Unveiling the complexity of neurofibromatosis type 1: Innovations in genetic understanding and clinical management. A narrative review

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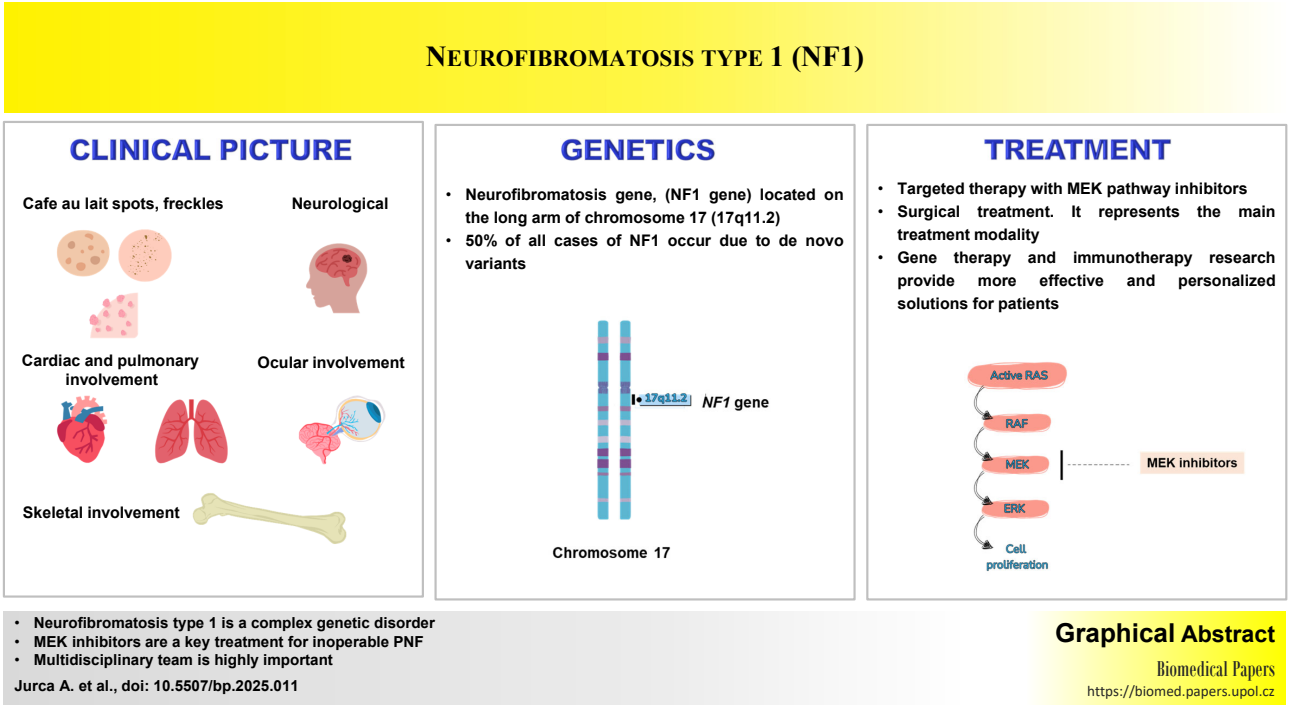
Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder caused by mutations in the NF1 gene. The most important signs are café-au-lait spots, intertriginous freckling, and neurofibromas. The disease has a progressive course, the penetrance is almost complete, and reduces life expectancy by approximately 15%. This review examines the current literature, including NIH (National Institute of Health) diagnostic criteria, genetic testing, genotype-phenotype correlations, and emerging therapies. Genetic testing has improved diagnostic accuracy, particularly for age-dependent clinical features. The genotype-phenotype correlation in NF1 underscores that specific genetic alterations, such as large deletions in the NF1 gene, are frequently linked to more severe clinical outcomes. These deletions often result in early onset of symptoms, a higher frequency of tumor development, and increased tumor burden, all of which contribute to a more complex clinical course. Consequently, individuals with these genetic changes require intensive and continuous monitoring to manage potential complications and prevent further health deterioration. Advances in therapies such as MEK inhibitors offer hope for inoperable plexiform neurofibromas, while surgery remains the primary option for localized tumors, despite the risk of recurrence. Multidisciplinary care and genetic advancements are crucial for improving the prognosis and quality of life of patients with NF1.



