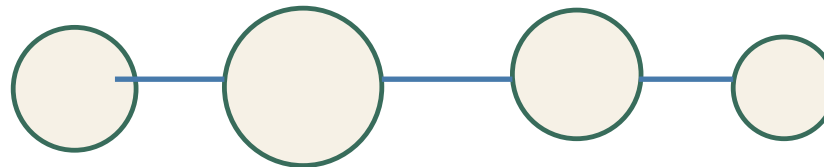


Neurofibromatosis Type 1

Genetics • Tumor biology • Neurofibroma morphology • Malignant progression



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Learning objectives

Relate NF1 tumor-suppressor loss to sustained RAS signaling.

Distinguish cutaneous, diffuse, and plexiform neurofibroma morphologies.

Explain neoplastic Schwann cells and stromal cooperation.

Connect multisystem phenotype to the risk of malignant nerve-sheath tumors.

Peripheral nerve sheath tumors: The framework

Schwannoma

Schwann-cell tumor;
Prominently associated with
NF2.

Neurofibroma

Heterogeneous tumor;
Sporadic or NF1-associated.

MPNST

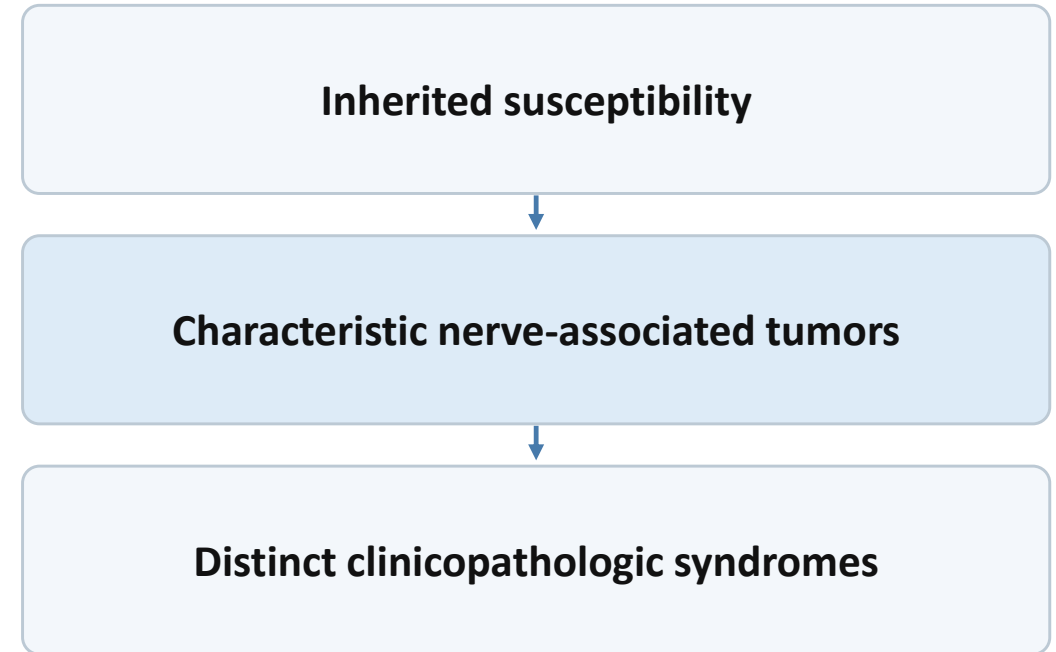
Malignant peripheral nerve
sheath tumor; May arise in
NF1.

NF1 belongs to a family of tumor syndromes

NF1, NF2, and schwannomatosis are distinct familial tumor syndromes.

Shared peripheral nerve associations do not imply identical tumor spectra.

NF1 particularly links neurofibroma formation with MPNST risk.



Schematic (editable; Not a tissue image)

NF1 is a multisystem neoplastic disorder

NF1 combines nonneoplastic manifestations with multiple tumor types.

The disease affects the skin, nerves, eye, skeleton, and nervous system.

Its manifestations cannot be explained by a single localized mass.

Cutaneous

Macules;
Neurofibromas

Neural

Nerve sheath
tumors; Gliomas

Ocular

Lisch nodules; Optic
glioma

Other

Skeletal defects;
Pheochromocytoma

NF1 is relatively common

A frequency of approximately 1 in 3,000 individuals.

Its clinical importance extends beyond the presence of cutaneous tumors.

The associated neoplastic spectrum includes benign and malignant entities.

~1 / 3,000

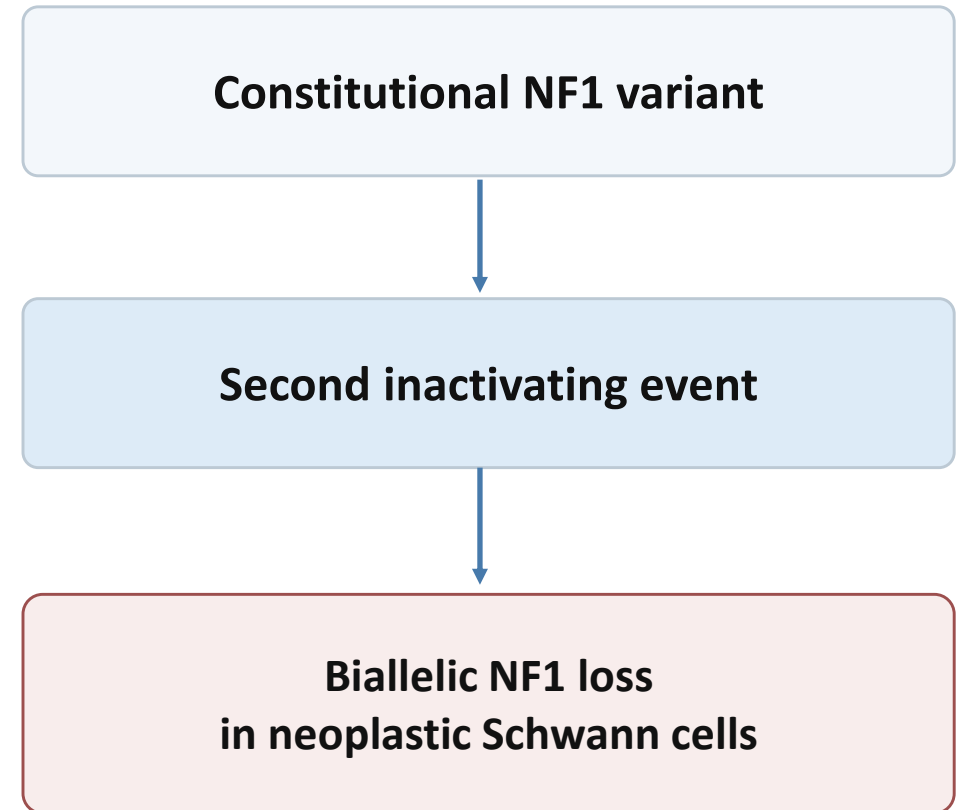
Reported frequency of NF1

Autosomal dominant inheritance

The disorder follows an autosomal dominant pattern.

One inherited pathogenic NF1 allele is sufficient for constitutional susceptibility.

Development of a given tumor is linked to further loss of NF1 function in neoplastic cells.



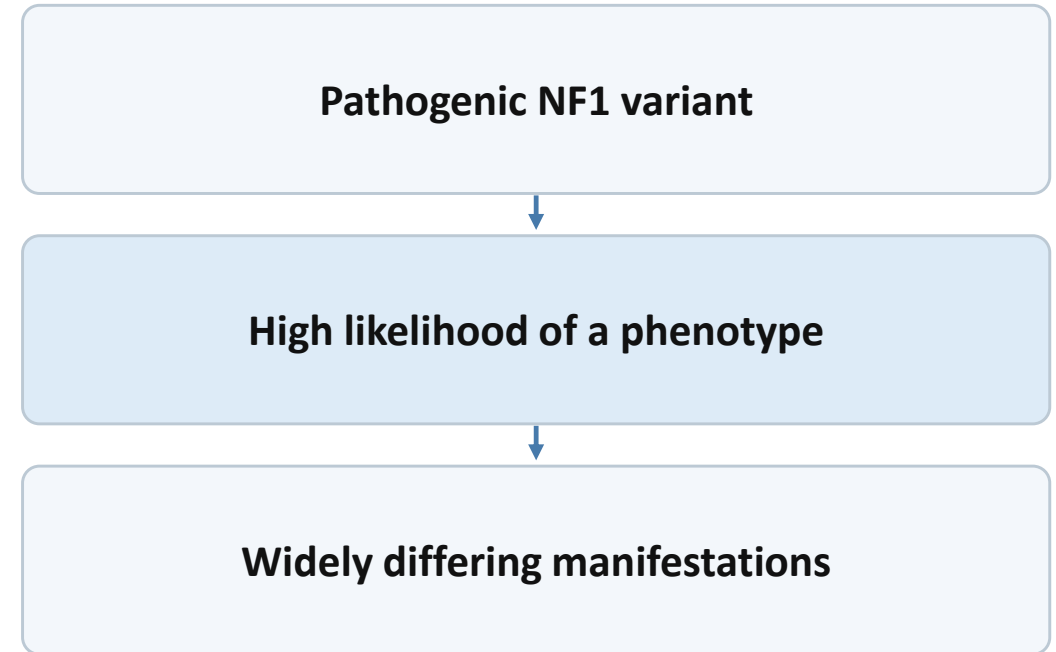
Schematic (editable; Not a tissue image)

High penetrance is not uniform severity

NF1 is characterized by high penetrance.

Clinical expression varies widely across affected individuals.

Severity must not be inferred solely from the inheritance pattern.



Schematic (editable; Not a tissue image)

Variable expressivity explains clinical diversity

Some affected individuals have relatively subtle cutaneous findings.

Others develop numerous tumors and serious systemic manifestations.

Phenotypic variability occurs within the same genetic disease.

Mild

Subtle pigmentation

Intermediate

Multiple neurofibromas

Severe

Extensive multi-organ disease

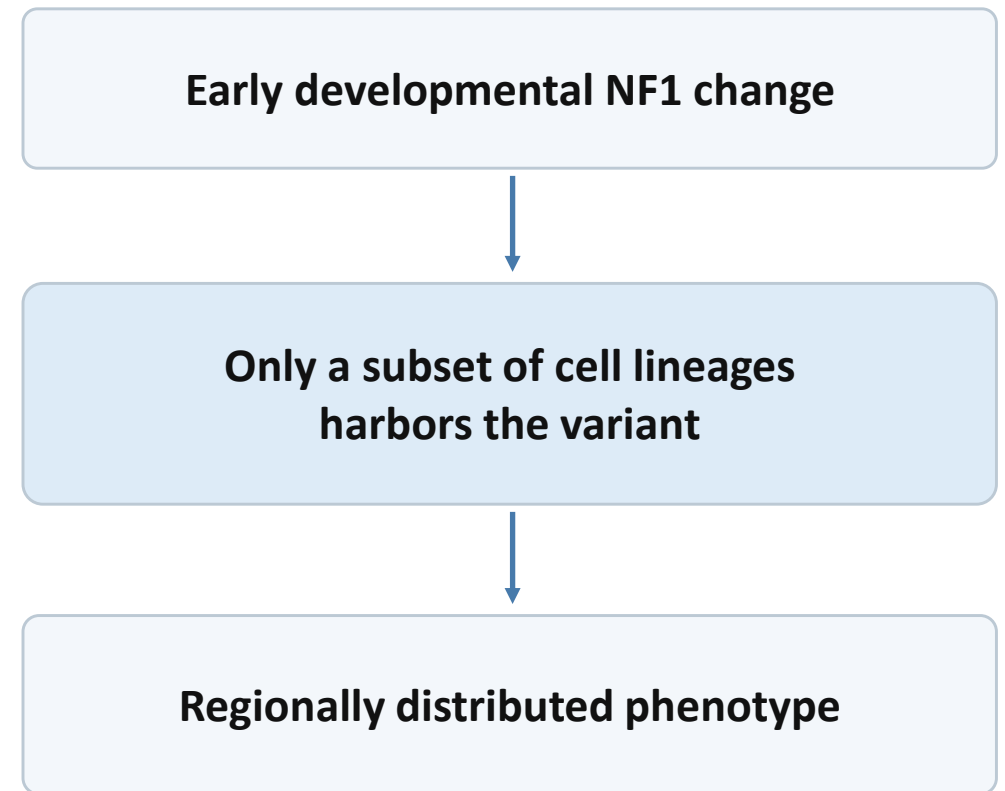
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Mosaic NF1 can produce regional disease

Some patients have manifestations limited to specific body regions.

Such localized patterns to mosaicism.

The clinical distribution reflects which cell populations harbor the alteration.



