

Inherited Peripheral Neuropathies

Genetic mechanisms, nerve pathology, and clinicopathologic patterns

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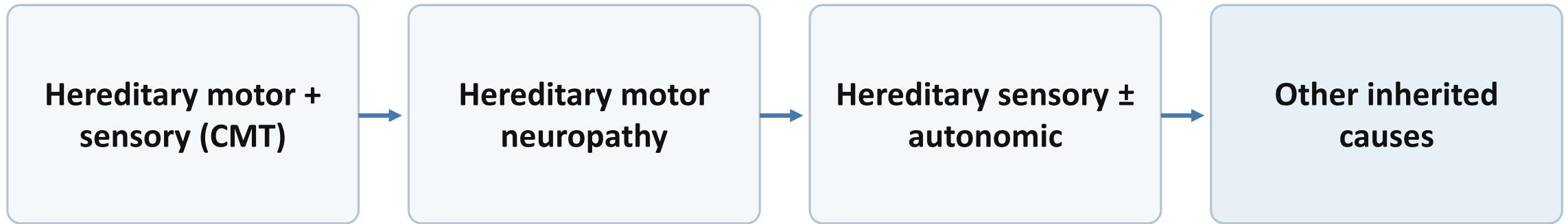
Learning objectives

- Differentiate axonal, demyelinating, and neuronopathic mechanisms in peripheral nerves.
- Classify major inherited neuropathies by phenotype, inheritance, and primary injury pattern.
- Link PMP22, MPZ, GJB1, and MFN2 abnormalities to characteristic CMT subtypes.
- Recognize the morphology and clinical implications of sensory and amyloid neuropathies.

Inherited neuropathy may appear sporadic

- Adult presentation does not exclude an inherited disorder.
- De novo mutations may occur without an affected family member.
- Overlapping phenotypes mean the same presenting symptom can reflect different genetic causes.
- Inherited disease remains part of the differential diagnosis for unexplained peripheral neuropathy.

Four broad groups of inherited neuropathy



Other inherited causes explicitly include familial amyloidosis and inherited metabolic diseases.

Historical and genetic classification serve different purposes

- Historical classification used the inheritance pattern and clinical presentation.
- Modern molecular assessment identifies defects in numerous unrelated genes.
- More than 100 genes linked to inherited neuropathies.
- No single molecular pathway explains all inherited neuropathy phenotypes.

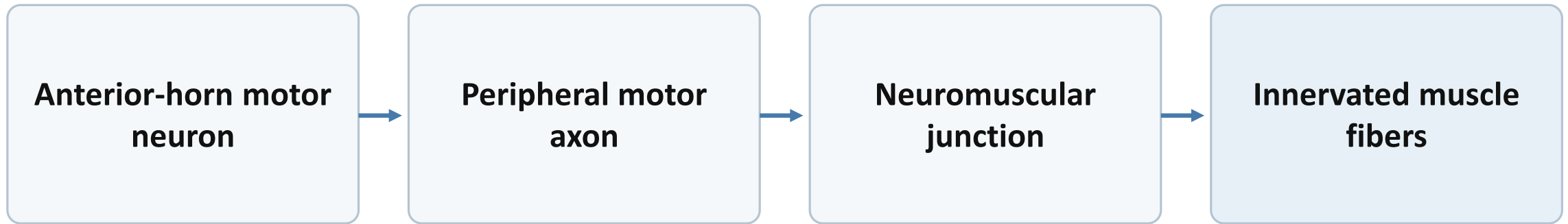
Three complementary descriptors of neuropathy

Clinical phenotype	Inheritance	Injury pattern
Motor + sensory	Autosomal dominant	Demyelinating
Motor-predominant	X-linked	Axonal
Sensory $\pm$ autonomic	Other / variable	Mixed injury may occur

What can fail within a peripheral nerve?