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INTRODUCTION

Neurofibromatosis type 1 is a multisystemic disease with neurocutaneous involvement, one of the neurocutaneous syndromes, a group of disorders affecting all tissues derived from the neuroectoderm. The disease is characterized by skin changes such as café-au-lait spots, intertriginous freckling, and the presence of various neurofibromas both in the central nervous system and the peripheral nervous system (brain, spinal cord, various internal organs, skin) (ref.[1,2]). Additionally, alongside Noonan, Costello, Legius, and Cardiofaciocutaneous syndromes, it belongs to the broader group of RASopathies, being the first condition identified as part of this signaling pathway. The RAS/MAPK pathway plays an extremely important role in cellular signaling, ensuring cell differentiation, proliferation, migration, and apoptosis[3,4]. The disease arises due to mutations in the *NF1* gene, inherited in an autosomal dominant manner[5]. NF1 is a disease that, in the vast majority of cases, is diagnosed clinically, based on the criteria proposed by the National Institutes of Health (NIH) in 1988 (ref.[6]). By the age of 8, approximately 97% of patients can be diagnosed using clinical criteria[7]. Genetic testing is an important criterion for confirming the diagnosis of the disease, having been included in the revised NIH diagnostic criteria in 2021 (Table 1) (ref.[8-10]).

MATERIAL AND METHODS

For the preparation of this article, the authors conducted a comprehensive search across the PubMed and Scopus databases. The article is a narrative review of the most important findings in the clinical management and genetics of NF1.The search strategy was designed to capture relevant studies, focusing on keywords such as “neurofibromatosis”, “NF1”, “mutations”, “diagnosis”, “treatment” and “associated complications”. The search targeted publications from 2014 to 2024, with a focus on studies that utilized inclusion criteria limited to peer-reviewed articles, clinical studies, observational studies, and reviews that specifically addressed the management of patients with neurofibromatosis type 1. Only studies published in English were included. Case reports, editorials, and studies unrelated to clinical aspects or treatments for neurofibromatosis type 1 were excluded. This selection process ensured that the sources included were scientifically well-founded and pertinent to the scope of the article.

GENETICS OF NEUROFIBROMATOSIS TYPE 1

The disease results from mutational variants in the *NF1* gene. This gene is located on the long arm of chromosome 17 (17q11.2). It is a large gene, approximately 350 Kb, containing 55 constitutive exons and 5 alternatively spliced exons. It also has one of the greatest variation rates in the human genome[10]. This, coupled with the absence of mutational hotspots, makes the molecular diagnosis of NF1 particularly challenging[11]. Approximately half of the cases of neurofibromatosis type 1 arise due to de novo variants, unrelated to heredity. In cases where a patient with a pathogenic variant in the *NF1* gene develops a second somatic (non-germline) mutation in another tumor suppressor gene, the "second hit" mechanism significantly increases the risk of uncontrolled cell growth and tumor development[12].

The *NF1* gene encodes neurofibromin, a large protein involved in regulating intracellular signaling pathways. The Human Gene Mutation Database (HGMD) catalogs over 3600 pathogenic variants of the *NF1* gene, distributed throughout its length, affecting both exons and introns, including splice junctions[13]. These variants include: microdeletions that may encompass the entire *NF1* gene, copy number variants (CNVs), frameshift mutations, nonsense and missense mutations, and splice-site mutations[8,14,15].

Although clinical diagnosis is essential and the clinical criteria are very clear, genetic diagnosis in neurofibromatosis is extremely important, and the techniques used are diverse. If clinical signs are conclusive for this diagnosis, targeted molecular testing of the *NF1* gene is recommended. For this, sequencing of the genomic DNA (gDNA) of the *NF1* gene is performed. An alternative

Table 1. Diagnosis criteria for Neurofibromatosis type 1 (ref.[8-10]).

