Spinocerebellar Ataxia, Autosomal Recessive 27 (SCAR27) — Comprehensive Disease Report

Disease: Spinocerebellar Ataxia, Autosomal Recessive 27 (SCAR27) **Causal gene: GDAP2** (ganglioside-induced differentiation-associated protein 2) **Identifiers:** MONDO:0032706 · phenotype OMIM #618369 · gene OMIM *618128* · *HGNC:18010* · *Ensembl ENSG00000196505* · *UniProt Q9NXN4 Category:** Mendelian, monogenic, autosomal recessive

Summary

Spinocerebellar ataxia, autosomal recessive 27 (**SCAR27**) is an ultra-rare, adult-onset, slowly progressive neurodegenerative disorder caused by **biallelic loss-of-function (LOF) variants in GDAP2**, the gene encoding ganglioside-induced differentiation-associated protein 2. The disease was first defined in 2018, when Eidhof and colleagues reported two unrelated patients with gene-disruptive GDAP2 mutations and onset of ataxia in the fourth decade of life; GDAP2 had not previously been implicated in any human disease (PMID: 30084953). Despite its name ("spinocerebellar ataxia"), SCAR27 is unambiguously a GDAP2 disorder — this report follows the MONDO ID (MONDO:0032706) and causal gene provided, and should not be confused with other serially-numbered spinocerebellar ataxias caused by different genes.

Clinically, SCAR27 presents in the third-to-fourth decade with cerebellar ataxia, dysarthria, and gait difficulty, frequently accompanied by eye-movement abnormalities, lower-limb spasticity, difficulty writing (dysgraphia), and cognitive impairment that can progress to dementia. Some patients lose independent ambulation and become wheelchair-dependent. Reported neuropathology extends well beyond the cerebellum to include the inferior olive, thalamus, substantia nigra, and pyramidal tracts, with limbic (hippocampus/amygdala) tau pathology. The molecular mechanism, best characterized in a *Drosophila* knockdown model, centers on **impaired cellular stress handling** — GDAP2-deficient cells show heightened vulnerability to oxidative stress (reactive oxygen species) and nutrient deprivation. GDAP2 is a 497-amino-acid protein containing a macro domain and a CRAL-TRIO/Sec14-like domain, and (distinct from its mitochondrial paralog GDAP1) localizes to the **lysosomal membrane**.

SCAR27 is caused exclusively by loss-of-function alleles: ClinVar's pathogenic/likely-pathogenic GDAP2 variants are uniformly truncating (nonsense, frameshift) or canonical splice-site changes, and population genetic constraint data (gnomAD) are consistent with a recessive LOF mechanism rather than haploinsufficiency. There is no disease-modifying therapy; management is supportive and rehabilitative, and diagnosis rests on whole-exome sequencing or hereditary-ataxia gene panels. No faithful mammalian neurodegeneration model yet exists — all published LOF animal models are invertebrate (*Drosophila* and silkworm) — representing a major gap for mechanistic and therapeutic research.

Key Findings

Finding 1 — SCAR27 is an adult-onset autosomal recessive cerebellar ataxia caused by biallelic GDAP2 loss-of-function

The defining study established the disease entity in two unrelated patients with biallelic, gene-disruptive GDAP2 mutations, both with onset of ataxia in the fourth decade and additional features of progressive spasticity and dementia. GDAP2 was explicitly described as "a gene previously not implicated in disease." As the authors state: *"we report two unrelated patients with a new subtype of autosomal recessive cerebellar ataxia caused by biallelic, gene-disruptive mutations in GDAP2, a gene previously not implicated in disease. Both patients had onset of ataxia in the fourth decade. Other features included progressive spasticity and dementia"* (PMID: 30084953).

This finding anchors the disease definition: an autosomal recessive, adult-onset cerebellar ataxia with a monogenic GDAP2 cause. Subsequent reports have reproduced this picture in independent families — a Chinese family (PMID: 32437512), an additional adult-onset case (PMID: 32428220), and a Spanish family with a novel null variant (PMID: 40469082) — confirming the gene-disease relationship across populations.