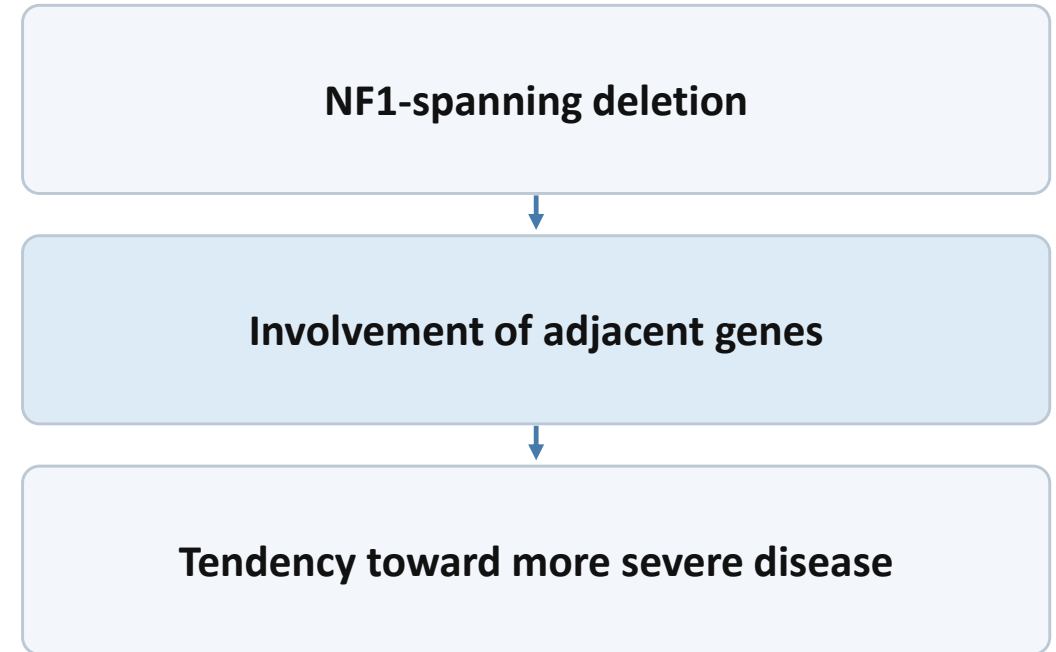
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Large NF1 deletions may confer severe phenotypes

Large chromosomal deletions can extend beyond the NF1 locus.

Loss of adjacent genes is associated with more severe manifestations.

Variant architecture therefore contributes to phenotypic severity.



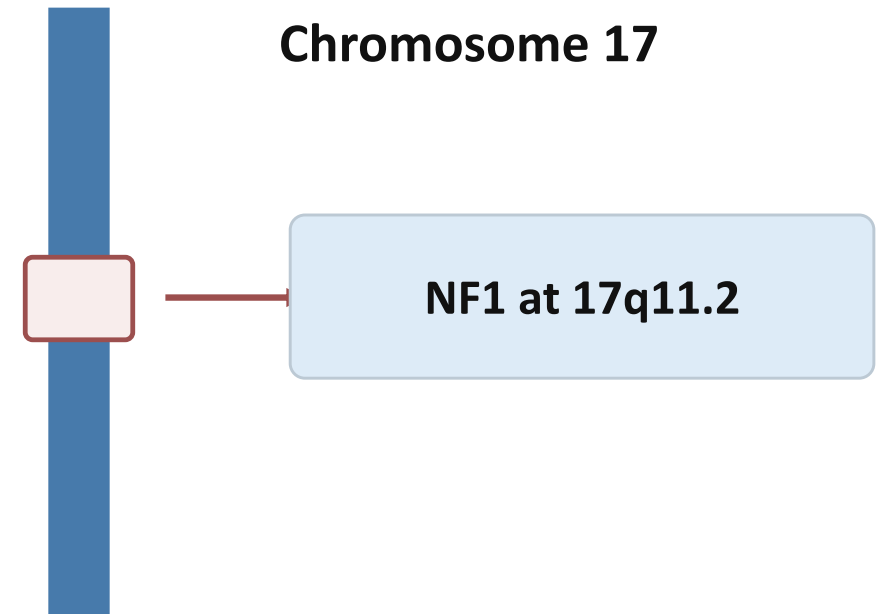
Schematic (editable; Not a tissue image)

The NF1 locus is on chromosome 17

NF1 resides at 17q11.2.

It encodes the protein neurofibromin.

Its loss-of-function status establishes NF1 as a tumor-suppressor syndrome.



Gene product: Neurofibromin

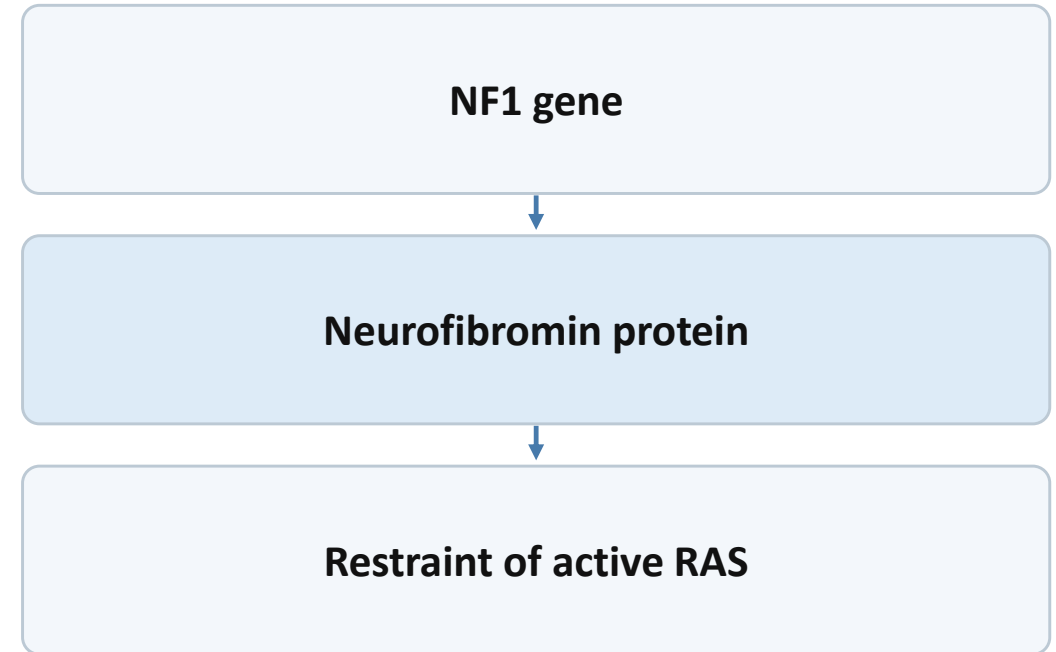
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Neurofibromin is the NF1 gene product

Neurofibromin is a negative regulator of RAS signaling.

Normal neurofibromin limits activation of a growth-promoting signaling switch.

Its absence is central to NF1-associated neoplasia.



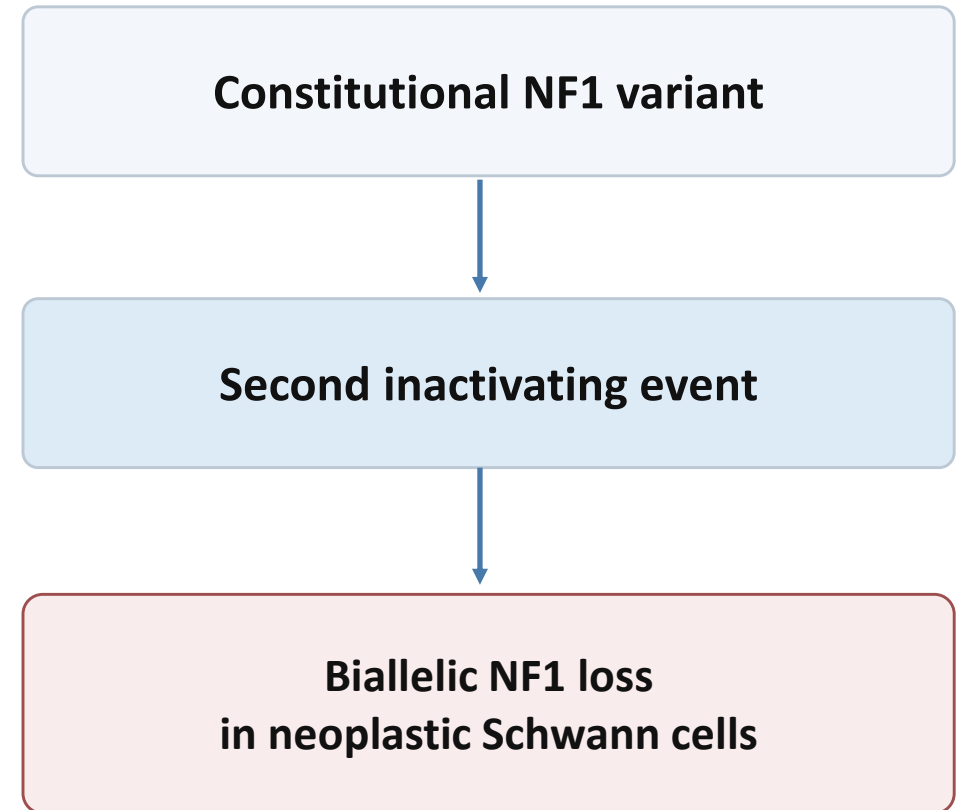
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NF1 functions as a tumor suppressor

Inherited loss of one NF1 copy predisposes tissues to tumor formation.

NF1-related neoplastic cells have biallelic defects.

The decisive tumor-cell effect is complete loss of neurofibromin.



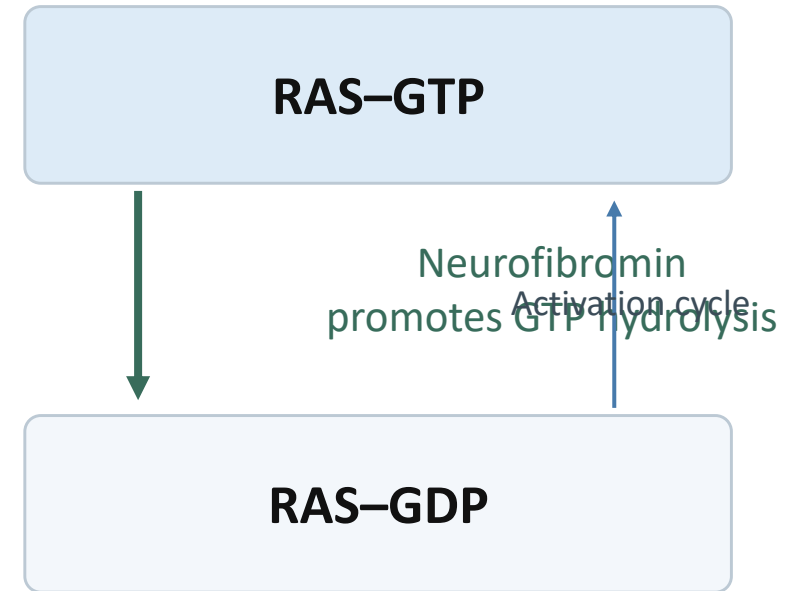
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RAS signaling has active and inactive states

RAS switches between GTP-bound active and GDP-bound inactive forms.

Neurofibromin accelerates RAS GTP hydrolysis and limits signaling.

The relevant pathology is failure to terminate RAS activity.



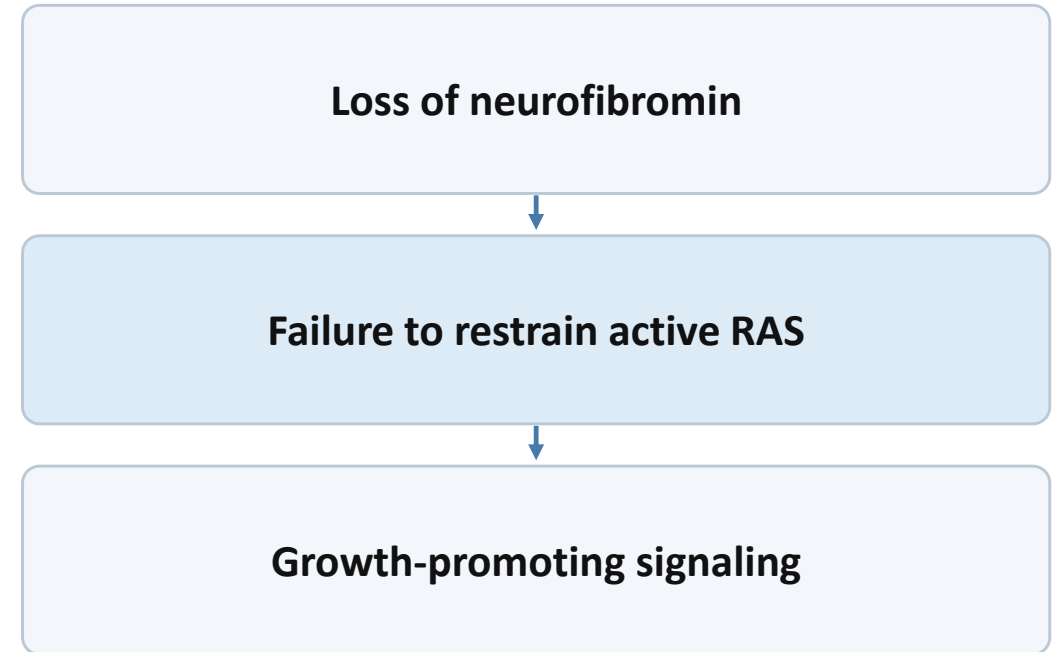
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Neurofibromin loss prolongs RAS activity

With NF1 loss, RAS remains in its active state for longer.

Prolonged signaling can promote cell growth and survival.

This provides the molecular link from tumor-suppressor loss to tumor formation.



