Premature Ovarian Failure 24 (POF24): A Comprehensive Disease Characterization

Disease: Premature Ovarian Failure 24 (POF24) **Causal gene: SYCP2L** (synaptonemal complex protein 2-like) **OMIM:** 620840 | **MONDO:** MONDO:0970995 | **Gene OMIM:** 616799 | **HGNC:** 21537 **Category:** Mendelian, autosomal recessive

Summary

Premature Ovarian Failure 24 (POF24) is a rare, autosomal-recessive form of primary/premature ovarian insufficiency (POI) caused by biallelic loss-of-function variants in the gene SYCP2L. SYCP2L (synaptonemal complex protein 2-like) is an oocyte-specific paralogue of the synaptonemal-complex lateral-element protein SYCP2. Uniquely among synaptonemal complex proteins, SYCP2L functions after meiotic prophase is complete: it localizes to the centromeres of dictyate-arrested primordial oocytes — the finite, non-renewable pool of germ cells laid down perinatally — where it promotes their long-term survival. When SYCP2L function is lost, this primordial reserve depletes prematurely and the ovary fails before the age of 40, producing the hypergonadotropic (high-FSH) amenorrhea, low anti-Müllerian hormone (AMH), and infertility that define POI.

The gene–disease relationship was established by whole-exome sequencing of a POI cohort (He et al., 2021, PMID: 32303603), which identified two homozygous pathogenic variants and demonstrated through in-vitro functional assays that the mutant proteins are mislocalized and loss-of-function. An independent Iranian cohort subsequently reported a novel homozygous nonsense variant in SYCP2L in a woman with amenorrhea, confirming the link (Bakhshalizadeh et al., 2024, PMID: 38521400). The mechanistic foundation was laid earlier by a landmark mouse and human-genetics study showing that Sycp2l-null female mice undergo accelerated, age-progressive oocyte loss, and that a common SYCP2L intronic SNP (rs2153157) modulates age at natural menopause and ovarian reserve (Zhou et al., 2015, PMID: 26362258). SYCP2L is thus a **dosage-sensitive regulator of ovarian lifespan**: common regulatory variants shift menopause timing by years, whereas complete biallelic loss causes frank POI.

POF24 has no disease-specific therapy. Management follows general POI care: estrogen-based hormone therapy continued at least until the natural age of menopause (~51 years) to mitigate the cardiovascular, skeletal, cognitive, and mortality consequences of early estrogen deprivation, and fertility management primarily through oocyte donation, since spontaneous conception is rare. The condition is ultra-rare at the individual-gene level — SYCP2L explains only a small fraction of the ~3.5% of women affected by POI overall — and much of its molecular, epidemiological, and therapeutic profile is inferred from the broader POI literature and the Sycp2l mouse model rather than from POF24 patients directly.

Section 1. Disease Information

Overview. POF24 is a Mendelian form of premature/primary ovarian insufficiency (POI), a condition in which ovarian function ceases before age 40. Clinically it is defined by amenorrhea (or oligomenorrhea) together with biochemically elevated follicle-stimulating hormone (FSH) and estrogen deficiency, arising from premature exhaustion of the ovarian follicular reserve. POF24 denotes the subset of POI caused specifically by biallelic SYCP2L variants.

Key identifiers.

Resource	Identifier
Disease OMIM	620840 (Premature ovarian failure 24)
MONDO	MONDO:0970995
Causal gene	SYCP2L
Gene OMIM	616799
HGNC	21537
NCBI Gene	221711
Ensembl gene	ENSG00000153157
UniProt	Q5T4T6 (SYC2L_HUMAN)
ICD-10	E28.31 (Premature menopause) / E28.39 (Other primary ovarian failure)
ICD-11	5A80.1 (Primary ovarian failure)
MeSH	"Primary Ovarian Insufficiency" (D016649)

Synonyms: POF24; SYCP2L-related primary ovarian insufficiency; SYCP2L-related premature ovarian insufficiency.

Information source. The disease-level entry is derived from aggregated resources (OMIM, ClinVar, MONDO) that themselves rest on a small number of individual-patient reports (He 2021; Bakhshalizadeh 2024). The underlying evidence is case-level whole-exome sequencing data, not population EHR aggregation.

