Mini-Review

The Pathoetiology of Neurofibromatosis 1

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Although a mutation in the *NF1* gene is the only factor required to initiate the neurocutaneous-skeletal neurofibromatosis 1 (NF1) syndrome, the pathoetiology of the multiple manifestations of this disease in different organ systems seems increasingly complex. The wide spectrum of different clinical phenotypes and their development, severity, and prognosis seem to result from the cross talk between numerous cell types, cell signaling networks, and cell–extracellular matrix interactions. The bi-allelic inactivation of the *NF1* gene through a “second hit” seems to be of crucial importance to the development of certain manifestations, such as neurofibromas, café-au-lait macules, and glomus tumors. In each case, the second hit involves only one cell type, which is subsequently clonally expanded in a discrete lesion. Neurofibromas, which are emphasized in this review, and cutaneous neurofibromas in particular, are known to contain a subpopulation of *NF1*-diploinsufficient Schwann cells and a variety of *NF1*-haploinsufficient cell types. A recent study identified a multipotent precursor cell population with an *NF1*^{+/-} genotype that resides in human cutaneous neurofibromas and that has been suggested to play a role in their pathogenesis. (*Am J Pathol* 2011, 178:1932–1939; DOI: 10.1016/j.ajpath.2010.12.056)

Neurofibromatosis 1 as a Clinical Entity

Neurofibromatosis 1 (NF1; Online Mendelian Inheritance of Man no. 162200; <http://www.ncbi.nlm.nih.gov/omim>, last accessed March 10, 2011), previously known as von Recklinghausen disease, is an autosomal dominant disorder that affects approximately 1 in 3500 persons worldwide.^{1,2} Half of the patients with NF1 have inherited their *NF1* mutation, and the other half are caused by a *de novo* *NF1* mutation. The findings and the degree of severity of NF1 are highly variable. The hallmarks of NF1 include

café-au-lait macules and multiple benign cutaneous neurofibromas, which, typically, are detectable in adulthood by simple visual inspection.

NF1 can affect nearly every organ system, and the complications vary between individuals, even within a single family. The clinical diagnosis is based on the presence of two or more of the following findings: six or more café-au-lait macules with diameters >5 mm in prepubertal patients and >15 mm in postpubertal patients; two or more neurofibromas of any type or one plexiform neurofibroma; axillary or inguinal freckling; optic glioma; two or more Lisch nodules of the iris; a distinctive osseous lesion, such as sphenoid wing dysplasia or pseudarthrosis; or a first-degree relative diagnosed as having NF1 according to the preceding criteria.³ It has been suggested that a pathogenic mutation in the *NF1* gene be added to the list of diagnostic criteria.⁴

The most common complications of NF1 are included in the previously listed diagnostic criteria. Additional features include short stature, scoliosis, headache, speech disorders, attention deficit disorder and attention-deficit/hyperactivity disorder, and learning disabilities. Rare complications, affecting <5% of patients, include epilepsy, hydrocephalus, cardiovascular problems, and dystrophic scoliosis.⁵ The lifetime risk of malignant tumors arising from peripheral nerves is estimated to be 10% to 13%.⁶ The pathoetiology of the complications in NF1 is, however, largely unknown.

Genetic Background

NF1 is caused by mutations in the *NF1* gene that encodes the tumor suppressor protein neurofibromin.^{7,8} The *NF1* gene is located on chromosome band 17q11.2, spanning approximately 280 kb of genomic DNA, and is composed of 57 constitutive exons and 4 alternatively spliced exons (9a, 10a2, 23a, and 48a).⁹ However, the large size of the *NF1* gene alone does not explain the high frequency of *de*

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novo mutations. The inheritance of NF1 follows an autosomal dominant trait, and all affected individuals are apparently heterozygous for an *NF1* mutation because persons with constitutive inactivation of both alleles of the *NF1* gene have not been found. Homozygous *Nf1*^{-/-} mice die *in utero*, indicating that neurofibromin is essential for life.^{10,11} On the other hand, mice with an *Nf1*^{+/-} genotype do not develop neurofibromas and appear otherwise normal during the first year of life.¹¹ Later, however, *Nf1*^{+/-} mice develop tumor types similar to those typically seen in old wild-type mice but with a higher frequency.