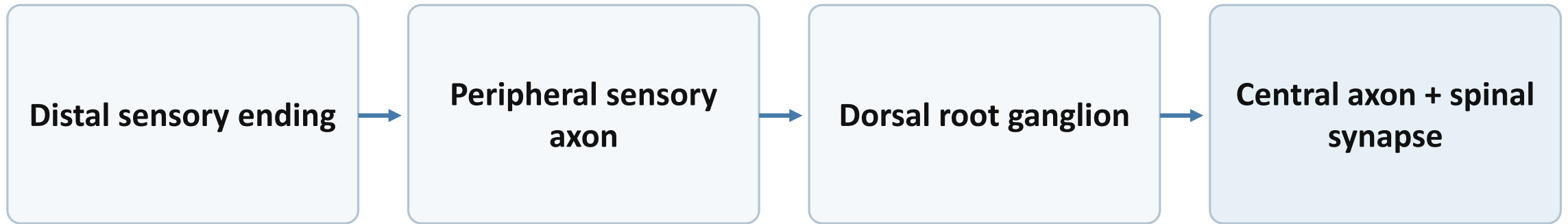
- The axon conducts impulses from the neuronal cell body to its target.
- Schwann cells form and maintain peripheral myelin.
- Peripheral nerve dysfunction may begin in the axon, myelin, or neuronal cell body.
- The location of primary injury influences morphology and nerve-conduction findings.

Functional organization of a motor unit



In hereditary neuropathy, axonal/myelin damage compromises conduction to the distal motor unit.

Functional organization of somatic sensation



Sensory disturbances may reflect the peripheral axon or the primary sensory neuron.

Myelin thickness and functional specialization

Large myelinated fiber



Fast conduction: Motor, light touch, proprioception

Thin unmyelinated fiber



Slow conduction: Autonomic signals and some pain/temperature

Segmental myelin loss interrupts internodal continuity

Intact myelinated axon



Axon with segmental myelin injury



Exposed axonal segment

Segmental loss of myelin may leave the axon relatively intact.

A Schwann cell establishes one myelinated internode

- Each myelinating Schwann cell wraps a single axonal segment.
- The internodes are separated by nodes of Ranvier.
- Saltatory conduction depends on intact myelin and appropriately spaced nodes.
- Myelin abnormalities therefore impair conduction even if axons persist.

Peripheral nerve compartments and their significance

Component	Anatomic role	Why it matters
Axon	Long neuronal process	Primary target in axonal neuropathy
Myelin / Schwann cell	Insulation around axon	Primary target in demyelination
Endoneurium	Around individual nerve fibers	Contains nerve-fiber microenvironment
Perineurium	Encloses nerve fascicles	Organizes groups of axons
Epineurium	Covers entire nerve	Fibrovascular outer support

Distinct gene defects converge on peripheral neuropathy

PMP22

Myelin protein dosage



MPZ

Major myelin protein



GJB1

Schwann-cell gap junction



MFN2

Mitochondrial fusion



Disturbance of axon and/or
myelin homeostasis

Axonal versus demyelinating neuropathy

Axonal injury

- Primary reduction or degeneration of axons
- Injury can progress despite attempted axonal regeneration
- Nerve response loses signal amplitude as axons drop out

Demyelinating injury

- Primary injury to Schwann cells or myelin
- Repeated segmental loss with remyelination
- Conduction slowing from impaired saltatory transmission

Axonal neuropathy: The functional deficit reflects fiber loss

- Axons may fragment and their myelin disintegrates after severe injury.
- Chronic injury may show both degenerating and regenerating axons.
- Ongoing injury can outpace regeneration, progressively reducing the axonal population.
- The source describes reduced nerve-signal amplitude with relative preservation of conduction velocity.

Demyelination can spare the underlying axon

- Myelin sheath damage may involve discontinuous internodal segments.
- Schwann-cell proliferation contributes to attempted repair.
- Remyelinated internodes are typically shorter and thinner than their predecessors.
- Marked slowing of nerve conduction is the classic physiologic signature.

Segmental demyelination: Loss of internodes

Intact myelinated axon



Axon with segmental myelin injury



Exposed axonal segment

Segmental loss of myelin may leave the axon relatively intact.

Remyelination produces shorter, thinner sheaths

Intact myelinated axon



After demyelination and remyelination



Replacement internodes are shorter and thinner.