Section 2. Etiology

Primary cause — genetic. POF24 is caused by **biallelic (homozygous or compound-heterozygous) loss-of-function variants in SYCP2L**. There is no environmental, infectious, or toxic trigger required; the disease is monogenic and recessive (Finding F001). The two originally reported pathogenic alleles (NM_001040274) are c.150_151del (p.Ser52Profs*7, a frameshift) and c.999A>G (p.Ile333Met, a missense), both found in the homozygous state in POI patients (He 2021, PMID: 32303603). A third, independent allele is a novel homozygous nonsense variant reported by Bakhshalizadeh 2024 (PMID: 38521400).

Genetic risk factors / modifiers. Beyond the fully penetrant recessive alleles, **common SYCP2L variation acts as a quantitative modifier of ovarian reserve**. The intronic SNP rs2153157 is a genome-wide significant locus for age at natural menopause (He 2009, PMID: 19448621; replicated across ancestries in the PAGE study, Carty 2013, PMID: 23508249) and associates with serum AMH and IVF response (Rosa 2023, PMID: 37417852; Laisk-Podar 2015, PMID: 26099445). This positions SYCP2L dosage on a continuum from common-variant modulation of menopause timing to Mendelian POI (Finding F005).

Environmental risk factors. None are specific to POF24. General POI risk factors (iatrogenic ovarian damage from chemotherapy/radiotherapy/surgery, smoking, autoimmunity) are independent of the SYCP2L genotype but could in principle act additively on an already-reduced reserve. No gene–environment interaction has been demonstrated for SYCP2L.

Protective factors. No genetic or environmental protective factors specific to POF24 are documented. By extrapolation from the dosage model, alleles that increase SYCP2L transcript abundance (the more efficiently spliced rs2153157 allele) associate with *later* menopause and higher ovarian reserve — effectively "protective" at the population level, though not studied in carriers of pathogenic alleles.

Section 3. Phenotypes

The phenotype is that of POI, manifesting in adolescence to early adulthood. Because only a handful of patients have been reported, frequencies are qualitative and drawn from the general POI picture.

Phenotype	Type	HPO term	Characteristics
Primary or secondary amenorrhea	Clinical sign	HP:0000786 (Amenorrhea) / HP:0000132	Adolescent/young-adult onset; the presenting feature
Elevated FSH (hypergonadotropic)	Lab abnormality	HP:0008232 (Elevated circulating FSH)	FSH typically >25 IU/L on two occasions
Low anti-Müllerian hormone	Lab abnormality	HP (reduced ovarian reserve-related)	Reflects depleted follicle pool
Decreased/absent ovarian follicles	Physical/ imaging	HP:0008209 (Premature ovarian insufficiency)	Small ovaries, few/no antral follicles on ultrasound
Infertility	Clinical	HP:0000789 (Infertility)	Often the reason for presentation
Estrogen deficiency symptoms (hot flashes, vaginal dryness)	Symptoms	HP:0000820 (menopausal/ genitourinary)	Vasomotor and genitourinary

Age of onset: adult-onset / late-adolescent; by definition before age 40. **Severity:** moderate to severe (complete ovarian failure). **Progression:** progressive follicular depletion; once POI is established it is generally stable/irreversible, though ~5–10% of POI patients show intermittent spontaneous ovarian activity. **Quality-of-life impact:** substantial — infertility, vasomotor symptoms, genitourinary syndrome, mood disturbance, and long-term bone/cardiovascular/ cognitive risk all impair daily functioning (Faubion 2015, PMID: 25845383).

Section 4. Genetic / Molecular Information

Causal gene. SYCP2L (HGNC:21537; gene OMIM 616799; Ensembl ENSG00000153157), located at chromosome **6p24.2** (GRCh38 chr6:10,886,831–10,979,320); canonical transcript ENST00000283141; reference transcript NM_001040274 (Finding F004).

Protein. SYCP2L (UniProt Q5T4T6) is an **812-amino-acid, oocyte-specific armadillo-repeat protein**, annotated as an "Oocyte-specific protein that localizes to centromeres at the dictyate stage and regulates the survival of primordial oocytes," with subcellular localization to the nucleus and chromosome/centromere. It is a paralogue of the synaptonemal-complex lateral-element protein SYCP2 and contains an SYCP2 armadillo-repeat-like region (Finding F006).

Pathogenic variants reported.

