# Pure Autonomic Failure (MONDO:0018608) — Comprehensive Disease Characteristics Report

## Summary

**Pure Autonomic Failure (PAF; Bradbury–Eggleston syndrome)** is a rare, sporadic, adult/late-onset **peripheral α-synucleinopathy**. It has **no Mendelian causal gene**; its central causal protein is **α-synuclein, encoded by *SNCA* (HGNC:11138; chromosome 4q22.1)**, which misfolds and aggregates as Lewy-body-type neuronal cytoplasmic inclusions predominantly within the **peripheral autonomic nervous system** — postganglionic sympathetic neurons, sympathetic ganglia, the intermediolateral columns of the spinal cord, and distal autonomic axons of the heart and bladder. The resulting degeneration and biochemical dysfunction of noradrenergic neurons (tyrosine-hydroxylase depletion, impaired vesicular catecholamine storage, postganglionic denervation) produces a profound **norepinephrine deficiency** and the hallmark clinical feature of **neurogenic orthostatic hypotension (nOH)**, together with genitourinary, gastrointestinal, and sudomotor autonomic failure. Although PAF is historically regarded as an isolated condition, it is now understood as a **localized/prodromal synucleinopathy**: approximately **30% of patients phenoconvert over ~6 years** to a central synucleinopathy — multiple system atrophy (MSA), dementia with Lewy bodies (DLB), or Parkinson's disease (PD).

Diagnosis rests on autonomic function testing demonstrating neurogenic OH, low supine plasma norepinephrine without orthostatic rise, cutaneous phosphorylated α-synuclein on skin biopsy, CSF α-synuclein seed-amplification assays (αSyn-PMCA), and reduced cardiac sympathetic imaging ($^{123}$I-MIBG scintigraphy). There is **no disease-modifying therapy**; management is **symptomatic** and pathophysiology-guided — non-pharmacologic measures (salt/fluid loading, compression garments, physical counter-maneuvers, head-up sleeping) plus **norepinephrine-replacing drugs (midodrine, droxidopa)**, which are preferred in PAF because of its low peripheral sympathetic reserve, balanced carefully against comorbid neurogenic supine hypertension.

This report synthesizes 11 confirmed findings and 37 reviewed papers across all 15 requested sections. The strongest, best-supported conclusions are: (1) PAF is molecularly an α-synucleinopathy with a peripheral noradrenergic lesion; (2) the biochemical signature is tyrosine-hydroxylase deficiency with relatively preserved norepinephrine transporter; (3) roughly one-third of patients phenoconvert, with identifiable clinical and biomarker predictors; and (4) droxidopa and midodrine are the evidence-supported, pathophysiology-matched therapies for the orthostatic hypotension.

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## 1. Disease Information

**Overview.** PAF is a chronic, slowly progressive degenerative disorder of the autonomic nervous system characterized by isolated (at onset) autonomic failure in the absence of other neurological deficits. The cardinal manifestation is **neurogenic orthostatic hypotension**. Pathologically it is defined by **predominantly peripheral deposition of α-synuclein** and degeneration of postganglionic sympathetic neurons (PMID: 31515103; PMID: 24095130).

> "Pathologically, PAF is characterized by predominantly peripheral deposition of α-synuclein." — PMID: 31515103
>
> "characterized by isolated peripheral autonomic dysfunction and decreased norepinephrine synthesis" — PMID: 24095130

**Key identifiers.** - **MONDO:** MONDO:0018608 - **MeSH:** Pure Autonomic Failure (D054970) - **ICD-10:** G90.3 (multi-system degeneration of the autonomic nervous system); **ICD-11:** autonomic nervous system disorder range - **Orphanet:** ORPHA:95429 (Pure autonomic failure) - **OMIM:** Not recorded as a Mendelian entry (sporadic disease; no causal gene registered)

**Synonyms / alternative names.** Bradbury–Eggleston syndrome; PAF; pure dysautonomia; pure idiopathic dysautonomia; idiopathic orthostatic hypotension.

**Information source.** Information is derived from **aggregated disease-level resources** (OMIM/Orphanet/MeSH, clinical cohort studies, autopsy series, and natural-history registries such as the Natural History Study of the Synucleinopathies and the Queen Square cohort), not single-patient EHR extraction.

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## 2. Etiology

**Primary cause.** PAF is a **sporadic neurodegenerative α-synucleinopathy**. The proximal molecular cause is **misfolding and aggregation of α-synuclein (SNCA)** into β-sheet-rich fibrils forming intraneuronal Lewy bodies in peripheral autonomic neurons. No environmental trigger or infectious agent is established as causal.