Finding 2 — GDAP2 links cerebellar ataxia to defective cellular stress responses

Functional work in *Drosophila* linked GDAP2 loss to impaired stress handling. Ubiquitous knockdown of fly *Gdap2* caused shortened lifespan and motor anomalies (righting defects, reduced and uncoordinated walking, compromised flight). Critically, *Gdap2* expression itself

responded to stress treatments, and knockdown flies were hypersensitive to oxidative and metabolic stress: *"Gdap2 expression levels responded to stress treatments in control flies, and Gdap2 knockdown flies showed increased sensitivity to deleterious effects of stressors such as reactive oxygen species and nutrient deprivation"* (PMID: 30084953).

On the human side, neuropathological examination demonstrated degeneration extending to the cerebellum, inferior olive, thalamus, substantia nigra, and pyramidal tracts, with tau pathology in the hippocampus and amygdala. Together these data support a model in which GDAP2 normally protects neurons against cellular stress, and its loss renders long-lived post-mitotic neurons progressively vulnerable to oxidative and nutrient stress — a plausible explanation for the adult-onset, slowly progressive neurodegeneration.

Finding 3 — GDAP2 is a 497-aa macro-domain + CRAL-TRIO protein on 1p13.2, with constraint consistent with recessive LOF

GDAP2 (UniProt Q9NXN4) is a 497-amino-acid protein containing a **macro domain** (residues ~43–223) and a **CRAL-TRIO/Sec14-like domain** (residues ~333–481), plus a disordered region (~252–273). The gene maps to chromosome **1p13.2** (GRCh38 chr1:117,863,485–117,929,621; HGNC:18010; Ensembl ENSG00000196505). This locus assignment corrects earlier imprecise annotations.

Population constraint metrics from gnomAD v4 are consistent with a recessive, loss-of-function disease mechanism rather than dominant haploinsufficiency: pLI ≈ 0 (1.1×10^{-13}), LOEUF (oe_lof upper bound) = 0.96, observed/expected LoF = 51/67 (oe_lof = 0.76), LoF Z = 1.66, missense Z = 0.73. In plain terms, heterozygous loss of one GDAP2 allele is tolerated in the general population — as expected for a recessive disorder where disease requires loss of **both** copies.

The macro domain is a known ADP-ribose/NAD-metabolite-binding module (associated with poly-ADP-ribose signaling and stress responses), while CRAL-TRIO/Sec14 domains bind small hydrophobic ligands (e.g., lipids). These domain assignments provide a biochemical scaffold linking GDAP2 to the stress-response and lipid/membrane biology implicated in the phenotype.

Finding 4 — The SCAR27 clinical spectrum includes eye-movement abnormalities and dysgraphia beyond ataxia/spasticity/cognitive impairment

Curated clinical descriptions (UniProt, derived from primary literature) characterize SCAR27 as a *"progressive disease characterized by gait difficulties, eye movement abnormalities, dysarthria, and difficulty writing. Some patients may lose independent ambulation. Additional features include spasticity of the lower limbs and cognitive impairment."* This broadens the recognized phenotype to include **oculomotor abnormalities** and **dysgraphia** alongside the cardinal cerebellar, pyramidal, and cognitive features.

The phenotypic range continues to expand. A 2025 case report described progressive slurred speech (dysarthria) as an *atypical* presenting feature in a 47-year-old man — notably **without** cerebellar atrophy on MRI — whose brother had more advanced disease with dysphagia and wheelchair dependence; whole-exome sequencing identified a homozygous nonsense GDAP2 mutation (PMID: 42633453). This underscores that SCAR27 can present with isolated dysarthria and normal neuroimaging, and should be considered in the differential diagnosis of progressive dysarthria.

Finding 5 — Pathogenic GDAP2 variants are uniformly loss-of-function (truncating/splice), confirming the LOF mechanism

ClinVar (RefSeq NM_017686.4) lists 112 GDAP2 variants, of which 3 are Pathogenic and 6 Likely pathogenic (the remainder largely VUS/benign). Every pathogenic/likely-pathogenic single-nucleotide variant is loss-of-function:

Variant (cDNA)	Protein	Type	Classification
c.757C>T	p.Arg253Ter	Nonsense	Pathogenic
c.677C>A	p.Ser226Ter	Nonsense	Likely pathogenic
c.760C>T	p.Gln254Ter	Nonsense	Likely pathogenic
c.1048C>T	p.Arg350Ter	Nonsense	Likely pathogenic
c.134del	p.Pro45fs	Frameshift	Likely pathogenic
c.1107+1G>T	—	Canonical splice	Likely pathogenic
c.1030+1G>T	—	Canonical splice	Likely pathogenic

Two large multigene 1p13 copy-number variants are also classified Pathogenic in ClinVar but are not SCAR27-specific (they span additional genes). The uniform truncating/splice signature across unrelated families strongly supports **loss of function** (not gain of function or dominant negative) as the disease mechanism, consistent with the recessive inheritance and the gnomAD constraint profile.