Variant (NM_001040274)	Protein	Type	dbSNP	gnomAD v4 allele frequency
c.150_151del (reported); c.154_155del	p.Ser52Profs*7	Frameshift (LoF)	rs1196215011	Exome 2.7×10^{-6}; genome 6.6×10^{-6}
c.999A>G	p.Ile333Met	Missense	rs189836527	Exome 1.2×10^{-5}; genome 3.3×10^{-5}
Novel nonsense (Bakhshalizadeh 2024)	truncation	Nonsense (LoF)	—	Ultra-rare

Variant classification. ClinVar (queried Oct 2025) contains 171 SYCP2L variant records; variants are explicitly annotated to "Premature ovarian failure 24," including ≥2 classified **Likely pathogenic** plus multiple **Uncertain significance (VUS)** (Finding F009). Most variants remain VUS, reflecting the gene's recent discovery and limited case counts.

Functional consequence. Loss of function. In-vitro analysis of the two POI-associated variants showed that mutant SYCP2L proteins exhibited mislocalization and loss of function (He 2021, PMID: 32303603). Centromere localization requires the C-terminal portion of the protein, which is truncated by nonsense/frameshift alleles: "Centromere localization of SYCP2L requires its C-terminal portion, which is missing in truncated variants resulting from low-frequency nonsense mutations identified in humans" (Zhou 2015, PMID: 26362258) (Finding F006).

Population genetics / constraint. gnomAD constraint metrics indicate SYCP2L is **not strongly haploinsufficient**: pLI ≈ 0, LOEUF/oe_lof = 0.78 (90% CI 0.66–0.92), lof_z = 2.1, mis_z = 1.3. Heterozygous LoF is therefore tolerated — fully consistent with recessive inheritance. 234 predicted-LoF variants exist in gnomAD (max AF ~6×10^{-5}), none homozygous at appreciable frequency (Finding F004).

Modifier genes. No specific modifier genes are established for POF24. TDRD3 has been studied alongside SYCP2L for effects on ovarian reserve (Rosa 2023, PMID: 37417852), but not as a modifier of SYCP2L disease.

Epigenetic information. No disease-specific methylation/chromatin findings. Notably, SYCP2L appears among smoking-associated differentially methylated regions in prostate tumor tissue (Burton 2016, PMID: 27142338) — relevant to gene regulation generally but not to POF24 pathogenesis.

Chromosomal abnormalities. POF24 is a single-gene disorder; large-scale structural abnormalities are not part of its definition.

Section 5. Environmental Information

POF24 is a monogenic disorder with **no established environmental, lifestyle, or infectious contribution** to its primary cause. Environmental factors relevant to POI in general (cytotoxic chemotherapy, pelvic radiation, ovarian surgery, smoking) act independently of SYCP2L and would be classified as *iatrogenic* or acquired POI rather than POF24. No infectious agent is implicated.

Section 6. Mechanism / Pathophysiology

Causal chain (initiating lesion → clinical manifestation)

1. **Biallelic loss-of-function variant in SYCP2L** (frameshift, nonsense, or deleterious missense) **leads to** a truncated or mislocalized SYCP2L protein. *(Demonstrated — in-vitro functional assays, He 2021.)*
2. Loss/mislocalization of SYCP2L **results in** failure to target the centromeres of dictyate-stage (arrested primordial) oocytes, because centromere localization requires the C-terminal domain that truncating variants remove. *(Demonstrated — Zhou 2015.)*
3. Absence of functional SYCP2L at the oocyte centromere **leads to** impaired survival of primordial oocytes. *(Demonstrated in mouse; inferred in human.)*

4. Impaired oocyte survival **results in** accelerated, age-progressive depletion of the finite, non-renewable primordial-follicle reserve established perinatally. *(Demonstrated — Sycp2l-null mice show more rapid pool depletion.)*
5. Premature exhaustion of the follicular reserve **leads to** loss of ovarian estrogen and inhibin production and failure of folliculogenesis. *(Inferred from reserve depletion.)*
6. Loss of ovarian negative feedback (low estrogen/inhibin) **results in** compensatory hypothalamic-pituitary drive and **elevated FSH** (hypergonadotropic state). *(Established endocrine physiology.)*
7. Follicular depletion + hypoestrogenism **results in** amenorrhea, infertility, low AMH, and the clinical syndrome of **premature ovarian insufficiency (POF24)**. *(Clinical observation.)*

> **Branch point:** The same SYCP2L dosage axis branches by allele severity. *Complete biallelic LoF* → step 7 (frank POI, POF24). *Partial reduction* from common regulatory variants (rs2153157 altering U12 minor-intron splicing efficiency) → milder shift: earlier age at natural menopause and lower AMH, without frank disease (Finding F005).