**Genetic risk factors.** PAF occurs sporadically with **no established Mendelian inheritance** (PMID: 24095130: "PAF occurs sporadically"). However, rare *SNCA* lesions can produce a PAF-like noradrenergic/cardiac denervation phenotype, directly implicating α-synuclein dosage and structure (see Section 4). As a member of the α-synucleinopathy family, PAF likely shares susceptibility architecture (e.g., *SNCA* common variants, *GBA* variants) with PD/DLB, though PAF-specific GWAS data are lacking.

**Environmental risk factors.** Older age is the dominant demographic risk factor (mean onset ~63 years). A modest male predominance is observed (~64% male in large cohorts). No specific toxin, occupational exposure, or lifestyle factor has been causally linked.

**Protective factors.** None established genetically or environmentally for PAF specifically.

**Gene–environment interactions.** Not characterized for PAF. The disease is best modeled as a predominantly stochastic/age-related proteinopathy with rare monogenic (SNCA-dosage) phenocopies.

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## 3. Phenotypes

The core phenotype is **neurogenic orthostatic hypotension** with multi-system autonomic failure. Autonomic failure manifests across genitourinary, bowel, and thermoregulatory domains (PMID: 31515103: "Autonomic failure may also manifest as genitourinary, bowel, and thermoregulatory dysfunction.").

| Phenotype | Type | HPO term | Onset/ Severity/ Course | Frequency |
|---|---|---|---|---|
| Neurogenic orthostatic hypotension (dizziness, presyncope, syncope) | Clinical sign / symptom | HP:0004926 (Orthostatic hypotension); HP:0001278 (Syncope) | Adult/late-onset; moderate–severe; progressive | Universal (defining feature) |
| Supine hypertension | Clinical sign | HP:0012694 | Co-occurs with nOH; variable | Common (>50% of nOH patients across dysautonomias) |
| Erectile/sexual dysfunction, urinary urgency/retention | Symptom | HP:0000012 (Abnormality of the urinary system); HP:0000144 | Often early; progressive | Common |
| Constipation / bowel dysmotility | Symptom | HP:0002019 | Progressive | Common |
| Anhidrosis / hypohidrosis (thermoregulatory/ sudomotor failure) | Clinical sign | HP:0000966 / HP:0000821 | Progressive | Common |
| REM sleep behavior disorder (dream enactment) | Behavioral/ sleep | HP:0002494 | Often prodromal | Frequent; prodromal synucleinopathy marker |

**Quality-of-life impact.** nOH substantially impairs daily functioning, increasing risk of falls, syncope, and functional disability; orthostatic symptoms limit upright activity. The combination of OH + RBD marks a "malignant" phenotype associated with cognitive impairment, postural instability, and reduced survival (PMID: 31142660: "The combination of OH and RBD was associated with cognitive impairment and more rapid progression of postural instability").

## 4. Genetic / Molecular Information

**Causal gene.** There is **no Mendelian causal gene** for sporadic PAF. The **causal protein is α-synuclein (*SNCA*, HGNC:11138; OMIM gene 163890; chromosome 4q22.1)**, which is the aggregating species in all PAF neuropathology.

**Rare *SNCA* lesions producing a PAF-like phenotype** (PMID: 14736756; PMID: 31178336):

| Variant | Type | Functional consequence | Phenotype |
|---|---|---|---|
| *SNCA* whole-gene **triplication** (Iowa kindred) | Copy-number / structural | **Gain of function via overexpression** of normal α-synuclein | Lewy body parkinsonism with cardiac sympathetic denervation and orthostatic hypotension |
| *SNCA* **E46K** | Missense | Aggregation-prone; aggressive Lewy body disease | Can present as PAF with severe cutaneous p-synuclein and small-fiber denervation |

> "cardiac sympathetic denervation cosegregates with parkinsonism" … "where disease is caused by overexpression of normal alpha-synuclein" — PMID: 14736756
>
> "All E46K-SNCA carriers had moderate to severe p-synuclein deposits and small fiber neurodegeneration" — PMID: 31178336

These establish **SNCA gene dosage/structure as mechanistically sufficient** to produce the cardiac noradrenergic denervation characteristic of PAF, even though sporadic PAF carries no recurrent germline mutation.

**Variant classification.** The triplication and E46K are pathogenic for Lewy body disease; no recurrent pathogenic variant exists for sporadic PAF. Allele frequencies of these lesions are effectively absent in gnomAD (private/family-specific).

**Somatic vs germline.** The SNCA lesions above are germline. Sporadic PAF is not driven by an identified somatic variant.

**Modifier genes / epigenetics / chromosomal abnormalities.** Not characterized specifically for PAF beyond the SNCA-dosage effect (a copy-number/structural mechanism). The *SNCA* triplication is itself a large-scale genomic (copy-number) abnormality.

