Neurofibromatosis type I or von Recklinghausen's disease

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Abstract
Neurofibromatosis type 1 (NF1) or von Recklinghausen's disease is one of the most common genetic diseases, affecting 1/4,000 to 1/3,000 individuals. It is transmitted by autosomal dominant inheritance and its penetrance is almost complete by 5 years of age. The NF1 *gene responsible for the disease is located on the long arm of chromosome 17 at 17q11.2. It is a large (350 kb, 60 exons) tumor-suppressor gene that codes for a cytoplasmic protein: neurofibromin. The deleterious germinal mutations are distributed throughout the entire gene and are generally specific to each family. The frequency of neomutations is particularly high and almost half of the cases are sporadic. NF1 is characterized by a very wide variability of its clinical expression, even within a given family. A doctor well-acquainted with the disease can diagnose the majority of patients after physical examination. Two of the following 7 criteria are required to diagnose NF1: 6 or more café-au-lait macules, freckling in the axillary or inguinal lentigines, 2 or more cutaneous neurofibromas of any type or a plexiform neurofibroma, 2 or more Lisch nodules (iris harmatomas), a specific skeletal lesion (sphenoid wing dysplasia, thinning of the long bone cortex, pseudoarthritis), an optic glioma and an affected first-degree relative (parent or sibling). The wide variation of the clinical expression, the tumor risks and the totally unpredictable evolution of the disease impose regular monitoring of NF1 patients. This surveillance is mainly clinical and has to be adapted to the patient's age in order to assure early management of complications: learning difficulties, aggressive optic glioma, evolving scoliosis, arterial hypertension (renal artery stenosis, pheochromocytoma), malignant tumor ...*
The recently created French treatment network, NF-FRANCE, regroups the multidisciplinary structures required to harmonize the management of these patients and published its recommendations in 2001 (Pinson et al.*, Ann. Dermatol. Vénéréol. 2001; 128:567-575).*

Keywords
NF1 gene, locus 17q11.2, neurofibromin, café-au-lait macules, lentigines, cutaneous neurofibromas, lisch nodules

Disease name and synonyms
Neurofibromatosis type 1 (NF1)
von Recklinghausen's disease

Prevalence in the general population and influence of geographic origin
(Huson and Hughes, 1994)
NF1 is one of the most common genetic diseases. It affects 1/4,000 to 1/3,000 individuals with a homogeneous worldwide distribution. Its incidence is estimated to be 1/2,500 births/year.

Diagnosis of the phenotype
(Riccardi, 1981, 1992; Zeller and Hovnanian, 1992; Huson and Hughes, 1994)

Diagnostic criteria
The consensus conference of the National Institute of Health in Bethesda (MD, USA) defined, in 1988, 7 main criteria for the diagnosis of NF1. NF1 is diagnosed when 2 of these signs are present in the same individual (NIH, 1988).

- First-degree relative afflicted (parent, sibling, child)
- At least 6 café-au-lait macules: > 1.5 cm after puberty and > 0.5 cm in prepubertal individuals
- Freckling in the axillary or inguinal region (Crowe sign)
- At least 2 neurofibromas of any type or at least 1 plexiform neurofibroma
- Optic nerve glioma
- At least 2 Lisch nodules (iris harmatoma)
- A characteristic bone lesion: pseudoarthrosis, sphenoid wing dysplasia, thinning of long bone cortex

