

Familial Acute Necrotizing Encephalopathy (ANE1): A Comprehensive Disease Report

Disease: Familial Acute Necrotizing Encephalopathy **MONDO ID:** MONDO:0011953 | **OMIM:** 608033 | **Category:** Mendelian (autosomal-dominant, incompletely penetrant) **Causal gene:** *RANBP2* (Nup358), HGNC:9848, NCBI Gene 5903, chromosome 2q13

Summary

Familial acute necrotizing encephalopathy (ANE1) is a rare, autosomal-dominant, incompletely penetrant predisposition to a fulminant post-infectious brain injury. It is caused by heterozygous missense variants in *RANBP2* (RAN-binding protein 2 / Nup358), the largest nucleoporin of the nuclear pore complex, with a recurrent mutational hotspot at p.Thr585Met (c.1880C>T). The disorder is unmasked when an affected individual — typically a previously healthy young child (median onset ~24 months) — contracts a common febrile viral infection such as influenza A/B, human herpesvirus-6 (HHV-6), parainfluenza, respiratory syncytial virus (RSV), or SARS-CoV-2. The infection triggers a systemic hyperinflammatory ("cytokine storm") response that drives blood-brain-barrier breakdown and produces the disease's hallmark: multiple bilaterally **symmetric** necrotic lesions, most characteristically in the thalami, plus the brainstem tegmentum, external capsules, insular cortices, periventricular white matter, and cerebellum.

The mechanistic model connects two arms of *RANBP2* biology: (1) its canonical roles in nucleocytoplasmic transport and SUMOylation, and (2) its non-canonical role in central nervous system (CNS) energy metabolism, where RanBP2 binds hexokinase I ("the pacemaker of glycolysis") and the mitochondrial metallochaperone Cox11. A mouse model demonstrated that *RanBP2* haploinsufficiency selectively lowers hexokinase I and ATP levels in the CNS, providing a biological rationale for the brain's vulnerability. On top of this metabolic predisposition, the infection-driven cytokine storm (IL-6, TNF- α , hyperferritinemia) produces endothelial activation and vasogenic/cytotoxic edema with petechial hemorrhage ("dysoria"), culminating in symmetric thalamic necrosis.

ANE1 carries high morbidity and mortality (~30–40% mortality in some cohorts; frequent severe neurologic sequelae in survivors). Diagnosis rests on the characteristic symmetric thalamic MRI signature combined with *RANBP2* sequencing and a supportive laboratory profile (elevated CSF protein without pleocytosis, elevated transaminases/CPK, thrombocytopenia, hyperferritinemia, no hyperammonemia). There is no approved disease-specific therapy; management combines intensive supportive care with early immunomodulation (high-dose corticosteroids, IVIG, and IL-6 blockade with tocilizumab). Prophylactic pulse steroids during febrile infections in known carriers, and influenza vaccination, are emerging preventive strategies. Notably, ~19% of familial/recurrent cases lack a *RANBP2* variant, indicating locus heterogeneity and additional susceptibility loci still to be discovered.

Key Findings

Finding 1 — ANE1 is caused by dominant *RANBP2* missense mutations, most commonly p.Thr585Met

The landmark study by Neilson et al. (2009) mapped a 7-Mb ANE1 susceptibility locus in a family segregating recurrent ANE as an incompletely penetrant, autosomal-dominant trait, and found that all affected individuals and obligate carriers were heterozygous for the missense variant c.1880C>T, p.Thr585Met in *RANBP2*. As the authors state: *"We now report that all affected individuals and obligate carriers in this family are heterozygous for a missense mutation (c.1880C-->T, p.Thr585Met) in the gene encoding the nuclear pore protein Ran Binding Protein 2 (RANBP2)"* (PMID: 19118815). The same mutation recurred widely: *"Patients from 9 of 15 additional kindreds with familial or recurrent ANE had the identical mutation. It arose de novo in two families"* — establishing p.Thr585Met as a true mutational hotspot that can also arise de novo.

Allelic heterogeneity exists. Reported pathogenic variants beyond the p.Thr585Met hotspot include **p.Trp681Cys** (a de novo variant causing recurrent ANE), **p.Glu3014Gly** (c.9041A>G, identified in a four-generation Chinese family: *"A novel missense variation, c.9041A > G, p. (Glu3014Gly) in RANBP2 was identified in this family"* — PMID: 35348941), and p.Thr585Met reported co-occurring with a *CPT2* thermolabile modifier in the first Japanese case.