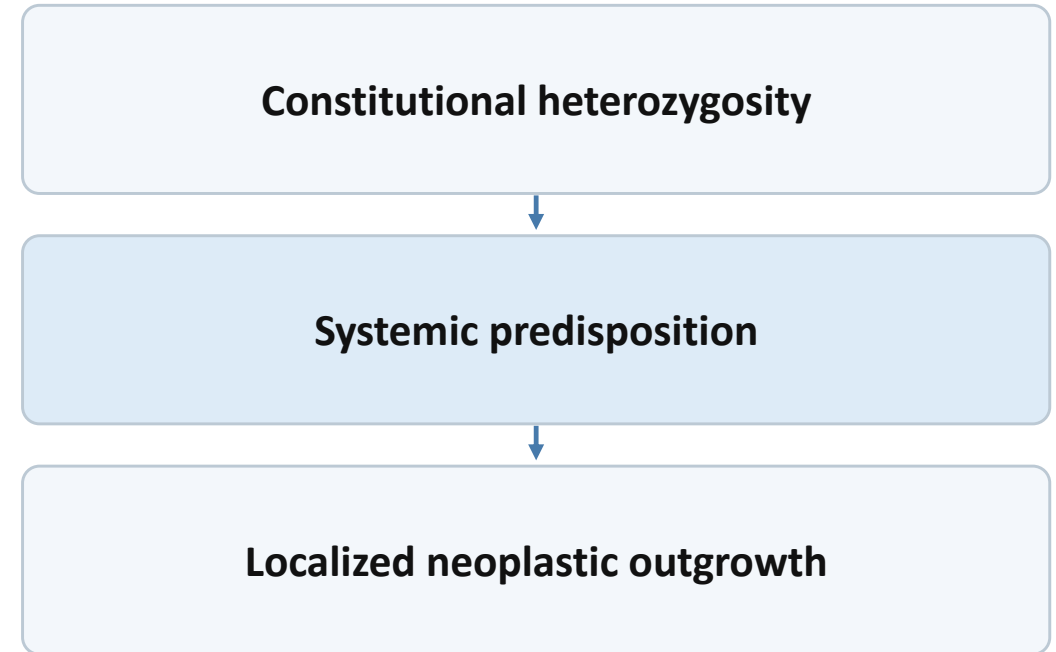
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An inherited variant creates susceptibility

Constitutional NF1 loss of function affects multiple cell lineages.

Syndromic findings can occur without a tumor at every anatomic site.

Tumor development requires a separate explanation at the cellular level.



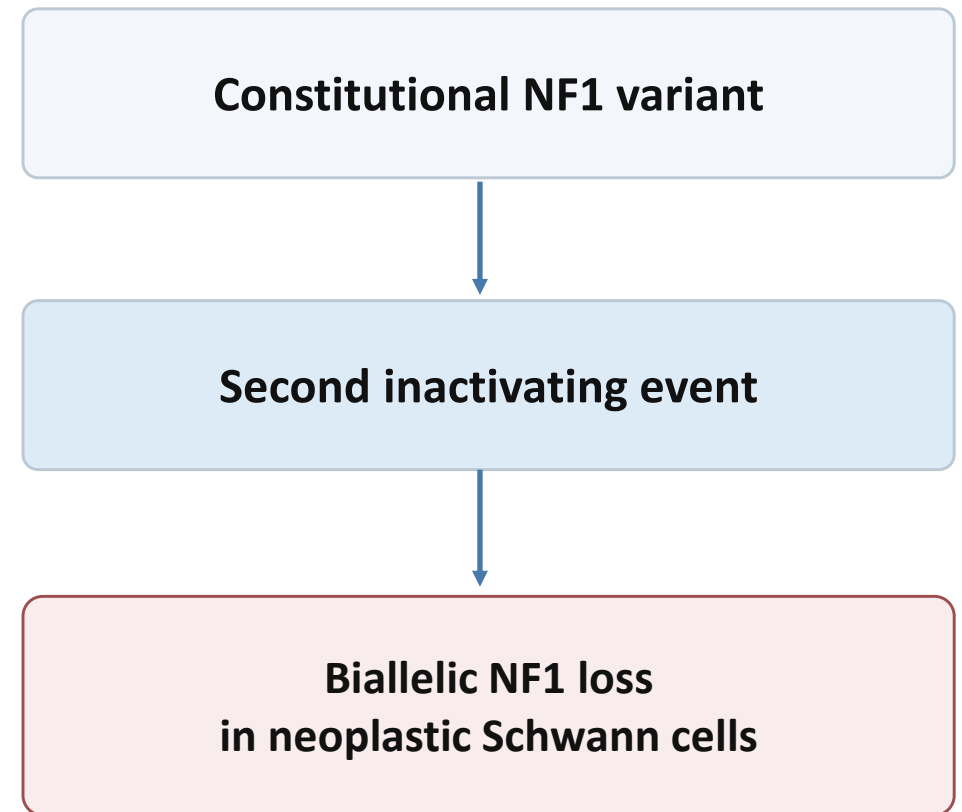
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Biallelic NF1 defects occur in tumor cells

Biallelic NF1 defects in NF1-related neoplastic cells.

Both copies of the tumor-suppressor gene lose effective function.

This explains why a focal tumor can arise in a systemic disorder.



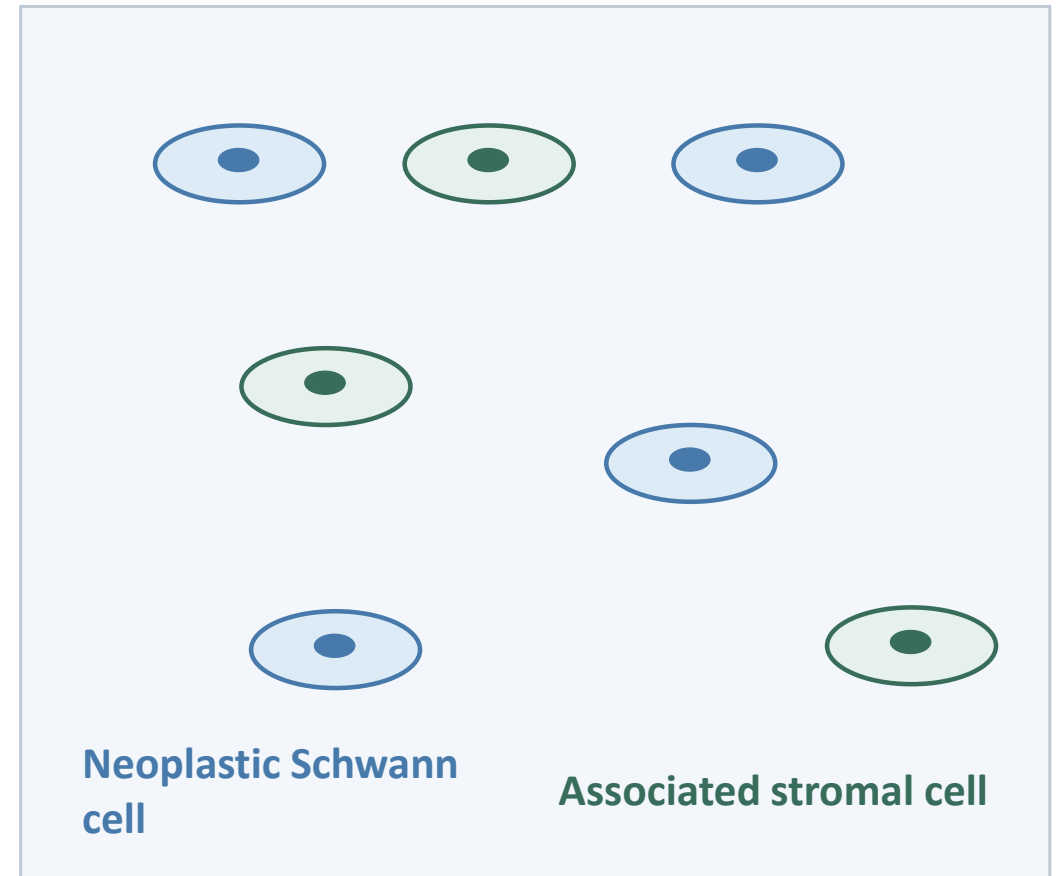
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The neoplastic population is not the entire lesion

Neurofibromas contain several cellular populations.

Complete loss of neurofibromin identifies the neoplastic Schwann cells.

Other intermixed populations participate in the tumor environment.



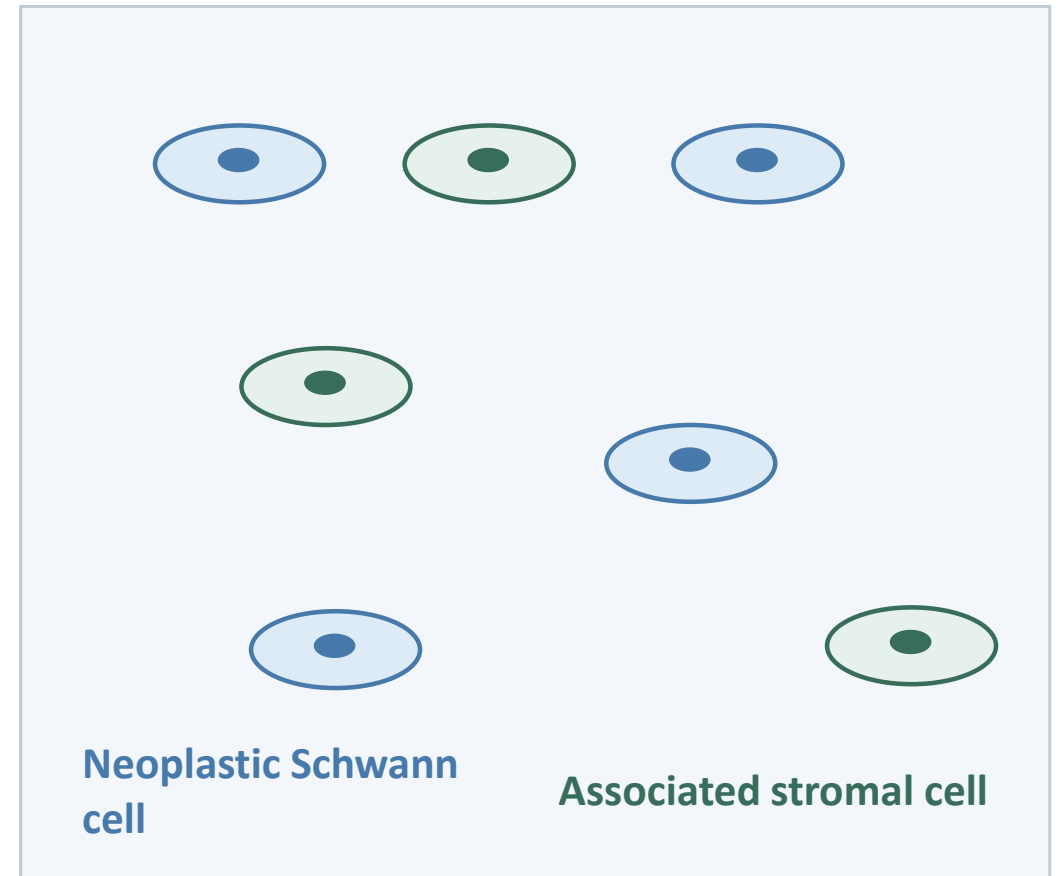
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Schwann cells are the neoplastic component

Neurofibroma Schwann cells show complete neurofibromin loss.

They are admixed with stromal and inflammatory cells.

Morphologic heterogeneity does not imply that every cell is neoplastic.



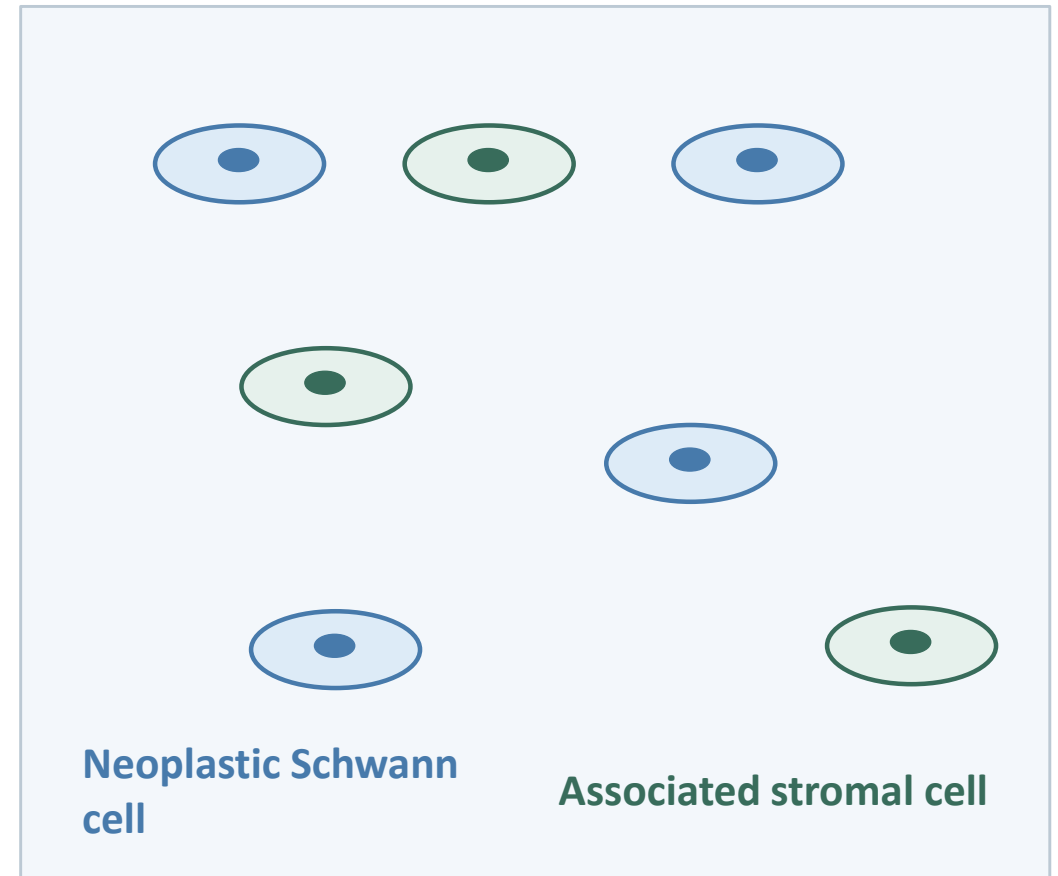
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The neurofibroma microenvironment is mixed

Neurofibromas include perineurial-like cells, fibroblasts, and mast cells.