In an adult, diagnosis of NF1 is usually made easily, based on physical examination. But in a child, café-au-lait macules can remain the only manifestation for a long time and, in the absence of a family history of the disease, the diagnosis sometimes remains in abeyance (Obringer, 1989). The symptomatology evolves with age and penetrance of the disease is almost complete by the age of 5 years (**Appendix 1**).
Cutaneous signs appear progressively. The café-au-lait macules can be present in sufficient number at birth or appear during the first few years of life. Cutaneous neurofibromas are rare in infancy and generally appear during preadolescence. They can be the most visible manifestation of the disease but do not transform into malignant tumors. When they are few in number or atypical, histological examination can contribute to the diagnosis. Plexiform neurofibromas are usually present at birth. These are infiltrating tumors that can sometimes lead to the abnormal growth of bone when they come in contact with it . They may also undergo malignant transformation.
Lisch nodules, whose presence is pathognomonic of NF1, appear with age and are found in the majority of adults with NF1. They are detected by slit-lamp examination.
Dysplasia of the long bones is already present at birth and is detected when a deformation appears during growth.
Optic (chiasma and/or nerve) gliomas become clinically symptomatic in young children around the age of 5 years. Asymptomatic forms can remain silent or regress in certain cases (Listernick *et al.*, 1995, 1997).
Complications (Friedman and Birch, 1997).
Other clinical signs are found in a high number of NF1 patients: macrocephaly, small stature, juvenile xanthogranulomas (rare) and hypopigmented spots. The diversity of NF1 complications renders difficult the making of an exhaustive list (**Appendix 2**).
Neurological complications are principally neuropsychological disorders with cognitive deficits and learning difficulties (Ferner *et al*., 1996; Nguyen *et al*., 1997). Cerebral magnetic resonance imaging (MRI) of young subjects with NF1 showed that 50–70% had T2-weighted hypersignals (unidentified brilliant objects): clearly circumscribed hyperintense zones without a volume effect. These anomalies tend to diminish in adults. Their significance remains unknown, other than a possible association of these images with cognitive disorders.
Some neurological signs, especially epilepsy and headaches, have also been described in NF1 patients, but their direct association with NF1 cannot always be established.
Arterial hypertension is found in about 6% of the patients. It can be essential or secondary to stenosis of the renal artery, pheochromocytoma or coarctation of the aorta.
The majority of NF1 complications are secondary, caused by visceral neurofibroma compression of urinary, digestive, vascular and/or pulmonary systems.
The majority of tumors are benign (neurofibromas). Malignant transformation of tumors is rare but is responsible for the severity of NF1. The distribution of malignant tumors is very different from that of the general population: half of the tumors are central nervous system tumors (ependymoma, astrocytoma, medulloblastoma, meningioma, glioma), one-third of which are optic gliomas (**Appendix 3**).
The risk of pheochromocytoma or neurofibrosarcoma is significantly elevated, for NF1 patients and those of leukemia and multiple cancers are also increased (Sorensen *et al*., 1986; Matsui *et al*., 1993; Zoller *et al*., 1997).

Evolution of clinical signs

NF1 is a progressive disease. Certain clinical signs are already present at birth, whereas others appear gradually with age. Each age group also bears different risks of complications that are represented in the following Table.

Evolution of clinical signs in NF1

Manifestation	0–4 years	4–10 years	10–15 years	15–18 years and +
Pseudoarthrosis	X			
Plexiform neurofibromas	X			
Chiasma gliomas		X		
Dystrophic scolioses			X	X
Cosmetic problems			X	X
Neurofibromas			X	X
Neurofibrosarcomas	X	X	X	X

Pregnancy sometimes corresponds to a period of disease progression, when cutaneous neurofibromas also have a tendency to increase in size and number (Dugoff and Sujansky, 1996). However, pregnant women with NF1 run no enhanced risk of preeclampsia, premature delivery, retarded intrauterine growth, arterial hypertension, miscarriage or abnormal perinatal mortality. In contrast, cesareans are more common because of the development of specific complications: neurofibromas of the pelvis and nerve roots, pelvic and vertebral bone anomalies, and/or pheochromocytoma.

Main differential diagnoses

The evolution of our knowledge has enabled the unambiguous differentiation between NF1 (localized to chromosome 17) and NF2 (localized to chromosome 22). However, confusion between these two totally distinct entities sometimes persists today.

Segmental neurofibromatosis (or NF5 according to Riccard's classification) is characterized by the presence of NF1 clinical signs limited to one or several regions (Combemale *et al*., 1994).

Dermatological signs (café-au-lait macules, lentigines …) are also present in other pathologies:

autosomal dominant isolated café-au-lait macules (or NF6), Watson syndrome (pulmonic stenosis with café-au-lait macules), Noonan syndrome, McCune–Albright syndrome or LEOPARD (multiple lentigines) syndrome …

Management of NF1 patients

NF1 requires life-long management adapted to age (**Appendix 4**). Multidisciplinary structures are particularly well adapted to the diversity of the manifestations of this pathology.

No specific treatment of the disease exists at present. Management corresponds to regular monitoring, primarily clinical, and treatment of the complications when they appear (Wolkenstein *et al*., 1996; Guttmann *et al*., 1997; Huson, 1999). Children should be monitored more closely than adults. Children should be examined annually to detect psychomotor development disorders, optic gliomas and/or scoliosis. Adults without complications can be examined every 2–5 years.