- **Variant type:** missense (point mutations)
- **Classification (ACMG/AMP):** pathogenic / likely pathogenic for the recurrent variants

- **Origin:** germline (inherited or de novo)
- **HGNC:** RANBP2 (HGNC:9848); **OMIM gene:** 601181; **OMIM phenotype (ANE1):** 608033

Finding 2 — ANE1 is triggered by common viral febrile infections and presents with bilateral symmetric thalamic lesions

ANE is a rapidly progressive encephalopathy in previously healthy children following common viral infections. Neilson et al. frame it precisely: *"Acute necrotizing encephalopathy (ANE) is a rapidly progressive encephalopathy that can occur in otherwise healthy children after common viral infections such as influenza and parainfluenza"* (PMID: 19118815). The clinical episode follows a stereotyped sequence: a viral prodrome with fever → rapid deterioration of consciousness, seizures, and focal deficits → coma. In the familial (ANE1) form, episodes can **recur** with each new infection.

The neuroimaging signature is diagnostic. In an ANE1 case: *"Brain magnetic resonance imaging (MRI) showed a characteristic involvement of the bilateral thalami, external capsules, insular cortices, and brainstem, suggesting ANE"* (PMID: 34059398). The lesions are symmetric and multifocal, affecting both gray and white matter: *"symmetric multifocal brain lesions are seen in the bilateral thalami as well as other characteristic regions, involving both gray and white matter"* (PMID: 32426208). Documented viral triggers across case reports include influenza A (including H1N1), influenza B, HHV-6/HHV-7, parainfluenza, RSV, varicella zoster, dengue, and SARS-CoV-2.

Finding 3 — Prognosis is predicted by the ANE Severity Score, brainstem involvement, and hyperferritinemia; early steroids improve outcome

The **ANE Severity Score (ANE-SS)** stratifies risk on a 0–9 scale: 3 points for shock, 2 for brainstem lesions, 2 for age >48 months, 1 for platelet count <100,000/μL, and 1 for CSF protein >60 mg/dL, yielding low (0–1), medium (2–4), and high (5–9) risk strata (PMID: 24931733).

Hyperferritinemia — a marker of the underlying cytokine storm — is a key outcome predictor. Lee et al. (2024, n=29) found that *"ferritin, aspartate aminotransferase (AST), and ANE severity score (ANE-SS) were the predictors associated with outcomes"* (PMID: 38295717), with 69% of patients having poor neurological outcomes; thresholds of ferritin >1823 ng/mL, AST >78 U/L, and ANE-SS >4.5 predicted poor outcome, and higher ferritin/ANE-SS correlated with brainstem involvement. A Malaysian cohort (n=13) reported 38.5% mortality with 5 brainstem

deaths, and all survivors in a vegetative state or with severe disability at discharge (PMID: 33358123). Critically, *"Early treatment with high dose steroids is associated with a more favorable outcome"* (PMID: 32426208), especially in patients without brainstem involvement.

ANE-SS component	Points
Shock	3
Brainstem lesions	2
Age >48 months	2
Platelets <100,000/ μ L	1
CSF protein >60 mg/dL	1
Risk strata	Low 0–1 · Medium 2–4 · High 5–9

Finding 4 — Pathophysiology: *RANBP2* variant + viral fever → cytokine storm → BBB breakdown → symmetric thalamic necrosis

The proposed causal chain integrates genetics, immunology, and tissue pathology. The original neuropathologic description of ANE emphasized blood–brain–barrier failure: *"Both the gray and white matter are involved, with neuropathological evidence of local breakdown of the blood-brain barrier (dysoria)"* (PMID: 9105653). The *RANBP2*-specific mechanisms remain only partially demonstrated; Levine et al. enumerate several non-mutually-exclusive hypotheses: *"There are several non-mutually exclusive hypotheses suggesting possible etiologies for this phenotype based on the many functions of RANBP2 within the cell. These include dysfunctions in nucleocytoplasmic trafficking and intracellular metabolic regulation, as well as cytokine storm, and abnormal distribution of mitochondria"* (PMID: 32426208).

