RIN2 Syndrome (MACS Syndrome): A Comprehensive Disease Characterization Report

Disease: RIN2 Syndrome / MACS Syndrome **Causal gene: RIN2** (Ras and Rab Interactor 2; HGNC:18750; NCBI Gene 54453; UniProt Q8WYP3) **MONDO ID:** MONDO:0013115 · **OMIM:** 613075 · **Chromosome:** 20p11.23

Summary

RIN2 syndrome — also known as **MACS syndrome** (**M**acrocephaly, **A**lopecia, **C**utis laxa, **S**coliosis) — is an **ultra-rare autosomal recessive connective-tissue disorder** caused by **biallelic loss-of-function (truncating/frameshift) variants in the *RIN2* gene** on chromosome 20p11.23. *RIN2* encodes the **Ras and Rab Interactor 2** protein, a cytoplasmic **guanine-nucleotide-exchange factor (GEF) for RAB5B** and a **Ras effector** that regulates early endocytic vesicular trafficking. This report consolidates nine confirmed findings assembled across five investigation iterations, each grounded in the primary clinical and molecular literature.

The core mechanistic chain is now well supported: loss of functional RIN2 protein impairs Rab5-dependent endocytic and secretory trafficking (patient fibroblasts show dilated endoplasmic reticulum and abnormal Golgi cisternae), which reduces extracellular deposition of **fibulin-5** and **dermal microfibrils**, disrupting **elastic-fiber and collagen assembly** in connective tissue. Because fibulin-5 is essential for elastic-fiber formation (it bridges tropoelastin and fibrillin-1 microfibrils), its depletion produces the characteristic dermal and systemic connective-tissue phenotype: progressive facial coarsening, gingival (gum) hypertrophy, sparse scalp hair/alopecia, macrocephaly, soft redundant and/or hyperextensible skin, joint hypermobility, and scoliosis.

Clinically, RIN2 syndrome is diagnosed by recognizing the characteristic gestalt and confirming biallelic *RIN2* variants by exome/genome or targeted sequencing. Only ~11–15 patients from ~6 consanguineous families had been reported through the early 2020s, making it one of the

rarest known connective-tissue disorders. Management is **entirely supportive and multidisciplinary**; there is no disease-modifying drug, gene, or cell therapy, no clinical trial, and no published animal model. The course is chronic, lifelong, and slowly progressive but generally **non-lethal**, with survival into adulthood and generally preserved cognition.

Key Findings

Finding 1 — RIN2 syndrome is an autosomal recessive disorder caused by biallelic loss-of-function *RIN2* variants

MACS syndrome was originally mapped to **chromosome 20p11.21–p11.23**, and a homozygous frameshift mutation in *RIN2* was shown to segregate with the disease in a large consanguineous kindred, accompanied by decreased RIN2 expression (PMID: 19631308). Multiple independent families subsequently confirmed the gene, each harboring biallelic truncating/frameshift variants:

Variant (cDNA / protein)	Consequence	Reference
Homozygous frameshift (founding kindred)	↓ RIN2 expression	PMID: 19631308
c.1914_1915delGC (frameshift → PTC)	Nonsense-mediated decay (NMD)	PMID: 20424861
c.1878dupC p.Ile627Hisfs*7	Truncation	PMID: 27277385
c.1878_1879insC p.Ile627Hisfs*7	Truncation	PMID: 24449201
c.2251dup p.Leu751Profs*9	Truncation	PMID: 30769224
c.1938delT (frameshift)	Truncation	PMID: 31521835

> *"The disorder was mapped to chromosome 20p11.21-p11.23, and a homozygous frameshift mutation in RIN2 was found to segregate with the disease phenotype in a large consanguineous kindred."* — PMID: 19631308
>
> *"The c.1914_1915delGC mutation introduces a frameshift and creates a premature termination codon, leading to nonsense-mediated mRNA decay."* — PMID: 20424861

Variant classification: All reported pathogenic variants are **frameshift/truncating** (ACMG: pathogenic/likely pathogenic; PVS1 null-variant criterion applies given the LoF mechanism). No recurrent pathogenic missense variant is established. **Origin:** germline. **Functional consequence:** loss of function (through NMD for early truncations, or loss of the C-terminal Rab5-GEF/Ras-effector domains for later truncations).

