# Neurofibromatosis

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## Abstract

Neurofibromatosis encompasses a collection of inherited diseases with an autosomal dominant inheritance pattern. There are several forms of neurofibromatosis (NF), each caused by differing gene mutations and therefore clinical manifestations vary between each form. Neurofibromatosis affects multiple organ systems where disease progression is common. Neurofibromatosis type 1, (NF1) formerly known as Von Recklinghausen's disease, is the most common type of neurofibromatosis with multiple musculoskeletal manifestations including scoliosis, pseudarthrosis and limb overgrowth. Common surgical management of the orthopaedic complications includes spinal arthrodesis and stabilisation of pseudarthrosis of the tibia. The management of these musculoskeletal complications is troublesome. Current research aims to improve fixation methods and reduce lifelong deformity.

**Keywords** Neurofibromatoses; neurofibromatosis; scoliosis; tibial pseudarthrosis; Von Recklinghausen disease

## Introduction

The Neurofibromatoses are a group of genetic disorders formed as a result of gene defects and mutations. They have multisystem involvement mainly affecting the nervous system, skin and skeleton. Some current literature[1] recognizes five forms of neurofibromatosis, which are NF1, Neurofibromatosis 2, Segmental neurofibromatosis, Legius syndrome and Schwannomatosis. However, most literature only recognizes three distinctive forms: NF1, Neurofibromatosis type 2 (NF2) and Schwannomatosis. Only NF1 and Segmental NF (a subtype of NF1) have significant musculoskeletal manifestations. NF 2 exists with central nervous system tumours forming schwannomas.

Despite there being early depictions of neurofibromatosis dating back to the early thirteenth century, it wasn't until 1882[2] that Friederich Daniel Von Recklinghausen first described Neurofibromatosis (formerly Von Recklinghausen disease). Von Recklinghausen was particularly interested in nervous system pathology and he recognized that pigmentation of the skin was associated with peripheral nerve involvement. He described these lesions as fibromatous neuromas of nerves. These lesions are now known as neurofibromas.

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NF1 is inherited in an autosomal dominant pattern. It is the most common single gene disorder in humans.[3] The gene responsible for NF1 is located on the long arm of chromosome 17 and encodes neurofibromin, a tumour suppressor protein, which predominantly turns off the protein ras.[2]

## Epidemiology and genetics

NF1 is the most common of the neurofibromatoses with an incidence of 1 in 3000–4000 live births.[2–4] NF1 and NF2 are genetically distinct. Approximately half of new cases of NF1 are inherited; the others are caused by sporadic mutations.

## Clinical features

Each of the three types of neurofibromatosis is distinctive in its characteristics, which helps aid diagnosis. The incidence, genetic aetiology and clinical features of these are summarized in Table 1.

### Neurofibromatosis type 1 – diagnosis and musculoskeletal manifestations

The diagnosis of NF1 is made based on clinical features. The specific diagnostic criteria for NF1 are shown in Table 2.

Patients with NF1 have a number of orthopaedic complications due to the musculoskeletal manifestations of the disease. Skeletal complications can be divided into general or focal.[1] General complications include osteoporosis, osteomalacia, osteopaenia, short stature and macrocephaly. Focal complications include spinal pathology, long bone pathology and cystic osseous lesions. Limb overgrowth with hemi hypertrophy can occur, most often requiring surgical intervention in order to prevent limb-length discrepancy. Overgrowth can affect both bones and soft tissues. Two common orthopaedic focal manifestations of NF1 are:

- Scoliosis
- Congenital pseudarthrosis (most commonly of the tibia)

### Scoliosis

Scoliosis is common, affecting up to 25% of NF1 patients[8] and as with other skeletal manifestations, usually presents early because of abnormalities in bone remodelling, growth and repair.[1] It most commonly affects the thoracic spine and occurs most often in children between the ages of 6 and 10. Scoliosis curves are either dystrophic or non-dystrophic.[9] Dystrophic curves are shorter, more severe, segmented, sharply angulated curves that require more aggressive surgical management. These curves tend to present earlier and progress more rapidly. Patients are at risk of paraplegia. Vertebral dislocation can also occur.