Evidence for the cytokine-storm step comes from severe pediatric viral encephalopathy, where *"Serum concentrations of cytokines/chemokines including interleukin 6 and tumor necrosis factor- α were significantly higher within 24 hours of onset than for controls"* (PMID: 41714597).

Finding 5 — Epidemiology: rare pediatric disorder; sporadic form predominant in East Asia; familial ANE1 very rare

ANE of childhood was first established as a disease entity predominantly affecting infants and young children in Japan and Taiwan: *"This disease predominantly affects infants and young children living in Japan and Taiwan, and manifests itself as acute encephalopathy following viral*

infections" (PMID: 9105653). Importantly, the geographic distribution of the familial (RANBP2-associated) form differs from the sporadic form: *"Although sporadic ANE predominantly affects Asian children, ANE1 is very rare in east Asia"* (PMID: 34059398). The familial form has been reported across European, North American, Chinese, and (first in 2021) Japanese kindreds. No precise prevalence/incidence figures exist; ANE is classified as a rare disease (Orphanet).

Finding 6 — RANBP2/Nup358 is a multidomain nucleoporin that binds hexokinase I and Cox11; haploinsufficiency lowers CNS ATP (mouse model)

RANBP2 (Nup358, ~358 kDa) is the largest nucleoporin, forming the cytoplasmic filaments of the nuclear pore complex and regulating nucleocytoplasmic transport: *"RANBP2 (also known as Nup358) is the largest nucleoporin of the nuclear pore complex (NPC), where it constitutes the main component of the cytoplasmic filaments and regulates nucleocytoplasmic transport"* (PMID: 40976348). Its domains include a zinc finger, four Ran-binding domains, an E3 SUMO ligase domain, and a cyclophilin-like domain; it localizes to the nuclear envelope, annulate lamellae, mitochondria–ER junctions, and kinetochores.

The metabolic link is decisive for understanding CNS vulnerability. Aslanukov et al. showed that *"RanBP2 associates in vitro and in vivo and colocalizes with the mitochondrial metallochaperone, Cox11, and the pacemaker of glycolysis, hexokinase type I (HKI) via its leucine-rich domain"* and, critically, that *"haploinsufficiency of RanBP2 in an inbred strain causes a pronounced decrease of HKI and ATP levels selectively in the central nervous system"* (PMID: 17069463). This provides a mechanistic basis for why the brain — and energy-demanding structures such as the thalamus — are selectively vulnerable.

Finding 7 — Marked intrafamilial phenotypic variability; prophylactic pulse steroids may prevent recurrences

Alrifai et al. (2026) reported three siblings sharing the identical pathogenic RANBP2 variant but with markedly divergent courses — one progressed to brain death with influenza A, one responded to corticosteroids with mild residual cognitive dysfunction, and a third remained neurologically intact despite recurrent infections: *"Despite sharing the same genotype, the clinical spectrum was markedly variable"* (PMID: 42407393). This illustrates **variable expressivity** and **incomplete penetrance**. Importantly, the surviving siblings received a preventive strategy: *"The surviving cases were given a preventive treatment plan with pulse steroids during influenza infections. At 2 years of follow-up, they still have no new episodes of encephalopathy"* (PMID: 42407393) — proof-of-concept for anti-inflammatory prophylaxis during febrile illness.

Finding 8 — Systematic review (n=92): demographics and vaccine safety

Cavaliere et al. (2026) conducted a PRISMA systematic review of familial/recurrent/genetic ANE: *"Ninety-two patients were analysed (91 literature cases and 1 novel case) (median onset age 24 months; 62% male; RANBP2 mutations in 81% of tested individuals)"* (PMID: 42385467). Of 142 clinical events, 108 were definite/probable ANE and 34 were atypical (25 infection-triggered encephalopathy without bithalamic involvement; 9 other acute neurological events); in 13% of patients, atypical episodes preceded a subsequent ANE event. Regarding vaccination safety: *"5/20 resumed vaccination post-ANE (no vaccine-related relapses over a median follow-up of 19 months)"* (PMID: 42385467).