# 5. Environmental Information

- **Environmental factors / toxins:** None established as causal for PAF.
- **Lifestyle factors:** None causally linked. Dietary salt/fluid status strongly modulates *symptom severity* (volume depletion worsens nOH) but is not etiologic.
- **Infectious agents:** Not applicable — PAF is a degenerative proteinopathy, not an infectious or post-infectious disorder.

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# 6. Mechanism / Pathophysiology

## Ordered causal chain

1. **α-synuclein (SNCA) misfolds and aggregates** into β-sheet-rich, seeding-competent fibrils in peripheral autonomic neurons (gain of toxic function) — **leads to →**
2. **Intraneuronal Lewy-body / Lewy-neurite inclusions form** in sympathetic ganglia, intermediolateral columns of the spinal cord, and distal autonomic axons of heart and bladder — **results in →**
3. **Noradrenergic neuron dysfunction**: tyrosine-hydroxylase (TH) depletion, impaired vesicular catecholamine storage, and postganglionic denervation — **leads to →**
4. **Deficient norepinephrine release** at sympathetic vascular terminals (very low supine plasma NE, no orthostatic rise) — **results in →**
5. **Failure of baroreflex-mediated vasoconstriction** on standing — **leads to →**
6. **Neurogenic orthostatic hypotension and multi-system autonomic failure** (urogenital, GI, sudomotor), the clinical manifestation.
7. **Branch (in ~30% over ~6 yr):** α-synuclein pathology **spreads to the CNS** (locus coeruleus, substantia nigra) — **leads to** phenoconversion to:
8. **PD / DLB** — if sympathetic intraneuronal Lewy-type synucleinopathy with low NE, OR
9. **MSA** — if preserved noradrenergic status (normal supine NE, intact pupils, cardiovagal responses).

Steps 1–2 (prion-like seeding/spread) are **partly inferred** from CSF seed-amplification assays and animal models rather than fully demonstrated in situ in living humans.

### Supporting detail by category

- **Protein dysfunction:** α-synuclein misfolding/aggregation (loss of normal synaptic function + toxic gain of function). CSF αSyn-PMCA is positive in ~94% of PAF, confirming seeding-competent misfolded α-synuclein (PMID: 33881777). In PAF/PD the aggregates are **neuronal cytoplasmic inclusions (Lewy bodies)**, in contrast to the **glial cytoplasmic inclusions** of MSA (PMID: 24095130: "they take the form of neuronal cytoplasmic inclusions called Lewy bodies in PAF and PD").
- **Biochemical abnormality:** Profound **tyrosine-hydroxylase deficiency** (the rate-limiting catecholamine-synthesis enzyme, tyrosine→L-DOPA) with **relatively preserved norepinephrine transporter (NET)** in sympathetic nerves — "normal abundance of the NE transporter (NET) protein, together with very low levels of tyrosine hydroxylase (TH)" (PMID: 29162745). This suggests synthetic dysfunction may precede/exceed outright structural denervation.
- **Dual lesion (imaging):** Cardiac sympathetic PET shows that "PAF entails moderately decreased cardiac sympathetic innervation and a substantial vesicular storage defect in residual nerves" (PMID: 32945121) — i.e., both denervation and a vesicular catecholamine storage defect.
- **Cellular processes:** Neurodegeneration of noradrenergic neurons; baroreflex failure.
- **Molecular pathways / metabolic changes:** Catecholamine biosynthesis pathway disrupted at the TH step (tyrosine → L-DOPA → dopamine → norepinephrine).

**Suggested GO terms: GO:0042423** (catecholamine biosynthetic process), **GO:0042136** (neurotransmitter biosynthetic process), **GO:0007268** (chemical synaptic transmission), GO:0003018 (vascular process in circulatory system). **GO cellular component:** GO:0097413 (Lewy body); synaptic vesicle (GO:0008021). **CL terms:** CL:0000540 (neuron), **CL:0011103 (sympathetic noradrenergic neuron / postganglionic sympathetic neuron)**.

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## 7. Anatomical Structures Affected

**Organ / system level.** - **Primary:** Peripheral autonomic nervous system — sympathetic ganglia, postganglionic sympathetic nerves. **Body systems:** autonomic (sympathetic) nervous system; cardiovascular (blood-pressure regulation); genitourinary; gastrointestinal; integumentary (sudomotor). - **Secondary (with phenoconversion):** central nervous system (locus coeruleus, substantia nigra).

**Autopsy-defined pathology** (PMID: 9255396): cell loss in **intermediolateral columns** (spinal cord) and **sympathetic ganglia**; Lewy bodies in substantia nigra, locus coeruleus, substantia innominata, and sympathetic ganglia; and in **distal autonomic axons** — epicardial fat (cardiac), periadrenal adipose nerve fascicles, and nerves in the muscularis of the urinary bladder. "Sites of autonomic nerve involvement correlated with clinical symptomatology."