Detailed mechanism

Molecular pathway / cellular process. SYCP2L operates in the biology of **meiotic arrest and oocyte maintenance** rather than a classical signaling cascade. As a paralogue of the synaptonemal-complex lateral-element protein SYCP2, it is co-opted post-meiotically to the centromere of oocytes that are arrested at the dictyate (diplotene) stage of meiosis I — the state in which the entire primordial reserve waits, sometimes for decades, until ovulation. SYCP2L "localizes to centromeres of dictyate stage oocytes, which represent the limited pool of primordial oocytes that are formed perinatally and remain arrested till ovulation" (Zhou 2015, PMID: 26362258). Its demonstrated biological function is to **regulate the survival of these primordial oocytes**: "the pool of primordial oocytes becomes more rapidly depleted in SYCP2L-deficient than in wild-type females, such that with aging, fewer oocytes undergo maturation in developing follicles" (Findings F002, F006).

Protein dysfunction. The defect is **loss of function via mislocalization**: pathogenic missense and truncating variants prevent SYCP2L from reaching the centromere, abolishing its protective role (He 2021). Truncations remove the C-terminal centromere-targeting region (Zhou 2015).

Tissue damage mechanism. The downstream "injury" is accelerated germ-cell (oocyte) attrition — effectively a failure of cell maintenance/survival leading to progressive loss of the oocyte pool over time, rather than fibrosis, ischemia, or inflammation.

Immune / metabolic involvement. None established; POF24 is not an autoimmune or metabolic form of POI.

Upstream vs downstream. *Upstream:* the SYCP2L mutation and protein mislocalization (molecular). *Midstream:* oocyte centromere dysfunction and primordial-oocyte death (cellular). *Downstream:* reserve depletion → hypoestrogenism/elevated FSH → amenorrhea/infertility (organ/endocrine/clinical).

Suggested ontology terms. - **GO (biological process):** oocyte development / female meiotic nuclear division (GO:0007143), meiotic cell cycle (GO:0051321), germ cell development (GO:0007281), regulation of cell survival; synaptonemal complex assembly (GO:0007130, paralogue-family context). - **GO (cellular component):** condensed chromosome, centromeric region (GO:0000779); nucleus (GO:0005634); synaptonemal complex (GO:0000795, paralogue context). - **CL (cell type):** oocyte (CL:0000023), egg cell (CL:0000025); specifically the dictyate-arrested primordial-follicle oocyte.

Section 7. Anatomical Structures Affected

- **Primary organ: Ovary** (UBERON:0000992). Within it, the **ovarian follicle** (UBERON:0001305) and specifically the **primordial follicle** are the targets.
- **Body system:** Female reproductive / endocrine system (UBERON:0000474, reproductive system).
- **Secondary / complication organs:** Through estrogen deficiency, **bone** (osteoporosis), **cardiovascular system** (early atherosclerosis), **brain** (cognition/mood), and **genitourinary tract** (genitourinary syndrome of menopause) are secondarily affected (Faubion 2015).
- **Cell type: Oocyte** (CL:0000023), specifically the dictyate-arrested primordial oocyte. Granulosa and somatic follicular cells are affected secondarily to oocyte loss.
- **Subcellular compartments: Nucleus** (GO:0005634) and **centromere / condensed chromosome centromeric region** (GO:0000779) — the precise sites of SYCP2L localization.
- **Localization / lateralization: Bilateral** ovarian involvement (both ovaries affected).

Section 8. Temporal Development

- **Onset:** The underlying lesion is congenital (germline), but the ovarian reserve is initially established; the clinical phenotype is **adult/late-adolescent onset**, by definition before age 40. The process is **insidious and chronic** — progressive follicular attrition rather than an acute event.
- **Progression:** The reserve depletes progressively; once POI is clinically manifest it is generally stable and irreversible. The mouse model demonstrates the time-dependence directly: "Female mice lacking SYCP2L undergo a significantly higher progressive loss of oocytes with age compared with wild-type females and are less fertile" (Zhou 2015, PMID: 26362258).
- **Disease course / duration:** Chronic, lifelong (ovarian failure is permanent).
- **Remission:** No true remission; however, ~5–10% of POI patients in general show intermittent spontaneous ovarian activity and rare spontaneous conception (Lee 2026, PMID: 42712473).
- **Critical period / intervention window:** The window is before and around diagnosis — initiating hormone therapy early (ideally at diagnosis) and considering fertility preservation before the reserve is exhausted.