Finding 9 — Diagnosis rests on characteristic MRI plus *RANBP2* sequencing; key labs distinguish from Reye syndrome

The diagnosis is clinical-radiological, supported by a characteristic laboratory profile. A classic case description notes: *"His serum CPK was markedly elevated, but there was no hyperammonaemia or hypoglycaemia. His CSF showed an increased protein level, but the cell count and glucose level were normal"* (PMID: 10834515) — the elevated CSF protein without pleocytosis and the absence of hyperammonemia/hypoglycemia distinguish ANE from Reye syndrome. The para-infectious (non-neuroinvasive) nature is supported by PCR-negative CSF: *"Antibody production without detectable levels of influenza virus in cerebrospinal fluid suggests that virus infection occurred, but the virus did not replicate in sufficient numbers in his central nervous system"* (PMID: 10834515). Molecular confirmation of ANE1 is by *RANBP2* single-gene sequencing or multigene panel/WES. A rapid bedside functional assay for *RANBP2*-ANE1 has been proposed (PMID: 38046586).

Finding 10 — ANE1 is a gene–environment disorder with modifiers and locus heterogeneity

ANE1 is a paradigmatic gene–environment interaction: it requires both a genetic predisposition (*RANBP2* variant) and an environmental trigger (febrile viral infection), with incomplete penetrance. Ohashi et al. reported a modifier: a patient carrying both *RANBP2* p.Thr585Met and a thermolabile *CPT2* polymorphism — *"The patient also harbored a CPT2 polymorphism that is linked to acute encephalopathy in Japanese patients. Thus, he had a genetic background with two susceptibility variants for acute encephalopathy, RANBP2 (frequent in the Caucasians), and CPT2 (frequent in the Japa[nese])"* (PMID: 34059398). Locus heterogeneity is established by López-Laso et al., who described a familial/recurrent ANE family **without**

RANBP2 mutations: "Mutations in *RANBP2* are not the sole susceptibility alleles for familial or recurrent ANE" (PMID: 19643689) — consistent with the systematic review's finding of *RANBP2* variants in only 81% of tested cases.

Finding 11 — Management is supportive plus early immunomodulation; prophylactic steroids in carriers are emerging prevention

No *RANBP2*-targeted or disease-specific approved therapy exists. Acute management combines ICU-level supportive care with immunomodulation. For SARS-CoV-2-related ANE: "Treatment with a combination of early steroid therapy, intravenous immunoglobulin therapy, and targeted interleukin 6 (IL-6) blockade yielded good neurological improvements" (PMID: 36529001). Preventive strategies include prophylactic pulse steroids during infections in carriers (PMID: 42407393) and influenza vaccination, which did not provoke relapses (PMID: 42385467).

Report by Template Section

1. Disease Information

ANE1 is a rare, autosomal-dominant, incompletely penetrant Mendelian predisposition to infection-triggered acute necrotizing encephalopathy. **Identifiers:** MONDO:0011953; OMIM 608033 (phenotype); *RANBP2* gene OMIM 601181; Orphanet (rare disease). **Synonyms:** acute necrotizing encephalopathy type 1; familial/recurrent/genetic acute necrotizing encephalopathy; *RANBP2*-associated ANE; infection-induced acute encephalopathy 3 (IIAE3). Information is derived from **aggregated disease-level resources** (case reports, kindred studies, and systematic reviews) rather than EHR.

2. Etiology

Primary cause: heterozygous germline missense variants in *RANBP2* (recurrent p.Thr585Met). **Genetic risk factors:** the causal *RANBP2* variants; modifier/co-susceptibility alleles such as the thermolabile *CPT2* p.Phe352Cys polymorphism (PMID: 34059398). **Environmental risk factors:** common febrile viral infections (influenza A/B, HHV-6/7, parainfluenza, RSV, varicella zoster, dengue, SARS-CoV-2); fever/hyperthermia is a key trigger. **Protective factors:** avoidance/mitigation of febrile viral illness (vaccination, antipyresis, antivirals) reduces trigger

exposure; no genetic protective alleles are established. **Gene–environment interaction:** disease requires BOTH the genetic predisposition AND an infectious trigger — a canonical GxE disorder with incomplete penetrance ([PMID: 19643689](#)).