Length dependence helps explain distal symptoms

- Peripheral axon disorders frequently affect the longest axons first.
- Weakness or sensory loss therefore often begins in the feet.
- Distal involvement can extend proximally and eventually involve the hands.
- This principle helps explain the stocking–glove pattern of many polyneuropathies.

Anatomic patterns guide localization

Pattern	Distribution	Illustrative cause in Robbins
Mononeuropathy	Single named nerve	Trauma or compression
Mononeuritis multiplex	Patchy individual nerves	Vasculitis
Polyneuropathy	Multiple nerves, usually symmetric	Metabolic or inherited disease
Polyradiculoneuropathy	Roots and peripheral nerves	Immune-mediated disease

CMT is the largest hereditary motor-sensory group

- Charcot–Marie–Tooth (CMT) denotes hereditary motor and sensory neuropathies.
- Prevalence of up to 1 in 2500 people.
- The classic presentation links distal muscle atrophy, sensory loss, and foot deformities.
- Multiple molecular mechanisms can converge on this shared clinical phenotype.

CMT phenotype is not a single genetic diagnosis

- Mutations in more than 50 genes can produce CMT phenotypes.
- Gene products participate in peripheral axonal or myelin structure and function.
- Inheritance and injury pattern help divide this heterogeneous clinical group.
- Phenotypic resemblance does not establish a specific pathogenic variant.

Motor and sensory abnormalities in CMT

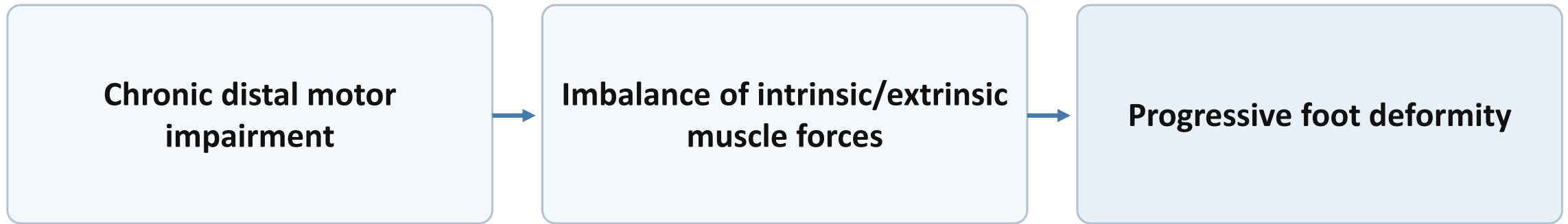
Motor emphasis

- Distal muscle atrophy
- Progressive distal motor impairment
- Foot deformities can accompany chronic motor neuropathy

Sensory emphasis

- Sensory deficits may coexist with weakness
- Axonal and myelin disease both impair peripheral signaling
- The relative balance varies among genetic subtypes

Why distal motor neuropathy alters foot architecture



Conceptual clinicopathologic sequence based on the textbook-described association of distal muscle atrophy with deformity.

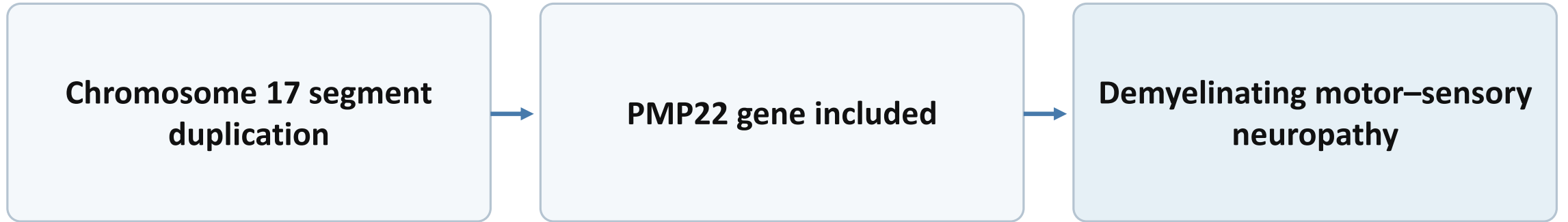
Major CMT subtypes at a glance

Group	Inheritance	Primary injury	Representative gene
CMT1	Autosomal dominant	Demyelinating	PMP22, MPZ
CMT1X / CMTX	X-linked	Peripheral nerve dysfunction	GJB1
CMT2	Autosomal dominant	Axonal	MFN2

CMT1 is the dominant demyelinating category

- CMT1 encompasses autosomal dominant demyelinating neuropathies.
- The CMT1 group is the most common hereditary motor-sensory subtype.
- Characteristic histology includes recurrent demyelination and remyelination.
- CMT1A and CMT1B are important defined molecular examples.