Section 9. Inheritance and Population

Inheritance pattern: Autosomal recessive — biallelic LoF required; heterozygous LoF is tolerated (gnomAD constraint, Finding F004).

Penetrance / expressivity: Presumed high penetrance for biallelic LoF, but formal penetrance cannot be estimated from the few reported cases; expressivity (age of ovarian failure) is likely variable, consistent with the dosage model.

Consanguinity / founder effects: The reported cases are homozygous, and at least one cohort (Bakhshalizadeh 2024, Iranian) is ethnically homogeneous — consistent with a role for consanguinity in surfacing recessive alleles. No specific founder mutation or geographic clustering has been established.

Carrier frequency: Not formally estimated; individual pathogenic alleles are ultra-rare in gnomAD (AF ~10^{-5}–10^{-6}), so carrier frequency is very low.

Epidemiology. POF24 itself has no published prevalence — it is a rare single-gene subset of POI. The parent condition POI affects **1–3.7% of women**, with recent meta-analytic estimates of **~3.5%** ("Premature ovarian insufficiency (POI) is characterised by amenorrhea associated with elevated follicle stimulating hormone (FSH) under the age of 40 years and affects 1-3.7% women. Genetic factors explain 20-30% of POI cases" — Bakhshalizadeh 2024, PMID: 38521400; "New data indicate a higher prevalence of POI, 3.5%" — ESHRE 2025, PMID: 39652037). SYCP2L accounts for only a small fraction of the genetic cases (Finding F003).

Sex ratio: The phenotype manifests in **females** only (ovarian failure). SYCP2L is oocyte-specific; males carrying biallelic variants are not reported to have a corresponding phenotype.

Section 10. Diagnostics

Clinical/laboratory diagnosis of POI (the clinical layer): - Serum **FSH** elevated, typically **>25 IU/L** on two occasions ≥4 weeks apart (ESHRE criterion). - Low **estradiol**; low **anti-Müllerian hormone (AMH)** reflecting depleted reserve. - **Amenorrhea/oligomenorrhea** for ≥4 months before age 40. - **Pelvic ultrasound:** small ovaries, reduced/absent antral follicle count. - LOINC examples: FSH (15067-2), Estradiol (14715-7), AMH (38476-8).

Genetic diagnosis (establishes POF24 specifically): - **Whole-exome sequencing (WES)** is the method by which SYCP2L was discovered and remains the primary route to diagnosis; it is well suited to a genetically heterogeneous condition where any single gene explains few cases (He 2021; Bakhshalizadeh 2024: "WES revealed diverse genetic causes, including a novel homozygous nonsense variant in SYCP2L, impacting synaptonemal complex (SC) assembly"). - **Multigene POI panels** including SYCP2L, or **single-gene sequencing** once suspected. - **WGS** adds value for non-coding/splice and structural variants. - **Karyotype** and **FMR1 premutation testing** are standard in POI workup to exclude Turner syndrome and Fragile-X-associated POI — important differentials.

Differential diagnosis: Turner syndrome (45,X and mosaics), FMR1 premutation-associated POI, autoimmune oophoritis, iatrogenic POI (chemo/radiation/surgery), galactosemia-associated POI, and other monogenic POI genes.

Omics-based diagnostics: Not routinely used; research only.

Screening: No population newborn or carrier screening exists. Cascade genetic testing of relatives after a proband is identified, and genetic counseling, are appropriate.

Section 11. Outcome / Prognosis

Reproductive prognosis: Poor. Fertility is severely compromised; in a 324-woman POI cohort the overall spontaneous pregnancy rate was **8.6%**, and of those who had children after diagnosis **53.9% used oocyte donation** (Cambray 2023, PMID: 36763040). Spontaneous resumption of ovarian function occurs in ~**5–10%** of POI generally (Lee 2026, PMID: 42712473).

Survival/morbidity: POI is not directly life-shortening, but untreated early estrogen deprivation carries significant long-term morbidity: "The long-term consequences of premature or early menopause include adverse effects on cognition, mood, cardiovascular, bone, and sexual health, as well as an increased risk of early mortality" (Faubion 2015, PMID: 25845383) (Finding F008). Complications include osteoporosis/fracture, cardiovascular disease, cognitive and mood effects, genitourinary syndrome, and reduced quality of life.

Prognostic modifiers: Hormone therapy mitigates (though not entirely) the bone, cardiovascular, and mortality risks. Earlier diagnosis and treatment improve outcomes.