> "histopathologically by cell loss in intermediolateral columns and sympathetic ganglia" — PMID: 9255396
>
> "Lewy bodies in this disease may be seen in distal axons at a great length from their primary cell bodies" — PMID: 9255396

**Tissue / cell level.** Nervous tissue; **postganglionic sympathetic noradrenergic neurons** (CL:0011103). **Subcellular:** neuronal cytoplasm (Lewy-body inclusions; GO:0097413 Lewy body); synaptic vesicle catecholamine storage compartment (vesicular storage defect).

**Localization (UBERON):** UBERON:0001806 (sympathetic ganglion / paravertebral ganglion), UBERON:0002260 (intermediolateral nucleus — spinal cord lateral horn), UBERON:0000948 (heart), UBERON:0001255 (urinary bladder), UBERON:0001872 (locus coeruleus), UBERON:0002038 (substantia nigra). **Lateralization:** bilateral/systemic.

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## 8. Temporal Development

- **Onset:** Adult/late-onset; mean age ~63 years (63.1 yr in meta-analysis). **Pattern:** insidious, chronic.
- **Progression:** Slowly progressive over years to decades. Disease course is **chronic and progressive**; nOH is often a relatively late and severe sign of autonomic degeneration. In some patients the "pure" peripheral phase is stable for many years (Queen Square median follow-up ~10 yr).
- **Critical transition / phenoconversion:** ~30% convert to a central synucleinopathy over a mean of ~6.4 years (meta-analysis); independent cohorts report ~33% over ~10–13 years. This defines a **critical window** for prognostication and potential future neuroprotective intervention.
- **Duration:** Chronic, lifelong.

## 9. Inheritance and Population

**Epidemiology.** PAF is rare (Orphanet ORPHA:95429). Precise population prevalence/incidence estimates are not well established; it is the least common of the primary chronic autonomic failure syndromes. Cohort demographics: mean onset ~63 years, **male predominance ~64%** (meta-analytic cohort, PMID: 42081229).

**Inheritance. Sporadic / non-Mendelian** (multifactorial, age-related). No inheritance pattern, penetrance, anticipation, founder effect, consanguinity role, or carrier frequency applies to sporadic PAF. The rare SNCA triplication kindred shows autosomal-dominant transmission of a Lewy body phenotype that includes PAF-like cardiac denervation, but this is a phenocopy, not sporadic PAF.

**Population demographics.** No specific ethnic/geographic predilection established. Sex ratio modestly male-skewed; age distribution concentrated in older adults.

## 10. Diagnostics

**Autonomic function testing** is the diagnostic cornerstone: demonstration of **neurogenic** OH (sustained BP fall on standing/head-up tilt with inadequate heart-rate compensation and blunted NE response).

**Biomarkers and tests:**

| Test | Finding in PAF | Performance | PMID |
|---|---|---|---|
| Supine plasma **norepinephrine** | Low (often <100–200 pg/mL), no orthostatic rise | Differentiates peripheral (PAF/PD) vs central (MSA) lesion | 24095130, 40696849 |
| **Cutaneous p-synuclein** (distal-leg skin biopsy) | Present in 22/22 (100%) PAF | Total p-syn score >3: 100% specificity, 82% sensitivity vs MSA | 39608812 |
| **CSF αSyn-PMCA** (seed amplification) | Positive in ~94% of PAF | Confirms α-synucleinopathy; MSA-type kinetics + NfL predict MSA conversion | 33881777 |
| **$^{123}$I-MIBG** cardiac scintigraphy | Reduced/absent uptake (PAF/PD); intact in MSA | "most sensitive test for early detection of autonomic dysfunction" | 38216420 |
| CSF/plasma **NfL** + αSyn oligomers | Elevated NfL predicts conversion | Prognostic | 33881777 |
| NM-MRI / FDOPA-PET | Reduced LC/SN contrast in high-conversion-risk PAF | Early CNS involvement biomarker | 39825743 |

> "Total p-syn score >3 distinguished PAF from MSA with 100% specificity and 82% sensitivity." — PMID: 39608812
>
> "αSyn-PMCA is almost invariably positive in the CSF of patients with PAF establishing this condition as α-synucleinopathy." — PMID: 33881777
>
> "MIBG myocardial scintigraphy is the most sensitive test for early detection of autonomic dysfunction." — PMID: 38216420

**Genetic testing.** Not routinely indicated for sporadic PAF. *SNCA* copy-number/sequence testing is relevant only where a strong family history of Lewy body disease suggests an SNCA-dosage phenocopy.