Finding 6 — All GDAP2 loss-of-function animal models are invertebrate; no faithful mammalian neurodegeneration model exists

A model-organism audit found that every published GDAP2 loss-of-function model is an invertebrate:

- **Drosophila** *Gdap2* knockdown — the only neuromotor LOF model, showing shortened lifespan, motor defects, and stress hypersensitivity (PMID: 30084953).
- **Silkworm (Bombyx mori)** CRISPR/Cas9 knockout of *BmGDAP2* (2025) — extended lifespan, reduced body size, prolonged growth cycle, and 149 differentially expressed genes enriched (KEGG) in peroxidase activity, hormone synthesis, apoptosis, and longevity regulation (PMID: 40332832).
- **Silkworm** systemic GDAP2 knockout — delayed larval development, reduced body weight, and arrest at the 4th-instar stage; GDAP2 is a direct downstream target of the bHLH transcription factor Dimm integrating insulin/IGF and juvenile-hormone signaling (PMID: 40205793).

Importantly, the frequently-cited rodent study used GDAP2 **overexpression** (gain of dosage) in primary hippocampal neurons and an epileptic mouse — not a knockout — finding increased dendritic complexity, dysregulated excitatory synaptic transmission, and increased seizure frequency (PMID: 35158016). This models a dosage-gain condition, not the recessive LOF of SCAR27. Ortholog gene IDs: human GDAP2 (NCBI 54834), mouse *Gdap2* (14547), rat *Gdap2* (362004), zebrafish *gdap2* (447824), *Drosophila Gdap2* (59173), *Bombyx mori BmGDAP2* (101738783). The absence of a mammalian knockout that recapitulates adult-onset neurodegeneration is the single largest experimental gap in the field.

Finding 7 — GDAP2 localizes to the lysosomal membrane, distinguishing it from its mitochondrial paralog GDAP1

UniProt (Q9NXN4) records a single experimentally-supported Gene Ontology cellular-component annotation for GDAP2: **GO:0005765 "lysosomal membrane"** (evidence code HDA, high-throughput direct assay). This is mechanistically important because the better-known

paralog **GDAP1** (mutated in Charcot-Marie-Tooth disease) localizes to the **mitochondrial outer membrane**. Thus, despite the shared "GDAP" name and domain architecture, the two paralogs operate at different organelles. A lysosomal localization for GDAP2 reorients mechanistic thinking toward lysosomal/autophagic and membrane-lipid biology (consistent with the CRAL-TRIO/Sec14 lipid-binding domain), rather than assuming a mitochondrial role by analogy to GDAP1.

Mechanistic Model / Interpretation

Ordered causal chain (initiating lesion → clinical manifestation)

1. **Biallelic loss-of-function variant in GDAP2** (nonsense, frameshift, or canonical splice-site) *results in* absent or non-functional GDAP2 protein in all tissues. *(Demonstrated — ClinVar LOF alleles; recessive inheritance.)*
2. Loss of GDAP2 *leads to* deficient cellular stress-response capacity — the protein's macro domain (ADP-ribose/NAD metabolite binding) and CRAL-TRIO/Sec14 (lipid-binding) domains normally support stress handling at the lysosomal membrane. *(Inferred from domain architecture + GO:0005765 lysosomal localization.)*
3. Deficient stress handling *results in* heightened vulnerability of cells to **oxidative stress (reactive oxygen species)** and **nutrient deprivation**. *(Demonstrated in* Drosophila *knockdown —*

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   .)
4. In long-lived post-mitotic **neurons**, chronic exposure to oxidative/metabolic stress over decades *leads to* progressive neuronal dysfunction and death. *(Inferred — explains adult onset and slow progression.)*
5. Neurodegeneration *manifests in* the cerebellum, inferior olive, thalamus, substantia nigra, and pyramidal tracts, with limbic tau pathology. *(Demonstrated — human neuropathology,*

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   .)
6. Regional degeneration *produces* the clinical phenotype:
7. Cerebellar + olivary degeneration → **ataxia, dysarthria, oculomotor abnormalities, dysgraphia**
8. Pyramidal tract involvement → **lower-limb spasticity**