CMT1A: The gene-dosage lesion



This chromosome-17 duplication as the cause of CMT1A.

CMT1A: Expected clinical course

- Presentation usually occurs in the first or early second decade of life.
- Peripheral motor and sensory dysfunction progresses slowly.
- Demyelination is the dominant injury pattern.
- Motor manifestations are generally more conspicuous than sensory manifestations.

CMT1A frequency requires an explicit denominator

- Approximately 55% of genetically defined CMT as CMT1A.
- This figure concerns CMT cases with molecular characterization.
- It must not be presented automatically as 55% of all clinically suspected neuropathies.
- Frequency is a classification aid, not a substitute for establishing the causal duplication.

CMT1B: MPZ and the myelin scaffold



MPZ encodes a major structural peripheral-myelin protein; CMT1B with MPZ mutations.

CMT1B spans multiple ages of onset

- CMT1B has markedly variable timing of clinical presentation.
- Onset may occur in infancy, childhood, or adulthood.
- Approximately 9% of genetically defined CMT.
- Age at onset alone cannot reliably exclude MPZ-associated CMT.

CMT1A versus CMT1B

CMT1A (PMP22)

- Chromosome-17 duplication containing PMP22
- Typically early onset with slow progression
- Motor-predominant demyelinating presentation

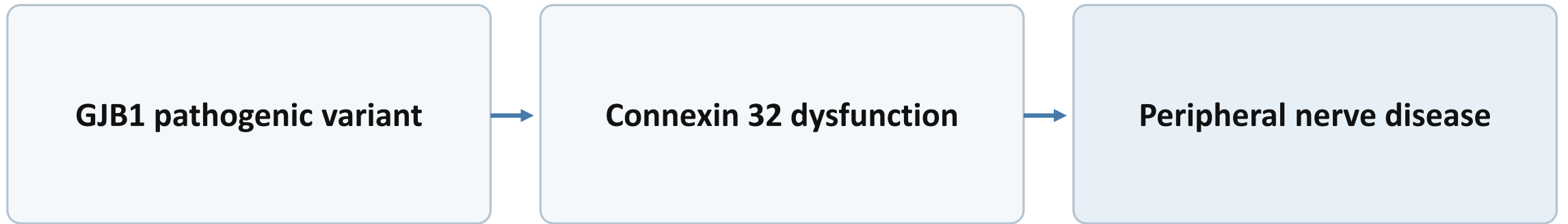
CMT1B (MPZ)

- Pathogenic variants of the MPZ structural gene
- Highly variable onset, including adulthood
- Demyelinating presentation

CMTX is defined by X-linked inheritance

- CMTX includes multiple X-linked Charcot–Marie–Tooth syndromes.
- CMT1X is the most common X-linked subtype.
- Its pathogenic variants involve the GJB1 gene.
- Inheritance context aids interpretation but does not replace molecular identification.

GJB1: A Schwann-cell gap-junction gene



GJB1 encodes connexin 32 (gap-junction protein $\beta 1$), which is expressed in Schwann cells.

CMT1X differs between males and females

- Males typically experience more severe manifestations.
- Females may also have clinically significant disease.
- Variable X-chromosome inactivation contributes to the range of severity in females.
- The text reports around 15% of genetically defined CMT cases as CMT1X.