3. Phenotypes

Core phenotypes and suggested HPO terms: - **Acute/recurrent encephalopathy** (HP:0006846 Acute encephalopathy) — rapid deterioration of consciousness; severe; episodic/recurrent with infections. - **Seizures** (HP:0001250) — common in acute episodes. - **Fever** (HP:0001945) — prodromal trigger. - **Coma / reduced consciousness** (HP:0001259) — severe episodes. - **Ataxia** (HP:0001251), **dysarthria** (HP:0001260), **developmental regression/delay** (HP:0002376) — sequelae. - **Elevated CSF protein** (HP:0002922), **elevated hepatic transaminases** (HP:0002910), **hyperferritinemia** (HP:0003281), **thrombocytopenia** (HP:0001873), **elevated CPK** (HP:0003236) — laboratory abnormalities. - **Age of onset:** infancy–early childhood (median 24 months). **Severity:** severe/variable. **Progression:** episodic/relapsing with infections, often with cumulative deficits. **Frequency:** RANBP2 variant in ~81% of tested familial cases. **QoL impact:** survivors frequently have severe disability or vegetative state.

4. Genetic/Molecular Information

Causal gene: *RANBP2* (HGNC:9848; OMIM 601181; NCBI Gene 5903). **Pathogenic variants:** p.Thr585Met (c.1880C>T, recurrent hotspot, pathogenic); p.Trp681Cys (de novo); p.Glu3014Gly (c.9041A>G). **Variant type:** missense. **Classification:** pathogenic/likely pathogenic (ACMG/AMP). **Allele frequency:** extremely rare in gnomAD (private/ultra-rare). **Origin:** germline (inherited or de novo). **Functional consequence:** altered function of a multidomain nucleoporin affecting nucleocytoplasmic transport, SUMOylation, and CNS energy metabolism (HKI/ATP). **Modifier genes:** *CPT2* thermolabile polymorphism. **Chromosomal abnormalities:** none characteristic; the 2q12-13 region harboring *RANBP2* is structurally dynamic with RGPD paralogs ([PMID: 37795679](#)).

5. Environmental Information

Environmental/infectious factors: viral febrile infections are the essential trigger — influenza A/B (including H1N1), HHV-6/HHV-7, parainfluenza, RSV, varicella zoster, dengue, and SARS-CoV-2. **Lifestyle factors:** not established; fever itself is the operative exposure. The para-infectious nature (PCR-negative CSF) indicates the brain injury is immune/inflammatory rather than directly virus-invasive.

6. Mechanism / Pathophysiology — Ordered Causal Chain

1. Germline heterozygous RANBP2 missense variant (e.g., p.Thr585Met)
 - creates an incompletely penetrant predisposition [demonstrated: genetics]
2. Baseline reduced RANBP2 function
 - lowers hexokinase I and ATP selectively in the CNS
[demonstrated in RanBP2+/- mouse; inferred for human variants]
3. A common febrile viral infection (influenza, HHV-6, SARS-CoV-2)
 - triggers a systemic hyperinflammatory response [demonstrated: clinical]
4. Excessive pro-inflammatory cytokines (IL-6, TNF- α ; hyperferritinemia)
 - "cytokine storm" [demonstrated: serum cytokines elevated <24h]
5. Cytokines cause endothelial activation + local BBB breakdown ("dysoria")
 - vasogenic/cytotoxic edema + petechial hemorrhage [demonstrated: neuropathology]

- |
 - |—(branch A: metabolic) energy failure in
| high-demand gray matter (thalamus, brainstem)
 - |
 - |—(branch B: inflammatory) direct cytokine-mediated
| endothelial/parenchymal injury
6. Multifocal SYMMETRIC necrosis → bilateral thalami, brainstem tegmentum, external capsules, insular cortex, periventricular white matter, cerebellum
 - coma, seizures, focal deficits; recurrence with each infection

- **Molecular pathways:** cytokine signaling (IL-6/JAK-STAT, TNF- α); nucleocytoplasmic transport; SUMOylation (RANBP2 E3 SUMO ligase); glycolysis (hexokinase I).
- **Cellular processes:** inflammation (GO:0006954), necrosis (GO:0070265), blood–brain-barrier disruption, apoptosis (GO:0006915).
- **Protein dysfunction:** altered function of the Nup358 cytoplasmic-filament nucleoporin.
- **Metabolic changes:** reduced CNS hexokinase I and ATP (GO:0006006 glucose metabolic process; GO:0006754 ATP biosynthetic process).
- **Immune involvement:** hyperinflammatory cytokine storm (not autoimmune, not immunodeficiency).
- **Tissue damage:** BBB breakdown (dysoria), vasogenic/cytotoxic edema, petechial hemorrhage, necrosis.
- **Cell types (CL):** vascular endothelial cells (CL:0000115), neurons (CL:0000540), astrocytes (CL:0000127), microglia (CL:0000129).
- **Subcellular (GO CC):** nuclear pore (GO:0005643), cytoplasmic filaments, mitochondrion (GO:0005739), mitochondria–ER junction.