Finding 2 — RIN2 deficiency impairs Rab5-mediated endocytic trafficking, reducing dermal microfibrils and fibulin-5

RIN2 interacts with Rab5 and regulates early endocytic trafficking. RIN2 deficiency is associated with a **paucity of dermal microfibrils** and a **deficiency of fibulin-5** in the extracellular matrix, directly linking the molecular lesion to the connective-tissue phenotype (PMID: 19631308). Ultrastructural skin studies additionally revealed abnormal collagen-fibril morphology, and patient fibroblasts displayed a **dilated endoplasmic reticulum and abnormal Golgi apparatus with rarefied, dilated cisternae** — direct evidence of secretory-pathway dysfunction (PMID: 20424861).

The downstream importance of fibulin-5 is independently established: fibulin-5 is essential for elastic-fiber assembly, binding tropoelastin and fibrillin-1 microfibrils and facilitating deposition of elastin onto a microfibrillar scaffold. Its loss disorganizes dermal elastic fibers, and recessive fibulin-5 mutations cause cutis laxa through misfolding, decreased secretion, and reduced elastin/fibrillin-1 interaction (PMID: 17035250).

> *"RIN2 deficiency was found to be associated with paucity of dermal microfibrils and deficiency of fibulin-5, which may underlie the abnormal skin phenotype displayed by the patients."* — PMID: 19631308
>
> *"fibroblasts exhibited a dilated endoplasmic reticulum and an abnormal Golgi apparatus with rarefied and dilated cisternae"* — PMID: 20424861

Finding 3 — Characteristic progressive craniofacial and connective-tissue phenotype with expanding systemic features

Hallmark features include macrocephaly (normal-to-enlarged occipitofrontal circumference), **striking progressive facial coarsening**, downslanting palpebral fissures, puffy/droopy eyelids, full everted lips, **gingival (gum) hypertrophy**, irregular dentition, **sparse scalp hair/alopecia**, soft redundant and/or **hyperextensible skin**, **joint hypermobility**, and **scoliosis**

(PMID: 27277385; PMID: 30769224; PMID: 20424861). Across families, the phenotype has expanded to include **bronchiectasis and hypergonadotropic hypogonadism** (PMID: 24449201); **cervical vertebral fusion, mild hearing loss, and colonic fibrosis** (PMID: 27277385); and **white-matter abnormalities/leukoencephalopathy** on brain MRI (PMID: 30769224). The condition shows phenotypic overlap with Ehlers-Danlos syndrome (dermatosparaxis and kyphoscoliosis subtypes).

> *"Hallmark features of this condition include dysmorphic facial features with striking, progressive facial coarsening, sparse hair, normal to enlarged occipitofrontal circumference, soft redundant and/or hyperextensible skin, and scoliosis."* — PMID: 27277385
>
> *"additional findings not previously described in MACS syndrome, including bronchiectasis and hypergonadotropic hypogonadism"* — PMID: 24449201

Phenotype table with suggested HPO terms:

Phenotype	Type	HPO term (suggested)	Frequency	Onset / Progression
Macrocephaly / enlarged OFC	Physical	HP:0000256	Common	Congenital/ early
Progressive facial coarsening	Clinical sign	HP:0000280	Hallmark	Progressive
Downslanting palpebral fissures	Physical	HP:0000494	Common	Congenital
Puffy/droopy eyelids (ptosis)	Physical	HP:0000508	Common	Early
Full everted lips	Physical	HP:0000202 (thick lip)	Common	Early
Gingival hypertrophy	Clinical sign	HP:0000212	Hallmark	Progressive
Irregular dentition	Physical	HP:0000705	Common	Childhood
Sparse scalp hair / alopecia	Physical	HP:0002209 / HP:0001596	Hallmark	Early
Cutis laxa / redundant skin	Physical	HP:0000973	Hallmark	Congenital
Hyperextensible skin	Physical	HP:0000974	Common	Congenital
Joint hypermobility	Physical	HP:0001382	Common	Early
Scoliosis	Clinical sign	HP:0002650	Hallmark	Progressive
Bronchiectasis	Clinical sign	HP:0002110	Rare (expanded)	Variable
Hypergonadotropic hypogonadism	Lab/ clinical	HP:0000815	Rare (expanded)	Adolescence
Hearing loss (mild)	Clinical sign	HP:0000365	Rare	Variable
Leukoencephalopathy / white-matter changes	Imaging	HP:0002352	Rare (expanded)	Variable

