ABRAXAS1 (Q6UWZ7) — Evaluation of "microtubule binding" (GO:0008017, IBA)

Focus: function-assignment hypothesis — *ABRAXAS1 directly has microtubule binding (GO:0008017)* **Source:** `genes/human/ABRAXAS1/ABRAXAS1-ai-review.yaml` → `existing_annotations[2].function_hypothesis` **Evidence type under review:** IBA (GO_REF:0000033, PAINT phylogenetic inference)

Executive Judgment

Verdict: REFUTED / OVER-ANNOTATED (paralog carry-over).

The IBA "microtubule binding" annotation on ABRAXAS1 is not supported by any primary experimental evidence for ABRAXAS1 itself. Programmatic provenance tracing shows the term was propagated by PAINT from a shared PANTHER ancestral node (**PTN001272083**) whose experimental support comes from the **paralog ABRAXAS2 (ABRO1 / FAM175B, UniProt Q15018)** — the scaffold of the cytoplasmic BRISC complex, which genuinely localizes to the spindle pole and has direct (IDA/IMP) microtubule and spindle annotations. ABRAXAS1, by contrast, is an **exclusively nuclear** scaffold of the BRCA1-A complex whose experimentally supported molecular function is **polyubiquitin-modification-dependent protein binding (GO:0031593, IDA)**.

Two co-propagated terms from the *same* node/source — GO:0008608 (spindle-microtubule attachment to kinetochore) and GO:0090307 (mitotic spindle assembly) — are part of the same over-annotation cluster and share the fate of GO:0008017.

Most important caveat: This is a decision about *direct annotation carry-over*, not a claim that ABRAXAS1 has zero mitotic role. ABRAXAS1 does participate in mitotic G2/M **DNA damage checkpoint signalling** (properly annotated IMP/NAS), but that is checkpoint regulation, not physical microtubule binding, and does not rescue GO:0008017.

Evidence Matrix

#	Citation	Evidence type	Supports/ Refutes	Claim tested	Key finding	Context
1	QuickGO provenance (GO_REF:0000033)	computational / database	**Refutes (as direct)**	Is GO:0008017 experimental for ABRAXAS1?	GO:0008017 on Q6UWZ7 is **IBA**, assignedBy GO_Central, `withFrom` = PANTHER **PTN001272083** + **UniProtKB:Q15018**	GO annotation record
2	UniProt Q15018 (ABRAXAS2/ ABRO1)	direct assay + localization	**Competing source**	Which protein actually binds microtubules?	ABRAXAS2 has GO:0008017 **IDA**, GO:0008608 **IMP**, GO:0090307 **IMP**; localizes to **spindle pole / cytoskeleton**	Human, BRISC complex
3	Computed NW alignment (this run)	structural / evolutionary	**Qualifies**	Are ABRAXAS1 & ABRAXAS2 paralogs sharing a PANTHER family?	Global identity ~**40.8%** (shorter-seq) / ~45.4% (aligned core); both = MPN domain (7–160) + coiled-coil scaffold	Sequence computatio
4	UniProt Q6UWZ7 features/ comments	database + localization	**Refutes**	What is ABRAXAS1's function/ location?	Function = BRCA1-A scaffold recognizing K63-Ub histones; **Loc: Nucleus only**; MF IDA = GO:0031593 (polyUb-dependent binding)	Human
5	PMID **31253574** (Rabl et al., 2019, *Mol Cell*)	structural / review-level synthesis	**Refutes**	Are ABRAXAS & ABRO1 distinct scaffolds?	"…BRCC36 subunit that is functionalized by scaffold subunits **ABRAXAS and**	Human, cryo-EM/ biochem

#	Citation	Evidence type	Supports/ Refutes	Claim tested	Key finding	Context
					ABRO1, respectively" — nuclear BRCA1-A vs cytoplasmic BRISC	
6	PMID **28009280** (Kyrieleis et al., 2016)	structural	**Refutes**	Where does ABRAXAS1 act?	Recruited to **damaged chromatin**; cleaves K63-Ub on histones H2A/ H2AX	Human, negative-stain EM
7	PMIDs 17525340, 19261746, 19261748, 19261749	direct assay (IDA)	**Refutes (context)**	ABRAXAS1's real MF/CC	Foundational BRCA1-A papers; basis for GO:0070531 (IDA nucleus) and GO:0031593 (IDA polyUb binding)	Human cell
8	P 34272385 / 37198153 / 31630195	mutant phenotype / patient cells	**Qualifies**	ABRAXAS1 loss-of-function phenotypes	Genome-stability/ HR pathway-choice, BRCA1 mislocalization, breast-cancer predisposition — all **nuclear DNA-repair**	Human patient cells

GO Curation Implications

Lead (requires curator verification):

- **GO:0008017 microtubule binding (MF, IBA) → REMOVE / do not accept for ABRAXAS1.** It is an IBA carry-over whose only experimental support lies in the paralog ABRAXAS2 (Q15018). No ABRAXAS1-specific experimental evidence exists.
- **Co-propagated from the same node/source — treat identically:**
- GO:0008608 attachment of spindle microtubules to kinetochore (BP, IBA) → remove/flag.
- GO:0090307 mitotic spindle assembly (BP, IBA) → remove/flag.
- **Retain the informative, experimentally grounded MF: GO:0031593 polyubiquitin modification-dependent protein binding (IDA)** — this is the appropriate, more-specific molecular function and should be the annotation curators keep. (Do **not** fall back to bare "protein binding".)
- **Retain CC:** GO:0070531 BRCA1-A complex (IDA), GO:0005634 nucleus (IDA).