CD34-positive spindle cells are another stromal population.

Neoplastic Schwann cells and associated cells form a cellular ecosystem.



Schematic (editable; Not a tissue image)

Haploinsufficiency modifies the stroma

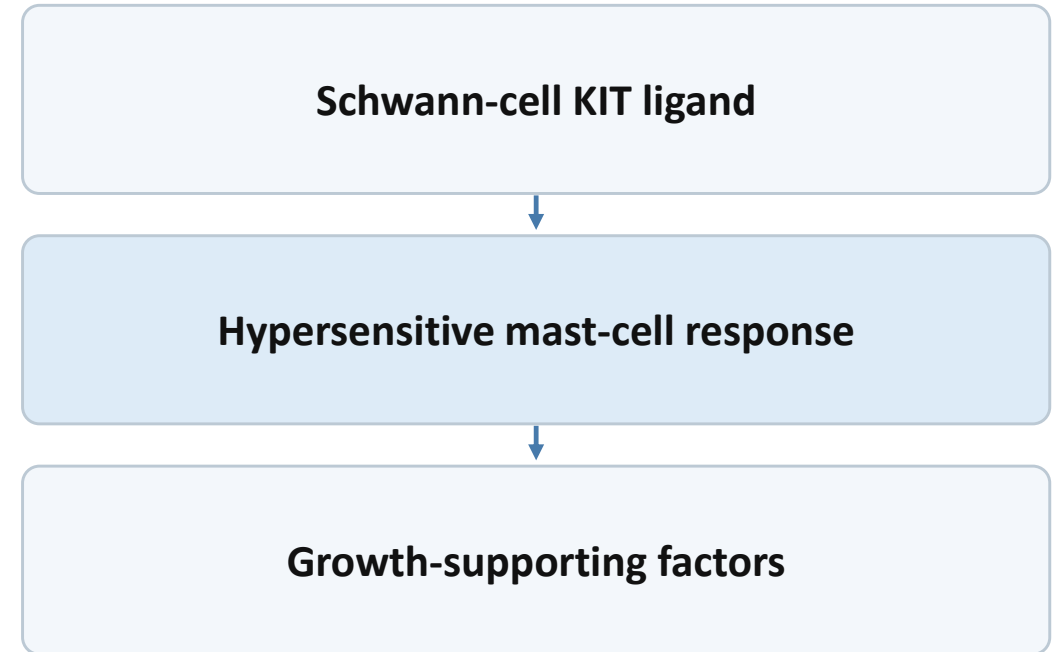
Feature	Schwann cells	Associated stromal cells
NF1 status	Biallelic loss	Often NF1 haploinsufficient
Neoplastic role	Tumor-forming population	Supportive tumor microenvironment
Mechanistic implication	Autonomous RAS dysregulation	Altered response to local signals

Mast cells contribute to reciprocal signaling

NF1-haploinsufficient mast cells may be hypersensitive to KIT ligand.

Schwann cells can provide the KIT ligand.

Activated mast cells may secrete factors that stimulate Schwann-cell growth.



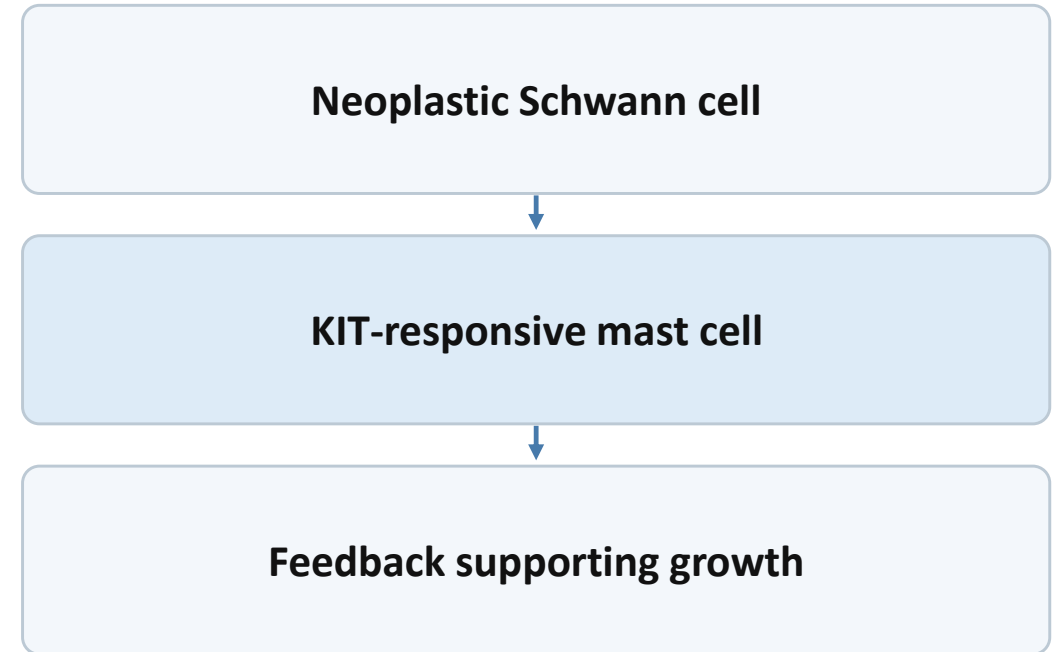
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Tumor–stroma cross-talk is mechanistically important

Tumor growth reflects reciprocal signals, not merely Schwann-cell proliferation.

The mast-cell/KIT example illustrates paracrine support.

KIT signaling as a potential therapeutic target, not as established curative therapy.



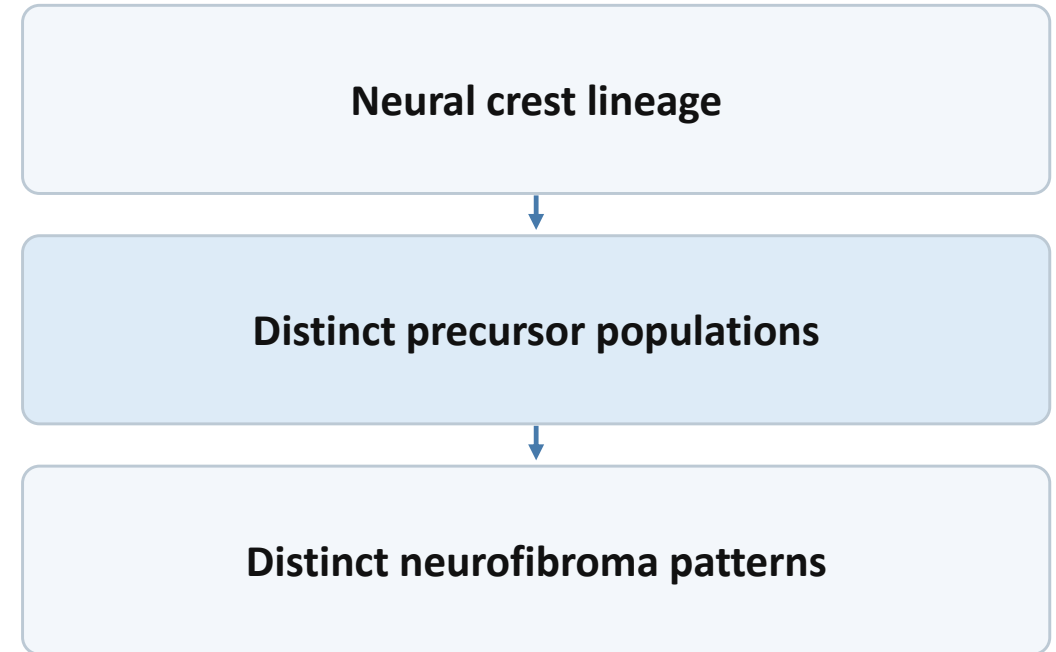
Schematic (editable; Not a tissue image)

Different neurofibromas may have distinct origins

Plexiform and dermal neurofibromas may arise from distinct precursors.

These proposed precursors are neural crest-derived.

Different progenitors help explain divergent growth patterns.



Schematic (editable; Not a tissue image)

NF1-associated tumors extend beyond nerves

Neurofibromas, MPNSTs, optic nerve gliomas, other gliomas, and pheochromocytomas.

The spectrum includes lesions of differing tissue origin and behavior.

Clinical evaluation should not equate NF1 solely with cutaneous neurofibromas.

Cutaneous

Macules;
Neurofibromas

Neural

Nerve sheath
tumors; Gliomas

Ocular

Lisch nodules; Optic
glioma

Other

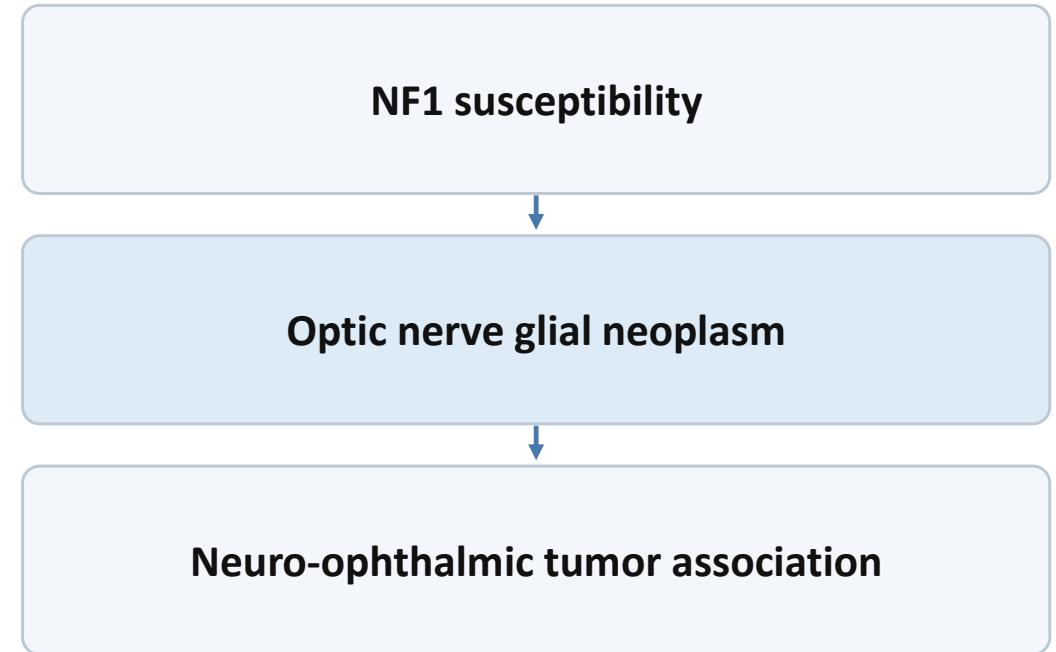
Skeletal defects;
Pheochromocytoma

Optic nerve gliomas are part of the NF1 spectrum

Optic nerve glioma is a characteristic associated tumor.

It illustrates involvement of the central nervous system.

Its inclusion is a tumor-spectrum association, not a histologic diagnosis from skin findings.



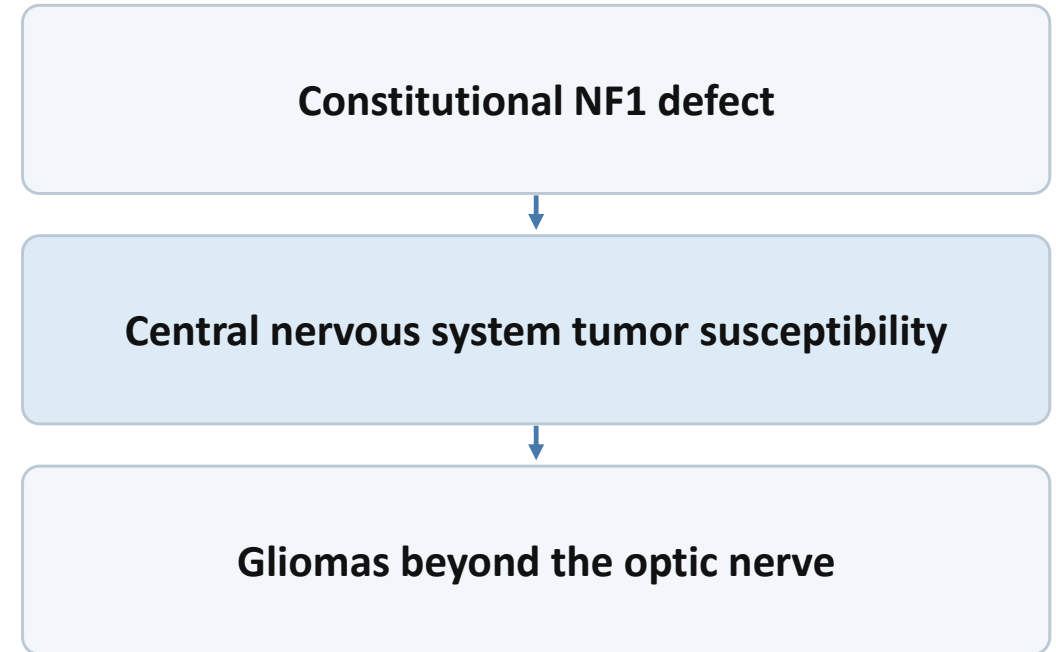
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Other gliomas also occur in NF1

The associated glioma spectrum is not confined to the optic nerve.