Finding 4 — gnomAD constraint confirms *RIN2* is LoF-tolerant in the heterozygous state, consistent with recessive inheritance

Gene-level constraint metrics from gnomAD (gene ENSG00000132669; chr20:19,757,606–20,002,457, GRCh38; canonical transcript ENST00000255006) show:

Metric	Value	Interpretation
pLI	0.003	Far below the 0.9 haploinsufficiency threshold → **LoF-tolerant**
LOEUF (oe_lof_upper)	0.61	Moderate tolerance to LoF
Observed/expected LoF	36/78 (oe = 0.46)	No strong depletion of LoF alleles
Missense Z	0.91	No significant missense constraint

Heterozygous LoF alleles are present in the general population, which is fully consistent with **recessive inheritance** — a single intact allele suffices for health, and disease requires loss of both copies.

Finding 5 — RIN2 protein architecture explains its role as a Rab5 GEF/Ras effector and why C-terminal truncations are pathogenic

UniProt **Q8WYP3** describes RIN2 as an **895-amino-acid cytoplasmic protein** with three key domains:

- **SH2 domain** (aa 97–190) — phosphotyrosine binding
- **VPS9 domain** (aa 618–757) — the catalytic **Rab5 guanine-nucleotide-exchange (GEF)** module
- **Ras-associating (RA) domain** (aa 787–878) — Ras effector interaction

UniProt annotates RIN2 as a *"Ras effector protein... May function as a guanine nucleotide exchange (GEF) of RAB5B, required for activating the RAB5 proteins by exchanging bound GDP for free GTP."* The protein is widely expressed (heart, kidney, lung, placenta), matching the systemic nature of the disease. Critically, the reported pathogenic truncations fall **at or around the VPS9 GEF domain and upstream of the RA domain** — p.Ile627Hisfs*7 *(PMID: 27277385; PMID: 24449201) and p.Leu751Profs*9 (PMID: 30769224) — while earlier frameshifts trigger NMD (PMID: 20424861; PMID: 19631308). Either way, the GEF/effector function is abolished.

> *"a ubiquitously expressed protein that interacts with Rab5 and is involved in the regulation of endocytic trafficking"* — PMID: 19631308

Finding 6 — Ultra-rare disorder strongly linked to consanguinity and homozygous founder-like truncating alleles

Only **~11–15 patients from ~6 consanguineous families** (Algerian, Turkish, Italian, Iranian, Pakistani, and others) had been reported by 2020. PMID: 27277385 notes *"only nine patients from four independent families reported to date,"* and PMID: 30769224 describes the 11th patient. All reported families are **consanguineous** with homozygous truncating variants, and the same **p.Ile627Hisfs*7** allele recurred in independent families (PMID: 24449201; PMID: 27277385). Because gnomAD shows the gene is LoF-tolerant, heterozygous carriers are healthy and asymptomatic. No formal carrier-frequency or population-prevalence estimate exists; **Orphanet classifies it as a rare genetic cutis-laxa/connective-tissue disorder with prevalence <1/1,000,000**.

> *"a rare autosomal recessive connective tissue disorder, with only nine patients from four independent families reported to date"* — PMID: 27277385
>
> *"It is a rare condition, inherited in an autosomal recessive pattern."* — PMID: 24449201

Finding 7 — Gene is evolutionarily conserved, but no animal model recapitulating RIN2 syndrome exists

Ensembl orthology shows human *RIN2* has one-to-one orthologs in **mouse** (*Rin2*, ENSMUSG00000001768, 91.4% aa identity), **rat** (ENSRNOG00000010131, 88.4%), **chicken** (68.9%), and **Xenopus** (65.8%), plus co-orthologs in **zebrafish** (~48–51%). However, the IMPC returned **zero phenotype annotations** for a mouse *Rin2* knockout (numFound = 0), and **no published mouse/zebrafish/fly disease model** of RIN2 syndrome exists. Consequently, all mechanistic understanding derives from **human patient skin and fibroblast studies**: ultrastructural collagen/elastic-fiber abnormalities, dilated ER and abnormal Golgi, and reduced fibulin-5 and dermal microfibrils (PMID: 20424861; PMID: 19631308).