Approximately 50% of human NF1 cases are caused by a new sporadic mutation in the *NF1* gene. Sporadic germline *NF1* gene mutations exhibit a sex bias, with most (>80%) of new mutations being of paternal origin,¹² whereas most of the so-called microdeletions seem to be of maternal origin.¹³ Microdeletions cover the entire *NF1* gene and its flanking regions, which contain 17 genes.¹⁴

Genetic Testing

The penetrance of NF1 is 100%, meaning that all patients with an *NF1* mutation have NF1. A comprehensive *NF1* mutation screen can detect gene mutations in more than 92% of tested patients fulfilling the NIH diagnostic criteria.^{15,16} Mutation analysis is especially important in very young children with a negative family history and who only partially fulfill the NIH diagnostic criteria. Molecular testing for NF1 is also useful for diagnostic confirmation in the case where an adult patient with café-au-lait macules and axillary freckles has no neurofibromas. These patients with a mild phenotype but fulfilling NF1 diagnostic criteria might have Legius syndrome; the mutation is, in this case, in another gene, *SPRED1*.¹⁷ Approximately 1% to 2% of patients meeting NIH clinical diagnostic criteria for NF1 in fact harbor *SPRED1* mutations.¹⁸

Functions of Neurofibromin

The *NF1* gene is transcribed into an 11- to 13-kb mRNA with an approximately 9-kb open reading frame and is translated into a ubiquitously expressed, 280-kDa protein called neurofibromin.^{9,19} Direct or indirect interactions have been reported between neurofibromin and several other proteins, including the transmembrane proteoglycan syndecan, actin, tubulin, and intermediate filaments, but very little is known about its function, and none of the known interactions alone can explain the different symptoms related to NF1. Only two potentially functional domains of neurofibromin have been described, RasGAP and Sec14,²⁰⁻²³ but the biological role of the Sec14 domain is unknown. The RasGAP-related domain (Ras-GRD) accelerates the conversion of active Ras-GTP to inactive Ras-GDP in various cell types and acts as a negative regulator of the p21ras signaling pathway. The Ras GTPases interact with multiple pathways, including the Raf/Mek/Erk mitogen-activated protein kinase cascade, which regulates cellular growth and differentiation.²⁴ NF1 belongs to a class of developmental syndromes called *RASopathies*, which are caused by germline

mutations in genes that encode protein components of the Ras/mitogen-activated protein kinase pathway.²⁵

Differential Diagnosis: Other Ras Pathway Syndromes

Several clinical syndromes with disease-causing mutations in genes encoding proteins of the Ras signaling pathway have phenotypes overlapping with those of NF1.^{26,27} These syndromes include Noonan syndrome, LEOPARD syndrome, cardiofaciocutaneous syndrome, Costello syndrome, and Legius syndrome. These conditions all share a variable degree of learning difficulty, cardiac defects, facial dysmorphism, short stature, macrocephaly, and skin abnormalities.⁴ The clinical features of the recently described Legius syndrome resemble and partially overlap with those of NF1, including multiple café-au-lait spots, axillary freckling, and macrocephaly.^{17,28} Legius syndrome also seems to be associated with cognitive abnormalities.¹⁷ However, patients with Legius syndrome have neither Lisch nodules in the iris nor neurofibromas or central nervous system tumors. The syndrome is caused by a mutation in the *SPRED1* gene at 15q14, and the gene product is part of the Sprouty/SPRED proteins, which are negative regulators of Ras.

Genotype-Phenotype Correlations in NF1

Only two genotype-phenotype correlations have been reported for the *NF1* gene, leading to speculations on possible modifiers of the haploinsufficient state of the *NF1* gene product. The first correlation relates to patients with NF1 and *NF1* microdeletions, which cover the entire *NF1* gene and lead to a severe form of NF1.^{29,30} Patients with an *NF1* microdeletion have a higher burden of cutaneous neurofibromas, may have dysmorphic features, and often develop learning disabilities. The second association involves a specific, 3-bp, in-frame deletion in exon 17 (c.2970-2972 delAAT) of the *NF1* gene, a condition that is characterized by a mild phenotype in many patients.³¹ These patients show typical pigmentary features of NF1 and Lisch nodules but do not develop cutaneous or clinically detectable plexiform neurofibromas.³²

Mild forms of NF1 can be caused by mosaicism, a situation in which the *NF1* mutation occurs after fertilization. Somatic mutations occurring early during embryonic development produce generalized mosaicism, which is characterized by a mild disease indistinguishable from classic NF1. Mutations occurring at a later stage of embryonic development result in segmental NF1, where manifestations are restricted to one segment of the body. Gonadal mosaicism is a rare form of mosaicism; the mutation is present only in the gonads, and it can be suspected if two or more children of unaffected parents have NF1.³³ It has been speculated but, to our knowledge, not published that mosaicism can explain at least some of the cases in which a mildly affected patient with no family history of NF1 has a child who develops a severe form of the disease.