The Robbins peripheral nerve chapter cross-references the CNS chapter.

Histologic classification of specific gliomas is outside this NF1 unit.



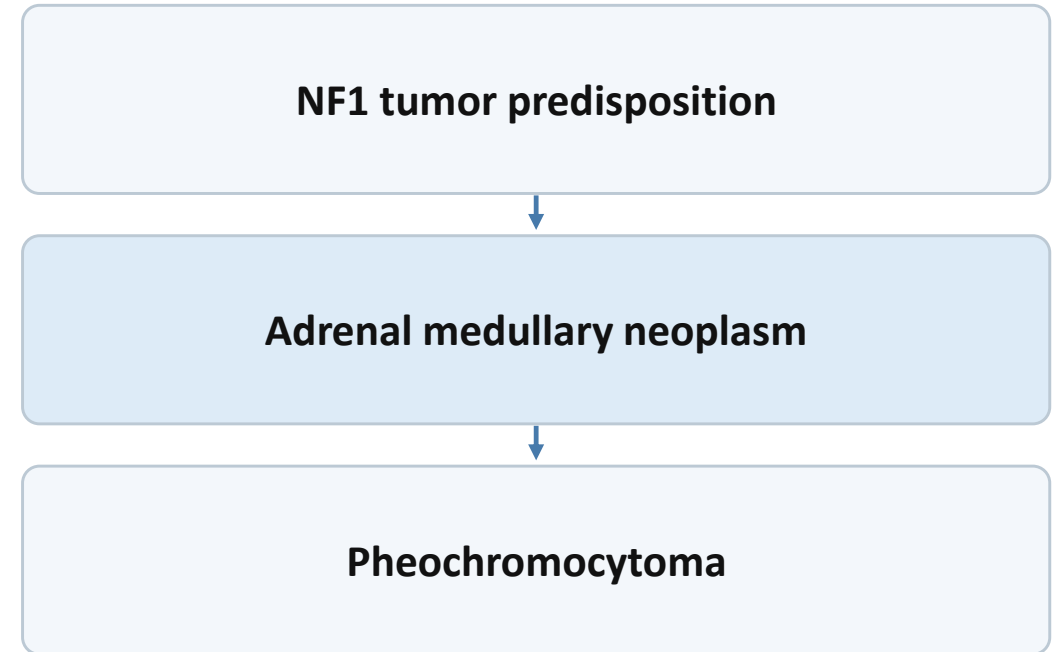
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Pheochromocytoma represents a distinct tumor lineage

Pheochromocytomas are included among NF1-associated neoplasms.

They show that the disease predisposes to tumors beyond nerve sheaths.

Do not mistake a pheochromocytoma for a neurofibroma morphologically.



Schematic (editable; Not a tissue image)

Café-au-lait spots are nonneoplastic signs

Feature	Café-au-lait macule	Neurofibroma
Category	Pigmented macule	Benign nerve sheath tumor
Pathologic process	Hyperpigmentation	Schwann-cell neoplasia with stroma
Role in NF1	Nonneoplastic manifestation	Associated tumor phenotype

Lisch nodules are ocular findings

Feature	Lisch nodule	Optic nerve glioma
Location	Iris	Optic nerve
Category	Pigmented ocular nodule	Glial tumor
Teaching point	Clinical phenotype	Neoplastic association

Skeletal defects belong to the NF1 phenotype

Skeletal abnormalities are included among the nonneoplastic manifestations.

They reinforce the systemic nature of the disease.

A tumor-only conceptual model misses an important category of findings.

Cutaneous

Macules;
Neurofibromas

Neural

Nerve sheath
tumors; Gliomas

Ocular

Lisch nodules; Optic
glioma

Other

Skeletal defects;
Pheochromocytoma

Neurologic manifestations are not all tumors

Feature	Nonneoplastic features	Neoplastic features
Examples	Intellectual disability; Seizures	Gliomas; Neurofibromas
Category	Clinical manifestations	Tumor lesions
Interpretation	Systemic disease effects	Tumor-type evaluation

The NF1 phenotype integrates several organ systems

Skin findings can coexist with ocular, skeletal, and nervous-system changes.

Associated tumors may involve peripheral nerves, CNS, or adrenal tissue.

The breadth of findings reflects multisystem constitutional susceptibility.

Cutaneous

Macules;
Neurofibromas

Neural

Nerve sheath
tumors; Gliomas

Ocular

Lisch nodules; Optic
glioma

Other

Skeletal defects;
Pheochromocytoma

Neurofibromas can be sporadic or syndromic

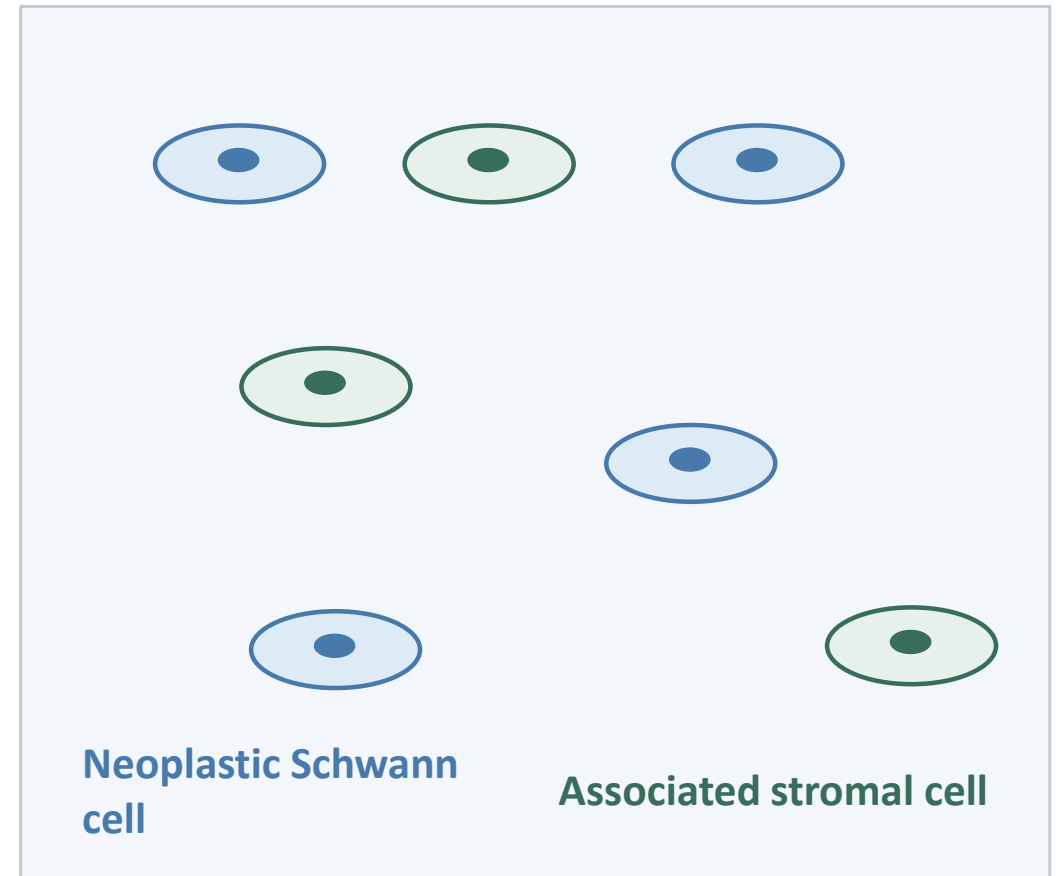
Feature	Sporadic neurofibroma	NF1-associated neurofibroma
Presentation	May be isolated	May be multiple or plexiform
Genetic context	No inferred systemic NF1 diagnosis	Constitutional NF1 susceptibility
Caution	Single lesion $\neq$ syndrome	Integrate systemic findings

Neurofibromas have heterogeneous cellularity

The neoplastic component shows Schwann-cell differentiation.

Additional cells include fibroblasts, perineurial-like cells, mast cells, and CD34-positive spindle cells.

This heterogeneity helps separate neurofibroma from a purely Schwann-cell tumor model.



Schematic (editable; Not a tissue image)

Three neurofibroma growth patterns

Localized cutaneous

Small dermal/subcutaneous,
often pedunculated nodules.

Diffuse

Broad infiltrative plaque
involving skin or soft tissue.

Plexiform

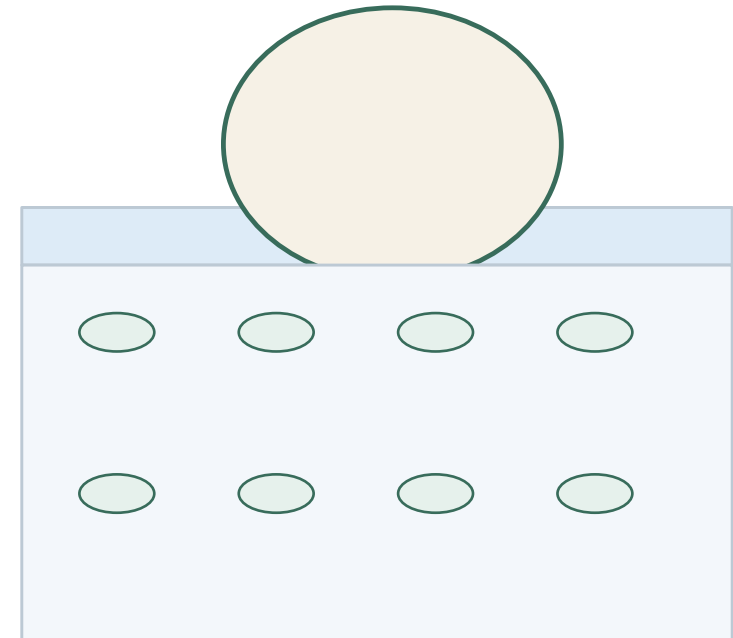
Multifascicular nerve-
associated growth;
Characteristically NF1.

Cutaneous neurofibroma: Clinical growth pattern

Superficial cutaneous neurofibromas often appear as pedunculated nodules.

They may occur singly in sporadic disease.

Multiple cutaneous neurofibromas may accompany NF1.



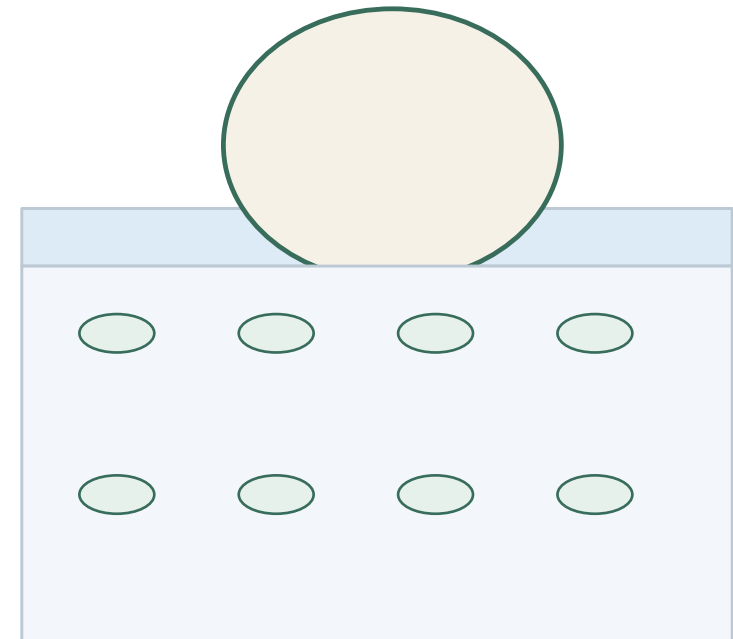
Schematic (editable; Not a tissue image)

Localized neurofibroma is well delimited but unencapsulated

Localized lesions arise in dermis and subcutaneous fat.

They are relatively well circumscribed without a complete capsule.

Histology typically shows low cellularity and a bland spindle-cell component.