A: The diagnostic criteria for NF1 are met in an individual who does not have a parent diagnosed with NF1 if two or more of the following are present:
• 2 or more of the criteria
• ≥ 6 café-au-lait spots (> 5 mm before puberty, > 15 mm after puberty)
• Freckling in the axillary or inguinal region
• Two or more neurofibromas of any type *or* one plexiform neurofibroma
• ≥ 2 Lisch nodules identified by slit lamp examination or two or more choroidal abnormalities (CAs)—defined as bright, patchy nodules imaged by optical coherence tomography (OCT)/near-infrared reflectance (NIR) imaging
• Optic glioma
• Typical bony changes (dysplasia of sphenoid bone, thinning of cortex in long bones (with or without psudoarthrosis)
• A heterozygous pathogenic *NF1* variant with a variant allele fraction of 50% in apparently normal tissue such as white blood cells.
B: A child of a parent who meets the diagnostic criteria specified in A merits a diagnosis of NF1 if one or more of the criteria in A are present

is to complement it with complementary DNA (cDNA) sequencing, along with specific deletion analysis of the gene, as pathogenic variants affecting the splicing region occur with increased frequency. If the phenotype resembles other disorders characterized by hyperpigmentation, tumors, and/or overlapping features, the use of a multigene panel may be indicated. This panel should include the *NF1* and *SPRED1* genes to account for potential differential diagnoses[12].

CLINICAL FEATURES IN NEUROFIBROMATOSIS TYPE 1

Cutaneous involvement

The first sign that suggests the disease is the presence of "café-au-lait" spots, which are visible from birth. These spots gradually increase in number, become more noticeable in early childhood, and grow proportionally with the body. Freckles, another sign are diffusely present on the trunk, proximal extremities, and neck, as well as in the axillary, inguinal, and breast regions. They usually appear in older children or adolescents[16,17].

Ocular involvement

Neurofibromatosis diagnosis presents a challenge for ophthalmologists in terms of early diagnosis, clinical features, and treatment. In recent years, significant advances in multimodal imaging in ophthalmology have led to the identification of new ocular manifestations in NF1, such as choroidal abnormalities (CA). Choroidal abnormalities are more common in adults (80–90%). In children, their prevalence is much lower, around 60–78.6%, but they are more frequent compared to Lisch nodules[10,18]. Lisch nodules are benign formations on the iris. They can be observed during slit-lamp examination and are frequently seen in adults with NF1, while being much rarer in the pediatric population. Choroidal freckles result from the proliferation of Schwann cells arranged in concentric rings around an axon. They can be detected in all patients with neurofibromatosis, both adults and children, using laser scanning ophthalmoscopy with infrared light or optical coherence tomography (OCT) (ref.[19,20,21]). Optic glioma, frequently associated with NF1, is asymptomatic in the vast majority of cases, which often leads to delayed diagnosis. In some instances, it remains asymptomatic throughout the patient's life[22,23]. Moreover, most of these tumors regress spontaneously, with their prevalence decreasing from approximately 20% in young children to less than 5% in older adults with NF1 (ref.[24,25]).

Tumoral Involvement in NF1

Neurofibromas cutaneous and subcutaneous neurofibromas are benign tumors derived from Schwann cells that can affect almost any nerve in the body[17,26,27]. These lesions are well-defined and typically range in size from a few millimeters (1–2 mm) to several centimeters. Their consistency varies from soft to elastic or firm. They may appear sessile or pedunculated, with overlying skin that can either match the surrounding healthy tissue or show discoloration[28]. Most neurofibromas are asymptomatic, but they can sometimes cause itching or become tender to touch. They usually emerge during puberty, increasing in number and size until around the age of 20 (ref.[1,29]). Subcutaneous neurofibromas are located beneath the skin and are usually nodular with well-defined edges, or they may appear diffuse with varying consistency. The skin over a diffuse superficial neurofibroma can display unusual pigmentation or abnormal hair growth. These neurofibromas may occur as isolated lesions, in groups, or as a "beaded" pattern along a nerve. Both cutaneous and subcutaneous forms can appear throughout life, although their emergence rate can vary significantly from year to year[30].