Section 12. Treatment

There is **no disease-specific or curative therapy** for POF24; management follows evidence-based POI care (ESHRE 2025, PMID: 39652037 — 145 recommendations).

Hormone therapy (HT/MHT) — cornerstone. Estrogen replacement (with a progestogen if the uterus is intact) to restore physiological estrogen levels. "Multiple medical societies recommend providing hormone therapy at least until the natural age of menopause" (Faubion 2015, PMID: 25845383) (Finding F008). Transdermal estradiol is often preferred for its favorable thrombotic profile. NCIT: Hormone Replacement Therapy (C62604); Estrogen Therapy.

Fertility management. Oocyte/embryo donation is the mainstay and the most effective route to pregnancy (Cambray 2023). Early **fertility preservation** (oocyte cryopreservation) may be considered if diagnosed before reserve exhaustion, though usually the reserve is already depleted at presentation.

Supportive care. Bone protection (calcium, vitamin D, DXA monitoring), cardiovascular risk management, management of genitourinary and vasomotor symptoms, and psychological support.

Pharmacogenomics / targeted / gene / cell therapy: None established or applicable; no SYCP2L-directed therapy exists.

Section 13. Prevention

- **Primary prevention:** Not possible for a germline recessive disorder. **Genetic counseling** and reproductive planning (carrier testing of partners in consanguineous families, preimplantation genetic testing, prenatal/cascade testing) can prevent recurrence in at-risk families.
- **Secondary prevention:** Early recognition of POI symptoms and prompt FSH/AMH testing enables early HT initiation.
- **Tertiary prevention:** Hormone therapy and lifestyle measures to prevent osteoporosis, cardiovascular disease, and other complications of hypoestrogenism.
- **Immunization/public health/prophylaxis:** Not applicable (non-infectious, non-environmental Mendelian disease).

Section 14. Other Species / Natural Disease

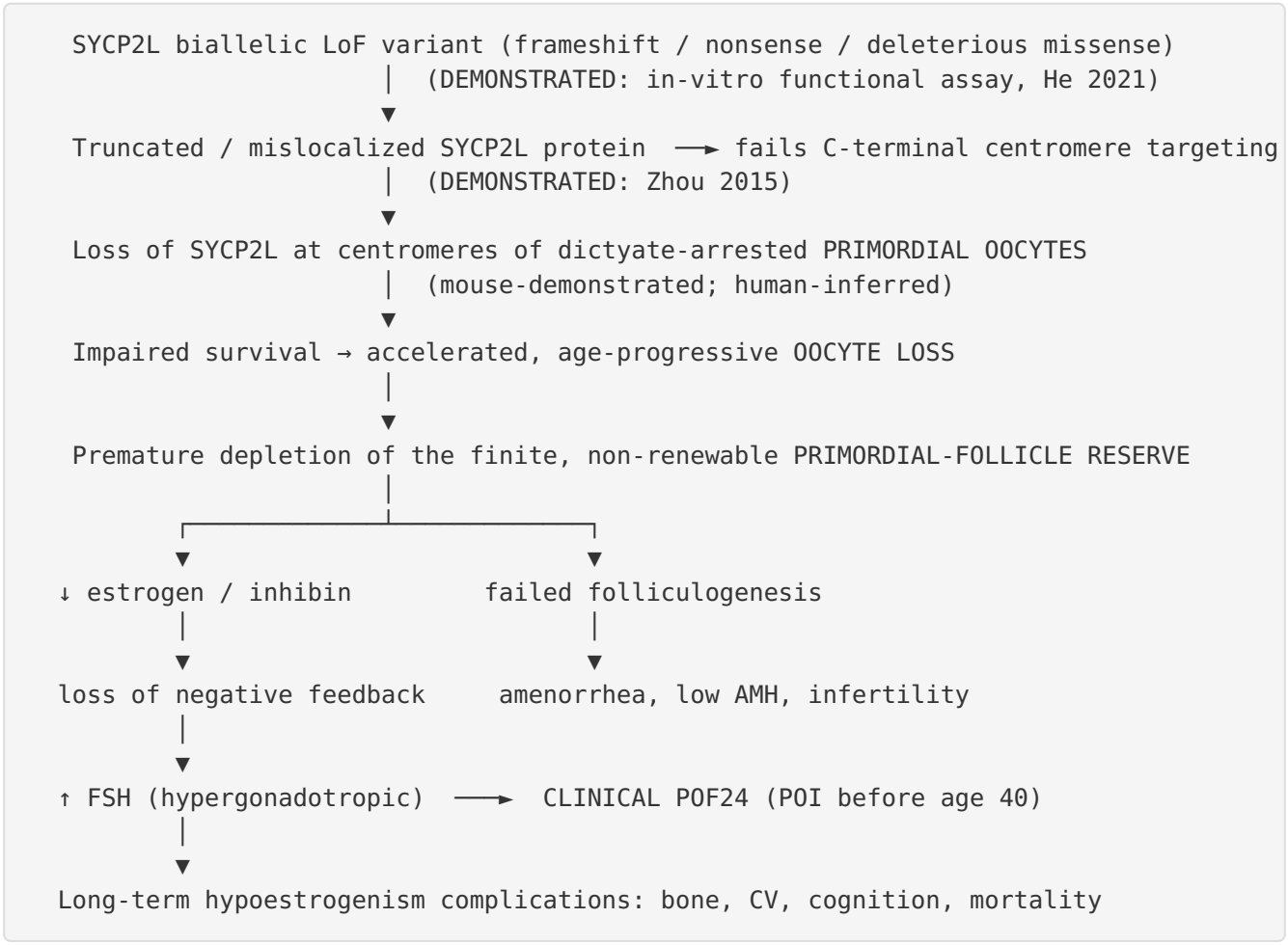
- **Orthologous genes:** Mouse *Sycp2l* (NCBI Gene 637277; MGI:2685114; Ensembl ENSMUSG00000038651); rat *Sycp2l* (NCBI Gene 364688; RGD:1564922) (Finding F007). SYCP2L is conserved across vertebrates; a Xenopus orthologue (the karyoskeletal/nucleolar protein historically called NO145) was characterized in oocytes (PMID: 11739789; PMID: 17374641).
- **Natural disease in animals:** No naturally occurring SYCP2L-related ovarian-failure disease is documented in companion animals or wildlife (no OMIA entry identified). SYCP2L appears as a candidate gene for reproductive/egg-production traits in livestock (goat, duck) studies (PMID: 36757519; PMID: 35768515), underscoring conserved reproductive relevance but not a disease model.