9. Cortical/thalamic/limbic + tau pathology → **cognitive impairment / dementia**
10. Progressive cerebellar/brainstem loss → **loss of independent ambulation, dysphagia**

Branch point

```
                Biallelic GDAP2 LOF
                        |
       (lysosomal-membrane stress-response deficit)
                        |
        Heightened vulnerability to ROS + nutrient stress
                        |
     +----------------+---------------------+
Cerebellum/        Pyramidal            Cortex/thalamus/
inferior olive      tracts              limbic + tau
     |                 |                      |
Ataxia, dysarthria,  Lower-limb          Cognitive decline/
eye movements,       spasticity           dementia
dysgraphia
```

Upstream vs downstream

- **Upstream (initiating):** GDAP2 LOF → lysosomal/stress-response deficit (the primary, generalizable lesion present in all cells).
- **Downstream (manifesting):** selective neuronal vulnerability and regional neurodegeneration, which is what produces symptoms. The selectivity for neurons — despite GDAP2 being ubiquitously expressed — is not fully explained and is a key open question.

Ontology term suggestions

- **Gene/protein:** HGNC:18010 (GDAP2); UniProt Q9NXN4
- **GO biological process:** response to oxidative stress (GO:0006979); cellular response to starvation/nutrient levels (GO:0009267 / GO:0031669); neuron death (GO:0070997)
- **GO cellular component:** lysosomal membrane (GO:0005765)
- **CL cell types:** cerebellar Purkinje cell (CL:0000121); granule cell; neuron (CL:0000540); inferior olivary neuron
- **UBERON anatomy:** cerebellum (UBERON:0002037); inferior olivary complex (UBERON:0002118); thalamus (UBERON:0001897); substantia nigra (UBERON:0002038);

pyramidal tract (UBERON:0002435); hippocampus (UBERON:0002421); amygdala (UBERON:0001876)

- **CHEBI:** reactive oxygen species (CHEBI:26523); ADP-ribose (CHEBI:16960)
- **Disease:** MONDO:0032706; OMIM #618369

Section-by-Section Disease Characterization

1. Disease Information

SCAR27 is an adult-onset, autosomal recessive, slowly progressive cerebellar ataxia caused by biallelic GDAP2 loss of function. **Identifiers:** MONDO:0032706; OMIM phenotype #618369; gene OMIM *618128; HGNC:18010; UniProt Q9NXN4. No specific ICD-10/ICD-11 or MeSH code is assigned to SCAR27 as a distinct entity; it falls under hereditary/recessive cerebellar ataxia categories (e.g., ICD-10 G11.1/G11.2, broadly). Synonyms:** autosomal recessive spinocerebellar ataxia-27; GDAP2-related cerebellar ataxia; GDAP2-related spinocerebellar ataxia. The disease-level information is derived from aggregated case reports and curated database resources (OMIM, UniProt, ClinVar), not from large patient registries or EHR cohorts — reflecting the ultra-rare status.

2. Etiology

Causal factor: purely genetic — biallelic (homozygous or compound heterozygous) loss-of-function variants in GDAP2. **Genetic risk factors:** the causal variants themselves; consanguinity substantially raises risk (several reported families are consanguineous, with homozygous null alleles). No susceptibility loci, modifier genes, protective alleles, or gene-environment interactions have been established. **Environmental/lifestyle/infectious factors:** none identified as causal or contributory. Given the stress-vulnerability mechanism, oxidative or metabolic stressors are a theoretical modifier, but this is **not demonstrated** in patients.

3. Phenotypes

Phenotype	Type	HPO suggestion	Onset	Progression	Frequency
Cerebellar ataxia / gait difficulty	Clinical sign	HP:0001251 / HP:0002066	3rd–4th decade	Progressive	Core (near-universal)
Dysarthria	Clinical sign	HP:0001260	Adult	Progressive	Common; can be presenting feature
Eye-movement abnormalities	Clinical sign	HP:0000496	Adult	Progressive	Common
Lower-limb spasticity	Clinical sign	HP:0002061	Adult	Progressive	Common
Dysgraphia / difficulty writing	Clinical sign	HP:0025131	Adult	Progressive	Reported
Cognitive impairment / dementia	Behavioral/ cognitive	HP:0001268 / HP:0000726	Adult	Progressive	Reported in multiple cases
Loss of independent ambulation	Functional	HP:0002540	Late	Progressive	Subset (wheelchair dependence)
Dysphagia	Clinical sign	HP:0002015	Late	Progressive	Advanced disease
Cervical dystonia	Clinical sign	HP:0002402	Adult	—	Reported (Spanish family)

Quality-of-life impact: progressive loss of mobility, speech, writing, and cognition causes substantial and increasing disability; advanced patients become wheelchair-dependent with dysphagia. No formal EQ-5D/SF-36/PROMIS data exist for this ultra-rare disease.

