INVESTIGATORS / CLINICIANS / DATA PARTNERS

ASH1L research collaboration brief

Eleven testable ASH1L questions connecting molecular consequence, cell state, natural history, measurement, and translation.

USE THIS WHEN

Scoping a study, feasibility review, or concept note.

TIME NEEDED

15-minute first read

TAKE OR SHARE

Send with a concise concept note.

Eleven questions. Five evidence stages. Clear criteria at every step.

Information about 63 connected people, shared by individuals and families, can generate testable questions. It cannot confirm those hypotheses or estimate prevalence. Each question needs an appropriate comparator, participant group, study design, and clear result that would support or weaken it.

01 / WHAT THE AVAILABLE INFORMATION CAN SUPPORT

What the current information can support

ASH1L.org publishes evidence summaries and does not publish private family records. The connected records can generate hypotheses, but they are not a prevalence sample or a confirmatory study.

63
CONNECTED PEOPLE
People currently represented; not prevalence.

53
PEOPLE WITH CLINICAL INFORMATION
At least one clinical feature is described.

62
MOLECULAR RESULTS
Description recorded; complete result not always verified.

52
PEOPLE SHOWN ON MAP
33 positioned LoF/truncating + 19 single-missense.

Not established
ORIGINAL REPORT TOTAL
Historical record indicators do not establish a verified original-report count. Reviewed September 7, 2026.

21
ORIGINAL CLINICAL RECORDS
At least one original clinical document beyond the genetic laboratory report is available.

These counts describe available information—not frequency or prognosis.

The connected group includes 38 males and 25 females across 19 countries. The public single-position map shows 52 people: 33 positioned LoF/truncating + 19 single-missense. Complex and mixed findings remain outside this two-class display.

HYPOTHESIS GENERATION

What this information can do

Prioritize molecular consequences, lifespan questions, repeated within-person measurements, physiological contexts, recovery windows, and outcomes that deserve independent study.

MORE EVIDENCE NEEDED

What it cannot do

Estimate prevalence, prove a shared mechanism, establish prognosis, qualify a biomarker, validate a target, or substitute for prospective independent enrollment.

How to read the numbers

Missing means unreported unless an adequate assessment establishes otherwise. Related people, repeated events, additional findings, the amount of original documentation available, and very small groups affect interpretation; multiple events in one person are not independent cases.

02 / TRANSLATIONAL EVIDENCE PATH

Discover → Confirm → Explain → Generalize → Translate

Every arrow is a separate claim. The records that generated a hypothesis cannot confirm it, and each stage requires an appropriate participant group, comparator, protocol, and advancement criterion.

01

Discover

Develop testable hypotheses from documented molecular, clinical, and longitudinal observations without treating the connected records as a population sample.

02

Confirm

Reproduce prospectively in an independent sample with fixed definitions, complete denominators, adequate controls, and pre-specified analysis.

03

Explain

Establish temporal order, compare plausible mediators, and test whether correction or rescue changes the proposed link.

04

Generalize

Replicate across alleles, cell states, ages, sexes, laboratories, and an independent human cohort wherever the question requires it.

05

Translate

Advance only after safety, target engagement, meaningful outcomes, feasibility, ethical oversight, and regulatory requirements are met.

Failure at one arrow narrows that proposed link.

It does not erase the established gene-disease relationship or authorize a leap to the next stage. Reassess the assay, timing, cell state, comparator, alternative explanations, and stop rule before advancing.

03 / CANDIDATE RESERVE MODEL

Measure challenge, response, and recovery

Reduced reserve is a working measurement model—not a diagnosis, a synonym for severity, or proof that intact ability is hidden. It must be defined separately at molecular, cellular, physiological, and human-functional scales.

Candidate reserve phenotype

A candidate cellular signal is a reproducible genotype × challenge × time effect after baseline adjustment, with viability, maturation, batch, clone, dosage, sham, and negative controls—and directional attenuation after a valid correction or rescue.

SIX ORDERED TIMEPOINTS · SAME CELLS · SAME ASSAYS

t0	t1	t2	t3	t4	t5
Baseline	**Perturb**	**Peak**	**Close**	**Recover**	**Re-challenge**
Residual dosage and stable function	Defined maturation step or challenge	Magnitude and pathway engaged	Transcriptional or functional shutoff	Return toward the starting state	Reset, memory, and recurrence threshold

01 / ALLELE

Preserve the molecular question

Patient-derived allele, CRISPR-corrected isogenic control, engineered dosage series, matched reference, and ASH1L rescue.