Table 1. Regulation of *NF1* Expression

Target	Effects	References
Promotor methylation	<i>NF1</i> gene silencing.	36, 37
Transcriptional control	bFGF-, PDGF-, and EGF-induced up-regulated transcription of <i>NF1</i> gene.	35, 38–45
RNA processing	Alternative splicing of exons 9a, 10a-2, 23a, and 48a. Exon 10a-2 is spliced in between exons 10a and 10b.	46–50
mRNA transport	<i>NF1</i> mRNA targeting to cell periphery via actin microfilaments in migrating and cell junction-forming cells; possible mediator, HuR.	51, 52
mRNA level	Rapidly oscillating steady-state levels of <i>NF1</i> mRNA. Down-regulation of <i>NF1</i> mRNA leading to the terminal differentiation of epithelial cells.	19, 52–54
mRNA degradation	Mutations in <i>NF1</i> gene may lead to non-sense-mediated RNA decay.	52, 55, 56
Translational control	Increased translational efficiency or protein stabilization. Increased neurofibromin levels after nerve injury.	39
Posttranslational modifications	Phosphorylation at the cysteine/serine-rich domains of the N-terminus and in the C-terminal region, possibly by PKC.	43, 56–58
Protein targeting	Targeting of neurofibromin near the plasma membrane via the cytoskeleton to enable interaction with Ras-GTP and syndecan. Targeting to the nucleus or nucleoli.	7, 48, 58–62
Protein degradation	Regulation by the ubiquitin-proteasome pathway triggered by PDGF, EGF, and LPA; requires sequences adjacent to the catalytic GAP-related domain of neurofibromin.	35

bFGF, basic fibroblast growth factor; PDGF, platelet-derived growth factor; EGF, epidermal growth factor; PKC, protein kinase C; LPA, lysophosphatidic acid.

Regulation of *NF1* Gene Expression

The expression of *NF1* is regulated at multiple levels, resulting in levels of *NF1* mRNA and protein that can vary considerably, even within minutes (Table 1).^{34,35} Proteins interacting with either *NF1* mRNA or the protein or causing their degradation can be considered as modifiers of *NF1* expression. Only one protein, the tumor antigen HuR, is known to interact with *NF1* mRNA, binding specifically to one of the five potential protein-binding sites of its 3' untranslated region.⁵¹ In general, HuR has been shown to be involved in posttranscriptional mRNA stabilization and transport from the nucleus. HuR has also been associated with the regulation of tumor growth.⁶³ In the cytoplasm of migrating and cell junction-forming cells, some of the *NF1* mRNA is targeted to the cell periphery via actin microfilaments.⁵²

Furthermore, the silencing of *NF1* mRNA expression and the rapid oscillation of *NF1* mRNA and protein levels highlight the complexity of regulation of the *NF1* tumor suppressor gene.^{53,59} A recent study has shown that a microRNA, miR-10b, may regulate *NF1* tumorigenesis by targeting the *NF1* mRNA 3' untranslated region and modulating the Ras signaling pathway.⁶⁴ In general, microRNAs hybridize to the 3' untranslated region of target mRNAs and can repress mRNA translation or mediate its cleavage.

NF1 as a Tumor Suppressor Gene

All individuals with *NF1* are heterozygous for an *NF1* mutation that causes haploinsufficiency, and, thus, the single functional copy of the gene does not produce enough neurofibromin to ensure normal development and the regulation of cell growth, thereby leading to a diseased state. Note that mutations of the *NF1* gene have also been detected in cancers unrelated to *NF1*.⁶⁵