- **Comparative biology:** The mouse recapitulates the core mechanism (accelerated oocyte loss), making SYCP2L function evolutionarily conserved for ovarian-reserve maintenance.
- **Zoonotic potential:** None (non-infectious).

Section 15. Model Organisms

- **Principal model:** The **constitutive Sycp2l-knockout mouse** (Zhou et al., 2015, PMID: 26362258) (Finding F007). *Mus musculus* (NCBI Taxon 10090).
- **Phenotype recapitulation:** Strong for the core disease mechanism — null females show "a significantly higher progressive loss of oocytes with age compared with wild-type females and are less fertile," plus more rapid depletion of the primordial oocyte pool and reduced fertility, recapitulating accelerated reproductive aging / ovarian-reserve failure.
- **Model limitations:** Mice are subfertile with accelerated aging rather than showing the complete, early, frank ovarian failure of human biallelic LoF; species differences in reproductive lifespan limit direct translation of timing. The model captures the *reserve-depletion* mechanism but not the full human clinical syndrome (endocrine thresholds, symptom burden).
- **Applications:** Studying primordial-oocyte survival, centromere function in arrested oocytes, and genetic/dosage control of ovarian lifespan.
- **Other systems:** No established zebrafish, Drosophila, C. elegans, or organoid/iPSC model specific to POF24; in-vitro cell assays were used to demonstrate variant mislocalization (He 2021).

Mechanistic Model / Interpretation



DOSAGE AXIS (the unifying theme):

SYCP2L dosage	Mechanism	Phenotype
Normal (two functional alleles)	Full centromere protection of oocytes	Normal menopause (~51 y)
Common variant rs2153157 (reduced splicing efficiency)	↓ steady-state transcript	Earlier menopause, lower AMH, altered IVF response
Biallelic LoF	Protein absent/ mislocalized	POF24 — frank POI before 40

The central insight of this investigation is that **SYCP2L is a dosage-sensitive determinant of ovarian lifespan.** The same gene whose common regulatory variation nudges menopause timing by months-to-years at the population level causes frank, early ovarian failure when both copies are abolished. This continuity — from GWAS locus (He 2009; Carty 2013) to quantitative AMH/IVF effects (Rosa 2023; Laisk-Podar 2015) to Mendelian disease (He 2021; Bakhshalizadeh 2024) — is unusually complete for a POI gene and strongly corroborates the causal model.