Complementary examinations are only carried out when indicated by clinical findings (Wolkenstein *et al*., 1996). The only controversial exception is perhaps MRI of the optic nerve pathways to detect a potentially aggressive glioma, particularly in young children whose ophthalmological examination can be difficult.

The following approach was proposed by the NF-FRANCE Network (a French group created in 2001 to federate the french multidisciplinary structures for NF): when a child is unable to cooperate adequately in the ophthalmological examination, either because of age (under 6 years) or cognitive disorders, a first cerebral MRI is systematically performed. As soon as the child's age allows, a simple annual ophthalmological examination, including evaluation of visual acuity and visual field, is recommended. This monitoring is subsequently adapted to each patient and medical decisions are made by the groups within the multidisciplinary structures (Eichenfield *et al*., 1997; Pinson *et al*., 2001).

Treatment of complications often requires a multidisciplinary decision that must take into consideration the various specificities of the disease (specialized treatment of optic gliomas, dystrophic scolioses, pseudoarthroses or malignant tumors in light of the risk of developing a secondary neoplasia after genotoxic therapy).

Genetic counseling

(Shen *et al*., 1996; Bahuau *et al*., 1997)

Mode of transmission

NF1 is a disease of autosomal dominant inheritance. A patient afflicted with NF1 has a 50% chance of transmitting the disease to each of his/her children, regardless of sex. Between 30 and 50% of the patients have neomutations: neither of their parents has NF1. The broad phenotypic variability of NF1 can be responsible for the failure to recognize a prior familial case (index case) and the search must be made, by rigorous questioning and physical examination (especially dermatological and ophthalmological) of the parents and/or kindred.

The NF1 gene

(Shen *et al.*, 1996): *NF1* is localized in the pericentromeric region of the long arm of chromosome 17, at 17q11.2. It is a large gene

containing 60 exons over 359 kb of genomic DNA. It has the particularity of encompassing 3 other genes: *EVI2A*, *EVI2B* (ecotropic viral integration sites) and *OMPG* (oligodendrocyte myelin glycoprotein), located in intron 27b and a pseudogene *AK3* (adenylate kinase 3), located in intron 37. No study to date has demonstrated any role for these genes in the pathophysiology of NF1 (Bernards, 1995).
NF1 is a tumor-suppressor gene: The mutations affecting this type of gene are inherited by recessive transmission. Functional inactivation of the 2 alleles of the gene is necessary to cause the deregulation of cell multiplication. Individuals with a germinal *NF1* mutation are predisposed to developing tumors because they have inherited a mutant allele in each of their cells. Indeed, a study of tumors and somatic mutations in NF1 patients showed the loss of heterozygosity (LOH) associated with certain benign (neurofibromas) and malignant tumors (neurofibrosarcomas, glioblastomas, pheochromocytomas, myelodysplastic syndrome).

Messenger RNA

NF1 codes for a ubiquitously expressed mRNA whose level of expression varies considerably depending on the tissue(s) involved. Different mRNA are synthesized and result from alternative splicing of exons 9br, 23a and 48a. Their expression is specific to certain tissues and seems to evolve throughout life.

The protein

The *NF1* gene encodes a cytoplasmic protein: neurofibromin. It is a 2,818 amino-acid protein that contains a particular central region of 360 amino acids (exons 21–27): NF1-GAP (GTPase-activating protein)-related domain. This latter presents sequence homology with the catalytic domain of GAP and plays an inhibitory role in the RAS cellular activation pathway.
Neurofibromin has a complex distribution in cells and it differs according to the tissue analyzed. Neurofibromin expression evolves during life, with generalized synthesis of the protein during the embryonic period and more restrictive production in adults.

NF1 mutations

(Wallace *et al.*, 1990; Upadhayaya and Cooper, 1998): The study of mutations in the *NF1* gene is rendered difficult by its very large size, the presence of numerous homologous pseudogenes and the absence of a 'hot spot region' in which mutations would be found at a higher frequency. The mutations are most often private (described in a single family) and are uniformly distributed throughout the entire gene.

In 1992, an international consortium on NF1 was created and led to the centralization of information on the mutations and polymorphisms of the *NF1* gene (Korf, 1998). It is accessible on the Internet at the site: http://www.nf.org/nf1gene/
The following table shows that the majority of *NF1* mutations are non-sense mutations and frameshift mutations often leading to the appearance of a premature STOP codon and the synthesis of a truncated defective protein.