4. Genetic / Molecular Information

Causal gene: GDAP2 (HGNC:18010; gene OMIM *618128; Ensembl ENSG00000196505; NCBI Gene 54834). Variant classes: nonsense, frameshift, and canonical splice-site — all loss-of-function (see Finding 5 table). Functional consequence: loss of function (LOF). Allele frequency: pathogenic alleles are ultra-rare/private in gnomAD. Origin: germline. Modifier/epigenetic/chromosomal:** none established specific to SCAR27; two large multigene 1p13 CNVs are pathogenic but not SCAR27-specific. gnomAD constraint (pLI≈0, LOEUF 0.96) confirms heterozygous LOF tolerance consistent with recessive disease.

5. Environmental Information

No environmental, lifestyle, or infectious factors are implicated in SCAR27. The disease is monogenic and fully genetically determined. (Oxidative/nutrient stress is mechanistically relevant at the cellular level but is not an established patient-level environmental risk factor.)

6. Mechanism / Pathophysiology

See the **Mechanistic Model** section above for the full ordered causal chain. In brief: biallelic GDAP2 LOF → loss of a lysosomal-membrane, macro-domain/CRAL-TRIO stress-response protein → impaired handling of oxidative and nutrient stress → progressive, region-selective neurodegeneration (cerebellum, inferior olive, thalamus, substantia nigra, pyramidal tracts; limbic tau) → ataxia, spasticity, and cognitive decline. Key molecular features: macro domain (ADP-ribose/NAD metabolite binding), CRAL-TRIO/Sec14 lipid-binding domain, lysosomal-membrane localization. Silkworm knockout transcriptomics highlighted peroxidase activity, apoptosis, and longevity-regulation pathways (PMID: 40332832), consistent with a stress/oxidative-homeostasis role.

7. Anatomical Structures Affected

Primary organ/system: central nervous system (nervous system). **Primary sites:** cerebellum (UBERON:0002037) and inferior olivary complex (UBERON:0002118). **Secondary involvement:** thalamus (UBERON:0001897), substantia nigra (UBERON:0002038), pyramidal tracts (UBERON:0002435), hippocampus (UBERON:0002421), amygdala (UBERON:0001876). **Tissue/cell:** nervous tissue; cerebellar neurons (Purkinje cells CL:0000121, granule cells), olivary and brainstem neurons. **Subcellular:** lysosomal membrane (GO:0005765). **Lateralization:** bilateral/symmetric (typical of neurodegenerative ataxia).

8. Temporal Development

Onset: adult, typically 3rd–4th decade (reported onsets ~32–47 years). **Onset pattern:** insidious/chronic. **Progression:** slowly progressive over years to decades; no remission. **Course:** chronic, lifelong, progressive. Advanced disease → loss of ambulation and dysphagia. No episodic or relapsing-remitting pattern. **Critical window:** none defined; because neurodegeneration is slow, there is in principle a long window for intervention if disease-modifying therapy becomes available.

9. Inheritance and Population

Inheritance: autosomal recessive. **Penetrance:** appears complete in biallelic LOF carriers (based on limited cases). **Expressivity:** variable (ranging from isolated dysarthria with normal MRI to full ataxia-spasticity-dementia). **Consanguinity:** an important contributor; homozygous null variants have been reported in consanguineous families. **Carrier frequency:** not formally established; pathogenic alleles are private/ultra-rare. **Epidemiology:** ultra-rare — only a handful of families reported worldwide (original/Netherlands, China, Spain, and others); true prevalence/incidence unknown and likely well under 1 per million. **No founder effect, anticipation, or sex bias** has been established; as an autosomal recessive disorder, males and females are affected equally.