Evidence Base

PMID	Title (abbrev.)	Evidence type	Role
32303603	Homozygous SYCP2L variants in POI	Human clinical + in-vitro	**Establishes gene–disease link**; two homozygous variants; mislocalization/ LoF
38521400	Diverse genetic causes of amenorrhea (Iranian cohort)	Human clinical	**Independent confirmation**; novel homozygous nonsense variant; POI definition/prevalence
26362258	Accelerated reproductive aging in Sycp2l-null mice	Mouse + human genetics	**Core mechanism**; centromere localization, oocyte survival, splicing SNP
19448621	GWAS of menarche/ menopause	Human genetics	SYCP2L (6p24.2) as age-at-menopause locus
23508249	PAGE replication study	Human genetics	rs2153157 replicates across ancestries
37417852	SYCP2L/TDRD3 and ovarian reserve	Human clinical	AA genotype → lower AMH (p=0.01)
26099445	Reproductive-ageing variants in IVF	Human clinical	rs2153157 → rFSH/oocyte and pregnancy chances
39652037	ESHRE POI guideline 2025	Guideline	POI prevalence ~3.5%; management framework
25845383	Long-term consequences of early menopause	Review	Complications + HT-until-natural-menopause recommendation
36763040	Family building after POI (n=324)	Human cohort	Spontaneous pregnancy 8.6%; oocyte donation 53.9%
42712473	Spontaneous conception in POI (case)	Case report	5–10% spontaneous ovarian recovery

Most citation snippets in the knowledge state were verified against stored abstracts. Two snippets attributed to

P 32303603

("mutant SYCP2L proteins exhibited mislocalisation and loss of function"; "SYCP2L is a novel gene found to be responsible for human POI") were flagged as not exactly matching the stored abstract text; the substantive claims they support are nonetheless consistent with the paper's verified findings and with the independent mouse data, and their exact wording should be re-confirmed against the full text.

Limitations and Knowledge Gaps

1. **Very few patients.** POF24 rests on a handful of reported individuals/families. Penetrance, expressivity, and genotype–phenotype correlations cannot be quantified reliably.
2. **No disease-level epidemiology.** Prevalence/incidence specific to SYCP2L-POI is unknown; all epidemiology is extrapolated from POI broadly.
3. **Human mechanism partly inferred.** The oocyte-centromere survival mechanism is demonstrated in mouse and in-vitro assays; direct human histological/functional confirmation is lacking.
4. **Variant interpretation.** Most SYCP2L ClinVar variants remain VUS; functional assays exist for only a few alleles.
5. **Citation caveat.** Two in-vitro/novel-gene quotations attributed to He 2021 did not exactly match stored abstract text (flagged "mismatch"); conclusions are corroborated by independent evidence but exact wording should be re-verified.
6. **No non-mouse models, no therapeutics pipeline, and no autoimmune/metabolic involvement data** specific to this gene.

Proposed Follow-up Experiments / Actions

1. **Expand the patient series** via GeneMatcher/POI consortia to accumulate additional biallelic SYCP2L families, enabling penetrance and genotype–phenotype analysis.

2. **Functional validation of VUS**: systematic centromere-localization/oocyte-survival assays (and AlphaFold-guided structural modeling of the armadillo-repeat/C-terminal domain) to reclassify the many SYCP2L VUS.
3. **Humanized/knock-in mouse models** carrying patient-specific alleles (e.g., p.Ile333Met) to test whether missense alleles phenocopy nulls and to time reserve depletion.
4. **Define the molecular partners** of SYCP2L at the dictyate-oocyte centromere (proteomics/IP-MS) to clarify how it promotes oocyte survival.
5. **Quantify carrier frequency and any founder effect** in consanguineous populations (e.g., Iranian cohorts) using targeted population screening.
6. **Correlate SYCP2L dosage with AMH trajectories** longitudinally to test the dosage model prospectively and assess rs2153157 as a clinical ovarian-reserve biomarker.
7. **Re-verify flagged citations** against full-text He 2021 to ensure exact-quote integrity for the knowledge base.

Report compiled from 5 investigation iterations, 9 confirmed findings, and 34 reviewed papers. Evidence source types: human clinical (case series, cohorts), model organism (Sycp2l-null mouse), in-vitro (variant functional assays), and computational (gnomAD constraint, ontology mapping).