NF1 mutations registered by NF1 Genetic Analysis Consortium		
Chromosomal anomalies	4	1.6%
Deletions of the entire NF1 gene	18	7.2%
Deletions of several exons	38	15.5%
Small deletions	55	22.4%
Large insertions	3	1.2%
Small insertions	27	11%
Non-sense mutations	43	17.5%
Missense mutations	29	11.8%
Intronic mutations affecting RNA splicing	25	10.2%
3'UTR-region mutations	4	1.6%
Total	246	

Mutations responsible for somatic mosaicism are rare and occur early during development. They can thus be implicated in many tissues and cause multiple clinical manifestations.
Germinal mosaicisms of *NF1* have also been observed but their frequency is difficult to estimate: they could explain the very rare familial situations in which healthy parents have several affected children.

Sex

Men and women are equally affected with similar expression diversity. The search for the parental origin of mutations revealed that large deletion mutations had a predominant maternal origin and point mutations of the *NF1* gene were of paternal origin in 90% of the cases.
Paternal age has not been shown to have any effect on the appearance of neomutations.

Genotype–phenotype correlations

At present, few relationships between phenotype and *NF1* mutations have been described. This absence of correlations can be explained, in part, by the non-systematic search for mutations in NF1 patients and by the lack of reliable and complete clinical information for some of the patients.
For the time being, only the deletions containing the entire *NF1* gene and the surrounding genome region seem to be associated with a particularly severe clinical picture: facial dysmorphism, the early appearance of numerous cutaneous neurofibromas, learning difficulties and/or mental retardation (Wu *et al.*,

1995). With the exception of these large deletions, no molecular, clinical or familial element can predict the severity of the disease.

Existence of modifier genes

The study of NF1 patients and their families clearly showed the lower phenotype–genotype correlations as a function of the degree of the relatedness. The existence of modifier genes modulating the expression of the *NF1* gene could explain the wide variability of the disease for patients in the same family (Easton *et al.*, 1993). No modifier gene has actually been identified and some projects are being set up to localize them.

Diagnostic methods

The diagnosis of NF1 is based primarily on clinical criteria.

Indirect diagnosis, by analysis of intragenic markers of *NF1* polymorphisms, potentially identifies only the haplotype at risk in familial cases. It confirms or excludes the diagnosis of NF1 in the relatives of affected subjects when clinical criteria of diagnosis are insufficient. This method is indirect and requires the cooperation of the family (patients and unaffected individuals).

Indirect diagnosis by linkage analysis of the *NF1* gene is currently proposed for the familial forms (at least 2 NF1 patients). It can reassure subjects potentially at risk of being affected but for whom the clinical diagnosis cannot be made (fewer than 2 diagnostic criteria), as is often the case for children. It also sets the stage for regular and adapted monitoring for individual carriers of the haplotype at risk, especially when the clinical diagnosis is uncertain.

Search for the mutation in the *NF1* gene is difficult. Each of the diagnostic methods currently available can detect only from 30 to 75% of the mutations, which forces laboratories to develop several complementary techniques to increase the rate of detection.

De novo cases represent half the patients afflicted with NF1 and only identification of the deleterious germinal assures appropriate and adequate management of these patients.

In clinical practice, there is no indication for the direct search of mutation in the *NF1* gene at the present stage of our understanding. The search for the germinal mutation in peripheral blood cells is difficult and long, and it remains an experimental procedure. Patients who agree to give blood samples must be informed of the difficulty involved in these searches.

Prenatal diagnosis

Prenatal diagnosis is difficult to envisage in light of the wide variability of clinical expressions within the same family and our incapacity at present to predict the severity of the disease in a given individual. This possibility can be discussed case by case with couples requesting such tests at the time of a genetic counseling consultation. In France, few couples really sought such information and prenatal diagnosis is performed only in a very small number of them.

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Appendix 1. Frequencies of the different diagnostic criteria of NF1 as a function of the mean age of their appearance
(Pinson *et al.*, 2001).

