in chondrocyte differentiation and to the formation of enchondromas (13). Transgenic mice expressing the mutant *Pthr1* develop tumors similar to those observed human enchondromatosis. Because it was found that regulation of *Ihh* by PTHrP was lost in enchondromas, transgenic mice overexpressing the Hedgehog (Hh) transcriptional regulator, *Gli2*, were generated. These mice develop ectopic cartilage islands similar to those of the mutant *Pthr1* mice. Thus, the *Ihh* signaling pathway as a whole seems to play a crucial role in the formation of enchondromatosis.

### Cytogenetics and molecular genetics

There are few cytogenetic reports of benign enchondromas (17), and there are no tumor-specific chromosomes or chromosomal regions associated with enchondromas, or chondrosarcomas. However abnormalities within certain chromosomes or chromosomal regions appear to be non-random and can be shared with both benign and malignant tumors (18-21).

### Molecular mechanisms involved in malignant transformation

Little is known on the molecular mechanisms involved in malignant transformation from

enchondromas to chondrosarcomas. Romeo *et al.* have shown that both PTHrP and the PTHR1 are expressed in chondroblastoma (22). Expression levels of PTHrP, PTHR1, and their downstream partner Bcl2 may be correlated with the grade of malignancy in chondrosarcoma (23-26).

#### Genetic counseling/antenatal diagnosis

Ollier's disease -and Maffucci syndrome- are usually non-familial disorders.

#### Unresolved questions

- Although a mutation in the *PTHR1* gene has been identified in two patients with Ollier's disease, this or another mutation in the *PTHR1* gene were not identified in other patients. This is consistent with a molecular heterogeneity in the defect causing Ollier's disease. The molecular basis for this heterogeneity is not known.
- The molecular mechanisms involved in malignant transformation are unknown.
- The link -if any- between Ollier's disease and Maffucci syndrome is unknown.

#### Treatment

There is no medical treatment for enchondromatosis. Surgical treatment is indicated in case of complications (pathological fracture, growth defect, malignant transformation).

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