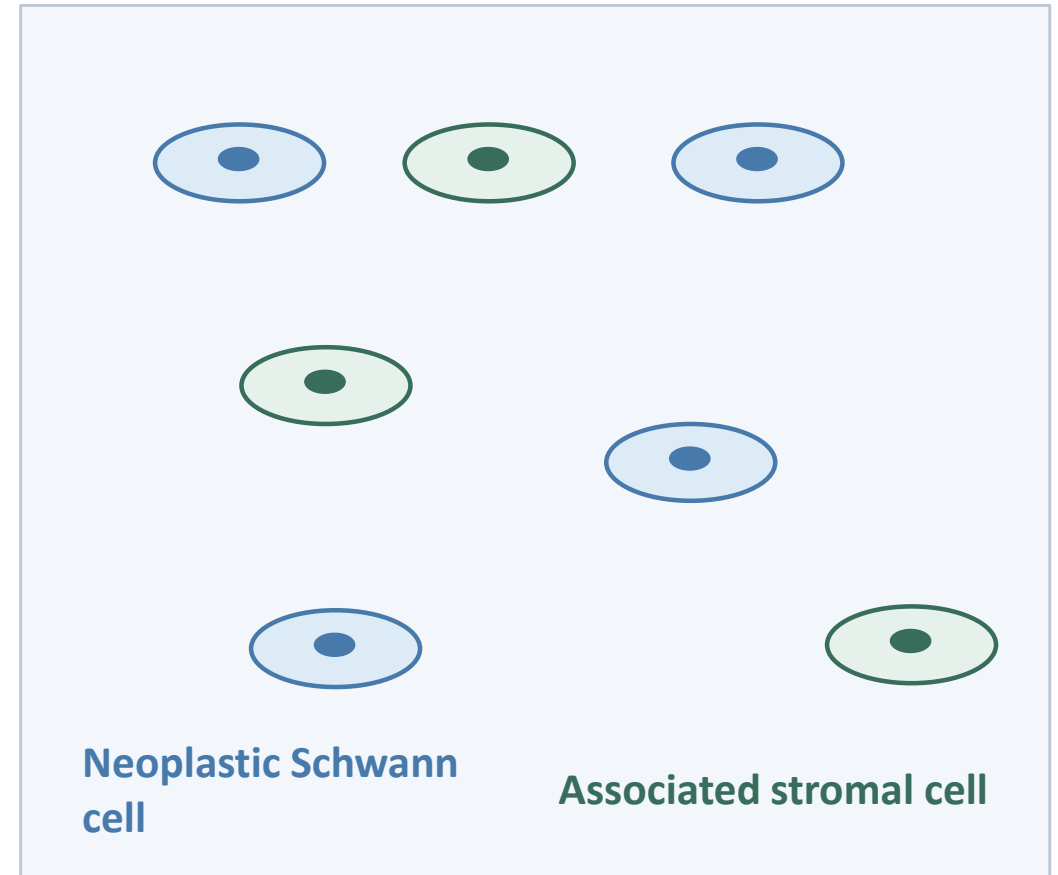
Schematic (editable; Not a tissue image)

The matrix of localized neurofibroma is loose

The supporting stroma includes loose collagen.

Schwann cells intermingle with other stromal elements.

Bland cytology and low cellularity should be interpreted with the growth pattern.



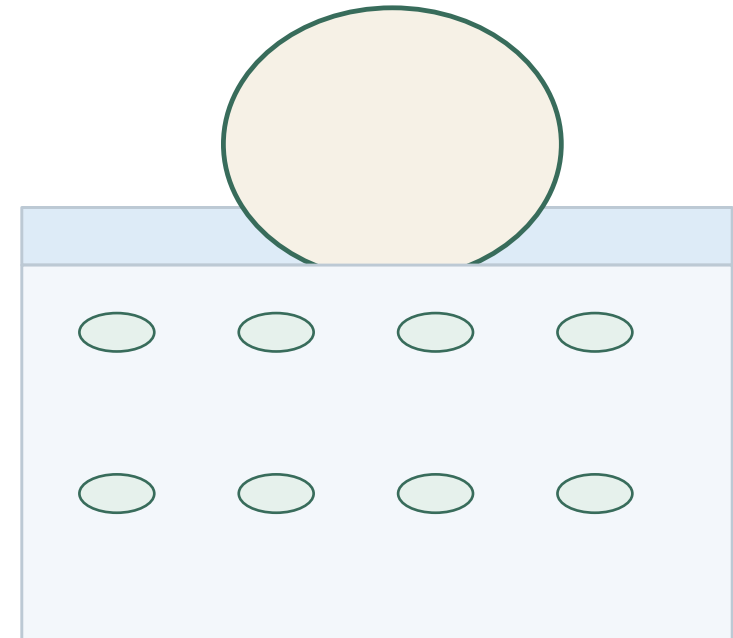
Schematic (editable; Not a tissue image)

Adnexal structures can be trapped at lesion edges

Localized cutaneous neurofibromas may entrap adnexal structures.

This does not automatically indicate malignant invasion.

The lesion remains a benign, often unencapsulated proliferation.



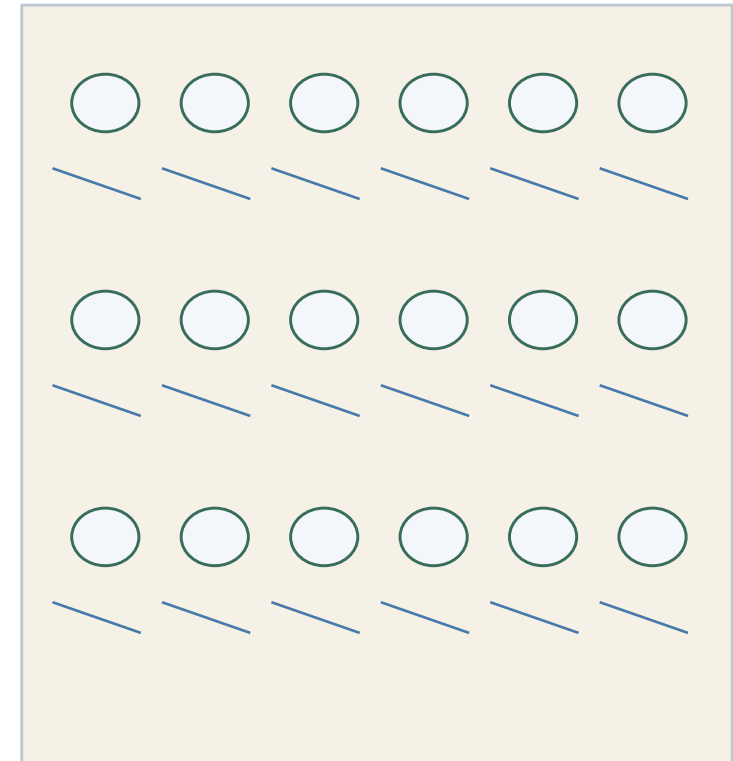
Schematic (editable; Not a tissue image)

Diffuse neurofibroma has an infiltrative growth pattern

Diffuse neurofibroma extends through dermis, subcutis, or deeper soft tissues.

The lesion forms a large, frequently plaque-like elevation.

Growth pattern—not cytologic atypia—distinguishes it from localized neurofibroma.



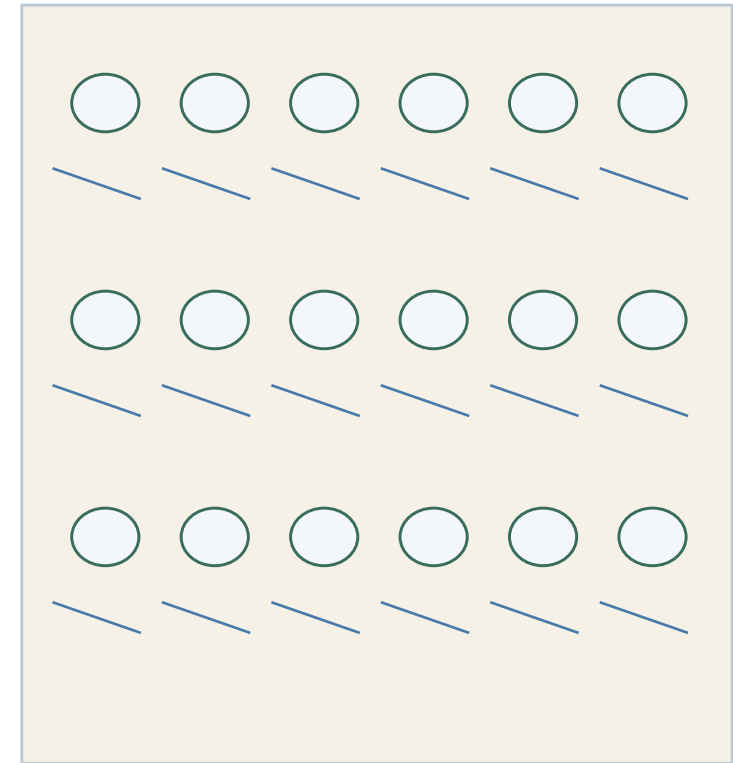
Schematic (editable; Not a tissue image)

Diffuse neurofibroma entraps normal tissues

The tumor may permeate fat and entrap skin appendages.

Entrapment is an architectural clue to diffuse extension.

Cytology may remain similar to localized neurofibroma.



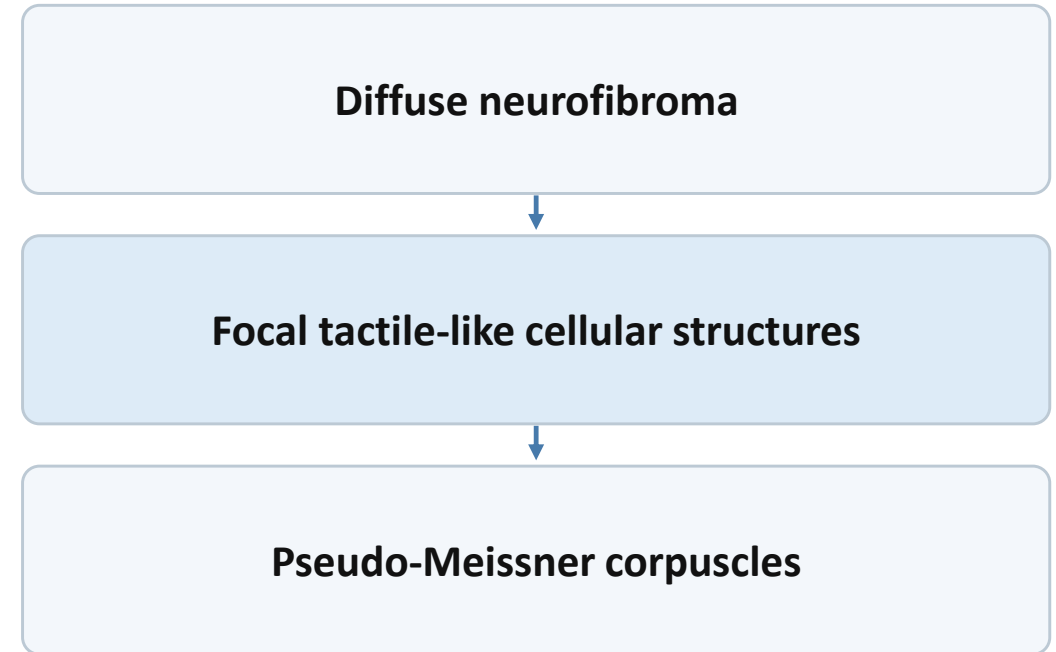
Schematic (editable; Not a tissue image)

Pseudo-Meissner corpuscles can occur in diffuse lesions

Focal cell clusters may resemble tactile corpuscles.

These are termed pseudo-Meissner corpuscles or tactile-like bodies.

They are an associated morphologic feature, not a separate neoplasm.



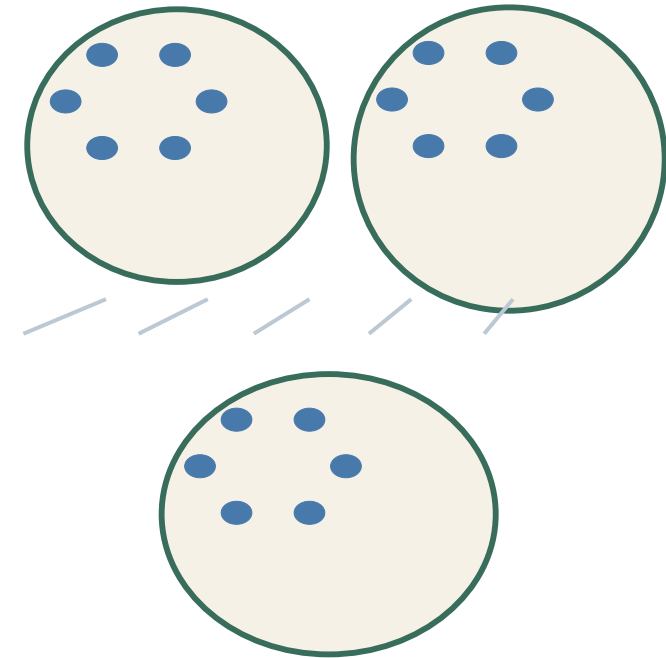
Schematic (editable; Not a tissue image)

Plexiform neurofibroma involves multiple fascicles

Plexiform lesions expand several nerve fascicles.

They may arise in superficial or deep nerves, including roots and larger nerves.

Their multifascicular architecture is a defining diagnostic concept.



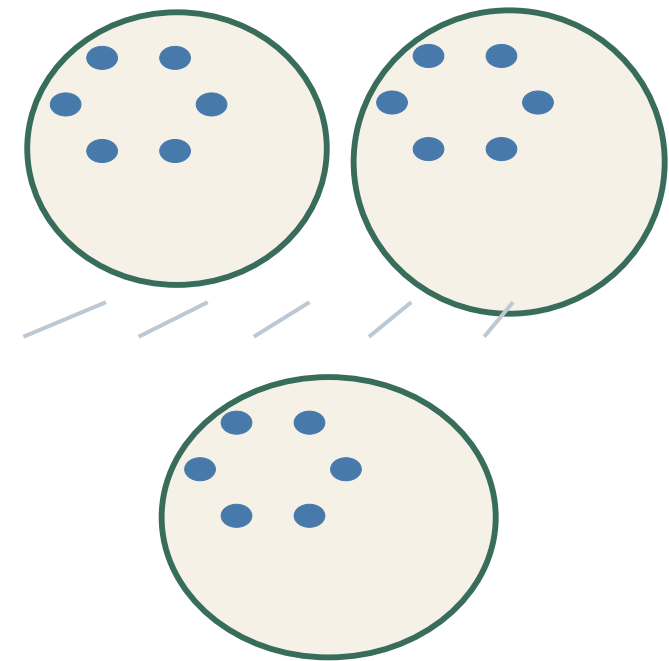
Schematic (editable; Not a tissue image)

Plexiform growth remodels nerve anatomy

Tumor cells expand fascicles within the nerve.

Associated axons are entrapped in the expanded structures.