This is an MF-term removal driven by paralog-based IBA over-annotation, with a better-supported MF already in place.

Mechanistic Scope

- **Immediate molecular activity actually tested/supported for ABRAXAS1:** a **scaffold/adaptor** that reads **K63-linked polyubiquitin** (via associated RAP80/BRCC36) and physically tethers BRCA1–BARD1 to ubiquitinated H2A/H2AX at DNA double-strand breaks. Molecular function = polyubiquitin-dependent protein binding; cellular component = nuclear BRCA1-A complex.
- **Microtubule binding is a *molecular activity of a different gene product* (ABRAXAS2)**, not a downstream phenotype of ABRAXAS1. There is no direct-binding, localization, or mutant evidence placing ABRAXAS1 on microtubules or the spindle.
- ABRAXAS1's only mitosis-adjacent role is **G2/M DNA-damage checkpoint signalling** — a regulatory/pathway consequence, distinct from GO:0008017.

Conflicts and Alternatives

- **Paralog confusion (primary explanation):** ABRAXAS1 (Q6UWZ7, nuclear BRCA1-A) vs ABRAXAS2 (Q15018, cytoplasmic BRISC, spindle pole). ~41% identical; same PANTHER family → PAINT propagated ABRAXAS2's experimental spindle/microtubule terms to ABRAXAS1. The `withFrom` field explicitly names Q15018 as the source.
- **Node separation is telling:** the *genuine* ubiquitin-binding term (GO:0031593) propagated from a **different** ancestral node (PTN001272081) and is independently IDA on ABRAXAS1; the microtubule cluster propagated from **PTN001272083** and is IDA/IMP only on ABRAXAS2. The annotations that are real are internally corroborated; the microtubule ones are not.
- **No isoform/organism rescue found:** UniProt lists ABRAXAS1 localization as Nucleus only; no spindle/cytoskeletal isoform is annotated.

Knowledge Gaps

Gap	What was checked	Why it matters	What would resolve it
Any direct ABRAXAS1–tubulin/microtubule interaction	Literature search (multiple queries) + UniProt + QuickGO	If a real interaction existed, removal would be wrong	An in vitro microtubule co-sedimentation/pelleting assay with purified ABRAXAS1; IF co-localization with tubulin in mitosis
Whether ABRAXAS1 ever localizes to spindle/centrosome	UniProt subcellular location (Nucleus only); HPA nuclear body	Localization would be a prerequisite for the term	High-resolution mitotic IF / live imaging of endogenous ABRAXAS1
PAINT node review status	Traced node PTN001272083 + Q15018	Curators may already have flagged the node	Inspect the PANTHER family tree annotation and whether a NOT/qualifier was applied

Discriminating Tests

1. **Microtubule co-sedimentation assay** with purified recombinant ABRAXAS1 ± taxol-stabilized microtubules — direct test of GO:0008017; ABRAXAS2 as positive control.
2. **Mitotic immunofluorescence / live imaging** of endogenous ABRAXAS1 vs ABRAXAS2 to test spindle-pole localization (expected: ABRAXAS2 yes, ABRAXAS1 no).
3. **Depletion phenotype comparison:** siABRAXAS1 vs siABRAXAS2 spindle-assembly / chromosome mis-attachment scoring — the spindle phenotype should segregate to ABRAXAS2.
4. **PANTHER tree audit** of PTN001272083 to confirm the experimental basis is exclusively ABRAXAS2-lineage and apply an experimental-evidence-based override for ABRAXAS1.

Curation Leads (require curator verification)

- **Action change:** Remove/reject IBA GO:0008017 (and co-clustered GO:0008608, GO:0090307) on ABRAXAS1 as paralog over-annotation; keep GO:0031593 (IDA) as the informative MF.
- **Candidate reference to cite for the over-annotation source (verify snippet):** PMID **31253574** — *"...the lysine-63 linkage-specific BRCC36 subunit that is functionalized by scaffold subunits ABRAXAS and ABRO1, respectively."*
- **Candidate reference for ABRAXAS1's true nuclear function (verify snippet):** PMID **28009280** — *"It is recruited to damaged chromatin as a component of the BRCA1-A deubiquitinase, which cleaves K63-linked ubiquitin chains attached to histone H2A and H2AX."*
- **Suggested curator question:** Does GO_Central want to add a `NOT` qualifier or experimental-override for ABRAXAS1 at node PTN001272083, given that Q15018 (ABRAXAS2) is the sole experimental source and ABRAXAS1 is nucleus-restricted?
- **Suggested experiment:** microtubule co-pelleting of purified ABRAXAS1 (definitive).

Provenance (computed this run)

- UniProt Q6UWZ7: 409 aa; MPN domain 7–160; coiled-coil 206–260; Loc = Nucleus; MF IDA = GO:0031593.

- QuickGO: GO:0008017 = IBA / GO_REF:0000033 / assignedBy GO_Central / withFrom PANTHER:PTN001272083 + UniProtKB:Q15018.
- UniProt Q15018 (ABRAXAS2): microtubule binding IDA; spindle attachment IMP; spindle assembly IMP; Loc = spindle pole/cytoskeleton.
- Needleman–Wunsch ABRAXAS1 vs ABRAXAS2: ~40.8% identity (shorter seq) / ~45.4% (aligned core) → true paralogs in one PANTHER family.