Plexiform neurofibromas. Plexiform neurofibromas are typically internal and therefore not visible during clinical inspection. They are found in approximately 50% of patients with NF1 and are usually detected via MRI. These tumors frequently grow during childhood and adolescence, stabilizing in adulthood[31]. Although usually asymptomatic, they can cause: pain, deformities, thickening or erosion of adjacent tissues, and impairment of nerve function or other structures. Plexiform neurofibromas can be diffuse or deeply located. Diffuse plexiform neurofibromas are soft, irregular, and often associated with thickening, enlargement, and/or abnormal pigmentation of the surrounding skin. When palpated, they may give the characteristic sensation of a "bag of worms", indicating involvement of multiple nerves and branches. These can appear as isolated lesions or extend along the entire length of a nerve, creating a "beaded" sensation upon touch. Deep Plexiform Neurofibromas: are not visible clinically, they may have a diffuse or nodular structure and can occur either as isolated lesions or in groups. They can affect any nerve, nerve root, or nerve plexus[12]. These tumors, though often asymptomatic, pose a potential risk for complications, including malignant transformation, and therefore require careful monitoring.

Malignant peripheral nerve sheath tumors (MPNSTs) are the most common types of cancer associated with NF1. They occur at a younger age than in the general population and are often accompanied by a more reserved prognosis in NF1 patients[32,33]. Almost all MPNSTs develop from pre-existing plexiform neurofibromas, either diffuse or nodular. The most common clinical sign of malignant transformation is persistent pain, which may be a new symptom or an intensification of pre-existing pain[31].

Brain tumors. In individuals with NF1, gliomas that do not affect the optic pathways are generally asymptomatic and are discovered incidentally, usually during MRIs conducted for other medical reasons. These tumors are usually of low grade, with very slow growth or stability over long periods. In rare cases, symptomatic or high-grade brain tumors may occur. More than 20% of NF1 patients who present with a non-optic glioma develop two or more similar tumors[12]. The incidence rate is between 2% and 5%, and these tumors can occur at any age, although they are less common in children than in adults[24,34,35].

Breast cancer

Women diagnosed with NF1 have a significantly higher risk of developing breast cancer before the age of 50 and have a higher mortality rate from this cause. The risk of developing contralateral breast cancer is also higher compared to the general population[36].

Other neurological manifestations

Can affect motor function, leading to difficulties in coordination, balance, and performing fine motor tasks. Hypotonia is also extremely common in children. Intellectual and learning difficulties may arise, with learning, memory, and language challenges being frequently encountered[35,37].

Behavioral disorders

Behavioral problems are commonly observed in NF1 patients, including social difficulties such as isolation and challenges in group integration. Attention Deficit Hyperactivity Disorder (ADHD) occurs in 30–50% of children and adolescents with NF1, and autism spectrum disorder (ASD) is found in 25% of children with NF1 (ref.[38]). Sleep disorders are present across all age groups in individuals with NF1(ref.[39]). Epileptic seizures are rare, with an incidence of approximately 5%, and are more common in adults[40].

Cardiac and pulmonary involvement. Although not common manifestations, these have been reported in certain specialized studies. Pulmonary valve stenosis and mitral valve stenosis are the most frequent cardiac anomalies observed in individuals with NF1, but intracardiac neurofibromas can also occur[41]. Diffuse pulmonary disease associated with NF1 is observed only in adults with NF1 (10–20%), with symptoms generally being nonspecific (exertional dyspnea, difficulty breathing, chronic cough, chest pain) (ref.[42]).

Skeletal involvement

Scoliosis, osteopenia, long bone and sphenoid wing dysplasias, and pseudarthrosis are consistently encountered in individuals with NF1 and manifest from early childhood (long bone dysplasia) to adulthood. They can be primary or associated with plexiform neurofibromas or vertebral or sphenoid wing dysplasia[43]. Surgical treatment of these abnormalities is a challenge, typically being successfully performed only by specialized doctors[44].