02 / CELL

Compare identities - not brain versus body

Direct neural anchors: progenitor, immature and mature glutamatergic, and mature GABAergic states. Priority gaps: astrocyte and barrier epithelium.

03 / STATE

Define what changes the system

Use a controlled maturation step or tissue-appropriate challenge with matched dose, duration, culture state, sham condition, viability, and recovery conditions.

04 / TIME

Sample the return - not only the peak

Repeated measurement must distinguish lower baseline output, delayed transition, excessive activation, delayed shutoff, incomplete recovery, and altered re-challenge behavior.

Control rule: compare every timepoint across the patient allele, isogenic correction, dosage series, matched reference, and rescue in the same prespecified cell identity and state. A peak-only experiment cannot distinguish delayed induction, altered amplitude, delayed shutoff, or slow recovery.

04 / MEASUREMENTS AT EVERY TIMEPOINT

Collect convergent molecular and functional readouts

The same assay families must be collected across the ordered time course. Each family answers a different link in the proposed chain, and no single readout can establish the mechanism by itself.

MOLECULAR DOSAGE

Is functional ASH1L actually reduced?

Allele-specific RNA and long-read transcript analysis, transcript stability, quantitative full-length protein, localization, catalytic function, and complex assembly.

LOCUS-LEVEL CHROMATIN

Where does chromatin regulation change?

Use CUT&RUN or CUT&Tag for H3K36me1/2, H3K27me3, H3K4me3, and ASH1L occupancy; pair with ATAC-seq at predefined loci and report bulk marks separately.

TRANSCRIPTIONAL KINETICS

Which programs mistime?

Use time-resolved RNA-seq, splicing, and pathway activity to separate delayed induction, altered amplitude, delayed shutoff, and incomplete recovery.

LINEAGE FUNCTION

Does the molecular difference matter to the cell?

Measure proliferation and differentiation; multielectrode-array or patch-clamp physiology; transmitter and ion handling; epithelial resistance, transport, and repair; or metabolic throughput as appropriate to the lineage.

HUMAN RETURN PATH

Is there an independently testable human correlate?

Repeat a defined clinical or physiological measure at baseline, during a prospectively specified naturalistic window, and through recovery. Do not claim cross-scale equivalence until a biomarker linking the cellular and human measures is analytically validated and independently reproduced.

What a cross-scale result does not establish

A cellular timing signal may motivate a human measurement. It does not prove that a cellular assay and a human functional change are the same phenomenon, establish one shared mechanism, or qualify a biomarker.

05 / RESCUE, REPLICATION, AND COMPETING EXPLANATIONS

Ask what the evidence would support or weaken

The design must specify what supports the model, what narrows it, and what weakens the proposed chain. Correction, rescue, replication, and valid controls are essential evidence.

SUPPORTS THE LINK

Correction or rescue attenuates the readout

Supports ASH1L dependence only when dose, timing, delivery, viability, and the assay's positive and technical controls are appropriate.

NARROWS THE LINK

The effect is restricted to one cell state

Defines a candidate lineage or maturation vulnerability; it does not establish a whole-body mechanism or predict every human presentation.

REFINES THE LINK

Peak is similar but recovery diverges

Supports a specific response-termination or resolution hypothesis that must reproduce across independent clones, batches, and challenge conditions.

WEAKENS THE LINK

The effect does not attenuate

Reassess rescue dose, timing, delivery, differentiation, background, additional findings, assay validity, and whether the proposed chain is wrong.

RESULT THAT WOULD WEAKEN THE MODEL 01

No reproducible allele consequence

The specified assay detects no reproducible allele-dependent molecular consequence under conditions in which its positive and technical controls perform.

RESULT THAT WOULD WEAKEN THE MODEL 02

No ordered regulatory link

In the specified cell state and time course, the candidate chromatin difference does not precede or predict the transcriptional or functional change.

RESULT THAT WOULD WEAKEN THE MODEL 03

No dose-appropriate attenuation

The specified response phenotype does not attenuate after correction or rescue across independent clones and batches.

A negative result is mechanistically informative.

Failure falsifies or narrows the specified assay-and-model chain. It does not erase the established ClinGen gene-disease relationship, every possible consequence of an allele, or all ASH1L biology.