The architecture is distinct from a tumor merely pushing a nerve aside.



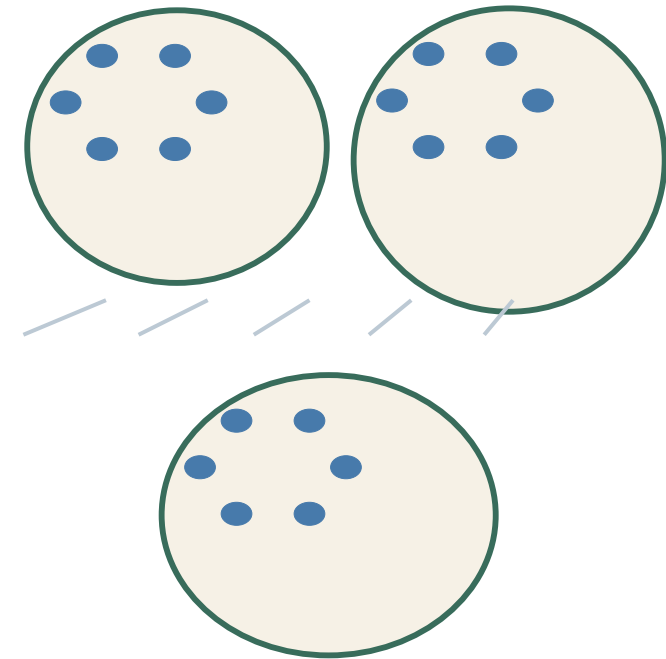
Schematic (editable; Not a tissue image)

The outer perineurium may be preserved

The external perineurial layer remains around expanded fascicles.

Individual fascicles may therefore appear encapsulated.

An apparent fascicular boundary does not mean the entire plexiform lesion is encapsulated.



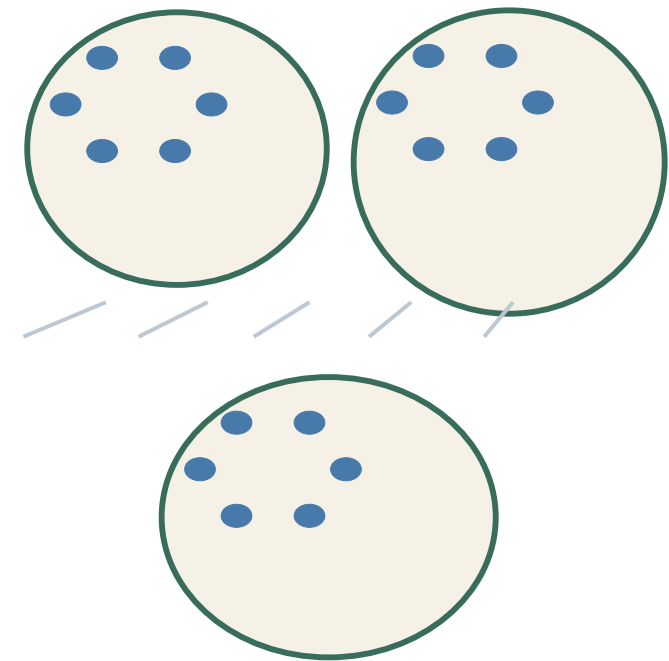
Schematic (editable; Not a tissue image)

Entrapped axons are an important architectural clue

Plexiform neurofibromas incorporate existing nerve fascicles.

Axons can remain entrapped amid the proliferating cells.

Understanding this feature clarifies their relationship to the parent nerve.



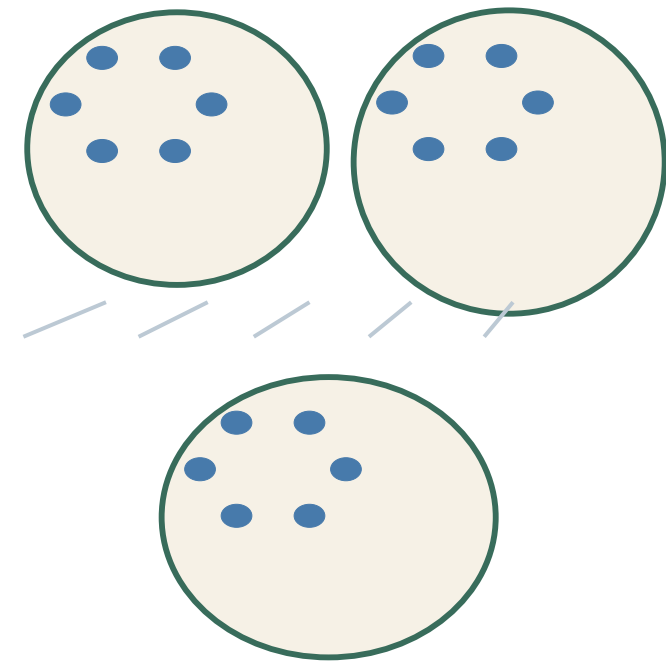
Schematic (editable; Not a tissue image)

Plexiform neurofibroma: “bag of worms” pattern

Multiple enlarged, tortuous fascicles produce aropy gross configuration.

The gross appearance as a “bag of worms.”

The term reflects the multifascicular growth pattern rather than a separate histologic subtype.



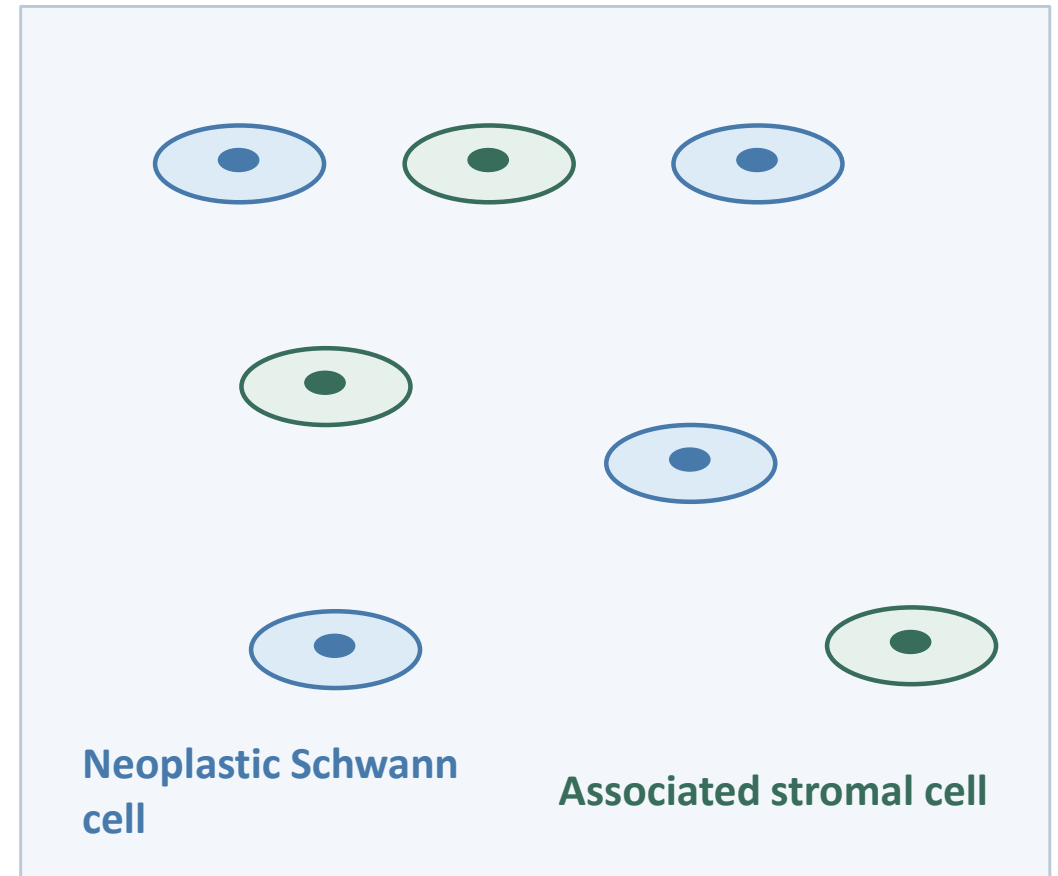
Schematic (editable; Not a tissue image)

Plexiform lesions show variable extracellular matrix

The stroma ranges from loose and myxoid to collagenous and fibrous.

Neurofibroma cells remain mixed with nonneoplastic stromal populations.

Matrix heterogeneity is compatible with the same neurofibroma category.



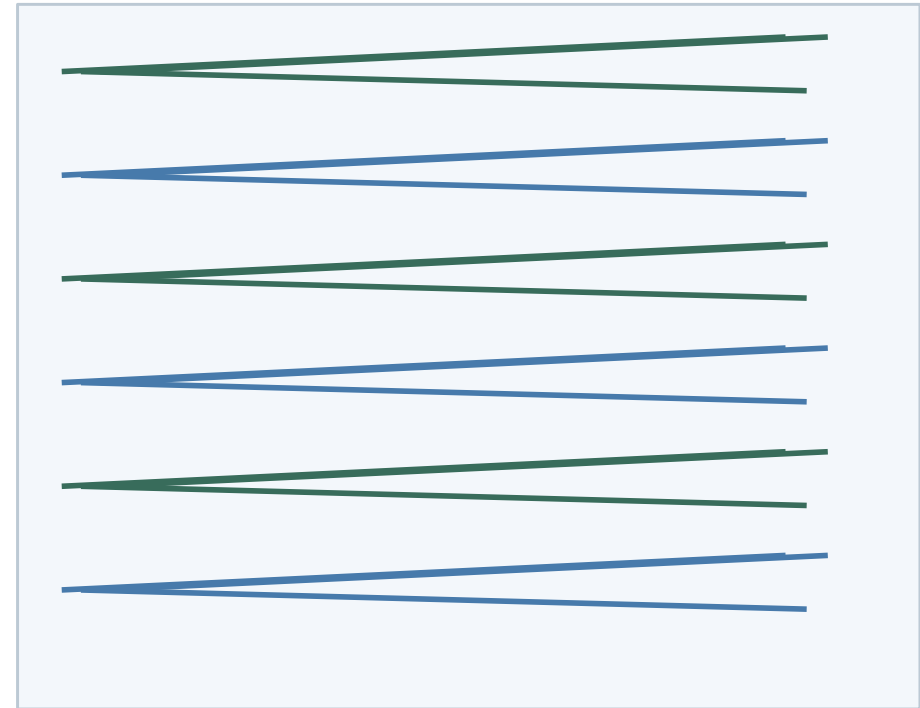
Schematic (editable; Not a tissue image)

“Shredded carrot” collagen is a morphologic metaphor

Plexiform neurofibromas may contain slender, wavy collagen bundles.

Robbins likens this collagen to shredded carrots.

The descriptor refers to collagen morphology; It is not a stain or molecular test.



Wavy collagen bundles (conceptual)

Schematic (editable; Not a tissue image)

Plexiform neurofibromas are strongly tied to NF1

Feature	Localized cutaneous	Plexiform
Anatomic pattern	Small skin nodule	Several enlarged nerve fascicles
Syndromic implication	May be sporadic	Strong NF1 association
Growth	Dermal/subcutaneous	Nerve-related, multifascicular

Growth pattern distinguishes neurofibroma variants

Localized

Nodular architecture; Well delimited but unencapsulated.

Diffuse

Broad tissue infiltration;
Trapped fat and appendages.

Plexiform

Many swollen nerve fascicles;
Axons remain entrapped.

Neurofibroma and schwannoma are not interchangeable

Feature	Neurofibroma	Schwannoma
Cell composition	Mixed stromal cell population	Predominantly Schwann cells
Nerve relationship	May incorporate nerve fascicles/axons	Typically displaces adjacent nerve
Syndromic association	NF1 (especially plexiform)	NF2 (especially vestibular)

Tumor architecture can predict surgical difficulty

Feature	Schwannoma	Plexiform neurofibroma
Pattern	Expansile mass adjacent to nerve	Enlargement of many fascicles
Axons	Parent nerve commonly displaced	Associated axons entrapped
Implication	Separable plane may exist	Integrated nerve anatomy complicates separation

Neurofibroma may progress to MPNST

In NF1, MPNSTs can arise through transformation of preexisting neurofibromas.

This benign-to-malignant progression is unusual among soft tissue tumors.

Plexiform neurofibromas are the usual precursor.

NF1-associated plexiform neurofibroma



Accumulation of malignant change



Malignant peripheral nerve sheath tumor

Schematic (editable; Not a tissue image)

MPNST risk is a clinically important NF1 consequence

An overall NF1-associated MPNST incidence of approximately 5%–10%.

The stated figure concerns NF1 patients, not all neurofibromas.

Benign morphology at one site does not negate the long-term systemic tumor risk.