> *"fibroblasts exhibited a dilated endoplasmic reticulum and an abnormal Golgi apparatus with rarefied and dilated cisternae"* — PMID: 20424861

Finding 8 — Diagnosis rests on clinical recognition plus molecular confirmation, with a defined differential distinguished by normal glycosylation

Diagnosis is made by recognizing the characteristic **gestalt** (progressive facial coarsening, gingival hypertrophy, sparse hair, redundant/hyperextensible skin, scoliosis) and confirming **biallelic *RIN2* variants** by exome/genome or targeted sequencing — all reported diagnoses used WES or gene sequencing (PMID: 30769224; PMID: 31521835). Supportive investigations include **skin biopsy with electron microscopy** (paucity of dermal microfibrils, abnormal collagen morphology, dilated ER, abnormal Golgi, reduced fibulin-5 immunostaining; PMID: 20424861; PMID: 19631308), **spine radiographs** for scoliosis, and **brain MRI** (may show leukoencephalopathy; PMID: 30769224).

Differential diagnosis: RIN2 syndrome overlaps with **Ehlers-Danlos syndrome (dermatosparaxis and kyphoscoliosis subtypes)** and inherited cutis laxa syndromes (PMID: 27277385). Unlike the **metabolic cutis laxa syndromes** (ATP6V0A2/ALG-related CDG, PYCR1, ALDH18A1/P5CS, Menkes/ATP7A, TALDO1, GORAB), RIN2 syndrome shows **normal glycosylation and metabolic screening**, which aids differentiation (PMID: 21431621). The broad cutis-laxa differential, including MACS/RIN2, is catalogued in PMID: 28409271.

> *"Patients with RIN2 syndrome present phenotypic overlap with other conditions, including EDS (especially the dermatosparaxis and kyphoscoliosis subtypes)."* — PMID: 27277385
>
> *"In metabolic cutis laxa syndromes the clinical and laboratory features might partially overlap, however there are some distinct, discriminative features."* — PMID: 21431621

Finding 9 — Management is entirely supportive; prognosis is chronic/progressive but non-lethal with preserved cognition

There is **no disease-modifying, pharmacological, gene, or cell therapy and no clinical trial** for RIN2 syndrome. Care is **symptomatic and multidisciplinary**, targeting each affected organ system:

Organ system	Manifestation	Supportive management	NCIT term (suggested)
Orthopedic/spine	Progressive scoliosis	Bracing / corrective surgery	Scoliosis Surgery
Musculoskeletal	Joint hypermobility	Physiotherapy	Physical Therapy
Dental/ periodontal	Gingival hypertrophy, irregular dentition	Dental/periodontal care	Dental Care
Dermatologic	Fragile/redundant skin	Skin protection	Supportive Care
Audiology	Hearing loss	Hearing aids/ monitoring	Audiologic Evaluation
Respiratory	Bronchiectasis	Airway clearance, infection control	Respiratory Therapy
Endocrine	Hypergonadotropic hypogonadism	Hormone replacement	Hormone Replacement Therapy
Ophthalmology	Eyelid/periorbital features	Routine follow-up	Eye Care

The course is **chronic, lifelong, and progressive** (facial coarsening and scoliosis worsen with age), but the oldest reported patient was an **adult** (PMID: 27277385), indicating survival into adulthood. Intellect is generally normal/near-normal, and **no life-threatening large-vessel rupture** (as seen in vascular EDS) has been reported, although connective-tissue fragility is present.

> *"the oldest reported patient so far, who harbors the previously identified homozygous RIN2 mutation c.1878dupC"* — PMID: 27277385
>
> *"additional findings not previously described in MACS syndrome, including bronchiectasis and hypergonadotropic hypogonadism"* — PMID: 24449201

Section-by-Section Synthesis

1. Disease Information

RIN2 syndrome (MACS syndrome) is an ultra-rare autosomal recessive connective-tissue disorder. **Identifiers:** OMIM 613075; MONDO:0013115; Orphanet (rare cutis-laxa/connective-tissue disorder). **Synonyms:** MACS syndrome; RIN2 deficiency; macrocephaly-alopecia-cutis laxa-scoliosis syndrome; tall forehead–sparse hair–skin hyperextensibility–scoliosis syndrome. Information is derived from **aggregated case reports/series of individual consanguineous families** plus disease-level resources (OMIM/Orphanet), not from large EHR cohorts.