7. Anatomical Structures Affected

- **Primary organ:** brain (UBERON:0000955); **body system:** central nervous system.
- **Specific sites (UBERON):** thalamus (UBERON:0001897) — bilateral and symmetric; brainstem/midbrain tegmentum (UBERON:0002298 brainstem); external capsule; insular cortex (UBERON:0002022); periventricular white matter; cerebellum (UBERON:0002037); mammillary bodies, periaqueductal gray, hippocampus (reported in some cases).
- **Lateralization:** bilateral, symmetric — a diagnostic hallmark.
- **Secondary involvement:** rare multiorgan involvement (e.g., acute fulminant myocarditis reported concomitantly).
- **Tissue level:** both gray and white matter; nervous tissue and cerebral vasculature.

8. Temporal Development

- **Onset:** pediatric, typically infancy–early childhood (median ~24 months); **pattern:** acute/fulminant, following a viral prodrome by days.
- **Progression:** episodic/relapsing — acute episodes recur with each new febrile infection; within an episode, rapid (hours–days) deterioration to coma.
- **Disease course:** lifelong predisposition; between episodes patients may be stable, but cumulative deficits can accrue.
- **Remission:** acute episodes may partially resolve (imaging shows resolution of swelling with residual cytotoxic edema); prophylactic steroids during infections may prevent new episodes.
- **Critical period:** the first 24–72 hours of a febrile illness is the window for intervention (early steroids/immunomodulation).

9. Inheritance and Population

- **Inheritance:** autosomal dominant, **incomplete penetrance**, **variable expressivity** (PMID: 19118815; PMID: 42407393).
- **Penetrance:** incomplete; some carriers never develop ANE despite recurrent infections.
- **De novo / mosaicism:** de novo occurrence documented in ≥ 2 families; germline mosaicism not specifically reported.
- **Epidemiology:** no precise prevalence/incidence; ultra-rare. Sporadic ANE predominates in East Asian children; familial ANE1 is rare worldwide and very rare in East Asia.

- **Demographics (systematic review, n=92):** median onset 24 months; 62% male; RANBP2 variant in 81% of tested.
- **Founder effect/consanguinity:** no founder effect established; reported in non-consanguineous families.

10. Diagnostics

- **Imaging (definitive):** brain MRI showing bilateral **symmetric** lesions of thalami, brainstem tegmentum, external capsules, insular cortex, periventricular white matter, cerebellum; thalamic "tricolour"/laminar/concentric pattern on ADC maps.
- **Laboratory:** CSF elevated protein **without** pleocytosis; elevated serum transaminases (AST/ALT) and CPK; thrombocytopenia; hyperferritinemia; **no** hyperammonemia or hypoglycemia (distinguishes from Reye syndrome); CSF typically virus-PCR-negative.
- **Genetic testing:** RANBP2 single-gene sequencing, multigene encephalopathy panels, or WES/WGS; a rapid bedside functional assay has been proposed ([PMID: 38046586](#)).
- **Differential diagnosis:** sporadic ANE; acute disseminated encephalomyelitis (ADEM); Leigh/MELAS mitochondrial disease; Wernicke encephalopathy; acute bilateral striatal necrosis; Reye syndrome; acute encephalopathy with biphasic seizures and late reduced diffusion (AESD); dengue necrotizing encephalopathy-like encephalitis.
- **Screening:** cascade genetic testing of at-risk relatives in known kindreds; prenatal/pre-symptomatic testing feasible once a familial variant is identified.

11. Outcome / Prognosis

- **Mortality:** high — ~38.5% in the Malaysian cohort (5 brainstem deaths); ~30–40% range reported; 69% poor neurological outcome in a 29-patient series.
- **Morbidity:** survivors frequently have severe disability or vegetative state at discharge, with variable later recovery.
- **Prognostic factors:** ANE-SS (>4.5), brainstem involvement, shock, hyperferritinemia (>1823 ng/mL), AST (>78 U/L), low GCS at presentation, higher MRI scores.
- **Recovery:** partial recovery possible with early immunomodulation, particularly when the brainstem is spared; ≥12-month follow-up recommended for accurate prognostication.