Some distinct lesions characteristic of *NF1* are associated with the loss of both functional *NF1* alleles in cer-

tain cell types. A somatic “second-hit” mutation has been demonstrated in several benign and malignant tumors in *NF1*,^{8,32,33} and it is best characterized in a subset of Schwann cells present in neurofibromas. These facts support the view that the *NF1* gene is a tumor suppressor gene that follows the Knudson two-hit hypothesis of tumor formation.⁶⁶ In general, somatic inactivation of a tumor suppressor can occur via three principal mechanisms: loss of heterozygosity (LOH), somatic intragenic mutations, and promoter hypermethylation. The mechanisms leading to LOH are mitotic recombination, chromosomal microdeletion, and chromosome loss with reduplication.⁶⁵

The Spectrum of *NF1* Second-Hit Mutations

The mutational spectrum differs between *NF1* germline mutations and somatic or second-hit mutations. A recent study revealed a high occurrence of somatic frameshift mutations and also showed that deletions comprising at least 4 nucleotides are remarkably more common as second-hit mutations, whereas the frequency of somatic missense mutations is lower than that observed in the *NF1* germline mutational spectrum.³² In the same study, two separate mutations were detected in 26 of 29 cutaneous neurofibromas, and the remaining 3 had LOH. In a recent study, *NF1* diploinsufficiency was found in all nine neurofibromas, seven of which had a unique second mutation and two LOH.⁶⁷ Thus, LOH does not emerge as a leading cause for the inactivation of both *NF1* alleles in cutaneous neurofibromas. Collectively, earlier studies have reported LOH to be responsible for somatic inactivation in approximately 20% of neurofibromas sampled from patients without microdeletions.³³ Furthermore, the spectrum of somatic mutations differs between *NF1* microdeletion patients and the general *NF1* population, revealing an absence of LOH as a second hit in patients with *NF1* microdeletions.⁶⁸

Pathoetiology of the Lesions in NF1

NF1 is characterized by the variability of its clinical manifestations, whose pathoetiologies remain, in many cases, rather elusive. These manifestations include Lisch nodules, learning disabilities, speech disorders, and a variety of skeletal manifestations, such as short stature, osteopenia/osteoporosis, and lytic bone lesions.^{69,70} A bi-allelic inactivation of the *NF1* gene has been demonstrated in neurofibromas, café-au-lait macules, and glomus tumors. In addition, LOH of the *NF1* gene has been shown in two patients with NF1 and pseudarthrosis.⁷¹ Bi-allelic inactivation has also been observed in certain NF1-related malignancies, such as malignant peripheral nerve sheath tumors (MPNSTs), pheochromocytomas, astrocytomas, and juvenile myelomonocytic leukemia.³³ These observations raise the important questions as to what symptoms and signs are caused by haploinsufficiency as such and what is the role played by the loss of both *NF1* alleles.

NF1 Lesions Caused by LOH or Somatic Second-Hit Mutations

Café-au-lait macules in adults are well circumscribed, uniformly light brown to dark brown macules, averaging 2 to 5 cm in diameter. They can be present at birth, although they usually become detectable during early childhood, growing proportionately to body growth, but they have no tendency toward malignancy. De Schepper et al^{72,73} showed that melanocytes cultured from café-au-lait macules of patients with NF1 carry a somatic or second-hit mutation in the *NF1* gene, suggesting that the melanocyte is the primary pathogenic cell in these pigmented lesions. This notion increases the understanding of the pathoetiology of these lesions. Loss of expression of the wild-type allele without a detectable second-hit mutation was shown to affect melanocytes derived from café-au-lait macules of one patient with NF1.

Glomus tumors are benign but painful tumors of the fingertips and toes. Affected individuals present with the triad of severe paroxysmal pain, cold intolerance, and localized tenderness. The tumors arise from the glomus body, a highly innervated thermoregulatory shunt containing concentric layers of contractile α -actin-positive glomus cells, which harbor bi-allelic inactivation of the *NF1* gene.⁷⁴ Glomus tumors may affect up to 5% of the adult NF1 patient population.⁷⁵