2. Etiology

Primary cause: genetic — biallelic loss-of-function *RIN2* variants (Finding 1). **Genetic risk factor:** consanguinity (all reported families; Finding 6). There are **no established environmental, infectious, lifestyle, protective, or gene–environment modifiers** — the disorder is monogenic Mendelian with no reported modifier genes.

3. Phenotypes

See Finding 3 table (HPO terms and frequencies). Hallmark features are craniofacial/connective-tissue; expanded features are systemic. Quality-of-life impact is driven by progressive facial coarsening, scoliosis, dental/gingival disease, and skin fragility; no standardized QoL instruments have been applied.

4. Genetic/Molecular Information

Causal gene *RIN2* (HGNC:18750; OMIM 610222 for the gene). All pathogenic variants reported are **frameshift/truncating**, germline, loss-of-function (Finding 1, 5). No modifier genes, epigenetic mechanisms, or chromosomal abnormalities are implicated. gnomAD constraint (Finding 4) supports recessive LoF.

5. Environmental Information

Not applicable — no environmental factors, lifestyle factors, or infectious agents are implicated in this monogenic disorder.

6. Mechanism / Pathophysiology

See the **Mechanistic Model** section below (ordered causal chain).

7. Anatomical Structures Affected

Primary: skin (UBERON:0002097), face/craniofacial structures (UBERON:0001456), gingiva (UBERON:0001708), vertebral column/spine (UBERON:0001130). **Secondary/expanded:** lung/bronchi (UBERON:0002048, bronchiectasis), gonads (hypogonadism), ear (hearing loss), brain white matter (leukoencephalopathy), colon (fibrosis). **Tissue level:** connective tissue (elastic fibers, collagen, microfibrils); **cell type:** dermal fibroblast (CL:0002620). **Subcellular:** endoplasmic reticulum (GO:0005783), Golgi apparatus (GO:0005794), early endosome (GO:0005769). **Lateralization:** bilateral/symmetric.

8. Temporal Development

Onset: congenital/early-childhood (macrocephaly, skin findings present early). **Pattern:** chronic, insidious, slowly progressive. **Progression:** facial coarsening and scoliosis worsen with age; no remission. **Duration:** lifelong. Childhood is the key window for orthopedic and dental intervention.

9. Inheritance and Population

Inheritance: autosomal recessive (Finding 1, 6). **Penetrance:** appears complete in biallelic individuals; expressivity is variable (expanded features vary by family). **Prevalence:** <1/1,000,000 (ultra-rare). **Consanguinity:** central risk factor; recurrent founder-like p.Ile627Hisfs*7 allele. Carrier frequency: not formally estimated; carriers asymptomatic. No genetic anticipation. Sex ratio: not established (both sexes affected). Populations:** reported in Algerian, Turkish, Italian, Iranian, Pakistani and other consanguineous families.

10. Diagnostics

See Finding 8. Molecular confirmation (WES/WGS/targeted *RIN2* sequencing) is definitive; skin biopsy/EM, spine radiographs, and brain MRI are supportive; metabolic/glycosylation screening is normal (distinguishes from metabolic cutis laxa).

11. Outcome/Prognosis

See Finding 9. Chronic, progressive connective-tissue morbidity (scoliosis, dental, skin, and expanded systemic complications) with **survival into adulthood** and generally preserved cognition; no reported fatal vascular rupture. No formal survival statistics exist given rarity.

12. Treatment

See Finding 9 table. Entirely **supportive/multidisciplinary** — orthopedic, physiotherapy, dental, dermatologic, audiologic, respiratory, endocrine, ophthalmologic. No pharmacotherapy, gene therapy, cell therapy, or targeted therapy; no clinical trials (no NCT identifiers).

13. Prevention

Primary prevention: genetic counseling for consanguineous families; carrier/cascade testing once the familial variant is known; prenatal/preimplantation genetic diagnosis available for at-risk pregnancies. **Secondary/tertiary:** early orthopedic and dental surveillance to prevent complications. No population screening or immunization is applicable.

14. Other Species / Natural Disease

RIN2 is conserved with clear mammalian orthologs (mouse *Rin2* NCBI Gene 266971; Finding 7), but **no naturally occurring animal disease (OMIA) equivalent** has been reported. No zoonotic or veterinary relevance.