10. Diagnostics

Genetic testing is the diagnostic cornerstone: whole-exome sequencing (WES) or hereditary-ataxia gene panels (e.g., adult-onset hereditary ataxia panels such as PanelApp) detect biallelic GDAP2 LOF variants; whole-genome sequencing and Sanger confirmation/segregation are adjuncts. **Imaging:** brain MRI may show cerebellar atrophy, but — importantly — can be normal early or in atypical presentations (PMID: 42633453); thus normal MRI does **not** exclude SCAR27. **Routine labs and neurophysiology** are typically unremarkable. **No specific biomarker** exists. **Differential diagnosis:** other autosomal recessive cerebellar ataxias (e.g., ATM/ataxia-telangiectasia, SACS/ARSACS, COQ8A, APTX/AOA1, SYNE1, Friedreich ataxia) — distinguished by genetic testing; GDAP2 is now included on adult-onset ataxia panels. **Screening:** cascade carrier testing within affected families; no newborn or population screening.

11. Outcome / Prognosis

SCAR27 is a chronic, progressive, disabling neurodegenerative disease. Patients experience accumulating disability — loss of gait, speech, writing, and cognition — with a subset becoming wheelchair-dependent and developing dysphagia. No formal survival, mortality, or life-expectancy data exist given the rarity, but as an adult-onset neurodegenerative ataxia, life expectancy may be reduced in advanced disease (e.g., via aspiration/dysphagia complications). **Prognostic factors** are not formally defined; earlier/more severe cognitive and pyramidal involvement likely portends worse functional outcome. No prognostic biomarkers are established.

12. Treatment

There is **no disease-modifying or curative therapy** for SCAR27. Management is **supportive and rehabilitative**: physical therapy for gait/spasticity, occupational therapy (including writing aids for dysgraphia), speech therapy for dysarthria/dysphagia, antispasticity agents (e.g., baclofen — skeletal muscle relaxant class), mobility aids, swallow management, and cognitive/social support. No pharmacotherapy, gene therapy, RNA-based therapy, or targeted therapy is approved or in trials specific to GDAP2. **NCIT intervention concepts:** Physical Therapy, Occupational Therapy, Speech Therapy, Supportive Care. Because the mechanism involves oxidative/metabolic stress vulnerability, antioxidant strategies are a theoretical direction but are **not evidence-based** for this disease.

13. Prevention

No primary prevention exists for a monogenic recessive disorder. **Genetic counseling** is the principal preventive tool: at-risk couples (especially consanguineous) can be offered carrier testing, and families with a known GDAP2 variant can pursue **cascade testing**, **prenatal diagnosis**, or **preimplantation genetic testing (PGT-M)**. Tertiary prevention = rehabilitative management to limit complications (falls, aspiration). No immunization or public-health intervention applies.

14. Other Species / Natural Disease

No naturally occurring GDAP2-related disease has been reported in companion animals or wildlife (no OMIA entry for a GDAP2 natural disease). GDAP2 is evolutionarily conserved with clear orthologs: mouse *Gdap2* (NCBI 14547), rat *Gdap2* (362004), zebrafish *gdap2* (447824),

Drosophila Gdap2 (59173), and *Bombyx mori BmGDAP2* (101738783). The macro + CRAL-TRIO domain architecture and stress-response role appear conserved from insects to humans. No zoonotic or cross-species transmission component (non-infectious disease).

15. Model Organisms

See Finding 6. Available LOF models are **all invertebrate**:

Model	Type	Key phenotype	PMID
Drosophila Gdap2 knockdown	RNAi knockdown	Shortened lifespan, motor defects, stress hypersensitivity	30084953
Silkworm *BmGDAP2*	CRISPR/Cas9 KO	Extended lifespan, reduced size, 149 DEGs (peroxidase/apoptosis/longevity)	40332832
Silkworm GDAP2	Systemic KO	Delayed development, 4th-instar arrest; Dimm target	40205793
Rodent (GDAP2 **overexpression**)	Gain of dosage (not KO)	Dendritic/synaptic changes, increased seizures	35158016

No mammalian knockout recapitulating adult-onset neurodegeneration exists. The *Drosophila* knockdown best models the neuromotor/stress phenotype; silkworm models inform development/longevity biology but not neurodegeneration. iPSC-derived neurons and conditional mouse knockouts are obvious unfilled needs.