12. Treatment

No disease-specific approved therapy. **Acute:** intensive supportive/ICU care + immunomodulation: - High-dose IV corticosteroids (earliest treatment associated with better outcome) — NCIT: Corticosteroid Therapy. - IVIG (intravenous immunoglobulin). - IL-6 blockade (tocilizumab) — effective in SARS-CoV-2-related ANE ([PMID: 36529001](#)). - Trigger-directed therapy: oseltamivir + antipyresis for influenza. - Severe multiorgan cases: ECMO support reported. **Prevention in carriers:** prophylactic pulse steroids during febrile infections ([PMID: 42407393](#)); influenza vaccination. **Pharmacogenomics / targeted / gene / cell / RNA therapies:** none established.

13. Prevention

- **Primary:** influenza vaccination (safe with respect to ANE relapse — [PMID: 42385467](#)); avoidance/early treatment of febrile viral illness.
- **Secondary:** early recognition and prompt immunomodulation during febrile illness in known carriers; prophylactic pulse steroids.
- **Tertiary:** rehabilitation; management of neurologic sequelae.
- **Genetic counseling:** autosomal-dominant transmission with incomplete penetrance and variable expressivity must be conveyed; cascade testing in kindreds.

14. Other Species / Natural Disease

- **Taxonomy / orthologs:** *Ranbp2* mouse ortholog (*Mus musculus*, NCBI:txid10090). No naturally occurring companion-animal/wildlife equivalent of ANE1 is established (not reported in OMIA).
- **Comparative biology:** RANBP2 is conserved across metazoans; the primate-specific RGPD paralog family arose via duplication during ape evolution ([PMID: 37795679](#)).
- **Zoonotic potential:** not applicable (the human disorder is a host genetic predisposition, not a transmissible disease).

15. Model Organisms

- **Mouse (*Mus musculus*):** *RanBP2*-null mice are embryonic lethal; inbred *RanBP2*(+/-) haploinsufficient mice show selectively decreased CNS hexokinase I and ATP, growth deficits, and impaired glucose catabolism ([PMID: 17069463](#)) — recapitulating the **metabolic** arm of ANE1.

- **Additional mouse phenotype:** *RanBP2* haploinsufficiency is neuroprotective against light-elicited, age-dependent photoreceptor degeneration and alters retinal free-fatty-acid metabolism (PMID: 18949001).
- **Model types available:** knockout (lethal), haploinsufficient/heterozygous. **Limitation:** no mouse model fully reproduces the infection-triggered symmetric thalamic necrosis of human ANE1; the gene–environment (viral-trigger) dimension is not captured.
- **Resources:** MGI (mouse), Alliance of Genome Resources.

Mechanistic Model / Interpretation

ANE1 is best understood as a **two-hit, gene–environment disorder** superimposed on an underlying **metabolic vulnerability**:

Layer	Element	Evidence strength
Predisposition	Germline <i>RANBP2</i> variant (p.Thr585Met)	Demonstrated (genetics, PMID: 19118815)
Baseline vulnerability	Reduced CNS hexokinase I / ATP	Demonstrated in mouse (PMID: 17069463); inferred in humans
Trigger	Febrile viral infection	Demonstrated (clinical, PMID: 19118815)
Amplifier	Cytokine storm (IL-6, TNF- α , ferritin)	Demonstrated (serum cytokines, PMID: 41714597)
Effector	BBB breakdown ("dysoria")	Demonstrated (neuropathology, PMID: 9105653)
Lesion	Symmetric thalamic/brainstem necrosis	Demonstrated (MRI/pathology)

The convergence of a metabolic predisposition (why the brain, and specifically energy-hungry deep gray structures) with an inflammatory trigger (why infections, why symmetric and fulminant) explains both the anatomical selectivity and the episodic, infection-linked course. The therapeutic implication follows directly: interrupting the cytokine-storm amplifier early (steroids, IVIG, tocilizumab) and pre-empting it in carriers (prophylactic steroids during fevers) are the rational interventions, and both have preliminary clinical support.

The ~19% of familial cases without a *RANBP2* variant ([PMID: 42385467](#); [PMID: 19643689](#)) indicate genetic locus heterogeneity — additional susceptibility genes in the same mechanistic pathway remain to be identified.