Interpreting the X-linked phenotype

Male with GJB1-related disease

- Usually more severely affected description
- May show motor–sensory CMT manifestations
- Inheritance history can be informative

Female with GJB1-related disease

- Can be symptomatic
- Severity is variable
- X-inactivation contributes to phenotypic variation

CMT2 is defined by predominantly axonal injury

- CMT2 encompasses autosomal dominant hereditary motor-sensory neuropathies.
- Its primary lesion is axonal, rather than demyelinating.
- Affected nerves may show axonal loss rather than conspicuous primary myelin injury.
- CMT2A is the most common CMT2 subtype described in this Robbins section.

CMT2A: A mitochondrial mechanism

MFN2 pathogenic variant



Disrupted mitofusin 2 function



Axonal neuropathy

Mitofusin 2 is required for normal mitochondrial fusion; The CMT2A phenotype is axonal.

CMT2A: Clinically severe early presentation

- The typical phenotype begins in early childhood.
- The disease course is usually severe.
- Sensory manifestations often predominate.
- CMT2A at about 4% of all CMT disease (not specifically genetically defined cases).

Do not mix denominators in CMT frequencies

Entity	Reported estimate	Population denominator
CMT1A	≈55%	Genetically defined CMT
CMT1B	≈9%	Genetically defined CMT
CMT1X	≈15%	Genetically defined CMT
CMT2A	≈4%	All CMT disease

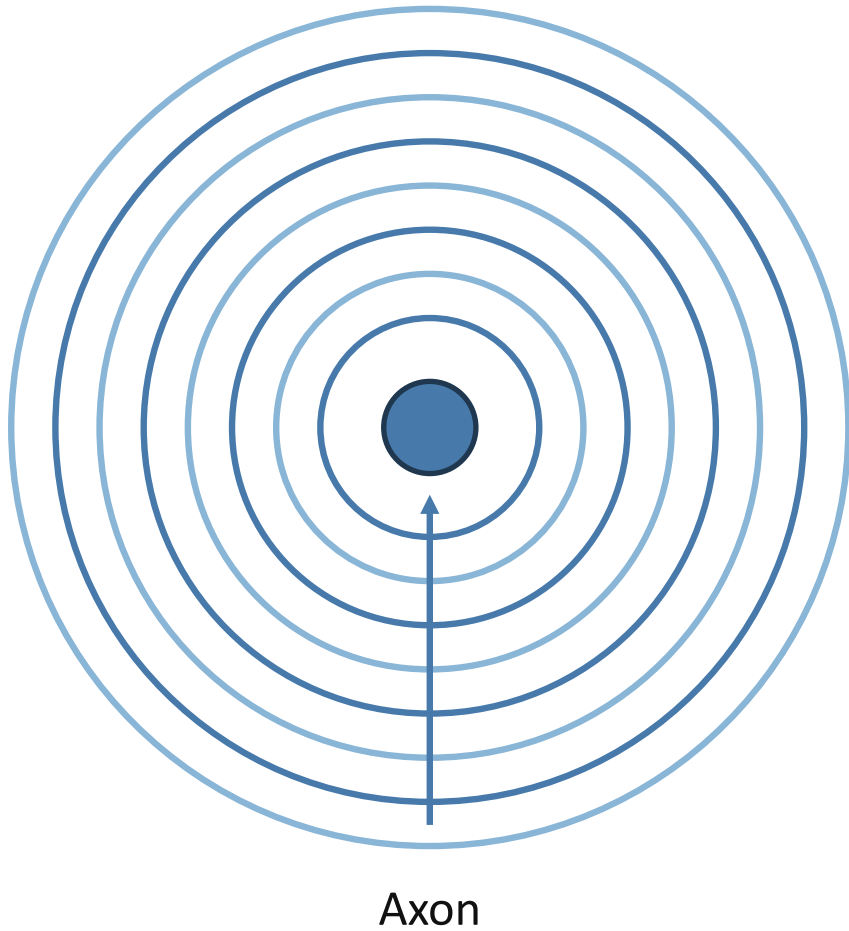
Four principal CMT gene–phenotype associations

Subtype	Gene / lesion	Physiologic or pathologic emphasis
CMT1A	PMP22 duplication	Demyelination; slowly progressive distal motor > sensory
CMT1B	MPZ variants	Demyelination; onset from infancy to adulthood
CMT1X	GJB1 variants	Schwann-cell connexin 32; X-linked severity variation
CMT2A	MFN2 variants	Axonal disease; early, often severe sensory symptoms

Onion bulbs are a morphologic clue to repeated injury

- Demyelinating CMT can produce repeated cycles of myelin loss and replacement.
- Schwann-cell proliferation accumulates around nerve fibers.
- Concentric layered Schwann-cell structures are called onion bulbs.
- The finding indicates a chronic demyelinating–remyelinating process, not a specific gene by itself.

