COMPUTATIONAL TARGET PROFILE

ABI3

An Alzheimer's Microglial Adaptor, Characterised Without An Experimental Structure

A top-tier AD genetic hit whose mechanism is unknown. A structureless, half-disordered adaptor — resolved into a domain map, a **construct-design plan**, and an interaction pocket on its SH3 domain, for a protein with **no solved structure**.

UniProt Q9P2A4 · 366 aa · Soluble (cytoplasmic) · IDG tier: T_{bio} · PDB: none · July 2026

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At A Glance

Fold / Class	Soluble cytoplasmic **non-enzyme** (p=1.00); an Abi-family adaptor — structural / signalling, not catalytic.
Architecture	**~46% disordered.** An N-terminal coiled-coil (33–61), a large disordered mid-region (161–302) and a C-terminal **SH3 domain (308–366)** — so **construct design is the first problem**.
Interaction Pocket	**High-confidence hypothesis (0.86).** A residue-level pocket **on the SH3 domain** (317–361) — the peptide-binding groove an adaptor uses to choose partners.
Modifications	Phosphorylation-rich, including sites in the disordered region (S213, S216) and the SH3 (S342).
Clean Signal	Soluble; no membrane or amyloid signal.

PREDICTION CONFIDENCE

Figure 1. Model-reported confidence for the headline calls. The SH3 interaction pocket (amber) is the load-bearing prediction — the partner-selection surface on a structureless adaptor.

1 The Gap

ABI3 is one of the strongest *genetic* leads in Alzheimer's disease and one of the weakest *mechanistic* ones. A rare coding variant (rs616338, p.Ser209Phe) is a genome-wide-significant risk factor for late-onset AD, reported alongside **PLCG2** and **TREM2** as the evidence that microglia drive AD risk [3]. ABI3 is expressed in microglia in AD and Nasu-Hakola brain [4]. Yet its mechanism **remains unresolved** — mouse models of *Abi3* loss give *opposing* amyloid phenotypes [5] — and it has **no experimental structure in the PDB**. It is studied biologically but undrugged (IDG T_{bio}) [2].

That combination — **high genetic priority, near-zero structural information** — is exactly where prediction earns its keep: everything below is computed from the canonical 366-residue sequence and derived structural predictions, with no experimental ABI3 structure used as input.

2 Domain Architecture And Disorder

The first thing anyone expressing ABI3 needs to know is that **roughly half of it is intrinsically disordered**. Astra predicts ~46% disorder: a short N-terminal coiled-coil, a large disordered mid-region, and a single ordered, foldable module at the C-terminus — the SH3 domain. That map *is* the construct-design plan.

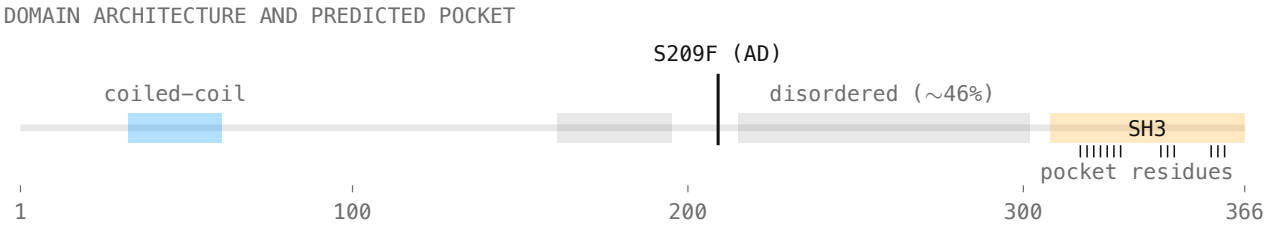

Figure 2. Domain architecture. A short coiled-coil (blue), a large disordered mid-region (grey, ~46% of the chain) and a C-terminal SH3 domain (amber) carrying the predicted interaction-pocket residues (ticks). The Alzheimer's risk variant **S209F** falls in the disordered region, not the folded domain — itself a mechanistic clue.

3 The Predicted Interaction Pocket

An adaptor's job is to choose partners, and an SH3 domain does that through a defined peptide-binding groove. The useful question is *which residues form it*. Astra places a **high-confidence pocket (0.86) on the SH3 domain** (residues 317–361) — the surface through which ABI3 would engage the actin-regulatory machinery its family is associated with. Because the pocket sits on the one ordered, foldable module, it is also the part of ABI3 most tractable to express and assay.

PREDICTED INTERACTION POCKET

Location	C-terminal SH3 domain (308–366)
Pocket residues	317, 319, 321–329, 341–345, 356–361
Confidence	HIGH (0.86); no known small-molecule binder

AlphaFold gives a fold; Astra adds the annotation. An AlphaFold model of ABI3 exists, but for a half-disordered protein a per-residue model is most useful when someone tells you *which* region is the foldable, functional module and which residues form its binding surface. This profile is that layer. As a control, the same pocket detection recovers the known peptide-binding grooves on SH3 domains whose structures *are* solved, so the ABI3 pocket is a like-for-like prediction. The net effect: a half-disordered GWAS hit becomes a **ranked, testable plan** — an expressible construct, a defined interaction surface, and the mutants to probe it.