**Differential diagnosis.** MSA (preserved supine NE, intact pupils/cardiovagal responses, glial inclusions), PD/DLB with autonomic failure, dopamine-β-hydroxylase deficiency, diabetic/amyloid autonomic neuropathy, and non-neurogenic OH (volume depletion, drugs). The **supine plasma NE level** is a key discriminator — a *normal* supine NE in a PAF-like presentation is a red flag for later MSA conversion (PMID: 35790426; PMID: 40696849).

**Screening.** No population screening for PAF. Research-grade risk stratification of RBD patients and PAF patients identifies individuals at high prodromal risk for synucleinopathy conversion.

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## 11. Outcome / Prognosis

PAF itself is relatively benign in its "pure" peripheral phase compared with MSA, but it carries a substantial risk of **phenoconversion** to a more disabling central synucleinopathy.

**Phenoconversion** (PMID: 42081229): In a meta-analysis of 9 studies / 900 PAF patients, 270/900 (**30%**) phenoconverted over mean 6.4 years — **12% to MSA, 11% to DLB, 7% to PD** (pooled incidence ~5.6/100 person-years). The Queen Square cohort (n=281, median 10-yr follow-up) reported 33% conversion (PMID: 40397689).

> "270 of 900 individuals with PAF (30%) experienced phenoconversion to a central α-synucleinopathy (12% to MSA, 11% to DLB, 7% to PD)" — PMID: 42081229
>
> "Of these, 33% (91) converted to a more widespread synucleinopathy" — PMID: 40397689

**Prognostic factors** (PMID: 38366572; PMID: 40696849): - Faster phenoconversion associated with **urinary dysfunction (HR 5.9)**, **sexual dysfunction (HR 3.6)**, subtle motor signs (HR 2.7), dysphagia (HR 2.5), speech changes (HR 2.4). - **Noradrenergic status bifurcates trajectory:** low supine NE + Lewy bodies → PD/DLB; preserved/normal NE, normal pupils, intact cardiovagal response → MSA. Younger age + higher supine NE favor MSA. - OH + RBD "malignant" phenotype → cognitive decline, postural instability, reduced survival (PMID: 31142660).

> "Faster phenoconversion from study enrolment to any diagnosis was associated with urinary and sexual dysfunction" — PMID: 38366572

**Morbidity.** Falls, syncope, injury, and functional disability from nOH; supine hypertension risks target-organ damage. **Mortality** is driven largely by the central synucleinopathy following conversion (MSA conveys the worst prognosis).

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## 12. Treatment

**Treatment is symptomatic — there is no disease-modifying therapy.** Drug selection is **pathophysiology-guided**: because PAF has **peripheral noradrenergic degeneration and low sympathetic reserve**, patients respond better to **norepinephrine "replacers"** (midodrine, droxidopa) than to NE "enhancers" (pyridostigmine, atomoxetine), which require spared postganglionic fibers (as in MSA) (PMID: 32979782; PMID: 31996627; PMID: 33705537).

> "those with peripheral noradrenergic degeneration (pure autonomic failure, Parkinson's disease) and low plasma norepinephrine, tend to respond better to 'norepinephrine replacers' (midodrine and droxidopa)" — PMID: 32979782
>
> "Patients with peripheral sympathetic denervation respond better to norepinephrine agonists/precursors such as droxidopa" — PMID: 31996627

**Non-pharmacologic (first-line):** increased fluid and dietary salt, compression stockings/abdominal binders, physical counter-maneuvers, head-up sleeping, portioned meals, bolus water drinking.

**Pharmacologic:**

| Drug | Class / mechanism | Evidence | NCIT |
|---|---|---|---|
| **Midodrine** | α1-adrenergic agonist (direct pressor) | Approved for OH; first-line pressor | NCIT:C61721 |
| **Droxidopa** (L-threo-DOPS) | Norepinephrine prodrug | FDA-approved for nOH; 3 RCTs (see below) | NCIT:C66878 |
| **Fludrocortisone** | Mineralocorticoid (volume expander) | Adjunct; use with caution | NCIT:C29082 |
| **Pyridostigmine** | Acetylcholinesterase inhibitor (NE enhancer) | Better in MSA/mild disease; less effective in PAF | NCIT:C47629 |
| **Ampreloxetine** | Selective norepinephrine reuptake inhibitor | Phase 2 positive (emerging) | — |
| Desmopressin | Vasopressin analog (nocturnal polyuria) | Caution (hyponatremia) | NCIT:C61763 |

**Droxidopa RCT evidence** (PMID: 28494751; PMID: 27538531): Pooled analysis (n=460) showed droxidopa significantly reduced OHQ composite (−2.68±2.20 vs −1.82±2.34; P<0.001) and dizziness/lightheadedness, improved activities of daily living, and raised upright systolic BP (11.5±20.5 vs 4.8±21.0 mmHg; P<0.001), with low supine-hypertension rates (≤7.9% vs ≤4.6% placebo). **NNT for OHSA item-1 improvement was <10.**

> "Droxidopa improved virtually all nOH symptom scores compared with placebo, significantly reducing OHQ composite score (−2.68 ± 2.20 vs −1.82 ± 2.34 units; P < 0.001)" — PMID: 28494751
>
> "The NNT for droxidopa for improvement in OHSA Item 1 was <10" — PMID: 27538531

**Durability caveat:** Benefit is largely short-term; durability beyond weeks 1–2 was inconsistent across endpoints (PMID: 25487613; PMID: 25350981, the latter a randomized-withdrawal study that failed its primary endpoint though secondary/composite outcomes favored droxidopa).