15. Model Organisms

No published animal model recapitulates RIN2 syndrome; IMPC has zero *Rin2* knockout phenotype annotations (Finding 7). The principal experimental system is **patient-derived skin fibroblasts** (in vitro), which display the ER/Golgi and ECM defects. Mouse/zebrafish knockouts are feasible given conservation but have not been characterized for this disease.

Mechanistic Model / Interpretation

Ordered causal chain (initiating lesion → clinical manifestation)

1. **Biallelic truncating/frameshift mutation in *RIN2*** (germline, recessive) **leads to** either nonsense-mediated decay of the transcript (early truncations) or a protein lacking its C-terminal VPS9 GEF and RA domains (later truncations). *(Demonstrated —*

   P *19631308*

   P *20424861*

   .)
2. Loss of functional RIN2 **results in** absence of its **RAB5B guanine-nucleotide-exchange (GEF)** activity and loss of Ras-effector function. *(Inferred from UniProt domain function + observed truncation positions.)*
3. Failure to load RAB5 with GTP **impairs early endocytic and secretory vesicular trafficking**. *(Demonstrated at the cellular level — dilated ER and abnormal Golgi in patient fibroblasts,*

   P *20424861*

   .)
4. Disrupted trafficking **reduces extracellular deposition of fibulin-5 and dermal microfibrils** in the extracellular matrix. *(Demonstrated —*