06 / EVIDENCE ANCHORS AND LIMITS

Anchor the design to direct evidence - and its limits

These studies support the choice of cell states, chromatin measurements, and time-resolved assays. Their species, perturbation direction, and model context remain attached to every conclusion.

2026 / HUMAN NEURAL CRISPR

Complete ASH1L knockout effects varied across modeled neural states; this is not a heterozygous patient-allele dosage series. Fernandez Garcia et al.

2025 / STRUCTURE & DIFFERENTIATION

Chromatin-engagement domains were resolved and Ash1l depletion altered selected timing markers in mouse ES models; these are not human patient cells. Vann et al.

2024 / H3K36 METHYLTRANSFERASE MAP

ASH1L-associated H3K36me2 was locus-specific in a sensitized multi-enzyme-knockout mouse mesenchymal context; bulk abundance would miss that mapped signal. Shipman et al.

EXPERIMENTAL ANCHORS

What the direct evidence contributes

State- and lineage-dependent ASH1L consequences, resolved chromatin-engagement domains, timing-sensitive differentiation effects, and locus-specific H3K36me2 mapping justify an allele-aware, cell-aware, time-resolved design.

OPEN TESTS

What remains proposed

Patient-allele dosage thresholds, astrocyte and barrier-epithelial vulnerability, one shared challenge-and-recovery mechanism, a validated cross-scale biomarker, and a human treatment target remain unestablished.

Scientific and human-safety limits

This is proposed study architecture, not a completed cohort experiment, shared human mechanism, biomarker, or treatment recommendation. Failure narrows the specified assay-and-model chain; it does not challenge the ClinGen gene-disease relationship or every possible ASH1L consequence. Neurons, astrocytes, barrier epithelium, chromatin timing, and recovery kinetics remain candidate systems or measurements. Never deliberately recreate illness, pain, bowel loading, anesthesia, medication withdrawal, sleep deprivation, or another unsafe exposure.

SECTION 07 / DISCOVER, CONFIRM, EXPLAIN, GENERALIZE

Research questions 01–06

Each question names the uncertainty, a way to test it, and the result that would support it. Full specifications also retain the participant group, comparison, and results that would weaken the proposal.

01 What molecular consequence does each ASH1L alteration produce?

ALLELE EFFECT

HOW TO TEST Allele-specific RNA, protein, localization, chromatin, and function in patient lines plus corrected isogenic controls.

SUPPORT IF Replicates across clones and batches and attenuates with correction or justified rescue.

02 Which molecular programs are shared, allele-specific, and direct?

MOLECULAR PROGRAM

HOW TO TEST Integrate occupancy, locus-resolved chromatin, accessibility, transcription, splicing, and function across alleles and time.

SUPPORT IF A mechanism-appropriate direct anchor precedes the outcome, repeats, and attenuates.

03 Which cells and developmental states cross a dosage threshold?

CELL STATE

HOW TO TEST Test the same allele-control pairs across prespecified cell identities and maturation states with composition controls.

SUPPORT IF Genotype × state interaction survives quality adjustment, replicates, and attenuates.

04 Does ASH1L dysfunction reduce challenge-and-recovery reserve?

RESPONSE KINETICS

HOW TO TEST Baseline-adjusted, time-resolved challenge with dose, sham, viability, recovery, re-challenge, correction, and rescue.

SUPPORT IF Genotype × challenge × time is reproducible, not toxicity, and moves toward control.

05 What lifespan and multisystem spectrum is supported by records?

NATURAL HISTORY

HOW TO TEST Prospective natural history with a common clinical core, source type, molecular group, repeated function, and explicit participant counts.

SUPPORT IF Definitions and visit schedule apply prospectively; estimates remain stable when missing information and documentation level are considered.

06 How do sex, age, and developmental transitions modify the course?

MODIFIERS

HOW TO TEST Longitudinal age- and puberty-aware models with molecular group, relatedness, additional findings, documentation level, and baseline function.

SUPPORT IF Interaction is pre-specified, powered, robust to covariates, and independently reproduced.

SECTION 08 / CONFIRM, EXPLAIN, GENERALIZE, TRANSLATE

Research questions 07–11

The later questions move from repeatable within-person signals toward temporal explanation, measurement qualification, and cautious translational readiness.

07 Which state-dependent functional changes reproduce within a person?

WITHIN PERSON

HOW TO TEST Repeat the same brief measures at stable baselines, naturally occurring managed windows, negative-control days, and recovery.