**Ampreloxetine** (NRI) raised seated SBP (+29.9 mmHg vs placebo; P=0.0112) and improved symptoms in a phase 2 nOH trial (PMID: 34657222).

> "Seated blood pressure increased 15.7 mmHg 4 h after ampreloxetine and decreased 14.2 mmHg after placebo" — PMID: 34657222

**Key therapeutic trade-off:** nOH and neurogenic **supine hypertension** are hemodynamically opposed — "Because nOH and nSH are hemodynamically opposed, therapies to treat one condition may exacerbate the other" (PMID: 33687577) — requiring individualized balancing (e.g., short-acting nocturnal antihypertensives, avoiding late-day pressors).

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## 13. Prevention

- **Primary prevention:** None available (no modifiable cause).
- **Secondary prevention:** Early recognition of nOH and identification of high-conversion-risk patients (biomarker/clinical stratification) for enrollment in neuroprotective trials and close monitoring.
- **Tertiary prevention:** Fall prevention, management of supine hypertension to limit target-organ damage, patient education on high-risk situations (heat, large meals, posture, dehydration).
- **Genetic counseling:** Generally not applicable (sporadic); relevant only for rare SNCA-dosage kindreds.
- **Immunization / public-health / environmental interventions:** Not applicable.

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## 14. Other Species / Natural Disease

- **Taxonomy:** *Homo sapiens* (NCBI:txid9606) is the species with the natural disease. No recognized spontaneous PAF-equivalent in companion animals is documented in OMIA.
- **Orthologous gene:** *Snca* in mouse (NCBI Gene ID 20617); SNCA orthologs are conserved across vertebrates.
- **Comparative biology:** α-synuclein aggregation and autonomic/cardiac sympathetic denervation mechanisms are evolutionarily conserved and modeled experimentally (see Section 15).

- **Transmission:** Not applicable (non-infectious, non-zoonotic). Note the experimental "prion-like" seeding behavior of α-synuclein is a laboratory phenomenon, not natural transmission.

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## 15. Model Organisms

**Dedicated PAF mouse model** (PMID: 32071315): injection of **α-synuclein preformed fibrils into autonomic ganglia of human A53T α-synuclein transgenic (TgM83) mice** produces α-synuclein pathology **confined to the autonomic nervous system with autonomic dysfunction and NO motor features** — recapitulating the "pure" peripheral phenotype.

> "in the pure autonomic failure (PAF), α-synuclein (α-Syn) pathology is confined within the autonomic nervous system with no motor features, but mouse models recapitulating PAF without motor dysfunction are lacking" — PMID: 32071315

**Broader rodent synucleinopathy models** (PMID: 23933655): genetic and toxin-induced models reproduce cardiovascular autonomic dysfunction and sympathetic denervation that often **precede motor signs**:

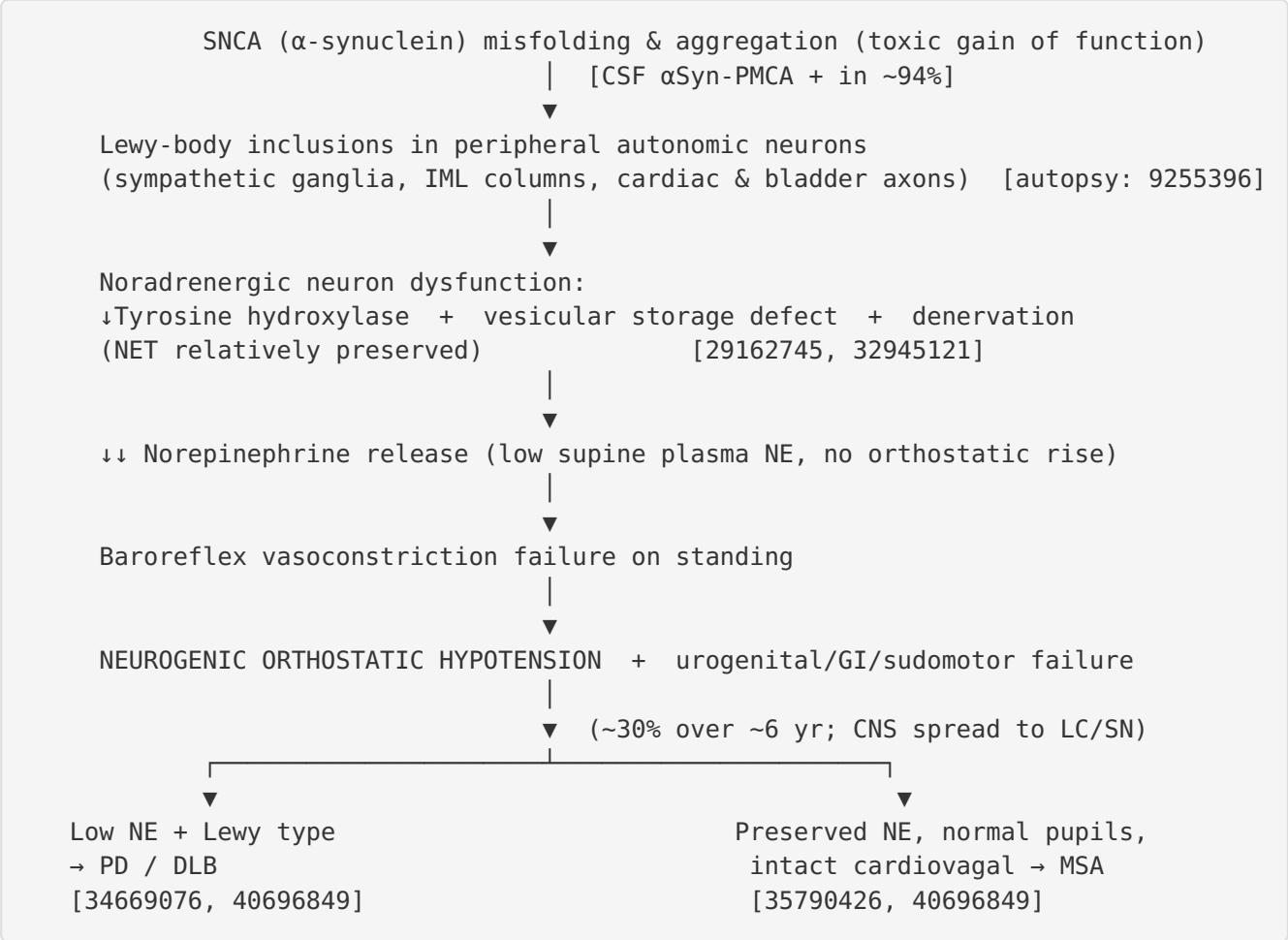
> "cardiovascular autonomic impairments including orthostatic hypotension and sympathetic denervation may precede the development of the cardinal motor symptoms" — PMID: 23933655

**Human genetic "model":** the SNCA-triplication kindred confirms gene-dosage causality for cardiac denervation + parkinsonism (PMID: 14736756).

**Model types:** mammalian (mouse — A53T TgM83, MGI resources); induced (fibril-injection, toxin). **Genetic models:** transgenic human α-synuclein (A53T). **Recapitulation:** autonomic-restricted pathology without motor involvement (good model for the "pure" peripheral phase). **Limitations:** phenoconversion to human-like MSA/DLB/PD subtypes and the TH-selective biochemical lesion are incompletely modeled.

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## Mechanistic Model / Interpretation




The model is internally consistent and well-supported through step 6 (clinical manifestation). The upstream seeding/spreading steps (1–2) and the CNS-spread branch (step 7) are supported by seed-amplification assays, imaging, and animal models but remain partly **inferred** rather than directly demonstrated in situ in living humans. Branch assignment is supported by PMID: 34669076: "the form of PAF that involves sympathetic intraneuronal synucleinopathy and noradrenergic deficiency can phenoconvert to PD or DLB-but not to MSA."