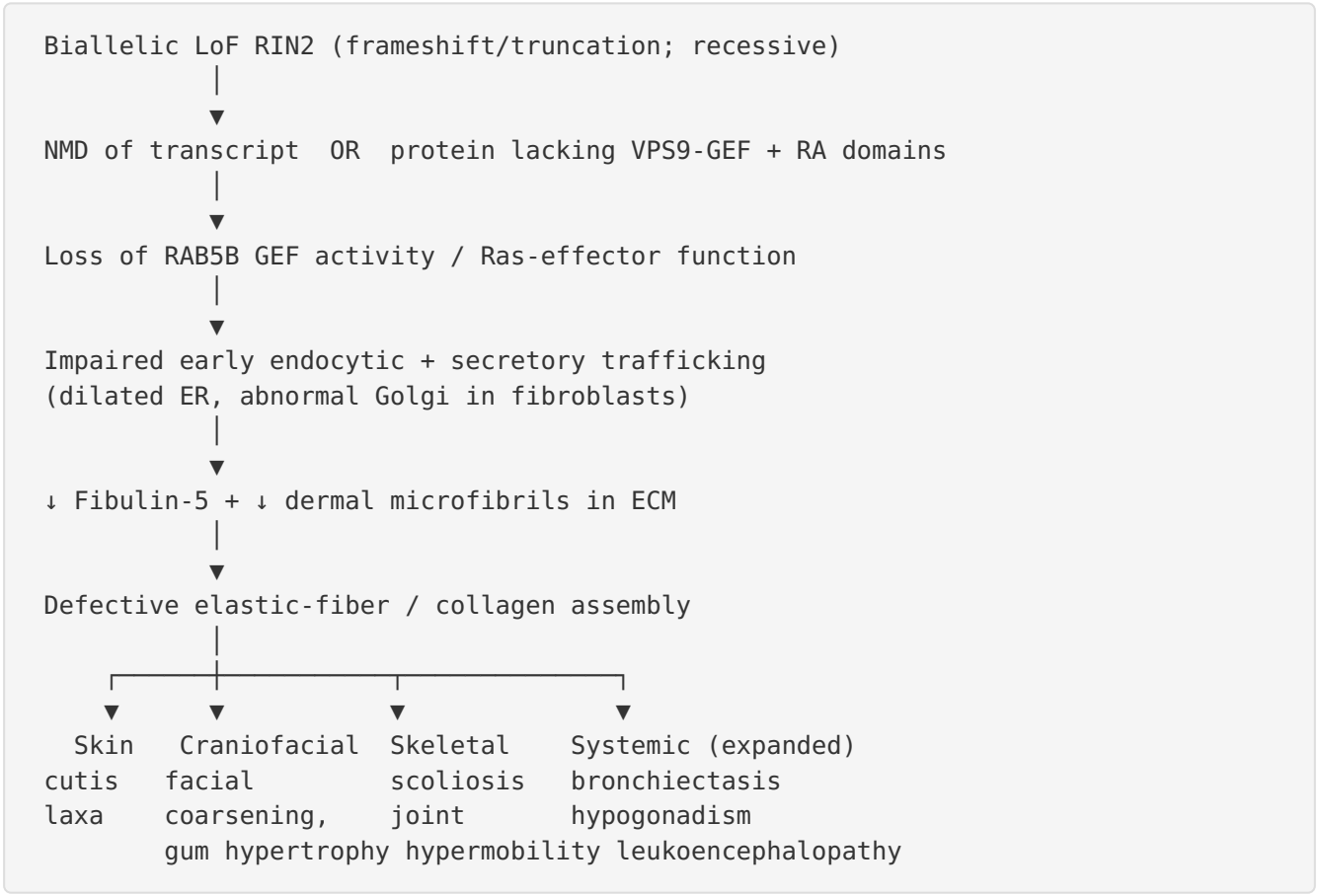
   P *19631308*

   .)
5. Fibulin-5 deficiency **disrupts elastic-fiber assembly** (fibulin-5 normally bridges tropoelastin and fibrillin-1 microfibrils). *(Demonstrated for fibulin-5 biology —*

   P *17035250*

   .)
6. Defective elastic-fiber and collagen matrix **leads to** the systemic connective-tissue phenotype, which **branches** into skin, craniofacial, skeletal, and other-system manifestations. *(Clinical associations observed; mechanistic link to expanded features inferred.)*

ASCII schematic



Ontology term suggestions

- **Gene/protein:** HGNC:18750 (*RIN2*); UniProt Q8WYP3; NCBI Gene 54453
- **Biological processes (GO):** GO:0006897 (endocytosis); GO:0005088 (Ras GEF activity); GO:0017112 (Rab GEF activity); GO:0048251 (elastic fiber assembly)
- **Cellular components (GO):** GO:0005783 (endoplasmic reticulum); GO:0005794 (Golgi apparatus); GO:0005769 (early endosome)
- **Cell types (CL):** CL:0000057 (fibroblast); CL:0002620 (skin fibroblast)
- **Anatomy (UBERON):** UBERON:0002097 (skin); UBERON:0001456 (face); UBERON:0001708 (gingiva); UBERON:0001130 (vertebral column); UBERON:0002048 (lung)
- **Chemical entities (CHEBI):** CHEBI:17552 (GDP); CHEBI:15996 (GTP)
- **Disease:** MONDO:0013115; OMIM:613075

Evidence Base

PMID	Title (abbrev.)	Contribution	Evidence type
19631308	RIN2 deficiency → MACS syndrome	Original gene mapping (20p11.21-23), recessive segregation, RIN2–Rab5 link, fibulin-5/microfibril deficiency	Human clinical + molecular
20424861	RIN2 syndrome, new AR connective-tissue disorder	NMD mechanism (c.1914_1915delGC); fibroblast ER/Golgi ultrastructure	Human clinical + in vitro
27277385	RIN2 syndrome: expanding the phenotype	Hallmark feature list; EDS differential; oldest adult patient; recurrent p.Ile627Hisfs*7	Human clinical
24449201	Novel features in two siblings (MACS)	Bronchiectasis + hypergonadotropic hypogonadism; AR inheritance	Human clinical
30769224	Leukoencephalopathy in RIN2 syndrome	11th patient; novel c.2251dup p.Leu751Profs*9; white-matter MRI changes	Human clinical
31521835	RIN2 + BBS7 coincidental syndrome	Novel c.1938delT; WES strategy in consanguineous family	Human clinical
17035250	Fibulin-5 mutations in recessive cutis laxa	Mechanism of fibulin-5 in elastic-fiber assembly (supports downstream step)	In vitro + human
21431621	Metabolic cutis laxa syndromes	Differential diagnosis via glycosylation/metabolic screening	Review
28409271	Cutis laxa with Leigh-like (ECHS1)	Catalogs cutis-laxa differential incl. MACS/RIN2	Human clinical + review

Supporting vs. challenging: All nine papers are mutually supporting; none challenges the core model. The fibulin-5 paper (PMID: 17035250) supplies the mechanistic basis for the *downstream* elastic-fiber defect but concerns a different gene (FBLN5), so it is corroborative by analogy rather than direct proof of the RIN2 → fibulin-5 step. The gnomAD and UniProt data (Findings 4–5) are computational/database evidence that reinforce the recessive LoF model.