4 Post-Translational And Structural Features

The predicted modification map points to how this adaptor is regulated:

- **Phosphorylation in the disordered region.** Sites such as S213 and S216 sit in the disordered mid-region — a classic regulatory pattern for adaptor proteins (phospho-switching of partner binding).
- **Phosphorylation on the SH3 module (S342).** A candidate control point for the interaction surface itself.
- **No membrane or amyloid signal.** A soluble adaptor; the disorder is regulatory, not aggregation-prone.

5 Recommended Experimental Follow-Up

This turns a structureless GWAS hit into a ranked, executable plan: each prediction is paired with the experiment that would test it and the readout to watch for.

Prediction	Experiment	Readout
SH3 = the foldable module (308–366)	Express the SH3 domain vs full-length	A well-behaved, assay-ready construct
SH3 interaction pocket (317–361)	Alanine scan + partner pulldown (AP-MS)	Loss of specific partner binding
~46% disorder map	Limited proteolysis / truncation series	Confirmed domain boundaries
S209F in the disordered region [3]	S209F vs WT binding / phospho-state	A structural hypothesis for the variant
Phospho-switch (S213/S216/S342)	Phosphomimetic / phospho-null mutants	Change in partner selection

Its microglial expression and AD genetics [3, 4] indicate where a validated interaction map would first be worth pursuing.

6 Where This Fits In A Discovery Workflow

Team	What they get from this profile
Target biology	Testable residue-level hypotheses and a validation plan
Structural biology	The foldable module, construct boundaries, and disorder map
Medicinal chemistry	SH3 pocket residues for docking and interaction-inhibitor design
BD / platform evaluation	Evidence Orbion can prioritise dark targets quickly

7 Methods

All predictions were generated with Orbion's Astra suite from the canonical ABI3 sequence (UniProt Q9P2A4 [1]). Modules used, with method publications cited where available: **AstraSUIT2** and **AstraROLE2** [6] (membrane and functional class, oligomeric state), **AstraUNFOLD** (topology, disorder, aggregation), **AstraPTM2** [7] (modification sites) and **AstraBIND** [8] (binding pocket). Reported values are model outputs; model internals are out of scope. Confidence scores are model-estimated probabilities (0–1) that rank and gate each call — not calibrated rates of experimental success.

PREDICTION PROVENANCE

Target & input	ABI3 · UniProt Q9P2A4, canonical isoform (366 aa)
Structure source	AlphaFold2 predicted model (no experimental PDB entry)
Feature inputs	ESM-2 embeddings + AlphaFold2-derived structural features [6–8]
Models	AstraSUIT2 · AstraROLE2 · AstraUNFOLD · AstraPTM2 · AstraBIND
Binding-site model	GATv2 detector trained on >250k protein–ligand complexes [8]
Confidence & calibration	Per-call model probability; per-model calibration, thresholds and benchmarks reported in [6]–[8]

Scope And Limitations

- **Prediction, not experiment.** These are computational hypotheses to prioritise experiments — not a substitute for a structure or an assay. No result here has been validated in the wet lab.

- **The pocket is predicted; no binder or partner is proven.** The SH3 surface is a residue-level interaction hypothesis. ABI3's specific incorporation into the WAVE regulatory complex is inferred from Abi-family homology, not from an ABI3-specific reconstitution.
- **Biology caveats.** ABI3's mechanism in AD microglia is unresolved (knockout models give opposing amyloid phenotypes [5]); treat the disease mechanism as an open question.

8 References

[1] UniProt Consortium. UniProtKB entry Q9P2A4 (ABI3, human). uniprot.org.

[2] Pharos / Illuminating the Druggable Genome. ABI3 target record — T_{bio}. pharos.nih.gov/targets/Q9P2A4.

[3] Sims R., van der Lee S.J., Naj A.C., et al. Rare coding variants in PLCG2, ABI3, and TREM2 implicate microglial-mediated innate immunity in Alzheimer's disease. *Nat. Genet.* **49**(9), 1373–1384 (2017). doi:10.1038/ng.3916.

[4] Satoh J.-I., Kino Y., Yanaizu M., et al. Microglia express ABI3 in the brains of Alzheimer's disease and Nasu-Hakola disease. *Intractable Rare Dis. Res.* **6**(4), 262–268 (2017). doi:10.5582/irdr.2017.01073.

[5] Ibanez K.R., Jansen-West K., et al. Deletion of *Abi3* gene locus exacerbates neuropathological features of Alzheimer's disease in a mouse model of Aβ amyloidosis. *Sci. Adv.* **8**(8), eabe3954 (2022). doi:10.1126/sciadv.abe3954.

[6] Bozkurt Ç., Vasilyeva A., Goteti A. AstraROLE2 & AstraSUIT2: Multi-Task Annotation Models for Functional Profiling of Proteins. *bioRxiv* 2025.06.21.660734 (2025). doi:10.1101/2025.06.21.660734.

[7] Bozkurt Ç., Vasilyeva A., Goteti A. AstraPTM2: A Context-Aware Transformer for Broad-Spectrum PTM Prediction. *bioRxiv* 2025.10.03.680341 (2025). doi:10.1101/2025.10.03.680341.

[8] Goteti A., Vasilyeva A., Bozkurt Ç. AstraBIND: Graph Attention Network for Predicting Ligand Binding Sites. *bioRxiv* 2025.11.10.687555 (2025). doi:10.1101/2025.11.10.687555.