Neurofibromas are lesions characterized by bi-allelic inactivation of the *NF1* gene in a subpopulation of Schwann cells.⁷⁶ The current understanding of the key role of Schwann cells is based on studies with conditional knockout mice and the genetic analysis of cells cultured from human neurofibromas.^{32,76,77} These studies have collectively shown that bi-allelic inactivation of the *NF1* gene is a prerequisite for neurofibroma formation but that tumorigenesis can occur only in an *NF1*^{+/-} background. Neurofibromas can be classified into two main categories: cutaneous and plexiform.⁷⁸ Both are benign hamartomatous tumors traditionally considered to arise from the supporting and connective tissue cells of peripheral

nerves. Neurofibromas contain all elements of peripheral nerves but organized in a haphazard manner: histochemical analysis, immunohistochemical analysis, and electron microscopy have revealed cellular differentiation characteristic of Schwann cells, which are the most numerous, fibroblasts, perineurial cells, mast cells, axonal processes, and blood vessels, all embedded in an abundant collagenous extracellular matrix.^{79,80} However, the cutaneous and plexiform neurofibromas display marked differences: their maximal growth rates follow different timetables, their average size is quite different, and the plexiform neurofibromas have a marked potential for malignant transformation, whereas the cutaneous neurofibromas never turn malignant. The pathogenesis of these different tumor types should, therefore, be considered separately. Several mouse models have been generated to elucidate the pathogenesis of neurofibromas. However, these models only partially reflect the human disease, and most mouse studies have focused exclusively on plexiform neurofibromas.

Pathogenesis of Plexiform Neurofibromas

Approximately one-third of patients with NF1 develop clinically detectable plexiform neurofibromas. These tumors may form large disfiguring masses involving nerve trunks and infiltrating the surrounding tissues.⁶⁵ Plexiform neurofibromas are thought to be congenital lesions, and the risk of their malignant transformation highlights their clinical importance. The bi-allelic inactivation leading to the development of plexiform neurofibromas apparently takes place in embryonic cells that have the potential to generate large populations of cells carrying a single *NF1* second-hit mutation.^{77,81} The growth of plexiform neurofibromas during early childhood distinguishes these tumors from cutaneous neurofibromas, which are undetectable before puberty.⁵

Mouse studies have demonstrated that *Nf1*^{-/-} Schwann cells are necessary, but not sufficient, for tumor formation to occur. Parada and coworkers⁷⁷ demonstrated that *Nf1*^{fllox/-};Krox20cre mice, in which 5% to 10% of Schwann cells are nullizygous for *Nf1* in an *Nf1* heterozygous background, developed plexiform neurofibromas. In contrast, *Nf1*^{fllox/fllox};Krox20cre mice with both *Nf1* alleles inactivated only in Schwann cells (other cells are wild type) failed to develop neurofibromas. Thus, tumor progression apparently requires interactions between *Nf1*^{-/-} Schwann cells and *Nf1*^{+/-} cell lineages in the tumor microenvironment. Mouse plexiform neurofibromas fail to develop if the *Nf1*^{+/-} bone marrow is replaced with bone marrow from an *Nf1*^{+/+} animal, suggesting that the growth and maintenance of neurofibromas is partially dependent on the presence of *Nf1*^{+/-} mast cells.⁸² Schwann cells with an *Nf1*^{-/-} genotype secrete soluble kit ligand, which is chemotactic to mast cells, enhancing mast cell migration, proliferation, and survival.⁸³ On the other hand, mast cells are also components of normal human and mouse peripheral nerves.⁸⁴

Imatinib mesylate (Gleevec/Glivec; Novartis, East Hanover, NJ), a potential inhibitor of c-kit, was used to treat *Nf1*^{fllox/-};Krox20cre mice.⁸² Volumetric analysis per-

formed with 2-[^{18}F]-fluoro-2-deoxy-D-glucose positron emission tomography showed that imatinib mesylate reduced tumor volume and metabolic activity by approximately 50% in treated mice. This led to the first clinical trial in which a 3-year-old girl with a highly vascularized, nonresectable, and progressively growing neurofibroma was treated with imatinib mesylate. After 3 months of treatment, magnetic resonance imaging indicated a 70% reduction in tumor volume.⁸² However, it is still unclear whether these results can be replicated in a wider population of patients with NF1 of varying ages and tumor burdens.

Approximately 2% to 5% of plexiform neurofibromas progress to MPNSTs.⁸⁵ However, because bi-allelic inactivation of the *NF1* gene occurs in benign neurofibromas, mutations in the *NF1* gene alone are not sufficient for the progression from a plexiform neurofibroma to an MPNST. Additional mutations in other regulatory genes have been described in MPNSTs, including the homozygous deletion of *CDKN2A*, which encodes p16^{INK4A}, and p14ARF and TP53 loss.³⁴ Furthermore, karyotypes in many MPNSTs are complex. It remains to be elucidated whether NF1-related MPNSTs are always derived from plexiform neurofibromas or whether they can arise directly from peripheral nerves.