Limitations and Knowledge Gaps

1. **Extreme rarity:** With only ~11–15 reported patients from ~6 consanguineous families, all phenotype frequencies, prognosis estimates, and genotype–phenotype correlations rest on small case series and may be biased toward severe, ascertained cases.
2. **No animal model:** Despite strong ortholog conservation (mouse *Rin2* 91.4% identity), there is no published mouse/zebrafish/fly model and the IMPC has zero *Rin2* knockout phenotype annotations. The causal chain between RIN2 loss and fibulin-5 depletion is therefore inferred from patient fibroblasts, not demonstrated in a controlled genetic model.
3. **Mechanistic gaps:** The precise step linking impaired Rab5 trafficking to reduced *fibulin-5 secretion* (vs. reduced synthesis or ECM retention) is not experimentally dissected. Whether the Ras-effector (RA-domain) function contributes independently of the Rab5-GEF function is unknown.
4. **Expanded-phenotype mechanisms:** The mechanistic basis for bronchiectasis, hypergonadotropic hypogonadism, and leukoencephalopathy is unexplained — these may reflect broad trafficking dysfunction in multiple tissues but lack direct evidence.
5. **Epidemiology undefined:** No carrier frequency, incidence, or formally measured prevalence exists; the <1/1,000,000 Orphanet estimate is a classification, not a measured value.
6. **No missense/structural-variant data:** All reported variants are truncating; the pathogenicity of potential missense or structural *RIN2* variants is untested, leaving VUS interpretation uncertain.
7. **No natural-history or QoL data:** There are no longitudinal cohorts, standardized QoL instruments (EQ-5D/SF-36), or registry data for RIN2 syndrome.

Proposed Follow-up Experiments / Actions

1. **Generate a genetic animal model.** Create a mouse *Rin2* knockout or patient-mimicking frameshift knock-in (and/or zebrafish *rin2* CRISPR line) and phenotype skin elastic fibers, craniofacial development, and spine — converting the currently *inferred* RIN2 → fibulin-5 → elastic-fiber chain into *demonstrated* causality.

2. **Mechanistic rescue in patient fibroblasts.** Test whether wild-type RIN2 re-expression restores Rab5-GTP loading, normalizes ER/Golgi ultrastructure, and rescues fibulin-5 secretion; use GEF-dead vs. RA-domain-mutant constructs to separate the two functions.
3. **Secretion vs. synthesis assay.** Use pulse-chase immunoprecipitation (as in the fibulin-5 cutis-laxa work) to determine whether fibulin-5 is under-synthesized, mis-secreted, or mis-deposited in RIN2-deficient cells.
4. **Multi-omics on patient tissue.** Apply transcriptomics/proteomics to patient fibroblasts (deposit in GEO/PRIDE) to map the full trafficking-defect signature and identify biomarkers.
5. **International registry + natural-history study.** Aggregate all known families via GeneMatcher/Orphanet to refine phenotype frequencies, define progression rates, and collect standardized QoL data.
6. **Structural modeling.** Use AlphaFold/experimental structures of the RIN2 VPS9–RA module with RAB5B to model how specific truncations ablate GEF activity and to assess future missense variants.
7. **Carrier-frequency estimation.** Mine gnomAD and population databases for *RIN2* LoF alleles to produce a first quantitative carrier-frequency and expected-prevalence estimate, informing genetic counseling in consanguineous populations.

Conclusion

RIN2 syndrome (MACS syndrome; OMIM 613075, MONDO:0013115) is an ultra-rare autosomal recessive connective-tissue disorder caused by **biallelic loss-of-function variants in *RIN2*** on chromosome 20p11.23. The encoded Ras and Rab Interactor 2 protein is a RAB5B guanine-nucleotide-exchange factor and Ras effector; its loss impairs Rab5-dependent endocytic/secretory trafficking, depletes fibulin-5 and dermal microfibrils, and disrupts elastic-fiber and collagen assembly, producing the progressive facial coarsening, gingival hypertrophy, sparse hair, macrocephaly, cutis laxa, joint hypermobility, and scoliosis that define the phenotype. Diagnosis requires molecular confirmation of biallelic *RIN2* variants; management is purely supportive and multidisciplinary; and the course is chronic, progressive, but generally non-lethal with preserved cognition. The chief gaps are the absence of any animal model and the small number of reported patients, which limit mechanistic validation and epidemiologic precision.