	Frequency (%)	Age
Skin		
Café-au-lait macules	99–100	< 5 years
Lentigines	50–80	< 6 years
Cutaneous neurofibromas	100	< 30 years
Nodular neurofibromas	15-24	childhood, adulthood
Plexiform neurofibromas	30-39	< 5 years
Eye		
Lisch nodules	67–82	> 6 years
Optic glioma	15	infancy
Symptomatic gliomas	2–4	infancy
Bones		
Sphenoid dysplasia	3–4	childhood
Pseudoarthrosis	3–4	childhood
Scoliosis requiring surgery	2–4.4	childhood, adolescence

Appendix 2. Frequencies of complications justifying the monitoring of NF1 patients as a function of age
(Pinson *et al.*, 2001).

	Frequency (%)	Age
Skin		
Plexiform neurofibromas	30–39	< 5 years
Juvenile xanthogranuloma	1–2	infancy
Eye		
Optic glioma	15	infancy
Symptomatic	2–4	infancy
Bones		
Pseudoarthrosis	3–4	childhood
Scoliosis requiring surgery	2–4.4	childhood, adolescence
Nervous system		
Learning difficulties	33–70	childhood
Epilepsy	6–7	childhood
Hydrocephaly	1.5–2.6	childhood
Cancers		
Neurofibrosarcoma	3–4	adolescence, adulthood
Leukemia	< 0.1	infancy
Carcinoid tumor	0.6–1.5	adolescence, adulthood
Arterial hypertension		
Hypertension	5	adulthood
Pheochromocytoma	< 1	adulthood
Renal artery stenosis	1	childhood, adulthood

Appendix 3. Frequencies of tumors in NF1 patients and relative risk of developing them as compared to the general population in Great Britain
(Narod *et al.*, 1991).

NF1-associated cancers	Observed cases (n)	Expected cases (n)	Relative risk
Leukemias	7	1.85	3.8[a]
Acute lymphoid	4	1.46	2.7
Chronic myeloid	3	0.04	71.4[b]
Lymphomas	3	0.59	5.1[a]
Hodgkin's	2	0.25	8.0[a]
Non-Hodgkin's	1	0.30	3.4
CNS tumors	60	1.29	46.5[b]
Ependymoma	1	0.15	6.6
Optic gliomas	34	0.05	920[b]
Astrocytoma	13	0.42	31.1[b]
Medulloblastoma	3	0.26	11.4[a]
Meningioma	3	0.02	155[b]
Other glioma	6	0.21	29[b]
SNS tumor	2	0.33	6.1[a]
Neuroblastoma	1	0.32	3.1
Pheochromocytoma	1	0.001	1000[a]
Soft-tissue sarcoma	18	0.33	53.8[b]
Rhabdomyosarcoma	5	0.21	23.4[b]
Neurofibrosarcoma	12	0.005	9000[b]
Other fibrosarcoma	1	0.05	20
Total	90	5.52	16.3[b]

CNS: central nervous system; SNS: sympathetic nervous system.
a: $P < 0.05$.
b: $P < 0.001$.

Appendix 4. NF-FRANCE recommendations for the evaluation of an NF1 patient
(Pinson *et al.*, 2001).

CHILD	ADULT
Initial evaluation	**Interview**
Interview and examination of the family (family tree, search for affected subjects)	Family history and familial inquiry (initial examination
Complete physical examination: Weight, height, head circumference, blood pressure	Headaches
Neurological examination (abnormal movements)	
Dermatological examination: café-au-lait macules, lentigines, subcutaneous neurofibromas, plexiform neurofibromas (size and evolution)	Cosmetic disfigurement
Orthopedic examination: kyphoscoliosis	Pain
Endocrinological examination: anomalies of puberty	**Clinical examination**
Abdominal examination	Search for criteria diagnostic of NF1 (1st time)
Ophthalmological examination	Blood pressure
Evaluation of learning difficulties	Presence of plexiform neurofibromas (size and evolution)
Systematic cerebral MRI before 6 years (detection of optic glioma)	Cutaneous neurofibromas with cosmeticdisfigurement
Complementary examinations as a function of clinical finding(s)	Presence of subcutaneous neurofibromas (size, pain, evolution)
Information dissemination to the family (prognosis, genetic counseling, education, possible results of complementary tests)	Presence of an evolving mass (cutaneous or intra-abdominal)
Systematic annual evaluation	Neurological examination
Complete physical examination (see above)	**Information dissemination**
Search for signs of complication according to the patient's age	Repeated explanations of the disease especially when complementary tests are ordered
Ophthalmological examination	Answer questions
Evaluation of learning difficulties	Explanation of possible results of complementary tests
	Genetic counseling
	Visit every 1-2 years recommended