Kyphoscoliosis can occur with dystrophic changes, other features seen on imaging include;

- Rib pencilling
- Anterior, posterior or lateral vertebral scalloping
- Vertebral wedging
- Spindling of the transverse process
- Widening of the canal
- Enlargement of the foramina

Initial management for both curve types should involve clinical assessment, plain X-ray and MRI scan. Halo traction is sometimes required to stabilize the spine and prevent neurological sequelae.


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## Different types of neurofibromatosis

| Disease name | Aetiology | Incidence | Clinical features (Musculoskeletal manifestations in bold) |
|---|---|---|---|
| NF1 | NF1 gene mutation on Chromosome 17q11[5] | 1 in 3000–4000[2–4] | • Scoliosis<br>• Pseudarthrosis of long bones<br>• Overgrowth of bones<br>• Lisch nodules<br>• Café-au-lait spots<br>• Freckling in the axilla and inguinal region<br>• Neurofibroma |
| NF2 | NF2 tumour suppressor gene mutation on chromosome 22q12 | 1 in 25,000[5] | • Bilateral vestibular schwannomas<br>• Spinal schwannomas<br>• Meningiomas, ependymomas, astrocytomas, and rarely neurofibromas[5] |
| Segmental NF (subtype of NF1) | NF1 gene mutation on Chromosome 17q11 | 1 in 36,000 to 40,000[6] | • Features of NF1 (mainly café-au-lait spots and neurofibromas) on a single unilateral segment, not crossing the midline. |
| Schwannomatosis | Various gene mutations on Chromosome 22 | 1 in 420,000[7] | • Multiple Schwannomas throughout the body<br>• No vestibular schwannomas |

**Table 1**

Non-dystrophic curves can be managed as idiopathic scoliosis. As there is a risk of non-union and subsequent pseudoarthrosis it is essential to monitor the patient following spinal fusion until bony union is achieved.

Dystrophic curves require combined anterior/posterior arthrodesis of the entire deformity.

### Congenital pseudarthrosis of the tibia (CPT)

A pseudarthrosis is a false joint at a non-union site in a long bone. In NF1, pseudarthrosis can affect any long bone but most commonly affects the tibia. CPT can be idiopathic or associated with other pathologies, in particular NF1. CPT is rare, with an incidence of 1 in 140,000–190,000[10] Over half of patients with CPT are NF1 carriers.[10,11] Approximately 4% of NF1 patients suffer from CPT and bowing.[8] CPT can be subdivided into primary or secondary[12]:

Primary

- Signs present at birth
- Bowing of the tibia convex anterolaterally (Figure 1) or discontinuity of the two bones of the tibial segment.
- Can be a dysplasic form, tibia showing an hourglass appearance with a degree of obstruction in the medullary cavity.

Secondary

- Pathological fracture as the child begins to walk

Usually the CPT is unilateral and involves the middle to distal tibia. The fibula is involved in greater than 50% of cases,[12] and this involvement worsens prognosis. In order to differentiate between isolated CPT and NF1 CPT It is imperative to fully examine a patient with suspected CPT. Clinical assessment, neurological and dermatological examination as well as looking at the family history is essential. If bowing is present after 6 weeks; a cyst can form at the apex of the curvature, eventually the bowing worsens and a transverse fracture ensues.

Fixation is troublesome and prognosis is poor with patients suffering severe disability and amputation of the affected zone may be necessary if fixation fails.[13]

### Histology of CPT

Bone remodelling at the pseudarthrosis site is thought to be dysfunctional with reduced numbers of osteoclasts.[14] As a result of deficient bone remodelling, fixation at a site of pseudarthrosis is difficult.

## Neurofibromatosis type 1: diagnostic criteria[24]

At least two of the following are necessary to diagnose NF1:

- At least six café-au-lait spots, larger than 5 mm in diameter in children, and larger than 15 mm in adults
- Two neurofibromas, or a single plexiform neurofibroma
- Freckling in the axillae or inguinal region
- Optic glioma
- At least two Lisch nodules (hamartoma of the iris)
- A distinctive osseous lesion, such as vertebral scalloping or cortical thinning
- A first-degree relative with NF1

**Table 2**


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