Onion bulbs: Repetitive Schwann-cell proliferation



Cross-sectional schematic — not a histologic image

Recurrent demyelination and
remyelination

Concentric Schwann-cell processes around
nerve fibers

May produce marked nerve enlargement
in CMT

In some CMT nerves, onion bulbs become extensive

- Pronounced Schwann-cell hyperplasia can expand the affected nerve.
- The nerve may become palpably enlarged in severe demyelinating CMT.
- Enlargement therefore reflects chronic structural remodeling as well as functional impairment.
- Morphology should be interpreted together with phenotype and inheritance pattern.

Mechanism predicts the electrodiagnostic tendency

Primary process	Structural effect	Electrophysiologic hallmark
Axonal injury	Axon dropout	Reduced amplitude; relatively maintained velocity
Demyelination	Disrupted myelin internodes	Slowed conduction velocity; amplitude relatively preserved

The clinical classification remains provisional

- Similar distal weakness and sensory loss can result from numerous pathogenic genes.
- Inheritance pattern, injury type, and clinical course narrow the possibilities.
- An apparently negative pedigree cannot exclude inherited neuropathy.
- Molecular identification provides etiologic specificity beyond the shared CMT phenotype.

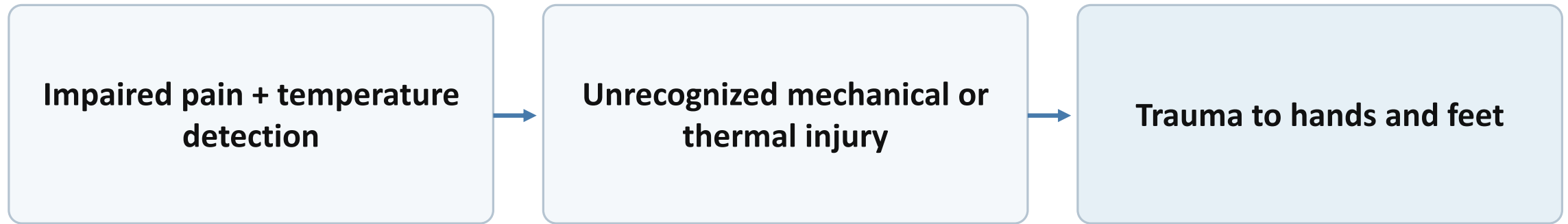
Hereditary motor neuropathies are a distinct group

- Hereditary motor neuropathies separately from the motor–sensory CMT syndromes.
- The category emphasizes predominantly motor dysfunction.
- Its molecular subtypes are not developed in detail in this textbook section.
- It should not be merged automatically with a sensory or autonomic phenotype.

Hereditary sensory neuropathy: Loss of protective perception

- Sensory loss dominates, with motor strength generally preserved.
- Pain and temperature deficits are especially characteristic.
- Many cases have predominantly axonal neuropathic injury.
- Autonomic dysfunction may or may not accompany the sensory deficit.

Why sensory loss causes tissue damage



Damage arises because the protective warning function of pain is lost.