GENOTYPE – PHENOTYPE CORRELATION

Understanding the relationship between genotype and phenotype is crucial for guiding treatment and managing the disease effectively. Several studies have explored this genotype-phenotype correlation, shedding light on the implications of different genetic mutations. For instance, Well et al. in a retrospective study that included 38 patients with NF1, demonstrated that large deletions encompassing the entire gene are associated with a much more severe clinical phenotype, a much higher tumor burden, and an acceleration in tumor growth rate compared to

Tabel 2. Genes involved in the differential diagnosis of neurofibromatosis type 1(ref.[12]).

Gene(s)	Disorder	MOD	Clinical aspects
AKT1	Proteus syndrome		Abnormal growth of multiple tissues, including hamartomas, connective tissue nevi, epidermal nevi, hyperostosis.
BRAF, MAP2K1, PTPN11, RAF1	Noonan syndrome with multiple lentigines	AD	Multiple lentigines, wide-set eyes hearing loss, and congenital heart defects.
BRAF, KRAS, LZTR1, MAP2K1, NRAS, PTPN11, RAF1, RIT1, SOS1	Noonan syndrome (NS)	AD (AR)	Dwarfism, congenital heart defects, pterygium coli, and distinct facial features. Individuals with NF1 may have facial traits similar to those of NS.
GNAS	McCune-Albright syndrome		Large cafe au lait spots, polyostotic fibrous dysplasia, and precocious puberty.
KIT, SNAI2	Piebald trait	AD	Skin pigmentation and depigmentation.
LZTR1, SMARCB1	Schwannomatosis	AD	Predisposition to develop multiple schwannomas. The most common feature is pain or a asymptomatic mass.
MLH1, MSH2, MSH6, PMS2	Constitutional mismatch repair deficiency (CMMRD)	AR	It is cancer predisposition syndrome. Skin features mimic NF1, but CMMRD is distinguished by parental consanguinity, family history or features of Lynch syndrome.
NF2	Neurofibromatosis 2 (NF2)	AD	Bilateral vestibular schwannomas, tumors on cranial and peripheral nerves, skin schwannomas or meningiomas, and juvenile cataracts.
PDGFRB	Infantile myofibromatosis	AD	Numerous tumors involving the skin, muscles, bones, and internal organs.
SPRED1	Legius syndrome (LS)	AD	CALMs are presents but neurofibromas, tumors, or Lisch nodules are absent. Additional traits often include freckling, lipomas, macrocephaly, and cognitive impairments.

MOD, mode of inheritance; CALMs, Café-au-lait macules.

patients with atypical deletions. The authors recommend close monitoring of these patients to assess tumor progression, the risk of malignant transformation, and, if necessary, recommend treatment with MEK inhibitors[30,45]. Peduto et al. also demonstrated that large deletions of the gene correlate with a severe phenotype and that not all mutational variants have the same effects. The genotype-phenotype associations are currently in an upward curve, slowly but profoundly changing the clinical and genetic approach to NF1 patients[46,47].

DIFFERENTIAL DIAGNOSIS

In the clinical evaluation of patients with NF1, differential diagnosis plays a crucial role, considering that numerous genetic conditions and syndromes may present with similar clinical features, such as café-au-lait spots and other characteristic manifestations of NF1. Although there are over 100 genetic conditions and syndromes with multiple congenital anomalies, including café-au-lait spots or other traits associated with NF1, the conditions that must be considered in the differential diagnosis of NF1 are relatively few. According to Friedeman et al., there are several genetic conditions that may have clinical manifestations similar to NF1, with the involved genes, inheritance patterns, and specific clinical characteristics of each condition being exemplified in Table 2 (ref.[2]).

TREATMENT

There is no specific treatment for neurofibromatosis. However, recent advancements in research have led to the development of innovative therapies aimed at managing symptoms and slowing disease progression.