Evidence Base

PMID	Role	Key contribution
19118815	Landmark	Identifies <i>RANBP2</i> p.Thr585Met as causal; AD, incomplete penetrance; viral trigger
35348941	Support	Novel p.Glu3014Gly variant — allelic heterogeneity
34059398	Support	First Japanese ANE1; <i>CPT2</i> modifier; MRI signature; geographic contrast
32426208	Review	Mechanistic hypotheses; symmetric lesions; early steroids beneficial
24931733	Tool	Defines ANE Severity Score
38295717	Support	Ferritin/AST/ANE-SS as outcome predictors
9105653	Foundational	Defines ANE entity; BBB breakdown (dysoria); East Asian predominance
41714597	Support	IL-6/TNF- α elevated <24h — cytokine storm evidence
17069463	Mechanism	RanBP2–HKI–Cox11; haploinsufficiency lowers CNS ATP (mouse)
40976348	Background	RANBP2 identity, domains, localization
42407393	Support	Variable expressivity in 3 siblings; prophylactic steroids
42385467	Review	n=92 demographics; RANBP2 in 81%; vaccine safety
10834515	Support	Lab profile; para-infectious (PCR-negative CSF)
38046586	Support	Proposed rapid bedside RANBP2-ANE1 diagnostic
19643689	Support	Locus heterogeneity — RANBP2 not the sole susceptibility allele
36529001	Support	Steroids + IVIG + tocilizumab effective (SARS-CoV-2 ANE)
33358123	Support	Malaysian cohort: 38.5% mortality; severe sequelae
37795679	Background	RANBP2 evolution, RGPD paralogs, disease associations
18949001	Model	RanBP2 haploinsufficiency effects in mouse retina/metabolism
26923722	Support	Variable course; novel p.Trp681Cys de novo variant

Limitations and Knowledge Gaps

1. **No precise epidemiology.** Prevalence and incidence of ANE1 are unknown; evidence is from case reports, kindreds, and a single systematic review (n=92).
2. **Mechanism partly inferred.** The link from human *RANBP2* variants to the metabolic (HKI/ATP) deficit is demonstrated only in mice; direct human tissue evidence is lacking. The exact molecular pathway from variant to cytokine storm remains "elusive."
3. **Locus heterogeneity unresolved.** ~19% of familial/recurrent cases lack a *RANBP2* variant; the additional gene(s) are unidentified.
4. **Treatment evidence is low-grade.** Steroids, IVIG, and tocilizumab are supported by case reports/small series, not randomized trials; one cohort found early immunomodulation did not change outcome, highlighting inconsistency.
5. **Penetrance/expressivity modifiers poorly characterized.** Beyond *CPT2*, genetic and environmental modifiers that determine whether a carrier develops ANE are largely unknown.
6. **No faithful animal model** reproduces the infection-triggered symmetric thalamic necrosis.
7. **Some citation snippets were normalized/approximate** (e.g.,

P 24931733

P 35348941

P 38046586

flagged during verification), so exact wording should be re-verified against source abstracts.

Proposed Follow-up Experiments / Actions

1. **Establish an infection-challenge model** in *RanBP2* mutant (knock-in p.Thr585Met) mice, challenged with influenza/poly(I:C), to test whether the symmetric thalamic lesion and cytokine storm can be recapitulated and pharmacologically prevented.
2. **Identify the non-RANBP2 loci** in the ~19% of familial cases via WGS/trio sequencing and GeneMatcher collaboration.

3. **Prospective registry + natural history study** to generate true prevalence/incidence, penetrance estimates, and standardized outcomes.
 4. **Biomarker study** correlating serial serum IL-6, TNF- α , and ferritin trajectories with ANE-SS and MRI severity to define treatment-response thresholds.
 5. **Randomized/adaptive trial** (or structured prospective cohort) of early high-dose steroids $\pm$ tocilizumab $\pm$ IVIG, stratified by brainstem involvement.
 6. **Carrier prophylaxis protocol** formally evaluating prophylactic pulse steroids and influenza vaccination during febrile illness in genotyped carriers.
 7. **Functional validation** of the proposed rapid bedside RANBP2-ANE1 assay against genetic gold standard across multiple variants.
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Report compiled from 11 confirmed findings and 42 reviewed papers across 5 investigation iterations. Evidence source types span human clinical case reports/cohorts, systematic review, mouse model organism, and in vitro biochemistry.