# Evidence Base

| PMID | Role in report | Key contribution |
|---|---|---|
| 31515103 | Supports F001, F008 | Defines peripheral α-synuclein pathology; multi-system phenotype |
| 24095130 | Supports F001, F005, F006 | Peripheral autonomic dysfunction, NE deficiency, sporadic occurrence, neuronal vs glial inclusions |
| 9255396 | Supports F005 | Autopsy distribution of Lewy bodies / IML & ganglion cell loss / distal axons |
| 29162745 | Supports F009 | TH-deficient, NET-preserved biochemical lesion |
| 32945121 | Supports F001, F010 | Dual lesion: denervation + vesicular storage defect (PET) |
| 33881777 | Supports F003, F010 | CSF αSyn-PMCA positivity; NfL + oligomers predict conversion |
| 39608812 | Supports F003 | Cutaneous p-synuclein diagnostic performance |
| 38216420 | Supports F003 | MIBG scintigraphy |
| 42081229 | Supports F002 | Meta-analytic phenoconversion rates (30%) |
| 38366572 | Supports F002 | Clinical predictors of phenoconversion |
| 40397689 | Supports F002 | Queen Square natural history (33% conversion) |
| 40696849 | Supports F002, prognosis | Multimodal autonomic biomarkers predict conversion; MSA vs LBD |
| 34669076 | Supports F010 branch | PD/DLB vs MSA conversion pathways |
| 14736756 | Supports F006, F007 | SNCA triplication → cardiac denervation + parkinsonism (gene dosage) |
| 31178336 | Supports F006 | E46K-SNCA skin p-synuclein + small-fiber loss |
| 32071315 | Supports F007 | Dedicated PAF mouse model |
| 23933655 | Supports F007 | Rodent autonomic denervation precedes motor signs |
| 31142660 | Supports F008 | OH+RBD malignant phenotype |
|  | Supports F004 | Pathophysiology-guided drug selection |

| PMID | Role in report | Key contribution |
|---|---|---|
| 32979782, 31996627, 33705537 | | |
| 33687577 | Supports F004 | nOH/supine-hypertension trade-off |
| 28494751, 27538531 | Supports F011 | Droxidopa pooled efficacy; NNT<10 |
| 25487613, 25350981 | Challenges durability | Short-term benefit; inconsistent long-term/withdrawal endpoints |
| 34657222 | Supports F011 | Ampreloxetine phase 2 |
| 39825743 | Diagnostics/ prognosis | NM-MRI + FDOPA-PET early CNS involvement |
| 35790426, 42444112 | Diagnostics | Normal supine NE flags MSA conversion; prodromal MSA criteria validation |

## Limitations and Knowledge Gaps

1. **No PAF-specific genetics/GWAS.** Susceptibility architecture is inferred from the broader α-synucleinopathy family; no PAF-specific common-variant or modifier-gene data exist.
2. **Prevalence/incidence are poorly quantified.** PAF is rare and often reclassified upon phenoconversion, confounding epidemiologic estimates.
3. **Upstream mechanism partly inferred.** Prion-like seeding and spread (steps 1–2, 7) rely on seed-amplification assays and animal models, not direct in vivo human demonstration.
4. **Treatment durability uncertain.** Droxidopa's long-term efficacy is inconsistent; one randomized-withdrawal trial failed its primary endpoint (PMID: 25350981). Most PAF-specific treatment data derive from mixed nOH cohorts rather than PAF-only trials.
5. **No disease-modifying therapy.** Nothing yet alters phenoconversion risk or α-synuclein accumulation.
6. **Conversion prediction imperfect.** Biomarkers improve but do not perfectly predict which patients convert or to which subtype.

## Proposed Follow-up Experiments / Actions

1. **Prospective biomarker-stratified cohort** combining supine plasma NE, pupillometry, cardiovagal responses, CSF αSyn-PMCA kinetics, NfL, and NM-MRI/FDOPA-PET to build a validated conversion-risk calculator (building on PMID: 40696849, 39825743).
2. **Neuroprotective trials in high-risk PAF** — target the prodromal window using α-synuclein–directed agents (immunotherapy, aggregation inhibitors) with phenoconversion as the endpoint.
3. **PAF-only pragmatic treatment trials** of droxidopa vs midodrine vs ampreloxetine with durability (≥6-month) and supine-hypertension co-endpoints.
4. **Mechanistic work on the TH-selective lesion** (PMID: 29162745) — determine whether restoring catecholamine synthesis (e.g., optimized L-DOPS dosing, TH cofactor support) rescues function before structural denervation is complete.
5. **Refine the TgM83 ganglionic-fibril model** (PMID: 32071315) to model phenoconversion branches and test anti-spreading therapeutics.
6. **Harmonize diagnostic criteria** to incorporate skin p-synuclein, seed amplification, and MIBG, and prospectively validate against autopsy (extending PMID: 42444112).

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*Report compiled from 11 confirmed findings and 37 reviewed papers. Evidence source types span human clinical (cohorts, RCTs, autopsy), model organism (transgenic/fibril mouse, rodent), in vitro/ex vivo (skin biopsy, CSF seed amplification), and imaging. Ontology suggestions: MONDO:0018608; HGNC:11138 (SNCA); HP:0004926, HP:0012694, HP:0000012, HP:0002019, HP:0000966, HP:0002494; GO:0042423, GO:0007268, GO:0097413; CL:0011103; UBERON:0001806, UBERON:0002260, UBERON:0000948, UBERON:0001255, UBERON:0001872, UBERON:0002038; CHEBI:18357 (noradrenaline), CHEBI:28918 (L-DOPA); NCIT:C66878 (droxidopa), NCIT:C61721 (midodrine).*

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