Evidence Base

PMID	Title (abbreviated)	Role in this report
30084953	*GDAP2 mutations implicate susceptibility to cellular stress in a new form of cerebellar ataxia*	**Landmark** — defines SCAR27; biallelic LOF; adult onset, spasticity, dementia; Drosophila stress model; human neuropathology
32437512	*Novel GDAP2 pathogenic variants … SCAR27 in a Chinese family*	Independent replication of gene-disease relationship
32428220	*Homozygous GDAP2 LOF variant in adult-onset cerebellar ataxia*	Additional adult-onset LOF case
40469082	*ARCA-27 … novel LOF of GDAP2 in a Spanish family*	Novel premature-stop homozygous variant; onset age 32; dysarthria→ataxia, spasticity, dystonia, cognitive impairment
42633453	*Progressive slurred speech as atypical presentation of GDAP2 ataxia*	Expands spectrum — isolated dysarthria, **normal MRI**, homozygous nonsense variant
35158016	*GDAP2 overexpression affects neurons / synaptic transmission*	Over-expression (gain-of-dosage) rodent study — informs GDAP2 neuronal function but **not** the recessive LOF mechanism
40332832	*CRISPR/Cas9 knockout of BmGDAP2 (silkworm)*	Invertebrate KO; stress/longevity transcriptomics
40205793	*Dimm targets GDAP2 to regulate larval development (silkworm)*	GDAP2 regulation and developmental KO phenotype
32428197 / 32658981	Reply/erratum correspondence	Document ongoing variant/family reporting

Evidence source types: human clinical/genetic (30084953, 32437512, 32428220, 40469082, 42633453; ClinVar; UniProt; OMIM); model organism (30084953 Drosophila; 40332832, 40205793 silkworm; 35158016 rodent overexpression); computational/database (gnomAD constraint; UniProt domain and GO annotation).

Limitations and Knowledge Gaps

1. **Very small patient numbers.** The disease rests on a handful of families worldwide. Phenotype frequencies, penetrance, expressivity, natural history, survival, and QoL are estimates from case reports, not cohort data.
2. **No mammalian LOF model.** All knockout models are invertebrate; the only rodent study used overexpression (opposite dosage direction). This limits mechanistic dissection and preclinical therapeutic testing.
3. **Mechanism is largely inferred.** The stress-vulnerability model is best supported in flies; the lysosomal-membrane localization is from a single high-throughput assay (GO evidence code HDA) and warrants targeted validation. Exactly how GDAP2's macro and CRAL-TRIO domains execute stress protection, and why neurons are selectively vulnerable despite ubiquitous expression, remain unknown.
4. **No biomarkers or disease-modifying therapy.** Diagnosis is genetic; there are no fluid/imaging biomarkers and no targeted treatment.
5. **Imaging can be normal**, complicating recognition; clinicians may under-diagnose SCAR27 in progressive dysarthria/ataxia without cerebellar atrophy.
6. **Epidemiology unknown** — prevalence, incidence, carrier frequency, and any founder effects are not established.

Proposed Follow-up Experiments / Actions

1. **Generate a conditional mouse knockout** (neuronal/cerebellar Cre) and characterize for adult-onset ataxia, Purkinje/olivary degeneration, tau pathology, and stress vulnerability — the single highest-priority gap.
2. **iPSC-derived cerebellar/Purkinje neurons and organoids** from patients (and isogenic LOF lines) to test oxidative/nutrient-stress sensitivity, lysosomal/autophagic function, and candidate protective compounds (e.g., antioxidants).
3. **Validate subcellular localization and interactome** of GDAP2 at the lysosomal membrane (confocal + proximity labeling/BioID), contrasting with GDAP1's mitochondrial role; define macro-domain ADP-ribose/NAD and CRAL-TRIO lipid ligands biochemically.

4. **International patient registry / GeneMatcher-driven case collection** to establish phenotype frequencies, natural history, penetrance, imaging spectrum, and genotype-phenotype correlations.
5. **Biomarker discovery** — oxidative-stress markers, neurofilament light chain (axonal injury), and lysosomal-function readouts in patient CSF/blood.
6. **Clinical awareness** — include GDAP2 on all adult-onset hereditary-ataxia panels and consider SCAR27 in progressive dysarthria/ataxia even with normal MRI; offer genetic counseling and cascade/PGT options to affected families.

Report compiled from database-verified findings (OMIM, UniProt, HGNC, Ensembl, ClinVar, gnomAD, NCBI Gene) and primary literature across 5 investigation iterations. GDAP2 is the causal gene of SCAR27 (MONDO:0032706; OMIM #618369).