SUPPORT IF Pre-specified change repeats in independent windows with timing, recovery, and competing explanations preserved.

08 Do distinct physiological contexts precede a recurring multidomain signature?

REPEATED SIGNATURE

HOW TO TEST Predefine the signature; use time-lagged nested models, discordant windows, and held-out confirmation.

SUPPORT IF Context precedes and predicts an independent window and survives dominant-person and definition checks.

09 Which measured variables are plausible temporal intermediates?

POSSIBLE MEDIATOR

HOW TO TEST Time-order candidate intermediates across baseline, exposure, functional change, and recovery while modeling competitors.

SUPPORT IF Candidate precedes outcome, adds within-person variance, reproduces, and survives competing-variable models.

10 Which biomarkers and outcomes measure meaningful change?

MEASUREMENT

HOW TO TEST Prospectively test analytic validity, reliability, feasibility, error, practice, longitudinal sensitivity, and meaningfulness.

SUPPORT IF Reliable within intended range, changes beyond error, links to meaningful function, and replicates independently.

11 Which intervention points are causally validated and trial-ready?

TARGET EVIDENCE

HOW TO TEST Require convergent patient-allele, correction, rescue, relevant-model, exposure, safety, engagement, and outcome evidence.

SUPPORT IF Replicated rescue in more than one relevant model without unacceptable toxicity and with a credible protocol path.

Criteria for proceeding are not a forecast.

Failure narrows or rejects the proposed link. It does not turn a discovery signal into absence, erase the gene-disease relationship, or justify advancing a biomarker, target, or human protocol without its required evidence.

SECTION 09 / EVIDENCE AND CAPACITY

Eight foundations for translational research

Progress depends on evidence convergence and practical capacity. These foundations are not a promise of treatment or a calendar.

01

Prospective natural history with shared definitions

Common clinical core, explicit source types, adequately assessed participant counts, longitudinal timing, and appropriate study review.

02

Allele-level functional classification

Comparable RNA, protein, chromatin, and residual-function evidence across molecular mechanisms.

03

Reproducible human models

Patient-derived and corrected isogenic systems with multiple clones, batches, dosage levels, and relevant cell states.

04

Time-resolved response assays

Pre-specified threshold, magnitude, shutoff, recovery, and re-challenge readouts with criteria for correction or rescue.

05

Qualified biomarkers

Analytically valid readouts that reproduce across laboratories and track a clinically meaningful domain.

06

Causally validated targets

Convergent correction, rescue, pharmacology, safety, and model evidence.

07

Trial-ready outcomes

Reliable measures, age and ability bands, meaningful-change rules, and natural-history estimates suitable for design.

08

Operational infrastructure

Data standards, secure sample stewardship, clear roles, recruitment, safety oversight, and independent replication.

No milestone stands alone.

A technically strong assay without longitudinal meaning, independent replication, secure data stewardship, and usable outcomes is not translational readiness. Preclinical rescue remains a research finding—not a treatment claim.

10 / COLLABORATION

From research question to a useful first conversation

A useful proposal explains the question, comparison group, information needed, participant time, safety, and the result the study is designed to interpret.

01 **Question** — Bounded claim

02 **Fit** — People and comparison

03 **Design** — Measures and safeguards

04 **Materials** — Only what is needed

05 **Next step** — Clear expectations

A useful concept note explains

- [ ] Institution, investigator, scientific question, and current evidence stage
- [ ] Participant group, comparison, inclusion criteria, relatedness, additional findings, and denominators
- [ ] Exact variables, samples, or source materials needed—not a request for a complete archive
- [ ] Expected family time, visits, procedures, risks, supports, and community value
- [ ] How private information and samples would be handled and who is responsible
- [ ] What participants will hear back, how results will be reported, and the proposed next step

FOCUSED REQUEST

Ask for only what the question needs

An initial conversation should not require a complete private archive. Name the exact records, measurements, or samples needed and why.

REPRODUCIBLE AND READABLE

Clear reporting

State participant counts, missing information, contradictions, documentation level, authorship, and the limits of the result.

When a study involves people or private records

Appropriate ethics review, informed participation, secure handling, and a clear responsible institution are required. Ordinary care always takes priority over research sampling.

1 ASH1L.org 11-question research program
https://ash1l.org/research

2 ASH1L.org methods and privacy
https://ash1l.org/methods

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