Targeted therapy with MEK pathway inhibitors

Since 2020, Ras pathway I inhibitors have been successfully used as therapeutic agents in the treatment of inoperable plexiform tumors in children. The US Food and Drug Administration approved the first monoclonal antibody, Selumetinib, a MEK1/2 inhibitor, in 2020. This treatment represents a breakthrough in the treatment of inoperable plexiform tumors in children older than 2 years[48].

Another therapeutic agent is Rapamycin, an inhibitor of the mTOR pathway, which also plays a role in the activation of AKT, making it another potential drug used in the treatment of plexiform tumors. **Surgical treatment**

Surgery remains the main treatment for neurofibromas, but the risk of tumor recurrence postoperatively is extremely high[46]. It is still considered the only curative treatment for patients with NF1 (ref.[49]).

Gene therapy and immunotherapy

Research in the fields of gene therapy and immunotherapy offers promising prospects for the future treatment of neurofibromatosis. Although these approaches are still in the early stages of study, they have the potential to provide more effective and personalized solutions for patients.

MONITORING AND SUPERVISION

Neurofibromatosis type 1 (NF1) is a complex, progressive genetic disorder with varied clinical manifestations that can affect multiple systems of the body. Regular monitoring allows for the early identification of potential pathological manifestations and quick intervention to prevent or alleviate their effects. In this context, recommendations for the m of patients with NF1 are essential for optimizing treatments and minimizing risks. Monitoring

Table 3. Recommended monitoring for neurofibromatosis type 1 (ref.[12]).

System	Evaluation	Frequency
Eyes	Ophthalmological examination	Annually, until adolescence; for older children and adults: as needed
Tumors	Clinical evaluation for neurofibromas, new or changing plexiform neurofibromas, and other signs/symptoms of malignancy	Annually
Neurological	Neurological evaluation: seizures, headaches, and pain	Annually. Brain MRI if clear clinical symptoms occur
Neurodevelopment	Psychological and neuropsychiatric evaluation	As needed
Breast Cancer	Mammography. Breast MRI with contrast	Mammography: annually, starting at age 30. Breast MRI: annually between ages 30 and 50
Bone	Clinical examination by orthopedic or rehabilitation specialist for asymmetry and scoliosis. Fractures: periodic evaluation	Annually throughout childhood, until growth completion, then as needed
Cardiovascular	Clinical evaluation for heart disease; monitoring of cardiovascular/vascular conditions by a cardiologist	Annually, before surgical procedures
Endocrine	Evaluation of height and head circumference; evaluation of pubertal development	Annually, throughout childhood

should be personalized based on the patient's age, the type and severity of clinical manifestations, as well as the progression of the disease. Table 3 details the necessary evaluations, their frequency, and specific monitoring parameters that are crucial for the correct management of the condition, providing a useful framework for healthcare professionals in tracking patient progression and adjusting treatment according to their needs[12].

Genetic counseling plays a central role in the management of neurofibromatosis type 1, providing patients and families with essential information about the disease, genetic implications, and management options. NF1 is an autosomal dominant condition, meaning that an affected parent has a 50% chance of having an affected child. If the parents are healthy, the possibility of a de novo mutation or germline mosaicism should be considered[50].

CONCLUSION

Neurofibromatosis type 1 is a complex genetic condition with varied clinical manifestations and a significant impact on the quality of life of patients. Recent advances in understanding the genetics and pathophysiology of the disease have led to new diagnostic and therapeutic approaches, including targeted therapy with MEK pathway inhibitors. However, the management of NF1 remains challenging, requiring a multidisciplinary approach that integrates long-term monitoring and innovative therapies to address both clinical complications and the individual needs of patients. Ongoing research in genetics and personalized therapy offers promising prospects for improving the prognosis and life expectancy of patients with NF1.

Search strategy and selected criteria

For the preparation of this article, the authors conducted a comprehensive search across the PubMed and Scopus databases. The search targeted publications from 2014 to 2024, with a focus on studies that utilized inclusion criteria limited to peer-reviewed articles, clinical studies, observational studies, and reviews that specifically addressed the management of patients with neurofibromatosis type 1.

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