Pathogenesis of Cutaneous Neurofibromas

Cutaneous neurofibromas occur in virtually all adults with NF1. They appear at puberty and increase in number and size with age and pregnancy. However, cutaneous neurofibromas have restricted growth potential; the tumor diameter usually varies between a few millimeters and approximately 2 cm, rarely exceeding 3 cm. A subpopulation of cells cultured from human cutaneous neurofibromas displays characteristics typical of Schwann cells and harbor a bi-allelic inactivation of the *NF1*

gene.^{16,32,67} The limited growth of cutaneous neurofibromas may reflect the developmentally late occurrence of the *NF1* second-hit mutation essential for their growth. The *NF1* diploinsufficient Schwann cells may, thus, have a limited potential for clonal cell division. The clonality of *NF1*^{-/-} Schwann cells in a discrete neurofibroma is supported by the facts that each cutaneous neurofibroma has its own unique second-hit mutation and that only one second-hit mutation is found in each tumor. The *NF1*^{-/-} genotype obviously provides these cells with a growth advantage, but it is not known what proportion of the Schwann cells in a cutaneous neurofibroma carries an *NF1*^{-/-} genotype and how much of the tumor growth can be explained by the increase in the number of other cells with an *NF1*^{+/-} genotype.

The previous understanding has been that the cutaneous neurofibromas may arise from small nerve twigs. However, Schwann cells do not represent a continuously dividing cell population, which makes them unlikely hosts for the second-hit mutation. The question of the cellular origin of cutaneous neurofibromas has been approached using a mouse model with an *Nf1*^{+/-} background and a tamoxifen-inducible second hit in dermal stem/progenitor cells.⁸⁶ These mice developed cutaneous neurofibromas on topical application of tamoxifen and subsequent double *Nf1* gene inactivation. Analogous lineage tracing experiments using human tissues are, however, not currently possible. In addition to the dermis, other potential sources of multipotent cells with high mitotic potentials include subcutaneous fat and hair roots.^{87,88} Previous histological analyses of apparently normal skin from patients with NF1 revealed minute neurofibromas, presumably in the early stages of development, in the immediate vicinity of the hair follicular apparatus.⁸⁹ In a recent study, we showed that human cutaneous neurofibromas contain multipotent *NF1*^{+/-} precursor cells capable of differentiating *in vitro* into cell types found in neurofibromas, in-

Figure 1. Proposed model for the development of cutaneous neurofibromas. As opposed to the traditional understanding of neurofibromas being formed by the dissociation of peripheral nerve components, the proposed model views neurofibromas as resulting from divergent cellular differentiation of multipotent precursor cells. The requirements for the development of neurofibromas include the presence of a clonal population of *NF1*^{-/-} Schwann cells in a microenvironment harboring other cell types with an *NF1*^{+/-} genotype. The potential sources of *NF1*^{+/-} Schwann cells are small cutaneous nerve twigs, hair roots, and subcutaneous fat. The close proximity of hair and incipient neurofibromas may suggest that the multipotent *NF1*^{+/-} cells residing in this area are the major source of neurofibroma-derived progenitors (NFPs), which can give rise to the different cell types found in the neurofibromas. Animal studies have suggested that the neurofibroma mast cells may be derived from bone marrow. These cellular components alone are, apparently, not sufficient to allow the cutaneous neurofibromas to develop into visible tumors because the latter do not appear before puberty, when marked changes in the hormonal status of an individual take place.

cluding Schwann cells, fibroblasts, and epithelial cells.⁶⁷ Together, these results suggest that the multipotent cells present in the hair follicles may contribute to the development of cutaneous neurofibromas.

Conclusions

Figure 1 summarizes the interplay between multiple cell types with *NF1*^{+/−} genotypes and *NF1*^{−/−} Schwann cells. In addition to the *NF1* nullizygous Schwann cells, neurofibromas contain a high number of other cells with an *NF1*^{+/−} genotype, including Schwann cells, neurons, perineurial cells, fibroblasts, adipocytes, epithelial cells, and mast cells.

Although the mutations in the *NF1* gene are sufficient to cause NF1 syndrome, the pathoetiology of the multiple manifestations of the disease in different organ systems seems increasingly complex. The question emerges as to whether the different cellular phenotypes originate from disintegrated peripheral nerves or whether they represent divergent cellular differentiation pathways of multipotent precursor cells.

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