Sensory/autonomic neuropathy versus CMT

Hereditary sensory $\pm$ autonomic

- Predominantly sensory deficit
- Preserved motor strength
- Traumatic injury from impaired protective sensation

Charcot–Marie–Tooth

- Combined motor and sensory dysfunction
- Distal muscle atrophy may be prominent
- Foot deformity is a classic manifestation

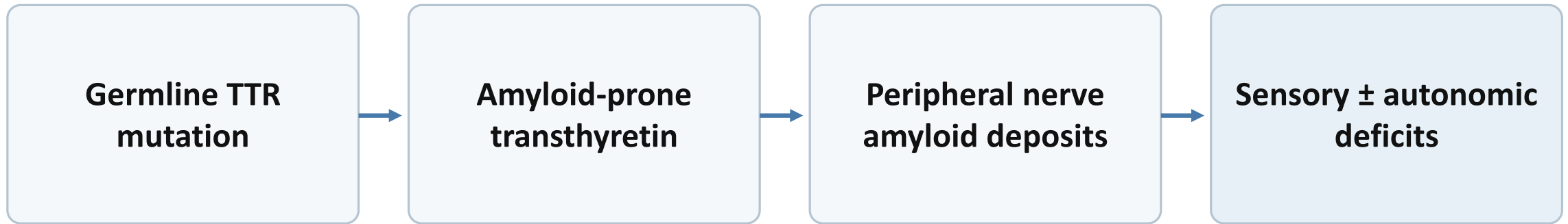
Autonomic involvement varies across inherited syndromes

- Hereditary sensory neuropathies may be accompanied by autonomic dysfunction.
- Not every hereditary sensory phenotype has important autonomic symptoms.
- Predominant sensory loss with spared motor strength is the defining pattern emphasized.
- Peripheral autonomic and sensory fibers can be affected together in selected genetic neuropathies.

Familial amyloid polyneuropathy: Protein deposition in nerve

- This inherited group is characterized by amyloid within peripheral nerves.
- Most familial amyloid polyneuropathies are linked to germline TTR mutations.
- Abnormal transthyretin is prone to assemble into extracellular amyloid fibrils.
- Peripheral nerve is one of several tissues in which the abnormal protein may deposit.

TTR mutation to amyloid-associated nerve dysfunction



Clinical overlap with hereditary sensory and autonomic neuropathies.

Transthyretin has a physiological transport role

- The TTR gene encodes transthyretin.
- Thyroid hormone binding and transport among its normal functions.
- Hereditary pathogenic variants can render the protein susceptible to amyloid fibril deposition.
- Hereditary protein misfolding translates a systemic molecular disorder into nerve pathology.

Familial amyloid disease may mimic a sensory neuropathy

- Clinical symptoms can resemble hereditary sensory/autonomic neuropathies.
- A family history may support inherited disease, but its absence does not eliminate a genetic explanation.
- Histopathologic demonstration of amyloid can distinguish the deposition mechanism.
- TTR-associated disease represents a different pathology from primary inherited myelin disorders.

Congo red is the key amyloid histochemical method

- Congo red staining as a method for detecting peripheral nerve amyloid.
- Polarized-light examination provides characteristic optical findings in amyloid-positive deposits.
- Electron microscopy can provide additional characteristic evidence of fibrillar material.
- This presentation uses a schematic explanation; No specimen image is represented as authentic.

CMT demyelination versus amyloid deposition

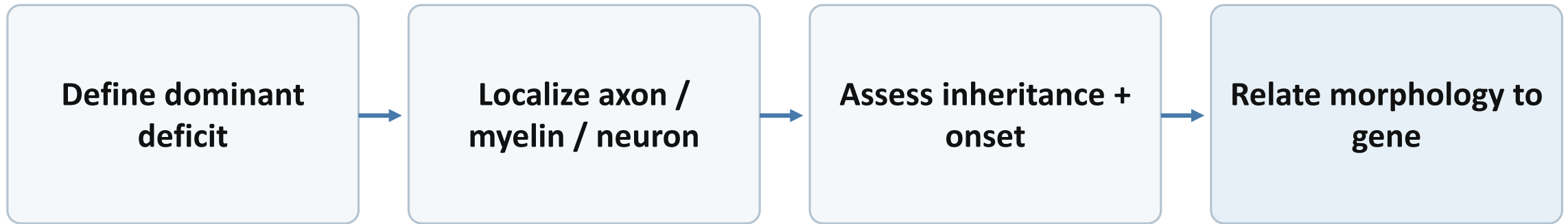
Demyelinating CMT

- Altered peripheral myelin and Schwann-cell homeostasis
- Onion bulbs may develop after repeated injury
- Molecular examples: PMP22 and MPZ

Familial amyloid polyneuropathy

- Protein fibrils deposited in peripheral nerve
- Congo red / polarized light; Electron microscopy
- Frequent genetic mechanism: Pathogenic TTR variant

A pathology-focused framework for inherited neuropathy



The phenotype and morphology guide classification; Neither by itself proves a particular molecular genotype.