5%–10%

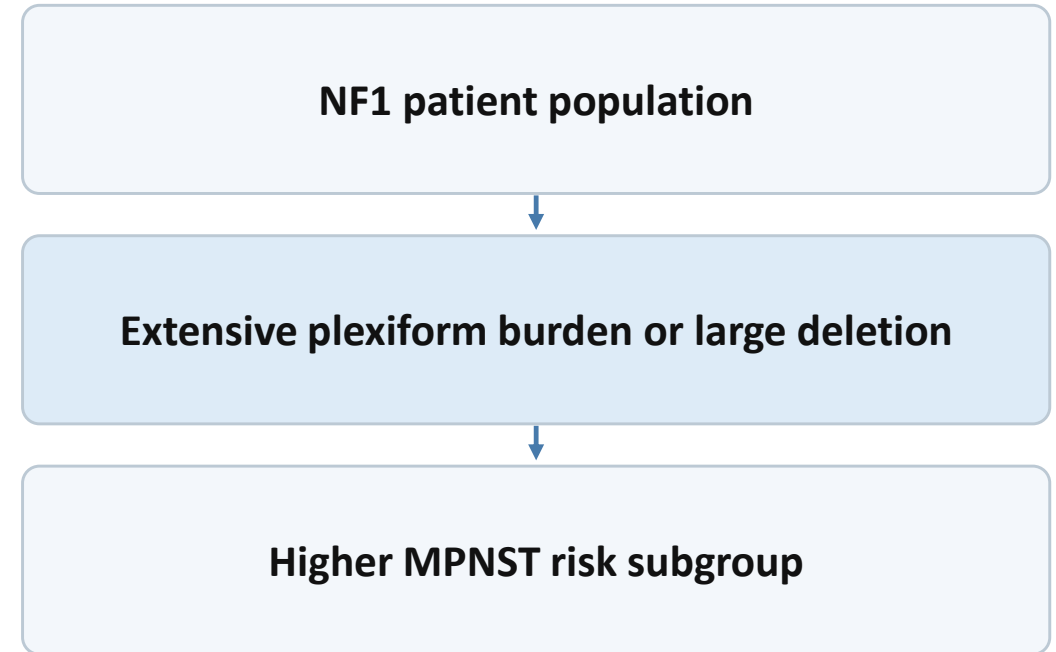
Reported overall incidence of MPNST
among patients with NF1

MPNST risk is not equally distributed

Large numbers of plexiform neurofibromas are associated with greater risk.

Large NF1 deletions are also associated with increased risk.

These modifiers should not be converted into individual numerical forecasts.



Schematic (editable; Not a tissue image)

MPNST is a distinct malignant tumor category

Feature	Benign neurofibroma	MPNST
Biologic category	Benign peripheral nerve sheath tumor	Malignant peripheral nerve sheath tumor
Typical pattern	Bland mixed spindle-cell lesion	Frequently high-grade malignancy
Relation to NF1	Common association	Major malignant complication

NF1 and NF2 differ in their hallmark tumors

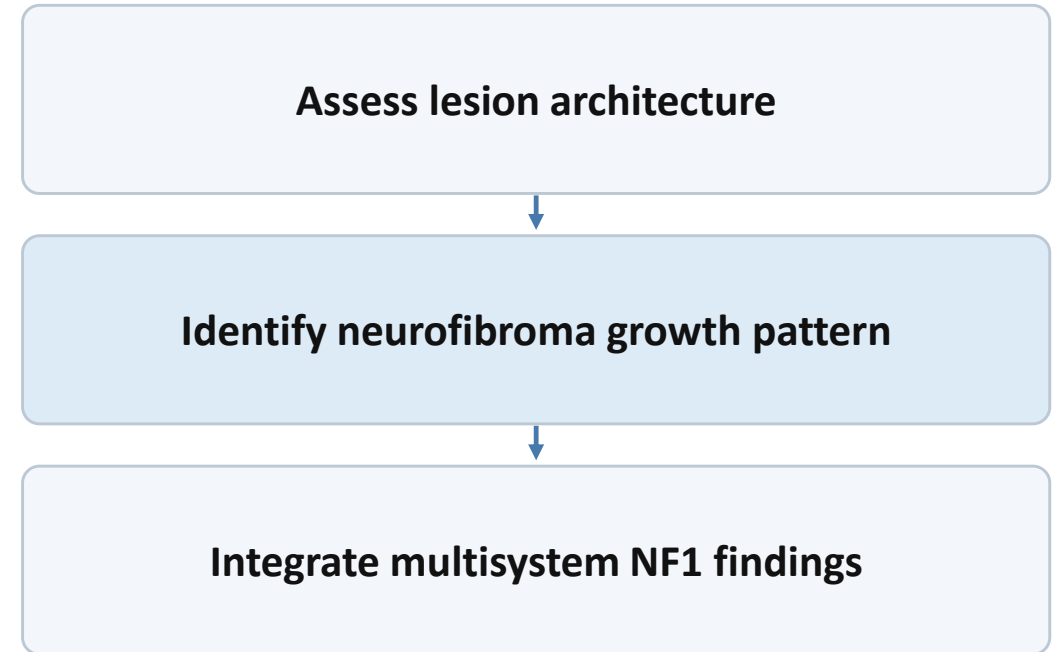
Feature	NF1	NF2
Gene	NF1; Neurofibromin; 17q11.2	NF2; Merlin; 22q12
Nerve tumor	Neurofibroma (especially plexiform)	Vestibular schwannoma
Other tumors	MPNST; Optic glioma; Pheochromocytoma	Meningioma; Spinal ependymoma
Inheritance	Autosomal dominant	Autosomal dominant

Histologic categories must be inferred cautiously

Morphologic clues establish a pattern but do not substitute for complete clinicopathologic correlation.

A single sporadic neurofibroma does not establish NF1.

A multifascicular plexiform lesion warrants particular attention to syndromic context.



Schematic (editable; Not a tissue image)

Case: A child with skin findings and nerve enlargement

Case vignette

A child has several café-au-lait macules and an enlarging, rope-like mass tracking along a peripheral nerve.

What two categories of findings are present?

Interpretation

Pigmentary finding:
Nonneoplastic macules.
Nerve mass: Morphologically suggestive of a plexiform neurofibroma. Together, they support consideration of NF1.

Case: Why is only one cell population neoplastic?

Case vignette

A neurofibroma contains Schwann cells, mast cells, fibroblasts, and perineurial-like cells. Genetic assessment finds complete NF1 loss only in the Schwann cells.

Which population is neoplastic, and why?

Interpretation

The Schwann cells are the neoplastic population. Other associated cells can influence growth without the same biallelic NF1 loss.

Case: Distinguish a diffuse lesion from plexiform growth

Case vignette

Two benign spindle-cell lesions are reviewed. One permeates dermis and adipose tissue; The other expands several discrete nerve fascicles and traps axons.

What growth-pattern labels fit these lesions?

Interpretation

First: Diffuse neurofibroma.
Second: Plexiform neurofibroma. Architecture matters more than generic spindle-cell appearance.

Case: Interpret the inherited and somatic defects

Case vignette

A patient has an inherited NF1 loss-of-function variant;
An associated neurofibroma shows biallelic inactivation
in its Schwann-cell component.

Why are the systemic phenotype and focal tumor different?

Interpretation

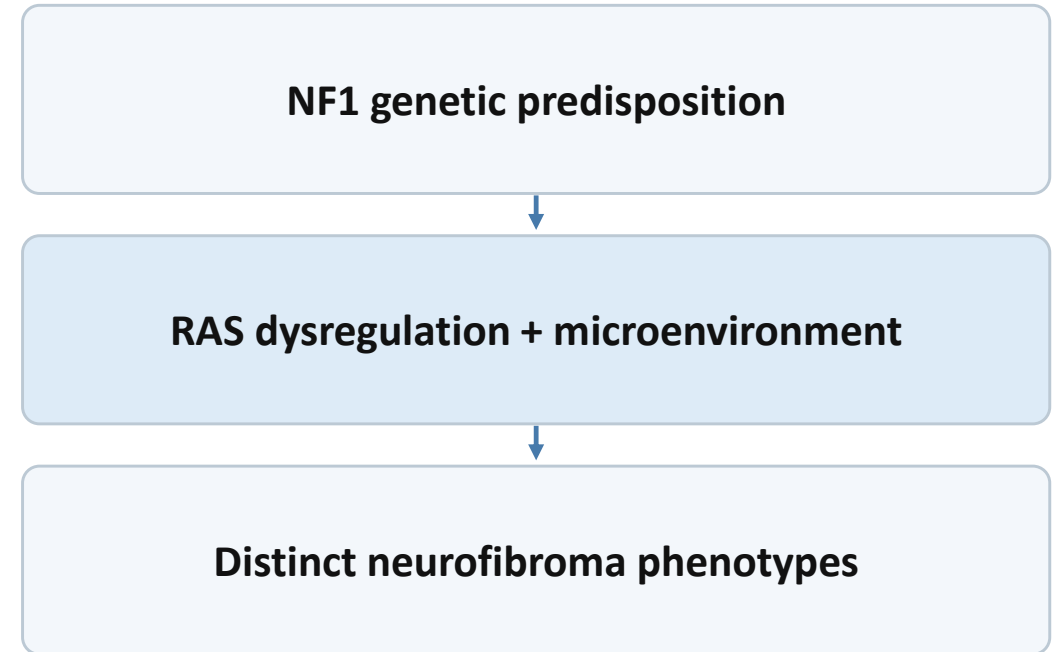
Constitutional heterozygosity
produces susceptibility; A
further localized defect
produces complete tumor-
suppressor loss in neoplastic
cells.

NF1 connects genotype, stroma, and morphology

Genotype: Inherited NF1 loss of function and biallelic tumor-cell loss.

Mechanism: Defective RAS restraint with stromal support.

Morphology: Heterogeneous neurofibromas whose architecture varies by growth pattern.



Schematic (editable; Not a tissue image)

Integrating the tumor spectrum with systemic signs

Benign nerve tumors coexist with pigmentary, ocular, skeletal, and neurologic features.

Associated gliomas and pheochromocytomas broaden the neoplastic spectrum.

MPNST is the central malignant nerve-sheath complication.

Cutaneous

Macules;
Neurofibromas

Neural

Nerve sheath
tumors; Gliomas

Ocular

Lisch nodules; Optic
glioma

Other

Skeletal defects;
Pheochromocytoma

Scope of pathology-based diagnostic reasoning

Robbins supports recognizing NF1 by its genotype, manifestations, and tumor spectrum.

This lecture does not substitute formal consensus diagnostic criteria.

The provided textbook excerpt does not enumerate criterion counts, age thresholds, or surveillance schedules.

Source-supported syndrome recognition



Clinicopathologic correlation



Separate verification of formal criteria

Schematic (editable; Not a tissue image)

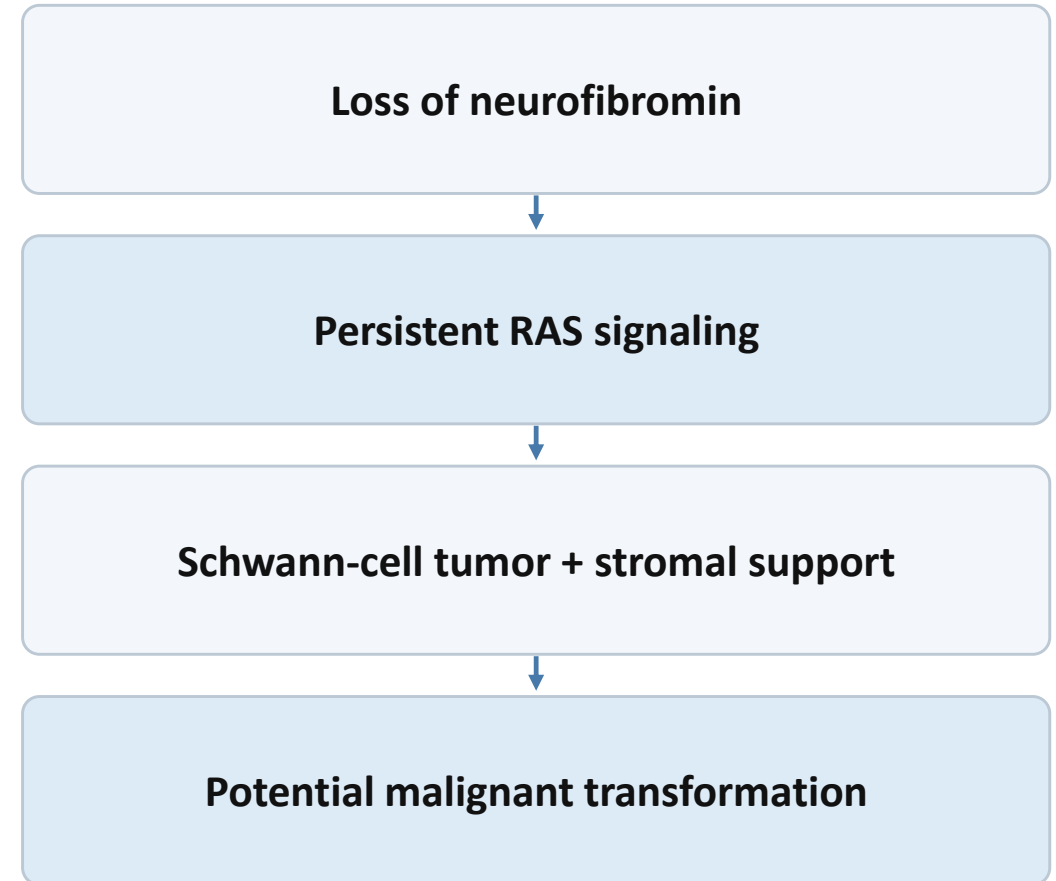
Mechanisms to retain

NF1 at 17q11.2 encodes neurofibromin, a RAS-negative regulator.

Neoplastic Schwann cells lose both NF1 alleles.

KIT-responsive mast cells illustrate tumor–microenvironment cooperation.

Plexiform neurofibromas are a major precursor setting for MPNST.



Schematic (editable; Not a tissue image)

References and source scope

Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th edition (2026).

Chapter 27: Peripheral Nerves and Skeletal Muscles; NF1 and neurofibroma sections, pp. 1125–1127.

Clinical and genetic distinctions are restricted to the supplied Robbins text and adjacent chapter context.

Diagrams are original editable schematics; no synthetic image is presented as histologic evidence.