Case: Early distal motor–sensory neuropathy

Clinical presentation

- First-decade onset
- Slowly progressive distal weakness and sensory loss
- Motor symptoms more prominent than sensory symptoms
- Demyelinating injury pattern

Interpretation task

Which CMT subtype and lesion are most compatible?

Case interpretation: Recognize the CMT1A pattern

- Early onset and slow progression are consistent with CMT1A.
- Predominant motor involvement and demyelination strengthen the pattern match.
- The genetic lesion specified by Robbins is duplication of the segment including PMP22.
- Clinical pattern supports a hypothesis; Identification of the duplication establishes the specific cause.

Case: Variable severity in an X-linked family

Clinical presentation

- Several affected relatives across the family
- Male relatives show more severe motor–sensory symptoms
- A female relative is mildly but clearly affected
- Molecular result implicates a Schwann-cell gap-junction gene

Interpretation task

Which gene and principle explain the variability?

Case interpretation: Female carriers can be symptomatic

- GJB1-related CMT1X commonly affects males more severely.
- Females are not necessarily asymptomatic.
- Variable X-inactivation provides a mechanism for variable female severity.
- Connexin 32 localization links the genotype to Schwann-cell function.

Case: Painful injury without protective sensation

Clinical presentation

- Marked loss of pain and temperature sensation
- Repeated unrecognized injury of hands or feet
- No substantial motor strength reduction
- Variable autonomic complaints

Interpretation task

**Which inherited
neuropathy group fits
best?**

Case interpretation: Preserved strength is discriminating

- Predominant pain/temperature sensory loss points to a sensory neuropathy.
- Repeated injury is explained by loss of protective nociception.
- Preserved muscle strength argues against the classic motor-predominant CMT pattern.
- Autonomic involvement is variable and need not be present.

Case: Inherited deposition neuropathy

Clinical presentation

- Progressive neuropathy with sensory/autonomic features
- Clinical resemblance to hereditary sensory neuropathy
- Amyloid deposits seen within peripheral nerve
- A pathogenic TTR germline alteration is detected

Interpretation task

What is the causal tissue-pathology mechanism?

Case interpretation: Prove the protein-deposition mechanism

- TTR mutation provides a heritable protein-based cause.
- Extracellular amyloid within peripheral nerve explains the distinctive pathology.
- Congo red with polarized light or characteristic electron microscopy supports amyloid identification.
- This should not be conflated with inherited primary demyelinating CMT.

Integrated classification: Lesion, phenotype, exemplar

Category	Dominant clinical finding	Pathology or molecular exemplar
CMT1	Distal motor + sensory	Demyelination; PMP22 or MPZ
CMT1X	Motor + sensory, X-linked	GJB1 / connexin32
CMT2	Motor + sensory, axonal	MFN2 mitochondrial fusion
Hereditary sensory ± autonomic	Pain/temp loss, motor preserved	Usually axonal
Familial amyloid	Sensory ± autonomic	TTR amyloid in nerve

Final synthesis: What to remember

- Inherited neuropathies are clinically overlapping, genetically heterogeneous, and may present in adulthood.
- CMT classification uses phenotype, inheritance, and axonal versus demyelinating injury.
- PMP22, MPZ, GJB1, and MFN2 connect distinct molecular lesions to characteristic CMT groups.
- Sensory injury with preserved strength and TTR-related amyloid deposition represent important alternative inherited patterns.

Primary textbook reference

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026).
- Source emphasis: inherited neuropathy phenotypes, gene associations, and nerve morphology.
- Peripheral nerve anatomy and patterns of axonal versus demyelinating injury supply the explanatory foundation.
- Diagrams in this lecture are original, editable schematics; they are not replacements for genuine clinical or histopathologic specimens.